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HTA Core Model® Online

Disclaimer
This information collection is a core HTA, i.e. an extensive analysis of one or more health technologies using all nine domains of the HTA Core Model. The core HTA is intended to be used as an information base for local (e.g. national or regional) HTAs.

Collection name
Use of Intravenous immunoglobulins for Alzeheimer's disease including Mild Cognitive Impairment
Scope

Immunoglobulins (IGG) compared to placebo, not doing anything or Usual supportive care in the treatment of Alzheimer's disease in elderly AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.

(See detailed scope below)

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Use of Intravenous immunoglobulins for Alzeheimer's disease including Mild Cognitive Impairment

Table of contents

Collection summary

Background

Like all dementias, Alzheimer's Disease is an important global public health problem.

Immunoglobulins, traditionally used to prevent or treat infectious diseases have been recently used for other non-communicable conditions including rare neurological diseases.

We report on reviews of the evidence of use and effect of immunoglobulins for Alzheimer's Disease and Mild Cognitive Impairment.

The existence and significance of Mild Cognitive Impairment are still debated

Results

Health Problem and Current Use of the Technology (CUR)

Alzheimer's Disease is an important public health problem, like all dementias. The existence and significance of Mild Cognitive Impairment are still debated

Description and technical characteristics of technology (TEC)

Immunoglobulins have been tradionatioally used for passive immunisation against infectious diseases, although in the last decades their use has expanded to include blood disorders, rare neurological disorders and cancer. **Safety of the technology (SAF)**

Effectiveness of the technology (EFF)

Despite several placebo controlled trials having been carried out and completed and some being underway so far there is no evidence of either positive or negative impact of IVIG on Alzheimer's Disease or Mild Cognitive Impairment.

Costs and economic evaluation (ECO)

In the absence of any discernible difference against placebo, no estimates of a trade-off between costs and benefits can be made at present.

Ethical aspects of the technology (ETH)

The only foreseeable ethical aspect which could be raised by the granting of a MA are the effects of industrial production on the limited supply of blood products used to treat other conditions such as clotting disorders.

Organisational aspects of the technology (ORG)

In the absence of any discernible difference against placebo, no estimates of organisational impact can be made at present

Social aspects of the technology (SOC)

In the absence of any discernible difference against placebo the social aspects cannot be defined

Legal aspects of the technology (LEG)

In the absence of any discernible difference against placebo the legal aspects cannot be defined

Discussion

The data gathered and synthetized in this Core HTA show that at present there is little evidence of any effect (positive or negative) of IVIG on Alzheimer's Disease and Mild Cognitive Impairment. Although the evidence base is still small and several trials are still to be completed or reported, the persisting speculative nature of the pathogenesis of dementia and consequent mechanism of action of any biological product suggest that investment in research of causation might be a better priority.

This is the second of our three JA2 scheduled pilot projects. We have experienced several hitherto unforeseen difficulties during the development of the project.

The first problem was related to the aftermath of choice of topic. There is little doubt that dementias are an important topic but we were also aware of the potential demands on plasma derivatives for the manufacture of IVIG. This would have a major influence in a delicately balanced market with many highly motivated patient organisations. Choice of an inert comparator, although dictated by the early phase of experimentation of AD IVIG, was also not a traditional choice in any HTA activity and much discussed. The choice has left unresolved disagreements.

The pre-Market Authorisation Application (MAA) nature of the intervention being assessed also meant that many trials were ongoing or unpublished, even if completed. This carried many implications which added to the difficulties. Data were either not available or were made available indirectly on registers such as clinicaltrials.gov after our manufacturer enquires drew a blank. Register "publication" took place in the autumn of 2014, long after completion of our primary searches in February 2014. Although data were quantitatively plentiful, they lacked detailed description of methods and a full study protocol which made its very inclusion and interpretation contentious. The difficulties came to a head with two distinct points of view regarding the inclusion of data after the main search had taken place. Some investigators were worried about risk of bias being introduced in the assessment, others thought the importance of reporting the largest trial ever conducted (yet inexplicably unpublished two years from completion) to be paramount.

To manage the problems, Coordination asked the Editorial Team for guidance. The Team, made up of all PIs, decided to allow inclusion of the register data. However, to minimize the risk of introducing bias by secondary searching (i.e. post primary search in February 2014) of only two domains, the Team recommended the conduct of an update search for all other domains to coincide with the date of the secondary search of registers. Although the

secondary search did not identify any new additional evidence, it generated additional work, further delay and dissatisfaction with the composition of the Team as all members of the domains on which the discussion centered wanted a say.

Several positive points arise from this experience. First, it is clear that the management infrastructure and input were insufficient to deal with the complexity and novelty of the work. Second, few members of the team had experience in dealing with what were essentially unpublished data. Third, the topic proved to be a good testing ground for dealing with unexpected problems. The experience gained should be reflected in future procedures.

Closing Remarks

The Core Model is not intended to provide a cookbook solution to all problems but to suggest a way in which information can be assembled and structured, and to facilitate its local adaptation. The information is assembled around the nine domains, each with several result cards in which questions and possible answers are reported.

The reasons for having a standardised but flexible content and layout are rooted in the way HTA is conducted in the EU and in the philosophy of the first EUnetHTA Joint Actions production experiment.

HTA is a complex multidisciplinary activity addressing a very complex reality – that of healthcare. Uniformly standardised evidence-based methods of conducting assessments for each domain do not exist1[1]. There are sometimes variations across and within Member States in how things are done and which aspects of the evaluation are privileged. This is especially so for the “softer” domains such as the ethical and social domains.

This pilot represents a useful lesson for methodological development in EUnetHTA Joint Action 2.

Collection methodology

Objective

To produce a Core Health Technology Assessment (HTA) assessing the effects of use of intravenous immunoglobulins for Alzeheimer’s disease including Mild Cognitive Impairment based on the EUnetHTA Core Model and working within the a mixed Collaborative Model organisational framework.

Methods

The work was based on the HTA Core Model on pharmaceuticals (HTA Core Model Application for Pharmaceuticals version 2.0), which was developed during the EUnetHTA Joint Actions 1 and 2.

The first phase was the selection of the technology to be assessed using the Core Model; this phase was carried out through a three-step process that is described in our MSP.

Then a check of Partners’ availability to assume responsibility for taking the lead in one of the nine evaluation domains was carried out. At the same time, the nine domain teams were built-up in accordance with partners’ preferences and some general guidelines (see the MSP).

Finally the specific work plan was shared, according with the general WP4 3-year work plan and objectives. This specific work plan included the phases scheduled in the “HTA Core Model Handbook” (Production of Core HTAs and structured HTA information).

An editorial team was set up for discussion and major decisions on basic principles and solutions related to the content of core HTA. The editorial team was chaired by Tom Jefferson (Agenas) and included all primary investigators of the domains.

To allow collaboration between partners a draft protocol for Core Model use was agreed by the researchers involved. The research questions for each of the eight domains of the Core Model were formulated and the corresponding relevant assessment elements (AEs) were selected. The legal domain was included in the assessment.

The research strategy was carried out by Agenas with input from the other partners.

Evidence from published and manufacturer sources was identified, retrieved, assessed, and included according to pre-specified criteria, and summarised to answer each AE. Domain assessments were done by a single agency and by different investigators from different agencies, in a mixed organisational model.

The final text has not been proof read or copyedited.

Introduction to collection

This brief document provides background information on the preparation and development of the Core HTA on use of Intravenous immunoglobulins for Alzheimer’s disease including Mild Cognitive Impairment. The core HTA document was produced during the course of the second EUnetHTA Joint Action (JA2) 2012-2015.

The idea behind EUnetHTA’s Core Model is to provide a framework for structuring relevant HTA information while at the same time facilitating local use and adaptation of the information or guiding its production.

The Model is based on nine dimensions or “domains” of evaluation:

1. Health Problem and Current Use of the Technology (CUR)
2. Description and technical characteristics of technology (TEC)
3. Safety (SAF)

4. Effectiveness (EFF)
5. Costs and economic evaluation (ECO)
6. Ethical analysis (ETH)
7. Organisational aspects (ORG)
8. Social aspects (SOC)
9. Legal aspects

The Core Model application on pharmaceuticals was tested by assessing the effects of use of intravenous immunoglobuliuns for Alzheimer's disease including Mild Cognitive Impairment. We produced a Core HTA structured as the eight documents that follow, one for each domain. The Legal Domain was not included in the used version of the Pharmaceuticals application but we produce it and add as appendix.

This Core HTA was prepared using a mixed Collaborative Model (COLMOD). Two different model of collaboration were tested during the first EUnetHTA Joint Action: in one, groups of researchers from different HTA Institutions produced the domain texts; in the other model, one of the national or sub-national HTA participating agencies took responsibility for the production of each domain. For the Core HTA on use of intravenous immunoglobuliuns for Alzheimer's disease including Mild Cognitive Impairment, some domains were produced using the first collaborative model, while other domains were produced using the secondcollaborative model, with a lead agency. The experimental organisational model added an element of challenge but probably helped to forge strong links across participants.

In the next few months an intensive validation programme including interviews and consultations will elicit comments and feedback both from those who contributed to the Core HTA and from those who read a Core HTA for the first time. As scheduled in the 3-year work plan, the Core HTA will be sent to the Stakeholder Advisory Group (SAG) for feedback before the final Public Consultation, during which the Core HTA will be made publicly available.

The results from the Validation and SAG consultation should provide useful information to improve the product.

Scope

Technology	Immunoglobulins (IGG) **Description** Naturally occurring proteins produced by the body's immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer's disease **Target condition** Alzheimer's disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.
Comparison	placebo, not doing anything or Usual supportive care **Description** There is no MA for IGGs for AD yet and there is no other intervention licensed for use in AD so the comparison would have to be against placebo or best supportive care
Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Health Problem and Current Use of the Technology

Authors: Antonio Migliore, Tapani Keranen, Sinikka Sihvo

Summary

Target Condition

Dementia is an overall term for a decline in mental ability severe enough to reduce a person's ability to perform everyday activities. Alzheimer's disease is the most common type of dementia, which accounts for 60 to 80 percent of cases. Alzheimer's is a progressive disease, where dementia symptoms gradually worsen over time. According to DSM-IV criteria for Alzheimer's disease, memory deficit must be objectively demonstrated plus at least one other cognitive deficit: aphasia (abnormal speech), executive function impairment (difficulty with planning, judgment, mental flexibility, abstraction, problem-solving, etc.), agnosia (impaired recognition of people or objects), or apraxia (impaired performance of learned motor skills). These cognitive deficits must result in impairment in performance of daily activities. The diagnosis is confirmed by post mortem evidence of neurofibrillary tangles and neuritic plaques in excess of those found in normal ageing of the brain (ICD-10). Those with Alzheimer's live an average of 3.6 to 6.6 years after the diagnosis, depending on age and other health conditions. In the newest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) "dementia" is replaced by "major neurocognitive disorder". Mild cognitive impairment (MCI) describes a transitional state between normal aging and pathological decline. Many terms and definitions have been used to describe mild forms of cognitive impairment. According to Petersen et al. mild cognitive impairment is classified as 1) MCI that primarily affects memory is known as "amnestic MCI", aMCI**,** and 2) MCI that affects thinking skills other than memory is known as "nonamnestic MCI". A person with MCI is at an increased risk of developing Alzheimer's disease and other dementias, however, many individuals revert to normal or do not progress. The conversion rate from MCI to Alzheimer's is low, about 7 % in community based samples and 15% in specialized care samples. Therefore, MCI diagnosis alone cannot be equaled with a pre-dementia stage. In order to allow treatments like medication, MCI diagnosis should be supplemented with predictors of a rapid cognitive decline, such as older age, vascular risk factors, neurological symptoms, apoE ε4 genotype, etc.). In the DSM-5 a term "mild neurocognitive disorder" is used instead of mild cognitive impairment. Intravenous immunoglobulins (IVIG) are expected to have potentially beneficial effects on the pathogenetic process of Alzheimer's disease by stabilizing cognitive functioning in patients with mild-to-moderate Alzheimer's disease. The neuroprotective mechanisms of IVIG are not well known. If MCI would be identified early this would allow earlier treatment to slow progression of AD or even prevent it. Early interventions are likely to be more effective than if the disease is already advantaged. Slowing the progression of AD with IVIG or other therapies could have major impact on the need for care and burden of the disease.

Target Population

Target populations for IVIG therapy are: i) Patients with Mild Cognitive Impairment; ii) Patients with mild-to-moderate Alzheimer's disease, as defined by validated criteria and with MMSE score between 15 and 26; iii) Patients with moderate-to-severe Alzheimer's disease, as defined by validated criteria and with MMSE score less than or equal to 14. The worldwide prevalence estimates are given usually for dementia than for Alzheimer's disease since the possibilities to make correct diagnosis can vary. In addition, estimates vary between studies. The age-standardised prevalence of dementia among populations > 60 years is 5-7%. In 2010 it was estimated that there are over 35 million people worldwide living with dementia. These numbers are expected to double every 20 years to 65.7 million in 2030 and to 115.4 million in 2050. According to worldwide meta-analysis of studies between 1984-2008, the prevalence of Mild Cognitive Impairment was 24.6% but varied between 21.5-71.5%. For people > 65 years the MCI incidence varied between 21.5-71.3/1000 person years.

Current Management of the Condition

There are no established treatments for MCI. In contrast to MCI, there are several pharmacological possibilities for the treatment of AD. Currently available drug treatments for AD are considered symptomatic. It is recommended that patients with AD and mild to moderate dementia are initially treated with one of the cholinesterase inhibitors (ChEIs), i.e. donepezil, galantamine, or rivastigmine. These drugs have been shown as having efficacy on cognitive function, global outcome, and ADL functions. ChEIs can be used also in the severe form of AD either alone or in combination with the glutamate antagonist memantine. Memantine can also be used alone in patients with severe AD and in patients who have contraindications or who are intolerant to ChEIs.

Utilisation

IVIG are not used for Alzheimer's disease including Mild Cognitive Impairment in any of the EUnetHTA partners answered the survey. However, while some partners explicitly excluded the use of IVIG for the mentioned indications, some others stated that, given the characteristics of the internal monitoring and reimbursement system, it's impossible exclude the off-label use of IVIG.

Regulatory Status

IVIG are currently used as first line therapy for various condition. However, some new indications are emerging and extensions in the indications could be proposed. At time of writing, no manufacturers have submitted requests to EMA for the market approval of the IVIG for Alzheimer's disease including Mild Cognitive Impairment.

Introduction

This domain aims to give a broad overview on Alzheimer's disease (AD) including Mild Cognitive Impairment (MCI) in terms of definition, diagnosis, current management, burden, as well as utilization and regulatory status of the IVIG.

Methodology

Frame

The collection scope is used in this domain.

Technology	Immunoglobulins (IGG) **Description**

	Naturally occurring proteins produced by the body's immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer's disease **Target condition** Alzheimer's disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.
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Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
A0002	Target Condition	What is the disease or health condition in the scope of this assessment?	yes	What is the disease in the scope of this assessment?
A0003	Target Condition	What are the known risk factors for the disease or health condition?	yes	What are the known risk factors for the Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI)?
A0004	Target Condition	What is the natural course of the disease or health condition?	yes	What is the natural course of the Alzheimer's disease (AD) and the Mild Cognitive Impairment (MCI)?
A0005	Target Condition	What are the symptoms and burden of disease for the patient at different stages of the disease?	yes	What are the symptoms and burden of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) for the patient at different stages of the disease?
A0006	Target Condition	What are the consequences of the disease or the health condition for the society (i.e. the burden of the disease)?	yes	What are the consequences of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) for the society (i.e. the burden of the disease)?
A0009	Target Condition	What aspects of the consequences / burden of disease are targeted by the technology?	yes	What aspects of the consequences / burden of disease are targeted by the intravenous immunoglobulin (IVIG) therapy?
A0007	Target Population	What is the target population in this current assessment of the technology?	yes	What is the target population in this current assessment of intravenous immunoglobulin (IVIG) therapy?
A0023	Target Population	How many people belong to the target population?	yes	How many people belong to the target population?
A0017	Current Management of the Condition	What are the differences in the management for different stages of the disease or health condition?	yes	What are the differences in the management for the different stages of the Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI)?
A0018	Current Management of the Condition	What are the other typical or common alternatives to the current technology?	yes	What are the other typical or common alternatives to intravenous immunoglobulin (IVIG) therapy?
A0024	Current Management of the Condition	How is the disease or health condition currently diagnosed according to published guidelines and in practice?	yes	How are Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) currently diagnosed according to published guidelines and in practice?
A0025	Current Management of the Condition	How is the disease or health condition currently managed according to published guidelines and in practice?	yes	How are the Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) currently managed according to published guidelines and in practice?
A0001	Utilisation	For which health conditions and for what purposes is the technology used?	yes	For which health conditions and for what purposes are intravenous immunoglobulins (IVIG) used?
A0011	Utilisation	How much is the technology utilised currently and in the future?	yes	How much are intravenous immunoglobulins (IVIG) utilised currently and in the future?
A0012	Utilisation	What kind of variations in use are there across countries/regions/settings?	yes	What kind of variations in the use of intravenous immunoglobulins (IVIG) are there across countries/regions/settings?
G0009	Utilisation	Who decides which people are eligible for the technology and on what basis?	yes	Who decides which people are eligible for intravenous immunoglobulin (IVIG) therapy and on what basis?
B0003	Utilisation	What is the phase of development and implementation of the technology and the comparator(s)?	yes	What is the phase of development and implementation of intravenous immunoglobulins (IVIG)?
F0001	Utilisation	Is the technology a new, innovative mode of care, an add-on to or modification of a standard mode of care or replacement of a standard mode of care?	yes	Is intravenous immunoglobulin (IVIG) therapy a new, innovative mode of care, an add-on to or modification of a standard mode of care or replacement of a standard mode of care?
A0020	Regulatory Status	What is the marketing authorisation status of the technology?	yes	What is the marketing authorisation status of intravenous immunoglobulins (IVIG)?
A0021	Regulatory Status	What is the reimbursement status of the technology across countries?	yes	What is the reimbursement status of intravenous immunoglobulins (IVIG) across countries?

Methodology description

Domain frame

The project scope is applied in this domain.

Information sources

The result cards CUR1, CUR2, CUR3, CUR4, CUR5, CUR6, CUR8, CUR9, CUR10, CUR11, CUR12, CUR14, and CUR18 have been produced using the results from the basic searches (done for the whole project) and additional, unsystematic literature searches performed by the authors {Appendix CUR-1}. Secondary studies were the main additional information sources considered. The result cards CUR7 and CUR13 have been produced using the findings reported in the document named “Use of Intravenous immunoglobulins for Mild Cognitive Impairment and Alzeheimer’s disease – Protocol” prepared by authors teams from SAF and EFF domains and presented in {Appendix SAF-7}. The result cards CUR15, CUR16, CUR17, CUR19, and CUR 20 have been produced using the results from the surveys carried out among the WP4 stakeholder advisory group (WP4 SAG) and EUnetHTA partners. The surveys are described in details in {Appendix CUR-3}.

Quality assessment tools or criteria

This domain presents descriptive information and rigorous quality assessment was believed not necessary by the domain’s authors. Quality assessment has not been performed for any of the considered citations.

Analysis and synthesis

Descriptive analysis was performed on different information sources. Results have been presented in narrative form. No numerical data analysis has been performed.

Result cards

Target Condition

Result card for CUR1: "What is the disease in the scope of this assessment?"

View full card

CUR1: What is the disease in the scope of this assessment?

Result

Dementia is an overall term for a decline in mental ability severe enough to reduce a person's ability to perform everyday activities**.** Alzheimer's disease is the most common type of dementia, which accounts for 60 to 80 percent of cases {76}.

Alzheimer's is a progressive disease, where dementia symptoms gradually worsen over time. In ICD-10-CM the code is G30 and in the ICD-10 classification of mental and behavioral disorders, diagnostic criteria for research the code is F00. According to DSM-IV criteria for Alzheimer’s disease memory deficit must be objectively demonstrated plus at least one other cognitive deficit: aphasia (abnormal speech), executive function impairment (difficulty with planning, judgment, mental flexibility, abstraction, problem-solving, etc.), agnosia (impaired recognition of people or objects), or apraxia (impaired performance of learned motor skills). These cognitive deficits must result in impairment in performance of daily activities. In the newest Diagnostic and Statistical Manual of Mental Disorders (DSM-5) “dementia” is replaced by “major neurocognitive disorder” {3} {75}.The diagnosis is confirmed by post mortem evidence of neurofibrillary tangles and neuritic plaques in excess of those found in normal ageing of the brain (ICD-10).

Those with Alzheimer's live an average of 3.6 to 6.6 years after the diagnosis, depending on age and other health conditions {78}.

Mild cognitive impairment (MCI) describes a transitional state between normal aging and pathological decline {10} {49} {81}. Many terms and definitions have been used to describe mild forms of cognitive impairment. According to Petersen et al. {63} mild cognitive impairment is classified as 1) MCI that primarily affects memory is known as "amnestic MCI, aMCI**"** and 2) MCI that affects thinking skills other than memory is known as "nonamnestic MCI, A person with MCI is at an increased risk of developing Alzheimer's disease and other dementias, however, many individuals revert to normal or do not progress {81}. The conversion rate from MCI to Alzheimer's is low, about 7% in community based samples and 15% in specialized care samples {49}. Therefore MCI diagnosis alone cannot be equaled with a pre-dementia stage {48}. In order to allow treatments like medication, MCI diagnosis should be supplemented with predictors of a rapid cognitive decline, such as older age, vascular risk factors, neurological symptoms, apoE ε4genotype, etc.) {48}. In the DSM-5 a term “mild neurocognitive disorder” is used instead of mild cognitive impairment {3} {75}.

Importance: Critical

Transferability: Completely

Result card for CUR2: "What are the known risk factors for the Alzheimer’s disease (AD) and Mild Cognitive Impairment (MCI)?"

View full card

CUR2: What are the known risk factors for the Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI)?

Result

The most important risk factor for Alzheimer's disease is age {43}. Up to 5 percent of people with the disease have early onset Alzheimer's, which often appears when someone is in their 40s or 50s. Many of the risk factors for cognitive impartment, Alzheimer's disease and dementia are similar as the cardiovascular disease risk factors: Smoking, hypertension, hypercholesterolemia and overweight {75}. Midlife diabetes is associated with elevated risk {43} {75}. Some of the risk factors are modifiable through life style changes or with medical treatment. Risk factors that cannot be modified include family history of dementia, genetic factors (APOE ε4), traumatic brain injuries and male sex. Other factors proposed to be related to increased AD risk include: low educational level, lack of cognitive activities, loneliness and lack of social networks, depression, low physical activity and heavy drinking {15} {43} {75}. Risk scores have been developed to predict risk of dementia {43}. It is not clear to what extent risk factors for clinically diagnosed AD increase the risk of developing neuropathological changes in AD or how comorbid conditions increase the risk of onset and progression of AD {75}. The role of modifiable life styles is also putative since the quantification of lifestyle factors varies largely in terms of intensity, frequency and duration of exposure.

The possible risk factors for minor cognitive impairment are partly the same as for dementia and Alzheimer's disease, such as age, hypertension and ApoE ε4 {48}. Many other risk factors of dementia and Alzheimer's disease have so far failed to show significant effect on MCI risk, such as gender, cardiovascular diseases, serum total cholesterol, cerebrovascular diseases, stroke, diabetes, smoking, psychiatric illness {48}.

Importance: Important

Transferability: Completely

Result card for CUR3: "What is the natural course of the Alzheimer's disease (AD) and the Mild Cognitive Impairment (MCI)?"

View full card

CUR3: What is the natural course of the Alzheimer's disease (AD) and the Mild Cognitive Impairment (MCI)?

Result

The major issue with MCI is that subjects with this disorder may progress to dementia in higher proportions than do cognitively normal people. A challenge in assessing the outcome of MCI – as in the case of the incidence and prevalence of MCI – is the non-uniform criteria applied in the diagnosis of the disorder. Furthermore, the symptomatology in the subjects is variable and in addition to Alzheimer's disease, MCI may appear in patients with other neurodegenerative disorders such as Parkinson's disease an also in cerebrovascular disorders. According to a meta-analysis of eight studies that examined the risk of dementia or Alzheimer's disease annual conversion rate (ACR) to dementia was 13.8 (95% 8.44–22.6), higher in subjects with MCI compared to healthy controls {56}. However, most of the individuals with MCI may not develop dementia. Studies report a wide variation in the risk of conversion after a one year follow-up (10.2 to 33.6%, median 19.0%), and after two years conversion frequency has varied from 9.8 to 36.3% (median 18.6%) {81}. A meta-analysis, based on the data of 41 studies with at least three years of follow-up concluded that about 30% of the MCI patients convert to dementia within 5 years after the diagnosis of MCI, and that the cumulative conversion rate to dementia in subjects followed up 5 years or more may not exceed 38% {56}. In general, population based studies show lower conversion rates of MCI to dementia: in the meta-analysis, the proportion of MCI subjects with conversion to dementia was 39.2% in the clinic based studies and 21.9% in community studies {56}. The ACR of MCI to dementia varies 2% to 31% across the studies {9}. Meta-analysis of community based studies reported an ACR of MCI to Alzheimer type dementia to be 6.9% (95% CI 4.1–10.4%) {56}. Several predictive factors for the risk of conversion from MCI to dementia have been identified. Multivariate analyses have shown that at baseline lower Mini Mental State Examination (MMSE), diastolic blood pressure, BMI {66}, ApoE ε4 allele {22}, temporal lobe /hippocampal volume in MRI {33} {37} {80}, abnormal FDG- or BIB PET {44} as well as CSF concentration of TAU and ApoE ε4 {33} {50} {54} {80} predict the risk of conversion to dementia. According to the meta-analysis of follow-ups studies, the ACR to dementia is similar in subjects with amnestic MCI and multiple-domain MCI (11.7% and 12.2%, respectively) and higher than in subjects with non-amnestic MCI {56}. Assessment of the risk of mortality associated with MCI is difficult due to limited number of population based studies as well as due to varying criteria for the diagnosis of MCI {34}. However, several studies have reporter increased mortality in subjects with MCI compared with cognitively non-impaired controls with hazard ratios varying from 1.2 to 2.2 {34} {35} {39} {83}. The mortality may be higher in subjects with multiple-domain amnestic MCI compared to those with single-domain amnestic MCI {39}. AD is characterized by insidious onset and progressive deterioration of cognitive function, functional abilities, behavior and mood. The progression varies inter-individually. Several scales are being used in clinical practice for the assessment of the severity of cognitive and functional decline in dementia. Most commonly used are MMSE, Clinical Dementia Rating (CDR), and Global Deterioration scale (GDS) {38} {68}. For clinical assessment and treatment consideration purposes, AD dementia is categorized as mild (MMSE 18–26, GDS 3–4, CDR 0.5–1), moderate (MMSE 10–22, GDS 4–6, CDR 1–2), and severe (MMSE 0–2, GDS 6–7, CDR 2–3). The decline in MMSE scores varies between 2.6 and 4.5 points in various studies, slower in community based studies than in clinic based surveys {1}. Some studies have suggested a non-linear decline in cognition in AD so that the progression is slower in patients with mild disease and on the other hand in severe disease but faster in patients with moderate disease {19} {57}. Functional decline is a prerequisite for the diagnosis of dementia and it is manifested already in early AD dementia. With the progression of cognitive symptoms in AD, social and occupational functioning continue to deteriorate {40}. Also behavioral and psychic symptoms correlate with the severity of cognitive deficits {47} {57}. Functional decline in patients with AD eventually leads to institutionalization. It has been estimated that approximately 50% of the demented patients of Northern Europe and North America are in institutionalized care but the percentage is lower in Southern European countries {1}.

The mortality risk in patients with AD is 1.5 to 5-fold compared with cognitively normal subjects {78}. Median survival time in AD ranges from 3.3 to 11.7 years {78}, and the annual mortality rate is 5.95% (95% CI 4.56–7.34) {18}. Predictive factors for mortality in patients with AD are age, male sex,

increased disease severity and functional impairment {78}.

Importance: Important

Transferability: Completely

Result card for CUR4: "What are the symptoms and burden of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) for the patient at different stages of the disease?"

View full card

CUR4: What are the symptoms and burden of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) for the patient at different stages of the disease?

Result

The hallmark of MCI is cognitive decline that is greater than expected for an individual's age and education level. The cognitive decline does not, however, interfere notably with activities of daily life {31}. Thus, the subjects with MCI have subjective cognitive complaints, which can be objectively verified, but no dementia. In most cases MCI is associated with isolated memory impairment (so called amnestic MCI) but also non-amnestic MCI (impairment in executive, language or visuospatial functions) may occur {63}. The impairment can be restricted to one cognitive domain or to multiple domains {63}.

In addition to its core features, i.e. cognitive symptoms, MCI can be associated with various behavioral symptoms. Systematic reviews of studies addressing neuropsychiatric manifestations in MCI have revealed that many patients with MCI have depression, anxiety, apathy and irritability {4} {58}. In fact, neuropsychiatric symptoms in MCI have similar pattern as in AD {58}. In caregivers and the family MCI may cause depression, stress, and burden {73}.

In AD dementia, there is a progressive decline in cognition. In mild dementia, the most prominent deficit is in the ability to recall new information. Other symptoms include impairment in language and visuospatial functions as well as involvement of attentional and executive domains {40}. Neuropsychiatric symptoms include depression, anxiety and irritability. Also sleep problems, apathy, delusions and paranoia may appear {40}. The patients may be able to do shopping, simple hobbies, bathing and dressing but they may have difficulties in complex financial arrangement {40}.

Patients with moderate AD dementia have impairment of all major cognitive domains. Also behavioral and psychic symptoms progress and frank hallucinations and delusions may appear. Behavior may involve socially inappropriate issues, and motor restless may occur. Behavioral and psychic symptoms may emerge as primary issues for caregivers {40}. Most of the ADL functions begin to be significantly affected e.g. cooking, cleaning and simple financial actions are impaired. The patients require daily help in dressing and daily hygiene, and eating may be involved. The patients may need 24 hour supervision {40}.

In severe AD dementia the patients may be disoriented to place and time and they may have difficulties in identifying close relatives. They may be able to conduct a casual conversation. Functionally the patients are dependent of others for almost all of their daily care and they suffer from incontinence. At the latest stages of the disease the patients become bedridden. Psychic symptoms include worsening hallucinations, agitation, or on the other hand, progressive apathy {40}.

Personality changes may accompany AD. Increased neuroticism, decreased extraversion and conscientiousness, and stable or slightly decreased openness and agreeableness have been observed in patients with AD {69}. These symptoms may be associated with social dysfunction due to AD. Literature suggests that high neuroticism or low conscientiousness may be early signs of dementia of the Alzheimer type as well as the best predictors of subsequent personality change in dementia {69}.

Importance: Important

Transferability: Completely

Result card for CUR5: "What are the consequences of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) for the society (i.e. the burden of the disease)?"

View full card

CUR5: What are the consequences of Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) for the society (i.e. the burden of the disease)?

Result

Alzheimer's disease has great consequences not only for the patient and the family members, but also for the health care system and the society. The direct medical costs (hospital care, medication, visits to clinics) are highest in the Western Europe and North America, however, majority of the costs are related to direct social care costs (homecare, food services, residential and nursing home care) and informal care (input of families) (CUR-5 Table 1). According to World bank data 42.3% of the total costs are direct social costs, 41.7% informal care and 16% direct medical costs {84}.

In the United Kingdom, the annual societal costs of dementia (£23 billion) were estimated to match those of cancer (£12 billion), heart disease (£8 billion) and stroke (£5 billion) combined {84}. Therefore early diagnosis and evidence-based interventions are in greater focus. Delaying the onset by

just a year or two could reduce the burden of AD on society and health care system.

CUR-5 Table 1. Estimated number of people with dementia and prevalence of dementia in population > 60 years (2010) {65} and the burden of disease (in billions US$) by WHO {84}.

Region	People with dementia	Prevalence, crude 2010	Proportionate increase 2010-2050, %	Direct medical costs	Direct social care costs	Informal care costs (all ADLs)
Europe, Western	9,727	7.2	93	3,019	9,288	8,705
Europe, Central	2,361	4.7	91	267	294	859
Europe , Eastern	3,930	4.7	66	342	294	796
North America	6,367	6.9	151	3,683	9,745	7,876
Asia, East	17,161	3.2	311	433	284	1,524
North Africa, Middle east	3,111	3.7	438	205	0.54	190
World	**75,854**	**4.7**	**225**	**9,641**	**25,569**	**25,189**

Key: *ADLs, activities of daily living.*

Importance: Critical

Transferability: Partially

Result card for CUR6: "What aspects of the consequences / burden of disease are targeted by the intravenous immunoglobulin (IVIG) therapy?"

View full card

CUR6: What aspects of the consequences / burden of disease are targeted by the intravenous immunoglobulin (IVIG) therapy?

Result

Intravenous immunoglobulins (IVIG) are expected to have potentially beneficial effects on the pathogenetic process of Alzheimer's disease by stabilizing cognitive functioning in patients with mild-to-moderate Alzheimer's disease {20} {46}. The benefits of IVIG in AD are believed to be related to fact that they contain both anti- tau and anti-Aβ natural antibodies and can help in reducing the misfolding, aggregation and deposition of amyloid-β, and deposition of misfolded tau protein in neurofibrillary tangles {Kayed}. The neuroprotective mechanisms of IVIG are not well known {82}.

If mild cognitive impartment would be identified early this would allow earlier treatment to slow progression of AD or even prevent it. Early interventions are likely to be more effective than if the disease is already advantaged. Slowing the progression of AD with IVIG or other therapies could have major impact on the need for care and burden of the disease.

At the moment it is not possible to assess impact of IVIG on AD mortality or other impacts on patients since we lack clinical studies.

A problem can arise in the supply of IVIG. IVIG is prepared from the plasma immunoglobulins of over 10 000 donors and the processing of plasma into IVIG takes about 9 months. IVIG treatment is therefore expensive. Supply could become a major problem if IVIG products would be used for AD unless new manufacturing processes are developed. {46}.

Importance: Critical

Transferability: Completely

Target Population

Result card for CUR7: "What is the target population in this current assessment of intravenous immunoglobulin (IVIG) therapy?"

View full card

CUR7: What is the target population in this current assessment of intravenous immunoglobulin (IVIG) therapy?

Result

Target populations for IVIG therapy are {Appendix SAF-1}:

- Patients with Mild Cognitive Impairment (ICD-9-CM Diagnosis Code 331.83; ICD-10-CM G31.84) as defined by validated criteria;
- Patients with mild-to-moderate Alzheimer's disease (ICD-9-CM Diagnosis Code 331.0; ICD-10-CM G30.9), as defined by validated criteria and with MMSE score between 15 and 26;

Patients with moderate-to-severe Alzheimer's disease (ICD-9-CM Diagnosis Code 331.0; ICD-10-CM G30.9), as defined by validated criteria and with MMSE score less than or equal to 14.

Importance: Critical

Transferability: Completely

Result card for CUR8: "How many people belong to the target population?"

View full card

CUR8: How many people belong to the target population?

Result

The worldwide prevalence estimates are given usually for dementia than for Alzheimer's disease since the possibilities to make correct diagnosis can vary. Also estimates vary between studies.

The age-standardised prevalence of dementia among populations > 60 years is 5-7% {65}. In 2010 it was estimated that there are over 35 million people worldwide living with dementia. These numbers are expected to double every 20 years to 65.7 million in 2030 and to 115.4 million in 2050 {65} {Table CUR-5}. In 2010 over half (58%) of people with dementia lived in low or middle income countries, this proportion is expected to rise to 71% in 2050. China has more cases of Alzheimer's disease than any other country; in 2010 there were 919 million (95% CI 5.92–12.48) people with dementia and the prevalence was 2.6% (0.0–28.2) at age 60-65 years and 60.5% (39.7–81.3) at age 95-99 year olds {12}. The incidence of dementia in China was 9.87 per 1000 person-years and that of Alzheimer's disease 6.25/1000 person-years {12}. The increase in numbers of people with dementia will occur much rapidly in low or middle income countries and faster than assumed {12} {84}.

According to worldwide meta-analysis of studies between 1984-2008, the prevalence of mild cognitive impairment was 24.6% but varied between 21.5–71.5%, and the prevalence of amnestic MCI (aMCI) alone was 4.6% (range 8.5–25.9%). For people > 65 years the MCI incidence varied between 21.5–71.3/1000 person-years. For aMCI the rates ranged from 8.5 to 25.9 per 1000 person-years {81}. In another systematic review the incidence rates were 51–76.8/1000 person-years and for aMCI between 9.9 and 40.6/1000 person-years {48}.

Importance: Critical

Transferability: Completely

Current Management of the Condition

Result card for CUR9: "What are the differences in the management for the different stages of the Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI)?"

View full card

CUR9: What are the differences in the management for the different stages of the Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI)?

Result

There are no established treatments for MCI.

In contrast to MCI, there are several pharmacological possibilities for the treatment of AD. Currently available drug treatments for AD are considered symptomatic. It is recommended that patients with AD and mild to moderate dementia are initially treated with one of the cholinesterase inhibitors (ChEIs), i.e. donepezil, galantamine, or rivastigmine {30} {38} {89}. These drugs have been shown as having efficacy on cognitive function, global outcome, and ADL functions {38}. ChEIs can be used also in the severe form of AD either alone or in combination with the glutamate antagonist memantine {38}. Memantine can also be used alone in patients with severe AD and in patients who have contraindications or who are intolerant to ChEIs {38}. See also {CUR12}.

Importance: Important

Transferability: Completely

Result card for CUR10: "What are the other typical or common alternatives to intravenous immunoglobulin (IVIG) therapy?"

View full card

CUR10: What are the other typical or common alternatives to intravenous immunoglobulin (IVIG) therapy?

Result

IVIG is considered as an experimental therapy in AD. Thus, the alternatives to IVIG in AD are the three ChEIs and memantine. It is recommended that patients with AD and mild to moderate dementia are initially treated with one of the cholinesterase inhibitors (ChEIs), i.e. donepezil, galantamine, or rivastigmine {30} {38} {89}. See {CUR12}.

Importance: Critical

Transferability: Completely

Result card for CUR11: "How are Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) currently diagnosed according to published guidelines and in practice?"

View full card

CUR11: How are Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) currently diagnosed according to published guidelines and in practice?

Result

MCI was introduced as a clinical entity more than 20 years ago, and during this time, multiple definitions for the syndrome have been proposed {63}. MCI is defined as a syndrome with cognitive decline greater than expected for an individual's age and education level but in the absence of significant effect on instrumental activities of daily living (ADL) {31}. The subjects with MCI have thus subjective cognitive complaints which can be objectively verified but no dementia. Subjects with MCI have most commonly isolated memory impairment (so called amnestic MCI) but also non-amnestic MCI (impairment in executive, language or visuospatial functions) may occur {63}. The impairment can be restricted to one cognitive domain or to multiple domains {63}. In considering this clinical and cognitive syndrome, it is important to emphasize that sharp demarcations between normal cognition and MCI and between MCI and dementia are difficult, and clinical judgment must be used to make these distinctions {2}.

Current definition and diagnostic criteria for MCI are present in {CUR-11 Table 2}. There are no specific operational criteria for the diagnosis of MCI that are applied in the clinical daily routine {63}. In the clinical diagnosis of MCI the first step is history taking followed by physical examination including cognitive assessment {32} {38} {85}. Information from spouses, other relatives and caregivers are important in assessing possible behavioral symptoms and ADL functions. For the demonstration of cognitive impairment, measures such as the Mini Mental State Examination (MMSE) score or Montreal Cognitive Assessment (MoCA) test can be used {13}. However, the evidence of the sensitivity of MMSE in the identification of MCI is not good and the value of MMSE in the diagnosis of MCI is very limited {53}. The clinician should also determine whether the impairment involves only one cognitive domain such as memory or are other cognitive domains impaired {63}. Thereafter, the etiology of MCI should be evaluated with neuroimaging and possibly by biomarkers {64}.

The key element in the diagnosis of AD is clinical history which needs to be supplemented with information impairment in ADL functions {38}. Diagnosis of AD requires an assessment of cognitive function in all patients {38}. Quantitative neuropsychological testing should be performed in subjects with questionable or very early dementia {38}. The proposed diagnostic criteria for probable and possible AD are presented in {CUR-11 Table 3} {51}. AD can be definitely diagnosed only post mortem {5}. Brain imaging studies are an essential part of diagnostic setup of bot MCI and AD and magnetic resonance imaging (MRI) is preferred because it is superior to computed tomography (CT) in demonstration of cerebral atrophy {28} {30} {38}. Hippocampal atrophy, as demonstrated by coronal T1-weighted MRI images is the best established and validated imaging marker of AD {28}. Functional neuroimaging, i.e. positron emission tomography (PET) with [18]-fluorodeoxyglucose (FDG) or [11C]PIB may increase the accuracy of separating subjects with MCI from healthy individuals {14} {28} {38}. Furthermore, MRI and PET may help to predict which cases of MCI will convert to AD {14} {28} {38}. A meta-analysis of MRI studies, using voxel-based morphomery in MCI patients, found that the left medial temporal lobe (especially hippocampus and parahippocampal gyrus) is the most affected region in MCI subjects who will convert to AD {27}. In addition to neuroimaging, the value of chemical biomarkers in the diagnosis of AD has been investigated. Low cerebrospinal fluid (CSF) concentration of amyloid-b (Ab1 – 42), in combination with high total CSF tau and phosphorylated tau, can discriminate AD patients from healthy subjects with reasonable sensitivity and specificity {7} {26} {54}. Due to issues such as variation in the results for different laboratories and cut off values, more validation work has to be done before the measurements can be considered mandatory in the diagnostics of dementia {5} {7} {27}. Subjects with cognitive problems usually see first their general practitioner (GP). Studies have shown that GPs correctly identify less than 50% of the individuals with MCI and they also have difficulties in identifying mild dementia {55}.

CUR-11 Table 2. Core clinical criteria for the diagnosis of MCI. Adapted from {2}.

MCI - Criteria for the clinical and cognitive syndrome	
Concern regarding a change in cognition.	There should be evidence of concern about a change in cognition, in comparison with the person's previous level. This concern can be obtained from the patient, from an informant who knows the patient well, or from a skilled clinician observing the patient.
Impairment in one or more cognitive domains	There should be evidence of lower performance in one or more cognitive domains that is greater than would be expected for the patient's age and educational background. If repeated assessments are available, then a decline in performance should be evident over time. This change can occur in a variety of cognitive domains, including memory, executive function, attention, language, and visuospatial skills. An impairment in episodic meory (i.e., the ability to learn and retain new information) is seen most commonly in MCI patients.
Preservation of independence in functional abilities	Persons with MCI commonly have mild problems performing complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping. They may take more time, be less efficient, and make more errors at performing such activities than in the past. Nevertheless, they generally maintain their independence of function in daily life, with minimal aids or assistance.
Not demented	The cognitive changes should be sufficiently mild that there is no evidence of a significant impairment in social or occupational functioning.

CUR-11 Table 3. Diagnostic criteria for probable and possible Alzheimer's disease dementia. Adapted from {51}.

Probable AD dementia	**Core clinical criteria:** Probable AD dementia is diagnosed when the patient meets criteria for dementia, and in addition, has the following characteristics: A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days; B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories. *a. Amnestic presentation:* • It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain. *b. Non-amnestic presentations:* • Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.
Possible AD dementia	**Core clinical criteria:** A diagnosis of possible AD dementia should be made. **Atypical course:** Atypical course meets the core clinical criteria in terms of the nature of the cognitive deficits for AD dementia, but either has a sudden onset of cognitive impairment or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline. **Etiologically mixed presentation:** Etiologically mixed presentation meets all core clinical criteria for AD dementia but has evidence of (a) concomitant cerebrovascular disease, defined by a history of stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) features of Dementia with Lewy bodies other than the dementia itself; or (c) evidence for another neurological disease or a non-neurological medical comorbidity or medication use that could have a substantial effect on cognition.

Importance: Critical

Transferability: Completely

Result card for CUR12: "How are the Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) currently managed according to published guidelines and in practice?"

View full card

CUR12: How are the Alzheimer's disease (AD) and Mild Cognitive Impairment (MCI) currently managed according to published guidelines and in practice?

Result

There are no effective interventions available for MCI {16}. Two meta-analyses of the three studies reporting conversion MCI to dementia gave no clear evidence of a beneficial effect of cholinesterase inhibitors (ChEI) on the progression to dementia at one, two or three years {70} {79}. The risk ratio (RR) for conversion at two years was significantly different from unity (0.67; 95% CI 0.55–0.83), but this is based on only two studies reported in the same article. There were essentially no clinically meaningful symptomatic effects of ChEI on cognitive test scores {70}. Other pharmacological interventions, such as huperzine A {88}, a chemical derived from a type of club moss (Huperzia serrate), vitamin E {24}, piribedil, nicotine, gingko biloba, B vitamins, nonsteroidal anti-inflammatory drugs, and omega-3 polysaturated fatty acids {16} have failed to reduce the risk of conversion to AD.

Non-pharmacological interventions physical activity and cognitive exercise may improve memory and executive functions in older people with MCI {67} {77}. Cognitive training interventions may improve some cognitive aspects in patients with MCI such as memory performance, executive functioning and attention but effects of these improvements on ADL functions is unclear {67}. Physical exercise may also have some positive effects {63} {77}. Treatment of modifiable risk factors in MCI, such as hypertension, diabetes mellitus, and hyperlipidemia, is recommended although there are no data of positive effects of interventions against these disorders {23}.

Currently available drug treatments for AD are considered symptomatic. It is recommended that patients with AD and mild to moderate dementia are initially treated with one of the cholinesterase inhibitors (ChEIs), i.e. donepezil, galantamine, or rivastigmine {30} {38} {89}. These drugs have been shown as having efficacy on cognitive function, global outcome, and ADL functions {38}. The effects of ChEis have been demonstrated mainly in studies lasting up to six months and the magnitude of the effects seems to be at the best modest {21} {38}. ChEIs have generally shown no meaningful improvement in the quality of life in patients with AD. The most common adverse effects of ChEIs are nausea, vomiting, diarrhea, abdominal pain, malaise, fatique, dizziness and headache. There is no conclusive evidence of any differenced in the efficacy or safety of the three ChEis {30} {38}. There are some discrepancies in the conclusions of different guidelines in respect to the use of ChEIs in severe AD: The NICE guidance {89} limits the use of ChEIs for mild to moderate AD whereas the European Federations of Neurological Sciences (EFNS) guideline and a Canadian guideline recommend the use of ChEIs also in the severe AD {30} {38}.

Memantine is a non-competetive N-methyl-D-aspartate receptor agonist which has been approved for use in moderate to severe AD. Evidence for the efficacy of memantine monotherapy in mild AD is lacking {71}. Recently, its efficacy as monotherapy in moderate to severe AD has been challenged {45}. The benefits of adding memantine to ChEI treatment are not clear {38} {61}. Systematic reviews suggest that the combination treatment with memantine and ChEIs may have beneficial effects on cognition, functional outcome and neuropsychiatric symptoms in patients with moderate to severe AD but the clinical relevance of the effects is unclear {25} {60}. The NICE guidance recommends the use of memantine in patients moderate AD who are intolerant or have a contraindication for ChEIs or for patients who have severe stage of AD {89}. The Canadian guideline concludes that there is insufficient evidence to recommend for or against the combined use of ChEIs and memantine {30}. Behavioral and psychic symptoms are prevalent in patients with AD the symptomatology tends to worsen with the progression of the disease. ChEIs have been shown to reduce behavioral and psychological symptoms in patients with mild to severe AD but the clinical relevance of the effects us unclear {11} {38}. ChEIs may have beneficial effects on psychosis and apathy {38}. Memantine may have efficacy on delusions, agitation, aggression and irritability in patients with severe AD {38}. Antidepressants may reduce agitation in patients with AD {74}. Risperidone and olanzapine are useful in reducing aggression in AD, and risperidone reduces psychotic symptoms in AD patient, but these drugs are associated with serous adverse cardiovascular events and extrapyramidal as well as with a small increase in the risk of death symptoms {6} {72}. Guidelines suggest that atypical antipsychotics can be used for severe agitation, aggression and psychosis at low doses and with careful monitoring {30} {38}. Mood stabilizers are ineffective or even harmful in AD {87}.

It has been shown that occupational therapies and exercise interventions may slow functional decline in AD but the clinical significance of the findings is uncertain {52}.

Importance: Important

Transferability: Completely

Utilisation

Result card for CUR13: "For which health conditions and for what purposes are intravenous immunoglobulins (IVIG) used?"

View full card

CUR13: For which health conditions and for what purposes are intravenous immunoglobulins (IVIG) used?

Result

Since their introduction, IVIG have been proposed as a treatment for an array of disorders, including primary and secondary immune deficiency states, and a variety of autoimmune and inflammatory disorders.

It is suggested that IVIG (0.2 g to 2.0 g per kg bodyweight, any regimen) might have beneficial effects on the pathogenic processes of Alzheimer's disease {20}, also at the stage of Mild Cognitive Impairment, by interfering positively with metabolism of amyloid β that seems to be reduced in subjects at risk for Alzheimer's disease. It is hypothesised that IVIG use for passive immunotherapy in Alzheimer's disease could slow the disease progression {20} {46} and use in patients with Mild Cognitive Impairment could avoid or delay the onset of Alzheimer's disease {Appendix SAF-1}.

Importance: Critical

Transferability: Completely

Result card for CUR14: "How much are intravenous immunoglobulins (IVIG) utilised currently and in the future?"

View full card

CUR14: How much are intravenous immunoglobulins (IVIG) utilised currently and in the future?

Result

IVIG are currently used as first line therapy for various condition {90}. However, some new indications are emerging and extensions in the indications could be proposed {91}. At time of writing, no manufacturers have submitted requests to EMA for the market approval of the IVIG for Alzheimer's disease including Mild Cognitive Impairment {Appendix CUR-3}.

Importance: Critical

Transferability: Completely

Result card for CUR15: "What kind of variations in the use of intravenous immunoglobulins (IVIG) are there across countries/regions/settings?"

View full card

CUR15: What kind of variations in the use of intravenous immunoglobulins (IVIG) are there across countries/regions/settings?

Result

IVIG are not used for Alzheimer's disease including Mild Cognitive Impairment in any of the EUnetHTA partners answered the survey. However, while some partners explicitly excluded the use of IVIG for the mentioned indications, some others stated that, given the characteristics of the internal monitoring and reimbursement system, it's impossible exclude the off-label use of IVIG {Appendix CUR-3}.

Importance: Critical

Transferability: Completely

Result card for CUR16 / ORG12: "Who decides which people are eligible for intravenous immunoglobulin (IVIG) therapy and on what basis?"

View full card

CUR16 / ORG12: Who decides which people are eligible for intravenous immunoglobulin (IVIG) therapy and on what basis?

Result

As IVIG have not been approved for Alzheimer's disease including Mild Cognitive Impairment, IVIG therapy does not have a formal prescription pathway for such indications. Considering the contextual differences among the countries, a generalisation of the off-label prescription strategies of the IVIG therapy is not possible and remains out of the scope of the present results card.

The current setting for the administration of IVIG therapy (for any condition) is use within hospitals {Appendix CUR-3}.

Importance: Important

Transferability: Completely

Result card for CUR17 / TEC3: "What is the phase of development and implementation of intravenous immunoglobulins (IVIG)?"

View full card

CUR17 / TEC3: What is the phase of development and implementation of intravenous immunoglobulins (IVIG)?

Result

Individual manufacturers are exploring the feasibility of developing IVIG therapy for Alzheimer's disease including Mild Cognitive Impairment but, at time of writing, no manufacturers applied for market authorisation to EMA {Appendix CUR-3}. No data are available regarding the monitoring of off-label or compassionate use of IVIG for Alzheimer's disease including Mild Cognitive Impairment {Appendix CUR-3}.

IVIG is presently very widely used for the treatment of a variety of immunologic disorders. IVIG is being used as a treatment in many different conditions, including mainly primary and secondary antibody deficiency states, haematology (acquired red cell aplasia, alloimmune thrombocytopenia, autoimmune haemolytic anaemia, haemolytic disease of the newborn, immune thrombocytopenic purpura), neurology (Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculneuropathy, inflammatory myopathy, Myastenia gravis, multifocal motor neuropaty) and other conditions (Kawasaki disease, transplantation, toxic epidermal necrolysis, staphylococcal or streptococcal toxic shock syndrome, autoimmune congenital heart block, autoimmune uveitis). See {TEC2}.

For more than thirty years, IVIG has been used for the treatment of post-exposure to infectious diseases, immune disorders and the management of patients with neurological conditions. IVIG treatment is used routinely for some immune-mediated neurological disorders such as Guillain-Barre syndrome, and recently IVIG has been investigated for the treatment of neurodegenerative disorders.

IVIG has not been approved for prevention or treatment of AD and mild cognitive impairment.

IVIG treatment of AD patients was first reported in a pilot study in 2004 {20}. Five patients with mild to moderate AD – Mini Mental State Examination (MMSE) mean score 19.4 – received Octagam (Octapharma; dose = 0.4 g/kg) on 3 successive days, every 4 weeks for 6 months. MMSE scores improved slightly in four of the AD patients and were unchanged in the fifth one, while their Alzheimer's Disease Assessment Scale-Cognitive sub-scale (ADAS-cog) scores decreased, suggesting increased cognitive functioning, in four patients and did not change in the fifth one. In 2009 results were published from a pilot study in which eight AD patients (mean MMSE score 23.5) were administered Gammagard S/D (Baxter Healthcare). After 6 months of treatment the mean MMSE score increased to 26.0, reflecting increased scores for six patients and no change in scores for two patients. After a 3-month washout period, the mean MMSE score returned to baseline (23.9). Following an additional 9 months of treatment, MMSE scores were essentially unchanged (mean 24.0).

Before publishing these results, in 2006 Baxter began a double-blind Phase II AD trial with Gammagard. Improved outcomes were noted in the Gammagard-treated subjects compared to those initially treated with placebo at 3, 6, and 9 months.

The results of a double-blind, placebo-controlled, 24- week phase II AD trial with Octagam were published in January 2013 {20}. Octagam had no apparent effects on cognitive or functional scores in the AD patients. No increase was found for plasma Aβ1-40; this had been reported in the pilot studies and suggested that IVIG products might increase efflux of Aβ from the brain. The only positive finding reported in this study, less reduction in glucose metabolism in some brain regions in the Octagam-treated individuals, was of uncertain significance. In conclusion, this trial showed favourable safety and tolerability of intravenous immunoglobulin and the absence of severe autoimmune reactions. Longer studies of larger populations are needed to assess effects on cognition and function in patients with Alzheimer's disease.

In May 2013, the results of a placebo-controlled phase III AD trial with Gammagard were announced. Three hundred ninety patients had been treated every 2 weeks for 18 months with 200 mg/kg Gammagard, 400 mg/kg Gammagard, or placebo. No significant differences were found for the rate of cognitive decline between the Gammagard-treated group and placebo group.

Two AD-related IVIG trials are still in progress. Flebogamma (Grifols Biologicals) is being evaluated, together with albumin, in an AD phase III trial, and NewGam (Octapharma) is being investigated by Sutter Health in a phase II trial to determine its effects in patients with amnestic mild cognitive impairment (MCI) and its influence on the risk for these patients to develop AD. A possible reason for the failures in the most recent IVIG trials is that by the time AD's clinical features become evident, its pathology, including extensive neuronal loss, is already well established. The trial with MCI patients should provide an indication of whether earlier IVIG treatment may be beneficial.

Newer research and developing human trials are becoming established for the use of intravenous immunoglobulins (IVIG) for the treatment and prevention of Alzheimer's disease.

The IVIG trials reported to date in AD patients have produced conflicting findings. Because the most recent trials produced negative results, enthusiasm for IVIG as a treatment for AD has been reduced. Polyvalent antibody therapy for AD, as typified by IVIG, should have advantages over administration of individual monoclonal antibodies. To identify which antibodies should be included in an AD-specific IVIG preparation, more must be known about the range of anti-AD antibodies in IVIG and their effects on AD pathology in animal models.

Importance: Critical

Transferability: Completely

Result card for CUR18: "Is intravenous immunoglobulin (IVIG) therapy a new, innovative mode of care, an add-on to or modification of a standard mode of care or replacement of a standard mode of care?"

View full card

CUR18: Is intravenous immunoglobulin (IVIG) therapy a new, innovative mode of care, an add-on to or modification of a standard mode of care or replacement of a standard mode of care?

Result

IVIG therapy is proposed as a new mode of care for Alzheimer's disease including Mild Cognitive Impairment. Current management involves the treatment of cognitive, non-cognitive and behavioural symptoms. Non-pharmacological treatment includes social support, increasing assistance with day-to-day activities, information and education, carer support groups, community dementia teams, home nursing and personal care, community services such as meals-on-wheels, befriending services, day centres, respite care and care homes {89}. At the current stage of development, it is not possible to state whether the IVIG therapy will be proposed alone or in combination with the current management solutions.

Importance: Critical

Transferability: Completely

Regulatory Status

Result card for CUR19: "What is the marketing authorisation status of intravenous immunoglobulins (IVIG)?"

View full card

CUR19: What is the marketing authorisation status of intravenous immunoglobulins (IVIG)?

Result

Immunoglobulins (IVIG) are authorised in Europe as {Appendix CUR-3}:

Replacement therapy in adults, and children and adolescents (0-18 years) in the following conditions:

- Primary immunodeficiency syndromes with impaired antibody production;
- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed;
- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation;
- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT);
- Congenital AIDS and recurrent bacterial infections;

Immunomodulation in adults, and children and adolescents (0-18 years) in the following conditions:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count;
- Guillain Barré syndrome;
- Kawasaki disease;
- Multifocal Motor Neuropathy (MMN).

Importance: Critical

Transferability: Completely

Result card for CUR20: "What is the reimbursement status of intravenous immunoglobulins (IVIG) across countries?"

View full card

CUR20: What is the reimbursement status of intravenous immunoglobulins (IVIG) across countries?

Result

IVIG are reimbursed across countries for a list of approved indications. As IVIG are not formally used for Alzheimer's disease including Mild Cognitive Impairment, no specific reimbursement schemes have been developed. Reimbursement of the IVIG therapy for off-label use cannot be excluded {Appendix CUR-3}.

Importance: Critical

Transferability: Completely

Discussion

According to the information available at the time of writing, IVIG are not used for Alzheimer's disease including Mild Cognitive Impairment in any of the EUnetHTA partners who answered the survey. However, while some partners explicitly excluded the use of IVIG for the mentioned indications, some others stated that, given the characteristics of the internal monitoring and reimbursement system, it's impossible to exclude the off-label use of IVIG {Appendix CUR-3}. No manufacturers have submitted requests to EMA for the market approval of the IVIG for Alzheimer's disease including Mild Cognitive Impairment {Appendix CUR-3}.

References

1. Aguero-Torres H, Fratiglioni L, Winblad B. Natural history of alzheimer's disease and other dementias: Review of the literature in the light of the findings from the kungsholmen project. Int J Geriatr Psychiatry. 1998 Nov;13(11):755-66.

2. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to alzheimer's disease: Recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. Alzheimers Dement. 2011 May;7(3):270-9.

3. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. Washington DC: American Psychiatric Association; 1994.

4. Apostolova LG, Cummings JL. Neuropsychiatric manifestations in mild cognitive impairment: A systematic review of the literature. Dement Geriatr Cogn Disord. 2008;25(2):115-26.

5. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet. 2011 Mar 19;377(9770):1019-31.

6. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;(1)(1):CD003476.

7. Blennow K, Dubois B, Fagan AM, Lewczuk P, de Leon MJ, Hampel H. Clinical utility of cerebrospinal fluid biomarkers in the diagnosis of early alzheimer's disease. Alzheimers Dement. 2014 May 2.

8. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of alzheimer's disease. Alzheimers Dement. 2007 Jul;3(3):186-91.

9. Bruscoli M, Lovestone S. Is MCI really just early dementia? A systematic review of conversion studies. Int Psychogeriatr. 2004 Jun;16(2):129-40.

10. Burns Alistair, Zaudig Michael. Mild cognitive impairment in older people. Lancet. 2002;360:1963-5.

11. Campbell N, Ayub A, Boustani MA, Fox C, Farlow M, Maidment I, et al. Impact of cholinesterase inhibitors on behavioral and psychological symptoms of alzheimer's disease: A meta-analysis. Clin Interv Aging. 2008;3(4):719-28.

12. Chan KY, Wang W, Wu JJ, Liu L, Theodoratou E, Car J, et al. Epidemiology of alzheimer's disease and other forms of dementia in china, 1990-2010: A systematic review and analysis. Lancet. 2013 Jun 8;381(9882):2016-23.

13. Chertkow H, Nasreddine Z, Joanette Y, Drolet V, Kirk J, Massoud F, et al. Mild cognitive impairment and cognitive impairment, no dementia: Part A, concept and diagnosis. Alzheimers Dement. 2007 Oct;3(4):266-82.

14. Cohen AD, Klunk WE. Early detection of alzheimer's disease using PiB and FDG PET. Neurobiol Dis. 2014 May 10.

15. Coley N, Andrieu S, Gardette V, Gillette-Guyonnet S, Sanz C, Vellas B, et al. Dementia prevention: Methodological explanations for inconsistent results. Epidemiol Rev. 2008;30:35-66.

16. Cooper C, Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: Systematic review. Br J Psychiatry. 2013 Sep;203(3):255-64.

17. Cooper C, Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: Systematic review. Br J Psychiatry. 2013 Sep;203(3):255-64.

18. Cortes F, Nourhashemi F, Guerin O, Cantet C, Gillette-Guyonnet S, Andrieu S, et al. Prognosis of alzheimer's disease today: A two-year prospective study in 686 patients from the REAL-FR study. Alzheimers Dement. 2008 Jan;4(1):22-9.

19. Delva F, Auriacombe S, Letenneur L, Foubert-Samier A, Bredin A, Clementy A, et al. Natural history of functional decline in alzheimer's disease: A systematic review. J Alzheimers Dis. 2014;40(1):57-67.

20. Dodel R, Rominger A, Bartenstein P, Barkhof F, Blennow K, Forster S, et al. Intravenous immunoglobulin for treatment of mild-to-moderate alzheimer's disease: A phase 2, randomised, double-blind, placebo-controlled, dose-finding trial. Lancet Neurol. 2013 Mar;12(3):233-43.

21. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: Management of dementia (an evidence-based review). report of the quality standards subcommittee of the american academy of neurology. Neurology. 2001 May 8;56(9):1154-66.

22. Elias-Sonnenschein LS, Viechtbauer W, Ramakers IH, Verhey FR, Visser PJ. Predictive value of APOE-epsilon4 allele for progression from MCI to AD-type dementia: A meta-analysis. J Neurol Neurosurg Psychiatry. 2011 Oct;82(10):1149-56.

23. Etgen T, Sander D, Bickel H, Forstl H. Mild cognitive impairment and dementia: The importance of modifiable risk factors. Dtsch Arztebl Int. 2011 Nov;108(44):743-50.

24. Farina N, Isaac MG, Clark AR, Rusted J, Tabet N. Vitamin E for alzheimer's dementia and mild cognitive impairment. Cochrane Database Syst Rev. 2012 Nov 14;11:CD002854.

25. Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for alzheimer's disease: A systematic review. BMJ Open. 2012 Jun 11;2(3):10.1136/bmjopen,2012-000917. Print 2012.

26. Ferreira D, Perestelo-Perez L, Westman E, Wahlund LO, Sarria A, Serrano-Aguilar P. Meta-review of CSF core biomarkers in alzheimer's disease: The state-of-the-art after the new revised diagnostic criteria. Front Aging Neurosci. 2014 Mar 24;6:47.

27. Ferreira LK, Diniz BS, Forlenza OV, Busatto GF, Zanetti MV. Neurostructural predictors of alzheimer's disease: A meta-analysis of VBM studies. Neurobiol Aging. 2011 Oct;32(10):1733-41.

28. Filippi M, Agosta F, Barkhof F, Dubois B, Fox NC, Frisoni GB, et al. EFNS task force: The use of neuroimaging in the diagnosis of dementia. Eur J Neurol. 2012 Dec;19(12):e131,40, 1487-501.

29. Gauthier S, Patterson C, Chertkow H, Gordon M, Herrmann N, Rockwood K, et al. 4th canadian consensus conference on the diagnosis and treatment of dementia. Can J Neurol Sci. 2012 Nov;39(6 Suppl 5):S1-8.

30. Gauthier S, Patterson C, Chertkow H, Gordon M, Herrmann N, Rockwood K, et al. 4th canadian consensus conference on the diagnosis and treatment of dementia. Can J Neurol Sci. 2012 Nov;39(6 Suppl 5):S1-8.

31. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. Mild cognitive impairment. Lancet. 2006 Apr 15;367(9518):1262-70.

32. Ghosh S, Libon D, Lippa C. Mild cognitive impairment: A brief review and suggested clinical algorithm. Am J Alzheimers Dis Other Demen. 2013 Dec 26.

33. Gomar JJ, Bobes-Bascaran MT, Conejero-Goldberg C, Davies P, Goldberg TE, Alzheimer's Disease Neuroimaging Initiative. Utility of combinations of biomarkers, cognitive markers, and risk factors to predict conversion from mild cognitive impairment to alzheimer disease in patients in the alzheimer's disease neuroimaging initiative. Arch Gen Psychiatry. 2011 Sep;68(9):961-9.

34. Guehne U, Angermeyer MC, Riedel-Heller S. Is mortality increased in mildly cognitively impaired individuals? A systematic literature review. Dement Geriatr Cogn Disord. 2006;21(5-6):403-10.

35. Guehne U, Luck T, Busse A, Angermeyer MC, Riedel-Heller SG. Mortality in individuals with mild cognitive impairment. results of the leipzig longitudinal study of the aged (LEILA75+). Neuroepidemiology. 2007;29(3-4):226-34.

36. Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: A systematic review of prospective evidence. Psychol Med. 2009 Jan;39(1):3-11.

37. Heister D, Brewer JB, Magda S, Blennow K, McEvoy LK, Alzheimer's Disease Neuroimaging Initiative. Predicting MCI outcome with clinically available MRI and CSF biomarkers. Neurology. 2011 Oct 25;77(17):1619-28.

38. Hort J, O'Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, et al. EFNS guidelines for the diagnosis and management of alzheimer's disease. Eur J Neurol. 2010 Oct;17(10):1236-48.

39. Hunderfund AL, Roberts RO, Slusser TC, Leibson CL, Geda YE, Ivnik RJ, et al. Mortality in amnestic mild cognitive impairment: A prospective community study. Neurology. 2006 Nov 28;67(10):1764-8.

40. Jicha GA, Carr SA. Conceptual evolution in alzheimer's disease: Implications for understanding the clinical phenotype of progressive neurodegenerative disease. J Alzheimers Dis. 2010;19(1):253-72.

41. Kayed R, Jackson GR, Estes DM, Barrett AD. Alzheimers disease: Review of emerging treatment role for intravenous immunoglobulins. J Cent Nerv Syst Dis. 2011 May 8;3:67-73.

42. Kelley BJ, Petersen RC. Alzheimer's disease and mild cognitive impairment. Neurol Clin. 2007 Aug;25(3):577,609, v.

43. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: A longitudinal, population-based study. Lancet Neurol. 2006 Sep;5(9):735-41.

44. Landau SM, Harvey D, Madison CM, Koeppe RA, Reiman EM, Foster NL, et al. Associations between cognitive, functional, and FDG-PET measures of decline in AD and MCI. Neurobiol Aging. 2011 Jul;32(7):1207-18.

45. Lockhart IA, Orme ME, Mitchell SA. The efficacy of licensed-indication use of donepezil and memantine monotherapies for treating behavioural and psychological symptoms of dementia in patients with alzheimer's disease: Systematic review and meta-analysis. Dement Geriatr Cogn Dis Extra. 2011 Jan;1(1):212-27.

46. Loeffler DA. Intravenous immunoglobulin and alzheimer's disease: What now? J Neuroinflammation. 2013 Jun 5;10(1):70,2094-10-70.

47. Lovheim H, Sandman PO, Karlsson S, Gustafson Y. Behavioral and psychological symptoms of dementia in relation to level of cognitive impairment. Int Psychogeriatr. 2008 Aug;20(4):777-89.

48. Luck T, Luppa M, Briel S, Riedel-Heller SG. Incidence of mild cognitive impairment: A systematic review. Dement Geriatr Cogn Disord. 2010;29(2):164-75.

49. Matthews FE, Stephan BC, McKeith IG, Bond J, Brayne C, Medical Research Council Cognitive Function and Ageing Study. Two-year progression from mild cognitive impairment to dementia: To what extent do different definitions agree? J Am Geriatr Soc. 2008 Aug;56(8):1424-33.

50. Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. CSF biomarkers and incipient alzheimer disease in patients with mild cognitive impairment. JAMA. 2009 Jul 22;302(4):385-93.

51. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR,Jr, Kawas CH, et al. The diagnosis of dementia due to alzheimer's disease: Recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9.

52. McLaren AN, Lamantia MA, Callahan CM. Systematic review of non-pharmacologic interventions to delay functional decline in community-dwelling patients with dementia. Aging Ment Health. 2013;17(6):655-66.

53. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res. 2009 Jan;43(4):411-31.

54. Mitchell AJ. CSF phosphorylated tau in the diagnosis and prognosis of mild cognitive impairment and alzheimer's disease: A meta-analysis of 51 studies. J Neurol Neurosurg Psychiatry. 2009 Sep;80(9):966-75.

55. Mitchell AJ, Meader N, Pentzek M. Clinical recognition of dementia and cognitive impairment in primary care: A meta-analysis of physician accuracy. Acta Psychiatr Scand. 2011 Sep;124(3):165-83.

56. Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia--meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 2009 Apr;119(4):252-65.

57. Mohs RC, Schmeidler J, Aryan M. Longitudinal studies of cognitive, functional and behavioural change in patients with alzheimer's disease. Stat Med. 2000 Jun 15-30;19(11-12):1401-9.

58. Monastero R, Di Fiore P, Ventimiglia GD, Ventimiglia CC, Battaglini I, Camarda R, et al. Prevalence and profile of mild cognitive impairment in parkinson's disease. Neurodegener Dis. 2012;10(1-4):187-90.

59. Moore A, Patterson C, Lee L, Vedel I, Bergman H. Fourth canadian consensus conference on the diagnosis and treatment of dementia: Recommendations for family physicians. Can Fam Physician. 2014 May;60(5):433-8.

60. Muayqil T, Camicioli R. Systematic review and meta-analysis of combination therapy with cholinesterase inhibitors and memantine in alzheimer's disease and other dementias. Dement Geriatr Cogn Dis Extra. 2012 Jan;2(1):546-72.

61. O'Brien JT, Burns A, BAP Dementia Consensus Group. Clinical practice with anti-dementia drugs: A revised (second) consensus statement from the british association for psychopharmacology. J Psychopharmacol. 2011 Aug;25(8):997-1019.

62. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry. 2006 May;63(5):530-8.

63. Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: A concept in evolution. J Intern Med. 2014 Mar;275(3):214-28.

64. Portet F, Ousset PJ, Visser PJ, Frisoni GB, Nobili F, Scheltens P, et al. Mild cognitive impairment (MCI) in medical practice: A critical review of the concept and new diagnostic procedure. report of the MCI working group of the european consortium on alzheimer's disease. J Neurol Neurosurg Psychiatry. 2006 Jun;77(6):714-8.

65. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement. 2013 Jan;9(1):63,75.e2.

66. Ravaglia G, Forti P, Maioli F, Martelli M, Servadei L, Brunetti N, et al. Conversion of mild cognitive impairment to dementia: Predictive role of mild cognitive impairment subtypes and vascular risk factors. Dement Geriatr Cogn Disord. 2006;21(1):51-8.

67. Reijnders J, van Heugten C, van Boxtel M. Cognitive interventions in healthy older adults and people with mild cognitive impairment: A systematic review. Ageing Res Rev. 2013 Jan;12(1):263-75.

68. Rikkert MG, Tona KD, Janssen L, Burns A, Lobo A, Robert P, et al. Validity, reliability, and feasibility of clinical staging scales in dementia: A systematic review. Am J Alzheimers Dis Other Demen. 2011 Aug;26(5):357-65.

69. Robins Wahlin TB, Byrne GJ. Personality changes in alzheimer's disease: A systematic review. Int J Geriatr Psychiatry. 2011 Oct;26(10):1019-29.

70. Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. Cochrane Database Syst Rev. 2012 Sep 12;9:CD009132.

71. Schneider LS, Dagerman KS, Higgins JP, McShane R. Lack of evidence for the efficacy of memantine in mild alzheimer disease. Arch Neurol. 2011 Aug;68(8):991-8.

72. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: Meta-analysis of randomized placebo-controlled trials. JAMA. 2005 Oct 19;294(15):1934-43.

73. Seeher K, Low LF, Reppermund S, Brodaty H. Predictors and outcomes for caregivers of people with mild cognitive impairment: A systematic literature review. Alzheimers Dement. 2013 May;9(3):346-55.

74. Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P. Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev. 2011 Feb 16;(2):CD008191. doi(2):CD008191.

75. Solomon A, Mangialasche F, Richard E, Andrieu S, Bennett DA, Breteler M, et al. Advances in the prevention of alzheimer's disease and dementia. J Intern Med. 2014 Mar;275(3):229-50.

76. Sosa-Ortiz AL, Acosta-Castillo I, Prince MJ. Epidemiology of dementias and alzheimer's disease. Arch Med Res. 2012 Nov;43(8):600-8.

77. Teixeira CV, Gobbi LT, Corazza DI, Stella F, Costa JL, Gobbi S. Non-pharmacological interventions on cognitive functions in older people with mild cognitive impairment (MCI). Arch Gerontol Geriatr. 2012 Jan-Feb;54(1):175-80.

78. Todd S, Barr S, Roberts M, Passmore AP. Survival in dementia and predictors of mortality: A review. Int J Geriatr Psychiatry. 2013 Nov;28(11):1109-24.

79. Tricco AC, Soobiah C, Lillie E, Perrier L, Chen MH, Hemmelgarn B, et al. Use of cognitive enhancers for mild cognitive impairment: Protocol for a systematic review and network meta-analysis. Syst Rev. 2012 May 30;1:25,4053-1-25.

80. Vos SJ, van Rossum IA, Verhey F, Knol DL, Soininen H, Wahlund LO, et al. Prediction of alzheimer disease in subjects with amnestic and nonamnestic MCI. Neurology. 2013 Mar 19;80(12):1124-32.

81. Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: Disparity of incidence and prevalence estimates. Alzheimers Dement. 2012 Jan;8(1):14-21.

82. Widiapradja A, Vegh V, Lok KZ, Manzanero S, Thundyil J, Gelderblom M, et al. Intravenous immunoglobulin protects neurons against amyloid beta-peptide toxicity and ischemic stroke by attenuating multiple cell death pathways. J Neurochem. 2012 Jul;122(2):321-32.

83. Wilson RS, Aggarwal NT, Barnes LL, Bienias JL, Mendes de Leon CF, Evans DA. Biracial population study of mortality in mild cognitive impairment and alzheimer disease. Arch Neurol. 2009 Jun;66(6):767-72.

84. Wimo A, Jonsson L, Bond J, Prince M, Winblad B, Alzheimer Disease International. The worldwide economic impact of dementia 2010. Alzheimers Dement. 2013 Jan;9(1):1,11.e3.

85. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, et al. Mild cognitive impairment--beyond controversies, towards a consensus: Report of the international working group on mild cognitive impairment. J Intern Med. 2004 Sep;256(3):240-6.

86. World Health Organization. The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization; 1992.

87. Xiao H, Su Y, Cao X, Sun S, Liang Z. A meta-analysis of mood stabilizers for alzheimer's disease. J Huazhong Univ Sci Technolog Med Sci. 2010 Oct;30(5):652-8.

88. Yue J, Dong BR, Lin X, Yang M, Wu HM, Wu T. Huperzine A for mild cognitive impairment. Cochrane Database Syst Rev. 2012 Dec 12;12:CD008827.

89. NICE technology appraisal guidance 217 Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111). 2011.

90. Department of Health. Clinical guidelines for immunoglobulin use: update to second edition. August 2011. London (UK).

91. Bašić-Kes V, Kes P, Zavoreo I, Lisak M, Zadro L, Ćorić L, Demarin V. Guidelines for the use of intravenous immunoglobulin in the treatment of neurologic diseases, Croatian Medical Association. Acta Clin Croat 2012; 51:673-683.

Appendices

Appendix CUR-1 (strategy of the additional, unsystematic literature searches performed by the authors of this domain).

Appendix SAF-7 (document named "Use of Intravenous immunoglobulins for Mild Cognitive Impairment and Alzeheimer's disease – Protocol" prepared by the authors team from SAF domain).

Appendix CUR-3 (surveys carried out by the WP4 Leader among the stakeholder advisory group, SAG, and EUnetHTA partners).

Description and technical characteristics of technology

Authors: Jesús González-Enríquez, Nadine Berndt, Houria Mouas

Summary

Features of the technology

Intravenous immunoglobulins (IVIG), human normal immunoglobulin for intravascular administration (ATC code J06BA02), is a medicinal product derived from human plasma of at least thousands of healthy voluntary donors, prepared industrially, containing polyclonal antibodies to produce passive immunity and other protective effects. Human normal immunoglobulin is a highly purified protein extracted from human plasma. It contains immunoglobulin G (IgG), which is a type of antibody. IgG works by restoring abnormally low IgG levels to their normal range in the blood.

There are several IVIG producers and many market authorized presentations of the product. The resulting products are generally believed to be equally effective for treatment of the autoimmune and immunodeficiency disorders. Products presentations vary in concentration of human normal immunoglobulins in 1 ml of solution.

There has been a rapid expansion in the use of intravenous immunoglobulin (IVIG) for an ever growing number of conditions and often used more extensively than the authorized indications ("off-label use"). IVIG has had a major impact in neurology, haematology, immunology, rheumatology and dermatology. Intravenous immunoglobulin (IVIG) has been successfully used to treat a number of immune-mediated diseases of the central and peripheral nervous system. Although underlying mechanisms of action of IVIG have not been fully explained, it is known that IVIG can interfere with the immune system at several levels. IVIG is being used as a treatment in many different conditions, including primary and secondary antibody deficiency states, haematological diseases, neurological diseases and other conditions.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

There is reassuring clinical experience regarding the lack of hepatitis A or Parvovirus.

B19 transmission with immunoglobulins and it is also assumed that the antibody content makes an important contribution to the viral safety.

It is strongly recommended that every time that IVIG preparation is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Serious reactions are uncommon. Adverse reactions occur more often when a patient is either receiving IVIG for the first time, or switching from one preparation to another or when there has been a long interval since the previous infusion. Certain patient groups are at higher risk for serious complications, such as those receiving high dose IVIG, patients with dehydration, the elderly, and those with preexisting renal or cardiovascular disorders, previous IVIG treatment complications, history of migraine, diabetes, concomitant use of nephrotoxic drugs, sepsis and fluid volume depletion. Many reactions are dose rate-related. Hematologic and thrombotic complications include hemolysis, neutropenia, and thrombotic and thromboembolic events. Some risk factors, such as high doses of IVIG, and certain underlying disorders, have been identified. The most important renal complication is acute renal failure, which is caused by sucrose-containing preparations, but can occur with any IVIG product.

Intravenous immunoglobulin (IVIG) products are being investigated as potential agents for treatment or prevention of AD. Polyclonal naturally occurring autoantibodies against amyloid β are found in serum of healthy persons and are reduced in AD patients.

IVIG has not been approved for prevention or treatment of AD and mild cognitive impairment. IVIG products are thought to contain the full range of antibodies present in the human repertoire. IVIG's mechanisms of action in different disorders are generally poorly understood. It contains several antibodies that have the potential to reduce AD-type pathology, but whether these antibodies can actually do so is unclear. The IVIG trials reported to date in AD patients have produced conflicting findings. Newer research and developing human trials are becoming established for the use of intravenous immunoglobulins (IVIG) for the treatment and prevention of Alzheimer's disease. At present there is no cure for AD. Symptomatic treatment of dementia with cholinesterase-inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists is considered as standard of care, particularly in mild to

moderate Alzheimer's disease. In addition to the symptomatic treatments currently marketed, a host of potentially disease-modifying therapies have been studied, and numerous others are in development. At present time there is no effective drug to treat or delay the progression from mild cognitive impairment (MCI) to dementia.

Investments and tools required to use the technology

IVIG is usually administered in an infusion center or health care facility, indicated by specialized medical staff and supervised by health professionals. IVIG can be given in the hospital, doctor's office, or patients' home. In any setting, nurses administer most of the transfusions. They should complete an accredited blood transfusion education program and be assessed upon their competency. Accredited nurses are responsible for checking blood and blood products, administering IVIG, monitoring patients during transfusion, and carrying out the appropriate actions should an adverse effect occur, ensuring adequate documentation in the medical notes, and reporting of transfusion reactions or other incidences related to the transfusion.

Detailed documentation of IVIG infusions should include the patient's current health status and any changes in this status in the period between IVIG infusions; serological testing; record of brand, manufacturer, lot number, expiry date, dose and identification of the patient, any pre-medications which were given; time duration the infusion and specific rate titrations which were made; and any problems or adverse reactions the patient experienced during the infusion and how they were managed. A signed informed and written consent should be obtained from the patient, who should have received full information on the description of IVIG, their nature of blood product, the associated risks and benefits as well as alternatives to this treatment. The administration of IVIG should be carefully monitored and observed for any symptoms or alteration of vital signs throughout the infusion period and after administration. In addition, a monitoring of the renal function and diuresis is required as well as a good hydration of the patient.

Quality controls are required to guarantee the consistency of IVIG batches and to limit the risks of adverse reactions that have shown to be linked to the presence of certain proteins, biological/microbial or chemical impurities. A set of quality control assays are needed to guide manufacturers in the development of IVIG preparations, to control the conditions of production and to guarantee the quality, safety and consistency of the products. Prescribed manufacturing procedures at the plasma collection centers and plasma-testing laboratories need to be designed in that way that they reduce the risk of transmitting viral infection. Risk reducing measures include careful selection of donors for plasma pools, testing for viral markers at multiple stages which allow for the detection of plasma viruses and the application of rigorously validated methods of testing. Quality controls for plasma derivatives include determination of chemical parameters, protein content, content of stabilizers and residues of chemicals used for the production or viral inactivation and various safety parameters. Some IVIGs products require refrigeration whereas others can be stored at room temperature. As such, lyophilized products are generally stored at room temperature before reconstitution. However, all liquid IVIG products optimally require refrigerated transport and storage between 2°C and 8°C. Blood products should be transported in dedicated and validated containers and be stored within glass containers, which are closed with rubber stoppers. It is important to follow the manufacturer's specifications regarding storage and refrigeration requirements of each product, since the recommendations may vary per IVIG product.

Training and information needed for utilizing the technology

The health professional using IVIG requires specific knowledge and skills in order to be competent to treat patients with IVIGs. A hospital based IVIG program should provide education, training and protocols for staff to ensure the appropriate management and use of IVIGs, including transport, storage, use of equipment and infusion techniques. The training should include education related to documentation, patient consent, difference among IVIG brands, selection of a brand on the basis of patients' risk factors, contraindications, needs, action plans for adverse events, rapid infusion protocols, and setup of infusion pumps, tubing and filter equipment.

Patients should be eligible for IVIGs only in case they give consent for transfusion of blood and/or blood products. One or several patient and/or family education sessions may be required to inform patients and/or family about what IVIG are and what they are used for, the fact that IVIGs are not licensed for use in the treatment of Alzheimers' disease and mild-cognitive-impairment (off-label use), what one needs to know before using IVIGs, how and how often it is administered, the approximate duration of each infusion times, potential risks and benefits of its use, the potential of virus transmissions, contra-indications, so that informed consent may be obtained. Information about such things as new modalities of treatment, legislative initiatives and insurance issues may also be valuable. Patients and their families should equally be provided with written information brochures concerning the IVIGs. A risk assessment may be carried out to ensure the patient and family understand the need for treatment and how it is administered.

Introduction

Intravenous immunoglobulins (IVIG), human normal immunoglobulin for intravascular administration (ATC code J06BA02), is a medicinal product derived from the pool of human plasma of at least thousands of healthy voluntary donors, prepared industrially, containing polyclonal antibodies to induce passive immunity and other protective effects. Human normal immunoglobulin is a highly purified protein extracted from human plasma. It contains immunoglobulin G (IgG), which is a type of antibody. IgG acts by restoring abnormally low IgG levels to their normal range in the blood.

There are several IVIG producers and many market authorized presentations of the product. The resulting products are generally believed to be equally effective for treatment of the autoimmune and immunodeficiency disorders. Products presentations vary in concentrations of human normal immunoglobulins in 1 ml of solution.

There has been a rapid expansion in the use of intravenous immunoglobulin (IVIG) for an ever growing number of conditions. IVIG has had a major impact in neurology, haematology, immunology, rheumatology and dermatology.

Intravenous immunoglobulin (IVIG) has been successfully used to treat a number of immune-mediated diseases of the central and peripheral nervous system. Although underlying mechanisms of action of IVIG have not been fully explained, it is presumed that IVIG can interfere with the immune system at several levels. IVIG has not been approved for prevention or treatment of AD and mild cognitive impairment. IVIG products contain the full range of antibodies present in normal population. IVIG's mechanisms of action in different disorders are generally poorly understood. It contains several antibodies that have the potential to reduce AD-type pathology, but whether these antibodies can actually do so is unclear. Newer research and human clinical trials are conducted for the use of intravenous immunoglobulins (IVIG) for the treatment and prevention of Alzheimer's disease.

The aim of this Domain is to describe and review the technical characteristics of IVIG. The aspects considered in this domain are correlated with the selected relevant issues and research questions. We try to describe the technology and its technical characteristics to get an overall understanding on its functioning, indications and use.

Methodology

Frame

The collection scope is used in this domain.

Technology	Immunoglobulins (IGG) **Description** Naturally occurring proteins produced by the body's immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer's disease **Target condition** Alzheimer's disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.
Comparison	placebo, not doing anything or Usual supportive care **Description** There is no MA for IGGs for AD yet and there is no other intervention licensed for use in AD so the comparison would have to be against placebo or best supportive care
Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
B0001	Features of the technology	What is this technology and the comparator(s)?	yes	What are Intravenous Inmunoglobulins (IVIG)? What are the potential comparators for IVIG use in Alzheimer's disease and Mild Cognitive Impairment?
B0002	Features of the technology	What is the approved indication and claimed benefit of the technology and the comparator(s)?	yes	What is the approved indication and claimed benefit of IVIG?
B0003	Features of the technology	What is the phase of development and implementation of the technology and the comparator(s)?	yes	What is the phase of development and implementation of intravenous immunoglobulins (IVIG)?
B0004	Features of the technology	Who performs or administers the technology and the comparator(s)?	yes	Who performs or administers IVIG?
B0005	Features of the technology	In what context and level of care are the technology and the comparator used?	yes	In what context and level of care are IVIG used?
A0022	Other	Who manufactures the technology?	yes	Who manufactures IVIG?
B0007	Investments and tools required to use the technology	What material investments are needed to use the technology?	yes	What material investments are needed to use IVIG?
B0008	Investments and tools required to use the technology	What kind of special premises are needed to use the technology and the comparator(s)?	yes	What kind of special premises are needed to use IVIG?
B0009	Investments and tools required to	What equipment and supplies are needed to use the	yes	What equipment and supplies are needed to use IVIG?

	use the technology	technology and the comparator?		
B0010	Investments and tools required to use the technology	What kind of data and records are needed to monitor the use of the technology and the comparator?	yes	What kind of data and records are needed to monitor the use of IVIG ?
B0011	Investments and tools required to use the technology	What kind of registers are needed to monitor the use the technology and comparator?	yes	What kind of registers are needed to monitor the use IVIG?
B0012	Training and information needed to use the technology	What kind of qualification and quality assurance processes are needed for the use or maintenance of the technology?	yes	What kind of qualification and quality assurance processes are needed for the use or maintenance of IVIG?
B0013	Training and information needed to use the technology	What kind of training and information is needed for the personnel/carer using this technology?	yes	What kind of training and information is needed for the personnel/carer using IVIG?
B0014	Training and information needed to use the technology	What kind of training and information should be provided for the patient who uses the technology, or for his family?	yes	What kind of training and information should be provided for the patients who uses IVIG o for their families?
B0015	Training and information needed to use the technology	What information of the technology should be provided for patients outside the target group and the general public?	no	Potential intervention for a specific clinical situation. In the current situation it is not relevant to examine the needs of information provision for the general population or patients outside the target group, because the intervention is highly specific. However, if the intervention will turn out to be effective in the future, there might be an interest to provide information on the IVIGs to the relevant target population and probably also to the general public, thus they are informed about the existence of this treatment.

Methodology description

Domain frame

The project scope is applied in this domain.

Information sources

- Basic systematic search. Common (basic) literature search strategy run for the whole project (Immuno database).

- Additional search for published literature in PubMed and internet search of grey literature using Google, HTA database. Review of the reference lists and bibliographies of selected studies identified through the basic systematic search.

- Manufacturers and companies web sites, Micromedex Drugdex Database.

- Search for IVIG authorization of immunoglobulins in EU website, EMEA data files, national and European law, other European notified bodies.

Quality assessment tools or criteria

No quality assessment tool was used. We use unsystematic approach and selection of relevant updated general reviews and specific documents.

Analysis and synthesis

The sources were sufficient to answer the questions. We did not perform additional data analysis. No quality assessment of the sources was made.

The results are presented in text format, supplemented by overview tables.

Descriptive analysis on different information sources. The assessment elements questions are answered and reviewed by cooperation of Domain investigators.

Result cards

Features of the technology

Result card for TEC1a: "What are Intravenous Inmunoglobulins (IVIG)?" and TEC1b: "What are the potential comparators for IVIG use in Alzheimer’s disease and Mild Cognitive Impairment?"

View full card

TEC1a: What are Intravenous Inmunoglobulins (IVIG)?

Method

Refer to domain search and domain methodology section.

Result

1. INTRODUCTION AND PRODUCT DESCRIPTION

Intravenous immunoglobulins (IVIG), human normal immunoglobulin for intravascular administration (ATC code J06BA02), is a medicinal product derived from human plasma of at least thousands of healthy voluntary donors, prepared industrially, containing polyclonal antibodies to produce passive immunity and other protective effects. Human normal immunoglobulin is a highly purified protein extracted from human plasma. It contains mainly immunoglobulin G (IgG), with a broad spectrum of antibodies against infectious agents. IVIG has been used as a medicine since the 1980s and has a wide range of activity against organisms that can cause infection. In 1982, IVIG use in the US was approximately 40,000 g, and in 2006 consumption was estimated to reach 36 million grams annually {Duff, 2006}{1}. IgG works by restoring abnormally low IgG levels to their normal range in the blood.

Human normal immunoglobulin contains mainly IgG with a broad spectrum of antibodies against infectious agents. Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donors, usually thousands of blood donors. It has a distribution of IG subclasses closely proportional to that in native human plasma. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated, but includes immunomodulatory effects.

Human normal immunoglobulin is immediately and completely bioavailable in the recipient’s circulation after intravenous administration. It is distributed relatively rapidly between plasma and extravascular fluid, after approximately 3-5 days equilibrium is reached between the intra- and extravascular compartments. The median IgG half-life after administration varies around 30 to 40 days approximately. This half-life may vary from patient to patient and clinical condition, in particular in primary immunodeficiency.

The rate of metabolism does not appear to increase with chronic administration. However, detailed pharmacokinetic studies are not available in patients with autoimmune diseases given repeated high dosages of IVIG.

Intravenous preparations of immune globulin (IVIG) first became available in the 1979 {The Consensus Working Group, 1997; Laupland KB, 2002}{2,3}, although these contained impurities that caused severe anaphylactoid reactions and protein aggregates that cause thromboembolies. Subsequent refinements allowed for safe administration of higher doses intravenously that more closely approximated physiologic levels.

Immune globulin may be administered by different routes: Intravenously (immune globulin, intravenous [human] "IVIG" or "IGIV"); subcutaneously (SCIG or IGSC) or intramuscularly (IGIM). Multiple products are available, which vary in concentration of IgG, additives and stabilizers, and IgA content. Most products are labeled for a specific route of administration. Subcutaneous and intramuscular products are generally more concentrated than intravenous preparations and should not be given intravenously.

1.1 IVIG production and composition

Production of IVIG begins with pooled human plasma from several thousand screened volunteer donors. Cold alcohol fractionation is used to isolate the immunoglobulin-containing fraction. This is followed by further purification techniques, including additional precipitation steps to remove non-IgG proteins and ion exchange chromatography. Most IgG preparations also undergo several specific treatments to inactivate or removal potentially present blood-borne pathogens. These include low pH treatment, fatty acid treatment, solvent-detergent treatment, heat-treatment (pasteurization) and/or nanofiltration.

The World Health Organization has published minimum standards for manufacturing IVIG preparations {WHO 2008}{4}.

IVIG should be extracted from a pool of at least thousands of healthy screened donors.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

It should contain as little IgA as possible.

The IgG molecules should be modified biochemically as little as possible and possess opsonizing and complement-fixing activities.

It should be free from preservatives or stabilizers that might accumulate in vivo.

There are slight differences in the manufacturing procedures utilized by the different producers, and different stabilizers are used in the excipients. However, the final preparations are highly purified (>90 percent) polyvalent IgG. Products differ in storage requirements and shelf life. Stabilizers may include sugars, such as sucrose, glucose, or maltose. Some IVIG products contain amino acids such as glycine or proline. The sodium content of different products also varies.

The resulting products are generally believed to be equally effective for treatment of the autoimmune and immunodeficiency disorders. However, they differ from each other in ways that may be important in a particular patient.

Product presentation varies in concentration of human normal immunoglobulins. The product is packaged in different volume vials (glass) as solution for infusion. The content is high purity IgG. The distribution of IgG subclasses also is variable. The solution is clear or slightly opalescent and colourless or pale yellow.

1.2 Main therapeutic indications

(From Core Summary of Product Characteristics. Clinical Particulars)

Replacement therapy in adults, and children and adolescents (0-18 years) in:

- Primary immunodeficiency syndromes with impaired antibody production.

- Hypogammaglobulinaemia and recurrent bacterial infections in patients with chronic lymphocytic leukaemia, in whom prophylactic antibiotics have failed.

- Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation.

- Hypogammaglobulinaemia in patients after allogeneic haematopoietic stem cell transplantation (HSCT).

- Congenital AIDS with recurrent bacterial infections.

Immunomodulation in adults, and children and adolescents (0-18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.

- Guillain Barré syndrome.

- Kawasaki disease.

- Product specific auto-immune indications (e.g. multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), myasthenia gravis exacerbations) and other product specific indications – see Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) EMA/CHMP/BPWP/94033/2007 rev. 2.

There has been a rapid expansion in the use of intravenous immunoglobulin (IVIG) for an ever growing number of conditions and often used more extensively than the authorized indications (“off-label use”). IVIG use has had a major impact in neurology, haematology, immunology, rheumatology and dermatology. (See B002)

1.3 Dosing

The dose and dose regimen is dependent on the indication. (See TEC-1 Figure 1)

TEC-1 Figure 1">

Replacement therapy in primary immunodeficiency syndromes:

The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l. The recommended starting dose is 0.4-0.8 g/kg given once, followed by at least 0.2 g/kg given every three to four weeks. Trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels.

Subcutaneous preparations are widely used in immunodeficiency because the gradual and steady introduction of immune globulin into the patient's circulation appears to have advantages. In addition, subcutaneous immune globulin (SCIG) is frequently self-administered at home, which could be more convenient for some patients.

Infusion rates for intravenous immunoglobulin:

Replacement therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency.

Initial intravenous infusion rates are low, and if well tolerated, the rate of administration may be increased, as specified in the products’ Summary of Product Characteristics (SPC). For certain products, the SPC indicates that if the higher rate is tolerated, the rate may be further increased in primary immunodeficiency (PID) patients to the maximum infusion rate. Higher infusion rates may lead to improved convenience for patients and may reduce nursing time and the need for hospital resources. Patients at high risk for tromboembolic events should not receive rapid infusion of IVIG. Infusion rates for each of the licensed immunoglobulins are provided in the table below. Immunoglobulin should be administered according to the manufacturers’ recommendations. The table below gives the infusion rates, and the infusion time at maximum infusion rate of 1 g/kg dose in a 70 kg person {Department of Health, 2011}{5}.(See TEC-1 Figure 2).

TEC-1 Figure 2">

Patients with particular clinical conditions are at risk for certain adverse events. Adverse events can be reduced by downgrading the dose, the rate and the volume of the infusion. IVIG is well tolerated by the majority of patients, but it is important to note that, just as each patient may require a different immunoglobulin product, each may also require an individualized infusion regimen in order to achieve the desired therapeutic response. Once a successful regimen has been developed, it should be carefully followed with every infusion. This includes not only the rate of the infusion and necessary premedications, but the specific product, as well.

1.4 Adverse effects

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped viruses HAV and parvovirus B19.

It is strongly recommended that every time that IVIG preparation is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Serious reactions are uncommon. Adverse reactions occur more often when a patient is either receiving IVIG for the first time, or switching from one preparation to another or when there has been a long interval since the previous infusion.

It is important to maintain patients consistently on one IVIG product to reduce the risk of adverse events.

Certain patient groups are at higher risk for serious complications, such as those receiving high dose IVIG, patients with dehydration, the elderly, and those with preexisting renal or cardiovascular disorders, previous IVIG treatment complications, history of migraine, diabetes, concomitant use of nephrotoxic drugs, sepsis and fluid volume depletion.

Many reactions are dose rate-related. Common adverse reactions include fever, chills, malaise, headache, dizziness, nausea vomiting, allergic reactions, arthralgia, influenza-like illness, chest discomfort, chest tightness, chest pain, asthenia, malaise, peripheral oedema, infusion site pain, infusion site swelling, infusion site reaction, rigors, pruritus, rash, urticaria, back pain, myalgia, muscle spasms, muscular weakness. These reactions usually respond to temporary discontinuation of the infusion. If reactions are anticipated, a patient can be premedicated with antihistamines and intravenous hydrocortisone.

Patients with active infections may experience fever, rigors, and "flu-like" symptoms during infusion of IVIG, which is believed to result from lysis of bacteria and release of cytokines. When possible, infections should be treated with antibiotics before administration of IVIG.

Hematologic and thrombotic complications include hemolysis, anaemia, lymphadenopathy, neutropenia, and thrombotic and thromboembolic events such as myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis {Micromedex Drugdex Database, 2014; Loeffler DA, 2013}{6,7}.

2. IVIG IN NEUROLOGICAL DISEASES

Intravenous immunoglobulin (IVIG) has been successfully used to treat a number of immune-mediated diseases of the central and peripheral nervous system.

Although underlying mechanisms of action of IVIG have not been fully explained, it is known that IVIG can interfere with the immune system at several levels. The effect of IVIG in one of particular diseases may not be attributed to only one of its mechanisms of action, because the pathophysiology of these diseases is complex.

The efficacy of IVIG has been proven in Guillain-Barre´ syndrome (level A), chronic inflammatory demyelinating polyradiculoneuropathy (level A), multifocal mononeuropathy (level A), acute exacerbations of myasthenia gravis (MG) and short-term treatment of severe MG (level A recommendation), and some paraneoplastic neuropathies (level B). IVIG is recommended asa second-line treatment in combination with prednisone in dermatomyositis (level B) and treatment option in polymyositis (level C). IVIG should be considered as a second or third-line therapy in relapsing–remitting multiple sclerosis, if conventional immunomodulatory therapies are not tolerated (level B), and in relapses during pregnancy or post-partum period (good clinical practice point). IVIG seems to have a favourable effect also in paraneoplastic neurological diseases (level A), stiff-person syndrome (level A), some acute-demyelinating diseases and childhood refractory epilepsy (good practice point) {EFNS, 2008}{8}.

2.2 IVIG AND ALZHEIMER’S DISEASE

IVIG products are thought to contain the full range of antibodies present in the human repertoire. IVIG’s mechanisms of action in different disorders are generally poorly understood. It contains several antibodies that have the potential to reduce AD-type pathology, but whether these antibodies can actually do so is unclear {Loeffler DA, 2013}{7}.

IVIG products contain antibodies to Aβ oligomers and fibrils and perhaps also to monomeric Aβ. These drugs differ in their levels of anti-Aβ antibodies. IVIG has been shown in vitro to disaggregate preformed Aβ fibrils, promote Aβ phagocytic removal, protect against Aβ neurotoxicity, and prevent formation of Aβ soluble oligomers {Dodel R, 2010} {9}.

IVIG’s antibodies recognize multiple sites on conformational Aβ epitopes, and its main binding to Aβ is reportedly to Aβ25-40. This differs from the monoclonal anti-Aβ antibodies that have been used in clinical trials, Bapineuzumab and Solanezumab, which recognize only one epitope in linear Aβ and bind to Aβ1-5 and Aβ13-28, respectively. A recent review {Moreth J, 2013}{10} suggested that using the IVIG polyclonal antibody approach in an effort to deplete the spectrum of aggregated Aβ species might be more promising than using monoclonal antibodies targeting a single Aβ species.

Other proposed mechanisms of action are anti-inflammatory effects, possible anti-tau effects, alteration of Aβ passage in and out of the brain and other non-antibody-mediated effects.

IVIG contains other non-antibody proteins in addition to sLRP, which could influence its actions in AD in ways that are not clear. Interferon-γ, an inflammatory cytokine that also has some anti-inflammatory actions, is present in IVIG. Soluble human leukocyte antigen (HLA) class I and II molecules are present in some IVIG products, as are their “physiological ligands,” CD4 and CD8. Soluble CD4 in IVIG might interfere with HLA class II molecules on antigen-presenting cells, competing with HLA-class II-restricted T cells and possibly causing immunosuppression. Transforming growth factor (TGF)-β1 and TGF-β2 are also present in IVIG. TGF-β1 is increased in AD brain, where it is associated with plaques, but it also may promote Aβ clearance, so its significance in AD is unclear.

Intravenous immunoglobulin (IVIG) products are being investigated as potential agents for treatment or prevention of Alzheimer´s Disease (AD). Polyclonal naturally occurring autoantibodies against amyloid β are found in serum of healthy persons and are reduced in AD patients. The IVIG product Octagam (Octapharma) was shown by Dodel et al. in 2002 to contain antibodies against amyloid β (Aβ), suggesting that IVIG might be useful for treatment of AD. These antibodies might interfere with metabolism of Aβ and be reduced in patient with AD {Dodel R, 2002}{11}. This provided the

rationale for IVIG pilot studies in AD patients. Three small clinical trials have tested the efficacy of intravenous immunoglobulin for mild-to-moderate Alzheimer's disease. In an initial uncontrolled trial, five patients received 1-2 g/kg intravenous immunoglobulin every 4 weeks for 6 months. The concentration of total Aβ decreased in CSF and increased in blood compared with baseline. The patients had no cognitive deterioration {Dodel R, 2004} {12}. These results were independently reproduced in an uncontrolled trial {Relkin NR, 2009}{13} with eight patients (given 0.4–2. 0 g/kg per month for 6 months). Finally, a placebo-controlled (saline) multiple dose study {Weksler M, 2010}{14} of 24 patients (given 0.2 g/kg or 0.4 g/kg once every 2 weeks or 0.4 g/kg or 0.8 g/kg per month for 6 months) has been done. Patients who were treated with intravenous immunoglobulin 0.4 g/kg every 2 weeks had the best outcome, with no decline in cognitive and functional measures. The results of these studies were encouraging leading to phase II AD trials with these products {Dodel R, 2013}{15}. Additional phase III AD trial with another IVIG product is in progress. Now it is unclear whether any IVIG products will offer a breakthrough for treatment of AD. Differences have been reported between IVIG products for the concentrations of some of their antibodies and their biological activities. These may be due to differences in manufacturing practices and/or the antigenic exposure of the plasma donors. With regard to AD, differences between IVIG preparations have been found for anti-Aβ and anti-tau antibodies. Determination of whether IVIG products differ in their ability to slow AD's progression will require comparative studies, as have been done for other diseases (Kawasaki disease and primary immune deficiency){Loeffler DA, 2013}{7}.

Importance: Important

Transferability: Completely

TEC1b: What are the potential comparators for IVIG use in Alzheimer's disease and Mild Cognitive Impairment?

Method

Refer to domain search and domain methodology section.

Result

1. The Interventions on Alzheimer´s Disease

At present there is no cure for AD. The current mainstays of drug treatment are pharmaceuticals intended to address the cognitive symptoms of AD, in combination with supportive medical and behavioral intervention {Upadhyaya P, 2010} {16}.

HTA and coverage bodies value trials of a new therapy given in combination with already-employed therapies that target different physiological processes than the new drug. Disease-modifying therapies should be assessed in combination with symptomatic therapies such as cholinesterase inhibitors or NMDA receptor antagonists. Add-on studies are one strategy to accomplish this assessment. Other strategies include limited placebo period studies, randomized withdrawal, factorial designs, and three-arm trials. The specific goals of the trial should determine the relative timing of the combination of drugs, but will typically involve adding the investigational drug to a stable dose of a commonly prescribed drug with regulatory approval {Green Park Collaborative (GPC), 2013}{17}.

Symptomatic treatment of dementia with cholinesterase-inhibitors is considered as standard of care, particularly in mild to moderate Alzheimer's disease. Therefore in the future new treatments for dementia may be evaluated more and more by using add-on-designs, particularly in long term studies the "pure" use of placebo control for demonstration of efficacy may be difficult to justify.

Two major classes of drugs are currently available to treat the symptoms of AD:

Marketed Drugs

Acetylcholinesterase inhibitors (AChEIs): These include donepezil, rivastigmine, and galantamine. An older AChEI, tacrine, is rarely used due to concerns about liver toxicity. AChEIs boost the amount of acetylcholine, an important neurotransmitter in the areas of the brain that control learning and memory. These drugs have been approved for use in patients with mild-to-moderate AD on the basis of short-term (i.e., 6 months or less) improvements in memory and cognition in clinical trials. There are no data suggesting that use of AChEIs modifies or delays disease progression.

N-methyl-D-aspartate (NMDA) receptor antagonists: A single NMDA receptor antagonist, memantine, is currently approved for the treatment of symptoms of moderate-to-severe AD. Memantine binds to NMDA receptors that are associated with excessive stimulation and eventual death of neurons. Findings from clinical trials suggest small positive effects of memantine on cognition, activities of daily living, and behavior. Memantine is not thought to affect disease trajectory or progression.

Disease-Modifying Therapy

In addition to the symptomatic treatments currently marketed, a host of potentially disease-modifying therapies have been studied, and numerous others are in development. These include treatments that modulate inflammation and oxidative damage, as well as treatments that interfere with Aβ deposition such as anti-amyloid aggregation agents, drugs to reduce Aβ production, drugs to promote Aβ clearance as active vaccination or passive immunization with monoclonal anti-amyloid antibodies, and other potential therapeutic approaches { Moreth J, 2013; Salomone S, 2011; Nygaard HB, 2013} {10,18,19}.

Non drugs interventions

There is much interest in the use of cognitive therapies in AD. Preliminary studies seem to suggest a beneficial effect of cognitive stimulation, also known as Reality Orientation. Although promising, cognitive stimulation and exercise have limited evidence to support their use in persons with mild to moderate dementia or mild cognitive impairment.

Treatment of behavioural and psychological symptoms.

Management of BPSD begins with careful search for trigger and/or exacerbating factors including environmental cues, physical problems (infections, constipation), medication and depression or psychosis. As studies of BPSD indicate a high placebo response, safe non-pharmacological management (education, exercise, aromatherapy, sensory stimulation, personalized music) should be tried wherever possible in the first instance as symptoms may naturally resolve within a short time {Hort J, 2010; NICE, 2014; Lin JS, 2013}{20,21,22}.

2. The Interventions on Mild Cognitive Impairment

At present time there is no effective drug to treat or delay the progression from mild cognitive impairment (MCI) to dementia. There are no evidence-based interventions for MCI. Cognitive enhancers are agents that are often used to treat dementia, but did not improve cognition or function among patients with mild cognitive impairment and were associated with a greater risk of gastrointestinal harms. {Tricco AC, 2013; Russ TC, 2012; Birks J, 2006; Cooper C 2013 }{23,24,25,26}.

Importance: Important

Transferability: Partially

Result card for TEC2: "What is the approved indication and claimed benefit of IVIG?"

View full card

TEC2: What is the approved indication and claimed benefit of IVIG?

Method

Refer to domain search and domain methodology section.

Result

There has been a rapid expansion in the use of intravenous immunoglobulin (IVIG) for an ever growing number of conditions. IVIG has had a major impact in neurology, haematology, immunology, rheumatology and dermatology.

In the last ten years many reviews and evidence based clinical guidelines on the use and indications of IVIG have been published {Micromedex Drugdex Database, 2014; Patwa HS, 2012; Anderson D, 2007}{6,27,28}. In the European context some guidelines have been produced by medical societies {EFNS 2008}{8} or they have been supported and adopted as a reference for best practice guideline to be implemented. The UK Clinical Guidelines for Immunoglobulin Use were first implemented in 2008. The Guidelines were developed utilising an evidence review and extensive consultations with clinicians and other stakeholders. This update fulfils the commitment made in the Second Edition to undertake a biennial review from 2009. The 2011 update limited its focus on defining selection criteria for appropriate use; efficacy outcomes to assess treatment success; and reassignment of existing indications /inclusion of new indications. We show her as a reference the summary of conditions for which IVIG use is considered appropriate {Department of Health, 2011}{5}.(See TEC-2 Figure 1)

TEC-2 Figure 1">

SUMMARY OF GREY INDICATIONS

Grey indications are those diseases for which the evidence is weak, in many cases because the disease is rare. Approval from both the local Immunoglobulin Assessment Panels and the Primary Care Trust is required for immunoglobulin treatment. In cases of 'unlisted' diseases, those not listed in the guidelines are to be considered as Grey. {5}. (See TEC-2 Figure 2)

TEC-2 Figure 2">

Importance: Important

Transferability: Partially

Result card for CUR17 / TEC3: "What is the phase of development and implementation of intravenous immunoglobulins (IVIG)?"

View full card

CUR17 / TEC3: What is the phase of development and implementation of intravenous immunoglobulins (IVIG)?

Result

Individual manufacturers are exploring the feasibility of developing IVIG therapy for Alzheimer's disease including Mild Cognitive Impairment but, at time of writing, no manufacturers applied for market authorisation to EMA {Appendix CUR-3}. No data are available regarding the monitoring of off-label or compassionate use of IVIG for Alzheimer's disease including Mild Cognitive Impairment {Appendix CUR-3}.

IVIG is presently very widely used for the treatment of a variety of immunologic disorders. IVIG is being used as a treatment in many different conditions, including mainly primary and secondary antibody deficiency states, haematology (acquired red cell aplasia, alloimmune thrombocytopenia, autoimmune haemolytic anaemia, haemolytic disease of the newborn, immune thrombocytopenic purpura), neurology (Guillain-Barré syndrome, chronic inflammatory demyelinating polyradiculneuropathy, inflammatory myopathy, Myastenia gravis, multifocal motor neuropaty) and other conditions (Kawasaki disease, transplantation, toxic epidermal necrolysis, staphylococcal or streptococcal toxic shock syndrome, autoimmune congenital heart block, autoimmune uveitis). See {TEC2}.

For more than thirty years, IVIG has been used for the treatment of post-exposure to infectious diseases, immune disorders and the management of patients with neurological conditions. IVIG treatment is used routinely for some immune-mediated neurological disorders such as Guillain-Barre syndrome, and recently IVIG has been investigated for the treatment of neurodegenerative disorders.

IVIG has not been approved for prevention or treatment of AD and mild cognitive impairment.

IVIG treatment of AD patients was first reported in a pilot study in 2004 {20}. Five patients with mild to moderate AD – Mini Mental State Examination (MMSE) mean score 19.4 – received Octagam (Octapharma; dose = 0.4 g/kg) on 3 successive days, every 4 weeks for 6 months. MMSE scores improved slightly in four of the AD patients and were unchanged in the fifth one, while their Alzheimer's Disease Assessment Scale-Cognitive sub-scale (ADAS-cog) scores decreased, suggesting increased cognitive functioning, in four patients and did not change in the fifth one. In 2009 results were published from a pilot study in which eight AD patients (mean MMSE score 23.5) were administered Gammagard S/D (Baxter Healthcare). After 6 months of treatment the mean MMSE score increased to 26.0, reflecting increased scores for six patients and no change in scores for two patients. After a 3-month washout period, the mean MMSE score returned to baseline (23.9). Following an additional 9 months of treatment, MMSE scores were essentially unchanged (mean 24.0).

Before publishing these results, in 2006 Baxter began a double-blind Phase II AD trial with Gammagard. Improved outcomes were noted in the Gammagard-treated subjects compared to those initially treated with placebo at 3, 6, and 9 months.

The results of a double-blind, placebo-controlled, 24- week phase II AD trial with Octagam were published in January 2013 {20}. Octagam had no apparent effects on cognitive or functional scores in the AD patients. No increase was found for plasma Aβ1-40; this had been reported in the pilot studies and suggested that IVIG products might increase efflux of Aβ from the brain. The only positive finding reported in this study, less reduction in glucose metabolism in some brain regions in the Octagam-treated individuals, was of uncertain significance. In conclusion, this trial showed favourable safety and tolerability of intravenous immunoglobulin and the absence of severe autoimmune reactions. Longer studies of larger populations are needed to assess effects on cognition and function in patients with Alzheimer's disease.

In May 2013, the results of a placebo-controlled phase III AD trial with Gammagard were announced. Three hundred ninety patients had been treated every 2 weeks for 18 months with 200 mg/kg Gammagard, 400 mg/kg Gammagard, or placebo. No significant differences were found for the rate of cognitive decline between the Gammagard-treated group and placebo group.

Two AD-related IVIG trials are still in progress. Flebogamma (Grifols Biologicals) is being evaluated, together with albumin, in an AD phase III trial, and NewGam (Octapharma) is being investigated by Sutter Health in a phase II trial to determine its effects in patients with amnestic mild cognitive impairment (MCI) and its influence on the risk for these patients to develop AD. A possible reason for the failures in the most recent IVIG trials is that by the time AD's clinical features become evident, its pathology, including extensive neuronal loss, is already well established. The trial with MCI patients should provide an indication of whether earlier IVIG treatment may be beneficial.

Newer research and developing human trials are becoming established for the use of intravenous immunoglobulins (IVIG) for the treatment and prevention of Alzheimer's disease.

The IVIG trials reported to date in AD patients have produced conflicting findings. Because the most recent trials produced negative results, enthusiasm for IVIG as a treatment for AD has been reduced. Polyvalent antibody therapy for AD, as typified by IVIG, should have advantages over administration of individual monoclonal antibodies. To identify which antibodies should be included in an AD-specific IVIG preparation, more must be known about the range of anti-AD antibodies in IVIG and their effects on AD pathology in animal models.

Importance: Critical

Transferability: Completely

Result card for TEC4: "Who performs or administers IVIG?"

View full card

TEC4: Who performs or administers IVIG?

Method

Refer to domain search and domain methodology section.

Result

IVIG is usually administered in an infusion center or health care facility, indicated by specialized medical staff and supervised by health professionals. IVIG can be given in the hospital, doctor's office, or patients' home. In any setting, nurses administer 90% of the transfusions {White-Reid K, 2008} {29}. They should complete an accredited blood transfusion education program and be assessed upon their competency. Accredited nurses are responsible for checking blood and blood products, administering IVIG, monitoring patients during transfusion, and carrying out the appropriate actions should an adverse effect occur, ensuring adequate documentation in the medical notes, and reporting of transfusion reactions or other incidences related to the transfusion. (See TEC13. B0013). IVIG may be infused in the home setting, usually by an experienced infusion nurse. In some situations, this practice has been found to be more cost effective and result in improved quality of life measures. The first few infusions should be administered with medical supervision, regardless of the longer-term plan.

Many institutions require signed consent before any blood product is administered, and they document in the records of all of the patients that potential risks have been explained and that the patient/parent has received this information, has been given the opportunity to ask questions, and has given consent to receiving IGIV before initiating therapy.

The risk of transmission of viruses and prions from IVIG treatment is felt to be extremely low. Nevertheless, patients should be tested for exposure to known blood borne pathogens before starting IVIG therapy. Serologic tests for exposure to or infection with common pathogens such as Epstein-Barr virus, CMV and Hepatitis B will become positive in recipients of immune globulin therapy because of the passively transferred antibody. Therefore, if it is important to know if a patient has been infected with one of these organisms, antigen tests, such as PCR, should be done before IgG is administered.

It is recommended to perform testing for HIV and hepatitis A, B, and C, and measure complete blood count, hepatic transaminases and renal function before initiating immune globulin therapy by any route. In hematologic disease, Coombs' testing should be done prior to IVIG therapy. This may identify preexisting infection or Coombs' positivity before the immune globulin was administered and not transmitted iatrogenically. (See TEC10, B0010).

Solution products and reconstituted solutions of lyophilized products that have been stored in refrigerators should be allowed to reach room temperature before administration, to minimize adverse events. However, immune globulin solutions should not be microwaved or otherwise heated because the immunoglobulin protein could become denatured. Reconstituted lyophilized products should be inspected before administration to assure that the product has been completely dissolved and that the solution is uniform, although vigorous mixing causing excessive foaming should be avoided. All products should be inspected for the presence of particulates and evidence of tampering before pooling or administration to the patient.

(See TEC13, B0013)

Importance: Important

Transferability: Partially

Result card for TEC5: "In what context and level of care are IVIG used?"

View full card

TEC5: In what context and level of care are IVIG used?

Method

Refer to domain search and domain methodology section.

Result

IVIG is usually administered in hospitals, in an infusion center or health care facility, including hospital–based outpatient clinics (immunology, hematology, oncology) and ambulatory infusion centers {Duff 2006}{1}. Patients may benefit from receiving infusion treatment in outpatient settings if these settings maintain a consisting nursing staff and a physician is available during the infusion to monitor patient vital signs, in case of emergencies. For some patients, IVIG may be also infused in the home setting, usually by an experienced infusion nurse. In some situations, this practice has been found to be more cost effective and could result in improved quality of life measures. To determine whether the patient is a homecare candidate, the physician must be comfortable with the patient´s reaction to the IVIG infusion. The first few infusions should be administered with medical supervision, in a controlled setting, regardless of the longer-term plan, after which the physician assesses the overall risk. Patients also need to feel confident about starting their treatment options and should be educated about which location, if alternatives are available, would best serve to their interests (See also TEC7, B007- TEC14, B014).

In the European context this products are usually administered in public or private hospitals or hospital-based outpatient clinics, for a limited number of approved indications, under clinical protocols to ensure the appropriate management and use of IVIG.

Importance: Optional

Transferability: Partially

Other

Result card for TEC6: "Who manufactures IVIG?"

View full card

TEC6: Who manufactures IVIG?

Method

Refer to domain search and domain methodology section.

Result

IVIG products authorized by EMEA

{ European Medicines Agency} {30}

TEC-6 Figure 1">

Flebogamma DIF presentations:

Flebogamma DIF*: 50 mg/ml; solution for infusion; intravenous use; vial (glass); content: 10, 50, 100, 200, 400 ml

Flebogamma DIF*: 100 mg/ml; solution for infusion; intravenous use; vial (glass); content: 50, 100, 200 ml

Privigen presentations:

Privigen*: 100mg/ml; solution for infusion; intravenous use; vial (glass); content: 25, 50, 100, 200 ml

Kiovig presentations:

Kioviog*: 100mg/ml; solution for infusion; intravenous use; vial (glass); content: 10, 25, 50, 100, 200, 300 ml

Other IVIG products authorized by national regulatory agencies in the European Union

BAXTER:

-Gammagard* S/D: 2,5g/50ml; 5g/96ml; 10g/192ml;

-Gammagard liquid*: 10 gr/100ml

BIOTEST PHARMA:

-Intratect*: 1g/20ml; 2,5g/50ml; 5g/100ml; 10g/200ml

-Intratect* 100gr/l solution for infusion

-Pentaglobin* 50mg/ml (10, 50, 100 ml)

BIO PRODUCTS LABORATORY:

-Gammaplex*: 5gr/100ml

-Vigam*: 5gr/100ml solution for infusion

CSL BEHRING:

-Sandoglobulin* 1 g/33ml; 3g/100ml; 6g/200ml;12g/200ml

GRIFOLS:

-Flebogamma IV 5%* (10, 50, 100, 200 ml)

-Gamunex*: 100 mg/ml (10, 50, 100, 200 ml)

KEDRION:

-Igvena*: 50gr/l (20, 50, 100,200 ml)

-Keiven*: 50 g/l (20, 50, 100,200 ml)

-Venita*l: 50gr/l (20, 50, 100,200 ml)

OCTAPHARMA:

-Octagam*: 50mg/ml (50, 100 y 200ml); 100mg/ml (20, 50, 100 y 200ml)

-Gamten*: 100mg/ml (20, 50, 100, 200 ml)

IVIG products authorized by FDA

{ Micromedex Drugdex Database, 2014; FDA, 2014}{6, 31}

Baxter Healthcare Corporation:

Gammagard Liquid*

Gammagard S/D*

Bio Products Laboratory:

Gammaplex*

Biotest Pharmaceuticals Corporation:

BIVIGam*

CSL Behring AG:

Carimune NF*

PrIVIGen*

Grifols Therapeutics, Inc:

Gamunex-C*

Gammaked*. (Distributed by Kedrion Biopharma)

Flebogamma DIF* 5% & 10%

Octapharma Pharmazeutika Produktionsges.m.b.H:

Octagam*

Importance: Important

Transferability: Partially

Investments and tools required to use the technology

Result card for TEC7: "What material investments are needed to use IVIG?"

View full card

TEC7: What material investments are needed to use IVIG?

Method

Refer to domain search and domain methodology section.

Result

The material investment needed for the use of IVIG is mainly {NZ Clinical Immunology Group, 2013; ACT Health, 2013; Octapharma 2007; Octapharma 2014; Baxter 2011}{ 32,33,34,35,36}:

- For the proper storage of IVIG products according to the product SPC (storage and handling part) which may require for some - including all IVIG supplied as liquids, refrigerated storage between 2°C and 8°C, whereas others, could be stored at room temperature. In some instance, when refrigeration is required, eg. in the case of the product is diluted, the preparation should be used as soon as practicable, in order to reduce microbiological hazard,but if storage is necessary, it should be stored at 2°C to 8°C for not more than eg. 24 hours(depends on stability studies). Accredited blood refrigerators are needed and a close temperature monitoring shall be performed in order to guarantee a correct temperature range for this storage. IVIG that requires refrigeration and that are stored at a temperature below 2°C should not be used because of the likelihood of the product damage. Solutions must be kept away from freezing.

- For the use of IVIG, an infusion pump (see TEC9) may be needed and standardized emergency equipment should be readily available during the infusion.

- For traceability of IVIG use: establishment and maintenance by the hospital or the institution of a system, ideally a computer program in order to ensure both patient and product traceability. The system shall allow linking each patient to the product received and vice versa.

- For potential (recurrence of) shortage of IVIG: discussion of a risk management plan to identify, characterize, prevent and minimize the risks of shortage. This plan may include, in some premises / hospitals back-up investments.

(Please also refer to TEC12, B0012).

Importance: Important

Transferability: Partially

Result card for TEC8: "What kind of special premises are needed to use IVIG?"

View full card

TEC8: What kind of special premises are needed to use IVIG?

Method

Refer to domain search and domain methodology section.

Result

IVIG infusions are usually given every 3 to 4 weeks and usually require three to four hours for infusion to the patient. Therefore, comfort measures during the infusion are needed, especially if side effects occur (medical bed or chair, blankets or pillows).

The infusion of IVIG are usually administered at hospital or in a health care facility at least during the first infusions with one brand, when it should be performed under strict medical supervision, with a medical doctor accessible at all times during IVIG transfusion and with resuscitation equipment available, in an area where the patient can be easily observed and monitored {ACT Health, 201; Younger MEM, 2012}{33,37}.

Under some specific conditions and in case of no occurrence of adverse reaction, subsequent IVIG infusion could be performed in the “home setting” if supervised by an experienced nurse.

Importance: Important

Transferability: Partially

Result card for TEC9: "What equipment and supplies are needed to use IVIG?"

View full card

TEC9: What equipment and supplies are needed to use IVIG?

Method

Refer to domain search and domain methodology section.

Result

The equipment and supplies needed for the intravenous use of immunoglobulins are {NZ Clinical Immunology Group, 2013; ACT Health, 2013; Younger MEM, 2012}{32,33,37}:

-Needles, bandages, peripheral sterile Intravenous (IV) infusion set and intravenous infusion pump as the use of permanent indwelling ports or central venous lines are usually discouraged due to the risk of infection (especially in antibody deficient patients) and thrombotic events . A specific intravenous line for the only use of IVIG is required and administration of concomitant medications through the same IV line should be avoided.

- Intravenous saline fluids for hydration.

- Appropriate waste disposal.

- Premedication as deemed necessary by the physician and/or IVIG specific products.

- Prescription of symptomatic treatment for headache, fever, flu-like symptoms should be done and drugs available for use if needed.

- Emergency equipment and drugs for treatment of a potential anaphylaxis should be readily available for use during the infusion.

(Please also refer to TEC12, B0012).

Importance: Important

Transferability: Partially

Result card for TEC10: "What kind of data and records are needed to monitor the use of IVIG ?"

View full card

TEC10: What kind of data and records are needed to monitor the use of IVIG ?

Method

Refer to domain search and domain methodology section.

Result

Detailed documentation of IVIG infusions should include the patient’s current health status and any changes in this status in the period between IVIG infusions; the name, dose and the lot numbers of the product; any pre-medications which were given; time duration of the infusion and specific rate titrations which were made; and any problems or adverse reactions the patient experienced during the infusion and how they were managed.

Prior to the first administration { NZ Clinical Immunology Group, 2013; ACT Health, 2013; Octapharma 2014; Baxter 2011;Younger, 2012 } {32,33,36,37}:

- Serological testing for prior exposure to or infection with known blood pathogens (such as EBV, CMV, HBV, HCV, HIV) and appropriate vaccinations should be considered

Prior to each administration:

- A signed informed and written consent should be obtained from the patient, who should have received full information on the description of IVIG, their nature of blood product, the associated risks and benefits as well as alternatives to this treatment.

- The prescription from the physician for

• the IVIG with the date, the identification of the patient, the particular IVIG product, the dose based on the patient weight, rate and duration of infusion

• a premedication if needed.

• specific instructions must be in place in case adverse events occur (headache, flu-like symptom, allergic reaction, malaise, nausea).

- Record of brand and assessment that it matches the physician prescription, the manufacturer, lot number, expiry date, dose of the product and identification of the patient.

For each administration:

- The integrity and quality of the IVIG should be assessed prior to the use, all refrigerated products should be at room temperature, the reconstitution of the product should be done per manufacturer’s guidelines, prescriber’s orders and following aseptic technique.

- The health status and the body weight of the patient prior to the infusion should be assessed and recorded. The dosage of the product should be adapted in case of any significant change of the body weight.

- The administration of the product should be carefully monitored and observed for any symptoms or alteration of vital signs throughout the infusion period and for at least 20 minutes after administration. In addition, a monitoring of the renal function and of the diuresis is required as well as a good hydration of the patient. As certain adverse reactions are more frequent in case of a high rate of infusion, during the first administration of IVIG, in case of switch between specific products and /or re-challenge infusion, or depending on patient medical condition and pre-existing risk factors, a low initial rate of infusion - which depends of each product - should be respected and may be gradually increased if the infusion is well tolerated by the patient. Should an adverse reaction happening (e.g. hypersensitivity with anaphylactic reaction, hyperviscosity complications such as thromboembolic events, acute renal failure, aseptic meningitis syndrome, haemolysis), then the vital signs should be checked and documented, the rate of infusion should be decreased or stopped and standard medical treatment should be implemented.

After the administration:

- Records of the infusion and declaration of any adverse reaction.

- Assess and record the need for a premedication for future infusions and ensure its prescription and availability for the next infusion.

- Records of the discard of any remaining product.

- Every 6 to 12 months:

- Long term complications of IVIG such as renal impairment, hemolytic anemia.

- Blood-borne infections.

Importance: Important

Transferability: Partially

Result card for TEC11: "What kind of registers are needed to monitor the use IVIG?"

View full card

TEC11: What kind of registers are needed to monitor the use IVIG?

Method

Refer to domain search and domain methodology section.

Result

Please refer to TEC10 (B0010).

Importance: Unspecified

Transferability: Unspecified

Training and information needed to use the technology

Result card for TEC12: "What kind of qualification and quality assurance processes are needed for the use or maintenance of IVIG?"

View full card

TEC12: What kind of qualification and quality assurance processes are needed for the use or maintenance of IVIG?

Method

Refer to domain search and domain methodology section.

Result

Manufacturing and Preparation

Quality controls are required to guarantee the consistency of IVIG batches and to limit the risks of adverse reactions that have shown to be linked to the presence of certain proteins (e.g. IgA) or to biological/ microbial (e.g. endotoxins) or chemical (e.g. residues of viral inactivation treatments) impurities. A set of quality control assays are needed to guide manufacturers in the development of IVIG preparations, to control the conditions of production and to guarantee the quality, safety and consistency of the products. In fact, international and national Pharmacopoeias define quality assays that must be performed by manufacturers, and all assay methods should be validated {WHO, 2013} {38}. Reference preparations and WHO standards, based on plasma preparations or purified fractions, are available from the National Institute for Biological Standards and Control (NIBSC, UK), the Center for Biologics Evaluation and Research, Food and Drug Administration (CBER/FDA, US), or from the European Directorate for the Quality of Medicines and HealthCare (EDQM, France). Batches should comply with the quality specifications defined and approved from regulators in the marketing authorization file of each product. Since IVIG products are manufactured using components of human blood, they may potentially contain the causative agents of hepatitis and other viral diseases, potentially even Creutzfeldt-Jacob Disease (CJD). For that reason prescribed manufacturing procedures at the plasma collection centers and plasma-testing laboratories need to be designed in that way that they reduce the risk of transmitting viral infection. Risk reducing measures include careful selection of donors for plasma pools, testing for viral markers at multiple stages which allow for the detection of plasma viruses {Baxter, 2011}{36}, and the application of rigorously validated methods of testing. Quality controls for plasma derivatives include determination of chemical parameters (like pH), protein content, content of stabilizers and residues of chemicals used for the production or viral inactivation and various safety parameters (e.g. protein identity, visual appearance) {Radosevich M, 2010}{39}.

Maintenance, storage and transport

Immunoglobulin products are supplied as solutions or as lyophilized products that need to be stored appropriately. Some IGs products require refrigeration whereas others can be stored at room temperature. As such, lyophilized products are generally stored at room temperature before reconstitution. However, all liquid IVIG products optimally require refrigerated transport and storage between 2°C and 8°C. Lower temperatures are likely to damage the product, and any IVIG liquid which has been frozen should be discarded {NZ Clinical Immunology Group, 2013}{32}. IVIG products should ideally be stored in accredited blood fridges that meet required standards. Domestic fridges and ward fridges should not be used for storage since these refrigerators are not closely monitored and accepted temperature range cannot be guaranteed. Blood products should be transported in dedicated and validated containers and be stored within glass containers, which are closed with rubber stoppers {ACT Health, 2013}{33}. It is important to follow the manufacturer's specifications regarding storage of each product, since the recommendations may vary per IG product {NZ Clinical Immunology Group, 2013}{32}. While being stored and transported, the IVIGs should be protected from light {ACT Health, 2013}{33}.

Examples for Storage:

Kiovig (Baxter)

- Store in a refrigerator for the duration of the shelf life (36 months) (2°C – 8°C). Do not freeze.

- At room temperature: Kiovig may be stored at room temperature (below 25°C) for up to 12 months within the first 24 months. However, once stored at room temperature, the product must remain stored at room temperature and must be used within the first 24 months from the date of manufacture. The total storage time of Kiovig depends on the point of time the vial is transferred to room temperature. The new expiration date must be recorded on the package when the product is transferred to room temperature. Product cannot be stored at room temperature after 24 months from date of manufacture. Once the product has been stored at room temperature, the product should not be re-refrigerated {Baxter, 2011} {36}.

Octagam (Octapharma)

- Store in a refrigerator for the duration of the shelf life (48 months) (2°C – 8°C). Do not freeze.

- At room temperature: Octagam may be removed from the refrigerator for a single period of up to 3 months (without exceeding the expiry date) and stored at a temperature below 25°C. At the end of this period, the product should not be refrigerated again and should be disposed of {Octapharma, 2014} {35}. In certain cases, Octagam may be stored for 24 months at +2°C to +25°C from the date of manufacture {Octapharma, 2007} {34}. The date at which the product was taken out of the refrigerator should be recorded {Octapharma, 2014} {35}.

Use and documentation

Before administering IVIGs, it needs to be sure that the patient is not allergic to IGs, and not to the any of the ingredients in the product. Appropriate vaccinations should be considered for immune competent patients who receive regular/repeated treatment with IVIGs {Octapharma, 2014}{35}. It is strongly recommended that every time the patient receives a dose of IVIG the name, dose and batch number of the product are recorded in order to maintain a record of the batches used. The integrity (protective seals) and the quality of the product should always be assessed. IVIG products should not be used if the solution is cloudy, has deposits or is colored intensively. If the protective seals are not intact, the dispensing pharmacy should be notified and the product should not be given. The products should neither be used after the expiry date stated on the label {Octapharma, 2014; Baxter, 2011} {35,36}. All (refrigerated) products should be at room temperature before infusion, as adverse effects can be associated with the administration of products that are too cold. The products should be allowed to brought to room temperature by themselves and not by heating (e.g. in microwave) since this may degrade the product. However, once a product has been brought to room temperature it may not be returned to the fridge. The date the product is removed from refrigeration should be noted on the packet. It is important to note that each product should be administered once removed from refrigeration and it is for a single use in one patient only, and therefore any remaining product should be discarded and recorded as such {Baxter, 2011} {36}.

IVIG products are not generic and there are notable differences among them. They must be considered as individual therapies and choice of or decision to change a particular IVIG product needs to be done with caution {Gelfand EW, 2005; 2006}{40,41}. In the case of the product is diluted, the preparation should be used as soon as practicable, in order to reduce microbiological hazard, as the product does not contain antimicrobial preservative. If storage is necessary, the diluted preparation should be stored at 2°C to 8°C for not more than 24 hours. It is possible for lyophilized products to be prepared at more than one concentration depending on the amount of diluent added. Possibilities for different concentrations should however be specified in the manufacturer's prescribing information. Lyophilized products should ideally be reconstituted in the infusion clinic. It is critically important to be aware of and to follow manufacturer's guidelines, prescriber's orders and aseptic technique when reconstituting these products {Younger MEM, 2012} {37}. IVIGs should be administered through a designated intravenous infusion, and should not be mixed with other medications or piggybacked into other infusions {Baxter, 2011}{36}. Since sterility of the IVIG is a concern, the solution should not be reconstituted until IV access has been established and it is ready to be administered. After adding the appropriate diluent to the powder by gently rotations, the vials should not be shaken to mix the solution, since this may damage the immunoglobulin proteins. Instead, the diluent should be able to dissolve the powder. It may take 5 up to 20 minutes

for the powder to completely be absorbed into solution. Depending on the manufacturer, IVIG may only be stable in solution for a few hours {Rosenthal K, 2007}{42}

Another quality assurance process includes detailed documentation of IVIG infusions. This should include the patient's current health status and any changes in this status in the period between IVIG infusions; the name, dose and the lot numbers of the product; any pre-medications which were given; time duration of infusion and specific rate titrations which were made; and any problems or adverse reactions the patient experienced during the infusion and how they were managed {Younger MEM, 2012}{37}.

Importance: Important

Transferability: Partially

Result card for TEC13: "What kind of training and information is needed for the personnel/carer using IVIG?"

View full card

TEC13: What kind of training and information is needed for the personnel/carer using IVIG?

Method

Refer to domain search and domain methodology section.

Result

The health professional using IVIG requires specific knowledge and skills in order to be competent to treat patients with IVIGs. A hospital based IVIG program should provide education, training and protocols for staff to ensure the appropriate management and use of IVIGs, including for transport, storage, use of equipment and infusion techniques. The number of training sessions may vary between personnel depending upon their experience. Usually two up to eight sessions, individualized or in groups, are required. The training should include education related to documentation, patient consent, difference among IVIG brands, selection of a brand on the basis of patients' risk factors, contraindications, needs, action plans for adverse events, rapid infusion protocols, and setup of infusion pumps, tubing and filter equipment {Reid B, 2006}{43}. IVIG can be given in the hospital, doctor's office, or patient's home. In any setting, nurses administer 90% of the transfusions {White-Reid K, 2008}{29}. They should complete an accredited blood transfusion education program and be assessed upon their competency {ACT Health, 2013}{33}. Accredited nurses are responsible for checking blood and blood products, administering IVIG, monitoring patients during transfusion, and carrying out the appropriate actions should an adverse effect occur, ensuring adequate documentation in the medical notes, and reporting of transfusion reactions or other incidences related to the transfusion {ACT Health, 2013}{33}. Protocols including a list of recommendations for the administration of IVIGS to help nurses and institutions are valuable. These protocols should list the importance of providing information to patients and their families and obtaining patient consent for IVIG use after outlining its risks and benefits. Other key features should be the verification of the prescription and indications for IVIGs, a list of contraindications to IVIG use, the assessment of the patients' medical history and health conditions before IVIG infusion, the identification of patients at risk for adverse reactions, the careful choice of IVIG brands and infusion protocols that are appropriate for the patients' conditions, the equipment needed to perform the infusion and control checks of the product, the necessary preparations before the infusion starts, how the infusion should be carried out, how to deal with adverse reactions and how to complete the infusion, and post-transfusion care, {Reid B, 2006; Malcolmson C, 2014} {43,44}.

Training for administering IVIG {National Blood Authority, 2014}{45}

After having obtained training for administering IVIGs, one should be able to:

- describe the transportation and storage requirements of the specific IVIG

- define IVIG administration and location of site of infusion

- list the appropriate infusion sites and understand the rotation of sites

- demonstrate care of the infusion site

- describe appropriate supplies necessary to complete the procedure

- use the pump and the alternative "push method"

- check the product, prepare the product, and to report wastage or nonuse

- prepare the infusion site and draw up the product from single or multiple vials and prime tubing

- demonstrate insertion of subcutaneous catheter and act appropriately if blood is present

- demonstrate appropriate aseptic techniques

- perform accurate administration the treatment, and remove and dispose the needle safely

- understand potential situations/reactions which could result from the infusion

- manage any reaction to the treatment correctly.

Whether the nurse is administering an intravenous infusion or teaching patients or caregivers to administer subcutaneous infusions, safety has to be the first priority. Guidelines prior to, during and after administration of IVIG should be carefully followed. In that sense, core pre-infusion assessments may include assessment of the appropriateness of the IVIG for the patient, product integrity and product temperature, and the patients' health status. An important intra-infusion assessment may include a continuous assessment of the patient for any symptoms to ensure that the infusion is being tolerated {Baxter, 2011; Younger MEM, 2012}{36,37}. Core post-infusion assessments may include an assessment for any irritation or adverse reaction to the infusion and an assessment for pre-medications for future assessments. These guidelines should be offered to help infusion nurses, but also patients and givers to minimize problems and adverse effects, and safely provide a successful infusion experience for the patient {Younger MEM, 2012}{37}.

One needs to be familiar with the complications of IVIG treatment, possible adverse effects and post-infusion reactions, and one needs to know which interventions are effective in case the patient experiences particular adverse effects {Younger MEM, 2012}{37}. IVIG is not a generic drug and IVIG products are not interchangeable, thus a specific IVIG product needs to be tailored to patient characteristics to insure safety {Gelfand EW, 2005; 2006}{40,41}. Communication of potential issues and problems so that they can be proactively addressed is critical {Younger MEM, 2012}{31}. Training and experience is crucial in order to decrease the risk of adverse events. When an IVIG infusion is given the first time, more attention is needed since adverse events may occur. However, if a patient has already received several infusions, it is known how the patient reacts and thus doses etc. are adjusted. Since the manufacture for the individual product is different, individual patients may experience different adverse events to different products and may experience adverse events in some, but not in other products {Gelfand EW, 2005; 2006}{40,41}. Premedication is usually only given if there has been a previous adverse reaction. In case of an adverse reaction, the rate of infusion must either be reduced or infusion stopped. Lower doses may be administered on a more frequent basis. Risk of adverse events can also be reduced by ensuring adequate hydration and by paying attention to particular requirements depending upon the health condition and its associated increased risks. The treatment required depends on the nature and severity of the (risk of the) adverse reaction {Baxter, 2011; NHS Health Scotland, 2012}{36,46}. Lastly, anyone involved with the administration of IVIG to patients must be well informed about the manufacturing and regulation, proper dose and administration, adverse events, appropriate assessments and related patient education {Chipps E, 1994}{47}.

Importance: Important

Transferability: Partially

Result card for TEC14: "What kind of training and information should be provided for the patients who uses IVIG o for their families?"

View full card

TEC14: What kind of training and information should be provided for the patients who uses IVIG o for their families?

Method

Refer to domain search and domain methodology section.

Result

Patients should be eligible for IVIGs only in case they give consent for transfusion of blood and/or blood products. One or several patient and/or family education sessions may be required to inform patients and/or his or her family about what IVIG are and what they are used for, the fact that IVIGs are not licensed for use in the treatment of Alzheimers' disease and mild-cognitive-impairment (off-label use), what one needs to know before using IVIGs, how and how often it is administered, the approximate duration of each infusion times depending on the patient's assigned dose and body mass, potential risks and benefits of its use, the potential of virus transmissions, contra-indications (e.g. deficiency of Immunoglobulin A with anti-IgA antibodies, anaphylactic reaction) and contra-indications with other medications, so that informed consent may be obtained {Relkin NR, 2009; Gysler M, 2012}{13,48}. Information about such things as new modalities of treatment, legislative initiatives and insurance issues may also be valuable. Patients and their families should equally be provided with written information brochures concerning the IVIGs. A risk assessment may be carried out to ensure the patient and/or his/her family understand the need for treatment and how it is administered.

In case patients (and their family) agree upon an IVIG treatment, they should be informed about the fact that just as each patient may require a different IVIG, each may also require an individualized infusion regimen in order to achieve the desired outcome. IVIG is given through an intravenous infusion at an individualized rate, dose and time. If the treatment is successful, it may be repeated. At present IVIG is usually only given in hospital, thus no training and training materials need to be provided to the patient for using IVIG. However, in case patients may be able to receive IVIG for treating Alzheimer's disease or mild-cognitive-impairment subcutaneously in the future, the patients (depending upon their cognitive functioning) or their caregivers might be able to administer the product outside the hospital setting. This will be especially the case for those patients who are receiving IVIG without adverse events or with mild adverse reactions that can easily be managed {American Academy of Allergy Asthma & Immunology, 2011}{49}. In that case special training should be provided to patients and their families about how subcutaneous IVIG should be given in a safe and aseptic manner, including associated risks and benefits. In any administration of IVIG, another important education topic is ensuring that the patient and his/her family understand adverse reactions and/or its signs and complications, as well as how to react to adverse reactions. The possibility of rare adverse events such as stroke, thrombotic events and acute renal failure, which have been reported with IVIG should be discussed {Dodel R, 2010, Patwa HS, 2012; ACT Health, 2013} {9,27,33}. Patients over 65 years of age with particular co-morbidities are mostly at risk for adverse events. In these patients, there should be special attention for the potential risks and benefits of IVIG weighed against those of alternative therapies {Baxter, 2011}{36}. In case of the existence of an augmented risk, patients should know that they will be administered with IVIG products at the minimum concentration available and the minimum rate of infusion practicable. Life attenuated vaccines should be deferred up to three months after the administration of IVIG. Patients receiving measles vaccine should have their antibody status checked. {ACT Health, 2013}{36}. The ability to drive and operate machines may be impaired by some adverse reactions associated with IVIGs. Patients who experience adverse reactions during treatment should wait for these to resolve before driving or operating machines. Last but not least, a consent form documenting agreement to undergo treatment with IVIG and discussion of potential adverse effects must be completed by the patient and the responsible physician. Patients should be informed that they have the right to stop the treatment any time they wish {Younger MEM, 2012}{37}.

Importance: Important

Transferability: Partially

References

1. Duff K. You can make a difference in the administration of intravenous immunoglobulin therapy. J Infus Nurs 2006; 29 (3S), S5-S14.

2. The Consensus Working Group. Present and future uses of IVIG: A Canadian multidisciplinary consensus-building initiative. Can J Allergy Clin Immunol 1997; 2: 176-207.

3. Laupland, KB. Polyclonal intravenous immunoglobulin for the prophylaxis and treatment of infection in critically ill adults. Can J Infect Dis 2002; 13 (2):100-106.

4. WHO. Requirements for the collection, processing, and quality control of blood, blood components, and plasma derivatives. WHO technical Report Series 1989, No. 786, Annex 4.

5. Department of Health. Clinical guidelines for immunoglobulin use: update to second edition. DH, 2011.

6. Micromedex Drugdex Database, Truven Health Analytics, 2014. (Last Modified: July 03, 2014). Accessed the 3th of July 2014.

7. Loeffler DA. Intravenous immunoglobulin and Alzheimer's disease: what now? J Neuroinflamm 2013, 10:70.

8. EFNS task force on the use of intravenous immunoglobulin in treatment of neurological diseases. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases. Eur J Neurol 2008, 15: 893–908

9. Dodel R, Neff F, Noelker C, Pul R, Du Y, Bacher M, Du Y. Intravenous Immunoglobulins as a Treatment for Alzheimer's Disease: Rationale and Current Evidence. Drugs 2010; 70(5), 513-528.

10. Moreth J, Mavoungou C, Schindowski K. Passive anti-amyloid immunotherapy in Alzheimer's disease: What are the most promising targets? Immun Ageing 2013, 10:18

11. Dodel R, Hampel H, Depboylu C, Lin S, Gao F, Schock S, Jäckel S, Wei X, Buerger K, Höft C, Hemmer B, Möller HJ, Farlow M, Oertel WH, Sommer N, Du Y. Human antibodies against amyloid beta peptide: a potential treatment for Alzheimer's disease. Ann Neurol 2002, 52:253–256.

12. Dodel R, Du Y, Depboylu C, Hampel H, Frölich L, Haag A, Hemmeter U, Paulsen S, Teipel SJ, Brettschneider S, Spottke A, Nölker C, Möller HJ, Wei X, Farlow M, Sommer N, Oertel WH. Intravenous immunoglobulins containing antibodies against beta-amyloid for the treatment of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004, 75:1472–1474.

13. Relkin NR, Szabo P, Adamiak B, Burgut T, Monthe C, Lent RW, Younkin S, Younkin L, Schiff R, Weksler ME. 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiol Aging 2009, 30:1728–1736.

14. Weksler M, Szabo P, Relkin N. IVIG therapy of mild to moderate Alzheimer's disease patients showed significant benefits as measured by neuroimaging and neuropsychological testing in a phase II, randomized, double blind placebo controlled clinical study. Gerontologist 2010; 50: 449–50.

15. Dodel R, Rominger A, Bartenstein P, Barkhof F, Blennow K, Förster S, Winter Y, Bach JP, Popp J, Alferink J, Wiltfang J, Buerger K, Otto M, Antuono P, Jacoby M, Richter R, Stevens J, Melamed I, Goldstein J, Haag S, Wietek S, Farlow M, Jessen F. Intravenous immunoglobulin for treatment of mild to- moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial. Lancet Neurol 2013, 12:233–243.

16. Upadhyaya P, Seth V, Ahmad M. Therapy of Alzheimer's disease: an update, African Journal of Pharmacy and Pharmacology 2010; 4(6), 408-421.

17. Green Park Collaborative (GPC). Evidence guide document. Design of Clinical Studies of Pharmacologic Therapies for Alzheimer's Disease. April 2013.

18. Salomone S, Caraci F, Leggio GM, Fedotova J, Drago F. New pharmacological strategies for treatment of Alzheimer´s disease: focus on disease modifying drugs. Br J Clin Pharmacol 2011; 73, 4: 504-517.

19. Nygaard HB. Current and Emerging Therapies for Alzheimer's Disease. Clin Ther 2013; 35(19), 1480-1489.

20. Hort J, O`Brien JT, Gainotti G, Pirttila T, Popescu BO, Rektorova I, Sorbi S and Scheltens P on behalf of the EFNS Scientist Panel on Dementia. EFNS guidelines for the diagnosis and management of Alzheimer`s disease. Eur J Neurol 2010, 17: 1236–1248 doi: 10.1111.

21. NICE technology appraisal guidance 217. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of NICE technology appraisal guidance 111). April 2014.

22. Lin JS, O'Connor E, Rossom RC, Perdue LA, Eckstrom E. Screening for Cognitive Impairment in Older Adults: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2013; 159: 601-612.

23. Tricco AC, Soobiah Ch, Berliner S, Ho JM, Carmen H, Ashoor HM, et al. Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. CMAJ 2013; DOI:10.1503

24. Russ TC, Morling JR. Cholinesterase inhibitors for mild cognitive impairment. Cochrane Database Syst Rev 2012; 9: Cd009132)

25. Birks J, Flicker L. Donepezil for mild cognitive impairment. Cochrane Database Syst Rev 2006; (3):Cd006104.

26. Cooper C, Li R, Lyketsos C and Gill Livingston Gill. Treatment for mild cognitive impairment: systematic review. BJP 2013; 203, 255–264. doi: 10.1192/bjp.bp.113.127811

27. Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: Intravenous immunoglobulin in the treatment of neuromuscular disorders Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2012; 78:1009-1015.

28. Anderson D, Ali K, Blanchette V, Brouwers M, Couban S, Radmoor P et al. Guidelines on the Use of Intravenous Immune Globulin for Hematologic Conditions. Transfus Med Rev 2007; 21, No 2, Suppl 1 (April): S9-S56

29. White-Reid K, Scherf R. Giving intravenous immunoglobulin. Modern Medicine, 2008. Accessed the 20th of June 2014 from http://www.modernmedicine.com/modern-medicine/news/giving-intravenous-immunoglobulin

30. European Medicines Agency. Accessed the 4th of June 2014 from http://www.ema.europa.eu/

31. Food and Drug Administration. Accessed the 5th of June 2014 from www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm133691.htm

32. New Zealand Clinical Immunology Group. Nursing guidelines for administration of subcutaneous immunoglobulin (SCIg). 3rd Version. New Zealand: NZCIG. 2013. Accessed the 20th of June 2014 at: http://www.healthpoint.co.nz/

33. ACT Health. Standard Operating Procedure: Intravenous Immunoglobulin (IVIg) Administration: Canberra, Australia: ACT Health. 2013. Accessed the 20th of June 2014 from http://www.act.gov.au/

34. Octapharma. Immune Globulin Intravenous (Human) 5% Solvent/Detergent Treated. 2007. Accessed the 25th of June 2014 at: http://www.abopharmaceuticals.com/ProductSheets/Octagam_PI.pdf

35. Octapharma. Package leaflet: information for the user - Octagam 10% solution for infusion. 2014. Accessed the 18th of June 2014 at: http://www.medicines.org.uk

36. Baxter Healthcare Corporation. Kiovig (Normal Immunoglobulin): Product Information. 2011. Accessed the 18th of June 2014 at: http://www.baxterhealthcare.com.au/downloads/healthcare_professionals/cmi_pi/kiovig_pi.pdf

37. Younger MEM, Buckley RH, Belser CM, Moran K, Duff C, Epland KB, et al. IDF guide for nurses: immunoglobulin therapy for primary immunodeficiency diseases. 3rd edition. Towson, MD: Immune Deficiency Foundation. 2012.

38. World Health Organization. The International Pharmacopoeia (4th Edition). WHO Department of Essential Medicines and Pharmaceutical Policies (EMP), NGO/WIT and its logistic partner HumanityCD Ltd, and the University of Waikato, New Zealand. 2013. Accessed the 25th of June 2014 from http://apps.who.int/phint/en/p/about/

39. Radosevich M, Burnouf T. Intravenous immunoglobulin G: trends in production methods, quality control and quality assurance. Vox Sang 2010; 98, 12-28.

40. Gelfand EW. Critical decisions in selecting an intravenous immunoglobulin product. J Infus Nurs 2005; 28(6), 366-374.

41. Gelfand EW. Differences between IGIV products: impact on clinical outcome. Int Immunopharmacol 2006; 6, 592-599.

42. Rosenthal K. Intravenous Immunoglobulin. Resource Nurse. 2007. Accessed the 20th of June 2014 from http://www.resourcenurse.com/feature_ivig.html.

43. Reid B, Van Allen S., LaGrange CA, Boissoneault N. Protocol recommendations for administration of intravenous immunoglobulin in Canada. J Infus Nurs 2006; 29(3), 158-64.

44. Malcolmson C, Jones A, Xu-Bayford J. Guideline for immunoglobulin infusions: intravenous and subcutaneous. London, UK: Great Ormond Street Hospital. 2014. Accessed the 20th of June 2014 at: http://www.gosh.nhs.uk/health-professionals/clinical-guidelines/immunoglobulin-infusions-intravenous-and-subcutaneous/

45. National Blood Authority. Training checklist for home administered subcutaneous immunoglobulin infusion treatment. Lyneham, Australia: National Blood Authority. 2014. Accessed the 18th of June 2014 at: http://www.blood.gov.au/subcutaneous-immunoglobulin

46. NHS Health Scotland. Clinical guidelines for immunoglobulin use - Second edition update Scotland. Edinburgh: NHS Health Scotland. 2012.Accessed the 20th of June 2014 at: http://www.nsd.scot.nhs.uk/Documents/clinimmumoMarch12.pdf

47. Chipps E, Skinner C. Intravenous Immunoglobulin: implications for use in the neurological patient. J Neurosci Nurs 1994, 26(1), 8-17.

48. Gysler, M. Infusion of Intravenous Immune Globulin (IVIG) CPG. The Credit Valley Hospital – Clinical Practice Guidelines. 2012. Accessed the 18th of June 2014 at: http://www.cvh.on.ca/pro/cpg/Infusion%20of%20Intravenous%20Immune%20Globulin%20__IVIG_%20CPG.pdf

49. American Academy of Allergy Asthma & Immunology. Guidelines for the site of care for administration of IGIV therapy. Milwaukee, WI: American Academy of Allergy Asthma & Immunology. 2011.Accessed the 20th of June 2014 at https://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20Resources/Guidelines-for-the-site-of-care-for-administration-of-IGIV-therapy.pdf

Safety

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Summary

Aim

To determine safety of treatment with intravenous immunoglobulin (IVIG) in adults with Mild Cognitive Impairment (MCI) or Alzheimer's disease (AD) (adverse events due to IVIG treatment compared with current practice).

A secondary objective was to map available evidence against the technology's evidence profile.

Methods

We performed a systematic review according to Cochrane methodology on evidence from biomedical and HTA databases; publicly available clinical trial (CT) registers were also accessed. Qualitative and quantitative syntheses were planned.

To assess risk of bias of included randomized controlled trials (RCTs) the risk of bias system proposed by the Cochrane Handbook for Systematic Reviews of Interventions was used. Overall quality of evidence for each outcome was assessed and synthesised according to the GRADE approach.

Results

Among the published clinical studies four met the inclusion criteria. One small multiple dose, placebo-controlled RCT treated 16 patients with mild-to-moderate AD for 12 weeks; one phase 2, dose-finding, placebo-controlled RCT treated 56 patients with mild-to-moderate AD for 24 weeks – 48 assigned to IVIG and 14 assigned to placebo; and two prospective interventional non-controlled studies included a total 13 patients with mild-to-moderate AD.

Missing publication was documented for other two completed RCTs in subjects with mild-to-moderate AD. One of the two unpublished studies {NCT00818662}, a phase 3 double-blind, placebo-controlled, two dose arm RCT, aiming at testing the safety and effectiveness of IVIG for patients with mild-to-moderate AD, had its results posted on a clinical trial register in October 23rd 2014, after completion of this report. The authors and the sponsor had been previously contacted (May 2014) but did not provide any data. As this study, according to decision of Editorial Team, met inclusion criteria, release of this report was postponed in order to include it in the analysis despite the fact that available data did not permit a comprehensive evaluation of the methodology and conduction of the study due to the absence of information posted. The Authors and the Sponsor had been previously contacted (May 2014) but did not provide any data. Manufacturer was not contacted again to provide additional information.

In the two published RCTs, the proportion of participants who experienced any AEs was similar in IVIG and placebo group. Most AEs in the IVIG group were mild or moderate. No deaths occurred in these trials. The incidence of AEs leading to study discontinuation was higher for IVIG group than placebo group; three patients on IVIG in one RCT and one patient in another RCT did not complete the study because of AEs. In one RCT, 10 SAEs were observed in eight patients with higher proportion (not statistically significant) in the placebo group (4/42, 10%, vs 4/14, 29%, respectively, p=0.078). In the same RCT, ischaemic stroke was registered in one patient on IVIG and microhaemorrhages at MRI occurred more than expected in the IVIG group (6/42, 14%, vs 0/14), but were asymptomatic. One small RCT used 0.25% human albumin as comparator, therefore bias could have been introduced due to inappropriate choice of placebo.

The unpublished RCT included 383 patients (completing the study: 302) that were randomized to one of two doses of IVIG (Gammagard Liquid 10%, 400 mg/kg bodyweight or 200 mg/kg bodyweight, every two weeks) or one of two doses of placebo (0.25% human albumin solution infused at 4mL/kg or at 2 mL/kg, every two weeks) for 70 weeks. Available data do not permit an evaluation of the methodology and conduction of the study due to the absence of information posted. The confidence in effect estimates at study level is *very low*, according to GRADE approach. The proportions of participants who experienced Serious AEs (53/262, 20.2% vs 26/121, 21.5%) and non-Serious AEs (230/262, 87.8% vs 103/121, 85.1%) were similar in IVIG and placebo group. Four patients in the IVIG group died and reasons were not reported, whilst no death occurred in placebo group. Most frequent AEs in experimental arm were as follows: headache (24%), rash (15.3%), infusion site extravasation (14.5%), diarrhoea (14.1%), hypertension (12.2%), blood pressure increased (11.8%), fall (11.5%), depression (11.5%), dizziness (11.1%), vomiting (10.7%), nausea (10.3%).

The confidence in effect estimate for overall evidence on all considered outcomes is *very low*, according to GRADE approach.

Data on 13 patients only were available from two other interventional prospective non-controlled studies.

Two additional ongoing RCTs have been identified: one including subjects with MCI, and one including subjects with mild-to-moderate AD. These trials are reported to and expected to end in November 2014 and December 2016, respectively. Patients with moderate-to-severe AD are not considered by any study.

Conclusion

No conclusion can be drawn on the safety of IVIG for subjects with MCI and AD due to the poor - in term of quantity and quality – evidence presently available. The safety analysis was based on studies with mild-to-moderate AD treated with different doses of IVIG . None of the retrieved studies included patients with MCI and moderate-to-severe AD. Conclusive evidence from unpublished and ongoing studies are necessary before setting up RCTs on long term safety of IVIG in patients with MCI, mild-to-moderate and moderate-to-severe AD.

Introduction

The Safety Domains describes the direct and indirect harms of a technology for patients, staff and environment, and how to reduce the risk of harms {HTA Core Model Handbook Online, Version 1.5}. The safety issues specific to pharmaceutical technologies (drug safety, patient safety, adverse drug reactions, patient susceptibility) were considered while working on the safety domain {“Endpoints used in REA of pharmaceuticals – Safety”, available at http://www.eunethta.eu/outputs/methodological-guideline-rea-pharmaceuticals-safety}.

Adverse reactions were reported in up to 20% of all IVIG infusions and potentially serious systemic reactions occur in 2% to 6% of patients. Serious adverse events reported were: acute renal failure, anaphylaxis; aseptic meningitis; backache; chest discomfort; chest pain; haemolysis; haemolytic anemia; hepatitis; hypokalemic nephropathy; hyponatremia; myocardial infarction; pulmonary embolism; tachycardia; thrombosis; transfusion related acute lung injury {Micromedex Drugdex database, 2014}. Some reactions appeared during the IVIG infusion (immediate reactions) others after the IVIG infusion (delayed reactions) {Singh-Grewal 2006}. Adverse reactions appearing during the infusion or within the 24 hours after infusion include rate-related reactions (phlogistic and anaphylactoid reactions, 2-20% of patients), headache (around 20% of patients) and true IgE-mediated anaphylaxis (in IgA-deficient patients) (< 1% of patients) {Silvergleid 2013}. Reactions emerging 24 hours after the infusion include headache/aseptic meningitis, acute kidney injury, hemolysis, venous thrombosis, and the possibility of myocardial infarction, transient ischemic attacks, and stroke {Silvergleid 2013}.

Objectives

Primary objective: to assess the safety of IVIG in adults with one the following conditions

- MCI
- Mild-to-moderate AD
- Moderate-to-severe AD

Secondary objectives:

- to map available evidence against the technology’s evidence profile, i.e. the body of evidence needed to demonstrate its safety in the above reported target conditions
- to identify research gaps

Methodology

Frame

The collection scope is used in this domain.

Technology	Immunoglobulins (IGG) **Description** Naturally occurring proteins produced by the body's immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer's disease **Target condition** Alzheimer's disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.
Comparison	placebo, not doing anything or Usual supportive care **Description** There is no MA for IGGs for AD yet and there is no other intervention licensed for use in AD so the comparison would have to be against placebo or best supportive care
Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
C0001	Patient safety	What kind of harms can use of the technology cause to the patient; what are the incidence, severity and duration of harms?	yes	What is the frequency of immediate and delayed serious and non-serious adverse events in patients with Mild Cognitive Impairment and in patients with Alzheimer's disease treated with IVIG?
C0002	Patient safety	Are the harms related to dosage or frequency of applying the technology?	yes	Do the incidence and severity of adverse events of IVIG change with different dosing and administration schemes when used in patients with Mild Cognitive Impairment or Alzheimer's disease?
C0008	Patient safety	How safe is the technology in relation to the comparator(s)?	yes	What are the incidence, severity and duration of adverse events when compared with placebo or with drugs approved (acetylcholinesterase inhibitors, memantine) for the treatment of Alzheimer's disease?
C0007	Patient safety	Are there special issues in the use of the technology that may increase the risk of harmful events?	yes	Do IVIG interfere with or are affected by other treatments used in patients with Mild Cognitive Impairment or in patients with Alzheimer's disease?
C0004	Patient safety	How does the frequency or severity of harms change over time or in different settings?	no	No special issues, only issues related to IV preparations; an issue could be the amount of IgA contained in IVIG preparation that will be explored in another question (C0060)
C0005	Patient safety	Are there susceptible patient groups that are more likely to be harmed through use of the technology?	no	Patients eligible for treatment with IVIG are old patients usually with co-morbidities thus we may considered all the treated patients as very susceptible to adverse events.
C0060	Safety risk management	How does the safety profile of the technology vary between different generations, approved versions or products?	yes	Does the safety profile of IVIG vary according to mode of production or between different IVIG approved versions or products when used in patients with Mild Cognitive Impairment and Alzheimer's disease?
C0061	Safety risk management	Can different organizational settings increase or decrease harms?	no	IVIG are supposed to be administered in an hospital setting (IV administration). Not sure if consider irrelevant this question: to be discussed, perhaps it could be important to state that the administration should be carried out in an hospital setting (not an ambulatory setting) where a resuscitating service is available
C0062	Safety risk management	How can one reduce safety risks for patients (including technology-, user-, and patient-dependent aspects)?	no	Better in TECH domain
C0063	Safety risk management	How can one reduce safety risks for professionals (including technology-, user-, and patient-dependent aspects)?	no	We consider that risks for professionals are quite low, comparable to those of every product to be administered through a parenteral route
C0064	Safety risk management	How can one reduce safety risks for environment (including technology-, user-, and patient-dependent aspects)	no	Same risks as every other biological waste
C0020	Occupational safety	What kind of occupational harms can occur when using the technology?	no	Occupational harms are supposed to be those related to IV drugs, not specific for IVIG
C0040	Environmental safety	What kind of risks for public and environment may occur when using the technology?	no	Same risks as every other biological waste.

Methodology description

Criteria for considering studies

Types of studies

All published and unpublished randomised controlled trials (RCTs), prospective controlled and non-controlled studies (interventional). For unpublished studies we accepted results from publicly available controlled trials' registers (decision made by Editorial Team). Report on animal models, pre-clinical and biological studies, narrative reviews, editorials, opinions, were excluded.

Types of participants (target population)

Adult (18+ years) patients of any sex who have one of the target conditions:

1. Patients with MCI (ICD-9-CM Diagnosis Code 331.83; ICD-10-CM G31.84) as defined by validated criteria.
2. Patients with AD (ICD-9-CM Diagnosis Code 331.0; ICD-10-CM G30.9), as defined by validated criteria.

Types of interventions

IVIG any dose, any regimen, any product, alone or in combination with non-pharmacological interventions, and/or with approved drugs (acetyl cholinesterase inhibitors, memantine).

Types of control treatments

- Placebo or drugs approved for symptomatic treatment of AD: acetylcholinesterase inhibitors, approved to be used in patients with mild-to-moderate AD, and memantine, approved to be used in patients with moderate-to-severe AD.

Types of outcomes and outcome measures

We looked for

1. immediate (emerging during the infusion of IVIG) and delayed (emerging after infusion) serious and non-serious adverse events [Issue domain Patient Safety C0001]
2. incidence and severity of adverse events with different dosing and administration schemes of IVIG [Issue domain Patient Safety C0002]
3. incidence, severity and duration of adverse events when compared with placebo or with drugs approved (acetylcholinesterase inhibitors, memantine) for the treatment of AD [Issue domain Patient Safety C0008]
4. incidence of interactions between IVIG and other treatments used in patients with MCI or AD [Issue domain Patient Safety C0007]

Search methods for identification of studies

Electronic searches

The following databases were searched:

Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE, TOXLINE, EMBASE, LILACS, ALOIS (the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group) and national and international trials registers (Australian New Zealand Clinical Trials Register (ANZCTR), http://www.anzctr.org.au/; metaRegister of Controlled Trials (mRCT), http://www.controlled-trials.com/mrct/; ClinicalTrials.gov. www.clinicaltrials.gov/; NIH Clinical Research Studies, http://clinicalstudies.info.nih.gov/; EU Clinical Trials Register, https://www.clinicaltrialsregister.eu/; International Clinical Trials Register Platform (ICTRP), http://www.who.int/ictrp/en/). We searched also the websites of the regulatory agencies (US Food and Drug Administration-MedWatch (http://www.fda.gov/Safety/MedWatch/default.htm), European Medicines Evaluation Agency (http://www.ema.europa.eu), Australian Adverse Drug Reactions Bulletin (http://www.tga.gov.au/safety/ews-monitoring.htm), and UK Medicines and Healthcare products Regulatory Agency (MHRA) pharmacovigilance and drug safety updates (http://www.mhra.gov.uk/Safetyinformation/index.htm).

Initial search was carried out on February 24th 2014 and an update was carried out close to the release of the report on December 16th 2014.

See Appendix 6 for detailed search strategies. The strategy for MEDLINE was translated for other databases. No language or date of publication restrictions were applied.

Searching other resources

In addition we checked conference proceedings for relevant abstracts, and contact individual researchers working in this field, organizations and pharmaceutical companies to identify additional RCTs, especially those unpublished. We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

The titles and abstracts of all studies identified by the search were screened independently by two investigators (ASSR). Full text was retrieved for all studies considered potentially relevant. Two investigators then identified studies for inclusion or exclusion (ASSR). Different selection results were discussed in order to achieve consensus. A third person was involved to resolve discrepancies (AAZ and SBU).

Data extraction and management

A data extraction form was developed and piloted specifically for this review. For each study, data were extracted on: participants (including inclusion and exclusion criteria, baseline investigations, co-treatments); interventions; outcomes; study design; results. For eligible studies, when data on outcomes

of interest were missing or incompletely reported investigators contacted the Authors for additional information. Data extracted were the number of participants with the outcome of interest in each group at each time point.

Assessment of risk of bias of included studies and of overall quality of evidence

To assess risk of bias of included RCTs the risk of bias system proposed by the Cochrane Handbook for Systematic Reviews of Interventions {Higgins et al. 2011} was used. Overall quality of evidence for each outcome was assessed and synthesised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach {Guyatt 2011a; Balshem 2011; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2013}, and presented in table. This approach specifies four levels of quality:

- High: further research is very unlikely to change our confidence in the estimate of effect;
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates;
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low: we are very uncertain about the estimate.

Data synthesis

Studies were grouped by target conditions included in this protocol. A descriptive summary of the included studies with details about study design, numbers and characteristics of enrolled patients, intervention/s and comparator/s, outcomes, and results is provided in tables and plain text format. We adopted definitions and terminology of safety according to the Medical Dictionary for Regulatory Activities (MedDRA) Terminology (http://www.meddra.org/).

Quantitative results are expressed as point estimates together with associated 95% confidence intervals (95% CI) and p-values. We had planned, if possible, to carry out a meta-analysis with graphical display of results and assessment of heterogeneity, according to the Cochrane Handbook for Systematic Reviews of Interventions {Higgins et al. 2011}.

To map available evidence against the technology's evidence profile, for each research question the results from *available evidence* and *upcoming evidence* were charted in order to describe stage of development and to highlight research gaps. *Available evidence* refer to published or unpublished studies with available data and *upcoming evidence* refer to unpublished without available data and ongoing studies.

Description of studies

Results of the search

The first electronic searches strategy (February 24th 2014) yielded 515 citations, after removal of duplicates. Of these, 388 were directly excluded, because judged not relevant.

Of the remaining 127 citations, 116 did not meet our inclusion criteria and were excluded from safety assessment (primary objectives). Three published studies (corresponding to 11 records) were included {Dodel 2004, Dodel 2013, Relkin 2009}. Periodic checks of registers of ongoing trials revealed that the results of one of the RCT {NCT00818662} tracked on clinical trial registries had been posted on ClinicalTrials.gov by the study sponsor in October 23rd 2014. Thus this study was included (decision made by Editorial Team) and the remaining 115 citations excluded. The second electronic search strategy (December 16th 2014) yielded 71 citations, after removal of duplicates. One published study {Arai 2014} was included. From the final periodic check of registers of ongoing trials (December 16th 2014) there was no further status change for included ongoing trials.

See PRISMA study flow diagram in Appendix 1{Figure A1}.

Excluded studies

The reasons for exclusion of the 115 records were as follows: in vitro/animal studies (n=13); other treatments (n=22); review papers (n=31); comments/editorials/news (n=14); other topics (n=4); studies on the current use of IVIG (n=2); case control studies (n=2); study without data on outcomes (n=1). The remaining 26 citations corresponding to 12 interventional studies did not fulfil our inclusion criteria. Of these 12 studies, 6 resulted as completed and published only as abstracts {Hara 2011, Kondo 2011, Kountouris 2000, Papatriantafyllou 2006, Rovira 2011, Relkin 2012}; 1 were completed but unpublished {NCT00299988 }; 2 studies are ongoing {NCT01300728, NCT01561053}, 2 studies had been planned but they were terminated prematurely {NCT01524887, NCT01736579}; and one published study was excluded because retrospective {Devi 2008}. The above 12 interventional studies were found eligible only for the evidence mapping against the technology's evidence profile.

Included studies with published results

The four included studies - summarised in Appendix 2**,** - were were two RCTs, one small multiple-dose and one dose-finding {Dodel 2013, Arai 2014}, and two prospective interventional non-controlled studies {Dodel 2004, Relkin 2009}.

The first RCT {Dodel 2013} was an exploratory phase 2 dose finding double-blind, block-randomised, placebo-controlled study aiming at testing the safety, effective dose, and infusion interval of treatment with intravenous immunoglobulin for patients with mild-to-moderate AD. Participants were 58 subjects (modified intention-to-treat population: 57; per protocol population: 45) with probable AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria), with a mini-mental state examination score 16–26 and age 50–85 years at baseline. Patients had to have been taking a stable dose of an approved AD drug for at least 3 months before screening; 36 out of 41 patients in IVIG (88%) used acetylcholinesterase inhibitor or memantine as well as 11 out of 14 (79%) patients in Placebo group.

Participants were randomized to one of six doses of IVIG (0.2 g/kg, 0.5 g/kg or 0.8 g/kg every 4 weeks; 0.1 g/kg, 0.25 g/kg, or 0.4 g/kg every 2 weeks) or to placebo (0.9% isotonic sodium chloride every 4 weeks or every 2 weeks). Treatment duration was 24 weeks. Primary outcome was the difference of the median area under the curve (AUC) of plasma concentration of Aβ1–40 between placebo groups and the six intervention groups, measured from last infusion to final visit. Other surrogate outcomes were the difference of AUC for plasma concentration of Aβ1–42 and of anti-Aβ autoantibodies; the difference of plasma concentration of Aβ1–40, Aβ1–42 and anti-Aβ autoantibodies at week 24 compared with baseline; the change in CSF concentration of Aβ1–40, Aβ1–42, anti -Aβ autoantibodies and p-tau181, 24 h after last infusion compared with baseline; the difference between baseline and week 24 of change in whole brain volume, hippocampus volume; glucose metabolism. Moreover some patient important outcomes were considered: difference in scores at baseline and at week 24 on the AD assessment scale-cognitive part (ADAS-cog), the clinical dementia rating scale-sum of boxes, the

Alzheimer's Disease Cooperative Study-activities of daily living scale, the mini-mental state examination; adverse events. The study - funded by Octapharma AG – was conducted in hospitals, research centres and private clinics of Germany and USA.

The second RCT {Arai 2014} was an exploratory multiple dose, double-blind, randomised, placebo-controlled study aiming at testing the safety and tolerability of treatment with IVIG for patients with mild-to-moderate AD. Participants were 16 subjects (intention-to-treat and per protocol population: 16) with probable AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria), with a mini-mental state examination score 16–26 and age 50–89 years at baseline. Patients could have been taking a stable dose of an approved AD drug (cholinesterase inhibitors, memantine) for at least 120 days prior baseline. However no data were reported about the use of these drugs.

Participants were randomized to one of two doses of IVIG (0.2 g/kg, 0.4 g/kg every 2 weeks) or to placebo (50 mL 0.25% human albumin solution every 2 weeks). Treatment duration was 12 weeks and follow up lasted up to 26 weeks. The outcome measures were safety and tolerability including adverse events (AE), assessed also by vital signs, physical and neurological examinations, 12-lead electrocardiogram, clinical laboratory evaluations, and brain MRI scans. AE were coded according to system organ classes using the Medical Dictionary for Regulatory Activities (version 14.1). Moreover MMSE score change 14 weeks after the end of treatment (week 26 of follow up) was considered. The study was conducted in 5 centres of Japan. No information was provided about funding. The study does not report a Study Registration number.

The other two studies {Dodel 2004, Relkin 2009} (interventional prospective non-controlled studies) had small populations (n = 13) of subjects with AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria) and tested the safety and the clinical effect of various schemes of IVIG administration (0.4 g/kg every 2 weeks; 0.4 g/kg on three consecutive days every 4 weeks; 0.4 g/kg every week; 1 g/kg every 2 weeks; 2 g/kg every 4 weeks) for 3-6 months of duration. The outcomes considered were difference between baseline and end of treatment of cognitive functions according to various scales/tools (Wechsler Adult Intelligence Scale; Wechsler Memory Scale; Boston Naming Test; ADAS-cog; MMSE; Visual construction abilities), immunologic surrogate outcomes (changes before and after infusion of serum or CSF anti-Abeta antibody, changes of CSF Abeta 40 and Abeta42), adverse events. Two studies {Dodel 2004, Relkin 2009} received both public and manufacturer's funding; in the third study {Devi 2008} the source of funding was not reported.

Included unpublished studies with results posted in clinical trials registers (Editorial Team decision)

The included unpublished study - summarised in Appendix 2**,** - were one RCT {NCT00818662}.

The following information refers to data posted by the study sponsor on one trial register (ClinicalTrials.gov) in October 23rd 2014. The Authors and the sponsor were previously contacted (May 2014). They responded but did not provide results. The Authors and the sponsor were not contacted again.

The included RCT {NCT00818662} was a phase 3 double-blind, placebo-controlled, two dose arm study aiming at testing the safety and effectiveness of IVIG for patients with mild-to-moderate AD. Participants were 383 patients (patients completing the study: 302; intention-to-treat population not declared) with probable AD (criteria not reported), with a mini-mental state examination score of 16–26 and age 50–89 years at baseline. Included patients had been taking a stable dose of an approved Alzheimer's disease drug for at least 3 months before screening (not reported number of patients on treatment). Participants were randomized to one of two doses of IVIG (Gammagard Liquid 10%, 400 mg/kg bodyweight every two weeks, or 200 mg/kg bodyweight every two weeks) or one of two doses of placebo (0.25% human albumin solution infused at 4 mL/kg every two weeks or at 2 mL/kg every two weeks), for 70 weeks. The randomization ratio was 2:2:1:1.

Co-primary outcomes were change from baseline at 18 months in the Alzheimer´s Disease Assessment Scale Cognitive Subscale (ADAS-Cog) and change from baseline at 18 months in the Alzheimer´s Disease Cooperative Study Activities of Daily Living (ADCS-ADL). Other patients important outcomes considered in the study were: change at 9 months in ADAS-Cog, change at 9 months in ADCS-ADL, change at 9 and 18 months in Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCSC-GIC), change at 18 months in the Neuropsychiatric Inventory (NPI), change at 18 months in the Logsdon Quality of Life in Alzheimer's Disease (QOLAD) of patients and caregivers. Other outcomes assessed in the study but not considered in this review were: Modified MiniMental State Examination (3MS), Wechsler Adult Intelligence Scale Revised Digit Span, FAS Verbal Fluency, Animals Category Fluency, Trail Making Test Part A and Part B, Clock Drawing Test. The study - funded by Baxter Healthcare Corporation and conducted in USA and Canada – started in December 2008 and ended in December 2012.

Included unpublished studies without results posted in clinical trials registers

Seven more studies - summarised in Appendix 3 - were carried out but not published as full papers, resulting as protocols in ClinicalTrial.gov {NCT00299988 } or abstracts at congress {Hara 2011, Kondo 2011, Kountouris 2000, Papatriantafyllou 2006, Relkin 2012, Rovira 2011}.

The NCT00299988 study {NCT00299988} was a phase 2 randomized, placebo-controlled trial, conducted in USA. Participants were 24 subjects with mild-to-moderate AD. Four schemes of intravenous immunoglobulin (ranging from 0.2 g/kg every 2 weeks to 0.8 g/kg every months) were compared to placebo. Treatment duration was 6 months. Primary outcome were ADAS-Cog and ADCS-CGIC. Other outcomes were cognitive functions measured by other scales/tools (MMSE; ADCS-ADL; NPI; GDS), quality of life (scales not reported), immunologic surrogate outcomes (plasma and CSF anti-amyloid antibody titers and beta amyloid levels), imaging surrogate outcomes (Positron Emission Tomography: FDG Cerebral Glucose Utilization, PIB Cerebral Amyloid Distribution, PK11195 Microglial Activation), adverse events. The study - funded by Weill Medical College of Cornell University Collaborators and by Baxter BioScience – was completed in April 2010 but results are still unpublished. For this study an open label extension of three years was carried out in 16 subjects in order to assess the long-term safety the IVIg infusion, but results are similarly unpublished as full paper (available only an abstract, Relkin 2012). Authors of the study were contacted in May 2014, and although they responded, they did not provide results.

Other four studies {Hara 2011, Kondo 2011, Papatriantafyllou 2006, Rovira 2011} applied a before-and-after design to small samples (n = 4 to 10) of subjects with AD testing the safety and effectiveness of various schemes of IVIg administration for 3-62 months of duration. The outcomes considered were difference between baseline and end of treatment of cognitive functions according to various scales/tools, surrogate outcomes, adverse events. These studies are still unpublished as full paper (available only as abstracts). The Authors of these studies were contacted. Two of them responded without providing results, stating that the studies will be probably published.

Finally, one study {Kountouris 2000} applied a non-randomized controlled design to 16 subjects with AD comparing the effectiveness of IVIg infusion together with piracetam versus the administration of piracetam only, for 12 months of duration. The outcome considered was the cognitive function assessed by the MMSE. This study is unpublished as full paper (available only as abstract). The Author of this study was contacted, without response.

Terminated studies

Two other studies - summarised in Appendix, Table 3: Characteristics of terminated studies – are terminated {NCT01736579, NCT01524887}, that is stopped prematurely.

An open label extension of three years of one of the above reported RCTs NCT00818662 was planned {NCT01736579} in order to assess the long-term safety of the IVIg infusion. The study was terminated in 2013 after enrollment of 6 patients because the preceding phase 3 study did not demonstrate efficacy on the co-primary endpoints.

The NCT01524887 study {NCT01524887} was a phase 3 randomized, placebo-controlled trial planned to include subjects with mild-to-moderate AD in order to test two unspecified schemes of intravenous immunoglobulin versus placebo for a treatment duration of 18 months. Primary outcome considered were ADAS-Cog and ADCS-ADL. The study - devised by Baxter Healthcare Corporation – was terminated in 2013 without enrollment of any patients because the first phase 3 study {NCT00818662} did not demonstrate efficacy on the co-primary endpoints.

Ongoing studies

Two more studies - summarised in Appendix 3– are still ongoing {NCT01300728, NCT01561053}.

The NCT01300728 study {NCT01300728}, is a phase 2 randomized, placebo-controlled trial, that is ongoing in USA. Participants are 50 subjects with MCI, amnestic type (single or multi domain) according to Petersen criteria (Petersen 1999) and supported by a CDR score of 0.5. IVIg infusion (0.4 g/kg every 14 days for a total of five infusions in two months) will be compared to placebo. Primary outcome is change in ventricular volumetric as measured by MRI (time frame: baseline and 24 month). Other outcomes are conversion from amnestic MCI to AD, cognitive functions measured by other scales/tools (ADAS-cog; MMSE; Clinical Dementia Rating and Sum of Boxes), other imaging surrogate outcomes, adverse events. The study - funded by Sutter Health – will be completed in November 2014.

The NCT01561053 study {NCT01561053}, is a phase 2/3 randomized, placebo-controlled trial, that is ongoing in USA and Spain. Participants are 350 subjects with mild-to-moderate Alzheimer Disease (National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria). IVIg (Flebogamma DIF) infusion (at unspecified high and low dose) together with plasmapheresis or plasmapheresis alone will be compared to a sham procedure. Primary outcome is increase in cognitive scores as measured by A<DAS-Cog (time frame 14 months). Other outcomes are change in: cognitive, functional and neuropsychiatric scores (measured by MMSE, NPS battery, ADCS-ADL, NPICDR-Sb, ADCS-CGIC, CSDD, C-SSRS), surrogate immunological outcomes (levels of AB1-40 and AB1-42, T-tau and P-tau in CSF; levels of AB1-40 and AB1-42 in plasma), surrogate imaging outcomes (structural changes in volume of the hippocampus, posterior cingulate area, and other associated areas at MRI; brain functional changes through FDG-PET), adverse events. The study - funded by Grifols Biologicals Inc. – will be completed in December 2016.

Risk of bias in included studies

The RCT NCT00818662 was a phase 3 double-blind, placebo-controlled, two dose arm study. Available data (posted on ClinicalTrials.gov, last access December 5 2014) do not permit an evaluation of the methodology and conduction of the study due to the absence of information posted. Authors and Manufacturer were not contacted again and risk of bias was assessed by Principal Investigator. A risk of attrition bias was present (81 out of 383 randomized patients did not complete the study). The study was industry sponsored. The overall risk of bias of this study was judged to be “high”. For details on study’s risk of bias please see Table 1.

Table 1. Risk of bias table for NCT00818662.

Bias	**Judgement**	**Support for judgement** Cochrane Risk of Bias; Criteria from EUnetHTA guideline, Internal validity of randomized controlled trials
Random sequence generation adequate (selection bias)	Unclear	No details on random generation.
Allocation concealment adequate (selection bias)	Unclear	No details on allocation concealment.
Blinding of patients (performance bias)	Unclear	No details on blinding.
Blinding of treating personnel (performance bias)	Unclear	No details on blinding.
Blinding of outcome assessment (detection bias)	Unclear	No details on blinding.
Incomplete outcome assessment unlikely (attrition bias)	High risk	383 patients were randomized: 127 IVIG 400mg/kg; 135 IVIG 200mg/kg; 58 Placebo 4mL/kg; 63 Placebo 2mL/kg. 82 (21.4%) patients did not complet the trial: 23 (18.1%) IVIG 400mg/kg; 33 (24.4%) IVIG 200mg/kg; 9 (15.5%) Placebo 4mL/kg; 16 (25.4%) Placebo 2mL/kg

ITT principle appropriately implemented (attrition bias)	Unclear risk	No details on ITT analysis.
Selective outcome reporting unlikely (reporting bias)	Low risk	No main discrepancies between the protocol and the reported results are present.
Other bias	High risk	Sponsored study Two Study Directors are reported Study Director: Norman Relkin, MD, PhD Alzheimer's Disease Cooperative Study (ADCS) Study Director: David Gelmont, MD Baxter Healthcare Corporation Role of the funding source "Restriction Description: Agreements with PIs may vary per requirements of individual PI, but contain common elements. For this study, PIs are restricted from independently publishing results until the earlier of the primary multicenter publication (by USCD) or 12 months after study completion. Baxter requires a review of results communications (e.g., for confidential information) ≥45 days prior to submission or communication. Baxter may request an additional delay of ≤45 days(e.g., for intellectual property protection)"

The second included RCT {Dodel 2013} was an exploratory dose-finding, phase 2 study with a small sample size, unbalanced baseline characteristics among the treatment groups (use of acetylcholinesterase inhibitors or memantine: 88% in IVIG group vs 79% in placebo group), risk of attrition bias (IVIG group: 6 withdrawals out of 42 subjects, 14.3%; placebo group: 5 withdrawals out of 14 subjects, 36%), industry sponsored. For details on study's risk of bias please see Table 2.

Table 2. Risk of bias table for Dodel 2013.

Bias	**Judgement**	**Support for judgement** Cochrane Risk of Bias; Criteria from EUnetHTA guideline, Internal validity of randomized controlled trials
Random sequence generation adequate (selection bias)	Low risk	"Patients were randomly allocated to receive one of three doses of intravenous immunoglobulin (0・2 g/kg, 0・5 g/kg, or 0・8 g/kg) or placebo (0・9% isotonic sodium chloride) every 4 weeks, or half of that dose (0・1 g/kg, 0・25 g/kg, or 0・4 g/kg) every 2 weeks. The randomisation was done with a computer-generated randomisation list created by the contract research organisation with SAS (version 9.1.3). Patients were allocated through an interactive web response service in block sizes of eight."
Allocation concealment adequate (selection bias)	Low risk	See above.
Blinding of patients (performance bias)	Low risk	"The study drug was contained in ethylene vinyl acetate bags masked by opaque pouches. It was prepared at local pharmacies and dispensed by pharmacists who were not masked to the allocation. Infusion was done by a physician who was masked to the patient's allocation and not involved in any assessments. Patients, caregivers, investigators assessing outcomes, staff of imaging facilities and of the clinical research organisation were masked to treatment allocation, but the statistician and the person responsible for the final PET analyses were not."
Blinding of treating personnel (performance bias)	Low risk	See above.
Blinding of outcome assessment (detection bias)	Low risk	See above.
Incomplete outcome assessment unlikely (attrition bias)	High risk	Flow chart, page 234. The drop-out rate in the trial was considerable; 89 patients were screened and 58 were randomly assigned; 2 patients were not treated; 42 assigned to intravenous immunoglobulin and 14 assigned to placebo; 6 withdraw in IVIgG group and 5 in Placebo group. 45 (77.6%) patients (out of 58) completed 24 weeks of treatment, with different rates of discontinuation between groups /6 out of 42 assigned IVIgG (14.28%): 5 out of 14 assigned to Placebo (35.7%)/. The characteristics of the dropped-out participants compared with the completed participants have not been reported.
ITT principle appropriately implemented (attrition bias)	Unclear risk	"For safety data, continuous variables were analysed with standard summary statistics and frequency tables. The safety analysis was based on 56 patients, of whom 42 patients were in the intravenous immunoglobulin group and 14 were in the placebo group." Flow chart, page 234. Authors mentioned Intention-to-treat analysis (ITT) and Per-protocol analysis (PPT) but from flow char is visible that the modified intent-to-treat (mITT) was used, which (marginally) differ from ITT, as patients randomised but not initiated on the study medication are excluded (2 patients).

		Proportion and p value are written, without CI.
Selective outcome reporting unlikely (reporting bias)	Unclear risk	3/42 patients on IVIG did not complete the study because of AEs: one 68-year-old women in the high-dose treatment group due to ischemic stroke (middle cerebral artery infarction), one patient due to 14 new asymptomatic microbleeds at week 12 on MRI scan and one due to reasons neither written in the article nor visible in trial registers. CI not shown for proportion of patient with documented AEs and SAEs. AEs were not prespecified primary or secondary endpoints.
Other bias	High risk	Some demographic and baseline characteristic were not similar between groups (for example sex, bodyweight, duration of symptoms, use of acetylcholinesterase inhibitor or memantine, total tau concentration, microbleeds, normalized whole brain volume). The patient characteristics (e.g. comorbidities) or medications at baseline or at end of study (e.g. doses used) in different study groups are not reported in sufficient detail. The trial is sponsored by pharmaceutical industry. The sample size was determined empirically, on the basis of a previous study. Small sample size of each treatment group and within IVIgG group, very small control (placebo) group. “Role of the funding source The study sponsor was partly responsible for the study design. The clinical research organisation (ClinResearch, now Aptiv Solutions, Cologne, Germany) had responsibility for data monitoring and analysis according to the statistical analysis plan developed by the sponsor as well as for writing trial reports for regulatory authorities. The sponsor had a role in data interpretation, but no role in data collection. After the database lock and study unmasking, all of the investigators had full access to the study data and had final responsibility for data analysis. The report was written and reviewed by the authors and the sponsor. The decision to submit the report for publication was made jointly by RD, FJ, MF, and the sponsor.” COI: 2 authors are employees of Octapharma; some authors received consultancy fee or funding for research or travel support to meetings or speaker fee, some are board member.

The third RCT {Arai 2014} was a multiple dose study with a small sample size, unclear selection bias, unclear performance and detection bias, and other bias. The study does not report a Study Registration number. For details on study’s risk of bias please see Table 3.

Table 3. Risk of bias table for Arai 2014.

Bias	**Judgement**	**Support for judgement** Cochrane Risk of Bias; Criteria from EUnetHTA guideline, Internal validity of randomized controlled trials
Random sequence generation adequate (selection bias)	Unclear risk	Not reported details about random sequence generation
Allocation concealment adequate (selection bias)	Unclear risk	Not reported details about allocation concealment
Blinding of patients (performance bias)	Unclear risk	Double blind but not reported details about appearance of IVIG treatment and placebo
Blinding of treating personnel (performance bias)	Unclear risk	Double blind but not reported details about appearance of IVIG treatment and placebo
Blinding of outcome assessment (detection bias)	Unclear risk	Double blind but not reported details about appearance of IVIG treatment and placebo
Incomplete outcome assessment unlikely (attrition bias)	Low risk	All included patients completed the study
ITT principle appropriately implemented (attrition bias)	Unclear risk	There is no Flow chart. “The population for safety analyses was defined as all randomly assigned subjects from whom post-treatment safety data has been collected at least once.” All included patients completed the study.
Selective outcome reporting unlikely (reporting bias)	Unclear risk	The study does not report a Study Registration number.
Other bias	High risk	All authors declare that they have no conflicts of interest associated with this manuscript, however five of them have affiliation with Baxter Limited, Tokyo, Japan. Small sample size. Very small control group which received as placebo 0.25% human albumin, that could induce AEs and SAE. Medications at baseline or at end of study (e.g. doses used) are not reported in sufficient detail for the different study groups. Short duration of study.

The two non-controlled interventional studies {Dodel 2004, Relkin 2009} had a very small sample size and absence of blinding of assessment of clinical outcomes; Dodel 2004 had an inadequate follow up duration (6 months); the other {Relkin 2009} was industry sponsored.

Result cards

Patient safety

Result card for SAF1: "What is the frequency of immediate and delayed serious and non-serious adverse events in patients with Mild Cognitive Impairment and in patients with Alzheimer's disease treated with IVIG?"

View full card

SAF1: What is the frequency of immediate and delayed serious and non-serious adverse events in patients with Mild Cognitive Impairment and in patients with Alzheimer's disease treated with IVIG?

Method

The same methodology was used as described in section for the whole domain.

Result

MCI

There are no data for patients with MCI.

AD

Placebo-controlled trials

Data from three RCTs (one multiple dose study {Arai 2014}, one phase 2, dose-finding study, {Dodel 2013}, and one phase 3 study {NCT00818662}) were available for analysis. See a synopsis of results on Table 4.

In Arai 2014, the proportion of participants who experienced any AEs was similar in IVIG and placebo group: 10/12 (83%) and 4/4 (100%), respectively. A total of 33 treatment-emergent AEs occurred, 26 in IVIG group and 7 in placebo group. Most AEs in the IVIG group were mild or moderate. No deaths occurred in this trial. The most common AEs in the IVIG group were nasopharyngitis (16.7%, three events in two subjects), injection-site swelling and erythema (16.7%, two events in two subjects). In the placebo group, the incidence of nasopharyngitis was reported to be 25.0% (one event in one subject), and no events of injection-site swelling or erythema occurred. The incidence of any AE did not significantly differ between the IVIG group and the placebo group or between the IVIG 0.2 g/kg and IVIG 0.4 g/kg groups.

Four SAEs were observed in three patients: one event (cataract) in the IVIG 0.2 g/kg group, and three events (patella fracture, radius fracture, and pneumonia) in two subjects in the placebo group. All these SAE were classified by the investigator as being unrelated to the study drug. There were no significant differences between the IVIG groups and the placebo group or between the IVIG 0.2 g/kg and IVIG 0.4 g/kg groups. The incidence of adverse drug reactions occurring in the IVIG group was 33.3% (nine events in four subjects) and 0 in the placebo group. However only one event (rash on the extremity and the trunk with mild elevations in aspartate amino transferase, alanine amino transferase, and lactose dehydrogenase) in one patient was considered 'possibly associated' to IVIG treatment. This patient was the only one that missed one infusion of the study drug because of that event. The other eight events (one event each for sinusitis, oral herpes, decreased neutrophil count, white blood cell count decreased, decreased neutrophil percentage, monocyte percentage increase, lymphocyte percentage increase, and erythema) were assessed as 'unlikely associated'. No microhaemorrhages were registered at MRI in both treatment groups.

The authors of the above mentioned RCT concluded that IVIG treatment is generally safe and well tolerated at doses of 0.2 and 0.4 g/kg in Japanese patients with mild to moderate AD. This small sample size study, with high risk of bias and short duration of treatment, included only 16 patients with control group who received 0.25% human albumin as placebo. Human albumin could induce AEs and SAE.

In Dodel 2013, the proportion of participants who experienced any AEs was similar in IVIG and placebo group: 25/42 (60%) and 9/14 (64%), respectively (p=0.75). Ten SAEs were observed in eight patients with higher proportion (not statistically significant) in the placebo group (4/14, 29%) versus IVIG group (4/42, 10%), p=0.078. Most AEs in the IVIG group were mild or moderate. No deaths occurred in this trial. The incidence of AEs leading to study discontinuation was higher with IVIG then with placebo; three patients on IVIG did not completed the study because of AEs. One 68-year-old women in the high-dose treatment group had a SAE, ischaemic stroke (middle cerebral artery infarction). One patient was removed from the study due to 14 new microbleeds at week 12 seen on MRI scan, without clinical symptoms. For the 3rd patient the specific AE that led to study discontinuation was not reported in the article nor was visible in trial registers. Authors did not record any changes in white matter (amyloid-related imaging abnormalities) nor aseptic meningitis and meningoencephalitis. No microbleeds were registered for patients treated with placebo whilst 6/42 (14%) patients treated with IVIG experienced microbleeds but were asymptomatic. 3/42 and 2/42 patients treated with IVIG experienced headache and hypoaestesia, respectively, versus no patient in the placebo arm. The following AEs were listed with a frequency of 2% or more in experimental arm: chills, influenza-like illness, tremor, muscle spasm, procedural hypertension, actinic keratosis, hyperkeratosis, pruritus, blood pressure fluctuation, impaired hearing, increased AST, increased LDH, dyspepsia, haematuria, fatigue, pyrexia, falls, infusion site extravasation. The authors of the above mentioned RCT concluded that IVIG has acceptable safety profile for patients with mild-to-moderate AD but stated limitations like small sample size in each group and short duration of treatment (only 6 months).

In NCT00818662 the proportions of participants who experienced Serious AEs (53/262, 20.2% vs 26/121, 21.5%) and non-Serious AEs (230/262, 87.8% vs 103/121, 85.1%) were similar in IVIG and placebo group. Four patients in the IVIG group died and reasons were not reported. No deaths occurred in placebo group. The incidence of AEs leading to study discontinuation was higher with IVIG then with placebo (7.3% vs 5.8%). Reasons were not

reported. Most frequent AEs in experimental arm were as follows: headache (24%), rash (15.3%), infusion site extravasation (14.5%), diarrhoea (14.1%), hypertension (12.2%), blood pressure increased (11.8%), fall (11.5%), depression (11.5%), dizziness (11.1%), vomiting (10.7%), nausea (10.3%).

Table 4. Summary of adverse events (AE) in one published RCTs on patients with mild-moderate AD

	N = 12	N = 4		N = 42	N =14		N=262	121	
Any AE	10 (83.3%)	4 (100%)	not reported	25 (60.0)	9 (64.0)	0.75 (not reported)	not reported	not reported	not reported
Serious AEs	1 (8.3%)	3 (75.0%)	not reported	4 (10.0)	4 (29.0)	0.078 (not reported)	53 (20.2)	26 (21.5)	not reported
Non Serious AEs	not reported	not reported	not reported	not reported	not reported	not reported	230 (87.8)	103 (85.1)	not reported
AEs leading to discontinuation	1 (8.3%)	0	not reported	3 (7.14)	0 (0)	not reported	not reported	not reported	not reported

Abbreviations: AEs=Adverse events

*Please note that patients had to have been taking a stable dose of an approved AD drug for at least 3 months before screening; use of acetylcholinesterase inhibitor or memantine as reported in Table 1 of Dodel 2013: 36/42 (88%) patients randomised to IVIG and 11/14 (79%) patients randomised to placebo.

Table 5. Description of Serious AEs, most frequent AEs and AEs leading to discontinuation of treatment.

	Arai 2014 **IVIG all doses (N = 12) vs Placebo (N =4)**	**Dodel 2013** **IVIG all doses (N = 42) vs Placebo (N =14)**	**NCT00818662** **IVIG all doses (N = 262) vs Placebo (N =121)**
Description of Serious AEs (No more than 1 or 2 per group) (**MedDRA 12.0**)		**n (%)**	**n (%)**
Microcytic anaemia	not reported	not reported	2 (0.8%) vs 0
Coronary Artery Disease	not reported	not reported	2 (0.8%) vs 0
Gastral antral vascular ectasia	not reported	0 vs 1 (7%)	not reported
Nausea / Vomiting	not reported	1 (2%) vs 0	1 (0.4%) vs 0
Chest pain	not reported	not reported	3 (1.1%) vs 0
MultiOrgan Failure	not reported	not reported	2 (0.8%) vs 0
Anaphylactic Reaction	not reported	not reported	1 (0.4%) vs 0
Subdural Haematoma	not reported	not reported	2 (0.8%) vs 0
Cerebral infarction	not reported	1 (2%) vs 0	not reported
Cerebral haemorrhage	not reported	not reported	1 (0.4%) vs 0
Convulsion	not reported	0 vs 1 (7%)	not reported
Partial seizures	not reported	not reported	2 (0.8%) vs 0
Dementia Alzheimer's progression	not reported	1 (2%) vs 0	not reported
Delirium	not reported	1 (2%) vs 0	not reported
Agitation	not reported	not reported	1 (0.4%) vs 2 (1.6%)

Confusional state	not reported	not reported	2 (0.8%) vs 0
Aggression	not reported	0 vs 1 (7%)	not reported
Knee arthroplasty	not reported	0 vs 1 (7%)	1 vs 0
Spinal laminectomy	not reported	1 (2%) vs: 0	not reported
Cataract	1 (8.3%) vs 0	not reported	not reported
Patella fracture	0 vs 1 (25.0%)	not reported	not reported
Radius fracture	0 vs 1 (25.0%)	not reported	not reported
Pneumonia	0 vs 1 (25.0%)	not reported	1 (0.4%) vs 1 (0.8%)
Description of most frequent AEs (above 5%)	**n (%)**	**n (%)**	**n (%)**
Eye disorders	2 (16.7%) vs 0	not reported	2 (0.8%) vs 0
Microbleeds / Cerebral Microhaemorrhage	not reported	6 (14%) vs 0	9 (3.4%) vs 4 (3.3%)
Dizziness	not reported	0 vs 1 (7%)	29 (11.1%) vs 12 (9.9%)
Paresthesia	not reported	0 vs 1 (7%)	not reported
Hypoaesthesia	not reported	2 (5%) vs 0	not reported
Increased CSF white-blood-cell count	not reported	0 vs 1 (7%)	not reported
Atrial fibrillation	not reported	0 vs 1 (7%)	2 (0.8%) vs 2 (1.6%)
Agitation	not reported	0 vs 1 (7%)	19 (7.3%) vs 10 (8.3%)
Bradycardia	not reported	not reported	5 (1.9%) vs 8 (6.6%)
Diarrhoea	not reported	not reported	37 (14.1%) vs 15 (12.4%)
Nausea	not reported	not reported	27 (10.3%) vs 10 (8.3%)
Vomiting	1 (8.3%) vs 0	not reported	28 (10.7%) vs 5 (4.1%)
Chills	not reported	not reported	25 (9.5%) vs 3 (2.5%9
Fatigue	not reported	not reported	23 (8.8%) vs 12 (9.9%
Infections and infestations	3 (25.0%) vs 2 (50.0%)	not reported	86 (32.8) vs 57 (47.1%)
Infusion site extravasation / swelling	2 (16.7%) vs 0	not reported	38 (14.5) vs 21 (17.4%)
Erythema	2 (16.7%) vs 0	not reported	not reported
Oedema peripheral	1 (8.3%) vs 0	not reported	12 (4.6%) vs 6 (5%)
Pyrexia	not reported	not reported	14 (5.3%) vs 4 (3.3%)
Nasopharyngitis	2 (16.7%) vs 1 (25.0%)	not reported	16 (6.1%) vs 9 (7.4%)
Upper Respiratory Tract Infection	not reported	not reported	16 (6.1%) vs 10 (8.3%)
Urinary Tract Infection	not reported	not reported	20 (7.6%) vs 15 (1..4%)
Contusion	not reported	not reported	22 (8.4%) vs 10 (8.3%)

Fall	not reported	not reported	30 (11.5%) vs 23 (19%)
Laceration	not reported	not reported	12 (4.6%) vs 9 (7.4%)
Blood pressure increased	not reported	not reported	31 (11.8%) vs 9 (7.4%)
Arthralgia	not reported	not reported	19 (7.3%) vs 4 (3.3%)
Back pain	not reported	not reported	23 (8.8%) vs 8 (6.6%)
Headache	not reported	not reported	63 (24%) vs 22 (18.2%)
Tremor	not reported	not reported	13 (5%) vs 5 (4.1%)
Anxiety	not reported	not reported	23 (8.8%) vs 10 (8.3%)
Confusional state	not reported	not reported	18 (6.9%) vs 4 (3.3%)
Depression	not reported	not reported	30 (11.5%) vs 19 (15.7%)
Cough	not reported	not reported	21 (8%) vs 13 (10.7%)
Epistaxis	not reported	not reported	15 (5.7%) vs 3 (2.5%)
Rash	1 (8.3%) vs 0	not reported	40 (15.3%) vs 6 (5%)
Hypertension	not reported	not reported	32 (12.2%) vs 11 (9.1%)
Hypotension	not reported	1 (2%) vs 1 (7%)	9 (3.4%) vs 7 (5.8%)
Description of AEs leading to discontinuation of treatment		**n (%)**	**n (%)**
Ischaemic stroke	not reported	1 (2%) vs 0	not reported
Microbleeds on MRI scan without symptoms	not reported	1 (2%) vs 0	not reported
Not reported	-	1 (2%) vs 0	19 (7.3%) vs 7 (5.8%)

The overall quality of evidence, assessed according to the GRADE approach, is *very low.*

Table 6. Evidence profile table on adverse events assessed with the GRADE approach (for Arai 2014, Dodel 2013, NCT00818662).

Adverse events								
Frequency of adverse events	**2/74**	**RCT** Arai 2014 Dodel 2013	High[1,2] -1	Direct	Limitations for inconsistency - 1	Limitations (CI NA) - 1	Limitations - 1 Small sample size, with small samples in intervention group and very small control group; short duration of treatment 1 RCT: Industry funded and COI; Evidence of publication bias	Very low
Frequency of serious adverse events	3/457	**RCT** Arai 2014 Dodel 2013, NCT00818662	High[1,2] -1	Direct	Inconsistencies - 1	Limitations (CI NA) - 1	Limitations -1 Industry funded and COI; small sample size, with small samples in intervention group and very small control group; short duration of treatment Evidence of publication bias	Very low

[1] Risk of bias at study level high.

[2] High risk of bias at outcome level.

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Active comparator trials

None were published or had visible results in publicly available registers.

Studies without comparator

Data from two interventional prospective non-controlled studies { Dodel 2004, Relkin 2009} were available for analysis.

{Dodel 2004}: Despite the fact that authors wrote that no SAE occurred during the study, one patient was admitted to the hospital 2 weeks after IVIG due to confusion that resolved within few days. Headaches was reported in 3 patients, duration less than one day, without any further neurological signs. One patient experienced tooth infection, but according the authors, this AE was not related to the treatment. Authors concluded that IVIG was well tolerated in these 5 patients.

{Relkin 2009}: No SAEs occurred during the study period; five AEs which were judged to be treatment related include one episode each of headache, chills, diaphoresis, fever and transient confusion (symptoms resolved spontaneously without sequelae). Authors stated that there were no AEs incurred during this study that have not been previously reported in association with IVIG therapy in other patient populations.

Table 7. Summary of adverse events (AEs) in two interventional prospective non-controlled studies in patients with mild-to-moderate AD (Dodel 2004, Relkin 2009).

Study (N pts)	Any AE, n	Treatment related AEs, n	Serious AEs, n	AEs leading to discontinuation, n
Dodel 2004 (N = 5)	5	4	1	0
Relkin 2009 (N = 8)	Not reported	5	0	0

AEs=Adverse events

Importance: Critical

Transferability: Completely

Result card for SAF2: "Do the incidence and severity of adverse events of IVIG change with different dosing and administration schemes when used in patients with Mild Cognitive Impairment or Alzheimer’s disease?"

View full card

SAF2: Do the incidence and severity of adverse events of IVIG change with different dosing and administration schemes when used in patients with Mild Cognitive Impairment or Alzheimer’s disease?

Method

The same methodology was used as described in section for the whole domain.

Result

MCI

No trials on patients with MCI were retrieved.

AD

Data from three RCTs (1 multiple dose study, Arai 2014, 1 phase 2 dose-finding study, Dodel 2013, and 1 phase 3 study, NCT00818662} and one interventional prospective non-controlled study {Relkin 2009} were available for analysis. The multiple dose RCT {Arai 2014} applied 2 different administration schemes for IVIG: 0.2 g/kg and 0.4 g/kg every 2 weeks. The authors stated that they did not record any adverse event due to dose effect. The phase 2 dose-finding RCT {Dodel 2013} applied 6 different administration schemes for IVIG: 0.2 g/kg, 0.5 g/kg, 0.8 g/kg every 4 weeks, and 0.1 g/kg, 0.25 g/kg, 0.4 g/kg every 2 weeks. The authors stated that they did not record any adverse event due to dose effect. The phase 3 RCT

{NCT00818662} applied 2 different administration schemes for IVIG: 200 mg/kg and 400 mg/kg, every 2 weeks. No data on possible adverse event due to dose effect were reported. The study by {Relkin 2009}, including 8 patients, applied four different administration schemes for IVIg: 0.4 g/kg/2 weeks, 0.4 g/kg/week, 1 g/kg/2 weeks and 2 g/kg/4 weeks for 6 months of treatment. Then IVIG was discontinued during a 3-month washout period including months 7, 8, and 9. And finally all patients were treated with 1 g IVIg/kg every 2 weeks starting in month 10 through month 12 and then with 0.4 g/kg/2 weeks starting in month 13 through month 18. Authors did not report any adverse event due to dose effect.

Importance: Critical

Transferability: Completely

Result card for SAF3: "What are the incidence, severity and duration of adverse events when compared with placebo or with drugs approved (acetylcholinesterase inhibitors, memantine) for the treatment of Alzheimer's disease?"

View full card

SAF3: What are the incidence, severity and duration of adverse events when compared with placebo or with drugs approved (acetylcholinesterase inhibitors, memantine) for the treatment of Alzheimer's disease?

Method

The same methodology was used as described in section for the whole domain.

Result

MCI

No trials on patients with MCI were retrieved.

AD

Placebo-controlled trials

Data from three RCTs (1 multiple dose study {Arai 2014}, 1 phase 2, dose-finding study {Dodel 2013}, and 1 phase 3 study {NCT00818662}) were available for analysis (see Table 8).

Table 8. Characteristic and adverse events data on one RCT (IVIG versus placebo) {Dodel 2013}.

Authors, Year, Reference number	**Arai 2014**	**Dodel 2013**	**NCT00818662, data posted on clinicaltrial.gov in October 23rd 2014**
Register number	Not reported	NCT00812565	**NCT00818662**
Design of the study	RCT placebo-controlled, multiple dose	RCT phase 2, placebo-controlled, dose-finding	RCT phase 3, placebo controlled
Disease severity	Mild-to-moderate	Mild-to-moderate	Mild-to-moderate
Intervention (N pts)	IVIG (two doses, N = 12)	IVIG (different doses, N = 42)	IVIG (two doses, N = 262)
Control (N pts)	Placebo (0.25% human albumin) (N =4)	Placebo (N =14)	Placebo (N = 121)
Duration (weeks)	26	24	70
Adverse events data			
Any AE, n (%)	10 (83.3) vs 4 (100), p not reported	25 (60.0) vs 9 (64.0), p=0.75	Not reported
Treatment related AEs, n (%)	1 (8.3) vs 0, p not reported	Non reported	Not reported
AEs leading to discontinuation, n (%)	1 (8.3) vs 0, p not reported	3 (7.1) vs 0*, p not reported	19 (7.3) : 7 (5.8), p not reported
Serious AEs, n (%)	1 (8.3) vs 3 (75.0), p not reported	4 (10.0) vs 4 (29.0), p=0.07	53 (20.2) vs 26 (21.5), p not reported

*AEs leading to discontinuation in three patients assigned to intravenous immunoglobulin (according the register and publication, N=3 in intervention group; 2 on 0.4 g/kg Octagam 10% every 2 weeks; 1 0.8 g/kg Octagam 10% every 4 weeks);

Comparative statistical analysis was reported only by Dodel at al. {Dodel 2013}. The proportions of individuals with one or more adverse event in the placebo group (n=9; 64%) and treatment group (n=25; 60%) were not significantly different (p=0·75). Similarly, the groups did not differ significantly in the proportion of serious adverse events: 4 (29%) patients in placebo group, 4 (10%) patients in IVIg group; p=0·078.

Active comparator trials

None were identified.

Importance: Critical

Transferability: Completely

Result card for SAF4: "Do IVIG interfere with or are affected by other treatments used in patients with Mild Cognitive Impairment or in patients with Alzheimer’s disease?"

View full card

SAF4: Do IVIG interfere with or are affected by other treatments used in patients with Mild Cognitive Impairment or in patients with Alzheimer’s disease?

Method

The same methodology was used as described in section for the whole domain.

Result

MCI

No trials on patients with MCI were retrieved.

AD

No trials reporting data regarding the interaction between IVIG and other drugs were retrieved.

Importance: Important

Transferability: Completely

Safety risk management

Result card for SAF5: "Does the safety profile of IVIG vary according to mode of production or between different IVIG approved versions or products when used in patients with Mild Cognitive Impairment and Alzheimer’s disease?"

View full card

SAF5: Does the safety profile of IVIG vary according to mode of production or between different IVIG approved versions or products when used in patients with Mild Cognitive Impairment and Alzheimer’s disease?

Result

see TECH domain

Importance: Optional

Transferability: Not

Discussion

No conclusion can be drawn on the safety of IVIG for subjects with MCI and AD due to the poor - in term of quantity and quality – evidence presently available. The safety analysis was based on patients with mild-to-moderate AD {Arai 2014, Dodel 2004, Relkin 2009, Dodel 2013, NCT00818662} treated with different doses of IVIG. Any evidence is lacking for MCI and moderate-to-severe AD.

The few available data – three RCTs {Arai 2014, Dodel 2013, NCT00818662} and two prospective interventional uncontrolled studies {Dodel 2004, Relkin 2009} - confirm the short-term safety profile of IVIG known from other populations of patients {Silvergleid 2013, Singh 2006}. One of the trials (NCT00818662), previously tracked completed but not published, had final results posted by the study sponsor in October 23rd 2014. Inclusion of this study in the assessment was decided by Editorial Team. Authors and sponsor were previously contacted (May 2014) but they did not provide any data. No further contacts were sought.

IVIG was generally well tolerated and in three RCTs {Arai 2014, Dodel 2013, NCT00818662} overall rates of IVIG AEs were similar to those in the placebo group. The majority of AEs that occurs during IVIG treatment was not serious and seemed to be manageable. Higher SAEs rates were observed in placebo group, without statistically significant difference. However the confidence in safety estimates for overall evidence on all considered outcomes is *very low*, according to GRADE method, due to high risk of bias.

In Arai 2014, one patient on IVIG did not complete the study because of rash on the extremity and the trunk with mild elevations in aspartate amino transferase, alanine amino transferase, and lactose dehydrogenase. This small sample size study, with high risk of bias and short duration of treatment, included only 16 patients with control group who received 0.25% human albumin as placebo. Human albumin could induce AEs and SAE.

In Dodel 2013, three patients on IVIG did not complete the study because of AEs: ischaemic stroke (1 patient), microhaemorrhages on MRI scan without symptoms (1 patient), not reported (1 patient). No deaths occurred during the treatment. A SAE which was observed in one patient on IVIG, ischaemic stroke, is a known serious adverse event for IVIG treatment. Increased risk for thrombotic events is known in patients with history of venous or arterial thrombosis, advanced age, prolonged immobilization, multiple cardiovascular risk factors, coagulation disorders, estrogen use, indwelling central vascular catheters, and possible or confirmed hyperviscosity {Micromedex Drugdex database, 2014}. Moreover cerebral microhaemorrhages at MRI (without clinical symptoms) were observed in six patients in IVIG arms versus none in placebo arms; one patient did not complete the study for this reason. The clinical significance of these findings is not clear, and the link to IVIG administration cannot be excluded.

In NCT00818662, four patients in the IVIG group died and reasons were not reported whilst no deaths occurred in placebo group.

In another prospective non-controlled study, one patient was admitted to the hospital two weeks following IVIG due to confusion, that resolved within few days {Dodel 2004}.

Due to the small samples, the possibility of other unexpected and SAEs, specific for the target population of interest, cannot be excluded.

We have documented the missing publication of another RCT {NCT00299988}, and of other six interventional non-controlled studies. All these studies included subjects with mild-to-moderate AD.

Other two ongoing RCTs have been recorded: one phase 2, dose-finding, including 50 subjects with MCI {NCT01300728}, and one phase 2/3, including 350 subjects with mild-to-moderate AD {NCT01561053}. Trials are reported to or expected to end in November 2014 and December 2016, respectively.

Included studies were conducted in hospitals, research centres and private clinics of Japan, Germany and USA. The tested therapeutic schemes and the duration of treatment are very different. The IVIGs used in included studies were *Gammagard* by Baxter Healthcare Corporation {NCT00818662} and *Octagam* by Octapharma AG {Dodel 2013}. The study by Arai et al. {Arai 2014} does not specify the label of the IVIG treatment. The ongoing RCTs are testing *Flebogamma* by Grifols S.A. and *NewGam* by Sutter Health. The latter study tests IVIG (high dose or low dose) together with plasmapheresis against plasmapheresis alone or against infusion of 20% albumin.

Implications for practice

At present there is limited evidence on safety of IVIG in adults with mild-to-moderate AD, and no evidence for adults with MCI and moderate-to-severe AD.

Implications for research

Publication bias was identified in the evidence base of subjects with mild-to-moderate AD. Two RCTs have been recently completed but not published {NCT00299988, NCT00818662}. One of them had its results recently posted on a clinical trial register {NCT00818662}; these data were included the present review. Another RCT including 350 patients will be ended within the next two years {NCT01561053}. Future access to these data might provide valuable evidence to assess safety of IVIG for these patients. No further trials would be advised before publication of these studies.

One small study on subjects with MCI {NCT01300728} is awaiting completion. It would produce only preliminary short term data. Other studies – if suitable – will have to be devised to assess safety in the long term.

The category of moderate-to-severe AD is not considered for future study, probably because the rationale of IVIG for advanced AD is weak or absent.

References

Arai H, Ichimiya Y, Shibata N, Nakajima T, Sudoh S, Tokuda T, Sujaku T, Yokokawa S, Hoshii N, Noguchi H, Bille A. Safety and tolerability of immune globulin intravenous (human), 10% solution in Japanese subjects with mild to moderate Alzheimer's disease. Psychogeriatrics 2014;14:165-74.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.

Dodel R, Hampel H, Depboylu C, Lin S, Gao F, Schock S, Jäckel S, Wei X, Buerger K, Höft C, Hemmer B, Möller HJ, Farlow M, Oertel WH, Sommer N, Du Y. Human antibodies against amyloid beta peptide: a potential treatment for Alzheimer's disease. Ann Neurol 2002;52:253-6.

Dodel R, Rominger A, Bartenstein P, Barkhof F, Blennow K, Förster S, Winter Y, Bach JP, Popp J, Alferink J, Wiltfang J, Buerger K, Otto M, Antuono P, Jacoby M, Richter R, Stevens J, Melamed I, Goldstein J, Haag S, Wietek S, Farlow M, Jessen F. Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial. Lancet Neurol 2013;12:233-43.

EUnetHTA Joint Action WP5. HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals. 1 March 2013 – V3.0. Available at http://www.eunethta.eu/outputs/new-application-hta-core-model-hta-core-model-rapid-relative-effectiveness-assessment-pharma; last access February 19th 2014.

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011a; 64:383-94.

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol 2011b; 64:407-15

Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011c; 64:1277-82.

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, Devereaux PJ, Montori VM, Freyschuss B, Vist G, Jaeschke R, Williams JW Jr, Murad MH, Sinclair D, Falck-Ytter Y, Meerpohl J, Whittington C, Thorlund K, Andrews J, Schünemann HJ. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol 2011d; 64:1283-93.

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011e; 64:1294-302.

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011f; 64: 1303-10.

Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, Atkins D, Kunz R, Brozek J, Montori V, Jaeschke R, Rind D, Dahm P, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Murad MH, Schünemann HJ; GRADE Working Group. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011g; 64:1311-6

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou P, Christensen R, Schünemann HJ. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013; 66:158-72.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Chapter 5: Defining the review question and developing criteria for including studies; last access February 19th 2014.

Micromedex Drugdex Database, 2014.

National Institute on Aging. AD - Unraveling the Mystery. U.S. Department of Health and Human Services NIH Publication Number: 08-3782; September 2011; available from www.nia.nih.gov/alzheimers, last access 29th January 2014.

National Institute for Health and Clinical Excellence (NICE). NICE technology appraisal guidance 217 Donepezil, galantamine, rivastigmine and memantine for the treatment of AD (review of NICE technology appraisal guidance 111). 2011; available from www.nice.org.uk/guidance/TA217, accessed 2014 Jan 30th.

NCT00299988. Available at http://prsinfo.clinicaltrial.gov/ct2/show/NCT00299988?term=NCT00299988&rank=1; last access December 16th 2014.

NCT00818662. Available at http://prsinfo.clinicaltrial.gov/ct2/show/record/NCT00818662?term=NCT00818662&rank=1; last access December 16th 2014.

NCT01300728. Available http://prsinfo.clinicaltrial.gov/ct2/show/NCT01300728?term=NCT01300728&rank=1, last access December 16th 2014.

NCT01524887. Available at http://prsinfo.clinicaltrial.gov/ct2/results?term=NCT01524887&Search=Search, last access December 16th 2014.

NCT01561053. Available at http://prsinfo.clinicaltrial.gov/ct2/show/NCT01561053?term=NCT01561053&rank=1, last access December 16th 2014.

NCT01736579. Available at http://prsinfo.clinicaltrial.gov/ct2/results?term=NCT01736579&Search=Search, last access December 16th 2014.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. MCI: clinical characterization and outcome. Arch Neurol 1999;56:303-8.

Relkin NR, Szabo P, Adamiak B, Burgut T, Monthe C, Lent RW, Younkin S, Younkin L, Schiff R, Weksler ME. 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiol Aging 2009;30:1728-36.

Singh-Grewal D, Kemp A, Wong M. A prospective study of the immediate and delayed adverse events following intravenous immunoglobulin infusions. Arch Dis Child 2006; 91:651-4.

Silvergleid AJ, Berger M. Intravenous immune globulin: Adverse effects. 2013 UpToDate®; available from www.uptodate.com, last access 9th October 2013.

Appendices

Appendix 1

Figure A1. Flow charts of study selection for the “safety domain”.

Appendix 2

Included studies

Table A2.1: Characteristics of included studies (see Appendix 5 for more details)

Reference	Study design	Participants	Intervention (duration)	Control	SAF issues	SAF outcome measure	Funding
Arai 2014	multiple dose, placebo controlled, RCT	16 patients (12 experimental group; 4 control group) with mild-to-moderate Alzheimer Disease	one of two doses of intravenous immunoglobulin (0·2 g/kg, 0·4 g/kg) every 2 weeks (12 weeks)	placebo (50-mL 0.25% human albumin solution) every 2 weeks	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Not reported
					Patient safety C0002	Frequency of immediate and delayed adverse events for different dosing and administration schemes	
					Patient safety C0008	Frequency, severity and duration of immediate and delayed adverse events of IVIG and comparators	
Dodel 2004	Interventional prospective non-controlled study	5 patients with Alzheimer Disease (4 mild-to-moderate; 1 moderate-to-severe)	IVIG (OctagamH) 0.4 g/kg on three consecutive days every 4 weeks (6 months)	None	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Public Octapharma (Lagenfeld, Germany) provided IVIG
Dodel 2013	phase 2, dose-finding; placebo controlled, RCT	58 patients (42 experimental group; 14 control group) with mild-to-moderate Alzheimer Disease	one of three doses of intravenous immunoglobulin (0·2 g/kg, 0·5 g/kg, or 0·8 g/kg) every 4 weeks, or half of that dose (0·1 g/kg, 0·25 g/kg, or 0·4 g/kg) every 2 weeks (24 weeks)	placebo (0·9% isotonic sodium chloride) every 4 weeks or every 2 weeks	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Octapharma AG
					Patient safety C0002	Frequency of immediate and delayed adverse events for different dosing and administration schemes	
					Patient safety C0008	Frequency, severity and duration of immediate and delayed adverse events of IVIG and comparators	
NCT00818662 (update on clinicaltrial.gov: October 23th 2014)	phase 3 RCT	383 patients with mild-to-moderate AD (262 experimental group; 121 control group)	IVIG (Gammagard Liquid) 200 mg or 400 mg/kg every 2 weeks (70 weeks)	Placebo: Human Albumin 0.25% 4 mL/kg or 2 mL/kg; every 2weeks (70 weeks)	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Baxter Healthcare Corporation
					Patient safety C0002	Frequency of immediate and delayed adverse events for different dosing and administration schemes	
					Patient safety C0008	Frequency, severity and duration of immediate and delayed adverse events of IVIG and comparators	

Relkin 2009	Prospective interventional dose finding study	8 patients with mild-to-moderate Alzheimer Disease	one of four IVIg (Gammagard S/D) doses (0.4 g/kg/2 weeks, 0.4 g/kg/week, 1 g/kg/2 weeks and 2 g/kg/4 weeks) (6 months + 9 months)	None	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Public and Baxter Bioscience Corporation
					Patient safety C0002	Frequency of immediate and delayed adverse events for different dosing and administration schemes	

Appendix 3

Excluded studies

Table A3.1: Characteristics of unpublished studies, randomized controlled studies (see Appendix 5 for more details).

Reference	Last update	Study design	Participants	Intervention (duration)	Control	SAF issues	SAF outcome measure	Funding
NCT00299988	2010	phase 2 RCT	24 patients with mild-to-moderate Alzheimer Disease	one of four doses of IVIg (from 0·2 g/kg every 2 weeks to 0·8 g/kg every month) (6 months)	Placebo	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Public, Baxter BioScience
						Patient safety C0002	Frequency of immediate and delayed adverse events for different dosing and administration schemes	
						Patient safety C0008	Frequency, severity and duration of immediate and delayed adverse events of IVIG and comparators	

Table A3.2: Characteristics of unpublished studies, other designs (see Appendix 5 for more details).

Reference	Last update	Study design	Participants	Intervention (duration)	Control	SAF issues	SAF outcome measure	Funding
Kountouris 2000	2000	Open label, non-randomized controlled tria	16 patients with Alzheimer Disease	IVIg (Octagam) 0,2 g/Kg + piracetam (12 months)	Piracetam	None	None	Not reported
Papatriantafyllou 2006	2006	Uncontrolled longitudinal study	6 patients with mild-to-moderate Alzheimer Disease	total dose of 0.4g/Kg IVIG in three consecutive days every 4 weeks (6 months)	None	None	None	Not reported
Hara 2011	2011	Uncontrolled longitudinal study	10 patients with Alzheimer Disease	IVIG (5.5-62.3 months)	None	None	None	Not reported
Kondo 2011	2011	Uncontrolled longitudinal study	4 patients with Alzheimer Disease	0.4 g/kg of IVIg for 3 consecutive days every month for 3 months	None	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Not reported
Rovira 2011	2011	Open label pilot uncontrolled longitudinal study	4 patients with mild-to-moderate Alzheimer Disease	0.5 g/kg of IVIG (Flebogamma DIF, Grifols) every 2 weeks (6 months)	None	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Not reported
Relkin 2012 (open extension of NCT00299988)	2012	12 month open label extension of a Phase II, double blind placebo controlled study	16 patients with mild-to-moderate Alzheimer Disease	IVIg (Gammagard, Baxter) 0.4g/kg/2 weeks (36 months)	None	None	None	Not reported

Table A3.3: Characteristics of terminated studies (see Appendix 5 for more details).

Reference	Last update	Study design	Participants	Intervention (duration)	Control	Funding

NCT01524887	2013 The study was terminated without enrol any patient because the first Phase 3 did not demonstrate efficacy on the co-primary endpoints	phase 3 RCT	patients with mild-to-moderate AD	Experimental: IVIG, 10% at Dose A (high dose) or Dose B (low dose) (18 months)	Placebo	Baxter Healthcare Corporation
NCT01736579	2013 The study was terminated after enrolment of 8 patients because the first Phase 3 did not demonstrate efficacy on the co-primary endpoints	open label extension previous study (NCT00818662)	patients with mild-to-moderate AD	IVIG (Gammagard Liquid) 200 mg or 400 mg/kg every 2 weeks (3 years)	None	Baxter Healthcare Corporation

Table A3.4: Characteristics of ongoing studies.

Reference	Study design	Participants	Intervention (duration)	Control	SAF issues	SAF outcome measure	Funding
NCT01300728 (estimated completion November 2014)	phase 2 RCT	50 patients with MCI	IVIG (NewGam) at 0.4 g/kg every 14 days for a total of five infusions (two months)	Placebo	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Sutter Health
					Patient safety C0008	Frequency, severity and duration of immediate and delayed adverse events of IVIG and comparators	
NCT01561053 (estimated completion December 2016)	phase 2/3 RCT	350 patients with mild-to-moderate Alzheimer Disease	Plasmapheresis alone or with infusion of 20% albumin and IVIG high dose or low dose (14 months)	Sham procedure	Patient safety C0001	Frequency of immediate and delayed serious and non-serious adverse events	Instituto Grifols, S.A.
					Patient safety C0002	Frequency of immediate and delayed adverse events for different dosing and administration schemes	
					Patient safety C0008	Frequency, severity and duration of immediate and delayed adverse events of IVIG and comparators	

Appendix 4

State of development of research on safety of IVIG

To describe the stage of development of current and future research on safety on IVIG for MCI and AD we tabled the studies against the evidence profile.

Available evidence

Comparative data about immediate and delayed adverse events of IVIG are available on patients with mild-to-moderate AD from one phase 1 RCT (16 patients), one phase 2 RCT (58 patients) and one phase 3 RCT (383 patients). The remaining two prospective interventional non-controlled studies on a total of 13 patients add very little information.

Upcoming evidence

Three RCTs will be able to add comparative data about immediate and delayed adverse events of IVIg – according to different dosing and administration schemes – for few hundreds of patients. The remaining prospective interventional non-controlled studies will add very little information.

Table A4.1: Stage of development of research on safety on IVIG for MCI and AD.

IVIg for MCI and AD			
Issue	**Outcome measure**	**Available evidence**	**Upcoming evidence**
Patient safety [C0001]	Frequency of immediate and delayed serious and non-serious adverse events at any time	3 interventional prospective non-controlled studies: Dodel 2004, Relkin 2009 (13 pts) 3 RCTs: Arai 2014 (16 pts), Dodel 2013 (58 pts) , NCT00818662 (383 pts)	3 interventional prospective non-controlled studies: Kondo 2011, Rovira 2011, Relkin 2012 (24 pts) 3 RCTs: NCT00299988 (24 pts), , NCT01300728 (50 pts), NCT01561053 (350 pts)
Patient safety [C0002]	Frequency of immediate and delayed adverse events for different dosing and administration schemes at any time	1 before-and-after study: Relkin 2009 (8 pts) 3 RCTs: Arai 2014 (16 pts), Dodel 2013 (58 pts); NCT00818662 (383 pts)	2 RCTs: NCT00299988 (24 pts), NCT01561053 (350 pts)
Patient safety [C008]	Frequency, severity and duration of immediate and delayed adverse events of IVIg and comparators at any time	3 RCTs: Arai 2014 (16 pts), Dodel 2013 (58 pts); NCT00818662 (383 pts)	3 RCTs: NCT00299988 (24 pts), NCT01300728 (50 pts), NCT01561053 (350 pts)

Patient safety [C0007]	Presence/absence of interference between drugs at any time	None	-

Appendix 5

Characteristics of included studies

Randomized controlled trials

Study title: NCT00818662
Study characteristics
Study design: 'A Randomized, Double-Blind, Placebo-Controlled, Two Dose Arm, Parallel Study of the Safety and Effectiveness of Immune Globulin Intravenous (Human), 10% (IGIV, 10%) for the Treatment of Mild-to-Moderate Alzheimer´s Disease'
Study Registration number: NCT00818662 (Last access December 5, 2014), study ID 160701
Country: USA & Canada
Centre: Multicentre, 44 locations
Ethics Committee Approval: health authorities in the above countries
Sponsor: Baxter Healthcare Corporation
Study period (study start, study end): December 2008 to December 2012

Patient characteristics
Patients with mild-to-moderate Alzheimer's disease Age of patients 50 to 89 Sex: Both sexes (M/F unclear) Disease severity: mild-to-moderate (as stated in the title, see above), and 'as determined by a Mini Mental State Examination (MMSE) score of 16 - 26 inclusive' (inclusion criterion) AD therapy (cholinesterase inhibitor; memantine): ' On stable doses of FDA approved AD medication(s) for at least 3 months prior to screening. These medications must be continued throughout this study.' (inclusion criterion)

Intervention
IVIG (Gammagard Liquid) 200 mg or 400 mg/kg every 2 weeks (70 weeks)

Control
Placebo: Human Albumin 0.25% 4 mL/kg; solution infused at 4 mL/kg/2weeks or 2 mL/kg solution infused at 2 mL/kg/2weeks (70 weeks)

Outcomes
Cognitive functions measured by ADAS-Cog Activities of daily living measured by ADCS-ADL

Flow of patients
No of patients enrolled: 702 participants enrolled; 308 were screen failures; 4 were discontinued before randomization; and 7 were withdrawn after randomization, but prior to receiving investigational product. Therefore 383 participants were randomized, 262 assigned to intervention group (127 to 400 mg/kg regimen; 135 to 200 mg/kg regimen), 121 to placebo (58 to 4 mL/kg regimen; 63 to 2 mL/kg regimen); 302 completed the study: 206 assigned to intervention group (104 to 400 mg/kg regimen; 102 to 200 mg/kg regimen), 96 to placebo (49 to 4 mL/kg regimen; 47 to 2 mL/kg regimen).
Number of analysed patients: 302 available for effectiveness data, 383 for safety data;. Results unpuplished and posted in clinicaltrial.gov record.

Author Disclosure (Conflict of interest): Not applicable

Study title: Arai 2014
Study characteristics
Study design: multiple dose, randomised, placebo-controlled trial
Study Registration number: not reported
Country: Japan
Centre: 5 research centres in Japan
Ethics Committee Approval: Not reported (Quote „This study was conducted in accordance with the applicable laws and regulations, including but not limited to the International Conference on Harmonization Guidelines for Good Clinical Practice, the ethical principles that have their origins in the Declaration of Helsinki, and Japan Good Clinical Practice. The institutional review board of each organization reviewed and approved the protocol and the informed consent form before any of the patients were enrolled.“
Sponsor: Not reported.
Study period (study start, study end): Not reported

Patient characteristics
Patients with mild-to-moderate Alzheimer’s disease Age of patients: Intervention groups 72.9 (9.2) years, placebo group 71.5 (11.3) years Sex: Intervention groups 9F/3M, Placebo group 4F/0M Disease severity: MMS score of 16-26, modified Hachinski-Rosen score of less than 5 (as stated in inclusion criteria) AD therapy (cholinesterase inhibitor; memantine): Quote „Any therapy appropriate to the subject’s condition was permitted during the study. Concomitant medications with the potential to affect cognition, other than cholinesterase inhibitors and/or memantine, were to be maintained on a stable dose regimen for 30 days prior to the baseline evaluations. This included injectable medications such as anxiolytics, sedatives, hypnotics, antipsychotics, antidepressants, over-thecounter sleeping aids, anti-allergy medications, thyroid supplements, and vitamin B12 supplements. The use of cholinesterase inhibitors for the symptomatic treatment of AD was allowed when the following conditions were met: (i) the subject’s dose regimen had been stable for 120 days prior to baseline; (ii) the subject was free of significant side effects attributable to such drugs; and (iii) the subject and caregiver agreed that, barring unforeseen circumstances, they would continue the advised regimen for the duration of the trial. In contrast, subjects who discontinued the use of cholinesterase inhibitors and/or memantine within 60 days of baseline were excluded from the trial“. The use of these drugs was not specified.

Intervention
One of two doses of intravenous immunoglobulin (0·2 g/kg, 0·4 g/kg) every 2 weeks (12 weeks)

Control
placebo (50-mL 0.25% human albumin solution (25% human albumin in a sterile nonpyrogenic formation for intravenous injection, mixed with sterile physiological saline (1:99)) every 2 weeks

Outcomes
safety and tolerability including adverse events (AE), vital signs, physical and neurological examinations, 12-lead electrocardiogram, clinical laboratory evaluations, and brain MRI scans Other: MMSE

Flow of patients
No of patients enrolled: assessed for eligibility not reported, 16 randomised, all treated, 12 assigned to intervention groups, 4 to placebo
Number of analysed patients 12 per protocol/12 ITT analysis in the intervention group, 4 per protocol/4 ITT analysis in the placebo group.

Author Disclosure (Conflict of interest) Yes, p. 165 (Quote “All authors declare that they have no conflicts of interest associated with this manuscript).

Study title: Dodel 2013

Study characteristics
Study design: Phase 2, dose finding, block randomised, placebo-controlled trial
Study Registration number: ClinicalTrials.gov (NCT00812565) and controlled-trials.com (ISRCTN64846759)
Country: USA & Germany
Centre: Hospitals, research centres and private clinics, 5 in Germany, seven in the USA
Ethics Committee Approval: Yes, by each site's ethics comitteee and the regulatory authorities (FDA and Paul-Ehrlich Institute)
Sponsor: Octapharma AG.
Study period (study start, study end): February 2009 to March, 2010

Patient characteristics
Patients with mild-to-moderate Alzheimer's disease
Age of patients: Intervention group 69.4(7.3) years, placebo group 72.0(10.2) years
Sex: Intervention group 15F/26M, Placebo group 9F/5M
Disease severity: MMS score of 16-26, modified Hachinski-Rosen score of less than 5 (as stated in inclusion criteria)
AD therapy (cholinesterase inhibitor; memantine): 'Patients had to have been taking a stable dose of an approved Alzheimer's disease drug for at least 3 monthsbefore screening; use reported in Table 1: intervention group 36(88%), Placebo group 11(79%)

Intervention
One of three doses of intravenous immunoglobulin (0·2 g/kg, 0·5 g/kg, or 0·8 g/kg) every 4 weeks, or half of that dose (0·1 g/kg, 0·25 g/kg, or 0·4 g/kg) every 2 weeks (24 weeks)

Control
placebo (0·9% isotonic sodium chloride) every 4 weeks or every 2 weeks

Outcomes
Cognitive functions measured by ADAS-Cog, CDR-GS
Other: MMSE
Activities of daily living measured by ADCS-ADL
Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)
Variation of imaging signs (change in ventricular volumetric as measured by MRI)

Flow of patients
No of patients enrolled: 89 assessed for eligibility, 58 randomised, 2 not treated, 42 assigned to intervention group, 14 to placebo
Number of analysed patients 36 per protocol/41 ITT analysis in the intervention group, 9 per protocol/14 ITT analysis in the placebo group.

Author Disclosure (Conflict of interest) Yes, p. 242-243

Other designs (interventional prospective non-controlled studies study)

Study title: Dodel 2004
Study characteristics
Study design Pilot interventional prospective non-controlled study

Study Registration number: Not reported in the paper
Country: Germany
Centre: Unclear; ' Six individuals were recruited from specialised outpatient clinics for cognitive disorders'
Ethics Committee Approval: Yes, ' by the local ethical committee of the Philipps-University, Marburg'
Sponsor: 'supported in part by the Alzheimer Forschungsinitiative (grant: 00806), Germany'; ' Octapharma (Lagenfeld, Germany) provided the intravenous immunoglobulins and Eli Lilly and Company (Indianapolis, USA) provided the Ab antibodies for this study.'
Study period (study start, study end): Not reported in the paper

Patient characteristics
Patient's with Alzheimer's disease (4 mild-to-moderate; 1 moderate-to-severe)
Age of patients: 55-64 years
Sex: 3M/2F
Disease severity: Unclear
AD therapy (cholinesterase inhibitor; memantine): 4 participants on Donepezil 10mg, 1 on Rivastigmine 12mg

Intervention
IVIG (OctagamH) 0.4 g/kg on three consecutive days every 4 weeks (6 months)

Control
none

Outcomes
Cognitive functions measured by ADAS-Cog
Other: MMSE, CERAD neuropsychological test battery
Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)

Flow of patients
No of patients enrolled: 6
Number of analysed patients:5, 1 refused to get a lumbar puncture at the end of study

Author Disclosure (Conflict of interest): Not clearly stated

Study title Relkin 2009
Study characteristics
Study design: Prospective interventional non-controlled 6 months IVIg dose ranging study, followed by a 3 months washout period, and then extension of 9 months of IVIg
Study Registration number: Not reported in the paper
Country: USA
Centre: Unclear (see below)
Ethics Committee Approval: Yes, ' by the Weill Cornell Institutional Review Board (IRB) and the Scientific Advisory Committee of the Weill Cornell General Clinical Research Center (GCRC)'

Sponsor: 'in part, by the General Clinical Research Center at the Weill Medical College of Cornell University, NIH/NCRR Grant M01 RR00047. Additional financial supportwas provided by Baxter Bioscience Corporation, by NIH grant AG-021033, and the Stern Family Fund (MW) as well as the gifts from the Hoyt, Chen, and Koplow families (NR). IVIg for the study was also supplied by Baxter Bioscience Corporation.'
Study period (study start, study end): Not reported in paper

Patient characteristics
Patients with mild-to-moderate Alzheimer's disease
Age of patients: 67 to 86 years (mean 74.3)
Sex: 1M/7F
Disease severity: mild, 'MMSE scores ranged from 20 to 29 (mean 23.5)?
AD therapy (cholinesterase inhibitor; memantine): ' All subjects were receiving stable doses of a cholinesterase inhibitor and in some cases memantine for at least 3 months prior to enrolling in the study.'

Intervention
one of four IVIG (Gammagard S/D) doses (0.4 g/kg/2 weeks, 0.4 g/kg/week, 1 g/kg/2 weeks and 2 g/kg/4 weeks) (6 months + 9 months)

Control
none

Outcomes
Cognitive functions measured by MMSE
Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)

Flow of patients
No of patients enrolled: 8, 2 in each dose group
Number of analysed patients: 8, 2 in each dose group

Author Disclosure (Conflict of interest): Marc E.Weksler, Paul Szabo, and Norman R. Relkin have received grants for research from Baxter Bioscience Corporation.

Characteristics of excluded studies

Published studies

Study title: Devi 2008
Study characteristics
Study design Observational retrospective study
Study Registration number Not applicable
Country: USA
Centre: Not clearly reported, probably Lenox Hill Hospital, New York (see below)
Ethics Committee Approval: Yes, ' institutional review board of Lenox Hill Hospital in New York, New York'
Sponsor: 'This study did not have a sponsor.'
Study period (study start, study end): Not reported

Patient characteristics
Patients with Alzheimer's disease
Age of patients 74 ±7.5
Sex 5M/5F
Disease severity: Unclear
AD therapy (cholinesterase inhibitor; memantine): Not reported

Intervention
IVIG 0.4 g/kg every 2 weeks (3-6 months)

Control
none

Outcomes
Cognitive functions measured by WAIS, WMS, Boston

Flow of patients
No of patients enrolled. Not applicable
Number of analysed patients 18 recieved IVIgs, 10 analysed

Author Disclosure (Conflict of interest): 'The editor in chief has reviewed the conflict of interest checklist provided by the author and has determined that none of the authors have any financial or any other kind of personal conflicts with this letter.'

Unpublished studies.

Randomized controlled trials

Study title: NCT00299988 2010
Study characteristics
Study design: 'A Placebo-controlled, Randomized, Double-Blind Phase II Clinical Study of Gammagard Intravenous Immunoglobulin (IVIg) for Treatment of Mild to Moderate Alzheimer's Disease'
Study Registration number: NCT00299988 (Last access September 18, 2014), study ID 0512008265
Country: USA
Centre: Unclear
Ethics Committee Approval: United States Institutional Review Board
Sponsor: Weill Medical College of Cornell University, Baxter BioScience, National Institutes of Health (NIH)
Study period (study start, study end): February 2006 to April 2010

Patient characteristics
Patients wth mild-to-moderate Alzheimer's disease
Age of patients. 50 and older

Sex: Both

Disease severity: mild to moderate (as stated in the title, see above), and 'as determined by a Mini Mental State Examination (MMSE) score of 14 - 26 inclusive' (inclusion criterion)

AD therapy (cholinesterase inhibitor; memantine): 'On stable doses of approved AD medications for at least 3 months.' (inclusion criterion ,details not provided)

Intervention
one of four doses of IVIG Gammagard (from 0•2 g/kg every 2 weeks to 0•8 g/kg every month) (6 months)

Control
placebo

Outcomes
Cognitive functions measured by ADAS-Cog
Other: ADCS-CGIC
Activities of daily living measured by ADCS-ADL
Behavioural changes measured by Neuropsychiatric Inventory (NPI)
Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)
Variation of imaging signs (change in SUVR at PIB-PET)
Generic health related quality of life
Disease specific health related quality of life
Activities of daily living measured by ADCS-ADL
Behavioural changes measured by Neuropsychiatric Inventory (NPI)
Generic health related quality of life
Disease specific health related quality of life

Flow of patients
No of patients enrolled: Estimated enrollment 24
Number of analysed patients. Not applicable, press release and publication documented, but no results posted in clinical.gov record.

Author Disclosure (Conflict of interest): Not applicable

Other designs

Study title: Kountouris 2000
Study characteristics
Study design: Open label, non-randomized controlled trial
Study Registration number: Not reported
Country: Greece
Centre: Unclear, Diagnostic Neurological Center, Michalakopoulou 45, 11528 Athens Greece?
Ethics Committee Approval: Not reported
Sponsor: Not reported
Study period (study start, study end): Not reported

Patient characteristics

Patients with Alzheimer's disease Age of patients. Not reported Sex: Not reported Disease severity: 'at the initial faze of the disease' AD therapy (cholinesterase inhibitor; memantine): Not reported. ' Both groups received 140 g of peracetam for the 1 year,

Intervention
IVIgG (Octagam) 0,2 g/Kg + piracetam (12 months)

Control
Piracetam

Outcomes
Cognitive functions measured by MMSE

Flow of patients
No of patients enrolled: 16, 8 in each group
Number of analysed patients. Not spceifically reported

Author Disclosure (Conflict of interest): Unclear. Octagam von OCTA farma A.G. provided the treatment?

Study title: Papatriantafyllou 2006
Study characteristics
Study design: A pilot, uncontrolled longitudinal study
Study Registration number: Not reported
Country: Greece
Centre: Unclear, Memory Clinic, Neurology Department, General Hospital of Athens?
Ethics Committee Approval: Unclear
Sponsor: Unclear
Study period (study start, study end): Unclear

Patient characteristics
Patients with mild-to-moderate Alzheimer's disease Age of patients: 55–78 Sex: 3M/3F Disease severity: Mini Mental State Examination scores 14—24 AD therapy (cholinesterase inhibitor; memantine): ' The patients were allowed to keep their previous medication which was steady for the last six months.'

Intervention
total dose of 0.4g/Kg IVIG in three consecutive days every 4 weeks (6 months)

Control
none

Outcomes
Cognitive functions measured by MMSE

Flow of patients
No of patients enrolled: 6
Number of analysed patients: 5, reasons for withdrawal/drop-out not reported.

Author Disclosure (Conflict of interest): None, disclosed by all authors

Study title: Hara 2011
Study characteristics
Study design: Uncontrolled longitudinal study
Study Registration number: Not reported
Country: USA
Centre: Shankle Clinic, Newport Beach, California?
Ethics Committee Approval: Not reported
Sponsor: Not reported
Study period (study start, study end): Not reported

Patient characteristics
Patients with Alzheimer's disease
Age of patients: Not reported
Sex: Not reported
Disease severity: Not reported
AD therapy (cholinesterase inhibitor; memantine): ' All patients also received Exelon and Namenda at all times.'

Intervention
IVIG (5.5-62.3 months)

Control
none

Outcomes
Cognitive functions measured by Memory Performance Index, and the Functional Assessment Staging test

Flow of patients

No of patients enrolled: 17 Patients (10 Alzheimer's disease, 4 Lewy body disease and 3 mixed Alzheimer's disease)
Number of analysed patients.8/17 for cognitive, 16/17 for functional tests, 8/17 for FAST staging

Author Disclosure (Conflict of interest): Not reported

Study title: Kondo 2011
Study characteristics
Study design: Uncontrolled longitudinal study
Study Registration number: Not reported
Country: Japan
Centre: Unclear
Ethics Committee Approval: Not reported
Sponsor: Not reported
Study period (study start, study end): Not reported

Patient characteristics
Patient's with Alzheimer's disease Age of patients: Not reported Sex: Not reported Disease severity: Not reported AD therapy (cholinesterase inhibitor; memantine): Not reported

Intervention
0.4 g/kg of IVIg for 3 consecutive days every month for 3 months

Control
none

Outcomes
Cognitive functions measured by MMSE

Flow of patients
No of patients enrolled: 4
Number of analysed patients. 4, full data for 3, one withrew because of generalized seizure after the first session

Author Disclosure (Conflict of interest): Unclear

Study title: Rovira 2011
Study characteristics

Study design: Single centre, open label pilot uncontrolled longitudinal study
Study Registration number: Not reported
Country: Spain
Centre: Single, unclear
Ethics Committee Approval: Not reported
Sponsor: Not reported
Study period (study start, study end): Not reported

Patient characteristics
Patients with mild-to-moderate Alzheimer's disease Age of patients: Not reported Sex: Not reported Disease severity: Mild to moderate AD therapy (cholinesterase inhibitor; memantine): ' receiving stable donepezil treatment who previously had participated in a proof-of-concept study on plasmapheresis with 5% Human Albumin Grifols'

Intervention
0.5 g/kg of IVIg (Flebogamma DIF, Grifols) every 2 weeks (6 months)

Control
none

Outcomes
Cognitive functions measured by ADAS-Cog, CDR-GS, MMSE

Flow of patients
No of patients enrolled: 4
Number of analysed patients.4

Author Disclosure (Conflict of interest): Unclear

Study title: Relkin 2012 (open extension of NCT00299988)
Study characteristics
Study design: 12 month open label extension of a Phase II, double blind placebo controlled study
Study Registration number: original study NCT00299988
Country: USA
Centre: Unclear
Ethics Committee Approval: Institution Review Bord; 'an IRB-approved extension protocol'

Sponsor: Unclear
Study period (study start, study end): Beginning at post-enrollment month 18

Patient characteristics
Patients with mild-to-moderate Alzheimer's disease
Age of patients: supposedly as in NCT00299988; 50 and older
Sex: supposedly as in NCT00299988; Both
Disease severity: supposedly as in NCT00299988; mild to moderate (as stated in the title, see above), and 'as determined by a Mini Mental State Examination (MMSE) score of 14 - 26 inclusive' (inclusion criterion)
AD therapy (cholinesterase inhibitor; memantine): supposedly as in NCT00299988; 'On stable doses of approved AD medications for at least 3 months.' (inclusion criterion, details not provided)

Intervention
IVIG (Gammagard, Baxter) 0.4g/ kg/2 weeks (36 months)

Control
none

Outcomes
Cognitive functions measured by ADAS-Cog, ADCS-CGIC
Activities of daily living measured by ADCS-ADL
Behavioural changes measured by Neuropsychiatric Inventory (NPI)
Generic health related quality of life
Disease specific health related quality of life

Flow of patients
No of patients enrolled: 16, 5 in placebo group; 11 in intervention group
Number of analysed patients: 16? Unclear

Author Disclosure (Conflict of interest): Unclear

Terminated studies

Randomized controlled trials

Study title: NCT01524887 2013
Study characteristics
Study design: ' A Phase 3 Randomized, Double-blind, Placebo-Controlled Study of the Safety and Effectiveness of Immune Globulin Intravenous (Human), 10% Solution (IGIV, 10%) for the Treatment of Mild to Moderate Alzheimer's Disease'
Study Registration number: NCT01524887 (Last access September 18, 2014)
Country: USA, Australia, Belgium, Canada, Japan, Poland, Spain, United Kingdom
Centre: Multiple (70 in total)
Ethics Committee Approval: Yes, by health authorities in respective countries
Sponsor: Baxter Healthcare Corporation

Study period (study start, study end): January 2012- March 2015

Patient characteristics
Age of patients: 50 to 89 years
Sex: Both, M/F not reported
Disease severity: Mild to moderate, as stated in the title (see above), and inclusion criterion 'Dementia of mild to moderate severity defined as Mini-Mental State Examination (MMSE) 16-26 inclusive at screening'
AD therapy (cholinesterase inhibitor; memantine): As stated in inclusion criterion: ' On stable doses of AD medication(s) for at least 12 weeks prior to screening. These medications must be continued throughout this study.'

Intervention
IVIG (unspecified High and Low doses) (18 months)

Control
Placebo

Flow of patients
No of patients enrolled: Estimated enrollment 530
Number of analysed patients: 'The study was terminated because the first Phase 3 did not demonstrate efficacy on the co-primary endpoints. The known safety profile remained unchanged.'

Author Disclosure (Conflict of interest): N/A

Other designs

Study title: NCT01736579 2013
Study characteristics
Study design: Interventional, parallel groups, non randomized, open label study (' A Study of the Long-Term Safety and Efficacy of Immune Globulin Intravenous (Human), 10% Solution (IGIV, 10%) in Mild to Moderate Alzheimer´s Disease')
Study Registration number: NCT01736579 (Last access September 18, 2014)
Country: USA & Canada
Centre: Unclear
Ethics Committee Approval: Yes, by health authorities in respective countries
Sponsor: Baxter Healthcare Corporation
Study period (study start, study end): November 2012 to April 2016 (final data collection date)

Patient characteristics
Age of patients: 51 and older
Sex: Both
Disease severity: mild to moderate (as stated in the title, see above)
AD therapy (cholinesterase inhibitor; memantine): Unclear

Intervention
IVIg IVIG (Gammagard Liquid) 200 mg or 400 mg/kg every 2 weeks (3 years)

Control
None

Flow of patients
No of patients enrolled: 6
Number of analysed patients. N/A ' The study was terminated because the first Phase 3 did not demonstrate efficacy on the co-primary endpoints. The known safety profile remained unchanged.'

Author Disclosure (Conflict of interest). N/A

Appendix 6

Search strategy

Database: Pubmed

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014*
1	"Immunoglobulins, Intravenous"[Mesh]	9526	
2	venimmun OR "modified immune globulin" OR "ivig" OR "endobulin" OR "alpha globin" OR venoglobulin OR sandoglobulin OR "intraglobin" OR "globulin n" OR "privigen" OR "gamunex" OR "gammagard" OR "gamimmune" OR "gamimune" OR "flebogamma dif" OR "intravenous ig" OR "iveegam" OR "immunoglobulins iv" OR "immunoglobulins ivig" OR "immunoglobulins ivigs" OR "iv immunoglobulin" OR "iv immunoglobulins"[All Fields]	15230	
3	1 OR 2	15230	
4	"Mild Cognitive Impairment"[Mesh]	1647	
5	"Alzheimer Disease"[Mesh]	64256	
6	“Mild Cognitive Impairment"[title/abstract] OR dementia*[Title/Abstract] OR Alzheimer*[Title/Abstract] OR MCI[Abstract/Title]	137580	
7	4 OR 5 OR 6	144293	
8	3 AND 7	82	24

*search re-run with the same date limit in February 18 2015, in order to capture references previously not indexed with Mesh terms.

Database: EMBASE

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	‘immunoglobulin'/exp/dd_iv	22907	
2	'endobulin':ab,ti OR 'ivig':ab,ti OR 'alpha globin':ab,ti OR venoglobulin:ab,ti OR sandoglobulin:ab,ti OR 'intraglobin':ab,ti OR 'globulin n':ab,ti OR 'privigen':ab,ti OR 'gamunex':ab,ti OR 'gammagard':ab,ti OR 'gamimmune':ab,ti OR 'gamimune':ab,ti OR 'flebogamma dif':ab,ti OR 'intravenous ig':ab,ti OR 'iveegam':ab,ti OR 'immunoglobulins iv':ab,ti OR 'immunoglobulins ivig':ab,ti OR 'immunoglobulins ivigs':ab,ti OR 'iv immunoglobulin':ab,ti OR 'iv immunoglobulins':ab,ti OR 'intravenous antibodies':ab,ti OR 'intravenous antibody':ab,ti OR 'intravenous immunoglobulin':ab,ti OR 'intravenous immunoglobulins':ab,ti AND [embase]/lim	14395	
3	1 OR 2	31178	
4	'dementia'/de OR 'alzheimer disease'/exp OR 'mild cognitive impairment'/exp	173965	
5	3 OR 4	359	42

Database: Cochrane Central Register of Controlled Trials

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	MeSH descriptor: [Immunoglobulins, Intravenous] explode all trees	616	
2	('endobulin':ab,ti or 'ivig':ab,ti or 'alpha globin':ab,ti or venoglobulin:ab,ti or sandoglobulin:ab,ti or 'intraglobin':ab,ti or 'globulin n':ab,ti or 'privigen':ab,ti or 'gamunex':ab,ti or 'gammagard':ab,ti or 'gamimmune':ab,ti or 'gamimune':ab,ti or 'flebogamma dif':ab,ti or 'intravenous ig':ab,ti or 'iveegam':ab,ti or 'immunoglobulins iv':ab,ti or 'immunoglobulins ivig':ab,ti or 'immunoglobulins ivigs':ab,ti or 'iv immunoglobulin':ab,ti or 'iv immunoglobulins':ab,ti or 'intravenous antibodies':ab,ti or 'intravenous antibody':ab,ti or 'intravenous immunoglobulin':ab,ti or 'intravenous immunoglobulins':ab,ti)	2379	
3	1 OR 2	2467	
4	MeSH descriptor: [Alzheimer Disease] explode all trees	2065	
5	MeSH descriptor: [Mild Cognitive Impairment] explode all trees	65	
6	Alzheimer or "mild cognitive impairment" or "mild cognitive impairments"	5163	
7	4 OR 5 OR 6	5198	
8	3 AND 7	10	5

Database: Lilacs, Ibec, Medcarib

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	tw: immunoglobulin* AND (alzheimer* OR dementia OR "mild cognitive impairment")	11	0

Database: Isi web of Knowledge

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	Topic=(Venimmun OR "modified immune globulin" OR "ivig" OR "endobulin" OR "alpha globin" OR venoglobulin OR sandoglobulin OR "intraglobin" OR "globulin n" OR "privigen" OR "gamunex" OR "gammagard" OR "gamimmune") OR "gamimune" OR "flebogamma dif" OR "intravenous ig" OR "iveegam" OR "immunoglobulins iv" OR "immunoglobulins ivig" OR "immunoglobulins ivigs" OR "iv immunoglobulin" OR "iv immunoglobulins" OR "intravenous antibodies" OR "intravenous antibody" OR "intravenous immunoglobulin" OR "intravenous immunoglobulin" OR "intravenous immunoglobulins")		
2	Topic=(mci[title/abstract] OR "Mild Cognitive Impairments"[title/abstract] OR "Mild Cognitive Impairment"[title/abstract] OR dementia*[Title/Abstract] OR alzheimer*[Title/Abstract])		
3	1 AND 2	138	30

Clinical Registers

ALOIS: a comprehensive register of dementia studies

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	immunlobulin*	7	0

metaRegister of Controlled Trials (mRCT), including ISRCTN (International Standard Randomised Controlled Trial Number Register)

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	(immunoglobulin*) and (Alzheimer or dementia or “mild cognitive impairment”)	2	0

ClinicalTrials.gov

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	(alzheimer* OR dementia* OR "mild cognitive impairment") AND (immunoglobulin*)	51	21

NIH Clinical research studies

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	immunoglobulin* and Alzheimer	0	0

EU Clinical Trials Register website

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	immunoglobulin* and Alzheimer	4	0

International Clinical Trials Register Platform (ICTRP)

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	immunoglobulin* and Alzheimer	4	0

Websites of the regulatory agencies

US Food and Drug Administration-MedWatch

http://www.fda.gov/Safety/MedWatch/default.htm:

Search terms: (Immunoglobulin OR Immunoglobulins OR Immune globulin OR Gammagard OR Octagam OR Newgam, OR Flebogamma) AND (dementia OR Alzheimer OR mild)

Search Date 25/02/2014: 0 documents.

Search Date 15/12/2014: 0 documents.

European Medicines Agency

http://www.adrreports.eu/IT/index.html

Search by topic: Immunoglobulin, Gammagard, Octagam, Newgam, Flebogamma

Search Date: 25/02/2014: 0 document

Search Date 15/12/2014: 0 document

Australian Adverse Drug Reactions Bulletin

http://www.tga.gov.au/safety/ews-monitoring.htm

Search by topic: Immunoglobulin, Gammagard, Octagam, Newgam, Flebogamma

Search Date: 25/02/2014: 2 documents, 0 relevant

Search Date 15/12/2014: 2 documents (same as above), 0 relevant

UK Medicines and Healthcare products Regulatory Agency (MHRA) pharmacovigilance and drug safety updates

http://www.mhra.gov.uk/Safetyinformation/index.htm)

Search terms: Immunoglobulin AND Alzheimer OR dementia OR mild cognitive.

Search Date: 25/02/2014: 7 documents retrieved; 0 relevant

Search Date: 15/12/2014: 4 documents retrieved; 0 relevant

Appendix 7

Use of Intravenous immunoglobulins for Mild Cognitive Impairment and Alzeheimer's disease - PROTOCOL

Clinical Effectiveness

Authors: Luca Vignatelli, Luciana Ballini, Susanna Maltoni, Jelena Barbaric, Mirjana Huic, Pernilla Östlund.

Summary

Aim

To determine whether treatment with intravenous immunoglobulins (IVIG) in adults with Mild Cognitive Impairment (MCI) or Alzheimer's disease (AD) improves clinical outcomes and quality of life, has impact on patients' satisfaction, hospitalization rate and institutionalization delay compared with current practice.

Secondary objective was to map available evidence against the technology's evidence profile.

Methods

We performed a systematic review according to Cochrane methodology on evidence from biomedical databases; publicly available clinical trials registers were also searched. Qualitative and quantitative syntheses were done. To assess risk of bias of included RCTs the risk of bias method proposed by the Cochrane Handbook for Systematic Reviews of Interventions was used. Overall quality of evidence for each outcome was assessed and synthesised according to the GRADE approach.

Results

Among the four published clinical studies none met the inclusion criteria. Missing publication was documented for two completed RCTs in subjects with mild-to-moderate AD. One of the two studies {NCT00818662}, a phase 3 double-blind, placebo-controlled, two dose arm RCT, aiming at testing the safety and effectiveness of IVIG for patients with mild-to-moderate AD, had its results posted on a clinical trial register in October 23rd 2014, after completion of this report. The authors and the sponsor had been previously contacted (May 2014) but did not provide any data. As this study, according to decision of Editorial Team, met inclusion criteria, release of this report was postponed in order to include it in the analysis. Available data do not permit an evaluation of the methodology and conduction of the study due to the absence of information posted. Manufacturer was not contacted again to provide more data. The confidence in effect estimate for overall evidence on all considered outcomes is *very low*, according to GRADE approach. Participants were 383 patients (completing the study: 302) that were randomized to one of two doses of IVIG (Gammagard Liquid 10%, 400 mg/kg bodyweight or 200 mg/kg bodyweight, every two weeks) or one of two doses of placebo (0.25% human albumin solution infused at 4mL/kg or at 2 mL/kg, every two weeks) for 70 weeks. Any important clinical outcomes such as cognitive functions (ADAS-Cog, ADCSC-GIC), activity of daily living (ADCS-ADL) and quality of life (both in patients and caregivers according to QOLAD) did not differ between IVIG and placebo groups.

Two additonal ongoing RCTs have been identified: one including subjects with MCI, and one including subjects with mild-to-moderate AD. These trials are reported to and expected to end in November 2014 and December 2016, respectively. Patients with moderate-to-severe AD are not considered by any study.

Conclusion

We found limited evidence of very low quality suggesting lack of effectiveness of IVIG in adults with mild-to-moderate AD and no evidence for adults with MCI or moderate-to-severe AD. Conclusive evidence from unpublished and ongoing studies are necessary before setting up RCTs on long term effectiveness of IVIG in patients with MCI, mild-to-moderate and moderate-to-severe AD.

Introduction

Background

The Clinical Effectiveness Domains describes the range and size of beneficial health effects expected through the use of the technology {HTA Core Model Handbook Online, Version 1.5}. The two key elements are that effective interventions should be directly compared and studied in patients who are typical of day-to-day health care settings {HTA Core Model Application for Pharmaceuticals, 2.0}.

AD is a chronic neurodegenerative disorder strongly associated with the formation and accumulation of extracellular plaques of amyloid-beta (Aβ) protein in the brain that is followed by synaptic dysfunction, inflammation and eventually neuronal death (Ballard 2011; Silvergleid 2013). It is suggested that IVIG might have beneficial effects on the pathogenic processes of AD (Dodel 2013) and even at the stage of MCI, by interfering positively with metabolism of amyloid β that seems to be reduced in subjects at risk for AD.

The causal chain suggesting a clinical benefit from the use of IVIG for MCI and AD appears as follows:

- amyloid β (Aβ) is the metabolic product of the amyloid precursor protein, an element placed in the normal cell membrane (Ballard 2011; National Institute on Aging 2011);

- abnormal increase of amyloid β in the brain - as beta-amyloid plaques - is probably the first expression of the pathological process that damages neurons in AD (Ballard 2011; National Institute on Aging 2011);

- biomarkers of the metabolism of Amyloid Precursor Protein are amyloid β40, amyloid β42, Anti-Aβ autoantibodies (Ballard 2011; Du 2002); all these products can be measured in cerebrospinal fluid and serum (Buchhave 2012; Dodel 2013; Du 2002; Jack 2013);

- amyloid β metabolism seems to be reduced in patients with AD; in particular it is reported that cerebrospinal fluid and serum amyloid β40 and amyloid β42 could be lower than normal in patients with MCI and AD, and that cerebrospinal fluid and plasma titers of anti–Aβ antibodies are lower in AD patients compared with controls (Jack 2013; Relkin 2009);

- natural polyclonal anti-Aβ autoantibodies are present in normal human blood (Dodel 2002; Weksler 2002);

- it is hypothesised that an immune-mediated amyloid-β degrading pathway may be physiologically present and its actions clinically significant in humans;

- early observations report that after IVIG treatment a significant increase in total anti-Aβ autoantibodies concentration can be produced in the plasma of patients with AD (Dodel 2002; Relkin 2009); peripherally administered antibodies against Aβ can induce a shift of Aβ from the CSF to the blood, thereby reducing the cerebral Aβ burden (the “peripheral sink hypothesis”) and with increased plasma concentration and decreased CSF concentration of Aβ;

- it is hypothesised that IVIG use for passive immunotherapy in AD could slow the disease progression (Dodel 2002; Dodel 2013; Loeffler 2013; Relkin 2009) and use in patients with MCI could avoid or delay the onset of AD.

Objectives

Primary objectives:

1. To assess the effectiveness of IVIG in adults with MCI.
2. To assess the effectiveness of IVIG (alone or in combination with other treatments) in adults with mild-to-moderate AD.
3. To assess the effectiveness of IVIG (alone or in combination with other treatments) in adults with moderate-to-severe AD.

Secondary objectives:

- to map available evidence against the technology’s evidence profile, i.e. the body of evidence needed to demonstrate its effectiveness in the above reported target conditions
- to identify research gaps.

Methodology

Frame

The collection scope is used in this domain.

Technology	Immunoglobulins (IGG) **Description** Naturally occurring proteins produced by the body’s immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer’s disease **Target condition** Alzheimer’s disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.

Comparison	placebo, not doing anything or Usual supportive care **Description** There is no MA for IGGs for AD yet and there is no other intervention licensed for use in AD so the comparison would have to be against placebo or best supportive care
Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
D0006	Morbidity	How does the technology affect the progression (or recurrence) of the target condition?	yes	Are IVIG effective in slowing or avoiding progression from Mild Cognitive Impairment to Alzheimer's disease when compared to placebo? Are IVIG effective in improving biomarkers of progression from Mild Cognitive Impairment to Alzheimer's disease when compared to placebo? Are IVIG effective in improving imaging markers of progression from Mild Cognitive Impairment to Alzheimer's disease when compared to placebo? Are IVIG effective in slowing disease progression from mild-to-moderate to moderate-to-severe Alzheimer's disease (measured with MMSE) when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving biomarkers of progression in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving imaging markers of progression in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving biomarkers of progression in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine? Are IVIG effective in improving imaging markers of progression in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?
D0005	Morbidity	How does the technology affect symptoms and findings (severity, frequency) of the target condition?	yes	Are IVIG effective in improving neuropsychiatric symptoms in patients Mild Cognitive Impairment when compared to placebo? Are IVIG effective in improving behavioural symptoms in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving behavioural symptoms in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?
D0001	Mortality	What is the expected beneficial effect of the intervention on overall mortality?	yes	Are IVIG effective in reducing overall mortality in patients with Mild Cognitive Impairment when compared to placebo? Are IVIG effective in reducing overall mortality in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in reducing overall mortality in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?
D0002	Mortality	What is the expected beneficial effect on the disease-specific mortality?	no	Disease-specific mortality is not a plausible outcome for Alzheimer Disease as death in these patients is expected due to complications and not to Alzheimer's disease itself.
D0003	Mortality	What is the effect of the technology on the mortality due to causes other than the target disease?	no	More relevant for the SAF domain
D0011	Function	What is the effect of the technology on patients' body functions	yes	Are IVIG effective in improving cognitive functions of patients with Mild Cognitive Impairment when compared to placebo? Are IVIG effective in improving cognitive functions of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving cognitive functions of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?
D0016	Function	How does use of the technology affect activities of daily living?	yes	Are IVIG effective in improving activities of daily living of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving activities of daily living of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?
D0014	Function	What is the effect of the technology on work ability?	no	Already covered by the assessment of daily activities.
D0015	Function	What is the effect of the technology on return to previous living conditions?	no	This issue is important for diseases with acute or relapsing course. Alzheimer disease has a progressive course.
D0012	Health-related Quality of life	What is the effect of the technology on generic health-related quality of life?	yes	Are IVIG effective in improving generic health-related quality of life of patients with Mild Cognitive Impairment when compared to placebo? Are IVIG effective in improving generic health-related quality of life of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving generic health-related quality of life of caregivers of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving generic health-related quality of life of caregivers of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?
D0013	Health-related Quality of life	What is the effect of the technology on disease specific quality of life?	yes	Are IVIG effective in improving disease specific health-related quality of life of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving disease specific health-related quality of life of caregivers of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Are IVIG effective in improving disease specific health-related quality of life of caregivers of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?
D0010	Change-in management	How does the technology modify the need for hospitalization?	yes	Does IVIG impact on the need for hospitalization in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Does IVIG impact on the need for institutionalization in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors? Does IVIG impact on the need for hospitalization in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine? Does IVIG impact on the need for institutionalization in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

D0023	Change-in management	How does the technology modify the need for other technologies and use of resources?	no	More relevant for the ORG domain
D0029	Benefit-harm balance	What are the overall benefits and harms of the technology in health outcomes?	yes	What are the overall benefits and harms of IVIG in health outcomes of patients with Mild Cognitive Impairment? What are the overall benefits and harms of IVIG in health outcomes of patients with mild-to-moderate Alzheimer's disease? What are the overall benefits and harms of IVIG in health outcomes of patients with moderate-to-severe Alzheimer's disease?
D0017	Patient satisfaction	Was the use of the technology worthwhile?	no	Not important

Methodology description

Criteria for considering studies

Types of studies

All published or unpublished full report of randomised controlled trials (RCTs) were considered for inclusion. For unpublished studies we accepted results from publicly available controlled trials' registers (decision made by Editorial Team). Report on animal models, pre-clinical and biological studies, narrative reviews, editorials, opinions, were excluded.

To establish stage of development of research of the technology, RCTs as well as interventional prospective controlled and uncontrolled studies were searched for.

Types of participants (target population)

Adult (18+ years) patients of any sex who have one of the target conditions:

1. MCI (ICD-9-CM Diagnosis Code 331.83; ICD-10-CM G31.84) as defined by validated criteria.
2. Mild-to-moderate AD (ICD-9-CM Diagnosis Code 331.0; ICD-10-CM G30.9), as defined by validated criteria and with MMSE score between 15 and 26.
3. Moderate-to-severe AD (ICD-9-CM Diagnosis Code 331.0; ICD-10-CM G30.9), as defined by validated criteria and with MMSE score less than or equal to 14.

Types of interventions

IVIG any dose, any regimen, any product, alone or in combination with non-pharmacological interventions, and/or with approved drugs (acetyl cholinesterase inhibitors, memantine).

Types of control treatments

- MCI: placebo, non-pharmacological treatments or no treatment
- Treatment naïve patients with mild-to-moderate AD: placebo, acetyl cholinesterase inhibitors, non-pharmacological treatments or no treatment
- Patients with mild-to-moderate AD treated with acetyl cholinesterase inhibitors: placebo plus acetyl cholinesterase inhibitors or acetyl cholinesterase inhibitors
- Patients with mild-to-moderate AD intolerant to acetyl cholinesterase: placebo and/or non-pharmacological treatment or no treatment.
- Patients with moderate-to-severe AD treated with memantine: placebo plus memantine, non-pharmacological treatments plus memantine, or memantine
- Patients with moderate-to-severe AD intolerant to memantine: placebo and/or non-pharmacological treatment or no treatment.

Types of outcomes and outcome measures

MCI

Primary outcomes (timeframe: 3 years)

- Progression to AD (timeframe: within 3 years) according to available AD validated criteria (NINCDS-ADRDA, ICD, DSM) [Issue domain Morbidity D0006]

Secondary outcomes

- Overall mortality [Issue domain Mortality D0001];
- Cognition improvement (Cognitive functions measured by ADAS-Cog, MMSE, Clinical Dementia Rating, and Global Change scales measured by Clinical Global Impression of Change (CGI-C), Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), Global Deterioration Scale (GDS)) [Issue domain Function D0011];
- Neuropsychiatric symptoms measured by scales (Neuropsychiatric Inventory – NPI - or other validated scales in the target population) [Issue domain Morbidity D0005];
- Generic health related quality of life measured by common scales (SF-36; EQ-5D) [Issue domain Health-related Quality of life D0012].

Other outcomes

- Variation of biomarkers (change of cerebrospinal fluid Aβ1-42; change of serum anti-Aβ autoantibodies) [Issue domain Morbidity D0006];
- Variation of imaging signs (change in standardized uptake value (SUVR) at PIB-PET; change in ventricular volumetric as measured by MRI) [Issue domain Morbidity D0006].

Mild-to-moderate AD

Primary outcomes (timeframe: at least 1 year)

- Progression to moderate-to-severe AD according to MMSE [Issue domain Morbidity D0006];
- Cognitive outcomes changes (Cognitive functions measured by ADAS-Cog or CDR-GS [Issue domain Function D0011];
- Functional ability changes (Activities of daily living measured by DAD, ADCS-ADL or other validated scales in the target population [Issue domain Function D0016];
- Behavioural changes (Neuropsychiatric Inventory - NPI, the Behavioural Pathology in AD Rating Scale - BEHAVE-AD, and the Behavioural Rating Scale for Dementia -BRSD) (GPC 2013) [Issue domain Morbidity D0005].

Secondary outcomes (timeframe: at least 1 year)

- Overall mortality [Issue domain Mortality D0001];
- Generic health related quality of life measured by common scales (SF-36; EQ-5D) both in patients and caregivers [Issue domain Health-related Quality of life D0012];
- Disease specific health related quality of life scales both in patients (ADRQL, CBS, DCM, DQoL PWB-CIP, QUALID Scale, QOL-AD, QOLAS, DEMQOL) and caregivers (DEMQOL-Proxy-U; Zarit Burden Interview) [Issue domain Health-related Quality of life D0013];
- Hospitalization [Issue domain Change in management D0010];
- Delay on institutionalization [Issue domain Change in management D0010].

Other outcomes

- Variation of biomarkers (change of cerebrospinal fluid Aβ1-42; change of serum anti-Aβ autoantibodies) [Issue domain Morbidity D0006];
- Variation of imaging signs (change in standard uptake value ratio - SUVR) at PIB-PET; change in ventricular volumetric as measured by MRI) [Issue domain Morbidity D0006].

Moderate-to-severe AD

Primary outcomes (timeframe: at least 1 year)

- Cognitive outcomes changes (Cognitive functions measured by SIB, ADAS-Cog, MMSE[Issue domain Function D0011];
- Functional ability changes (Activities of daily living measured by DAD, ADCS-ADL or other validated scales in the target population [Issue domain Function D0016].
- Behavioural changes (Neuropsychiatric Inventory - NPI, the Behavioural Pathology in AD Rating Scale - BEHAVE-AD, and the Behavioural Rating Scale for Dementia -BRSD) (GPC 2013) [Issue domain Morbidity D0005].

Secondary outcomes (timeframe: at least 1 year)

- Overall mortality [Issue domain Mortality D0001];
- Generic health related quality of life measured by common scales (SF-36; EQ-5D) in caregivers [Issue domain Health-related Quality of life D0012];
- Disease specific health related quality of life scales both in caregivers (DEMQOL-Proxy-U; Zarit Burden Interview) [Issue domain Health-related Quality of life D0013];
- Hospitalization [Issue domain Change in management D0010];
- Delay of institutionalization [Issue domain Change in management D0010].

Other outcomes

- Variation of biomarkers (change of cerebrospinal fluid Aβ1-42; change of serum anti-Aβ autoantibodies) [Issue domain Morbidity D0006];
- Variation of imaging signs (change in SUVR at PIB-PET; change in ventricular volumetric as measured by MRI) [Issue domain Morbidity D0006].

Search methods for identification of studies

Electronic searches

The following databases and clinical trials registers were searched:

Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE, EMBASE, LILACS, ALOIS (the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group) and national and international trials registers (Australian New Zealand Clinical Trials Register (ANZCTR), http://www.anzctr.org.au/; metaRegister of Controlled Trials (mRCT), http://www.controlled-trials.com/mrct/; ClinicalTrials.gov. www.clinicaltrials.gov/; NIH Clinical Research Studies, http://clinicalstudies.info.nih.gov/; EU Clinical Trials Register, https://www.clinicaltrialsregister.eu/; International Clinical Trials Register Platform (ICTRP), http://www.who.int/ictrp/en/).

Initial search was carried out on February 24th 2014 and an update was carried out close to the release of the report on December 16th 2014.

See Appendix 6 for detailed search strategies. The strategy for MEDLINE was adapted to other databases. No language or date of publication restrictions were applied.

Searching other resources. In addition we checked conference proceedings for relevant abstracts, and contact individual researchers working in this field, organizations and pharmaceutical companies to identify additional RCTs, especially those unpublished. We also checked the reference lists of all studies identified by the above methods.

Data collection and analysis

Selection of studies

The titles and abstracts of all studies identified by the search were screened independently by two investigators (ASSR). Full text was retrieved of all studies which any investigator considered potentially relevant. Two investigators then identified studies for inclusion or exclusion independently (ASSR). Different selection results were discussed in order to achieve consensus. A third person was involved to resolve discrepancies (AAZ and SBU).

Data extraction and management

A data extraction form was developed and piloted specifically for this review. For each study, data were extracted on: participants (including inclusion and exclusion criteria, baseline investigations, co-treatments); interventions; outcomes; study design; results. For eligible studies, when data on outcomes of interest were missing or incompletely reported investigators contacted the Authors for additional information. For dichotomous outcomes, data extracted were the number of participants with the outcome of interest in each group at each time point. For continuous outcomes, data extracted were the mean and standard deviation (SD) in each group at each time point. If only change-from-baseline data were available, those were extracted.

Assessment of risk of bias of included studies and of overall quality of evidence

To assess risk of bias of included RCTs the risk of bias system proposed by the Cochrane Handbook for Systematic Reviews of Interventions {Higgins et al. 2011} was used. Overall quality of evidence for each outcome was assessed and synthesised according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach {Guyatt 2011a; Balshem 2011; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2013}, and presented in table. This approach specifies four levels of quality:

- High: further research is very unlikely to change our confidence in the estimate of effect;
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates;
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low: we are very uncertain about the estimate.

Data synthesis

Quantitative results were expressed as point estimates together with associated 95% confidence intervals (95% CI) and p-values. We had planned, if possible, to carry out a meta-analysis with graphical display of results and assessment of heterogeneity, according to the Cochrane Handbook for Systematic Reviews of Interventions {Higgins et al. 2011}.

Studies used to map available evidence against the technology's evidence profile, i.e. the body of evidence needed to demonstrate its effectiveness in the above reported target conditions were grouped by target conditions included in this protocol. A descriptive summary of these studies with details about study design, numbers and characteristics of enrolled patients, intervention/s and comparator/s, outcomes, outcomes' measures and results is provided in tables and plain text format. In order to map available evidence against the technology's evidence profile, for each research question the results from *available evidence* and *upcoming evidence* were charted in order to describe stage of development and to highlight research gaps. *Available evidence* refer to published or unpublished studies with available data and *upcoming evidence* refer to unpublished without available data and ongoing studies..

Description of studies

Results of the search

The first electronic searches strategy (February 24th 2014), yielded 515 citations, after removal of duplicates. Of these, 388 were directly excluded, because judged not relevant. Of the remaining 127 citations, none meet our inclusion criteria and were excluded from relative effectiveness assessment (primary objectives). Checking periodically the registers of ongoing trials, the results of one of the RCT {NCT00818662}, tracked on clinical trial registries, were posted on ClinicalTrials.gov by the study sponsor in October 23rd 2014. Thus this study was included (decision by Editorial Team) and remaining the 126 citations excluded. The second electronic search strategy (December 16th 2014) yielded 71 citations, after removal of duplicates; 70 were excluded, because judged not relevant, and 1 excluded after evaluation of the full text. From the final periodic check of registers of ongoing trials (December 16th 2014) there was no further status change for included ongoing trials.

See PRISMA study flow diagram in Appendix 1 {Figure A1}.

Excluded studies

The reasons for exclusion of the 128 records were as follows: in vitro /animal studies (n=13); other treatments (n=22); review papers (n=31); comments/editorials/news (n=14); other topics (n=4); studies on the current use of IVIG (n=2); case control studies (n=2); study without data on outcomes (n=1); interventional studies not fulfilling design inclusion criteria (38 citations corresponding to 16 studies). The latter group of 16 studies were found eligible for the evidence mapping against the technology's evidence profile: 7 studies resulted as completed and unpublished {Hara 2011, Kondo 2011, Kountouris 2000, Papatriantafyllou 2006, Rovira 2011, NCT00299988, Relkin 2012 }, 2 studies are ongoing {NCT01300728, NCT01561053}, 2 studies had been planned but they were terminated prematurely {NCT01524887, NCT01736579}, and 5 studies were published {Arai 2014, Devi 2008, Dodel 2004, Dodel 2013, Relkin 2009}.

Included studies

No studies fitting our inclusion criteria were found.

Included unpublished studies with results posted in clinical trials registers (Editorial Team decision)

The following information refers to data posted by the study sponsor on one trial register (ClinicalTrials.gov) in October 23rd 2014. The Authors and the sponsor were previously contacted (May 2014). They responded but did not provide results. The Authors and the Sponsor were not contacted again. The

included RCT {NCT00818662} was a phase 3 double-blind, placebo-controlled, two dose arm study aiming at testing the safety and effectiveness of IVIG for patients with mild-to-moderate AD. Participants were 383 patients (patients completing the study: 302; intention-to-treat population not declared) with probable AD (criteria not reported), with a mini-mental state examination score of 16–26 and age 50–89 years at baseline. Included patients had been taking a stable dose of an approved Alzheimers disease drug for at least 3 months before screening (not reported number of patients on treatment). Participants were randomized to one of two doses of IVIG (Gammagard Liquid 10%, 400 mg/kg bodyweight every two weeks, or 200 mg/kg bodyweight every two weeks) or one of two doses of placebo (0.25% human albumin solution infused at 4 mL/kg every two weeks or at 2 mL/kg every two weeks), for 70 weeks. The randomization ratio was 2:2:1:1. Co-primary outcomes were change from baseline at 18 months in the Alzheimer´s Disease Assessment Scale Cognitive Subscale (ADAS-Cog) and change from baseline at 18 months in the Alzheimer´s Disease Cooperative Study Activities of Daily Living (ADCS-ADL). Other patients important outcomes considered in the study were: change at 9 months in ADAS-Cog, change at 9 months in ADCS-ADL, change at 9 and 18 months in Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCSC-GIC), change at 18 months in the Neuropsychiatric Inventory (NPI), change at 18 months in the Logsdon Quality of Life in Alzheimer's Disease (QOLAD) of patients and caregivers. Other outcomes assessed in the study but not considered in this review were: Modified MiniMental State Examination (3MS), Wechsler Adult Intelligence Scale Revised Digit Span, FAS Verbal Fluency, Animals Category Fluency, Trail Making Test Part A and Part B, Clock Drawing Test. The study - funded by Baxter Healthcare Corporation and conducted in USA and Canada – started in December 2008 and ended in December 2012.

Characteristics of published, unpublished and ongoing studies used for mapping available evidence against the technology's evidence profile

Published studies

Five studies (interventional n=4; observational, n=1) were found and summarised in Appendices 3 and 4.

The second RCT by Arai et al. {Arai 2014} was an exploratory multiple dose double-blind, randomised, placebo-controlled study aiming at testing the safety and tolerability of treatment with IVIG for patients with mild-to-moderate AD. Participants were 16 subjects (intention-to-treat and per protocol population: 16) with probable AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria), with a mini-mental state examination score 16–26 and age 50–89 years at baseline. Patients could have been taking a stable dose of an approved AD drug (cholinesterase inhibitors, memantine) for at least 120 days prior baseline. However no data were reported about the use of these drugs. Participants were randomized to one of two doses of IVIG (0.2 g/kg, 0.4 g/kg every 2 weeks) or to placebo (50 mL 0.25% human albumin solution every 2 weeks). Treatment duration was 12 weeks and follow up lasted up to 26 weeks. The outcome measures were safety and tolerability. Moreover MMSE score change 14 weeks after the end of treatment (week 26 of follow up) was considered. The study was conducted in 5 centres of Japan. No information was provided about funding. The study does not report a Study Registration number.

The RCT by Dodel et al. {Dodel 2013} was an exploratory phase 2 dose finding double-blind, block-randomised, placebo-controlled study aiming at testing the safety, effective dose, and infusion interval of treatment with IVIG for patients with mild-to-moderate AD. Participants were 58 subjects (modified intention-to-treat population: 57; per protocol population: 45) with probable AD (National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria), with a mini-mental state examination score 16–26 and age 50–85 years at baseline. Patients had to have been taking a stable dose of an approved Alzheimers disease drug for at least 3 months before screening; 36 out of 41 patients in IVIG (88%) used acetylcholinesterase inhibitor or memantine as well as 11 out of 14 (79%) patients in Placebo group. Participants were randomized to one of six doses of IVIG (0.2 g/kg, 0.5 g/kg or 0.8 g/kg every 4 weeks; 0.1 g/kg, 0.25 g/kg, or 0.4 g/kg every 2 weeks) or to placebo (0.9% isotonic sodium chloride every 4 weeks or every 2 weeks). Treatment duration was 24 weeks. Primary outcome was the difference of the median area under the curve (AUC) of plasma concentration of Aβ1–40 between placebo groups and the six intervention groups, measured from last infusion to final visit. Other surrogate outcomes were the difference of AUC for plasma concentration of Aβ1–42 and of anti-Aβ autoantibodies; the difference of plasma concentration of Aβ1–40, Aβ1–42 and anti-Aβ autoantibodies at week 24 compared with baseline; the change in CSF concentration of Aβ1–40, Aβ1–42, anti -Aβ autoantibodies and p-tau181, 24 h after last infusion compared with baseline; the difference between baseline and week 24 of change in whole brain volume, hippocampus volume; glucose metabolism. Moreover some patient important outcomes were considered: difference in scores at baseline and at week 24 on the AD assessment scale-cognitive part (ADAS-cog), the clinical dementia rating scale-sum of boxes, the AD Cooperative Study-activities of daily living scale, the mini-mental state examination; adverse events. The study - funded by Octapharma AG – was conducted in hospitals, research centres and private clinics of Germany and USA.

The other three studies {Devi 2008, retrospective observational study; Dodel 2004 and Relkin 2009, interventional prospective non-controlled studies} applied to small samples (n = 5 to 10) of subjects with AD (National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria) and tested the safety and the clinical effect of various schemes of IVIg administration (0.4 g/kg every 2 weeks; 0.4 g/kg on three consecutive days every 4 weeks; 0.4 g/kg every week; 1 g/kg every 2 weeks; 2 g/kg every 4 weeks) for 3-6 months of duration. The outcomes considered were difference between baseline and end of treatment of cognitive functions according to various scales/tools (Wechsler Adult Intelligence Scale; Wechsler Memory Scale; Boston Naming Test; ADAS-cog; CDR-GS; MMSE; Visual construction abilities), immunologic surrogate outcomes (changes before and after infusion of serum or CSF anti-Abeta antibody, changes of CSF Abeta 40 and Abeta42), adverse events. Two studies {Dodel 2004, Relkin 2009} received both public and manufacturer's funding; in the third study {Devi 2008} the source of funding was not reported.

Unpublished studies

Seven more studies - summarised in Appendix 3 - were carried out but not published as full papers, resulting as protocols in ClinicalTrial.gov {NCT00299988 } or abstracts at congress {Hara 2011, Kondo 2011, Kountouris 2000, Papatriantafyllou 2006, Relkin 2012, Rovira 2011}. None of them had results posted in clinical trials registers.

The NCT00299988 study {NCT00299988} was a phase 2 randomized, placebo-controlled trial, conducted in USA. Participants were 24 subjects with mild-to-moderate AD. Four schemes of intravenous immunoglobulin (ranging from 0.2 g/kg every 2 weeks to 0.8 g/kg every months) were compared to placebo. Treatment duration was 6 months. Primary outcome were ADAS-Cog and ADCS-CGIC. Other outcomes were cognitive functions measured by other scales/tools (MMSE; ADCS-ADL; NPI; GDS), quality of life (scales not reported), immunologic surrogate outcomes (plasma and CSF anti-amyloid antibody titers and beta amyloid levels), imaging surrogate outcomes (Positron Emission Tomography: FDG Cerebral Glucose Utilization, PIB Cerebral Amyloid Distribution, PK11195 Microglial Activation), adverse events. The study - funded by Weill Medical College of Cornell University Collaborators and by Baxter BioScience – was completed in April 2010 but results are still unpublished. For this study an open label extension of three years was carried out in 16 subjects in order to assess the long-term safety the IVIg infusion, but results are similarly unpublished as full paper (available only an abstract, Relkin 2012). Authors of the study were contacted in May 2014, and although they responded, they did not provide results.

Other four studies {Hara 2011, Kondo 2011, Papatriantafyllou 2006, Rovira 2011} applied a before-and-after design to small samples (n = 4 to 10) of subjects with AD testing the safety and effectiveness of various schemes of IVIg administration for 3-62 months of duration. The outcomes considered were difference between baseline and end of treatment of cognitive functions according to various scales/tools, surrogate outcomes, adverse events.

These studies are still unpublished as full paper (available only as abstracts). The Authors of the these studies were contacted. Two of them responded without providing results, stating that the studies will be probably published.

Finally, one study {Kountouris 2000} applied a non-randomized controlled design to 16 subjects with AD comparing the effectiveness of IVIg infusion together with piracetam versus the administration of piracetam only, for 12 months of duration. The outcome considered was the cognitive function assessed by the MMSE. This study is unpublished as full paper (available only as abstract). The Author of the this study was contacted, without response.

Terminated studies

Two other studies - summarised in Appendix 3– are terminated {NCT01736579, NCT01524887}, that is stopped prematurely.

An open label extension of three years of one of the above reported RCTs {NCT00818662} was planned {NCT01736579} in order to assess the long-term safety of the IVIg infusion. The study was terminated in 2013 after enrollment of 6 patients because the preceding phase 3 study did not demonstrate efficacy on the co-primary endpoints.

The NCT01524887 study {NCT01524887} was a phase 3 randomized, placebo-controlled trial planned to include subjects with mild-to-moderate AD in order to test two unspecified schemes of intravenous immunoglobulin versus placebo for a treatment duration of 18 months. Primary outcome considered were ADAS-Cog and ADCS-ADL. The study - devised by Baxter Healthcare Corporation – was terminated in 2013 without enrollment of any patients because the first phase 3 study {NCT00818662} did not demonstrate efficacy on the co-primary endpoints.

Ongoing studies

Two more studies - summarised in Appendix 3 – are still ongoing {NCT01300728, NCT01561053}.

The NCT01300728 study {NCT01300728} is a phase 2 randomized, placebo-controlled trial, that is ongoing in USA. Participants are 50 subjects with MCI, amnestic type (single or multi domain) according to Petersen criteria (Petersen 1999) and supported by a CDR score of 0.5. IVIg infusion (0.4 g/kg every 14 days for a total of five infusions in two months) will be compared to placebo. Primary outcome is change in ventricular volumetric as measured by MRI (time frame: baseline and 24 month). Other outcomes are conversion from amnestic MCI to AD, cognitive functions measured by other scales/tools (ADAS-cog; MMSE; Clinical Dementia Rating and Sum of Boxes), other imaging surrogate outcomes, adverse events. The study - funded by Sutter Health – will be completed in October 2014.

The NCT01561053 study {NCT01561053} is a phase 2/3 randomized, placebo-controlled trial, that is ongoing in USA and Spain. Participants are 350 subjects with mild-to-moderate Alzheimer Disease (National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association criteria). IVIg (Flebogamma DIF) infusion (at unspecified high and low dose) together with plasmapheresis or plasmapheresis alone will be compared to a sham procedure. Primary outcome is increase in cognitive scores as measured by ADAS-Cog (time frame 14 months). Other outcomes are change in: cognitive, functional and neuropsychiatric scores (measured by MMSE, NPS battery, ADCS-ADL, NPICDR-Sb, ADCS-CGIC, CSDD, C-SSRS), surrogate immunological outcomes (levels of AB1-40 and AB1-42, T-tau and P-tau in CSF; levels of AB1-40 and AB1-42 in plasma), surrogate imaging outcomes (structural changes in volume of the hippocampus, posterior cingulate area, and other associated areas at MRI; brain functional changes through FDG-PET), adverse events. The study - funded by Grifols Biologicals Inc. – will be completed in December 2016.

Risk of bias in included studies

The included RCT {NCT00818662} was a phase 3 double-blind, placebo-controlled, two dose arm study. Available data (posted on ClinicalTrials.gov, last access December 5 2014) do not permit an evaluation of the methodology and conduction of the study due to the absence of information posted. Authors and Manufacturer were not contacted again and risk of bias was assessed by Principal Investigators. A risk of attrition bias was present (81 out of 383 randomized patients did not complete the study). The study was industry sponsored. The overall risk of bias of this study was judged to be “high”. For details on study’s risk of bias please see Table 1.

Table 1. Risk of bias table for NCT00818662 trial

Bias	**Judgement**	**Support for judgement** Cochrane Risk of Bias; Criteria from EUnetHTA guideline, Internal validity of randomized controlled trials
Random sequence generation adequate (selection bias)	Unclear	No details on random generation.
Allocation concealment adequate (selection bias)	Unclear	No details on allocation concealment.
Blinding of patients (performance bias)	Unclear	No details on blinding.
Blinding of treating personnel (performance bias)	Unclear	No details on blinding.

Blinding of outcome assessment (detection bias)	Unclear	No details on blinding.
Incomplete outcome assessment unlikely (attrition bias)	High risk	383 patients were randomized: 127 IVIG 400mg/kg; 135 IVIG 200mg/kg; 58 Placebo 4mL/kg; 63 Placebo 2mL/kg. 82 (21.4%) patients did not complet the trial: 23 (18.1%) IVIG 400mg/kg; 33 (24.4%) IVIG 200mg/kg; 9 (15.5%) Placebo 4mL/kg; 16 (25.4%) Placebo 2mL/kg
ITT principle appropriately implemented (attrition bias)	Unclear risk	No details on ITT analysis.
Selective outcome reporting unlikely (reporting bias)	Low risk	No main discrepancies between the protocol and the reported results are present.
Other bias	High risk	Sponsored study Two Study Directors are reported Study Director: Norman Relkin, MD, PhD Alzheimer's Disease Cooperative Study (ADCS) Study Director: David Gelmont, MD Baxter Healthcare Corporation Role of the funding source “Restriction Description: Agreements with PIs may vary per requirements of individual PI, but contain common elements. For this study, PIs are restricted from independently publishing results until the earlier of the primary multicenter publication (by USCD) or 12 months after study completion. Baxter requires a review of results communications (e.g., for confidential information) ≥45 days prior to submission or communication. Baxter may request an additional delay of ≤45 days(e.g., for intellectual property protection)”

Result cards

Morbidity

Result card for EFF1a: "Are IVIG effective in slowing or avoiding progression from Mild Cognitive Impairment to Alzheimer’s disease when compared to placebo?", EFF1b: "Are IVIG effective in improving biomarkers of progression from Mild Cognitive Impairment to Alzheimer’s disease when compared to placebo?", EFF1c: "Are IVIG effective in improving imaging markers of progression from Mild Cognitive Impairment to Alzheimer’s disease when compared to placebo?", EFF1d: "Are IVIG effective in slowing disease progression from mild-to-moderate to moderate-to-severe Alzheimer’s disease (measured with MMSE) when compared to placebo or acetyl cholinesterase inhibitors?", EFF1e: "Are IVIG effective in improving biomarkers of progression in patients with mild-to-moderate Alzheimer’s disease when compared to placebo or acetyl cholinesterase inhibitors?", EFF1f: "Are IVIG effective in improving imaging markers of progression in patients with mild-to-moderate Alzheimer’s disease when compared to placebo or acetyl cholinesterase inhibitors?", EFF1g: "Are IVIG effective in improving biomarkers of progression in patients with moderate-to-severe Alzheimer’s disease when compared to placebo or memantine?" and EFF1h: "Are IVIG effective in improving imaging markers of progression in patients with moderate-to-severe Alzheimer’s disease when compared to placebo or memantine?"

View full card

EFF1a: Are IVIG effective in slowing or avoiding progression from Mild Cognitive Impairment to Alzheimer’s disease when compared to placebo?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with MCI.

Importance: Critical

Transferability: Completely

EFF1b: Are IVIG effective in improving biomarkers of progression from Mild Cognitive Impairment to Alzheimer's disease when compared to placebo?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with MCI.

Importance: Optional

Transferability: Completely

EFF1c: Are IVIG effective in improving imaging markers of progression from Mild Cognitive Impairment to Alzheimer's disease when compared to placebo?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with MCI.

Importance: Optional

Transferability: Completely

EFF1d: Are IVIG effective in slowing disease progression from mild-to-moderate to moderate-to-severe Alzheimer's disease (measured with MMSE) when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with mild-to-moderate AD.

Importance: Critical

Transferability: Completely

EFF1e: Are IVIG effective in improving biomarkers of progression in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with mild-to-moderate AD.

Importance: Optional

Transferability: Completely

EFF1f: Are IVIG effective in improving imaging markers of progression in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with mild-to-moderate AD.

Importance: Optional

Transferability: Completely

EFF1g: Are IVIG effective in improving biomarkers of progression in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with moderate-to-severe AD.

Importance: Optional

Transferability: Completely

EFF1h: Are IVIG effective in improving imaging markers of progression in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with moderate-to-severe AD.

Importance: Optional

Transferability: Completely

Result card for EFF2a: "Are IVIG effective in improving neuropsychiatric symptoms in patients Mild Cognitive Impairment when compared to placebo?", EFF2b: "Are IVIG effective in improving behavioural symptoms in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?" and EFF2c: "Are IVIG effective in improving behavioural symptoms in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?"

View full card

EFF2a: Are IVIG effective in improving neuropsychiatric symptoms in patients Mild Cognitive Impairment when compared to placebo?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with MCI.

Importance: Important

Transferability: Completely

EFF2b: Are IVIG effective in improving behavioural symptoms in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

Data on behavioural changes, measured by NPI, were available from 300 patients (out of 383) of one RCT {NCT00818662}.

Mean score change from baseline at 18 months in NPI assessment did not differ between IVIG 400 mg/kg group (104 patients) and placebo group (94 patients) (0.7 point score of difference, 95%CI -2.1 to 3.4, P = 0.640) and between IVIG 200 mg/kg group (102 patients) and placebo group (94 patients) (2.5 point score of difference, 95CI -0.3 to 5.3, P = 0.075). See Appendix 2 for details.

Table 2. Summary of findings: behavioural changes in patients with mild-to-moderate AD treated with IVIG

Outcome	Mean difference between IVIG 400mg/kg and Placebo	Mean difference between IVIG 200mg/kg and Placebo	Confidence in effect estimate
Behaviour: NPI mean score change from baseline to 18 months	0.7 (95% CI -2.1 to 3.4); P = 0.640	2.5 (95% CI -0.3 to 5.3); P = 0.075	Very low

Importance: Critical

Transferability: Completely

EFF2c: Are IVIG effective in improving behavioural symptoms in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with moderate-to-severe AD.

Importance: Critical

Transferability: Completely

Mortality

Result card for EFF3a: "Are IVIG effective in reducing overall mortality in patients with Mild Cognitive Impairment when compared to placebo?", EFF3b: "Are IVIG effective in reducing overall mortality in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?" and EFF3c: "Are IVIG effective in reducing overall mortality in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?"

View full card

EFF3a: Are IVIG effective in reducing overall mortality in patients with Mild Cognitive Impairment when compared to placebo?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with MCI.

Importance: Important

Transferability: Completely

EFF3b: Are IVIG effective in reducing overall mortality in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with mild-to-moderate AD.

Importance: Important

Transferability: Completely

EFF3c: Are IVIG effective in reducing overall mortality in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with moderate-to-severe AD.

Importance: Important

Transferability: Completely

Function

Result card for EFF4a: "Are IVIG effective in improving cognitive functions of patients with Mild Cognitive Impairment when compared to placebo?", EFF4b: "Are IVIG effective in improving cognitive functions of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?" and EFF4c: "Are IVIG effective in improving cognitive functions of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?"

View full card

EFF4a: Are IVIG effective in improving cognitive functions of patients with Mild Cognitive Impairment when compared to placebo?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with MCI.

Importance: Unspecified

Transferability: Unspecified

EFF4b: Are IVIG effective in improving cognitive functions of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

Data on cognitive function changes, measured by ADAS-Cog (co-primary outcome) and ADCSC-GIC, were available from 300 and 298 patients respectively (out of 383) of one RCT {NCT00818662}. See Appendix 2 for detailed results.

Mean score change from baseline at 18 months in the ADAS-Cog did not differ between IVIG 400 mg/kg group (105 patients) and placebo group (95 patients) (-0.8 point score of difference, 95%CI -3.1 to 1.5; P = 0.476) and between IVIG 200 mg/kg group (100 patients) and placebo group (95 patients) (0.7 point score of difference, 95%CI -1.6 to 3.0; P = 0.530). Accordingly mean score change from baseline at 9 months in the ADAS-Cog did not differ between IVIG 400 mg/kg group and placebo group and between IVIG 200 mg/kg group and placebo group.

Difference in means from baseline at 18 months in the ADCSC-GIC did not differ between IVIG 400 mg/kg group (105 patients) and placebo group (92 patients) (Difference in least square means: -0.1, 95% CI -0.3 to 0.2; P = 0.660) and between IVIG 200 mg/kg group (101 patients) and placebo group (92 patients) (0.0, 95% CI -0.2 to 0.3 ; P = 0.766). Accordingly mean score change from baseline at 9 months in the ADCSC-GIC did not differ between IVIG 400 mg/kg group and placebo group and between IVIG 200 mg/kg group and placebo group. See Appendix 2 for details.

Table 3. Summary of findings: cognitive function changes in patients with mild-to-moderate AD treated with IVIG

Cognitive functions: ADAS-Cog mean score change from baseline to 18 months	-0.8 (95% CI -3.1 to 1.5); P = 0.476	0.7 (95% CI -1.6 to 3.0)*; P = 0.530	Very low
Cognitive functions: ADCSC-GIC change from baseline to 18 months	-0.1 (95% CI -0.3 to 0.2); P = 0.660	0.0 (95% CI -0.2 to 0.3); P = 0.766	Very low

Importance: Critical

Transferability: Completely

EFF4c: Are IVIG effective in improving cognitive functions of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with moderate-to-severe AD.

Importance: Critical

Transferability: Completely

Result card for EFF5a: "Are IVIG effective in improving activities of daily living of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?" and EFF5b: "Are IVIG effective in improving activities of daily living of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?"

View full card

EFF5a: Are IVIG effective in improving activities of daily living of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

Data on activity of daily living changes, measured by ADCS-ADL (co-primary outcome), were available from 301 patients (out of 383) of one RCT {NCT00818662}. See Appendix 2 for details.

Mean score change from baseline at 18 months in ADCS-ADL did not differ between IVIG 400 mg/kg group (104 patients) and placebo group (95 patients) (0.4, 95% CI -2.9 to 3.7; P = 0.812) and between IVIG 200 mg/kg group (102 patients) and placebo group (95 patients) (-0.9, 95% CI -4.3 to 2.5; P = 0.602). Accordingly mean score change from baseline at 9 months in in ADCS-ADL did not differ between IVIG 400 mg/kg group and placebo group and between IVIG 200 mg/kg group and placebo group.

Table 4. Summary of findings: activity of daily living changes in patients with mild-to-moderate AD treated with IVIG

Activities of daily living: ADCS-ADL mean score change from baseline to 18 months	0.4 (95% CI -2.9 to 3.7); P = 0.812	-0.9 (95% CI -4.3 to 2.5); P = 0.602	Very low

Importance: Critical

Transferability: Completely

EFF5b: Are IVIG effective in improving activities of daily living of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with moderate-to-severe AD.

Importance: Critical

Transferability: Completely

Health-related Quality of life

Result card for EFF6a: "Are IVIG effective in improving generic health-related quality of life of patients with Mild Cognitive Impairment when compared to placebo?", EFF6b: "Are IVIG effective in improving generic health-related quality of life of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?", EFF6c: "Are IVIG effective in improving generic health-related quality of life of caregivers of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?" and EFF6d: "Are IVIG effective in improving generic health-related quality of life of caregivers of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?"

View full card

EFF6a: Are IVIG effective in improving generic health-related quality of life of patients with Mild Cognitive Impairment when compared to placebo?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence is available on effectiveness of IVIG for patients with MCI.

Importance: Important

Transferability: Completely

EFF6b: Are IVIG effective in improving generic health-related quality of life of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence on generic health related quality of life is available for patients with mild-to-moderate AD.

Importance: Important

Transferability: Completely

EFF6c: Are IVIG effective in improving generic health-related quality of life of caregivers of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence on generic health related quality of life is available for caregivers of patients with mild-to-moderate AD.

Importance: Important

Transferability: Completely

EFF6d: Are IVIG effective in improving generic health-related quality of life of caregivers of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence on generic health related quality of life is available for caregivers of patients with moderate-to-severe AD.

Importance: Important

Transferability: Completely

Result card for EFF7a: "Are IVIG effective in improving disease specific health-related quality of life of patients with mild-to- moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?", EFF7b: "Are IVIG effective in improving disease specific health-related quality of life of caregivers of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?" and EFF7c: "Are IVIG effective in improving disease specific health-related quality of life of caregivers of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?"

View full card

EFF7a: Are IVIG effective in improving disease specific health-related quality of life of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

Data on disease specific health related quality of life changes of patients, measured by QOLAD, were available from 284 patients (out of 383) of one RCT {NCT00818662}. See Appendix 2 for details.

Mean score change from baseline at 18 months in QOLAD did not differ between IVIG 400 mg/kg group (99 patients) and placebo group (86 patients) (1.1, 95% CI -0.2 to 2.3; P = 0.094) and between IVIG 200 mg/kg group (99 patients) and placebo group (86 patients) (1.1, 95% CI -0.2 to 2.3; P = 0.094).

Table 5. Summary of findings: Disease specific health related quality of life in patients with mild-to-moderate AD treated with IVIG

Disease specific health related quality of life in patients: QOLAD mean score change from baseline to 18 months	1.1 (95% CI -0.2 to 2.3); P = 0.094	1.1 (95% CI -0.2 to 2.3); P = 0.094	Very low

Importance: Important

Transferability: Completely

EFF7b: Are IVIG effective in improving disease specific health-related quality of life of caregivers of patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

Data on disease specific health related quality of life changes of caregivers, measured by QOLAD, were available from 290 patients (out of 383) of one RCT {NCT00818662}. See Appendix 2 for details.

Mean score change from baseline at 18 months in QOLAD did not differ between IVIG 400 mg/kg group (99 caregivers) and placebo group (92 caregivers) (-1.1 95% CI -2.3 to 0.2; P = 0.096) and between IVIG 200 mg/kg group (99 caregivers) and placebo group (92 caregivers) (-1.0, 95% CI -2.2 to 0.3; P = 0.123).

Table 6. Summary of findings: Disease specific health related quality of life in in caregivers of patients with mild-to-moderate AD treated with IVIG

Disease specific health related quality of life in caregivers: QOLAD mean score change from baseline to 18 months	-1.1 95% CI -2.3 to 0.2; P = 0.096	-1.0, 95% CI -2.2 to 0.3; P = 0.123	Very low

Importance: Important

Transferability: Completely

EFF7c: Are IVIG effective in improving disease specific health-related quality of life of caregivers of patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence on disease specific health related quality of life is available for caregivers of patients with moderate-to-severe AD.

Importance: Important

Transferability: Completely

Change-in management

Result card for EFF8a: "Does IVIG impact on the need for hospitalization in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?", EFF8b: "Does IVIG impact on the need for institutionalization in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?", EFF8c: "Does IVIG impact on the need for hospitalization in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?" and EFF8d: "Does IVIG impact on the need for institutionalization in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?"

View full card

EFF8a: Does IVIG impact on the need for hospitalization in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence on hospitalization is available for patients with mild-to-moderate AD.

Importance: Important

Transferability: Completely

EFF8b: Does IVIG impact on the need for institutionalization in patients with mild-to-moderate Alzheimer's disease when compared to placebo or acetyl cholinesterase inhibitors?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence on institutionalization is available for patients with mild-to-moderate AD.

Importance: Important

Transferability: Completely

EFF8c: Does IVIG impact on the need for hospitalization in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence on hospitalization is available for patients with moderate-to-severe AD.

Importance: Important

Transferability: Completely

EFF8d: Does IVIG impact on the need for institutionalization in patients with moderate-to-severe Alzheimer's disease when compared to placebo or memantine?

Method

The same methodology was used as described in section for the whole domain.

Result

No evidence on institutionalization is available for patients with moderate-to-severe AD.

Importance: Important

Transferability: Completely

Benefit-harm balance

Result card for EFF9a: "What are the overall benefits and harms of IVIG in health outcomes of patients with Mild Cognitive Impairment?", EFF9b: "What are the overall benefits and harms of IVIG in health outcomes of patients with mild-to-moderate Alzheimer's disease?" and EFF9c: "What are the overall benefits and harms of IVIG in health outcomes of patients with moderate-to-severe Alzheimer's disease?"

View full card

EFF9a: What are the overall benefits and harms of IVIG in health outcomes of patients with Mild Cognitive Impairment?

Result

x

Importance: Unspecified

Transferability: Unspecified

EFF9b: What are the overall benefits and harms of IVIG in health outcomes of patients with mild-to-moderate Alzheimer's disease?

Method

The same methodology was used as described in section for the whole domain.

Result

x

Importance: Unspecified

Transferability: Unspecified

EFF9c: What are the overall benefits and harms of IVIG in health outcomes of patients with moderate-to-severe Alzheimer's disease?

Method

The same methodology was used as described in section for the whole domain.

Result

x

Importance: Unspecified

Transferability: Unspecified

Discussion

There is limited evidence on IVIG in adults with mild-to-moderate AD and no evidence for adults with MCI or moderate-to-severe AD.

The systematic search of electronic databases retrieved 5 published studies: 2 RCTs {Arai 2014, Dodel 2013}, 2 prospective interventional non-controlled studies {Dodel 2004, Relkin 2009}, and 1 observational study {Devi 2008} – including patients with mild-to-moderate AD. They were not eligible for inclusion and were used to illustrate the state of development of research. No studies were found for MCI and moderate-to-severe AD.

During the periodical check of registers of ongoing trials, a previously tracked completed but not published RCT {NCT00818662} had final results posted by the study sponsor in October 23rd 2014. Inclusion of this study in the assessment was decided by Editorial Team. Authors and sponsor were previously contacted (May 2014) but they did not provide any data. No further contacts were sought. The included RCT is a phase 3 double-blind, placebo-controlled study, including 383 patients with mild-to-moderate AD. Data show that any important clinical outcomes such as cognitive functions (according to ADAS-Cog and ADCSC-GIC), activity of daily living (ADCS-ADL) and quality of life (both in patients and caregivers according to QOLAD) did not differ between IVIG groups (400 mg/kg or 200 mg/kg) versus placebo groups after 70 weeks of treatment. The confidence in effect estimate for overall evidence on all considered outcomes is *very low*, according to GRADE method, due to high risk of bias.

We have documented the missing publication of another RCT {NCT00299988} and of other six interventional non-controlled studies. All these studies included subjects with mild-to-moderate AD.

Other two ongoing RCTs have been recorded: one phase 2, dose-finding, including 50 subjects with MCI {NCT01300728}, and one phase 2/3, including 350 subjects with mild-to-moderate AD {NCT01561053}. Trials are reported to or expected to end in November 2014 and December 2016, respectively.

The published studies were conducted in hospitals, research centres and private clinics in Germany and USA. The tested therapeutic schemes and the duration of treatment varied substantially. The IVIGs used in published studies were Gammagard by Baxter Healthcare Corporation and Octagam by Octapharma AG. The unpublished study {NCT00818662} – by Baxter Healthcare Corporation - used Gammagard Liquid (200 mg or 400 mg/kg every 2 weeks). The ongoing RCTs are testing Flebogamma by Grifols S.A. and NewGam by Sutter Health. The latter study tests IVIG (high dose or low dose – no other details provided) together with plasmapheresis against plasmapheresis alone or against infusion of 20% albumin.

Implications for practice

At present there is limited evidence on lack of effectiveness of IVIG in adults with mild-to-moderate AD, and no evidence for adults with MCI and moderate-to-severe AD.

Implications for research

Publication bias was identified in the evidence base of subjects with mild-to-moderate AD. Two RCTs have been recently completed but not published {NCT00299988, NCT00818662}. One of them had its results recently posted on a clinical trial register. Another RCT including 350 patients will be ended within the next two years {NCT01561053}. Future complete access to all these data might provide valuable evidence to assess effectiveness of IVIG for these patients. No further trials would be advised before full publication of these studies. One small study on subjects with MCI {NCT01300728} is awaiting completion. It would produce only preliminary short term data on surrogate outcomes. Other studies – if suitable – will have to be devised to assess patient important outcomes in the long term. The category of moderate-to-severe AD is not considered for future study, probably because the rationale of IVIG's use for advanced AD is weak or absent.

References

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270-9.

Arai H, Ichimiya Y, Shibata N, Nakajima T, Sudoh S, Tokuda T, Sujaku T, Yokokawa S, Hoshii N, Noguchi H, Bille A. Safety and tolerability of immune globulin intravenous (human), 10% solution in Japanese subjects with mild to moderate Alzheimer's disease. Psychogeriatrics 2014;14:165-74.

Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. Lancet 2011; 377:1019-31.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64:401-6.

Bischkopf J, Busse A, Angermeyer MC. Mild cognitive impairment--a review of prevalence, incidence and outcome according to current approaches. Acta Psychiatr Scand 2002; 106:403-14.

Buchhave P, Minthon L, Zetterberg H, Wallin AK, Blennow K, Hansson O. Cerebrospinal fluid levels of β-amyloid 1-42, but not of tau, are fully changed already 5 to 10 years before the onset of Alzheimer dementia. Arch Gen Psychiatry 2012;69:98-106.

Cooper C, Li R, Lyketsos C, Livingston G. Treatment for mild cognitive impairment: systematic review. Br J Psychiatry 2013; 203:255-64.

Dodel R, Hampel H, Depboylu C, Lin S, Gao F, Schock S, Jäckel S, Wei X, Buerger K, Höft C, Hemmer B, Möller HJ, Farlow M, Oertel WH, Sommer N, Du Y. Human antibodies against amyloid beta peptide: a potential treatment for Alzheimer's disease. Ann Neurol 2002;52:253-6.

Dodel R, Rominger A, Bartenstein P, Barkhof F, Blennow K, Förster S, Winter Y, Bach JP, Popp J, Alferink J, Wiltfang J, Buerger K, Otto M, Antuono P, Jacoby M, Richter R, Stevens J, Melamed I, Goldstein J, Haag S, Wietek S, Farlow M, Jessen F. Intravenous immunoglobulin for treatment of mild-to-moderate Alzheimer's disease: a phase 2, randomised, double-blind, placebo-controlled, dose-finding trial. Lancet Neurol 2013;12:233-43.

Du Y, Dodel R, Hampel H, Buerger K, Lin S, Eastwood B, Bales K, Gao F, Moeller HJ, Oertel W, Farlow M, Paul S. Reduced levels of amyloid beta-peptide antibody in Alzheimer disease. Neurology 2001 11;57:801-5.

EUnetHTA Joint Action WP5. HTA Core Model for Rapid Relative Effectiveness Assessment of Pharmaceuticals. 1 March 2013 – V3.0. Available at http://www.eunethta.eu/outputs/new-application-hta-core-model-hta-core-model-rapid-relative-effectiveness-assessment-pharma; last access February 19th 2014.

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011a; 64:383-94.

Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol 2011b; 64:407-15

Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol 2011c; 64:1277-82.

Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, Devereaux PJ, Montori VM, Freyschuss B, Vist G, Jaeschke R, Williams JW Jr, Murad MH, Sinclair D, Falck-Ytter Y, Meerpohl J, Whittington C, Thorlund K, Andrews J, Schünemann HJ. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol 2011d; 64:1283-93.

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol 2011e; 64:1294-302.

Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol 2011f; 64: 1303-10.

Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, Atkins D, Kunz R, Brozek J, Montori V, Jaeschke R, Rind D, Dahm P, Meerpohl J, Vist G, Berliner E, Norris S, Falck-Ytter Y, Murad MH, Schünemann HJ; GRADE Working Group. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011g; 64:1311-6

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou P, Christensen R, Schünemann HJ. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013; 66:158-72.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Chapter 5: Defining the review question and developing criteria for including studies; last access February 19th 2014.

HTA Core Model Handbook Online, Version 1.5. Available at https://meka.thl.fi/htacore/ViewHandbook.aspx, access 8th October 2014.

HTA Core Model Application for Pharmaceuticals, 2.0. Available at https://meka.thl.fi/htacore/ViewApplication.aspx?id=14235, access 8th October 2014.

Jack CR Jr, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, Shaw LM, Vemuri P, Wiste HJ, Weigand SD, Lesnick TG, Pankratz VS, Donohue MC, Trojanowski JQ. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013 ;12:207-16.

Loeffler DA. Intravenous immunoglobulin and Alzheimer's disease: what now? J Neuroinflammation 2013 Jun 5;10:70.

McDade EM, Petersen RC. Mild cognitive impairment: Epidemiology, pathology, and clinical assessment. UpToDate® 2014; available from www.uptodate.com; accessed 2014 January 9th.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7:263-9.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(6): e1000097. doi:10.1371/journal.pmed1000097

National Institute on Aging. Alzheimer’s disease - Unraveling the Mystery. U.S. Department of Health and Human Services NIH Publication Number: 08-3782; September 2011; available from www.nia.nih.gov/alzheimers, last access 29th January 2014.

National Institute for Health and Clinical Excellence (NICE). NICE technology appraisal guidance 217 Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer’s disease (review of NICE technology appraisal guidance 111). 2011; available from www.nice.org.uk/guidance/TA217, accessed 2014 Jan 30th.

NCT00299988. Available at http://prsinfo.clinicaltrial.gov/ct2/show/NCT00299988?term=NCT00299988&rank=1; last access 16th December 2014.

NCT00818662. Available at http://prsinfo.clinicaltrial.gov/ct2/show/record/NCT00818662?term=NCT00818662&rank=1; last access 16th December 2014.

NCT01300728. Available http://prsinfo.clinicaltrial.gov/ct2/show/NCT01300728?term=NCT01300728&rank=1, last access 16th December 2014.

NCT01524887. Available at http://prsinfo.clinicaltrial.gov/ct2/results?term=NCT01524887&Search=Search, last access 16th December 2014.

NCT01561053. Available at http://prsinfo.clinicaltrial.gov/ct2/show/NCT01561053?term=NCT01561053&rank=1, last access 16th December 2014.

NCT01736579. Available at http://prsinfo.clinicaltrial.gov/ct2/results?term=NCT01736579&Search=Search, last access 16th December 2014.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303-8.

Relkin NR, Szabo P, Adamiak B, Burgut T, Monthe C, Lent RW, Younkin S, Younkin L, Schiff R, Weksler ME. 18-Month study of intravenous immunoglobulin for treatment of mild Alzheimer disease. Neurobiol Aging 2009;30:1728-36.

Silvergleid AJ, Berger M. General principles in the use of immune globulin. 2013a UpToDate®; available from www.uptodate.com, last access 9th October 2013.

Weksler ME, Goodhardt M. Do age-associated changes in 'physiologic' autoantibodies contribute to infection, atherosclerosis, and Alzheimer's disease? Exp Gerontol. 2002;37:971-9.

Appendices

Appendix 1

Figure A1.1. Flow chart of study selection for the effectiveness domain.

From: {Moher 2009}.

Appendix 2

Included Studies

Table A2.1. Characteristics of included studies (see Appendix 5 for more details).

Reference	Last update	Study design	Participants	Intervention (duration)	Control	EFF issues	EFF outcome measure	Funding
NCT00818662	October 23th 2014 (Clinicaltrials.gov)	phase 3 RCT	383 patients () with mild-to-moderate AD	IVIG (Gammagard Liquid) 200 mg or 400 mg/kg every 2 weeks (70 weeks)	Placebo: Human Albumin 0.25% 4 mL/kg or 2 mL/kg; every 2weeks (70 weeks)	Function D0011	Cognitive functions changes measured by ADAS-Cog at 9 and 18 months	Baxter Healthcare Corporation
						Function D0016	Activities of daily living changes measured by ADCS-ADL at 9 and 18 months	
						Function D0011	Cognitive functions changes measured by Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCSC-GIC) at 9 and 18 months	
						Morbidity D0005	Behavioural changes measured by Neuropsychiatric Inventory (NPI) at 18 months	
						Health-related Quality of life D0013	Disease specific health related quality of life changes in patients measured by Logsdon Quality of Life in Alzheimer's Disease (QOLAD) at 18 months	
						Health-related Quality of life D0013	Disease specific health related quality of life changes in caregivers measured by Logsdon Quality of Life in Alzheimer's Disease (QOLAD) at 18 months	

Table A2.2. GRADE Evidence profile on effectiveness of IVIG in mild-to-moderate AD, at overall and study level.

Cognitive functions: ADAS-Cog mean score change (± SD) from baseline to 18 months														

1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	7.4 ± 7.95 (105)	8.9 ± 8.20 (100)	8.4 ± 9.37 (95)	-0.8 (-3.1 to 1.5); P = 0.476^	0.7 (-1.6 to 3.0); P = 0.530^	No difference between groups	Very low	
Cognitive functions: ADAS-Cog mean score change (± SD) from baseline to 9 months														
1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	2.7 ± 5.20 (114)	4.5 ± 6.16 (114)	3.5 ± 6.44 (106)	-0.7 (-2.3 to 0.8); P = 0.368^	0.8 (-0.8 to 2.4); P = 0.319^	No difference between groups	Very low	
Cognitive functions: ADCSC-GIC change (units: patients) from baseline to 18 months														
1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	Very much better: 0 Much better: 1 A little better: 6 Same: 15 A little worse: 44 Much worse: 32 Very much worse: 7 (105)	Very much better: 0 Much better: 2 A little better: 1 Same: 15 A little worse: 43 Much worse: 33 Very much worse: 7 (101)	Very much better: 0 Much better: 1 A little better: 3 Same: 16 A little worse: 36 Much worse 32 Very much worse: 4 (92)	-0.1 (-0.3 to 0.2); P = 0.660#	0.0 (-0.2 to 0.3); P = 0.766#	No difference between groups	Very low	
Cognitive functions: ADCSC-GIC change (units: patients) from baseline to 9 months														
1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	Very much better: 0 Much better: 2 A little better: 7 Same: 33 A little worse: 52 Much worse: 19 Very much worse: 1 (114)	Very much better: 0 Much better: 1 A little better: 3 Same: 33 A little worse: 56 Much worse: 18 Very much worse: 3 (114)	Very much better: 0 Much better: 1 A little better: 7 Same: 36 A little worse: 48 Much worse 12 Very much worse: 0 (104)	0.1 (-0.1 to 0.3); P = 0.306#	0.3 (0.0 to 0.5); P = 0.028#	No difference between IVIG 400mg/kg group and Placebo group Difference between 200mg/kg group and Placebo group, in favour of Placebo group	Very low	
Activities of daily living: ADCS-ADL mean score change (± SD) from baseline to 18 months														
1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	-11.4 ± 10.49 (104)	-12.4 ± 11.41 (102)	-11.4 ± 12.19 (95)	0.4 (-2.9 to 3.7); P = 0.812^	-0.9 (-4.3 to 2.5); P = 0.602^	No difference between groups	Very low	
Activities of daily living: ADCS-ADL mean score change (± SD) from baseline to 9 months														
1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	-5.4 ± 7.03 (111)	-6.1 ± 8.13 (116)	-5.8 ± 8.32 (107)	0.3 (-1.8 to 2.4); P = 0.778^	-0.2 (-2.3 to 1.9); P = 0.851^	No difference between groups	Very low	
Behaviour: NPI mean score change (± SD) from baseline to 18 months														
1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	3.7 ± 12.93 (104)	4.9 ± 13.30 (102)	2.4 ± 10.77 (94)	0.7 (-2.1 to 3.4); P = 0.640^	2.5 (-0.3 to 5.3); P = 0.075^	No difference between groups	Very low	

Disease specific health related quality of life in patients: QOLAD mean score change (± SD) from baseline to 18 months														
1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	-0.5 ± 5.34 (99)	-0.7 ± 4.40 (99)	-1.5 ± 5.20 (86)	1.1 (-0.2 to 2.3); P = 0.094^	1.1 (-0.2 to 2.3); P = 0.094^	No difference between groups	Very low	
Disease specific health related quality of life in caregivers: QOLAD mean score change (± SD) from baseline to 18 months														
1/383	**RCT** NCT00818662	High§ -2	No indirectness	No inconsistency (only 1 trial)	No serious imprecision	Limitations* - 1	-3.0 ± 4.97 (99)	-2.5 ± 5.17 (99)	-1.6 ± 5.12 (92)	-1.1 (-2.3 to 0.2); P = 0.096^	-1.0 (-2.2 to 0.3); P = 0.123^	No difference between groups	Very low	

§ Not available details for assessing the major sources of bias; presence of risk of attrition bias

* Industry funded; detection of publication bias

^Method of analysis: ANCOVA (as reported in clinicaltrial.gov: results combined from 100 imputations from estimates & standard errors from 100 ANCOVA results for fixed effect of treatment, E4 allele of apolipoprotein E carrier status, & continuous covariates age at baseline, baseline ADASCog & education level)

Method of analysis: Mixed Models Analysis.

Appendix 3

Excluded studies

Table A3.1: Characteristics of published studies (see Appendix 5 for more details).

Reference	Study design	Participants	Intervention (duration)	Control	EFF issues	EFF outcome measure	Funding
Arai 2014	multiple dose, placebo controlled, RCT	16 patients (12 experimental group; 4 control group) with mild-to-moderate Alzheimer Disease	one of two doses of intravenous immunoglobulin (0·2 g/kg, 0·4 g/kg) every 2 weeks (12 weeks)	placebo (50-mL 0.25% human albumin solution) every 2 weeks	Function D0011	None of the prespecified ADAS-Cog, CDR-GS Cognitive functions measured MMSE	Not reported
Devi 2008	Observational-retrospective study	10 patients with AD	IVIG 0.4 g/kg every 2 weeks (3-6 months)	None	Function D0011	None of the prespecified ADAS-Cog, CDR-GS Cognitive functions measured by WAIS, WMS, Boston	Not reported
Dodel 2004	Interventional prospective non-controlled study	5 patients with AD (4 mild-to-moderate; 1 moderate-to-severe)	IVIG (OctagamH) 0.4 g/kg on three consecutive days every 4 weeks (6 months)	None	Function D0011	Cognitive functions measured by ADAS-Cog Other: MMSE, CERAD neuropsychological test battery	Public Octapharma (Lagenfeld, Germany) provided IVIG
					Morbidity D0006	Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)	
Dodel 2013	phase 2, dose-finding; placebo controlled, RCT	58 patients (42 experimental group; 14 control group) with mild-to-moderate AD	one of three doses of intravenous immunoglobulin (0·2 g/kg, 0·5 g/kg, or 0·8 g/kg) every 4 weeks, or half of that dose (0·1 g/kg, 0·25 g/kg, or 0·4 g/kg) every 2 weeks (24 weeks)	placebo (0·9% isotonic sodium chloride) every 4 weeks or every 2 weeks	Function D0011	Cognitive functions measured by ADAS-Cog, CDR-GS Other: MMSE	Octapharma AG
					Function D0016	Activities of daily living measured by ADCS-ADL	
					Morbidity D0006	Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)	
					Morbidity D0006	Variation of imaging signs (change in ventricular volumetric as measured by MRI)	
Relkin 2009	Interventional prospective dose finding study	8 patients with mild-to-moderate AD	one of four IVIG (Gammagard S/D) doses (0.4 g/kg/2 weeks, 0.4 g/kg/week, 1 g/kg/2 weeks and 2 g/kg/4 weeks) (6 months + 9 months)	None	Function D0011	None of the prespecified ADAS-Cog, CDR-GS	Public and Baxter Bioscience Corporation

						Cognitive functions measured by MMSE	
					Morbidity D0006	Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)	

Table A3.2: Characteristics of unpublished studies, randomized controlled studies (see Appendix 5 for more details).

Reference	Last update	Study design	Participants	Intervention (duration)	Control	EFF issues	EFF outcome measure	Funding
NCT00299988	2010	phase 2 RCT	24 patients with mild-to-moderate AD	one of four doses of IVIG (from 0·2 g/kg every 2 weeks to 0·8 g/kg every month) (6 months)	Placebo	Function D0011	Cognitive functions measured by ADAS-Cog Other: ADCS-CGIC	Public, Baxter BioScience
						Function D0016	Activities of daily living measured by ADCS-ADL	
						Morbidity D0005	Behavioural changes measured by Neuropsychiatric Inventory (NPI)	
						Morbidity D0006	Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)	
						Morbidity D0006	Variation of imaging signs (change in SUVR at PIB-PET)	
						Health-related Quality of life D0012	Generic health related quality of life	
						Health-related Quality of life D0013	Disease specific health related quality of life	
						Function D0016	Activities of daily living measured by ADCS-ADL	
						Morbidity D0005	Behavioural changes measured by Neuropsychiatric Inventory (NPI)	
						Health-related Quality of life D0012	Generic health related quality of life	
						Health-related Quality of life D0013	Disease specific health related quality of life	

Table A3.3: Characteristics of unpublished studies, other designs (see Appendix 5 for more details).

Reference	Last update	Study design	Participants	Intervention (duration)	Control	EFF issues	EFF outcome measure	Funding
Kountouris 2000	2000	Open label, non-randomized controlled trial	16 patients with AD	IVIG (Octagam) 0,2 g/Kg + piracetam (12 months)	Piracetam	Function D0011	None of the prespecified ADAS-Cog, CDR-GS Cognitive functions measured by MMSE	Not reported
Papatriantafyllou 2006	2006	uncontrolled longitudinal study	6 patients with mild-to-moderate AD	total dose of 0.4g/Kg IVIG in three consecutive days every 4 weeks (6 months)	None	Function D0011	None of the prespecified ADAS-Cog, CDR-GS Cognitive functions measured by MMSE	Not reported
						Function D0016	Activities of daily living measured by ADCS-ADL	

						Morbidity D0005	Behavioural changes measured by Neuropsychiatric Inventory (NPI)	
Hara 2011	2011	Uncontrolled longitudinal study	10 patients with AD	IVIG (5.5-62.3 months)	None	Function D0011	None of the prespecified ADAS-Cog, CDR-GS Cognitive functions measured by Memory Performance Index, and the Functional Assessment Staging test	Not reported
Kondo 2011	2011	Uncontrolled longitudinal study	4 patients with AD	0.4 g/kg of IVIGfor 3 consecutive days every month for 3 months	None	Function D0011	None of the prespecified ADAS-Cog, CDR-GS Cognitive functions measured by MMSE	Not reported
						Morbidity D0006	Variation of imaging signs (change in SUVR at PIB-PET)	
Rovira 2011	2011	open label pilot uncontrolled longitudinal study	4 patients with mild-to-moderate AD	0.5 g/kg of IVIG (Flebogamma DIF, Grifols) every 2 weeks (6 months)	None	Function D0011	Cognitive functions measured by ADAS-Cog, CDR-GS Other: MMSE	Not reported
						Morbidity D0006	Variation of imaging signs (change in ventricular volumetric as measured by MRI)	
Relkin 2012 (open extension of NCT00299988)	2012	12 month open label extension of a Phase II, double blind placebo controlled study	16 patients with mild-to-moderate AD	IVIG (Gammagard, Baxter) 0.4g/kg/2 weeks (36 months)	None	Function D0011	Cognitive functions measured by ADAS-Cog Other: ADCS-CGIC	Not reported
						Function D0016	Activities of daily living measured by ADCS-ADL	
						Morbidity D0005	Behavioural changes measured by Neuropsychiatric Inventory (NPI)	
						Health-related Quality of life D0012	Generic health related quality of life	
						Health-related Quality of life D0013	Disease specific health related quality of life	

Table A3.4: Characteristics of terminated studies (see Appendix 5 for more details)

Reference	Last update	Study design	Participants	Intervention (duration)	Control	Funding
NCT01524887	2013 The study was terminated without enrol any patient because the first Phase 3 did not demonstrate efficacy on the co-primary endpoints	phase 3 RCT	patients with mild-to-moderate AD	Experimental: IVIG, 10% at Dose A (high dose) or Dose B (low dose) (18 months)	Placebo	Baxter Healthcare Corporation
NCT01736579	2013 The study was terminated after enrolment of 8 patients because the first Phase 3 did not demonstrate efficacy on the co-primary endpoints	open label extension previous study (NCT00818662)	patients with mild-to-moderate AD	IVIG (Gammagard Liquid) 200 mg or 400 mg/kg every 2 weeks (3 years)	None	Baxter Healthcare Corporation

Table A3.5: Characteristics of ongoing studies

Reference	Study design	Participants	Intervention (duration)	Control	EFF issues	EFF outcome measure	Funding
NCT01300728 (estimated completion November 2014)	phase 2 RCT	50 patients with MCI	IVIG (NewGam) at 0.4 g/kg every 14 days for a total of five infusions (two months)	Placebo	Morbidity D0006	Rate of progression or frequency of patients progressed to AD according to according to available AD validated criteria (NINCDS-ADRDA, ICD, DSM) at 24 months	Sutter Health
					Function D0011	Cognitive functions measured by ADAS-Cog, CDR-GS at 24 months Other: MMSE	
					Morbidity	Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-	

					D0006	42; increase of serum Aβ1-40/Aβ1-42) at 24 months	
					Morbidity D0006	Variation of imaging signs (change in ventricular volumetric as measured by MRI) at 24 months	
NCT01561053 (estimated completion December 2016)	phase 2/3 RCT	350 patients with mild-to-moderate AD	Plasmapheresis alone or with infusion of 20% albumin and IVIG high dose or low dose (14 months)	Sham procedure	Function D0011	Cognitive functions measured by ADAS-Cog Other: MMSE	Instituto Grifols, S.A.
					Function D0016	Activities of daily living measured by ADCS-ADL	
					Morbidity D0005	Behavioural changes (Neuropsychiatric Inventory – NPI)	
					Morbidity D0006	Variation of biomarkers (decrease of cerebrospinal fluid Aβ1-40/Aβ1-42; increase of serum Aβ1-40/Aβ1-42)	
					Morbidity D0006	Variation of imaging signs (change in ventricular volumetric as measured by MRI)	

Appendix 4

Stage of development of research

To describe the stage of development of current and future research on effectiveness on IVIG for MCI and AD we tabled the studies against the evidence profile.

MCI

Available evidence

No evidence is available on effectiveness of IVIG for patients with MCI.

Upcoming evidence

One ongoing phase 2 RCT will be able to provide preliminary data on some important clinical outcomes (frequency of patients progressed to AD and cognitive functions, however in a short time frame (24 months of follow up).

Table A4.1: Stage of development of research on effectiveness on IVIG for MCI.

IVIG for MCI			
Issue	**Outcome**	**MCI**	
		Available evidence	Upcoming evidence
Morbidity [D0006]	Rate of progression or frequency of patients progressed	None	1 phase 2 RCT (50 pts)
Mortality [D0001]	Overall mortality rate	None	None
Function [D0011]	Cognitive functions	None	1 phase 2 RCT (50 pts)
Morbidity [D0005]	Neuropsychiatric symptoms/Behavioural changes	None	None
Health-related Quality of life [D0012]	Generic health related quality of life	None	None
Morbidity [D0006]	Variation of biomarkers	None	1 phase 2 RCT (50 pts)
Morbidity [D0006]	Variation of imaging signs	None	1 phase 2 RCT (50 pts)

Mild-to-moderate AD

Available evidence

Comparative data about cognitive functions and activity of daily living are available from one phase 2 RCT on 58 patients (see Table A4.2) and and one phase 3 RCT (383 patients), the latter included in the present study. These studies were preceded by three small non-controlled studies investigating mainly effect of IVIG on surrogate outcomes.

Table A4.2: Synopsis of results of the phase 2, dose-finding, RCT by Dodel et al. {Dodel 2013}.

Issues and outcome measures at 24 weeks	**IVIg Dose/4 weeks (No. of pts)** **0.2 g/kg (6)** **0.5 g/kg (8)** **0.8 g/kg (7)**	**Placebo 4 weeks (No. pts =7)**	**Difference (95% CI) Placebo vs IVIg 4 weeks** **0.2 g/kg** **0.5 g/kg** **0.8 g/kg**	**Interpretation**	**IVIg Dose/2 weeks (No. pts)** **0.1 g/kg (6)** **0.25 g/kg (7)** **0.4 g/kg (7)**	**Placebo 2 weeks (No. pts =7)**	**Difference (95% CI) Placebo vs IVIg 2 weeks** **0.1 g/kg** **0.25 g/kg** **0.4 g/kg**	**Interpretation**
Function D0011 - Cognitive functions ADAS-cog median change from baseline (range) Higher scores worse	5.3 (–4.7 to 8.7) 1.8 (–8.0 to 24.0) –1.5 (–4.3 to 18.3)	0.3 (–3.3 to 5.0)	–3.8 (–9.3 to 4.0) –0.3 (7.0 to 5.7) 0.8 (–13.3 to 7.3)	No statistically significant difference between groups	2.5 (–3.7 to 6.0) –1.3 (–7.3 to 4.0) 4.5 (–4.0 to 8.3)	–0.3 (–5.3 to 5.0)	–3.0 (–7.0 to 1.7) 2.0 (–4.0 to 7.0) –4.3 (–10.7 to 2.3)	No statistically significant difference between groups
Function D0011 - Cognitive functions CDR-sum of boxes median change from baseline (range) Higher scores worse	0.5 (–1.0 to 3.0) 0.0 (–1.0 to 5.0) 0.3 (–1.5 to 3.0)	–0.5 (–6.0 to 0.0)	–1.5 (–6.5 to 0.0) –0.5 (–6.0 to 0.0) –1.3 (–5.5 to 0.5)	No statistically significant difference between groups	0.0 (–1.0 to 5.0) 0.5 (–2.0 to 2.0) 0.8 (–1.5 to 4.0)	0.0 (–2.5 to 1.5)	–1.3 (–3.5 to 0.5) –0.5 (–2.5 to 1.0) –2.5 (–3.5 to 0.0)	No statistically significant difference between groups
Function D0016 - Activities of daily living ADCS-ADL median change from baseline (range) Higher scores better	–3.0 (–31.0 to 11.0) 0.0 (–15.0 to 11.0) –1.5 (–5.0 to 3.0)	–3.0 (–8.0 to 7.0)	–19.0 (–13.0 to –25.0) –4.5 (–14.0 to 7.0) –1.5 (–8.0 to 6.0)	No statistically significant difference between groups	–0.5 (–11.0 to 4.0) –3.0 (–17.0 to 3.0) –4.0 (–25.0 to 2.0)	2.0 (–6.0 to 10.0)	3.0 (–3.0 to 10.0) 5.0 (–1.0 to 13.0) 6.5 (0.0 to 18.0)	No statistically significant difference between groups
Morbidity D0006 – median change in AUC of plasma Aβ1-40 (range)	–18.0 (–1347.0 to 1068.5) –364.3 (–5834.5 to 1953.5) –351.8 (–1084.0 to 936.5)	–116.3 (–1379.0 to 5266.0)	–32.5 (–1358.0 to 4197.5) 195.3 (–1005.5 to 5302.0) 235.5 (–984.5 to 4329.5)	No statistically significant difference between groups	–13.8 (–1729.0 to 307.0) –32.5 (–1102.5 to 451.5) 47.0 (–341.0 to 72.5)	159.5 (51.5 to 303.0)	159.8 (–124.5 to 1838.5) 200.5 (–51.0 to 474.5) 134.5 (4.5 to 500.5)	Statistically significant difference in the group of 0.4 g/kg: the effect was favoring placebo
Morbidity D0006 - median change in AUC of plasma Aβ1-42 (range)	–41.8 (–244.4 to 336.6) –119.3 (–1220.6to 375.0) –107.5 (–173.5 to 231.0)	–20.5 (–183.7 to 489.0)	30.3 (–234.6 to 346.4) 114.8 (–64.5 to 622.0) 87.00 (–95.7 to 275.5)	No statistically significant difference between groups	3.0 (–109.5 to 74.5) –33.5 (–190.6 to –16.5) –9.5 (–57.0 to 5.0)	24.0 (2.0 to 125.5)	26.5 (–45.0 to 133.5) 63.0 (40.0 to 178.0) 39.0 (–11.5 to –135.0)	Statistically significant difference in the groups of 0.25 and 0.4 g/kg: the effect was favoring placebo. C.I for the latter group are probably misprinted in the paper
Morbidity D0006 – mean (SD) change from baseline normalized whole brain volume (cm3) at MRI	–1.4 (1.8) –1.1 (1.0) –1.6 (1.1)	–0.9 (0.8)	0.5 (–1.7 to 2.7) 0.2 (–1.1 to 1.5) 0.7 (–0.7 to 2.2)	No statistically significant difference between groups	–2.0 (0.8) –1.5 (0.7) –1.4 (1.7)	–1.4 (1.0)	0.6 (–0.8 to 2.0) 0.1 (–1.1 to 1.3) 0.0 (–2.3 to 2.2)	No statistically significant difference between groups

Differences between treatment groups were assessed by t test (two-sided, α=0·05) for biomarkers and MRI results and by calculating Hodges-Lehmann estimates and non-parametric 95% CIs, compared with Wilcoxon rank sum test (normal approximation, two-sided, α=0·05) for the cognitive and functional scales.

Upcoming evidence

One completed unpublished RCT and one ongoing phase 2/3 RCT will be able to add comparative data on some important outcomes (cognitive functions, activity daily living, behavioural changes) of IVIG – according to different dosing and administration schemes – for some hundreds of patients and on long term (14 months). In the last decade four non-controlled studies result to be completed and unpublished. They will be able to add only very few data on efficacy outcomes.

Table A4.3: Stage of development of research on effectiveness on IVIG for mild-to-moderate AD.

IVIG for mild-to-moderate AD			
Issue	**Outcome**	**Mild-to-moderate AD**	
		Available evidence	Upcoming evidence
Morbidity [D0006]	Rate of progression or frequency of patients progressed	None	None

Mortality [D0001]	Overall mortality rate	None	None	
Function [D0011]	Cognitive functions	1 interventional prospective non-controlled study study (5 pts), 1 phase 2 RCT (58 pts), 1 phase 3 RCT (383 pts)	2 uncontrolled longitudinal studies (20 pts), 2 RCTs (764 pts)	
Function [D0011]	Activities of daily living	1 phase 2 RCT (58 pts), 1 phase 3 RCT (383 pts)	2 uncontrolled longitudinal studies (22 pts), 2 RCTs (374 pts)	
Morbidity [D0005]	Neuropsychiatric symptoms/Behavioural changes	1 phase 3 RCT (383 pts)	2 uncontrolled longitudinal studies (22 pts), 2 RCTs (374 pts)	
Health-related Quality of life [D0012]	Generic health related quality of life	None	1 uncontrolled longitudinal studies (16 pts), 1 RCT (24 pts)	
Health-related Quality of life [D0013]	Disease specific health related quality of life	1 phase 3 RCT (383 pts)	1 uncontrolled longitudinal study (16 pts), 1 RCT (24 pts)	
Change in management [D0010]	Hospitalization	None	None	
Change in management [D0010]	Institutionalization	None	None	
Morbidity [D0006]	Variation of biomarkers	2 interventional prospective non-controlled studies (13 pts), 1 phase 2 RCT (58 pts)	3 RCTs (764 pts)	
Morbidity [D0006]	Variation of imaging signs	1 phase 2 RCT (58 pts)	2 uncontrolled longitudinal studies studies (20 pts), 2 RCTs (374 pts)	

Moderate-to-severe AD

Available evidence

No evidence is available on effectiveness of IVIG for patients with moderate-to-severe AD.

Upcoming evidence

No evidence is foreseen to be available on effectiveness of IVIG for patients with moderate-to-severe AD.

Table A4.4: Stage of development of research on effectiveness on IVIG for moderate-to-severe AD.

IVIG for moderate-to-severe AD			
Issue	**Outcome**	**Moderate-to-severe AD**	
.		Available evidence	Upcoming evidence
Mortality [D0001]	Overall mortality rate	None	None
Function [D0011]	Cognitive functions	None	None
Function [D0011]	Activities of daily living	None	None
Morbidity [D0005]	Neuropsychiatric symptoms/Behavioural changes	None	None
Health-related Quality of life [D0012]	Generic health related quality of life	None	None
Health-related Quality of life [D0013]	Disease specific health related quality of life	None	None
Change in management [D0010]	Hospitalization	None	None
Change in management [D0010]	Institutionalization	None	None
Morbidity [D0006]	Variation of biomarkers	None	None
Morbidity [D0006]	Variation of imaging signs	None	None

Appendix 5

Appendix 6

Search strategy

Database: Pubmed

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014*
1	"Immunoglobulins, Intravenous"[Mesh]	9526	
2	venimmun OR "modified immune globulin" OR "ivig" OR "endobulin" OR "alpha globin" OR venoglobulin OR sandoglobulin OR "intraglobin" OR "globulin n" OR "privigen" OR "gamunex" OR "gammagard" OR "gamimmune" OR "gamimune" OR "flebogamma dif" OR "intravenous ig" OR "iveegam" OR "immunoglobulins iv" OR "immunoglobulins ivig" OR "immunoglobulins ivigs" OR "iv immunoglobulin" OR "iv immunoglobulins"[All Fields]	15230	
3	1 OR 2	15230	
4	"Mild Cognitive Impairment"[Mesh]	1647	
5	"Alzheimer Disease"[Mesh]	64256	
6	"Mild Cognitive Impairment"[title/abstract] OR dementia*[Title/Abstract] OR Alzheimer*[Title/Abstract] OR MCI[Abstract/Title]	137580	
7	4 OR 5 OR 6	144293	
8	3 AND 7	82	24

* search re-run with the same date limit in February 18 2015, in order to capture references previously not indexed with Mesh terms.

Database: EMBASE

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	'immunoglobulin'/exp/dd_iv	22907	
2	'endobulin':ab,ti OR 'ivig':ab,ti OR 'alpha globin':ab,ti OR venoglobulin:ab,ti OR sandoglobulin:ab,ti OR 'intraglobin':ab,ti OR 'globulin n':ab,ti OR 'privigen':ab,ti OR 'gamunex':ab,ti OR 'gammagard':ab,ti OR 'gamimmune':ab,ti OR 'gamimune':ab,ti OR 'flebogamma dif':ab,ti OR 'intravenous ig':ab,ti OR 'iveegam':ab,ti OR 'immunoglobulins iv':ab,ti OR 'immunoglobulins ivig':ab,ti OR 'immunoglobulins ivigs':ab,ti OR 'iv immunoglobulin':ab,ti OR 'iv immunoglobulins':ab,ti OR 'intravenous antibodies':ab,ti OR 'intravenous antibody':ab,ti OR 'intravenous immunoglobulin':ab,ti OR 'intravenous immunoglobulins':ab,ti AND [embase]/lim	14395	
3	1 OR 2	31178	
4	'dementia'/de OR 'alzheimer disease'/exp OR 'mild cognitive impairment'/exp	173965	
5	3 OR 4	359	42

Database: Cochrane Central Register of Controlled Trials

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014

1	MeSH descriptor: [Immunoglobulins, Intravenous] explode all trees	616	
2	('endobulin':ab,ti or 'ivig':ab,ti or 'alpha globin':ab,ti or venoglobulin:ab,ti or sandoglobulin:ab,ti or 'intraglobin':ab,ti or 'globulin n':ab,ti or 'privigen':ab,ti or 'gamunex':ab,ti or 'gammagard':ab,ti or 'gamimmune':ab,ti or 'gamimune':ab,ti or 'flebogamma dif':ab,ti or 'intravenous ig':ab,ti or 'iveegam':ab,ti or 'immunoglobulins iv':ab,ti or 'immunoglobulins ivig':ab,ti or 'immunoglobulins ivigs':ab,ti or 'iv immunoglobulin':ab,ti or 'iv immunoglobulins':ab,ti or 'intravenous antibodies':ab,ti or 'intravenous antibody':ab,ti or 'intravenous immunoglobulin':ab,ti or 'intravenous immunoglobulins':ab,ti)	2379	
3	1 OR 2	2467	
4	MeSH descriptor: [Alzheimer Disease] explode all trees	2065	
5	MeSH descriptor: [Mild Cognitive Impairment] explode all trees	65	
6	Alzheimer or "mild cognitive impairment" or "mild cognitive impairments"	5163	
7	4 OR 5 OR 6	5198	
8	3 AND 7	10	5

Database: Lilacs, Ibec, Medcarib

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	tw: immunoglobulin* AND (alzheimer* OR dementia OR ”mild cognitive impairment”)	11	0

Database: Isi web of Knowledge

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	Topic=(Venimmun OR "modified immune globulin" OR "ivig" OR "endobulin" OR "alpha globin" OR venoglobulin OR sandoglobulin OR "intraglobin" OR "globulin n" OR "privigen" OR "gamunex" OR "gammagard" OR "gamimmune") OR "gamimune" OR "flebogamma dif" OR "intravenous ig" OR "iveegam" OR "immunoglobulins iv" OR "immunoglobulins ivig" OR "immunoglobulins ivigs" OR "iv immunoglobulin" OR "iv immunoglobulins" OR "intravenous antibodies" OR "intravenous antibody" OR "intravenous immunoglobulin" OR "intravenous immunoglobulin" OR "intravenous immunoglobulins")		
2	Topic=(mci[title/abstract] OR "Mild Cognitive Impairments"[title/abstract] OR "Mild Cognitive Impairment"[title/abstract] OR dementia*[Title/Abstract] OR alzheimer* [Title/Abstract])		
3	1 AND 2	138	30

Clinical Registers

ALOIS: a comprehensive register of dementia studies

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	immunlobulin*	7	0

metaRegister of Controlled Trials (mRCT), including ISRCTN (International Standard Randomised Controlled Trial Number Register)

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	(immunoglobulin*) and (Alzheimer or dementia or “mild cognitive impairment”)	2	0

ClinicalTrials.gov

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	(alzheimer* OR dementia* OR "mild cognitive impairment") AND (immunoglobulin*)	51	21

NIH Clinical research studies

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	immunoglobulin* and Alzheimer	0	0

EU Clinical Trials Register website

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	immunoglobulin* and Alzheimer	4	0

International Clinical Trials Register Platform (ICTRP)

#	Searches	Results Search Date: 24/02/2014	Update 16/12/2014
1	immunoglobulin* and Alzheimer	4	0

Appendix 7

Use of Intravenous immunoglobulins for Mild Cognitive Impairment and Alzeheimer's disease - PROTOCOL

Costs and economic evaluation

Authors: Anna-Theresa Renner, Neill Booth, Esther Kraft, Ingrid Rosian-Schikuta, Matthias Schwenkglenks

Summary

In the absence of any discernible difference against placebo, no estimates of a trade-off between costs and benefits can be made at present

Introduction

In principle, economic evaluations of medical interventions provide one basis for decisions which involve the distribution of scarce resources. However, an economic evaluation is not the only relevant input to informed decision making and itself relies on other evidence (see, e.g., Strech D., 2007 {1}. Prior to considering costs and efficiency, it is usually regarded as appropriate and useful to incorporate evidence from two other forms of evaluation:

- Efficacy ("Can it work?")
- Effectiveness ("Does it work?")

(From: Drummond et al., {2})

Of these two forms of evaluation, evaluation of efficacy, including related safety considerations, is generally considered as a prerequisite for undertaking economic evaluation. Without reliable evidence as to the (potential) effect of an intervention, spending scarce resources on an intervention can be seen as being economically irrational.

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this 'Costs and economic evaluation' -domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation. At this stage in the development of the intervention, we therefore refrained from producing (necessarily incomplete) assessment elements in this domain.

Methodology

Frame

The collection scope is used in this domain.

Technology	Immunoglobulins (IGG) **Description** Naturally occurring proteins produced by the body's immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer's disease **Target condition** Alzheimer's disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.
Comparison	placebo, not doing anything or Usual supportive care **Description** There is no MA for IGGs for AD yet and there is no other intervention licensed for use in AD so the comparison would have to be against placebo or best supportive care
Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
E0001	Resource utilization	What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)?	yes	What types of resources are used when delivering IGG and its comparators (resource-use identification)?
E0002	Resource utilization	What amounts of resources are used when delivering the assessed technology and its comparators (resource-use measurement)?	yes	What amounts of resources are used when delivering IGG and its comparators (resource-use measurement)?
E0009	Resource utilization	What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)?	yes	What were the measured and/or estimated costs of IGG and its comparator(s) (resource-use valuation)?
E0005	Measurement and estimation of outcomes	What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)?	yes	What is(are) the measured and/or estimated health-related outcome(s) of IGG and its comparator(s)?
E0006	Examination of costs and outcomes	What are the estimated differences in costs and outcomes between the technology and its comparator(s)?	yes	What are the estimated differences in costs and outcomes between IGG and its comparator(s)?
E0010	Characterising uncertainty	What are the uncertainties surrounding the costs and economic evaluation(s) of the technology and its comparator(s)?	yes	What are the uncertainties surrounding the costs and economic evaluation(s) of IGG and its comparator(s)?
E0011	Characterising heterogeneity	To what extent can differences in costs, outcomes, or 'cost effectiveness' be explained by variations between any subgroups using the technology and its comparator(s)?	yes	To what extent can differences in costs, outcomes, or 'cost effectiveness' be explained by variations between any subgroups using IGG and its comparator(s)?
E0012	Validity of the	To what extent can the estimates of costs, outcomes, or economic evaluation(s) be	yes	To what extent can the estimates of costs, outcomes, or economic

	model(s)	considered as providing valid descriptions of the technology and its comparator(s)?		evaluation(s) be considered as providing valid descriptions of IGG and its comparator(s)?

Result cards

Resource utilization

Result card for ECO1: "What types of resources are used when delivering IGG and its comparators (resource-use identification)?"

View full card

ECO1: What types of resources are used when delivering IGG and its comparators (resource-use identification)?

Result

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this ‘Costs and economic evaluation’ domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation.

Importance: Unspecified

Transferability: Unspecified

Result card for ECO2: "What amounts of resources are used when delivering IGG and its comparators (resource-use measurement)?"

View full card

ECO2: What amounts of resources are used when delivering IGG and its comparators (resource-use measurement)?

Result

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this ‘Costs and economic evaluation’ - domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation.

Importance: Unspecified

Transferability: Unspecified

Result card for ECO3: "What were the measured and/or estimated costs of IGG and its comparator(s) (resource-use valuation)?"

View full card

ECO3: What were the measured and/or estimated costs of IGG and its comparator(s) (resource-use valuation)?

Result

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this ‘Costs and economic evaluation’ domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation.

Importance: Unspecified

Transferability: Unspecified

Measurement and estimation of outcomes

Result card for ECO4: "What is(are) the measured and/or estimated health-related outcome(s) of IGG and its comparator(s)?"

View full card

ECO4: What is(are) the measured and/or estimated health-related outcome(s) of IGG and its comparator(s)?

Result

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this ‘Costs and economic evaluation’ domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation.

Importance: Unspecified

Transferability: Unspecified

Examination of costs and outcomes

Result card for ECO5: "What are the estimated differences in costs and outcomes between IGG and its comparator(s)?"

View full card

ECO5: What are the estimated differences in costs and outcomes between IGG and its comparator(s)?

Result

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this ‘Costs and economic evaluation’ domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation.

Importance: Unspecified

Transferability: Unspecified

Characterising uncertainty

Result card for ECO6: "What are the uncertainties surrounding the costs and economic evaluation(s) of IGG and its comparator(s)?"

View full card

ECO6: What are the uncertainties surrounding the costs and economic evaluation(s) of IGG and its comparator(s)?

Result

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this ‘Costs and economic evaluation’ domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation.

Importance: Unspecified

Transferability: Unspecified

Characterising heterogeneity

Result card for ECO7: "To what extent can differences in costs, outcomes, or ‘cost effectiveness’ be explained by variations between any subgroups using IGG and its comparator(s)?"

View full card

ECO7: To what extent can differences in costs, outcomes, or ‘cost effectiveness’ be explained by variations between any subgroups using IGG and its comparator(s)?

Result

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this ‘Costs and economic evaluation’ domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation.

Importance: Unspecified

Transferability: Unspecified

Validity of the model(s)

Result card for ECO8: "To what extent can the estimates of costs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of IGG and its comparator(s)?"

View full card

ECO8: To what extent can the estimates of costs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of IGG and its comparator(s)?

Result

Given the lack of available data and lack of published evidence on the efficacy and/or the effectiveness of the intervention, the researchers (and internal reviewers) of this ‘Costs and economic evaluation’ domain agreed that it would not be prudent to undertake research into costs or undertake an economic evaluation.

Importance: Unspecified

Transferability: Unspecified

References

1. Strech D., 2007 Four levels of value judgments in the medical outcome assessment--a systematic approach to the analysis of implicit normativity in evidence based medicine. Zeitschrift fur arztliche Fortbildung und Qualitatssicherung. 2007;101(7):473-80)
2. Drummond et al., 2005 Methods for the Economic Evaluation of Health Care Programmes

Ethical analysis

Authors: Plamen Dimitrov, Anelia Koteva

Summary

IVIG assessment in patients with early Alzheimer’s disease complies with the fundamental ethical principles, as already mentioned. Identified and discussed are the challenges that the use of this technology may provoke for both the patients themselves and their families, on the one hand as well as for the medical staff and the healthcare system management, on the other hand. Part of the problems related to the protection of human dignity of dementia patients could be regulated by some European and international legal documents such as the Charter of Fundamental Rights of the European Union and the Convention for the Protection of Human Rights and Biomedicine, while others, associated with a fair and balanced distribution of health resources for society as a whole, should be addressed and regulated at national/ regional level.

Introduction

Due to its prevalence, duration, lack of effective therapy and complex patient care, Alzheimer's disease has recently become a highly important public health issue. Together with the scientific efforts to clarify the causes of the disease and find the most effective treatment and adequate care for the sick, the researchers seek to better understand the psychological and social impact of the disease on the patients themselves, their families and society as a whole.

The ethical analysis aims at providing a balance between norms and values through the discussion of social, political, cultural, legal, religious and economic issues arising from the opposition to the generally accepted societal values, healthcare system goals and the application of new technologies.

The present domain focuses on the ethical issues associated with the application of the innovative IVIG technology for the treatment of patients with MCI by debating the following areas:

- Improving the quality of life of patients;
- Impaired decision-making competence and freedom of choice/autonomy of patients with MCI;
- Fair and balanced distribution of resources;
- Equal access to treatment;
- Stigmatization.

Methodology

Frame

The collection scope is used in this domain.

Technology	Immunoglobulins (IGG) **Description** Naturally occurring proteins produced by the body's immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer's disease **Target condition** Alzheimer's disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.
Comparison	placebo, not doing anything or Usual supportive care **Description** There is no MA for IGGs for AD yet and there is no other intervention licensed for use in AD so the comparison would have to be against placebo or best supportive care
Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
F0100	Beneficence/nonmaleficence	What is the severity level of the condition that the technology is directed to?	yes	What is the severity level of the condition that IGG is directed to?
F0010	Beneficence/nonmaleficence	What are the known and estimated benefits and harms for patients when implementing or not implementing the technology?	yes	What are the known and estimated benefits and harms for patients when implementing or not implementing IGG?
F0011	Beneficence/nonmaleficence	What are the benefits and harms of the technology for other stakeholders (relatives, other patients, organisations, commercial entities, society, etc.)?	yes	What are the benefits and harms of IGG for other stakeholders (relatives, other patients, organisations, commercial entities, society, etc.)?
F0003	Beneficence/nonmaleficence	Are there any other hidden or unintended consequences of the technology and its applications for different stakeholders (patients/users, relatives, other patients, organisations, commercial entities, society etc.)?	yes	Are there any other hidden or unintended consequences of IGG and its applications for different stakeholders (patients/users, relatives, other patients, organisations, commercial entities, society etc.)?
F0005	Autonomy	Is the technology used for patients/people that are especially vulnerable?	yes	Is IGG used for patients/people that are especially vulnerable?
F0004	Autonomy	Does the implementation or use of the technology affect the patient´s capability and possibility to exercise autonomy?	yes	Does the implementation or use of IGG affect the patient´s capability and possibility to exercise autonomy?
F0006	Autonomy	Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy when the technology is used?	yes	Is there a need for any specific IGGs or supportive actions concerning information in order to respect patient autonomy when IGG is used?
F0007	Autonomy	Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles?	yes	Does the implementation or withdrawal of IGG challenge or change professional values, ethics or traditional roles?
F0009	Respect for persons	Does the implementation or use of the technology affect the user´s moral, religious or cultural integrity?	yes	Does the implementation or use of IGG affect the user's moral, religious or cultural integrity?
F0008	Respect for persons	Does the implementation or use of the technology affect human dignity?	no	This question is more in the area of legal issues. Implementation of IG do not affect any aspects of human dignity.
F0101	Respect for persons	Does the technology invade the sphere of privacy of the patient/user?	no	Every technology to some extend is dealing with the privacy of the patients. The current one has much less potential to harm privacy comparing with many others
F0012	Justice and Equity	How does implementation or withdrawal of the technology affect the distribution of health care resources?	yes	How does implementation or withdrawal of IGG affect the distribution of health care resources?
F0013	Justice and Equity	How are technologies with similar ethical issues treated in the health care system?	yes	How are technologies with similar ethical issues treated in the health care system?
H0012	Justice and Equity	Are there factors that could prevent a group or persons to participate?	yes	Are there factors that could prevent a group or persons to participate?
F0102	Ethical consequences of the HTA	Does the economic evaluation of the technology contain any ethical problems?	yes	Does the economic evaluation of IGG contain any ethical problems?
F0103	Ethical consequences of the HTA	What are the ethical consequences of the assessment of the technology?	yes	What are the ethical consequences of the assessment of IGG?
F0017	Ethical consequences of the HTA	What are the ethical consequences of the choice of end-points, cut-off values and comparators/controls in the assessment?	no	This intervention may not have various cut-off values and end-points. Therefore no ethical consequences to consider.
F0014	Legislation	Does the implementation or use of the technology affect the realisation of basic human rights?	no	This question falls within the scope of Legal domain. Such intervention by our opinion is far from harming basic human rights stated in the UN Universal Declaration of Human Rights
F0016	Legislation	Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations?	no	

Methodology description

The Ethical domain has been developed in compliance with the fundamental ethical principles, basically following the method of principalism. Consistently presented are ethical arguments related to the autonomy and benefits for the patient as well as possible complications and limitations pertaining to the implementation of the health technology discussed, without aiming to give a definite answer or “ethical prescription”.

The domain comprises 19 issues, preliminarily divided into 4 sections, as listed below:

- Section 1 – Beneficence/Nonmaleficence;
- Section 2 – Autonomy;
- Section 3 – Respect for Persons;
- Section 4 – Justice and Equity.

We have answered 14 issues. The other 5 issues we consider either irrelevant or have marked them as a “skipped issue”. More specifically unanswered are:

- Issue 10 (marked as irrelevant);
- Issue 11 (marked as irrelevant);
- Issue 17 (marked as irrelevant);
- Issue 18 (marked as irrelevant);
- Issue 19 (marked as skipped).

The object of the analysis is the treatment with intravenous immunoglobulins of patients with early-stage Alzheimer's disease – an innovative immunotherapy, which is still at the experimental stage.

The intravenous immunoglobulin infusions by maintaining optimal level of antibodies in the patient's organism constitute a form of an experimental passive immunotherapy with a potential for reduction of beta-amyloid plaques, where the technology is expected to help completely heal or significantly improve the cognitive status of the treated subjects with all subsequent benefits, i.e. improved social interaction and quality of life.

The object of treatment are adults of both sexes, diagnosed with Alzheimer's disease at the stage of MCI with an estimate of progression of the disease.

Alzheimer's disease, the most common cause of dementia, belongs to the group of neurodegenerative diseases characterized by unknown etiology, hereditary predisposition and gradual progression over many years. The disease is of great medical and social importance with unnoticeable onset and irreversible course, being incurable at present, leading to death.

Result cards

Beneficence/nonmaleficence

Result card for ETH1: "What is the severity level of the condition that IGG is directed to?"

View full card

ETH1: What is the severity level of the condition that IGG is directed to?

Result

Technological advances in medicine and healthcare over the past decades have increased the life expectancy of the population in industrialized countries, shifting the focus of public attention from communicable to chronic non-communicable diseases, including dementia.

According to WHO data for 2010, the approximate number of people suffering from dementia worldwide is estimated at 35.6 million people, with the figure expected to double by 2030 reaching 65.7 million people and more than triple by 2050 (115.4 million people)[1]. The total number of new cases of dementia each year amounts to 7.7 million, which makes one case every 4 seconds[2]. More recent figures, but in a regional context, are provided by the Alzheimer's Association, where 5.2 million Americans from all age groups are reported[3] to have Alzheimer's disease for 2013 in the USA alone. The same report states that 1 in 9 Americans over 65 years of age, respectively, one-third of the persons aged 85 and older suffer from the disease. Among the total number of individuals covering the criteria[4] for AD diagnosis, the distribution is as follows: 4% - below 65 years of age, 13% - aged between 65 and 74 years , 44% - 75-84 years and 38% - aged 85 and over. In terms of gender distribution, females prevail over males (about two-thirds of women and one third of men).

Dementia is not isolated from individuals alone; rather, it affects their family members, relatives and friends by involving significant healthcare and social care resources for persons with dementia, thus influencing the general public as well. Costs that society bears in health, economic and social dimensions are substantial, representing a huge burden on the budget. According to the WHO report, the global costs associated with dementia reached the impressive figure of USD 604 billion in 2010 (corresponding to 1.0% of the aggregated worldwide GDP)[5], of which the share of direct medical costs, measured in high-income countries, amounts to only 15%. The rest, being a much more, are indirect costs.

Therefore, the high morbidity of dementia on a global scale, including Alzheimer's disease, combined with the high cost of this condition in all spheres of public life, the growing need to provide long-term care for the persons with dementia and the related social isolation and stigmatization to cope with, make dementia a global challenge, placing it among public health priorities.

Alzheimer's disease, the most common cause of dementia, belongs to the group of neurodegenerative diseases characterized by unknown etiology, hereditary predisposition and gradual progression over many years. The disease is of great medical and social importance with unnoticeable onset and irreversible course, being incurable at present, leading to death.

In accordance with the most common description used by clinicians, the disease is known to progress slowly, lasting on average 10-12 years from the time of diagnosis. Early signs are often ignored by the patient and his/her relatives, being mistakenly attributed to aging, thus making it difficult to correctly and adequately diagnose. The most common symptom is the short-term memory loss expressed in difficulties in remembering or reminding

recent events and inability to acquire new knowledge and memories. As the disease progresses, the clinical signs become more obvious, being complemented by spatial and temporal disorientation, confusion, mood swings, depression, irritability, aggression, behavioral disturbances, abstract thinking problems, difficulties in speech and loss of long-term memory as well as complete personal degradation with worsening social skills, causing permanent disability and inability to lead full-value life. Finally, organ functions gradually diminish and death occurs.

In order to classify individuals with memory impairment that normally does not progress to dementia, in 1962 *V.A. Kral* proposed the term “benign senescent forgetfulness”[6]. In addition to the cognitive deficit remaining stable and not deepening in the course of time, these adults show a slight memory decrease when evaluated by memory tests, without significant deviation from age-related norms.

It is this state of gradual transition from norm to pathology that is identified in the literature as “mild cognitive impairment”. MCI is typical of persons without other neurological, psychiatric, vascular, endocrine, communicable and neoplastic diseases, injuries, drug or alcohol intoxication carrying the potential for such diversions, with the MCI individuals exhibiting memory impairment that is more pronounced than what should normally be expected for a certain age and education level with preserved consciousness and cognitions, and routine daily activities remaining undisturbed.

As noted above, the term makes it possible to distinguish between dementia patients and fake dementia ones as well as those characterized by an isolated cognitive deficit due to physiological aging. The first one is an example of irreversible dementia, while in the other mentioned groups memory deficit remains stable or reversal occurs.

It should be emphasized that mild cognitive impairment is not actually a diagnosis (or a distinct nosological unit); rather, it is a concept for which specialized literature has suggested relevant diagnostic criteria that have undergone modifications over time. The MCI term denotes a preclinical, prodromal stage, not automatically presuming the medical diagnosis of Alzheimer’s disease.

To conclude, mild cognitive impairment causes a slight but noticeable and measurable decline in cognitive status, being associated with an increased risk of developing Alzheimer’s disease in the future. Long-term studies have found that in persons aged 65 and above, the frequency of MCI varies from 10 to 20%[7], and in a small percentage of cases mild cognitive impairment may progress to Alzheimer’s disease or other types of dementia, without it necessarily being so. The creation of this term is important in view of its practical importance as far as it is bound to the likelihood to early diagnose that type of degenerative dementia that allows for the application of a more effective treatment.

[1] According to WHO data for 2010, published in “*Dementia: A Public Health Priority*”, World Health Organization , 2012, p.2, available at: http://apps.who.int/iris/bitstream/10665/75263/1/9789241564458_eng.pdf .

[2] Ibid, p.2., available at: http://apps.who.int/iris/bitstream/10665/75263/1/9789241564458_eng.pdf .

[3] “*2013 Alzheimer’s Disease Facts and Figures*”, Report of the Alzheimer’s Association, vol. 9, issue 2, 2013, p. 15, available at: http://www.alz.org/downloads/facts_figures_2013.pdf .

[4] The report explicitly states that it is based on estimates and not actual number of cases of dementia diagnosed by a physician, which is due to the impossibility to cover all patients. It is also noted in the report that half of the 5.2 million Americans exhibiting clinical symptoms of Alzheimer’s disease are probably not aware of this fact – author’s note.

[5] See: the WHO Report for 2010: “*Dementia: A Public Health Priority*”, World Health Organization, p. 25, available at: http://apps.who.int/iris/bitstream/10665/75263/1/9789241564458_eng.pdf .

[6] Kral, V., “*Senescent Forgetfulness: Benign and Malignant*”, Journal of the Canadian Medical Association, February, 1962, vol. 86 (6): 257-260, available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1848846/pdf/canmedaj00930-0002.pdf .

[7] According to the data of Alzheimer’s Association: http://www.alz.org/dementia/mild-cognitive-impairment-mci.asp .

Importance: Unspecified

Transferability: Unspecified

Result card for ETH2: "What are the known and estimated benefits and harms for patients when implementing or not implementing IGG?"

View full card

ETH2: What are the known and estimated benefits and harms for patients when implementing or not implementing IGG?

Result

Although there is no available medication for the treatment of Alzheimer's disease that may stop or reverse the course of the pathology, the process related to the development and testing of new innovative drugs still continues. Research efforts are primarily devoted to the elucidation of the pathogenetic mechanisms of Alzheimer's disease and the establishment of a comprehensive theoretical foundation on which modern disease-modifying therapy should be based on, as contrasted to current symptomatic treatment. In this sense, future hopes are associated with immunotherapy, which is believed to limit the development and deposition of abnormal amyloid protein in the brain.

The experimental technology, i.e. intravenous immunoglobulin infusions by maintaining optimal level of antibodies in the patient's organism constitutes a form of passive immunotherapy with a potential for reduction of beta-amyloid plaques, where the technology is expected to help completely heal or significantly improve the cognitive status of the treated subjects with all subsequent benefits, i.e. improved social interaction and quality of life.

A pilot study examining the efficacy and safety of the treatment of Alzheimer's disease with immunoglobulins, conducted by *Dodel et al.*[1] on five patients, who have been treated for over six months with the blood product, reported stabilization of cognitive function as measured by the neuropsychological test "Mini-Mental State Examination" together with reduction in beta-amyloid deposits in the cerebral spinal fluid compared to baseline.

Promising results were also reported by *Relkin et al*.[2] on a sample of eight patients. The authors found improved cognition and seized cognitive decline in the majority of patients based on MMSE scale following a six-month IVIG administration, suggesting that the method could delay, withhold or even reverse the course of the pathology.

In mid-2013 were announced the results from the phase III of a large-scale randomized double-blind placebo-controlled clinical trial[3] that enrolled 390 patients with mild to moderate Alzheimer's disease, who have been treated by intravenous immunoglobulins for 18 months. The study, popularly known as "GAP" ("Gammaglobulin Alzheimer's Partnership"), like in previous clinical trials, traces the biomarkers' dynamics and the change in the cognitive status of involved individuals. The results to date are contradictory.

Although the above-mentioned data generally demonstrate relatively good tolerability of the blood product, specialized medical literature seems to argue that the potential of the new therapeutic alternative should not be generalized. Despite the somewhat reduced risks associated with passive immunotherapy vs. active one, hazards do exist, being still unknown and unpredictable. The following side effects or complications that may occur during treatment with both active and passive immunotherapy have been reported[4]: autoimmune diseases, brain inflammation (meningoencephalitis), microhemorhages, increased amyloid angiopathy, residual neurofibrillary tangles, brain volume reductions and problems with blood-brain barrier passage of antibodies, posing a threat to patients' health and worsening their quality of life. Therefore, in view of these considerations very cautious administration of IVIG products is required only after thorough testing on nonmurine animal species (primates) and further validation.

Given that IVIG treatment is still at an experimental stage, it may need additional confirmation based on quite more studies with expanding the number of both the people involved and the time period, with the authors warning that the new approach should not be taken for a universal treatment strategy on the principle "One size fits all." and therefore not to be viewed as a first-choice therapeutic alternative.

With a view to the above considerations, involved medical personnel needs to be responsible for balancing benefits and risks. In bioethics literature, this is known as a "risk-benefit analysis" where the researcher must weigh and balance the possible benefits and damages occurring in the course of research. One of the main tasks of the medical staff is to ensure that the principle of nonmaleficence has been observed or refrain from causing harm to the subjects in the study by assuring that potential benefits exceed unknown risks. Other negative consequences, such as in the case of patients with compromised decision-making capacity must also be envisaged, for example a decisionally impaired person, who has significantly recovered due to the treatment, might realize his/her deteriorating physical and mental state and as a result become distressed, feel anxiety, hopelessness and despair, thus causing increased suicidal risk among these patients. Physicians should be prepared for timely response to prevent this side effect.

[1] Dodel, R.C., Y.Du, C. Depboylu, H. Hampel, L. Frölich, A. Haag, U. Hemmeter, S. Paulsen, S.J. Teipel, S. Brettschneider, A. Spottke, C. Nölker, H.J. Möller, X. Wei, M. Farlow, N. Sommer and W.H. Oertel "*Intravenous Immunoglobulins Containing Antibodies against β-amyloid for the Treatment of Alzheimer's Disease" (Short Report)*, "Journal of Neurology, Neurosurgery and Psychiatry" 2004; 75: 1472-1474, available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1738770/pdf/v075p01472.pdf .

[2] Relkin, N.R., P. Szabo, B. Adamiak, T. Burgut, C. Monthe, R.W. Lent, S. Younkin, L. Younkin, R. Schiff and M.E. Weksler, "*18-Month Study of Intravenous Immunoglobulin for Treatment of Mild Alzheimer Disease*", "Neurobiology of Aging", volume 30, issue 11, November 2009, pp. 1728-1736, available at: http://www.ncbi.nlm.nih.gov/pubmed/18294736 .

[3] "*Updated Results from Phase 3 Trial of IVIG for Alzheimer's Disease*" *(Featured Research)*, Weill Cornell Medical College, July 2013, available at: http://www.sciencedaily.com/releases/2013/07/130716092743.htm .

[4] Foster, J.K., G. Verdile, K.A. Bates and R.N. Martins, "*Immunization in Alzheimer's Disease: Naïve Hope or Realistic Clinical Potential?*", "Molecular Psychiatry" (2009) 14, 239-251, available at: http://www.nature.com/mp/journal/v14/n3/full/mp2008115a.html .

Importance: Unspecified

Transferability: Unspecified

Result card for ETH3: "What are the benefits and harms of IGG for other stakeholders (relatives, other patients, organisations, commercial entities, society, etc.)?"

View full card

ETH3: What are the benefits and harms of IGG for other stakeholders (relatives, other patients, organisations, commercial entities, society, etc.)?

Result

Similar are the benefits and risks for the family, relatives, friends and caregivers of the patients participating in the experimental therapy. Benefits should be sought with regard to the improved quality of life for the patients as well as the positive impact on the social contacts of the persons concerned, while risks may refer to complications leading to reduced quality of life not only for the patient alone but for his/her kindred, as well (including need of extra care, financial loss, social isolation, stigmatization, etc.). Relatives providing care for persons with MCI should also be completely familiar with the pros and cons of the experiment, which lies within the responsibility of the researchers.

Apart from the direct benefits and risks for the patient and his/her relatives, passive immunotherapy with intravenous immunoglobulins may also produce indirect effects on society as a whole by involving significant health and social resources. If the experimental treatment turns out to be efficient and successful for AD patients in the long run and be approved of the respective regulatory authorities for routine clinical use, patients suffering from other diseases that are usually treated with the same blood product may be deprived of their treatment. Therefore, IVIG priority orientation towards AD patients would lead to a significant reduction in the therapeutic options for the persons suffering from autoimmune diseases, for instance. The high price of the mentioned blood product ranging between USD 3000 and USD 7000 per month[1] must also be taken into consideration – it not only makes treatment extremely expensive, but in light of scant or missing evidence of its effectiveness and safety so far puts its benefits into question.

[1] Foster, J.K., G. Verdile, K.A. Bates and R.N. Martins, "*Immunization in Alzheimer's Disease: Naïve Hope or Realistic Clinical Potential?*", "Molecular Psychiatry" (2009) 14, 239-251, available at: http://www.nature.com/mp/journal/v14/n3/full/mp2008115a.html .

Importance: Unspecified

Transferability: Unspecified

Result card for ETH4: "Are there any other hidden or unintended consequences of IGG and its applications for different stakeholders (patients/users, relatives, other patients, organisations, commercial entities, society etc.)?"

View full card

ETH4: Are there any other hidden or unintended consequences of IGG and its applications for different stakeholders (patients/users, relatives, other patients, organisations, commercial entities, society etc.)?

Result

Due to the still unknown etiology and pathogenesis of Alzheimer's disease, namely whether beta-amyloid protein is a key cause of the disease or its consequence, currently to both physicians and patients may be unclear if the proposed therapy will affect the specific pathology, i.e. if the new treatment will be etiopathogenetic or only symptomatic. Only by thorough testing of the method will it be possible to check the plausibility of the amyloid hypothesis.

Despite the initial scientific enthusiasm regarding immunotherapy and the very first promising results, medical literature maintains that immunotherapy potential in relation to Alzheimer's disease should not be generalized. Suspected, however, still unknown are some side effects or complications that may occur during treatment, such as autoimmune diseases, brain inflammation, microhemorhages, increased amyloid angiopathy, residual neurofibrillary tangles, brain volume reductions and problems with blood-brain barrier passage of antibodies. Given that, immunotherapy should not be seen as a universal therapeutic strategy on the principle "One size fits all." and it is not advisable that IVIG be the first choice for AD patients.

The authors[1] warn that even passive immunization may pose a risk for humans and recommend quite cautious application of the method only after extensive testing on nonmurine animal species such as primates.

[1] Foster, J.K., G. Verdile, K.A. Bates and R.N. Martins, "*Immunization in Alzheimer's Disease: Naïve Hope or Realistic Clinical Potential?*", "Molecular Psychiatry" (2009) 14, 239-251, available at: http://www.nature.com/mp/journal/v14/n3/full/mp2008115a.html .

Importance: Unspecified

Transferability: Unspecified

Autonomy

Result card for ETH5: "Is IGG used for patients/people that are especially vulnerable?"

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ETH5: Is IGG used for patients/people that are especially vulnerable?

Result

The need to test new drugs continues and will continue to be associated with increased demand for clinical trial participants who are vulnerable in a number of ways. First, medicine is a very complex field, not easily understood by the average person. Study participants often have neither sufficient knowledge to determine the best course of action for treating or preventing a disease, nor the necessary expertise to reasonably assess the hazards and risks borne by them in the experiment. Rather, they are placed in a position of dependence – depending on clinician researchers to advise them correctly. A second source of vulnerability is a function of the fact that study participants are often people having problems for which they are seeking a solution. These individuals place their lives in the hands of medical staff, trusting that researchers will act in the participants' best interest. Third, as far as clinical trials usually take place in a healthcare setting, researchers are in the position to easily gain access to sensitive information that may expose the participants in the study to social or economic risks, such as the presence of diseases that could have a negative impact on the public attitude towards the patient, namely his/her productivity, hence, employability, and, thus, contribute to deepening stigmatization. Fourth, clinician researchers, by virtue of their expertise and status, may abuse their position by exerting pressure on the patient and making him/her agree to the proposed intervention, even through the use of dishonest and unethical methods as coercion, deception, fraud and other forms of manipulation. As a result, patients may be reluctant to exercise their right to autonomy and, consequently, acquiesce to everything required of them – even when it may not be in their best interest. A fifth source of vulnerability when recruiting volunteers to participate in scientific experiments for testing new therapeutic alternatives could be generated by the need to balance between the patient's right to personal choice, his/her financial needs and the enthusiasm of researchers. Hopeless and desperate patients, not having enough money to pay for expensive treatment, may find it more beneficial to involve in a free trial of the new technology. Such situations normally raise the following ethical issues, i.e. to what extent has voluntary participation been guaranteed by researchers, especially in cases where clinician researchers may be quite enthusiastic and may, therefore, influence the decision of the patient by assuring him/her of the benefits and safety of a completely new, still unproven, therapy as well as how to ensure that potential risks are not to be belittled by the particular individual. Sixth, in the event of early diagnosed patients with anticipation for progressive deterioration over time, the practice of drawing up a legal document called "advance directive" is usually preferred – a written document, in which, while still healthy, a person without prominent cognitive dysfunctions but expected future ones formulates his/her future treatment preferences and desires. In similar situations, where it may take a period of several decades between an individual's preclinical diagnosis and the onset of clinical symptoms, there is a risk of discrepancy between the present and future "self" of the patient in the changed environment, posing the question how relevant with regard to a particular moment in the future would be the preliminarily given consent/refusal expressed by a person in the advance directive and whether earlier treatment preferences must always be respected by the medical personnel. Here the concept of future-oriented autonomy collides with the welfare of the patient. A seventh source of vulnerability is associated with the adopted practice of legal representation in the event of incompetence, which raises the question if an agent/representative of the patient would always act in the interest of the patient and how this could be ensured. Eighth, patients' vulnerability may be generated by excessive stereotyping and infantilization of the adults, especially through the application of restrictive procedures, such as the so-called "double consent" where consent is sought by the family, while the subsequent validation/approval of the consent (i.e. "assent") – by the patient himself/herself, quite analogous to the procedures in children.

In the event of diagnosed with AD individuals stands out the conflict between the right to autonomy of a patient and the limits of his/her capacity/competence – an issue that has been widely discussed in bioethics literature, however, without reaching unanimity. The positions of the authors are diverse, mostly depending on the adopted viewpoint. No universal prescriptions for action exist.

Under the legal doctrine, each subject shall be presumed competent until proven otherwise. For example, in law, unable to make a decision shall be considered the person who is unable to understand the information obtained and cannot hold it long enough (i.e. remember it), cannot use it or weigh it up as part of the decision-making process and is unable to communicate (express) his/her choice either by speech, or through sign language (for example by blinking eyes or squeezing a hand)[1].

Apart from the purely legal nature of the term "competence", in the literature prevails the view[2] that the progressive brain damages and ensuing cognitive and emotional disorders, accompanied by sensory impairment and dependence on family and caregivers, require careful and cautious application of the doctrine of competent, voluntary, informed consent in research on adult subjects given the consideration that the mental decline may affect a patient's ability to understand the medical alternatives by reducing the individual sense of caution and reasonable judgment of the potential risks and burdens associated with the intervention.

Even the prodromal stage of Alzheimer's disease, popular as MCI, might impair the capacity of patients to give consent. Distinguishing between competent and incompetent subjects is quite a complex process and despite standardized assessment tools, the question remains unresolved as to what upper limit of potential risk should be allowed and whether informed consent should be permitted in high-risk scientific research. Partial answer to this dilemma is contained in the current international codes and guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences Guidelines (CIOMS)[3] dealing with issues, such as research in vulnerable populations. They make it obvious that the balance between risks and benefits is especially important in the discussion on non-therapeutic vs. therapeutic research, where only minimal risks are allowed if the research won't be of benefit to the subjects involved.

Some authors[4] try to distinguish between an ideal, abstract model of autonomy and actual autonomy. Typically, an abstract model assumes the possession of a set of ideal capabilities that an autonomous agent is supposed to have, namely the ability to function as an independent and rational subject in his/her choices and actions, who knows his/her own desires and preferences, being fully competent in the decision-making process. These features, however, present a standard model, difficult to follow in some cases, such as Alzheimer's disease. The abstract, ideal definition is replaced by a new concept, popular as "actual autonomy" that views the individual as an owner of a particular history of development, personal beliefs, convictions and values, and who does not exist in isolation but in a dynamic relationship with the social world.

In accordance with the above, *George Agich* notes that although not exhibiting ideal capacity for giving consent due to existing memory deficit, confusion and disorientation, most volunteers participating in clinical trials of drugs are conscious subjects reported to be in excellent or good health, cognizant of everyday life, having their own preferences for specific foods, clothing, persons and activities and demonstrating relatively preserved capacity to interpret information and ask questions.

It would therefore be incorrect for dementia patients to always be deemed completely devoid of decision-making capacity. Moreover, if the information is presented slowly and repeatedly in a non-stressful manner, even people suffering from significant cognitive decline can grasp it. Thus, in compliance with the principle of autonomy, a cornerstone principle of medical ethics, it would be essential that procedures for informed consent be developed sensitive to preserving maximum freedom for the subject over his/her own body. According to the ethical guidelines of the Alzheimer Society of Canada[5], while still intact, the individual's freedom should not be limited by restrictive measures; rather, he/she should be given a choice and opportunity to decide. This position is shared in other guidance documents[6], adding that a person with preserved competence has the right to make even such a decision that may be perceived by others, including the health personnel, as unreasonable or irrational, with the particular individual not to be categorized as lacking capacity merely because the health professional has deemed his/her decision unwise.

[1] "*Reference Guide to Consent for Examination or Treatment*", second edition, Department of Health, United Kingdom, July 2009, p.9, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138296/dh_103653__1_.pdf .

[2] "*Dementia – Caring, Ethics, Ethnical and Economical Aspects: A Systematic Review",* Chapter 36 "Ethical and Societal Issues in Dementia", p. 446, volume 3, June 2008, SBU Statens beredning för medicinsk utvärdering (The Swedish Council on Technology Assessment in Health Care), available at: http://www.sbu.se/upload/Publikationer/Content1/1/Dementia_vol3.pdf .

[3] Ibid, p. 445, available at: http://www.sbu.se/upload/Publikationer/Content1/1/Dementia_vol3.pdf .

[4] Agich, G., "*Alzheimer Disease: Therapeutic Strategies*", edited by E. Giacobini and R. Becker, Boston, 1994, available at: http://personal.bgsu.edu/~agichg/Articles/AutAD.pdf .

[5] Sevick, M-A., T. McConnell and M. Muender, "*Conducting Research Related to Treatment of Alzheimer's Disease: Ethical Issues*", Journal of Gerontological Nursing 29(2), February 2003, pp. 6-12, available at: http://www.researchgate.net/publication/7957720_Conducting_research_related_to_treatment_of_Alzheimer%27s_disease._Ethical_issues .

[6] "*Reference Guide to Consent for Examination or Treatment*", second edition, Department of Health, United Kingdom, July 2009, p. 10, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138296/dh_103653__1_.pdf .

Importance: Unspecified

Transferability: Unspecified

Result card for ETH6: "Does the implementation or use of IGG affect the patient´s capability and possibility to exercise autonomy?"

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ETH6: Does the implementation or use of IGG affect the patient´s capability and possibility to exercise autonomy?

Result

Patient autonomy is a cornerstone principle of medical ethics and widely discussed issue in specialized literature. In general, patient autonomy can be defined as self-determination, an expression of one's own will, based on the ability of a person to guide and manage his/her own life in accordance with rational principles and rules, thus allowing him/her to consciously accept or refuse medical interventions.

The right to self-determination is ensured by the presence of valid consent by adherence to the principle of voluntariness and after the patient has been thoroughly introduced to the objective, nature of the procedures, potential risks, duration, anticipated effect of the intervention, etc.

In the context of neurodegenerative diseases particularly stands out the collision between the right to autonomy of a patient and the limits of his/her competence. The altered cognitive status expressed in memory deficit, sensory impairment, confusion, disorientation and compromised capacity to retain

long enough and assess information due to brain lesions raises the ethical question about the real boundaries of competence and personal identity of AD subjects.

This faces the preclinically diagnosed individuals with the challenge to make decisions regarding their own future. To what extent do the above-mentioned subjects have the capacity to decide in their own best interest is a disputable issue where the positions of the authors divide and which has been already covered in the answer to the previous question.

Although patient autonomy is considered to be a key point and prerequisite for any medical intervention and has therefore been well debated in the literature on bioethics, data on ethical aspects regarding the application of experimental therapeutic methods in patients with mild cognitive impairment are scarce at best or missing.

Importance: Unspecified

Transferability: Unspecified

Result card for ETH7: "Is there a need for any specific IGGs or supportive actions concerning information in order to respect patient autonomy when IGG is used?"

View full card

ETH7: Is there a need for any specific IGGs or supportive actions concerning information in order to respect patient autonomy when IGG is used?

Result

Intravenous immunoglobulin therapy is associated with invasive procedures that should be explained in detail to the patients – potential participants in a research. The partially compromised decision-making capacity of MCI persons makes the situation even more complicated as far as it may result in inadequately estimated (belittled) risks. In the context of bioethics, this conflict between the right to autonomy and the limits of competence of the subject needs to be envisaged, with the informed consent process involving a detailed description and clarification of all stages of the therapeutic procedure/experiment/study, including the provision of information on painful interventions, tests and manipulations, data on the effectiveness of the methodology, expected outcome, price, alternative treatments, etc. The information should be presented in an accessible form and in a way that does not hinder patients with a slight cognitive decline to understand the treatment options and make appropriate decisions regarding their quality of life accordingly. With the new experimental strategies, such as the blood product concerned, there is a risk of producing subtle side effects, which can hardly be caught/seen in patients with communication disorders. The potential risk of other unforeseen but serious complications and the harm to persons in the event of being placed into the placebo group in placebo-controlled trials, depriving them of treatment during the experiment, should also be discussed before the patient is asked to give final informed consent.

Involved medical personnel needs to be responsible for balancing benefits and risks. In bioethics literature, this is known as a “risk-benefit analysis” where the researcher must weigh and balance the probable benefits and damages occurring in the course of research. One of the main tasks of the medical staff is to ensure that the principle of nonmaleficence has been observed or refrain from causing harm to the subjects in the study by assuring that potential benefits exceed unknown risks. Other negative consequences, such as in the case of patients with compromised decision-making capacity must also be provided for, for example a decisionally impaired person, who has significantly recovered due to the treatment, might realize his/her deteriorating physical and mental state and as a result become distressed, feel anxiety, hopelessness and despair, thus causing increased suicidal risk among these patients and compromised quality of life. Physicians should be prepared for timely response to prevent this side effect.

These and other issues arising in the course of each experimental therapy and the common belief in the medical community that individuals with compromised capacity belong, by default, to a special class of subjects and should therefore be treated with utmost caution necessitate the provision and development of special protective measures when giving consent so as to properly balance the benefits and risks:

1. Maximum involvement of the persons with mild cognitive impairment in the risk assessment process – a risk that they are willing to take;
2. Providing an inventory of potential risks and burdens for each case study;
3. In light of the vague benefits of experimental drugs and therapies, volunteers must be fully acquainted in advance with the potential risks and burdens of the treatment by providing the individuals with relevant detailed information in the most accessible and understandable manner;
4. Guaranteed opportunity for patients to abstain from participation or reject further participation in the experimental study at any time;
5. Providing indemnity insurance by researchers. The latter are required to insure themselves against potential damage by making best efforts to identify possible adverse effects and determine the likelihood for participants to encounter similar events;
6. Ensuring that patients are aware of the purpose of the randomized controlled trial, whose subject they are, namely, hypothesis testing and providing general knowledge of a medication or therapeutic procedure;
7. Ensuring by researchers that potential participants understand that they may be allocated in the control/placebo group to be randomly determined, with each of them likely to fall into that group;

8. Control over the balancing of study benefits and risks should be carried out by an ethics commission/committee or similar body (it is commonly accepted that such committees approve and coordinate each experimental or epidemiological study with a focus on the population or groups of it).

In order to protect human dignity of dementia patients, in some European and international legal documents, i.e. the Charter of Fundamental Rights of the European Union and the Convention for the Protection of Human Rights and Biomedicine have been stipulated a number of key principles and requirements that must be observed during the intervention, whereas in the field of bioethics they can be summed up into several points as follows[1]:

1. Respect for the dignity of both the persons with dementia and their caregivers and the need for polite and respectful behavior towards them, observing their personality and cultural traditions (ensuring that they are treated tactfully, considerately, carefully and in a good manner);
2. Use by researchers of an appropriate language in the process of communication with dementia patients. Avoiding terms, such as “mad” and “dementia patient”, etc.;
3. Researchers through their own behavior and attitude should ensure the promotion and protection of the dignity of people with dementia;
4. Introducing standardized feedback forms enabling the participants in the experiment to anonymously share opinion, especially in cases when they have some critical remarks on the procedure or wish to express their dissatisfaction or disapproval;
5. Development and implementation of a customized procedure for each individual based on the principle of personal uniqueness and avoiding standardized programmes, except in the cases requiring such standardization;
6. Ensuring the principle of confidentiality when processing the personal data of AD patients by securing the privacy of their personal lives through transparent and legitimate procedures (personal data that have become known to researchers during the experiment);
7. Strict adherence to the principle of voluntariness through the avoidance of deception, fraud, manipulation, coercion and abstaining from unethical behavior on the part of researchers;
8. Viewing informed consent not as a single act but as an ongoing process during which each patient may withdraw whenever he/she wishes to. The informed consent procedure needs to be periodically revised, especially in cases of new information made known to the research team regarding treatment methods;
9. Questioning the need to conduct repeated, painful, stressful or invasive procedures for the patients in the context of missing prevention or efficient etiopathogenetic therapy, i.e. in the event of increased suffering for the patient;
10. Preliminary risk assessment by researchers and allowing only minimum risks in cases where the research does not contribute to the benefit of the subjects;
11. When recruiting volunteers for participation in scientific experiments with unknown risks should be favored the involvement of patients with less severe mental disorders, who are deemed to have basically preserved their competence;
12. Application of methods and techniques simplifying the process of decision-making by reducing the number of possible options and decomposing more complex decisions into a series of simple instructions and step-by-step guidance through the process (compliant with the ethical guidelines of the Alzheimer Society of Canada);
13. Critical use of the legal instrument “advance treatment directive” for expressing consent in advance when the individual is still cognitively intact (typical of early diagnosed patients) due to the possible discrepancy between the present and future “self” of the person;
14. Respect for the patient’s right to autonomy and control over his/her own body and soul, and addressing his/her legal representative only in the event of missing or severely impaired capacity without favoring the second option;
15. Safeguards against stereotyping and infantilizing adults through the practice of restrictive procedures for consent (the so-called “double consent”).

[1] “*Ethics*”, Alzheimer Europe, available at: http://www.alzheimer-europe.org/Ethics ; *Guide to Consent for Examination or Treatment*”, second edition, Department of Health, United Kingdom, July 2009, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138296/dh_103653__1_.pdf ; “*Dementia – Caring, Ethics, Ethnical and Economical Aspects: A Systematic Review”,* Chapter 36 “Ethical and Societal Issues in Dementia”, volume 3, June 2008, SBU Statens beredning för medicinsk utvärdering (The Swedish Council on Technology Assessment in Health Care), available at: http://www.sbu.se/upload/Publikationer/Content1/1/Dementia_vol3.pdf ; Agich, G., “*Alzheimer Disease: Therapeutic Strategies*”, edited by E. Giacobini and R. Becker, Boston, 1994, available at: http://personal.bgsu.edu/~agichg/Articles/AutAD.pdf .

Importance: Unspecified

Transferability: Unspecified

Result card for ETH8: "Does the implementation or withdrawal of IGG challenge or change professional values, ethics or traditional roles?"

View full card

ETH8: Does the implementation or withdrawal of IGG challenge or change professional values, ethics or traditional roles?

Result

Traditionally accepted is the notion that in order to be good professionals, healthcare workers besides good qualifications must possess a number of moral virtues and personal qualities, such as compassion, insight, trustworthiness, honesty, integrity and conscientiousness, with the care for patients

being based on responsibility, loyalty and mutual trust.

Development of medical science with the invention of new diagnostic and therapeutic procedures poses a number of challenges facing the healthcare workers that could consciously or unconsciously affect their attitude towards patients. The doctors' wish to find a new effective and successful therapy for treating Alzheimer's disease prior to the onset of irreversible damages in the brain of patients may cause in healthcare professionals ungrounded optimism, thus obscuring their humane intentions by permitting the enrollment of decisionally impaired persons or subjects deprived of sufficient information in the group for experimental clinical trials. Medical personnel should cautiously balance positive against negative outcomes from the experimental therapy and provide the individuals with accessible, comprehensive factual information on the features, benefits and harms of the new treatment, including the usage of non-verbal methods when needed.

Clinicians should also consider the fact that they are placed in a position intimidating patients in several ways: 1.) Patients do not have enough knowledge to decide for themselves what is good for their own prevention and therefore completely trust the honesty, benevolence and professional advice of physicians/researchers (particularly with regard to incapacitated persons, who, while seeking the best solution for their own health problem, entrust their health and lives in the hands of professionals with the conviction that the latter will act in their best interest.); 2.) Medical staff by virtue of its competence and social status may be intimidating to patients by silently forcing them to agree with everything, thereby depriving them of exercising their right to personal autonomy, even in cases when what is required by the patient may not be in his/her best interest (i.e. an abuse of official position – something that should not be allowed.); 3.) Researchers are obligated to ensure full confidentiality of the data acquired during the experiment since in the course of the study there is a risk of becoming aware of sensitive patient information, whose disclosure would endanger the patient's social and economic interests.; 4.) The staff must guarantee the principle of voluntariness upon signing the informed consent, bearing in mind that with a view to the patients' progressive mental deterioration, informed consent should be considered an ongoing process with an option to be potentially revised over time. Coercion, manipulation, fraud and other unethical methods are totally unacceptable or undesirable, with researchers being obliged to envisage measures for protection of the personal data of their patients.; 5.) In an effort to cure or slow disease progression, healthcare professionals might be influenced by the pharmaceutical companies advertising new drugs, without at the same time being sufficiently convinced of the effectiveness of the proposed treatments. Reasonable in this context would be questions such as: How will patients' quality of life change?; If and how effective are these drugs?; Do they induce the same side effects?; Is the cost, duration and treatment dose, etc. justified?; If, moreover, in an experiment involving the testing of new therapeutic methods, medical staff accepts funding from the pharmaceutical industry, a conflict of interest may arise, questioning both the objectivity of the experiment and the expected results.

Importance: Unspecified

Transferability: Unspecified

Respect for persons

Result card for ETH9: "Does the implementation or use of IGG affect the user's moral, religious or cultural integrity?"

View full card

ETH9: Does the implementation or use of IGG affect the user's moral, religious or cultural integrity?

Result

Despite the common belief that the principles of bioethics are universal and applicable to every culture and society and that have always existed in the religious and moral traditions in various forms, the possibility that some of them may collide with one another at a certain stage of development and/or treatment of AD patients cannot be completely excluded.

Major religions (Christianity, Judaism, Islam and Buddhism) do not differ significantly in terms of their generally positive attitude towards human, with slight variations about prioritizing human body or soul, which might result in minor discrepancies in their opinion as to what extent a person should be allowed to self-decide on issues such as the maintenance or termination of life (for example, the application of euthanasia in AD's terminal stage). With the mild cognitive impairment phase, however, this dilemma is out of the question, whereas the above-mentioned religions show a positive attitude with respect to all possible methods of treatment of the human body and soul.

Despite the principally expressed considerations, the concrete therapeutic technology under discussion might raise objections among some religious groups in light of the application of whatever therapy, i.e. some religious movements reject medical treatment, while others (such as "Jehovah's Witnesses") oppose blood transfusion practices. Therefore, there is a risk that the use of blood products in the form of immunoglobulins may be met with resistance from the supporters of the above-mentioned religious movement[1].

Ethical rules and virtues are likely to come into conflict with the moral of a particular social group. The enrollment of AD subjects or persons with MCI in a clinical trial group to be treated with immunoglobulins presumes these subjects to have already been diagnosed, which would mean that the above individuals are labelled as "mad" or "incurably ill". This could negatively impact on the individuals and their families, relatives and friends in their future

social contacts. Cultural differences linked to the use of information and decision-making in patients suffering from “formidable diseases” may further complicate the situation. In the USA, it is accepted among some groups such as Mexican Americans, Korean Americans and Navajo to inform family members about the health of their significant other before telling the diagnosis to the sick person himself/herself. In Ireland, 83% of the relatives of people suffering from dementia are against the disclosure of the diagnosis to the patients themselves, considering that learning/knowing it may harm the sick person causing him/her anxiety, stress, despair and depression. In this aspect, a conflict may be expected regarding the autonomy of the patient (i.e. his/her autonomy in the treatment decision-making process may be reduced). Therefore, autonomy of an individual depends largely on the people around him/her, their affiliation to a particular social group or community and cultural values, as well[2].

As another prerequisite for a potential conflict between the administered therapy and the pursued social policies in some countries could be mentioned the disparities in the burden between the costs of caring for patients suffering from Alzheimer’s disease and the social costs linked to other public health diseases. In recent years, Alzheimer’s disease has been recognized as a key public health issue because of its significant morbidity, high cost of related care and lack of effective definitive treatment. AD patients, due to their advanced age, are likely to have comorbid chronic diseases, such as diabetes, coronary problems, congestive heart failure and others, making it hard and expensive to treat.

[1] See: Alvargonzález, D. “*Alzheimer’s Disease and the Conflict between Ethics, Morality and Politics*”, Journal of Alzheimer’s Disease & Parkinsonism, March 2013, available at: http://www.omicsonline.org/alzheimers-disease-and-the-conflict-between-ethics-morality-and-politics-2161-0460.S10-004.pdf ; “*Personhood*”, Alzheimer Europe, January 2013, available at: http://www.alzheimer-europe.org/Ethics/Definitions-and-approaches/Other-ethical-principles/Personhood ; “*Ethical Issues in Practice*”, Alzheimer Europe, October 2009, available at: http://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice .

[2] Ibid.

Importance: Unspecified

Transferability: Unspecified

Justice and Equity

Result card for ETH10: "How does implementation or withdrawal of IGG affect the distribution of health care resources?"

View full card

ETH10: How does implementation or withdrawal of IGG affect the distribution of health care resources?

Result

One of the key principles in bioethics is the principle of justice linked to law and equality. From an ethical point of view, it can be considered in three different ways and subdivided into three distinct categories, respectively: fair allocation of scarce resources (distributive justice); respect for people’s rights (rights-based justice) and compliance with morally acceptable laws (legal justice). Although the right to equal treatment, respectively, equal access to treatment has been formally enshrined in many constitutions, actually, many factors, such as age, place of residence, social status, ethnicity, culture, sexual preference, disability, legal capacity, health budgets, treatment price, insurance coverage, etc. may limit access to treatment. Justice in these cases, without neglecting or underestimating the right of equal access for all, requires that the individual’s needs be balanced with the needs of the general public.

The EU enlargement has brought new opportunities and potential problems in healthcare, while at the same time efforts are underway to harmonize healthcare provisions, including the promotion of cooperation and reaching consensus on a variety of health issues. In 1992, the Maastricht Treaty on the European Union recognized public health as an object of the EU policy. In Europe, bioethics is largely based on the principle of solidarity, freedom of choice, tolerance, equal opportunities, social justice and human dignity. In the European Community, justice and law are seen through the prism of not only the patient alone but also of his/her family members and society as a whole.

Application of passive immunotherapy with intravenous immunoglobulins having still unproven benefits could induce broader effects on society by involving considerable health and social resources. If, in the long run, the experimental treatment turns out to be an efficient and successful strategy for AD patients and, consequently, be approved of the respective regulatory authorities for routine clinical use, individuals suffering from other diseases that are also treated by the same blood product may be deprived of their therapy. Therefore, IVIG priority orientation towards AD patients would lead to a significant reduction in the therapeutic options for the persons suffering from autoimmune diseases, for instance, while the extremely high cost of the blood product may violate the principles of equality, justice and solidarity, resulting in huge over-expenditures. On the other hand, one must take into account the fact that in case of failure to use the new technology, provided that the method has proven to be working and useful, there is a risk of infringing upon the rights of the people with Alzheimer’s disease to reliable and effective treatment providing improved quality of life.

Therefore, in view of the above and in order to ensure fair and reasonable healthcare spending, it is necessary that decisions are made on a case-by-case basis, particularly in situations characterized by limited resources, unequal opportunities and/or other moral discrepancies.

Importance: Unspecified

Transferability: Unspecified

Result card for ETH11: "How are technologies with similar ethical issues treated in the health care system?"

View full card

ETH11: How are technologies with similar ethical issues treated in the health care system?

Result

Intravenous immunotherapy is used in a number of diseases, being the only possible alternative in the treatment of primary immunodeficiency conditions (agammaglobulinemia and hypogammaglobulinemia) and secondarily acquired immunodeficiencies. Another major category of pathologies treated successfully with these blood products comprises the following autoimmune diseases: idiopathic thrombocytopenic purpura, Kawasaki disease, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré syndrome, multifocal motor neuropathy, myasthenia gravis, relapsing-remitting multiple sclerosis as well as other autoimmune disorders: pemphigus, autoimmune uveitis, Graves ophthalmopathy, polymyositis, dermatomyositis, etc. The third class of diseases, in which intravenous infusions have proved their therapeutic effect, are acute infectious diseases.

IVIG production for therapeutic purposes requires vast resources of blood plasma, for the preparation of which are necessary from 3000 to 10000-20000 healthy blood donors.[1] Unreasonable use of immunoglobulins may result in a rapid depletion of quantities produced, depriving a number of patients of the only available treatment for their disease. So as to distribute and use most efficiently the limited supplies of immunoglobulins in compliance with the ethical principles of justice and interdependence, some countries have established registries regulating the diseases for which IVIG therapy is deemed routine, namely immunodeficiencies in infants and children and diseases with the only possible alternative immunotherapy whose positive effect has been proven in controlled trials. The choice of method should furthermore be consistent with factors, such as patient's age, opportunities for peripheral venous access, presence of comorbidities (cardiovascular disorders, a history of allergy or renal disease), which may restrict IVIG administration due to expected complications.[2]

Since IVIG administration in AD patients is still at an experimental stage and marked by contradictory intermediate outcomes for the time being, the redirection of the limited quantities of the present blood product to the priority treatment of the huge and rising number of patients with Alzheimer's disease is likely to disturb the routine therapy of the persons suffering from the aforementioned autoimmune diseases, which lack another available alternative treatment strategy. Therefore, IVIG administration in AD subjects must not be a first therapeutic choice, whereas each country, depending on the financial capacity of its healthcare system, the available resources of immunoglobulins as well as the number of patients with immunodeficiency conditions and autoimmune diseases, for which no other alternative treatment exists, should determine as to whether to include passive intravenous immunotherapy among the therapies recommended for other groups of diseases (including Alzheimer's disease).

[1] Gómez-Puerta, J.A., R. Cervera and J. Font, "*Clinical Utility of Intravenous Immunoglobulins in Autoimmune Diseases (Utilidad Clínica de las Inmunoglobulinas Endovenosas en las Enfermedades Autoinmunes)*", Inmunología, vol. 22 /Núm 3/Julio-Septiembre 2003: 287-293, Spain. ; Kaveri, S.-V., G. Dietrich, V. Hurez and M. D. Kazatchkine, "*Intravenous Immunoglobulins (IVIg) in the Treatment of Autoimmune Diseases*", Clinical and Experimental Immunology (1991) 86, 192-198, available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2249.1991.tb05794.x/pdf .

[2] Koski, C.L., J.V. Patterson, "*Intravenous Immunoglobulin Use for Neurologic Diseases*", Journal of Infusion Nursing, volume 29, number 3 – supplement, pp. S21-S28, June 2006, available at: http://www.nursingcenter.com/lnc/journalarticle?Article_ID=663755 .

Importance: Unspecified

Transferability: Unspecified

Result card for ETH12 / SOC5: "Are there factors that could prevent a group or persons to participate?"

View full card

ETH12 / SOC5: Are there factors that could prevent a group or persons to participate?

Result

Despite the common belief that the principles of bioethics are universal and applicable to every culture and society and that have always existed in the religious and moral traditions in various forms, the possibility that some of them may collide with one another at a certain stage of development and/or treatment of AD patients cannot be completely excluded.

Major religions (Christianity, Judaism, Islam and Buddhism) do not differ significantly in terms of their generally positive attitude towards human, with slight variations about prioritizing human body or soul, which might result in minor discrepancies in their opinion as to what extent a person should be allowed to self-decide on issues such as the maintenance or termination of life (for example, the application of euthanasia in AD's terminal stage).

Despite the principally expressed considerations, the concrete therapeutic technology under discussion might raise objections among some religious groups in light of the application of whatever therapy, i.e. some religious movements reject medical treatment, while others (such as "Jehovah's Witnesses") oppose blood transfusion practices. Therefore, there is a risk that the use of blood products in the form of immunoglobulins may be resisted against by the supporters of the above-mentioned religious movement.

Ethical rules and virtues are likely to come into conflict with the moral of a particular social group. The enrollment of AD subjects or persons with MCI in a clinical trial group to be treated with immunoglobulins presumes these subjects to have already been diagnosed, which would mean that the above individuals are labelled as "mad" or "incurably ill", thus leading to depersonalization and other negative consequences for the individuals and their families, relatives and friends in their future social contacts. In the USA, it is accepted among some groups such as Mexican Americans, Korean Americans and Navajo to inform family members about the health of their significant other before telling the diagnosis to the sick person himself/herself. In Ireland, 83% of the relatives of people suffering from dementia are against the disclosure of the diagnosis to the patients themselves, considering that learning/knowing it may harm the sick person causing him/her anxiety, stress, despair and depression. In this aspect, a conflict may be expected regarding the autonomy of the patient (i.e. his/her autonomy in the treatment decision-making process may be reduced). Therefore, autonomy of an individual depends largely on the people around him/her, their affiliation to a particular social group or community and cultural values, as well.

In support of the above is the huge financial, ethical and social burden on the patient's family and relatives, who, also, consider it moral and ethical to participate in the treatment process options as much as this choice affects their quality of life. Alzheimer's disease is becoming a key public health issue because of its significant morbidity and duration, high cost of related care and lack of effective definitive therapy. AD patients, given their advanced age, are likely to have additional comorbid chronic conditions such as diabetes and cardiovascular diseases, making treatment harder and more expensive. The choice of therapy should furthermore take into account a number of other factors, such as age, place of residence, social status, ethnicity, culture, health budgets, insurance coverage, opportunities for peripheral venous access, allergy or renal disease, all of which not only make treatment costly but may limit IVIG administration due to expected complications.

In terms of healthcare, the costs of caring for AD patients exceed the social costs, which is also a prerequisite for a conflict between the applied therapy and the social policies in some states.

Importance: Unspecified

Transferability: Unspecified

Ethical consequences of the HTA

Result card for ETH13: "Does the economic evaluation of IGG contain any ethical problems?"

View full card

ETH13: Does the economic evaluation of IGG contain any ethical problems?

Result

Each new therapeutic technology is introduced as a routine clinical practice after indisputable evidence in favor of patients and following a detailed economic assessment of the efficiency of various treatment schemes (dose, frequency, duration). In an experimental study on intravenous infusion of immunoglobulins in patients with Alzheimer's disease were tested different therapeutic regimens for 36 months. The following schemes were applied: 0.2 g/kg every 2 weeks; 0.4 g/kg every 2 weeks; 0.4 g/kg every 4 weeks, and 0.8 g/kg every 4 weeks.[1]

The results from the randomized clinical trials conducted on very few patients, some of whom got complications during the experiment, show a trend towards improvement in the IVIG-treated individuals compared to the placebo group. Although to date no final selection of the most appropriate therapeutic regimen could be made, treatment is known to be quite expensive.

The price is above USD 75 per gram (i.e. approximately USD 15000 per infusion with a patient's weight about 100 kg and the therapy being administered in the lowest possible dose – 2g/kg).[2] Given the conflicting results of the trials and the small number of treated patients, researchers are too cautious when recommending an official introduction of immunoglobulin therapy for AD patients, highlighting the fact that this would deprive other needy patients of the only possible treatment for their disease.

[1] Gever, J., "*IVIG Stops Alzheimer's in Its Tracks*", published on 17th July 2012, available at: http://www.medpagetoday.com/MeetingCoverage/AAIC/33780 .

[2] "*Intravenous Immunoglobulin*", Wikipedia, available at: http://en.wikipedia.org/wiki/Intravenous_immunoglobulin .

Importance: Unspecified

Transferability: Unspecified

Result card for ETH14: "What are the ethical consequences of the assessment of IGG?"

View full card

ETH14: What are the ethical consequences of the assessment of IGG?

Result

Currently, administration of intravenous immunoglobulins in patients with Alzheimer's disease is still at an experimental stage marked by contradictory intermediate results. If clinical trials demonstrate indisputably the effectiveness of immunotherapy, its regular usage will be expected to provide improved quality of life for patients.

As already discussed in the previous sections, the reallocation of the limited quantities of immunoglobulins towards the treatment of the increasing number of AD subjects is likely to disturb the therapy of patients with immunodeficiencies or autoimmune diseases, placing IVIG as a treatment option for Alzheimer's disease in the background. This consideration is with a view to ensuring balanced distribution of healthcare resources for society as a whole, compliant with the principles of justice and interdependence in order to guarantee that they are fairly and rationally exploited by all.

Importance: Unspecified

Transferability: Unspecified

Discussion

As already stated, the analysis is based on different information sources pointing out that the IVIG innovative health technology is still at the experimental stage. Therefore, the future results of the final stage of the experiment are likely to affect all or some of the ethical considerations already debated on the effectiveness and adequacy of the use of IVIG technology in patients suffering from Alzheimer's disease in the prodromal MCI stage.

The therapeutic use of the innovative technology faces several ethical challenges. The major issue concerns the respect for the autonomy of the patients with impaired/reduced decision-making capacity, which requires that the engaged healthcare staff demonstrate more correctness and patience towards the sick ones. Moreover, the early stage of Alzheimer's disease is difficult to diagnose and may sometimes be carrying the risk of false diagnosis, thus resulting in stigmatization and social isolation of patients and their families, which contradicts the ethical principle of nonmaleficence. The third major ethical problem generated by the application of the very technology is associated with the principle of equitable distribution of resources. The use of immunoglobulins for the treatment of patients with Alzheimer's disease is likely to create a deficit of the same products by reducing the possible therapeutic options for other groups of patients, for whom there is no other alternative treatment.

We believe that the information discussed in the Ethical domain is therefore sufficient to support the process of assessment and the related decision-making process at national/regional level.

References

1. Agich, G., "*Alzheimer Disease: Therapeutic Strategies*", edited by E. Giacobini and R. Becker, Boston, 1994, available at: http://personal.bgsu.edu/~agichg/Articles/AutAD.pdf ;

1. Alvargonzález, D. "*Alzheimer's Disease and the Conflict between Ethics, Morality and Politics*", Journal of Alzheimer's Disease & Parkinsonism, March 2013, available at: http://www.omicsonline.org/alzheimers-disease-and-the-conflict-between-ethics-morality-and-politics-2161-0460.S10-004.pdf ;

1. Alzheimer's Association website: http://www.alz.org/ ;

1. Alzheimer Europe website: http://www.alzheimer-europe.org/ ;

1. "*2013 Alzheimer's Disease Facts and Figures*", Report of the Alzheimer's Association, vol. 9, issue 2, 2013, available at: http://www.alz.org/downloads/facts_figures_2013.pdf ;

1. "*Alzheimer's Disease Fact Sheet*", Alzheimer's Disease Education and Referral Center of the National Institute on Aging, July, 2011 (reprinted September, 2012), NIH Publication № 11-6423, available at: http://www.nia.nih.gov/sites/default/files/alzheimers_disease_fact_sheet_0.pdf ;

1. Alzheimer Society of Canada website: http://www.alzheimer.ca/en ;

1. Dalakas, M., "*Intravenous Immunoglobulin in Autoimmune Neuromuscular Diseases*", Journal of the American Medical Association (JAMA), May 2004; 291(19): 2367-2375 (doi:10.1001/jama.291.19.2367), available at: http://zhills.net/studies/IVIg_inAutoimmuneNeuroDiseases.pdf ;

1. "*Dementia: A Public Health Priority*", World Health Organization, 2012, available at: http://apps.who.int/iris/bitstream/10665/75263/1/9789241564458_eng.pdf ;

1. "*Dementia – Caring, Ethics, Ethnical and Economical Aspects: A Systematic Review",* Chapter 36 "Ethical and Societal Issues in Dementia", volume 3, June 2008, SBU Statens beredning för medicinsk utvärdering (The Swedish Council on Technology Assessment in Health Care), available at: http://www.sbu.se/upload/Publikationer/Content1/1/Dementia_vol3.pdf ;

1. Dodel, R.C., Y. Du, C. Depboylu, H. Hampel, L. Frölich, A. Haag, U. Hemmeter, S. Paulsen, S.J. Teipel, S. Brettschneider, A. Spottke, C. Nölker, H.J. Möller, X. Wei, M. Farlow, N. Sommer and W.H. Oertel, "*Intravenous Immunoglobulins Containing Antibodies against β-amyloid for the treatment of Alzheimer's Disease" (Short Report)*, "Journal of Neurology, Neurosurgery and Psychiatry" 2004; 75: 1472-1474, available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1738770/pdf/v075p01472.pdf ;

1. "*Ethical Issues in Practice*", Alzheimer Europe, October 2009, available at: http://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice ;

1. Farah, M., "*Emerging Ethical Issues in Neuroscience*", University of Pennsylvania, Center for Neuroscience and Society, published in "Nature Neuroscience", volume 5, issue 11, April 2004, pp. 1123-1130, available at: http://repository.upenn.edu/cgi/viewcontent.cgi?article=1007&context=neuroethics_pubs ;

1. "*Ethics*", Alzheimer Europe, available at: http://www.alzheimer-europe.org/Ethics ;

1. "*Florida Alzheimer's Disease Initiative: Understanding and Dealing with Alzheimer's Disease and Related Disorders" (Education Manual)*, University of Florida, USA, available at: http://elderaffairs.state.fl.us/doea/docs/adi_manual_2012_final.pdf ;

1. Foster, J.K., G. Verdile, K.A. Bates and R.N. Martins, "*Immunization in Alzheimer's Disease: Naïve Hope or Realistic Clinical Potential?*", "Molecular Psychiatry" (2009) 14, 239-251, available at: http://www.nature.com/mp/journal/v14/n3/full/mp2008115a.html ;

1. Gever, J., "*IVIG Stops Alzheimer's in Its Tracks*", published on 17th July 2012, available at: http://www.medpagetoday.com/MeetingCoverage/AAIC/33780 ;

1. Gómez-Puerta, J.A., R. Cervera and J. Font, "*Clinical Utility of Intravenous Immunoglobulins in Autoimmune Diseases (Utilidad Clínica de las Inmunoglobulinas Endovenosas en las Enfermedades Autoinmunes)*", Inmunología, vol. 22 /Núm 3/Julio-Septiembre 2003: 287-293, Spain;

1. Growdon, M., "*Ethical Issues in the Early Diagnosis of Alzheimer Disease" (Journal Discussion on Mattsson N., D. Brax, H. Zetterberg, "To Know or Not to Know: Ethical Issues Related to Early Diagnosis of Alzheimer's Disease)*", International Journal of Alzheimer's Disease*)*, "Virtual Mentor", Journal of Ethics of the American Medical Association, December 2011, volume 13, number 12: 868-872, available at: http://virtualmentor.ama-assn.org/2011/12/jdsc1-1112.html ;

1. "*Intravenous Immunoglobulin*", Wikipedia, available at: http://en.wikipedia.org/wiki/Intravenous_immunoglobulin ;

1. Kaveri, S.-V., G. Dietrich, V. Hurez and M. D. Kazatchkine, "*Intravenous Immunoglobulins (IVIg) in the Treatment of Autoimmune Diseases*", Clinical and Experimental Immunology (1991) 86, 192-198, available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2249.1991.tb05794.x/pdf ;

1. Kayed, R., G. Jackson, D. Mark Estes and A. Barrett, "*Alzheimers Disease: Review of Emerging Treatment Role for Intravenous Immunoglobulins*", Journal of Central Nervous System Disease, Libertas Academica, available at: http://www.la-press.com/alzheimers-disease-review-of-emerging-treatment-role-for-intravenous-i-article-a2632 ;

1. Kim, S.Y.H., C. Cox, E. Caine, "*Impaired Decision-Making Ability in Subjects with Alzheimer's Disease and Willingness to Participate in Research*", American Journal of Psychiatry, May 2002, 159: 797-802, doi: 10.1176/appi.ajp.159.5.797, available at: http://ajp.psychiatryonline.org/article.aspx?articleid=175528 ;

1. Klafki, H.-W., M. Staufenbiel, J. Kornhuber and J. Wiltfang, "*Therapeutic Approaches to Alzheimer's Disease" (Review Article)*, "Brain" (Journal of Neurology) (2006), 129, 2840-2855, available at: http://brain.oxfordjournals.org/content/129/11/2840.full.pdf ;

1. Koski, C.L., J.V. Patterson, "*Intravenous Immunoglobulin Use for Neurologic Diseases*", Journal of Infusion Nursing, volume 29, number 3 – supplement, pp. S21-S28, June 2006, available at: http://www.nursingcenter.com/lnc/journalarticle?Article_ID=663755 ;

1. Kral, V., "*Senescent Forgetfulness: Benign and Malignant*", Journal of the Canadian Medical Association, February, 1962, vol. 86 (6): 257-260, available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1848846/pdf/canmedaj00930-0002.pdf ;

1. Lobello, K., J.M. Ryan, E. Liu, G. Rippon and R. Black, "*Targeting Beta Amyloid: A Clinical Review of Immunotherapeutic Approaches in Alzheimer's Disease" (Review Article)*, International Journal of Alzheimer's Disease, Hindawi Publishing Corporation, volume 2012 (2012), article ID 628070, available at: http://www.hindawi.com/journals/ijad/2012/628070/ ;

1. Loeffler, D., "*Intravenous Immunoglobulin and Alzheimer's Disease: What Now?*", Journal of Neuroinflammation, June 2013, 10:70, doi: 10.1186/1742-2094-10-70, available at: http://www.jneuroinflammation.com/content/pdf/1742-2094-10-70.pdf ;

1. "Mild Cognitive Impairment", Alzheimer's Association; http://www.alz.org/dementia/mild-cognitive-impairment-mci.asp ;

1. "*Mild Cognitive Impairment (MCI)*", Alzheimer's Association, updated October, 2006, available at: http://www.alz.org/national/documents/topicsheet_mci.pdf ;

1. National Institute on Aging's website: http://www.nia.nih.gov/ ;

1. "*Personhood*", Alzheimer Europe, January 2013, available at: http://www.alzheimer-europe.org/Ethics/Definitions-and-approaches/Other-ethical-principles/Personhood ;

1. Petersen, R., "*Mild Cognitive Impairment: Transition between Aging and Alzheimer"s Disease*", Neurologia, vol. 15 (3): 93-101, March, 2000, an abstract available at: http://www.ncbi.nlm.nih.gov/pubmed/10846869 ;

1. Petersen, R., D. Knopman, B. Boeve, Y. Geda, R. Ivnik, G. Smith, R. Roberts, C. Jack, Jr., "*Mild Cognitive Impairment: Ten Years Later*", American Medical Association, Arch. Neurol., vol. 66 (12): 1447-1455, December, 2009, available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3081688/ ;

1. Peterson, R., G. Smith, St. Waring, R. Ivnik, E. Tangalos, E. Kokmen, "*Mild Cognitive Impairment: Clinical Characterization and Outcome*", American Medical Association, Arch. Neurol., vol. 56 (3): 303-8, March, 1999, available at: https://wiki.umn.edu/pub/LNPI/ExpertPanelPublications/G_Smith_-_Mild_cognitive_impairment_Clinical_characterization_and_outcome..pdf ;

1. Petersen, R., J. Stevens, M. Ganguli, E. Tangalos, J. Cummings, S. DeKosky, "*Practice Parameter: Early Detection of Dementia: Mild Cognitive Impairment (An Evidence-based Review)*", Report of the Quality Standards Subcommittee of the American Academy of Neurology, Neurology 2001, vol. 56: 1133-1142, available at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.196.7859&rep=rep1&type=pdf ;

1. Petersen, R., R. Doody, A. Kurz, R. Mohs, J. Morris, P. Rabins, K. Ritchie, M. Rossor, L. Thal, B. Winblad, "*Current Concepts in Mild Cognitive Impairment*", American Medical Association, Arch. Neurol., vol. 58 (12): 1985-92, December, 2001, available at: http://www.dal-bianco.at/mcipetersen.pdf ;

1. Portet, F., P. Ousset, P. Visser, G. Frisoni, F. Nobili, Ph. Scheltens, B. Vellas, J. Touchon, "*Mild Cognitive Impairment (MCI) in Medical Practice: A Critical Review of the Concept and New Diagnostic Procedure*", Report of the MCI Working Group of the European Consortium on Alzheimer's Disease, published in "Journal of Neurology, Neurosurgery & Psychiatry", June, 2006, 77 (6): 714-718, available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2077456/ ;

1. Potocnik, F.C.V., "*Ethical and Medico-Legal Aspects of Dementia*", "Continuing Medical Education" (South African Journal of Continuing Professional Development), vol. 31, №10 (2013), South Africa, available at: http://www.cmej.org.za/index.php/cmej/article/view/2870/3242 ;

1. "*Reference Guide to Consent for Examination or Treatment*", second edition, Department of Health, United Kingdom, July 2009, available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138296/dh_103653__1_.pdf ;

1. Relkin, N.R., P. Szabo, B. Adamiak, T. Burgut, C. Monthe, R.W. Lent, S. Younkin, L. Younkin, R. Schiff and M.E. Weksler, "*18-month Study of Intravenous Immunoglobulin for Treatment of Mild Alzheimer Disease*", "Neurobiology of Aging", volume 30, issue 11, November 2009, pp. 1728-1736, available at: http://www.ncbi.nlm.nih.gov/pubmed/18294736 ;

1. Schwartz, S.A., "*Intravenous Immunoglobulin (IVIG) for the Therapy of Autoimmune Disorders" (Special Article)*, Journal of Clinical Immunology, vol. 10, №2, 1990, available at: http://deepblue.lib.umich.edu/bitstream/handle/2027.42/44840/10875_2004_Article_BF00918189.pdf?sequence=1 ;

1. Sevick, M-A., T. McConnell and M. Muender, "*Conducting Research Related to Treatment of Alzheimer's Disease: Ethical Issues*", Journal of Gerontological Nursing 29(2), February 2003, pp. 6-12, available at: http://www.researchgate.net/publication/7957720_Conducting_research_related_to_treatment_of_Alzheimer%27s_disease._Ethical_issues ;

2. Small, G., "*What We Need to Know about Age-Related Memory Loss*", British Medical Journal, June, 2002, 324: 1502-5, available at: http://www.bmj.com/content/324/7352/1502 ;

1. "*The Ethical Issues Linked to Restrictions of Freedom of People with Dementia*", Alzheimer Europe, available at: http://www.alzheimer-europe.org/Ethics/Ethical-issues-in-practice/The-ethical-issues-linked-to-restrictions-of-freedom-of-people-with-dementia/Introduction ;

1. "*The Gammaglobulin Alzheimer's Partnership Study (Intravenous Immune Globulin (IVIG) Study)*", Alzheimer's Disease Education and Referral Center, available at: http://www.adcs.org/studies/igiv.aspx ;

1. "*Updated Results from Phase 3 Trial of IVIG for Alzheimer's Disease*" *(Featured Research)*, Weill Cornell Medical College, July 2013, available at: http://www.sciencedaily.com/releases/2013/07/130716092743.htm ;

1. Werner, P. and A. Korczyn, "*Mild Cognitive Impairment: Conceptual, Assessment, Ethical, and Social Issues"*, Journal of Clinical Interventions in Aging – Dove Press, September 2008, 3(3): 413-420, available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2682374/ ;

1. WHO website: http://www.who.int/en/ ;

1. Winblad, B., K. Palmer, M. Kivipelto, V. Jelic, L. Fratiglioni, "*Introduction: Mild Cognitive Impairment: Beyond Controversies, towards a Consensus*", Journal of Internal Medicine, 2004, vol. 256: 181-182, available at Wiley Online Library: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2004.01382.x/pdf ;

Organisational aspects

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Summary

It is not possible to determine with certainty whether use of Intravenous immunoglobulins for Alzheimer disease including Mild Cognitive Impairment affects significantly organisational aspects.

The current overview can be used as a starting point for further research on the organisational impact of use of Intravenous immunoglobulins for Alzheimer disease including Mild Cognitive Impairment.

Introduction

The most issues of this domain should not be included in the HTA on the “Use of Intravenous immunoglobulins for Alzheimer disease including Mild Cognitive Impairment”.

From a organisational point of view the “Health Problem and Current Use of the Technology” domain, “Description and technical characteristics of technology” domain already includes the use and technical characteristics of technology.

For Mild Cognitive Impairment, and Moderate to Severe there is no available evidence, while for Mild to Moderate Alzheimer disease there is upcoming evidence.

The technology under assessment is still in its early stage of development and evidence based answers to the AEs of ORG domain we selected during the protocol, cannot be given. On the other hand decisions about their use for treating one category of patients or another rise ethical questions related to how to use limited resources (ETH domain).

Methodology

Frame

The collection scope is used in this domain.

Technology	Immunoglobulins (IGG) **Description** Naturally occurring proteins produced by the body’s immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer’s disease **Target condition** Alzheimer’s disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.
Comparison	placebo, not doing anything or Usual supportive care **Description** There is no MA for IGGs for AD yet and there is no other intervention licensed for use in AD so the comparison would have to be against placebo or best supportive care
Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
G0001	Health delivery process	How does the technology affect the current work processes?	yes	How does IGG affect the current work processes?
G0100	Health delivery process	What kind of patient/participant flow is associated with the new technology?	yes	What kind of patient/participant flow is associated with IGG?
G0002	Health delivery process	What kind of involvement has to be mobilized for patients/participants and important others?	yes	What kind of involvement has to be mobilized for patients/participants and important others?
G0003	Health delivery	What is the process ensuring proper education and training of the staff?	yes	What is the process ensuring proper education and training of the staff?

	process			
G0004	Health delivery process	What kind of co-operation and communication of activities have to be mobilised?	yes	What kind of co-operation and communication of activities have to be mobilised?
G0012	Health delivery process	How is the quality assurance and monitoring system of the new technology organised?	yes	How is the quality assurance and monitoring system of IGG organised?
G0005	Structure of health care system	How does de-centralisation or centralization requirements influence the implementation of the technology?	yes	How does de-centralisation or centralization requirements influence the implementation of IGG?
G0101	Structure of health care system	What are the processes ensuring access to care of the new technology for patients/participants?	yes	What are the processes ensuring access to care of IGG for patients/participants?
G0006	Process-related costs	What are the processes related to purchasing and setting up the new technology?	yes	What are the processes related to purchasing and setting up IGG?
G0007	Process-related costs	What are the likely budget impacts of implementing the technologies being compared?	yes	What are the likely budget impacts of implementing the technologies being compared?
G0008	Management	What management problems and opportunities are attached to the technology?	yes	What management problems and opportunities are attached to IGG?
G0009	Management	Who decides which people are eligible for the technology and on what basis?	yes	Who decides which people are eligible for intravenous immunoglobulin (IVIG) therapy and on what basis?
G0010	Culture	How is the technology accepted?	yes	How is IGG accepted?
G0011	Culture	How are the other interest groups taken into account in the planning / implementation of the technology?	yes	How are the other interest groups taken into account in the planning / implementation of IGG?

Methodology description

The project scope is applied in this domain.

Result cards

Health delivery process

Result card for ORG1: "How does IGG affect the current work processes?"

View full card

ORG1: How does IGG affect the current work processes?

Result

Currently, IVIG is not an approved as a treatment option in Mild Cognitive Impairment and Alzheimer's disease (AD), therefore there are no relevant clinical guidelines on its position in the treatment pathway (for example whether it would replace existing pharmacological and other interventions or constitute an add-on therapy).

In terms of its impact on the patient pathway, with regard to AD, IVIG has a different route of administration compared to pharmacological treatments used in the management of AD. In specific, administration of IVIG for its approved indications is mainly done in the hospital setting or in infusion clinics ({White-Reid K, 2008}{1}, although depending on the clinical characteristics of the patients, alternative site of care (GP office, home care) can be used.

Taking into consideration recommendations on IVIG use for its licensed indications, patients may also need to undergo pre-treatment testing and routine monitoring for development of complications after treatment with IVIG {Silvergleid and Berger} {2}. Finally, delayed disease progression would affect AD prevalence and consequently impact the service delivery models {Brodaty *el al}*{ {3}.

Refer to TEC4, TEC5, TEC8.

Importance: Critical

Transferability: Partially

Result card for ORG2: "What kind of patient/participant flow is associated with IGG?"

View full card

ORG2: What kind of patient/participant flow is associated with IGG?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Result card for ORG3: "What kind of involvement has to be mobilized for patients/participants and important others?"

View full card

ORG3: What kind of involvement has to be mobilized for patients/participants and important others?

Result

Intravenous immunoglobulin (IVIG) is administered by infusion, predominantly in the hospital setting.

Since it is a product with limited availability and high cost, special management programs may be in place regarding its administration to patients such as the Department of Health Demand Management Plan for Immunoglobulin Use in the UK{Department of Health} {4}, the Immunoglobulin (Ig) Governance Program in Australia {National Blood Authority} {5} or the IVIG Utilization Management Program ran by the BC Provincial Blood Coordinating Office (PBCO) in Canada {Provincial Health Services Authority} {6}. Management programs may also be in place at the regional or the hospital level.

According to instructions relating to its administration in other groups of patients for its licensed indications in the aforementioned jurisdictions, patient written consent is required. Information provided to the patients relates to immunoglobulin products; reason for treatment; how the products are given; risks and benefits of the treatment; alternative treatments; side effects; and also requirements regarding collection and sharing of personal private information that apply for IVIG administration. Patients must also have instructions on how to act if serious reactions after treatment appear.

Importance: Important

Transferability: Not

Result card for ORG4: "What is the process ensuring proper education and training of the staff?"

View full card

ORG4: What is the process ensuring proper education and training of the staff?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Result card for ORG5: "What kind of co-operation and communication of activities have to be mobilised?"

View full card

ORG5: What kind of co-operation and communication of activities have to be mobilised?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Result card for ORG6: "How is the quality assurance and monitoring system of IGG organised?"

View full card

ORG6: How is the quality assurance and monitoring system of IGG organised?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Structure of health care system

Result card for ORG7: "How does de-centralisation or centralization requirements influence the implementation of IGG?"

View full card

ORG7: How does de-centralisation or centralization requirements influence the implementation of IGG?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Result card for ORG8: "What are the processes ensuring access to care of IGG for patients/participants?"

View full card

ORG8: What are the processes ensuring access to care of IGG for patients/participants?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Process-related costs

Result card for ORG9: "What are the processes related to purchasing and setting up IGG?"

View full card

ORG9: What are the processes related to purchasing and setting up IGG?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Result card for ORG10: "What are the likely budget impacts of implementing the technologies being compared?"

View full card

ORG10: What are the likely budget impacts of implementing the technologies being compared?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Management

Result card for ORG11: "What management problems and opportunities are attached to IGG?"

View full card

ORG11: What management problems and opportunities are attached to IGG?

Result

There is not information available about management problems of IVIGs for AD as this treatment has not been approved for AD but as an experimental therapy. In general, for various other conditions there is some information. The IVIG therapy is usually administered in hospitals or hospital-based outpatient clinics under clinical protocols, and is usually based on national policies {National Blood Authority} {7}.

By the management viewpoint the most critical points is to ensure availability of the IVIG products. There could be problems within the supply of IVIG. It is prepared from the purified plasma immunoglobulins of large numbers of healthy donors. The process of plasma into IVIG takes about 9 months. Solution to the problems of supply includes new manufacturing process, use of recombinant technology to produce IVIG, or an administration of specific antibodies in place of IVIG { Loeffler} {8}.

In addition, it has to be ensured that there are appropriate policies and procedures for the whole process. For example, IVIG products need specific storage and prescribing requirements and detailed documentation of infusions. {National Blood Authority} {7} (Refer to TEC7 and TEC10).

Adequate training and skills of the personnel have to be ensured. The personnel need specific knowledge and skills of treating patients with IVIG. Training of administrating IVG includes e.g. knowledge of infusion technique and use of equipment, as well as identification of possible adverse reactions of the product. (Refer to TEC13).

Importance: Important

Transferability: Partially

Result card for CUR16 / ORG12: "Who decides which people are eligible for intravenous immunoglobulin (IVIG) therapy and on what basis?"

View full card

CUR16 / ORG12: Who decides which people are eligible for intravenous immunoglobulin (IVIG) therapy and on what basis?

Result

As IVIG have not been approved for Alzheimer’s disease including Mild Cognitive Impairment, IVIG therapy does not have a formal prescription pathway for such indications. Considering the contextual differences among the countries, a generalisation of the off-label prescription strategies of the IVIG therapy is not possible and remains out of the scope of the present results card.

The current setting for the administration of IVIG therapy (for any condition) is use within hospitals {Appendix CUR-3}.

Importance: Important

Transferability: Completely

Culture

Result card for ORG13: "How is IGG accepted?"

View full card

ORG13: How is IGG accepted?

Result

None of our included studies provided information on this topic.

Importance: Unspecified

Transferability: Unspecified

Result card for ORG14: "How are the other interest groups taken into account in the planning / implementation of IGG?"

View full card

ORG14: How are the other interest groups taken into account in the planning / implementation of IGG?

Result

IVIG is an experimental therapy for AD and therefore there is not information about stakeholders.

In Australia {National Blood Authority} {7}, the key stakeholders involved with the supply, prescribing, dispensing, administration and use of IVIG are:

- National Blood Authority which e.g. manage contracts with suppliers;
- Funding Governments which e.g. provide funding for supply of IVIG;
- National and local committees which e.g. provide advice on options to strengthen prescribing practices;
- Prescribers who prescriber IVIG treatments in accordance with the Criteria;
- Patients who e.g. understand treatment risks and benefits;
- Authoriser which e.g. authorize access to government funded product for eligible patients;
- Dispenser who e.g. plan and manage product ordering appropriate to clinical demand;
- Distributor who e.g. plan and manage inventory levels according to the standards and clinical demand;
- Nurse who e.g. ensure patient's authorization and consent to IVIG treatment.

Importance: Important

Transferability: Partially

Discussion

According to the information available at the time of writing, IVIG are not used for Alzheimer's disease including Mild Cognitive Impairment in any of the EUnetHTA partners, and is quite difficult to find available information on the organizational aspects.

References

1. White-Reid K, Scherf R. Giving intravenous immunoglobulin. Modern Medicine, 2008; Accessed the 17th of November 2014 from http://www.modernmedicine.com/modern-medicine/content/giving-intravenous-immunoglobulin

2. Silvergleid, A.J, Berger, M. General principles in the use of immune globulin. UpToDate; Accessed 9 of October 2013.

3. Brodaty H, Breteler MM, Dekosky ST, Dorenlot P, Fratiglioni L, Hock C, Kenigsberg PA, Scheltens P, De Strooper B.; The world of dementia beyond 2020; 2011; J Am Geriatr Soc.

4. Department of Health. 2008. Demand Management Plan for Immunoglobulin Use. United Kingdom. Available from http://www.ivig.nhs.uk/documents/Demand_Management_Plan_SECOND_EDITION.pdf ; Accessed the 4th December 2014.

5. National Blood Authority. 2014. Home » Best Practice » Immunoglobulin Product Authorisation and Management » Ig Program. Commonwealth of Australia. Available from http://www.blood.gov.au/Ig-program; Accessed the 4th December 2014.

6. Provincial Health Services Authority. 2014. IVIG Provincial Program [Internet]. BC, Canada. Available from http://www.pbco.ca/index.php/programs/ivig-provincial-program; Accessed the 4th December 2014.

7. National Blood Authority. 2014. Home » Best Practice » Immunoglobulin Product Authorisation and Management » Ig Program. Commonwealth of Australia. Available from http://www.blood.gov.au/Ig-program; Accessed the 4th December 2014.

8. Loeffler DA. Intravenous immunoglobulin and Alzheimer's disease: what now? J Neuroinflamm 2013, 10:70.

Social aspects

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Summary

In the absence of any discernible difference against placebo the social aspects cannot be defined

Introduction

The technology under assessment is still in its early stage of development and evidence based answers to the AEs of SOC domain we selected during the protocol, cannot be given. The issues of this domain should not be included in the HTA on the "Use of Intravenous immunoglobulins for Alzheimer disease including Mild Cognitive Impairment". On the other hand decisions about their use for treating one category of patients or another rise ethical questions related to how to use limited resources (ETH domain).

From a micro-sociological point of view (related to the impact of the technology on patients QoL) the EFF domain had included the QoL outcome (D0012 and D0013) and the reader can be referred to this domain. In short, for Mild Cognitive Impairment, and Moderate to Severe there is no available evidence, while for Mild to Moderate Alzheimer disease there is upcoming evidence (ongoing RCT and before and after study by Relkin 2012). For the phase 3 double-blind, placebo-controlled, two dose arm RCT, aiming at testing the safety and effectiveness of IVIG for patients with mild-to-moderate AD whose results were posted on clinical trial register in October 23rd 2014, after completion of this report, see EFF domain's comment. As regard to outcomes such as activity of daily living (ADCS-ADL) and quality of life (both in patients and caregivers according to QOLAD), EFF domain's report that there is no difference between IVIG and placebo groups.

Methodology

Frame

The collection scope is used in this domain.

Technology	Immunoglobulins (IGG) **Description** Naturally occurring proteins produced by the body's immune system to combat foreign antigens
Intended use of the technology	Treatment Treatment of Alzheimer's disease **Target condition** Alzheimer's disease **Target condition description** **Alzheimer's disease** (**AD**) or **Alzheimer disease**, is the most common form of dementia. There is no cure for the disease, which worsens as it progresses, and eventually leads to death. **Target population** *Target population sex*: Any. *Target population age*: elderly. *Target population group*: Patients who have the target condition. **Target population description** AD is diagnosed mostly in people over 65 years of age, although there is an early-onset form that can occur much earlier. According to Wikipedia in 2006, there were 26.6 million sufferers worldwide.
Comparison	placebo, not doing anything or Usual supportive care **Description** There is no MA for IGGs for AD yet and there is no other intervention licensed for use in AD so the comparison would have to be against placebo or best supportive care
Outcomes	• Description of aims of technology (TECH) • Regulatory status (CUR) • Cognitive function (EFF) • Harms (SAF) • Cost effectiveness compared to alternatives (ECO) • Potential impact on plasma derivative market (ORG/Medico-legal) • Impact on family and carers (SOC) • Appropriateness of use in relation to solidity of evidence(ETH)

Assessment elements

	Topic	Issue	Relevant	Research questions or rationale for irrelevance
H0100	Individual	What kind of changes do patients or citizens expect?	yes	What kind of changes do patients or citizens expect?
H0002	Individual	Who are the important others that may be affected, in addition to the individual using the technology?	yes	Who are the important others that may be affected, in addition to the individual using IGG?
H0004	Individual	What kind of changes may the use of the technology generate in the individual's role in the major life areas?	yes	What kind of changes may the use of IGG generate in the individual's role in the major life areas?
H0006	Individual	How do patients, citizens and the important others using the technology react and act upon the technology?	yes	How do patients, citizens and the important others using IGG react and act upon IGG?
H0012	Individual	Are there factors that could prevent a group or persons to participate?	yes	Are there factors that could prevent a group or persons to participate?
H0003	Individual	What kind of support and resources are needed for the patient or citizen as the technology is introduced?	no	The technology doesn not seem to imply any support for patients
H0001	Major life areas	Which social areas does the use of the technology influence?	yes	Which social areas does the use of IGG influence?
H0009	Major life areas	What influences patients' or citizens' decisions to use the technology?	yes	What influences patients' or citizens' decisions to use IGG?
H0011	Major life areas	What kinds of reactions and consequences can the introduction of the technology cause at the overall societal level?	no	This technology should not have this effect
H0007	Information exchange	What is the knowledge and understanding of the technology in patients and citizens?	no	The use of the technology does not necessarily imply a specific understanding/knowledge
H0013	Information exchange	What are the social obstacles or prospects in the communication about the technology?	no	The use of this technology does not seem to depend on social obastcles

Result cards

Individual

Result card for SOC1: "What kind of changes do patients or citizens expect?"

View full card

SOC1: What kind of changes do patients or citizens expect?

Result

The technology under assessment is still in its early stage of development and evidence based answers to the AEs of SOC domain we selected during the protocol, cannot be given.

Importance: Unspecified

Transferability: Unspecified

Result card for SOC2: "Who are the important others that may be affected, in addition to the individual using IGG?"

View full card

SOC2: Who are the important others that may be affected, in addition to the individual using IGG?

Result

The technology under assessment is still in its early stage of development and evidence based answers to the AEs of SOC domain we selected during the protocol, cannot be given.

Importance: Unspecified

Transferability: Unspecified

Result card for SOC3: "What kind of changes may the use of IGG generate in the individual's role in the major life areas?"

View full card

SOC3: What kind of changes may the use of IGG generate in the individual's role in the major life areas?

Result

The technology under assessment is still in its early stage of development and evidence based answers to the AEs of SOC domain we selected during the protocol, cannot be given.

Importance: Unspecified

Transferability: Unspecified

Result card for SOC4: "How do patients, citizens and the important others using IGG react and act upon IGG?"

View full card

SOC4: How do patients, citizens and the important others using IGG react and act upon IGG?

Result

The technology under assessment is still in its early stage of development and evidence based answers to the AEs of SOC domain we selected during the protocol, cannot be given.

Importance: Unspecified

Transferability: Unspecified

Result card for ETH12 / SOC5: "Are there factors that could prevent a group or persons to participate?"

View full card

ETH12 / SOC5: Are there factors that could prevent a group or persons to participate?

Result

Despite the common belief that the principles of bioethics are universal and applicable to every culture and society and that have always existed in the religious and moral traditions in various forms, the possibility that some of them may collide with one another at a certain stage of development and/or treatment of AD patients cannot be completely excluded.

Major religions (Christianity, Judaism, Islam and Buddhism) do not differ significantly in terms of their generally positive attitude towards human, with slight variations about prioritizing human body or soul, which might result in minor discrepancies in their opinion as to what extent a person should be allowed to self-decide on issues such as the maintenance or termination of life (for example, the application of euthanasia in AD's terminal stage).

Despite the principally expressed considerations, the concrete therapeutic technology under discussion might raise objections among some religious groups in light of the application of whatever therapy, i.e. some religious movements reject medical treatment, while others (such as "Jehovah's Witnesses") oppose blood transfusion practices. Therefore, there is a risk that the use of blood products in the form of immunoglobulins may be resisted against by the supporters of the above-mentioned religious movement.

Ethical rules and virtues are likely to come into conflict with the moral of a particular social group. The enrollment of AD subjects or persons with MCI in a clinical trial group to be treated with immunoglobulins presumes these subjects to have already been diagnosed, which would mean that the above individuals are labelled as "mad" or "incurably ill", thus leading to depersonalization and other negative consequences for the individuals and their families, relatives and friends in their future social contacts. In the USA, it is accepted among some groups such as Mexican Americans, Korean Americans and Navajo to inform family members about the health of their significant other before telling the diagnosis to the sick person himself/herself. In Ireland, 83% of the relatives of people suffering from dementia are against the disclosure of the diagnosis to the patients themselves, considering that learning/knowing it may harm the sick person causing him/her anxiety, stress, despair and depression. In this aspect, a conflict may be expected regarding the autonomy of the patient (i.e. his/her autonomy in the treatment decision-making process may be reduced). Therefore, autonomy of an individual depends largely on the people around him/her, their affiliation to a particular social group or community and cultural values, as well.

In support of the above is the huge financial, ethical and social burden on the patient's family and relatives, who, also, consider it moral and ethical to participate in the treatment process options as much as this choice affects their quality of life. Alzheimer's disease is becoming a key public health issue because of its significant morbidity and duration, high cost of related care and lack of effective definitive therapy. AD patients, given their advanced age, are likely to have additional comorbid chronic conditions such as diabetes and cardiovascular diseases, making treatment harder and more expensive. The choice of therapy should furthermore take into account a number of other factors, such as age, place of residence, social status, ethnicity, culture, health budgets, insurance coverage, opportunities for peripheral venous access, allergy or renal disease, all of which not only make treatment costly but may limit IVIG administration due to expected complications.

In terms of healthcare, the costs of caring for AD patients exceed the social costs, which is also a prerequisite for a conflict between the applied therapy and the social policies in some states.

Importance: Unspecified

Transferability: Unspecified

Major life areas

Result card for SOC6: "Which social areas does the use of IGG influence?"

View full card

SOC6: Which social areas does the use of IGG influence?

Result

The technology under assessment is still in its early stage of development and evidence based answers to the AEs of SOC domain we selected during the protocol, cannot be given.

Importance: Unspecified

Transferability: Unspecified

Result card for SOC7: "What influences patients' or citizens' decisions to use IGG?"

View full card

SOC7: What influences patients' or citizens' decisions to use IGG?

Result

The technology under assessment is still in its early stage of development and evidence based answers to the AEs of SOC domain we selected during the protocol, cannot be given.

Importance: Unspecified

Transferability: Unspecified

Collection appendices

Appendix 1 - Legal aspects of the technology

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