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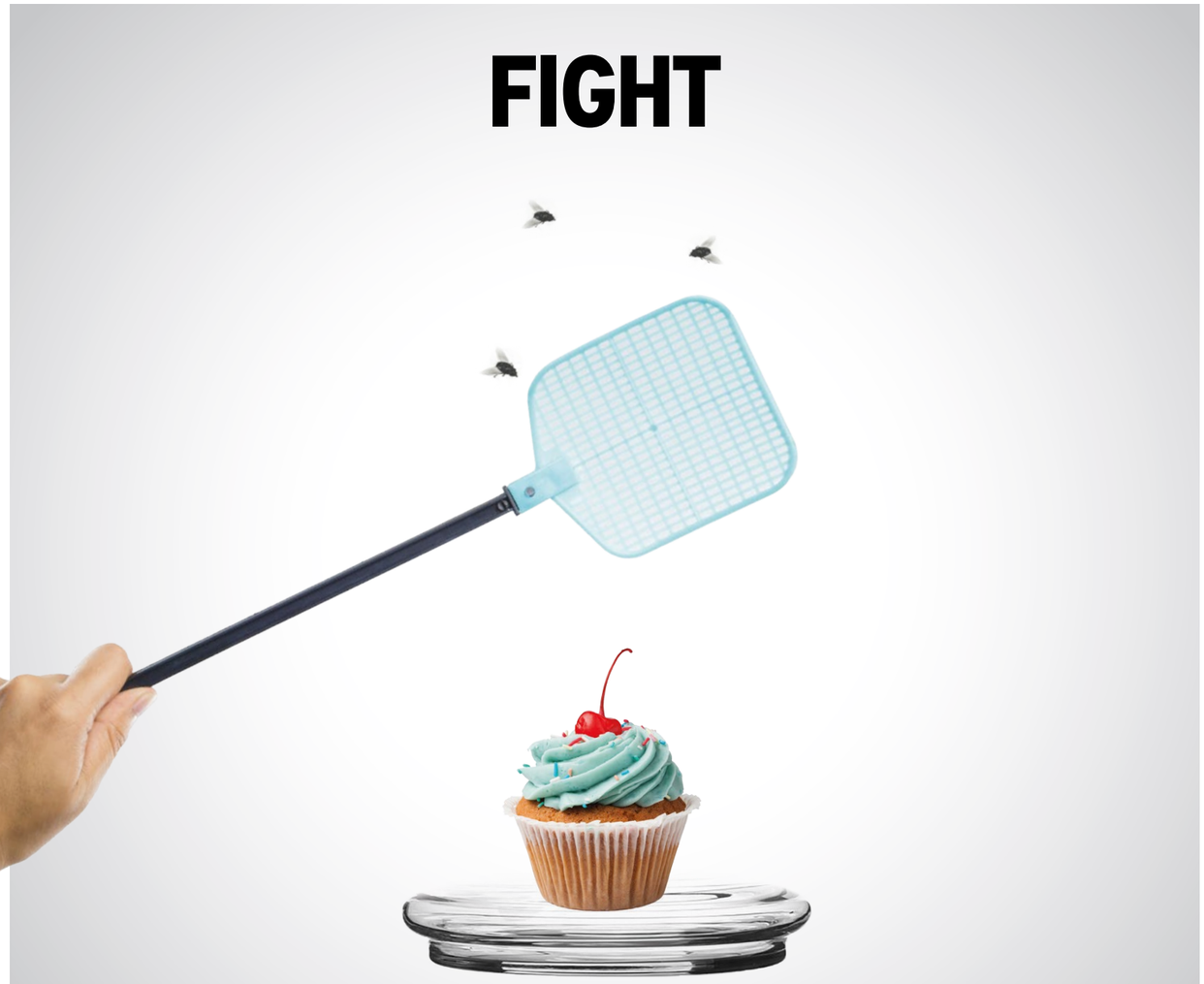
EMJ

Editor's Pick

A Case of Severe COVID-19 Infection in a Patient with Acute Myeloid Leukaemia: Critical Care Management and a Review of the Literature

Identifying Common Biomarkers Between COVID-19 and Commonly Associated Comorbidities

The Safety of Medications During Pregnancy and Lactation in Patients with Inflammatory Rheumatic Diseases



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Please refer to the full Summary of Product Characteristics (SmPC) approved in your country before prescribing. ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.**Indication:** Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. **Active ingredient:** Each pre-filled syringe contains 210mg brodalumab in 1.5ml solution. 1ml solution contains 140mg brodalumab. **Dosage and administration:** Posology: Adults: The recommended dose is 210mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210mg every 2 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. 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Reporting of Suspected Adverse Reactions
Adverse reactions should be reported according to local guidelines.

January 2021
MAT-40487

References:
1. Lebwohl M, et al. *N Engl J Med* 2015;373:1318–28. **2.** Kyntheum® (brodalumab) EU Summary of Product Characteristics. July 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kyntheum. Last Accessed: January 2021. **3.** Brembilla NC et al. *Front Immunol* 2018;9:1682. **4.** Pappu R et al. *Immunology* 2011;134:8–16. **5.** Baker KF and Isaacs JD. *Ann Rheum Dis* 2018;77:175–87.

PASI 100 at 12 weeks with Kyntheum®: 44% in AMAGINE-2 (n=612) and 37% in AMAGINE-3 (n=624) using NRI for missing data.[1]
IL, interleukin; NRI, non responder imputation; PASI, Psoriasis Area and Severity Index.

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EMJ Welcome letter

Dear Readers,

In my first ever welcome for EMJ, I would like to introduce myself as the Editor of the EMJ family of journals. It is my absolute pleasure to present the final issue of EMJ for 2021, which shares research in rheumatology, microbiology, nephrology, and gastroenterology, among other therapy areas.

To celebrate our Winter issue, we have chosen as our cover a photograph of a Stockholm landscape in snow as a nod to Jesse Huang, who is the author of an article featured in this issue on biomarkers in COVID-19 and other pre-existing conditions. Continuing the COVID-19 theme is our Editor's Pick for this issue authored by Gupta et al., which focuses on management of acute myeloid leukaemia in conjunction with severe COVID-19.

Looking back at the medical developments of this year, COVID-19 has again dominated the news and has been a major focus for healthcare professionals. We stand in awe of the key advancements in medicine underpinning the unprecedented vaccination roll-out at a global scale, which at the time of writing has seen more than 7.7 billion doses administered globally across 184 countries.

The EMJ Editorial team, who have worked tirelessly in putting this issue together, and myself, would like to express our gratitude to the authors of this issue. By contributing highly engaging insights and research they enable you, our readers, to learn more about key areas of focus and progress. We would also like to extend our thanks to the peer reviewers and Editorial Board for ensuring the quality of research shared in our journals remains high.

I hope that you enjoy reading through this issue. Looking at the year ahead, we are excited to be planning our upcoming issues for 2022, which will focus on topics of great interest in healthcare with a global appeal.

Koutsouki

Evgenia Koutsouki, PhD.

Editor

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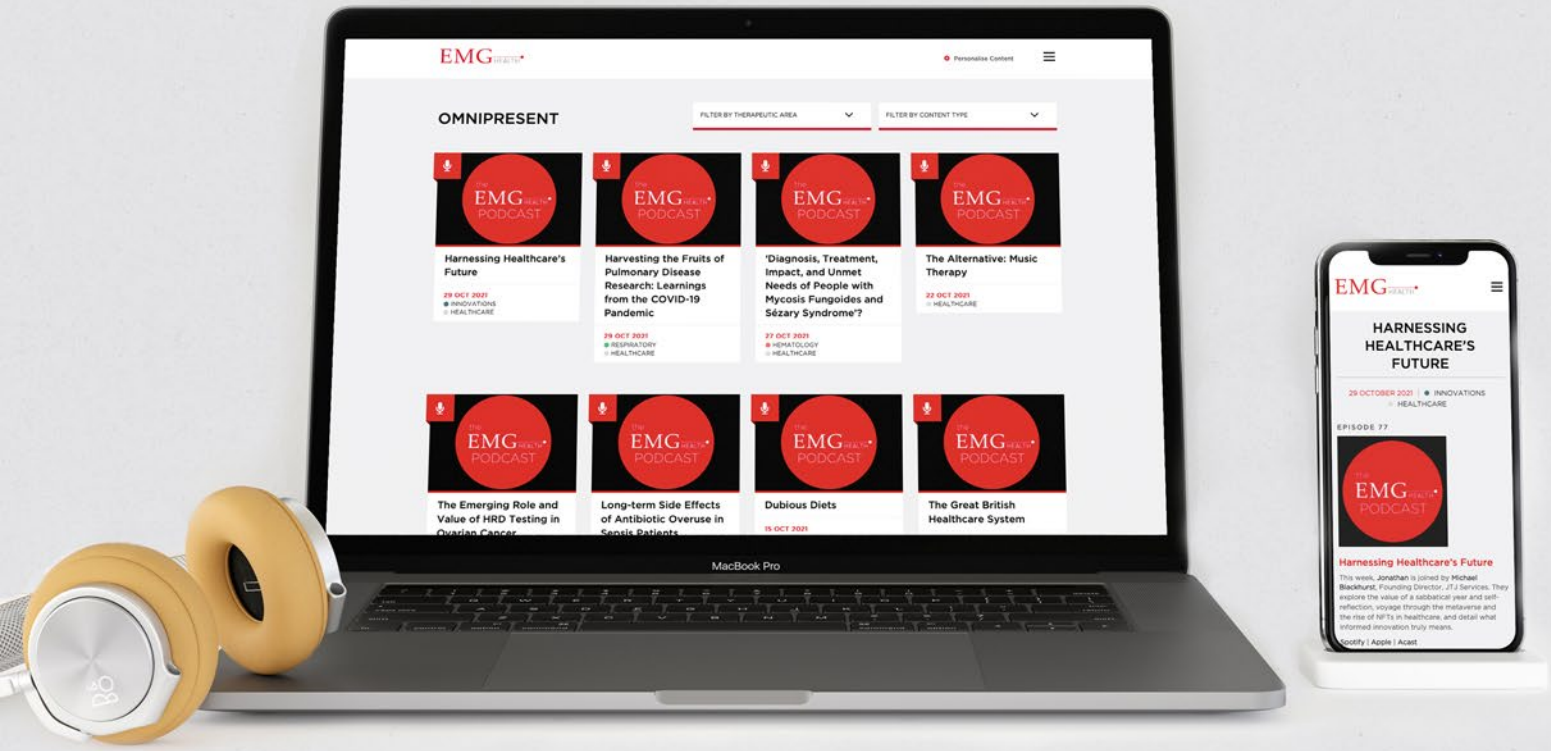

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The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. *Crohn's disease:* Induction treatment: 25 mg/week administered subcutaneously. Response to treatment can be expected after approximately 8 -12 weeks. Maintenance treatment: 15 mg/week. *Elderly:* Dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves. If changing the oral to parenteral administration a reduction of dose may be required due to the variable bioavailability. **Contraindications:** Hypersensitivity to methotrexate or any of the excipients; severe liver impairment; alcohol abuse; severe renal impairment (creatinine clearance < 30 ml/min); pre-existing blood dyscrasias (bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anaemia); serious, acute or chronic infections such as tuberculosis, HIV, other immunodeficiency syndromes; ulcers of the oral cavity and known active gastrointestinal ulcer disease; pregnancy, breastfeeding; concurrent vaccination with live vaccines. **Special warnings and precautions for use:** In the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease, Metoject PEN (methotrexate) must only be used once a week. 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Leukopenia, anaemia, thrombopenia, pancytopenia, agranulocytosis, severe courses of bone marrow depression, lymphoproliferative disorders, eosinophilia. Allergic reactions, anaphylactic shock, hypogammaglobulinaemia. Precipitation of diabetes mellitus. Depression, confusion, mood alterations. Headache, tiredness, drowsiness, dizziness, pain, muscular asthenia or paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis, encephalopathy/leukoencephalopathy. Visual disturbances, impaired vision, retinopathy. Pericarditis, pericardial effusion, pericardial tamponade. Hypotension, thromboembolic events. Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever, pulmonary fibrosis, Pneumocystis jirovecii pneumonia, shortness of breath and bronchial asthma, pleural effusion, epistaxis, pulmonary alveolar haemorrhage. Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain, oral ulcers, diarrhoea, gastrointestinal ulcers and bleeding, enteritis, vomiting, pancreatitis, gingivitis, haematemesis, haematorrhea, toxic megacolon. Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin), cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin, acute hepatitis, hepatic failure. Exanthema, erythema, pruritus, photosensitisation, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticarial, increased pigmentation, acne, petechiae, ecchymosis, allergic vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia, skin exfoliation/ dermatitis exfoliative. Arthralgia, myalgia, osteoporosis, stress fracture, osteonecrosis of jaw (secondary to lymphoproliferative disorders). Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition, renal failure, oliguria, anuria, electrolyte disturbances, proteinuria. Inflammation and ulceration of the vagina, loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge. Fever, wound-healing impairment, asthenia, injection site necrosis, oedema. Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed, decreasing during therapy. **Overdose:** Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate.

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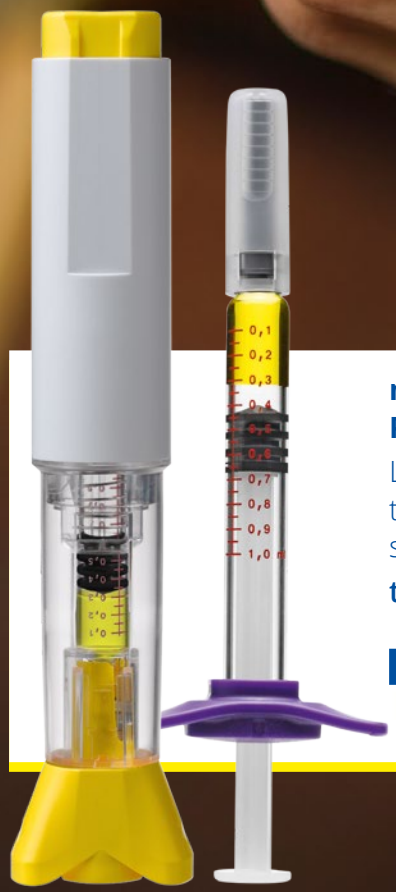

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Foreword

Dear Colleagues,

It is my pleasure to welcome you to this issue of *EMJ*, which comprises a collection of compelling articles exploring the latest advancements in a range of different therapeutic areas.

The Editor's Pick for this issue is a fascinating article titled 'A Case of Severe COVID-19 Infection in a Patient with Acute Myeloid Leukaemia: Critical Care Management and a Review of the Literature' by Gupta et al., which delves into this debilitating form of cancer, and the successful management of severe COVID-19 infections in patients. A definition of acute myeloid leukaemia was established, alongside symptoms and their overlap with COVID-19, and case and clinical management methods explained. Important consequences of the COVID-19 pandemic were also highlighted, including the impact of isolation on patient mental health.

Huang also explored the ever-relevant topic of COVID-19 in an interesting article comparing biomarkers for the disease with commonly associated conditions, including myocardial infarction, stroke, and hypertension. This paper provides a comprehensive review of systemic effects of the COVID-19 infection as well as identifying biomarkers for clinical evaluation of the disease.

A collection of rheumatology papers explore topics including the association between hypermobility and rheumatologic diseases such as Ehlers-Danlos syndrome. A review of the safety and risks associated with the use of medications to treat inflammatory rheumatic disease during pregnancy and lactation can also be found in this issue.

Other disease areas covered include a review of a pioneering topic titled 'Cannabinoids in the Treatment of Epilepsy: A Review', where Zhou et al. discuss innovative therapy strategies for the treatment of refractory epilepsy, and a case report of cefixime-induced hepatitis.

I would like to thank all of the authors, peer-reviewers, and researchers for committing their time to the production of this fantastic journal.

Markus Peck-Radosavlijevic

Professor of Medicine, Chairman of the Department of Gastroenterology and Hepatology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

Factor XI Inhibition: The Holy Grail of Haemostasis-Sparing Anticoagulation

These presentations took place on 20th July 2021, as part of the International Society on Thrombosis and Haemostasis (ISTH) Virtual Congress 2021

Speakers: Ajay Kakkar,[1] Jeffrey I. Weitz,[2] Harry R. Büller,[3] Jean M. Connors[4]

1. Thrombosis Research Institute, London, UK
2. McMaster University, Hamilton, Canada
3. Academic Medical Center, Amsterdam, The Netherlands
4. Harvard Medical School, Boston, Massachusetts, USA

Disclosure: Kakkar has received research support from Bayer and Sanofi; and personal fees from Bayer, Sanofi, and Anthos Therapeutics. Weitz has received research support or acted as principal investigator from Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, and Canadian Fund for Innovation; has served as a consultant for Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Pfizer, Portola Pharmaceuticals, Ionis Pharmaceuticals, Janssen Pharmaceutica, Merck & Co., Novartis, Anthos Therapeutics, and Tetherex Pharmaceuticals; and is on the scientific advisory board for Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi-Sankyo, Pfizer, Portola Pharmaceuticals, Ionis Pharmaceuticals, Janssen Parmaceutica, and Laboratoires Servier. Büller has received research support or acted as principal investigator from Sanofi-Aventis, Bayer HealthCare, Bristol Myers Squibb, Daiichi-Sankyo, GlaxoSmithKline (GSK), Pfizer, Roche, Ionis, Boehringer Ingelheim, Eli Lilly, and Novartis; and has served as a consultant and on the scientific advisory board for Sanofi-Aventis, Bayer, Bristol Myers Squibb, Daiichi-Sankyo, GSK, Pfizer, Roche, Ionis Pharmaceuticals, Boehringer Ingelheim, Eli Lilly and Company, Novartis, and Anthos Therapeutics. Connors has served on scientific advisory boards and as a consultant for Abbott, Anthos Therapeutics, Alnylam® Pharmaceuticals, Bristol Myers Squibb, Portola Pharmaceuticals, and Takeda; and has received research funding to the institution from CSL Behring.

Acknowledgements: This report was written by Jenny Lloyd, Compass Medical Communications, Ltd., UK.

Disclaimer: The views and opinions expressed are those of the speakers and not necessarily those of Anthos Therapeutics.

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Citation: EMJ. 2021;6[4]:12-20.

Summary

Ajay Kakkar opened this virtual meeting by discussing the history of the treatment and prevention of thrombosis. Early anticoagulants (unfractionated heparin and warfarin) reduced thrombosis risk but increased bleeding risk. Direct oral anticoagulants (DOACs) were more effective than warfarin and associated with a lower, but still present, bleeding risk. Jeffrey I. Weitz discussed the traditional view of the coagulation cascade, in which pathological thrombosis (i.e., harmful clots that occlude blood vessels) and physiological haemostasis (i.e., bleeding prevention) appear to be inextricably linked. He then introduced a more recent model with two distinct pathways, in which pathological thrombosis and physiological haemostasis could be uncoupled if certain factors are targeted, reducing bleeding

risk. Factor XI is a potential target, with strategies for its inhibition including antisense oligonucleotides, monoclonal antibodies (e.g., abelacimab, osocimab), aptamers, and small molecules (e.g., asundexian, milvexian). Harry R. Büller presented key trial data in patients undergoing total knee arthroplasty. Compared with enoxaparin, abelacimab significantly reduced the risk of venous thromboembolism (VTE) after a single post-operative 150 mg dose (4% versus 22%; p<0.001). FXI-ASO also reduced VTE compared with enoxaparin (4% versus 30%; p<0.001), but after nine 300 mg subcutaneous doses. Lastly, a single 1.8 mg/kg pre-operative dose of intravenous osocimab reduced VTE versus enoxaparin, but to a lesser extent (11% versus 26%; p<0.001). Jean M. Connors concluded that factor XI is a promising new target for the inhibition of pathological thrombosis, with minimal impairment of physiological haemostasis. The potential applications of factor XI inhibitors were then debated in a panel discussion.

The Prevention and Treatment of Thrombosis: Six Decades of Progress

Ajay Kakkar

There has been substantial progress in the field of venous and arterial thrombosis in the last 60 years. Back in 1960, Barritt and Jordan[1] published a study showing that the administration of an anticoagulant to patients with pulmonary embolism could significantly reduce death from this condition, from 5/19 untreated patients to 0/54 treated patients (p=0.0007). In the 1970s, the focus switched from the treatment of VTE to its prevention. In 1975, an international multicentre trial of 4,121 patients undergoing elective major surgical procedures showed that the administration of low-dose unfractionated heparin significantly reduced the number of patients with fatal pulmonary embolism compared with control (2 versus 16; p<0.005).[2]

A meta-analysis published in 2007 included six randomised trials, published during the 1990s, of patients with atrial fibrillation (AF) who had been randomised to warfarin or control/placebo.[3] Among a total of 2,900 patients, warfarin reduced the risk of stroke compared with control/placebo by 64% (95% confidence interval [CI]: 49–74).[3] A later meta-analysis included four Phase III randomised trials of patients with AF, published during 2009–2013, which compared direct oral anticoagulants, also referred to as non-vitamin K antagonist oral anticoagulants, with warfarin.[4] Among a total of 71,683 patients, DOACs significantly reduced the risk of stroke or systemic embolic events by 19% (95% CI: 9–27) compared with warfarin.[4] Together, these studies established the principle of intervention to prevent thromboembolic stroke with an anticoagulant in patients with AF.

However, anticoagulants can increase the risk of bleeding, particularly in certain patient groups. The GARFIELD-VTE registry included 10,684 patients with VTE, who were followed for up to 3 years.[5] Patients with active cancer were at increased risk of major bleeding (hazard ratio [HR]: 3.8; 95% CI: 2.9–5.0) compared with patients without cancer. Patients with active cancer also had an increased bleeding risk compared with patients with a history of cancer (HR: 2.9; 95% CI: 1.7–5.0).[5]

In the GARFIELD-AF registry, 52,032 patients with newly diagnosed AF were given a vitamin K antagonist (VKA) (±an antiplatelet agent), a DOAC (±an antiplatelet agent), an antiplatelet agent alone, or no antithrombotic treatment.[6] Various factors were significantly associated with increased bleeding risk, including a history of bleeding (HR: 2.38; 95% CI: 1.72–3.30), moderate or severe chronic kidney disease (HR: 1.72; 95% CI: 1.41–2.10), older age (HR: 1.23; 95% CI: 1.18–1.29), and anticoagulant used.[6] In terms of the anticoagulant, the bleeding risk was higher with a VKA than with a DOAC, and lowest with an antiplatelet agent alone.[6] The bleeding risk increased with the addition of an antiplatelet agent to a VKA or a DOAC.[6] Further, patients with major bleeding had a higher risk of all-cause mortality than those without major bleeding (adjusted HR [aHR]: 8.24; 95% CI: 6.76–10.04).[6] The presence of less severe bleeding also had an impact on all-cause mortality, including clinically relevant non-major bleeding (aHR: 2.59; 95% CI: 1.80–3.73) and minor bleeding (aHR: 1.53; 95% CI: 1.07–2.19).[6]

In GARFIELD-AF, both the proportion of patients receiving an anticoagulant and the choice of anticoagulant changed over time.[7] During 2010–2011, approximately 57% of patients were given an anticoagulant (either a VKA or DOAC),[7] but by 2015–2016 this had increased to around 71% (unpublished data). Among the patients who received an anticoagulant, this was mainly a VKA (approximately 93%) during 2010–2011, with approximately 7% receiving a DOAC.[7] By 2015–2016, patients were more likely to receive a DOAC (approximately 61%), with approximately 39% receiving a VKA (unpublished data). Most importantly, even in 2015–2016, approximately 25% of patients with AF, who are at increased risk of stroke, were not receiving any anticoagulant (unpublished data).

Even with the availability of DOACs, which have a lower bleeding risk than VKAs, the risk of major bleeding remains a deterrent to optimal anticoagulation, and prescription remains suboptimal. For example, in the NCDR PINNACLE registry, approximately 50% of outpatients with AF who were considered to be at high stroke risk (CHA_2DS_2-VASc: ≥5) received no anticoagulant.[8] Similarly, 40% of patients admitted to hospital with pre-existing AF (and CHA_2DS_2-VASc: ≥2) were receiving no anticoagulation at the time of admission.[9] Findings among other patient types at risk of VTE are similar, with 42% of surgical inpatients and 60% of non-surgical inpatients receiving no anticoagulation.[10]

In conclusion, despite substantial progress in the treatment and prevention of venous and arterial thrombosis over the last six decades, and the validation of the efficacy and safety of DOACs in clinical practice, there remains an unmet clinical need due to the risk and fear of bleeding. Therefore, there is a need for new anticoagulants with a lower bleeding risk.

Uncoupling Haemostasis from Thrombosis: The Potential of Factor XI Inhibition

Jeffrey I. Weitz

In traditional coagulation cascade models, the contact activation (or intrinsic) pathway (activated by factors inside the vascular system) and the tissue factor (or extrinsic) pathway (activated by external trauma) converge. This implies that pathological thrombosis and physiological haemostasis, both of which depend on clot formation, are inextricably linked through the common pathway. However, if just the contact pathway could be inhibited, this could be used to attenuate thrombosis with minimal disruption of haemostasis, thus reducing bleeding risk.

Various new initiators of the intrinsic pathway have been described. These are naturally occurring polyanions and include neutrophil extracellular traps extruded from activated leukocytes, DNA and RNA released from activated or damaged cells, and inorganic polyphosphates released from activated platelets. These anionic polyanions activate factor XII and induce thrombosis through the contact pathway.

Various lines of evidence support factor XI as an antithrombotic target. Firstly, individuals with factor XI deficiency (activity: ≤50%) have a reduced risk of VTE (aHR: 0.26; 95% CI: 0.08–0.84).[11] While such individuals can have some increased bleeding risk, this is rarely spontaneous or severe.[12,13] Secondly, individuals with elevated factor XI levels (above the 90th percentile) have a 2.2-fold higher adjusted risk (95% CI: 1.5–3.2) of deep venous thrombosis (DVT).[13] Thirdly, various animal studies support factor XI as an antithrombotic target with low bleeding risk.[14]

Strategies to target factor XI include: antisense oligonucleotides (ASO), which reduce hepatic synthesis of factor XI; aptamers, which bind factor XI and block activity; antibodies, which bind factor XI and block activation or activity; and small molecules, which bind reversibly to the active site of factor XIa and block activity.[15]

As mentioned above, the traditional view of the coagulation cascade suggests that the generation of the fibrin in an occlusive thrombus inside a vessel, or the fibrin in a haemostatic plug that seals leaks in damaged vessels both occur via a connected coagulation pathway. This led to the belief that it is not possible to have effective anticoagulation without an appreciable bleeding risk.

However, newer models of the coagulation cascade have delineated two distinct pathways, with only one main section in common: the downstream common pathway (Figure 1).[16] In this

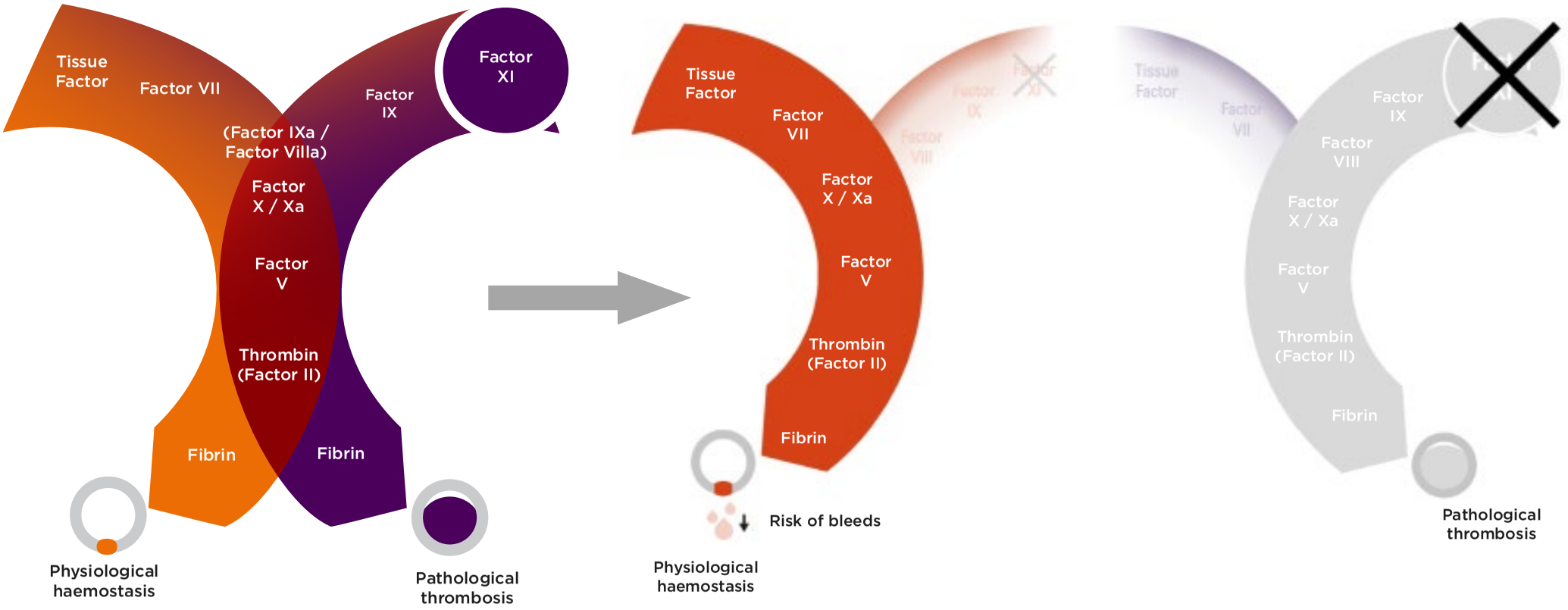

Figure 1: Newer model of the coagulation cascade.[16]

new model, haemostasis (i.e., the formation of a plug to seal leaks in damaged blood vessels) is mainly an extravascular process, triggered by high concentrations of tissue factor in the haemostatic envelope that surrounds blood vessels. Therefore, with high tissue factor concentrations, fibrin production occurs via the extrinsic pathway (left pathway in Figure 1). Pathological thrombosis (i.e., a clot inside a blood vessel) is triggered by much lower concentrations of tissue factor that are exposed when atherosclerotic plaques are disrupted or are presented on the activated endothelium that tethers tissue factor-expressing monocytes or microvesicles on the surface. With low concentrations of tissue factor, clotting initially occurs through the extrinsic pathway. However, the intrinsic pathway becomes very important for thrombus growth due to the back activation of factor XI by thrombin; and the activation of factor IX intensifies factor X activation and resultant fibrin formation (right path in Figure 1).[16]

DOACs and warfarin target factor X/Xa and prothrombin/thrombin (factor II/IIa), both of which are in the common pathway (centre of Figure 1). Warfarin additionally targets a number of other factors. Hence, DOACs and warfarin impact haemostasis as well as thrombosis. However, targeting factor XI, which is intimately involved in thrombosis but is generally non-essential for haemostasis, provides an opportunity to pharmacologically 'uncouple' the two coagulation pathways. This could enable the effective suppression of the pathological thrombosis pathway, while leaving the physiological haemostasis pathway largely unaffected, thus reducing bleeding risk.

Factor XI-directed strategies are being tested in various Phase II studies, as recently reviewed by Fredenburgh and Weitz.[17] Agents include monoclonal antibodies (e.g., abelacimab, osocimab), ASOs, and small molecules (e.g., asundexian, milvexian) (Table 1).[17] Abelacimab binds to factor XI and blocks its activation by factor XIIa and thrombin, whereas osocimab only inhibits factor XIa.[17] Both monoclonal antibodies can be given subcutaneously or intravenously, as single doses or once per month. They have a rapid onset and slow offset of action, and neither requires renal clearance nor poses a risk of drug–drug interactions. ASOs decrease factor XI synthesis, can be given weekly to monthly, and have a slow onset of action.[17] The small molecules inhibit factor XIa and are given orally, but require daily administration due to their rapid offset of action. They also undergo some renal clearance and have the potential for drug–drug interations.[17]

A potential new indication for factor XI inhibitors is the prevention of major adverse cardiovascular events in patients with end-stage renal disease (with or without AF), which could be highly beneficial as such patients cannot take DOACs as they are cleared via the kidneys, thus increasing the risk of accumulation and consequent bleeding. Factor XI inhibitors may also provide a safer platform for antiplatelet therapy in patients with acute coronary syndromes, secondary stroke prevention, the prevention or treatment of cancer associated VTE, and prevention of thrombosis on devices such as central venous catheters, mechanical heart valves, and left ventricular assist devices.

In conclusion, factor XI is emerging as a promising target for new anticoagulants. Several strategies to inhibit factor XI are under investigation, and ongoing trials will determine their benefit–risk profile and whether they can uncouple thrombosis and haemostasis.

Abelacimab: A Dual Factor XI/XIa Inhibitor

Harry R. Büller

Abelacimab is a unique, fully human monoclonal antibody that inhibits both the inactive (zymogen) and active forms of factor XI.[18] It binds to the catalytic domain of both factor XI and factor XIa with high affinity and selectivity.[18] It has two mutations in the fragment crystallisable region, which reduce the potential for fragment crystallisable-γ receptor binding and complement activation.

In the ANT-005 TKA study,[19] 412 patients who were undergoing total knee arthroplasty were randomly assigned 1:1:1:1 to a single intravenous infusion of post-operative abelacimab (30, 75, or 150 mg), or to once daily subcutaneous enoxaparin (40 mg). The primary efficacy outcome was objectively documented symptomatic VTE or asymptomatic DVT on mandatory venography

Table 1: Drugs that target factor XI.

	Abelacimab	Osocimab	FXI-LICA	Asundexian (BAY243334)	Milvexian (BMS-986177/ JNJ-70033093)
Agent	Monoclonal antibody (fully human)	Monoclonal antibody (fully human)	ASO	Small molecule	Small molecule
Mode of action	Dual factor XI/XIa inhibition	Factor XIa inhibition	Decreases factor XI synthesis	Factor XIa inhibition	Factor XIa inhibition
Administration	SC or IV	SC or IV	SC	Oral	Oral
Frequency of dosing	Monthly or once	Monthly or once	Weekly to monthly	Daily	Daily (QD, BID)
Onset of action	Rapid	Rapid	Slow	Rapid	Rapid
Offset of action	Slow	Slow	Slow	Rapid	Rapid
Renal clearance	No	No	No	Some	Some
Drug–drug interactions	No	No	No	Possible	Possible

ASO: antisense oligonucleotide; BID: twice daily; FXI-LICA: factor XI ligand-conjugated antisense; IV: intravenous; SC: subcutaneous, QD: once daily.

Adapted from Fredenburgh and Weitz.[17]

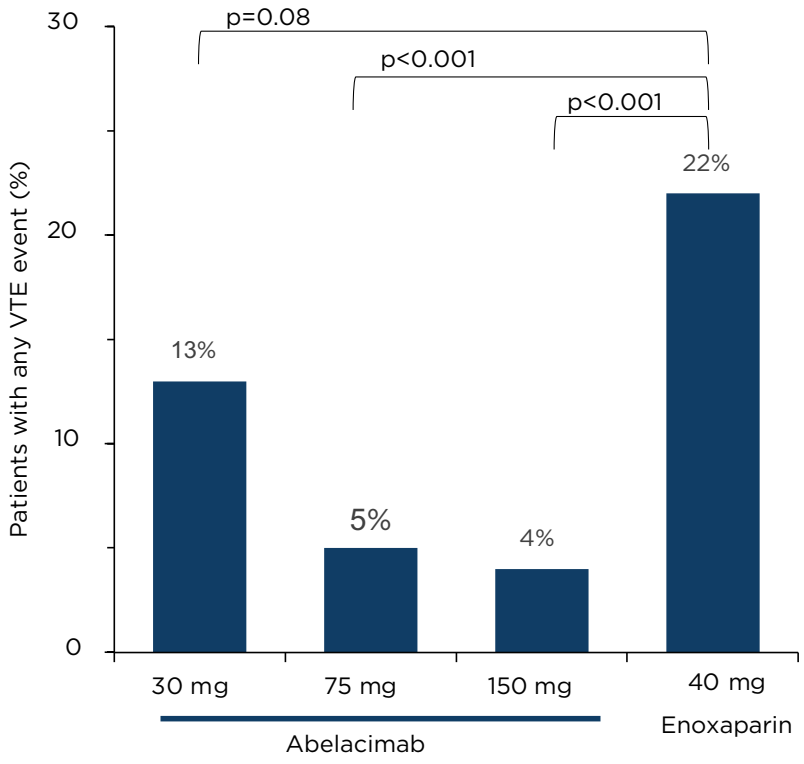

Figure 2: Rates of venous thromboembolism in the ANT-005 TKA study.[19]

VTE: venous thromboembolism.

on Day 10 (±2).[19] The principal safety outcome was a composite of major and clinically relevant non-major bleeding up to Day 30 after surgery.[19] At baseline on Day 1 prior to surgery, the median factor XI activity was approximately 120% in each of the three abelacimab dose groups. On Day 3, factor XI activity was <10% in all patients in all three dose groups. By Day 10, factor XI activity remained ≤10% in all patients in the two higher dose groups, while it had increased to a median of around 55% in the lowest dose group. By Day 30, median activity in the 150, 75, and 30 mg dose groups was approximately 5%, 75%, and 100%, respectively.[19] Rates of VTE were lower with all doses of abelacimab (4%, 5%, and 13%, with decreasing doses) than with enoxaparin (22%), reaching significance (p<0.001) in the two highest dose groups (Figure 2).[19]

Symptomatic VTE only occurred in one patient (in the enoxaparin group); the other 43 patients who met the primary endpoint had asymptomatic DVTs. Most of the DVTs were distal, with only three proximal DVTs (one in the abelacimab 30 mg group and two in the enoxaparin group).[19] Only four patients had a major or clinically relevant non-major bleed, two in each of the two lower abelacimab dose groups. Only one of these events was classified as major bleeding. It occurred in a patient in the 75 mg abelacimab group, who had two bleeding events: a clinically relevant non-major bleed and a joint infection and haemarthrosis that was classified as a major bleed.[19]

Other published clinical trials of factor XI inhibition in patients undergoing total knee arthroplasty include the FXI-ASO TKA study[20] and the FOXTROT osocimab trial.[21] In the FXI-ASO TKA study,[20] patients received nine subcutaneous doses of FXI-ASO (200 or 300 mg) during 36 days before to 3 days after surgery or enoxaparin 40 mg daily from the day before or the day of surgery for at least 8 days. VTE occurred in 4% of patients in the 300 mg group, 27% in the 200 mg group, and 30% in the enoxaparin group (p<0.001 for 300 mg versus enoxaparin).[20] In the FOXTROT trial, patients received a single intravenous dose of osocimab (0.3, 0.6, 1.2, or 1.8 mg/kg) on the day after surgery, a single intravenous dose of osocimab (0.3 or 1.8 mg/kg) on the day before surgery, daily enoxaparin (40 mg), or twice daily apixaban (2.5 mg).[21] The lowest rate of VTE occurred in the pre-operative osocimab 1.8 mg/kg group (11%), a rate significantly lower than that in the enoxaparin group (26%; p<0.001).[21]

Other ongoing or completed Phase II clinical trials of drugs targeting factor XI include those testing factor XI ligand-conjugated antisense (NCT04534114)[22] or osocimab (NCT04523220)[23] in patients with end-stage renal disease, milvexian in patients undergoing total knee arthroplasty (NCT03891524)[24] or for secondary stroke prevention (NCT03766581),[25] and asundexian in patients with AF (NCT04218266),[26] non-cardioembolic stroke (NCT04304508),[27] or acute myocardial infarction (NCT04304534).[17,28]

An ongoing Phase II study of abelacimab (ANT-006 AZALEA-TIMI 71) is comparing it with rivaroxaban in 1,200 patients with AF (NCT04755283).[29] There are also two planned Phase III trials in patients with cancer-associated thrombosis, one comparing abelacimab with apixaban in approximately 1,600 patients and one comparing it with dalteparin in approximately 1,000 patients.

In conclusion, current data support the concept of factor XI inhibition for reducing the risk of thrombosis. Rates of VTE after knee surgery with factor XI inhibitors are impressively low, with no evidence for increased risk of bleeding in this setting. Further, post-operative factor XI inhibition is very effective. Current data indicate that abelacimab could be a promising new drug in this field, and future studies will hopefully provide further support.

Conclusion

Jean M. Connors

Anticoagulants can significantly reduce the risk of stroke in patients with AF and reduce the risk of thromboembolic events. They are excellent treatments for acute thrombosis but can increase the risk of bleeding, which is of particular importance in patients with cancer. The avoidance of anticoagulants due to this increased bleeding risk has not been resolved with the introduction of DOACs. Further, patients at perceived risk of bleeding often receive inappropriately reduced doses of DOACs, which can reduce efficacy without necessarily reducing bleeding risk.

Factor XI is a promising new target for the inhibition of pathological thrombosis with minimal impairment of physiological haemostasis. Phase II data with abelacimab demonstrate impressive efficacy in patients undergoing total knee replacement, with no safety signals. Overall, abelacimab is a promising new treatment in many clinical situations to inhibit thrombosis without impairing haemostasis.

Panel Discussion

Abelacimab could potentially be useful in a range of patient populations including those with cancer-associated thrombosis, AF, or VTE. Patients with increased bleeding risk often also have an increased risk of thrombosis, making the uncoupling of physiological haemostasis and pathological thrombosis particularly important. Factor XI inhibitors could also be a safer option for reducing major adverse cardiovascular events in patients with end-stage kidney disease, who are at increased risk of bleeding. They may also be useful for preventing recurrent stroke in patients with non-cardioembolic stroke, in patients with acute coronary syndromes, or to prevent clotting on central venous catheters, etc. Current data on drugs targeting factor XI support the uncoupling of the coagulation model, with these drugs able to achieve very low VTE rates without increasing the risk of bleeding.

A major benefit of abelacimab over ASOs is that it can be given as a single dose on the day of surgery, rather than having to start approximately 1 month before a planned procedure. The possibility of once monthly subcutaneous dosing for other indications could also improve patient adherence, increase treatment satisfaction, and reduce patient burden. Monoclonal antibodies also have no risk of drug–drug interactions or issues with hepatic metabolism or renal clearance, thus improving safety. They can be given intravenously, if a very rapid onset of action is required, or subcutaneously for longer-term use.

In the real world, it is important to balance efficacy and safety. Current data indicate that abelacimab has very good efficacy, coupled with a favourable safety profile, making it a very promising candidate. The dosing of conventional anticoagulants is limited by bleeding risk, but if factor XI inhibitors can uncouple physiological haemostasis and pathological thrombosis, it may be possible to get high efficacy without increasing bleeding risk.

Much of the residual thromboembolic burden of thromboembolic disease is because, in trying to achieve safety with current drugs, physicians tend to under-dose, putting patients at risk of thromboembolic events. There are also patient populations who currently receive no anticoagulation due to their elevated bleeding risk. The factor XI inhibitors may prove particularly beneficial in both these populations.

The GARFIELD-AF registry highlights the suboptimal uptake of anticoagulants among patients with AF.[7] With a safer option available, both physicians and patients may be more likely to prescribe/accept treatment. Although aspirin is often perceived to have a lower bleeding risk, this is not actually true.

In conclusion, factor XI inhibition with abelacimab could potentially offer the holy grail of targeting and inhibiting pathological thrombosis and separating it from physiological haemostasis. These attributes could benefit many patients who require anticoagulation but are not receiving it due to bleeding concerns.

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Evra (Norelgestromin and Ethinyl Oestradiol) and Contraceptive Options Available to Females Today

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Interview Summary

The contraceptive landscape has evolved in the last two decades, and today, females have varied options, allowing them to choose the method that best fits their needs. Of those options, transdermal delivery of a combined hormonal contraceptive (CHC) is often favoured by females for the convenience of a weekly versus daily shedule. Ali Kubba, Consultant in obstetrics and gynaecology at London Bridge Hospital, UK, and Lead Consultant in colposcopy and reproductive healthcare at Guy's and St. Thomas' Private Healthcare, London, UK, spoke with EMJ about contraceptive use trends and developments in transdermal methods.

THE CURRENT CONTRACEPTIVE LANDSCAPE

Increased contraceptive choice is a pivotal shift in modern contraception that has improved the autonomy of females and may help to better match contraception to their individual and cultural identities. Females today have a variety of contraceptives to choose from. These include short-acting reversible contraceptives such as oral contraceptives (OC), vaginal rings, barrier methods, condoms, transdermal patches, and emergency contraception, and long-acting reversible contraceptives (LARC) such as intrauterine devices, injectable, or implantable methods.[1,2]

Kubba explained that in the last few years, the pattern of contraceptive use has changed. Females of all ages are looking for higher contraceptive efficacy and convenience to better fit their busy lifestyles. They favour non-daily methods and additional therapeutic effects (cycle regulation, controlling heavy bleeding, dysmenorrhoea reduction, and acne control). The National Survey of Sexual Attitudes and Lifestyles (Natsal) in the UK surveys a large representative sample of males and females every 10 years. Data from 1999–2000 and 2010–2012 from Natsal 2 and 3 revealed that the use of daily OCs, male and female sterilisation, and less effective methods (condom, rhythm, and withdrawal) decreased from 76.6% to 63.7%, and the use of LARC such as intrauterine devices (copper or hormonal) and implants increased from 5.4% to 13.2%.[3]

Healthcare professionals (HCP) should ensure collaborative decision making when counselling their patients about

contraceptives. Kubba uses a mnemotechnic formula, 'A, B, C, D, Go':

- A) Agenda. Discuss the females' priorities regarding health, sexual wellbeing, and therapeutic needs.
- B) Body and soul. First, consider medical history to identify health risks and contraceptive method contraindications. Next, consider mental health aspects (mood problems, premenstrual syndrome, libido).
- C) Choice. Discuss the available contraceptive options that fit the females' health status and priorities.
- D) 'Did you know?' HCPs can often provide additional information to make sure that they are counselling females as thoroughly as possible.

WHAT IS EVRA?

Evra® (Gedeon Richter Plc., Budapest, Hungary) is a transdermal hormonal contraceptive patch measuring 20 cm^2. It consists of a three-layered matrix that contains a combination of hormones, 6 mg norelgestromin and 600 µg ethinyl oestradiol.[4] It releases an average of 203 µg of norelgestromin and 33.9 µg of ethinyl oestradiol every 24 hours.[4]

Since Evra is a CHC, Kubba recommends HCPs should explain to their patients about the corresponding class effects regarding mechanism of action, efficacy, and side effects. It works by inhibiting ovulation through suppression of the hypothalamic/pituitary/ovarian axis. The oestrogenic and progestational components thicken cervical mucus and render the endometrium unsuitable for implantation.[4] It differs from combined OCs due to its convenient delivery system, based on a weekly schedule rather than daily ingestion. The patch is harder to forget than an OC because it is visible to the female. It could be a welcome choice for females who have gastrointestinal problems, take laxatives, or have eating disorders. As it circumvents the digestive tract, it protects females from hormonal fluctuations caused by sporadic indigestion or gastroenteritis. The ease of use and steady hormonal delivery aid compliance, which is essential for effective contraceptive use. Inconsistency exposes females to unplanned pregnancies.[5] Flexibility has been demonstrated in a systematic review that investigated missed patch scenarios. The reviewers found two studies that evaluated the effect of deliberate dosing errors outside the patch-free interval. Both found that mean concentrations of ethinyl oestradiol and norelgestromin stayed within reference ranges for ovulation inhibition with up to 3-day dosing errors removing anxiety should a patch change be delayed.[6] Moreover, females are instructed to change the patch every 7 days, and not to risk extending the patch-free interval.[4]

Regarding efficacy, Evra is comparable to other combined hormonal methods. On-therapy pregnancies occurred in only 15 participants out of 22,160 treatment cycles with Evra,[7,8] except in females who weigh ≥90 kg, in whom efficacy may be slightly decreased.[9] However, a Cochrane review of hormonal contraceptives in females who are overweight or obese did not find an association between higher BMI or weight and contraceptive efficacy.[10]

THE CLINICAL DATA ON EVRA'S SIDE EFFECT PROFILE

The most common side effects with Evra in clinical trials were headache (21.0%), nausea (16.6%), and breast tenderness (15.9%), but nausea and breast tenderness tend to improve after three cycles.[4] A pooled analysis by Sibai et al.[11] (N=3,330) found that 22.0% of females experienced breast symptoms (discomfort, engorgement, pain) mainly during the first two cycles. These symptoms were often mild or moderate (86.2%), and rarely led to discontinuation (1.9%).[11]

Regarding venous thromboembolism (VTE), a systematic review on VTE risk with non-oral CHCs found a statistically increased VTE risk in two of six studies.[12] This potentially increased risk represents few events in absolute terms.[12] Specifically, the number of VTEs per 10,000 females per year increases from 2 in non-CHC users, to 5–7 in levonorgestrel-containing CHC users, to 6–12 in norelgestromin-containing CHC users.[4] Accordingly, HCPs need to inform females, and consider VTE risk factors when prescribing CHCs. Kubba added that transdermal contraception should not be confused with transdermal hormone replacement therapy, which is associated with a lower VTE risk.

Cycle control is good with Evra, with the dose comparable to a standard combined OC

with 250 µg of norelgestromin and 35 µg of ethinyl oestradiol. In a large study (N=1,489) that compared Evra with an OC, there were no significant differences in cycle control. However, by Cycle 13, 8.2% in the patch group had breakthrough bleeding and spotting versus 12.0% in the OC group.[5] In another large study (N=610) of different contraceptive patch sizes and OCs, breakthrough bleeding was reported in Cycle 3 in 13.0%, 4.2%, 3.6%, and 6.6% of participants using 10, 15, and 20 cm^2 patches and OCs, respectively.[13]

COMPARABILITY WITH ORAL CONTRACEPTIVES

Evra is an alternative option with good satisfaction and consistent use rates. In an Italian study where 177 females using a contraceptive patch were followed for 6 months, 88% found it convenient or very convenient, 96% appreciated the once-weekly schedule, and 95% easily incorporated it into their lifestyle.[14] Their satisfaction compared to their baseline method increased during the study (45.1% at baseline versus 86.3% at the last visit) and 78.1% preferred the patch over their previous method.[14] A multinational European study found that 63.5% of OC users were satisfied or very satisfied, but compliance was poor, with only 22.2% of cycles fully compliant. After using the patch for six cycles, 88.2% were satisfied or very satisfied, and 90.5% of cycles were completed with perfect compliance.[15]

EVRA PATCH DESCRIPTION AND ADVICE FOR USERS

Evra can be applied to different parts of the body (buttock; abdomen; upper, outer arm; upper torso) on clean, dry, and healthy skin, without moisturisers, in a location where it will not be rubbed by tight clothing. It should never be applied to the breasts. Kubba advises females to apply the patch using the warmth of their hand to ensure it sticks, and to check the edges to ensure they are not turned up, as that would encourage detachment. The patch's location has to be rotated weekly to avoid potential irritation, and changed on a designated day every 7 days, with 3 weeks on and 1 week off.[4] Each consecutive transdermal patch should be applied to a different place on the skin to help avoid potential irritation, although they may be kept within the same anatomic site.[4] HCPs should remind females that satisfaction improves with continued use.

Detachment is rarely a problem. Complete detachment occurs in 1.8% of cases and partial detachment in 2.8%.[16] Nevertheless, females should regularly check the patch is in place, and if it detaches partially or completely, they have 24 hours to replace it. If >24 hours elapse, they should apply a new patch but also take additional non-hormonal precautions for 7 days.[4] Kubba emphasised that if there was unprotected sex during that time, the individual should consider emergency contraception.

Harsh conditions derived from activities such as swimming, using a sauna, and sports do not affect the attachment or efficacy of the patch, and hormone levels remain within the reference range for contraception.[17]

FEMALES WHO MAY BENEFIT FROM EVRA

Evra may appeal to many females regardless of age. In Kubba's experience, it is a good method for young females (<30 years of age) who have already used OCs for a few years and may fear missing doses and have had to use emergency contraception. They may prefer a method as efficacious as the pill with all its benefits, but that does not involve a daily routine. It is definitely a good method for those who are forgetful, have busy lives, have gastrointestinal problems, or experience breakthrough bleeding. For instance, female cabin crew on long-haul flights may be good candidates and it may also appeal to females looking after young children. Altogether, it is a good option for many females due to the flexibility of use, and overall better fit with their lives.

EVRA IN THE CURRENT CONTRACEPTIVE LANDSCAPE

Kubba considers that HCPs should provide females with the full range of contraceptive choices, so they can make the best selection for their individual needs. Evra fulfils an unmet need, and it is very important that it is offered as one of the methods available, while being

careful not to promote it as a panacea. It is an option for females who have special needs, or lifestyles that do not fit a daily routine, and for those who want to try a transdermal method while keeping in mind the advantages and risks. Evra is not a LARC, but may be more convenient than a daily method that empowers those who want independence from a daily routine, and reassurance regarding contraceptive efficacy. Ultimately, it is advantageous as a general contraception to all females who want an effective and convenient method.

Prescribing Information, UK-EVR-2100016, December 2021

Biography

Ali Kubba

Kubba works in the largest National Health Service (NHS) colposcopy clinic in London and is a global authority in contraception and reproductive health. He is an Honorary Professor in the Basra Medical School, Iraq, and he is founder and fellow of the Faculty of Sexual and Reproductive Healthcare (FSRH), London, UK. He is currently the Vice President of the European Society of Contraception and Reproductive Health (ESCRH), and a board member of the European Society of Gynecology (ESG).

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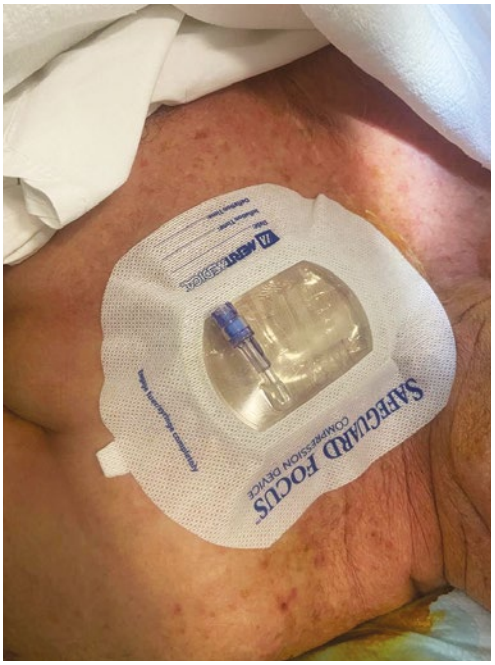

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Neurofibromatosis Type 1: Burden of Disease in Patients with Plexiform Neurofibromas

Interviewee: Rianne Oostenbrink

ENCORE – NF1 expertise center, Erasmus MC, Rotterdam, The Netherlands

Disclosure: Oostenbrink is an advisory consultant for AstraZeneca, a member of the European Union (EU) Patient-centric clinical trial platform (EU-PEARL), and a Full Member of the European Reference Network on Genetic Tumor Risk Syndromes (ERN GENTURIS). EU-PEARL has received funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking under grant agreement N°. 853966. This Joint Undertaking receives support from the EU's Horizon 2020 research and innovation programme and European Federation of Pharmaceutical Industries and Associations (EFPIA) and Children's Tumor Foundation, Global Alliance for TB Drug Development non-profit organisation, and Springworks Therapeutics Inc. This publication reflects the authors' views. Neither IMI nor the EU, EFPIA, or any Associated Partners are responsible for any use that may be made of the information contained herein.

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Summary

Neurofibromatosis Type 1 (NF1) is a genetic disorder, generally diagnosed during early childhood, that affects around 1 in 3,000 people worldwide. Around 30–50% of patients with NF1 develop NF1-associated plexiform neurofibromas (PN). These benign tumours, located on peripheral nerve sheaths, carry a lifelong risk for malignancy of 8–13%. PNs first present in childhood and, depending on their size and location, may cause pain, organ compression, disfigurement, and other complications. Though rare, the incidence is high enough that every general practitioner (GP) should expect to see at least one patient with NF1 in their practice. As such, it is important for all healthcare professionals (HCP) to understand the defining signs of NF1 and PNs, so as not to misdiagnose, and fail to refer or treat the patient in specialised centres, with dedicated multidisciplinary teams (MDT). Rianne Oostenbrink, Associate Professor and Paediatrician at Erasmus Medical Center in Rotterdam, the Netherlands, spoke to EMJ about the current diagnostic pathway for people with PNs, the burden of disease, and the HCPs involved in patient care. She also highlighted the presence and work of the Europe-wide organisations that can support HCPs, and patients alike.

INTRODUCTION

NF1 is an autosomal dominant disorder, arising from a mutation in the gene that encodes neurofibromin. It is a tumour-predisposing condition, associated with many different manifestations, including the risk of developing benign tumours in the peripheral and central nervous systems. PNs, one complication of NF1, are benign, diffuse tumours, located on peripheral nerve sheaths, that may be visible from the outside, or present internally (Figure 1). Other manifestations of NF1 include café-au-lait macules (CALM); cutaneous neurofibromas; Lisch nodules in the iris; axillary- or inguinal-area freckling; skeletal dysplasias; behavioural and cognitive deficits; low-grade gliomas; and organ involvement.[2]

NF1 occurs in around 1 in 3,000–4,000 people,[3] and around 30–50% with NF1 develop PNs.[4,5] In general, growth rate is higher at younger ages, although growth can be variable at any age.[6] Although some mutations are related with higher PN rates, for most patients, reported Oostenbrink, whether or not PNs will develop cannot be predicted based on other NF1 symptoms, such as the number of CALMs.

MEDICAL AND PSYCHOSOCIAL BURDENS ASSOCIATED WITH PLEXIFORM NEUROFIBROMAS

"The complexity of NF1," Oostenbrink explained, "is that it affects many body systems in variable

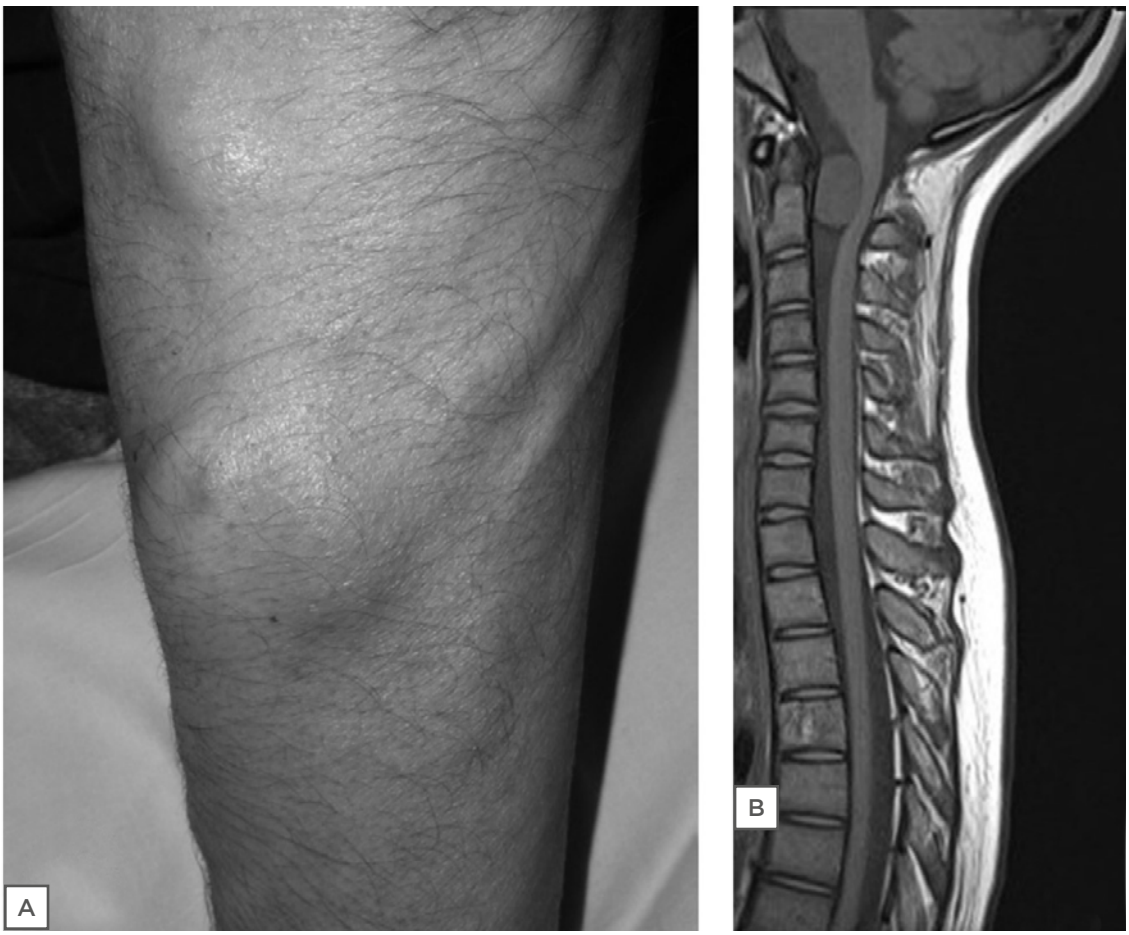

Figure 1: Plexiform neurofibroma in the forearm.

A) Subcutaneous NF in the upper limb in a patient with NF1. **B)** T1 sagittal MRI in an asymptomatic patient with C2 NF causing spinal cord flattening and distortion.

Adapted from Ferner et al. (2013).[1]

NF: neurofibromatosis; NF1: neurofibromatosis Type 1.

ways and times. It impacts on physical functioning and cognition and development combined. The burden of PNs," she continued, "is very variable. This can arise from PN visibility, size, and impact on functioning, but they may also have a large interindividual perception."

PNs can cause pain and disfigurement, particularly in older children, adolescents, or adults, due to nerve or surrounding tissue compression, bone erosion, or organ displacement.[6] NF1 can also cause fatigue, function loss, cognitive problems, and sleep difficulties, as well as burdens associated with stigma, appearance, social activity limitations and, later in life, career, and relationships.[6]

Another PN-associated burden Oostenbrink discussed is the lifelong need for medical monitoring, clinical investigations, and, where necessary, treatment; for instance, the time burden of an MRI that, for young children, is carried out under anaesthesia. Though not common (8–13%), there is a risk that PNs will develop into a malignant tumour,[2,6] and a further burden is the worry this can cause. This can be difficult for both the patient, and their parents or caregivers, to cope with.

With all of this in mind, the burden of PNs should always be considered when supporting patients throughout their life.

DIAGNOSIS, TREATMENT, AND MONITORING OF NEUROFIBROMATOSIS TYPE 1 IN PATIENTS WITH PLEXIFORM NEUROFIBROMAS

While the incidence of NF1 is low, Oostenbrink discussed how it is known as the 'largest small disease'. As there is roughly one NF1 patient for each GP, she underlined the importance of creating awareness at this level. One of the biggest barriers that HCPs face in recognising NF1 or PNs, especially for those with little prior experience of this condition, is in differentiating NF1 and PNs from other, similar, benign tumour-producing conditions such as lipoma (Table 1).

"Checking skin is part of general training," said Oostenbrink, "but some manifestations should lead to a specific diagnosis. CALMs are quite well known, but if a patient comes in just with a benign tumour in the skin, and CALMs are not that marked, or the main problem is in the leg, and the HCP doesn't think about looking under the shirt for CALMs, they might not recognise it." Just over half of people with NF1 have an inherited mutation,[8] so children of parents or siblings with NF1 may be checked more routinely.

If NF1 or PNs are suspected, patients must be referred to a specialist centre with an MDT. This should involve those skilled in diagnosing and monitoring PNs, and understanding their cause, working alongside specialist surgeons, and oncologists, depending on tumour type; and, if needed, other specialists such as an orthopaedic team and a pain management team. Together, they can help explain to the patient and caregivers about PNs, and discuss potential treatment options: for example, surgery versus systemic treatment or symptom management.

As the manifestation of PNs may be diverse, treatment, discussed Oostenbrink, requires a multidisciplinary approach. This must be based around understanding the spectrum of PNs, what is important to the patient, and what their outcome expectations are. Treatment is most often with surgery, although drug treatments, such with the mitogen-activated protein kinase inhibitor selumetinib, are becoming available for cases where tumours are inoperable and symptomatic.[7] Surgery may result in complete or partial removal, depending on specific circumstances, nerve and tissue involvement, and location. However, problems encountered with surgery can include large blood loss, nerve injury, disfigurement, and regrowth.[9]

Due to individual patient differences, even the same tumour in two people may need a different approach. The decision about treatment should be made with knowledge of the underlying condition, and its expected course. This is vital, because if the HCP knows it is a PN, says Oostenbrink, they then know there are some approaches that will not help. An example of where this was not carried out, she recalled, was the case of a child who underwent repeated surgery for a facial tumour that kept returning. On later presentation at an NF centre, the immediate recognition of CALMs helped to confirm the PN diagnosis and guide proper treatment.

Table 1: Clinical features of neurofibromatosis Type 1.

Genetics	Parent,* sibling,* or child* with NF1
Birth–infancy	Plexiform neurofibroma* (≥1)
	CALMs* (≥6, >5 mm in children, and >15 mm in adolescents and adults)
	Orbital dysplasia,* tibial dysplasia,* and/or pseudoarthrosis*
Infancy–early childhood	Optic pathway glioma*
	Learning deficits, ADHD or ADS, motor and/or speech delays
Childhood–adolescence	Skinfold freckling,* Lisch nodules* (≥2 on the iris)
	Dermal neurofibroma* (≥2), paraspinal neurofibroma
	Scoliosis
	MPNST, brainstem glioma
Adulthood	MPNST, breast cancer, high-grade glioma

*Diagnosis of NF1 requires two or more of the criteria, or one of the criteria and a proven genetic pathogenic mutation in the *NF1* gene.

Adapted from Gutmann et al. (2017)[1] and Brosseau et al. (2020).[7]

ADHD: attention deficit and hyperactivity disorder; ASD: autism spectrum disorder; CALM: café-au-lait macules; MPNST: malignant peripheral nerve sheath tumours.

Although the patient pathway may be different in different countries, one common feature is the need to have each patient evaluated by a dedicated and expert MDT. Once evaluated at a specialist centre, the result may be either further investigations, an intervention, or a referral back to a regional centre for monitoring. A patient may then return to the specialist centre after a defined time interval, if there is a change in PN, or other NF1 manifestations. To aid in this model, Oostenbrink described the development in the Netherlands of a national network, arising from her expertise centre, as nationwide as the number of patients was too high for one centre to manage. This network fulfils the need for patients to be monitored close to home if possible, and for care to be more centralised when necessary.

Once diagnosed with PN, Oostenbrink described how it will usually be the patient who picks up on a change in pain or growth. "Our role then is to discuss with the patient, and to make it more objective [when assessing] whether it is indeed a change in substantial growth, or clinical function. The key issue," she continued, "is to inform the patient with NF1 that they know how to recognise PN and its complications, and who they should go to for proper advice." As such, Oostenbrink emphasised the importance of educating patients and caregivers that they need to say: "I have NF1," so an HCP can then consider that the manifestation requires a specific approach.

PLEXIFORM NEUROFIBROMAS IN ADULTS

Diagnosis and treatment of PNs predominantly focuses on children, but there is growing awareness of the need for more monitoring, treatment, and care for adults. While young adults may especially want to feel independent of the need for monitoring, Oostenbrink warned that "this is the age that the manifestations can become higher risk if they are not monitored."

She also discussed how there are patients who say: "I was told that if I didn't have problems at puberty, there won't be a problem later on." She recounted that there are many examples where this is not true. For adults, there is a higher risk for malignancy in PNs,[2] so it is important to educate

patients on the need for follow-up when they are older, to monitor for complications and changes. It is also important to monitor adults with NF1, and associated PNs, to make sure complications do not arise, and to inform them about potential new treatments.

RESOURCES FOR PATIENTS AND HEALTHCARE PROFESSIONALS IN EUROPE

One valuable resource for patient education and support is dedicated NF1 organisations, to whom patients should be referred. As well as individual country organisations, Oostenbrink noted that there is also NF Patients United, which interconnects the patient organisations at a European Level.[10] For HCPs, there is also the European Reference Networks (ERN) for Rare and Low Prevalence Complex Diseases, where NF1 is identified as a rare genetic tumour risk syndrome.[11] This, Oostenbrink highlighted, also has patient representative and advocacy groups, and general information for patients. Additionally, she explained: "Some patient organisations have developed local materials to inform patients in their own language, which are now being copied, to make them more general for Europe."

The ERN basic concept, explained Oostenbrink, is to make sure that in every country there is at least one access point to share care. While this is a valuable initiative, as not all centres in one country need to be included, it does not connect all HCPs with NF1 experience. To include such HCPs, Oostenbrink discussed how there is now the Children's Tumor Foundation (CTF) Europe,[12] which includes a clinical care advisory board, and a clinical care network. They aim to open the network to all centres with experience of NF1, not just expertise centres.

Both the CTF Europe[13] and ERN GENTURIS have developed masterclasses to train and educate HCPs caring for patients with NF1, to which Oostenbrink contributes as an expert. There is also a biannual European NF meeting that connects HCPs with the clinical expertise of NF specialists, and researchers.

CONCLUSION

PNs may be a complex manifestation of NF1 to handle, and management requires a multidisciplinary approach, directed by a specialist centre and an MDT. Support also needs to be given to help patients cope with the medical and psychosocial burden of the disease, as this can be very high.

Though rare, most GPs should expect to see at least one patient with NF1. As such, they should be aware of how to recognise this condition, refer their patient(s) to a specialist centre, and potentially be involved with long-term monitoring.

European-wide HCP and patient organisations are connecting those less experienced in PNs with experts. These networks aim to enhance the recognition and care of people with PNs, and to discuss emerging therapies for those with inoperable PNs, such as mitogen-activated protein kinase inhibitors, which are currently being approved and may soon be widely available in clinical practice.[7]

In a follow-on article, Amedeo Azizi, Division of Neonatology, Pediatric Intensive Care and Neuropediatrics, Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Austria, discusses treatment options for PNs, and how these may evolve in the future.

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Management and Multi-specialty Approach in the Evolving Treatment Landscape of Neurofibromatosis Type 1 Plexiform Neurofibromas

Interviewee: Amedeo A. Azizi

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Disclosure: Azizi has served on the advisory board for selumetinib for AstraZeneca and received honoraria by AstraZeneca for a lecture held at EANO 2021.

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Interview Summary

Neurofibromatosis Type 1 (NF1) is a rare disease, occurring in approximately 1 in 3,000 people. Among the numerous manifestations of the disease, 30–50% of patients diagnosed with NF1 develop plexiform neurofibromas (PN). These are benign tumours that develop in infancy and childhood, differing in size, location (trunk, limbs, face, etc.), and growth rate. Treatment for PNs involves an evaluation by a multidisciplinary team (MDT) at an expert centre and most often involves surgical consultation depending on location, extent and growth of individual PNs, and patient-related factors. More recently, drug therapy with mitogen-activated protein kinase kinase enzyme (MEK) inhibitors has been included as a choice of treatment for PN. It may be used alongside, or as a replacement for, surgery if a symptomatic PN is judged as inoperable. The potential risk of malignisation (approximately 10% lifetime risk) also necessitates appropriate surveillance of PNs. In this article, Amedeo Azizi, Medical University of Vienna, Austria, spoke to EMJ about the current treatment options available for PNs and how these may evolve in the future.

INTRODUCTION

NF1 is caused by the inactivation of a tumour-suppressor gene that codes for neurofibromin. PNs are benign nerve sheath tumours, arising from nerve fascicles, which can also infiltrate adjacent tissue.[1] Symptomatic PNs most often occur in early infancy or childhood and may be disfiguring, impair motor function, or cause bowel or airway obstruction. Symptomatic lesions (with rapid growth, persistent pain, and motor dysfunction) may also be indicative of malignant transformation to malignant peripheral nerve sheath tumours (MPNST), which occur with approximately 10% lifetime risk.[2]

Treatment for PNs is co-ordinated in centres of expertise, housing a dedicated MDT. Alongside NF1 specialists and case managers, whether they are paediatricians, neurologists, or oncologists, the MDT should also include members such as experienced plastic surgeons, radiologists, and nuclear medicine specialists. Depending on

tumour location and extension, a MDT may also include speciality surgeons with expertise in, for example, neurosurgery, facial, abdominal, or thoracic surgery. Psychological support is also important, especially where the tumour (or the result of surgery) is visible and/or disfiguring as, explained Azizi, psychosocial issues often include problems with interactions with other children and schooling.

A risk-adapted approach to treatment is key, as some patients (e.g., those with NF1 microdeletions and extensive internal PN) can exhibit a more severe disease course.[2-4] Before any intervention, the NF1 specialist (and psychologist where feasible) meets the patient and family to discuss all possible options and implications. From age 5 years and even before, discussed Azizi, his team involves the child in consultations to discuss the potential benefits and adverse effects of different treatment options.

SURGERY FOR PLEXIFORM NEUROFIBROMA

Surgery is the bedrock of treatment options for PN and is currently the only potentially curative treatment.[2,4] Azizi recounted how some NF1 specialists argue that if a small child presents with an operable PN, no matter what the development might be, the PN should be removed to prevent further growth, related morbidities, and/or malignant evolution. However, there is no way to predict whether a PN will grow and, stressed Azizi, another strategy is to monitor the patient and evaluate whether there is any change over time of small PNs that initially do not cause any clinical symptoms.

If a PN is growing, surgery may be indicated, especially where the tumour is causing pain or deformity and/or intrudes on vital areas such as the trachea or bowel.[2] Of note though, by its very nature, PN is not a nodular tumour, and its web-like structure means that complete removal may not be easy or possible.[2,5] It is, therefore, necessary to consider that the surgical removal of a PN may result in related morbidity, bleeding, disfiguring, scarring, nerve damage, and/or loss of function, depending on PN size, location, and growth characteristics. Additionally, a recurrence of the tumour can occur.[5]

The decision to carry out surgery is usually made by an experienced MDT and may only occur after an investigation using ultrasound, MRI, and/or fluorodeoxyglucose-PET to ascertain the extent of both visible PNs and possible deeper, internal PNs, as well a potential evolution to a MPNST.[4,5] It is important, Azizi stressed, that the surgeon is highly skilled in PN removal, in general and specifically, for the location in the body where it arises. Such expertise may need to be sought outside of the centre where the patient is being treated, with discussions of complex cases even taking place at a national or international level when needed.

THE ROLE OF MITOGEN-ACTIVATED PROTEIN KINASE KINASE INHIBITORS IN THE TREATMENT OF PLEXIFORM NEUROFIBROMA

The *NF1* gene codes for neurofibromin, which interacts with the signal transduction protein rat sarcoma virus guanosine triphosphate (Ras-GTP), converting it to Ras-guanosine diphosphate. This results in decreased Ras-GTP mediated activation of the mitogen-activated protein kinase pathway, which is involved in the activation of a number of enzymes, including MEK. As this pathway ends in transcription factor activation, loss or disruption of the *NF1* gene (as seen in NF1), leads to increased mitogen-activated protein kinase pathway activation. As the pathway ends in transcription factor activation, this can lead to tumorigenesis. As Ras-GTP stays active with tumorigenesis, this pathway can be halted by targeting one of its components, which is where MEK inhibitors are useful.[6]

The MEK inhibitor selumetinib was recently approved in 11 countries, including the USA, European Union (EU) countries, and the UK, for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged ≥3 years (≥2 years in the USA).[7] This followed Phase I[8] and II[9] open label trials (total N=74; aged 3–18 years) that reported tumour shrinkage and positive outcomes for symptoms, including pain intensity, interference with daily functioning, health-related quality of life, strength, and range of motion.[8,9]

The MEK inhibitor might come in as a game changer, explained Azizi, in situations where the PN is symptomatic and inoperable. This

occurs where surgery may imply a high potential for morbidity, such as nerve dysfunction and/or bleeding, or could only reduce, not completely remove, the tumour. Location is also a consideration as surgery is potentially a more valuable option for superficial tumours, and drug therapy might be more valuable for PNs that are deep-seated in the trunk, or in crucial positions such as the orbital region.[6]

Some adverse events (AE) have been reported with MEK inhibitors that patients and their parents or carers should be made aware of. In clinical trials, the most frequent AEs were: (acneiform) rash; nausea or vomiting; diarrhoea; asymptomatic increases in creatine phosphokinase levels; and paronychia.[8,9] In the selumetinib Phase II SPRINT trial, AEs led to a dose reduction in under a third of patients and treatment discontinuation in 10% (five patients) where AEs were considered possibly selumetinib-related.[9]

AEs tend to be most severe at the beginning of treatment, discussed Azizi. Accordingly, patients should be informed about potential side effects and their management, so they do not discontinue the drug inappropriately but only after medical consultation and decision. "On the other hand," Azizi explained, "we know that paronychia, for example, occurs later in the treatment. This can be annoying and might necessitate stopping the drug for a while until it heals, then you can restart."

"Almost all AEs are manageable," Azizi emphasised, "and the more experience you have with the treatment, the better it will be." Notably, specialists may be required to address and manage specific AEs caused by MEK inhibitors, such as a dermatologist for an eczematous rash in infants and acneiform rash in adolescents. These effects are common to the entire class of MEK inhibitors and, discussed Azizi, it is important to balance the risk–benefit ratio of drug treatment to the possible morbidity caused by surgery.

For those who are candidates for a MEK inhibitor, Azizi explained how he would use the medication for at least 2 years or longer, if tolerated and efficacious. This is partially because a response may only occur after a few months of treatment. For instance, in the Phase II SPRINT trial with selumetinib, the median time to response was 8 cycles (range: 4–20, each cycle lasting 28 days) and time to best response was 16 cycles (range: 4–36).[9] New data presented at the 2021 Children's Tumor Foundation (CTF) Congress, with up to 5 years use of selumetinib, is helping to further evaluate longer term efficacy, safety profile, and AE occurrence.[10-13]

THE FUTURE OF MITOGEN-ACTIVATED PROTEIN KINASE KINASE INHIBITORS

While surgery will remain the key treatment for PNs, the coming years, discussed Azizi, will answer a number of questions regarding the use of MEK inhibitors, and how these two approaches may be integrated to provide patients with the best possible treatment regimen for their disease. For instance, in PNs currently considered inoperable, a MEK inhibitor may be able to shrink them to a size where they can be surgically removed. Conversely, where a tumour is resectable, MEK inhibitors may stop them regrowing, suggesting that further research may be directed to explore use of these novel treatments in the neoadjuvant and adjuvant settings.

Among the questions that may be addressed by future research and real-world data collection, Azizi explained that it is of great interest to clarify when to stop treatment, since tumour regrowth has been observed in some patients when MEK inhibitor treatment was stopped.[9] As such, he discussed how it may be feasible for patients to have a trial period of stopping the MEK inhibitor and returning to a 'watch-and-wait' strategy, only restarting treatment if the tumour starts growing again.

More data will be available in the coming years as MEK inhibitor use becomes more common and the benefits and AE profile of long-term therapy will become clearer. At the moment, Azizi explained, possible late AEs of MEK inhibitors are not yet known (e.g., on development and fertility in 20 years' time). It will also be interesting to assess the potential positive or negative impact MEK inhibitor use will have on the rate of development of malignancies and other NF1 manifestations, such as cognition.

It is also necessary to evaluate alternative treatment schedules to better manage and prevent AEs and improve adherence, for instance, to a 5-days on, 2-days off regimen, with such studies ongoing. Finally, further

research is being directed toward the study of liquid formulations of MEK inhibitors, which may facilitate administration to younger patients, as well as those who have difficulty swallowing capsules due to cognitive problems. Research is also needed to assess the utility of MEK inhibitors in children <2 years since, Azizi highlighted, the youngest patients are usually the ones experiencing fast-growing PNs and potentially presenting with the highest need of a MEK inhibitor.

CONCLUSION

PNs occur in 30–50% of patients with NF1;[14] however, not all PNs need immediate treatment, and it is up to an experienced MDT to decide which approach should be used and when to start treatment. In complex cases, expertise should be sought on a national or international level.

Surgery is the current treatment of choice, if safely feasible, and the only option if malignisation to MPNST is suspected. This must be carried out by a surgeon with expertise in PN surgery, with specific consideration of the anatomical site. The recent market authorisation of a MEK inhibitor adds to the armoury against PNs as they can be used to treat inoperable, symptomatic patients. More data are being collected in both clinical practices and through clinical trials to better understand the safety and efficacy profile of the first approved MEK inhibitor, selumetinib, and of novel treatment options, combinations, and schedules to help support patients with NF1 who are developing PNs.

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Aficamten: A New Cardiac Myosin Inhibitor for Obstructive Hypertrophic Cardiomyopathy

Interviewees: Iacopo Olivotto

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Interview Summary

Cardiac myosin inhibitors (CMI) are set to change the treatment landscape for patients with obstructive hypertrophic cardiomyopathy (oHCM). The newest entrant into this class of drugs is aficamten (CK-274). Safety and efficacy data from the Phase II REDWOOD-HCM trial were announced in July,[1] and additional findings were presented in a late-breaking clinical trial session at the Heart Failure Society of America (HFSA) Annual Scientific Meeting 2021 in Denver, Colorado, USA, and online.[2]

In this interview with the EMJ, Iacopo Olivotto, Head of the Cardiomyopathies Unit at Careggi University Hospital, Florence, Italy, provided his insights into the data and highlighted the aspects he believes are the most relevant for patients and physicians.

EFFICACY

REDWOOD-HCM was a multicentre, randomised, placebo-controlled, double-blind, dose-finding clinical trial of aficamten in patients with symptomatic oHCM on background medical therapy. Two cohorts were randomly allocated 2:1 to aficamten or placebo. Patients allocated to aficamten received up to three escalating doses once daily: 5, 10, and 15 mg in cohort one (n=21) and 10, 20, and 30 mg in cohort two (n=20). Echocardiography was performed after 2 weeks of treatment at each dose to assess eligibility to up-titrate to the next dose. Dose titration was performed at Weeks 2, 4, and 6. The overall treatment duration was 10 weeks with a 4-week follow-up period after the final dose. The baseline characteristics of patients in the trial were consistent with a symptomatic population with high resting and Valsalva gradients, reflecting a substantial burden of disease.

Regarding efficacy, the trial demonstrated consistent and clinically meaningful reductions in left ventricular outflow tract (LVOT) gradients within 2 weeks. For patients receiving aficamten in cohort one (n=14), the average Valsalva LVOT gradient changed from 74.4 mmHg at baseline to 38.1 mmHg at 10 weeks, while the corresponding reduction for those in cohort 2 (n=14) was from 82.3 mmHg at baseline to 29.8 mmHg at 10 weeks. For patients in the combined

placebo group (n=13), the average Valsalva LVOT gradient changed from 84.6 mmHg at baseline to 76.0 mmHg at 10 weeks (p=0.001; p<0.0001 in cohorts one and two, respectively, versus placebo). Significant changes in resting LVOT gradient were also observed in the aficamten groups.

The target goal of treatment, resting gradient <30 mmHg and post-Valsalva gradient <50 mmHg at Week 10, was achieved by the majority of patients receiving aficamten (78.6% and 92.9% of cohorts one and two, respectively) compared to just 7.7% of those in the placebo group.

"These gradient results would not have been achieved with any other drug regime in current practice, so that is what's most striking," said Olivotto. "The effect on the gradient and on the overall obstruction in patients with both dosing regimens was notable."

RAPID ONSET OF ACTION

A distinct feature was that the treatment effect was observed after just 2 weeks, highlighted by Olivotto: "That's because of the 3.4-day half-life of aficamten, which allows for rapid titration."

Reductions in LVOT gradient were maximised within 2–6 weeks and were sustained until Week 10. Reversibility of the pharmacodynamic effect was seen after a 2-week washout, with resting LVOT gradients, N-terminal pro-B type natriuretic peptide and left ventricular ejection fraction (LVEF) returning to baseline values. "It's good to have a drug that responds fairly quickly," said Olivotto, "and the effect will revert fast if patients drop their ejection fraction too much, which is important for safety."

SAFETY

Treatment with aficamten was generally well tolerated and the incidence of adverse events was similar between treatment arms. No patients receiving aficamten in cohort one had an LVEF <50%. In cohort two, one patient with an LVEF at baseline of 58% was up-titrated to 20 mg of aficamten and experienced transient LVEF reduction to <50% (remaining above 40%) requiring down-titration. Another patient had an LVEF <50% (49.3%) at Week 10 (end of treatment). The patient was on 20 mg of aficamten. No dose change was required per protocol and LVEF returned to baseline at Week 12. No interruptions or discontinuations of treatment with aficamten occurred in any patient.

Olivotto observed that the safety profile was "extremely favourable." He added: "There were only two patients with transient reduction of ejection fraction below 50%, which was totally reversible." Overall, the most remarkable findings, he said, were "the consistent and sustained reduction in gradient with only a very small reduction in ejection fraction". LVEF returned to baseline in all patients within 2 weeks after the end of treatment in both cohorts, which was consistent with the reversibility of effect observed in healthy participants in the Phase I study of aficamten.

SYMPTOMS AND QUALITY OF LIFE

Treatment with aficamten was associated with changes in New York Heart Association (NYHA) class. Improvement by at least one class was achieved by 31% of the placebo group, 43% of patients on aficamten in cohort one (p>0.1), and 64% of patients on aficamten in cohort two (p=0.08).

Olivotto noted that during treatment with aficamten, patients found that their symptoms gradually got better and better. "The sheer benefit in quality of life is what matters most to patients. They not only regain the ability to do things that they have not done for a long time but occasionally are even able to do things that they have never done before."

The weakness and fatigue experienced by patients with oHCM, particularly in hot weather, is often a side effect of β-blockers. However, Olivotto noted: "There are hopes that CMIs may not only decisive as add-on therapy, but may emerge as ideal in monotherapy and therefore avoid the side effects of β-blockers."

SELECTION OF MEDICINES IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

The standard first-line treatment for oHCM is β-blockers. Olivotto said: "β-blockers are effective for provocable obstruction, in

other words related to effort, but less so for resting obstruction. Disopyramide is usually added, which is more potent for resting obstruction." Calcium channel blockers are rarely used at his institution unless the patient is intolerant to β-blockers.

"The point is that β-blockers alone may provide some symptom relief but almost never provide relief of severe obstruction," explained Olivotto. "Disopyramide provides complete resolution of symptoms in only one-quarter of patients. It also has side effects, particularly very dry mouth, constipation, and prostatic problems in males. In addition, disopyramide tends to lose efficacy over time because of tachyphylaxis so we use it a lot as a bridge to myectomy."

Overall, Olivotto estimated that 70–75% of patients with oHCM have some response to standard medications, at least for a period of time. "But if we're talking about optimal response, meaning normal quality of life and exercise performance, in my experience less than 10% of patients achieve that with current drug therapies. Considering that the average age of these patients is about 45 years, this is not a trivial matter," outlined Olivotto.

EVALUATING THERAPEUTIC RESPONSE IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

Routine assessment in oHCM includes echocardiography. Responders in clinical trials are defined as patients in whom treatment reduces resting gradient to <30 mmHg and exercise gradient to <50 mmHg or ideally <30 mmHg. Reductions in gradient are usually accompanied by symptom relief. According to Olivotto, clinicians typically rely on patients' report of symptoms, particularly angina, shortness of breath, presyncope, palpitations, and fatigue, to evaluate the efficacy of pharmacological treatment. "The other thing that is very peculiar to oHCM is postprandial symptoms," he added. "We have patients with obstruction consistently telling us that they cannot eat normal meals at night because they get angina or shortness of breath, and socially that's a disaster."

NYHA class is routinely evaluated. In addition, more precise quality of life endpoints are entering the research arena, such as the Kansas City Cardiomyopathy Questionnaire (KCCQ).

Olivotto said: "In chronic, slowly progressive conditions such as genetic cardiomyopathies, in general, patient-reported outcomes are really the future and patients will be the pioneers advancing the field." Initiatives are underway to monitor sports participation, leisure activities, and lifestyle. "Wearables are probably the way to go," he commented. "This is a disease that changes day-to-day so tracking activities, side effects, and symptoms on a smartwatch or smartphone would be a more accurate representation of patient experience than periodic measurements."

HOW CARDIAC MYOSIN INHIBITORS FIT INTO THE TREATMENT LANDSCAPE

Initially, candidates for CMI treatment will be patients with symptomatic oHCM who are not responding well or optimally to medical treatment and are not immediate candidates for surgery. "The debate here is whether to use CMIs as an add-on to β-blockers, for example, or simply as a monotherapy thereby avoiding, for example, chronotropic incompetence and fatigue due to β-blockers," said Olivotto. "In the short term, I would see CMIs as an intermediate step between first-line pharmacological treatment and surgical options; hopefully, however, indications may broaden with time."

While REDWOOD-HCM was conducted in oHCM, which is a relatively homogenous population, Olivotto envisages CMI usage expanding to other conditions. "These are drugs that are aimed at treating the myocardium, not just the obstruction, so I think this is a pipeline of agents that will help us treat the whole spectrum of patients with HCM," he said.

Olivotto's hope for the future is that CMIs will be used to stop oHCM even before symptoms develop: "Ideally, we would identify mutation carriers with a very early propensity to develop the phenotype and treat them with a CMI to halt the progression of disease, as we observed in experimental models."

FUTURE DIRECTIONS FOR CARDIAC MYOSIN INHIBITORS

An update of the European cardiomyopathy guidelines is expected and for the first time will have randomised trial evidence to support recommendations on CMIs for relief of symptoms in oHCM. Olivotto would like to see an outcome study in approximately 500 patients performed in the next 5 years, to complement the "feel and function" trials performed so far. "Such a trial would need a composite endpoint to keep the required duration of follow-up manageable; for example, hospitalisations, implantable cardioverter-defibrillator shocks, transplant, and new-onset atrial fibrillation. Such trial design may ultimately allow accrual of evidence that CMIs improve outcome in patients with HCM, as well as resolve potential doubts regarding their long-term safety."

The Phase II REDWOOD-HCM open-label extension trial is ongoing and includes a cardiac MRI sub-study to evaluate changes in cardiac morphology, function, and fibrosis. The results of REDWOOD-HCM have informed dose selection and a Phase III registrational clinical trial is expected to start in 2021.

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Automated Echocardiography Analysis: Expanding Access and Saving Time

Interviewees: Carolyn Lam,[1,2] Li-Ming Gan[3,4,5]

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INTRODUCTION

December marks the launch of Us2.ai's automated cardiac analysis platform[1] as a cloud-based service on the EchoNous Kosmos device (Seattle, Washington, USA). The world's first fully automated solution for both 2D and Doppler images, cleared by the U.S. Food and Drug Administration (FDA) for 23 parameters (data on file), will now be available on the only handheld ultra-mobile tool offering diagnostic grade imaging with continuous-wave Doppler capability.

In these interviews with the EMJ, Carolyn Lam, Senior Consultant Cardiologist and Director of Women's Heart Health, National Heart Centre of Singapore, and Li-Ming Gan, Chief Physician, Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden, and Vice President and Head of Early Clinical Development, Cardiovascular, Renal and Metabolism, AstraZeneca, Gothenburg, Sweden, shared their experiences of using artificial intelligence (AI) tools in cardiology and their vision for the future.

Carolyn Lam

Use of Artificial Intelligence in Medicine

Lam pointed out that the use of AI in medical imaging is not new: "If we were to walk into a hospital now and get a chest X-ray, I think you'll be surprised at how much AI is used to pre-screen that X-ray to pick out, for example, nodules and other abnormalities, before the radiologist reads it and signs off on the report."

The purpose is to offset manual tasks that inherently involve human error. "We can never be fully reproducible in manual measurements; this refers not only to intra-observer variability (difference in repeated measurements by the same observer), but also to inter-observer variability (differences in measurements between observers)," she said. "AI affords a standardisation, with complete reproducibility, improved precision and increased efficiency. Regardless of which doctor you meet, you get some basic level of screening and detection."

Rather than replacing doctors, AI frees up time for doctors to spend with patients to look at complex and rare cases. Lam noted that not all AI works by a black box approach where it's hard to fully understand how results were derived, and doctors are expected to 'trust' the AI. Rather, other AI approaches recapitulate what the human does. Doctors examine the echo view, perform segmentation, trace the border of the heart, take measurements, and compare them against guidelines to determine if they are normal or not to decide what action is needed. Us2.ai recapitulates that process, with full explainability in the report, showing end-users exactly which views were used and how annotations were made to derive a particular measurement, further allowing users to edit the measurements if needed. This keeps doctors in full control, while relieving them of the tedium of repetitive manual tasks and increasing their efficiency manyfold.

Introducing Us2.ai and EchoNous Kosmos

Lam explained that Us2.ai, referring to 'us' and 'ultrasound', is the software, whilst EchoNous is the hardware. The software completely automates the analysis, measurement, and reporting of an echocardiogram. The hardware is the handheld device used to acquire the images from the patient. The Kosmos is mobile, the probe plugs into a tablet, and is the only mobile hardware that can acquire not just 2D but all Doppler images including pulse wave and continuous wave. It also comes with AI guidance to help the user point the probe in the correct way.

"Together the combined product is truly a match made in heaven," said Lam. "Because you have the best-in-class mobile hardware with AI to guide acquisition. And once you get those best quality images, Us2.ai gives you a full report, completely automatically."

She acknowledged that a criticism of AI in general is that it appears to work only in the population it was derived from. Us2.ai, however, has been externally validated in large real-world cohorts in Taiwan, Singapore, Canada, and the USA (data on file).

Vision for Automated Cardiac Analysis

"The short-term vision that we started with was to alleviate my carpal tunnel syndrome from sitting in a dark room doing 250 clicks and spending 30 minutes for each study just reading it and reporting it," said Lam. "I did it that way because that's how I was taught. We spend so many years training that we don't question that we have to spend hours just doing that." The experience sparked an ambition to automate those manual tasks, improve the workflow in the echocardiography lab, and make the measurements more reproducible.

The moonshot vision is to democratise echocardiography (ultrasound of the heart) so that it is no longer the preserve of cardiology institutes but is performed by general practitioners (GPs), pharmacists, community nurses, and even patients. "My vision has definitely grown as I've seen it come to life," said Lam. "It's not that far away that [patients] could even do a medical selfie of [their] heart with this mobile AI combination."

There were many challenges to meet along the way. Particularly memorable was showing the product to other clinicians, especially echocardiologists. Lam recalls, "I was so nervous because I anticipated that my colleagues reading 'echos' everyday may be insulted by 'AI created to what they do'. Indeed, I have met scepticism at first mention; yet, thankfully once they see the software in action, they become converts. Because, trust me, none of us like doing that manual stuff. We like to be in control, which our software gives you. We like full explainability, you show me what you did and only if I agree I accept it, which again our software provides. Doctors like that. But we don't like doing the manual stuff, which the software removes."

U.S. Food and Drug Administration Validation Study

The landmark study that led to FDA clearance for Us2.ai was performed at a top echo core lab and included 600 echo studies from the USA (data on file). The bar set by the FDA was that the automated readings for 23 variables had to be completely interchangeable with human readings. The variables are measurements deemed clinically important by international societies (European Association of Cardiovascular Imaging [EACVI],[2] American Society of Echocardiography [ASE][3]) for a comprehensive transthoracic adult echocardiogram. The primary performance metric used in the study was the individual bioequivalence co-efficient (IEC), where 0 means that the variance between a machine read and a human is the same as between two humans. "I want to remind you that these were top expert human readers so that's already a very small variance," added Lam.

The performance success requirement set by the regulators was a non-inferiority margin of IEC <0.25, and this was achieved for all 23 measurements with IEC for some variables near 0 or even negative. "That was a real eye opener to me because that means that the variance between a machine and a human was actually less than between human and human for quite a number of the measurements," she said. "And that's the way it's going to go because algorithms will keep improving. It's really quite amazing."

"That's not even touching on the time-saving," Lam continued. Performing the full suite of 23 measurements in each patient took human readers an average of 40.0 minutes compared with 1.2 minutes for Us2.ai. "You can imagine for 600 studies it's a massive gain because the software just had to run for 12 hours. We turned it on, went to sleep, and the results were all available the next day. That's the potential."

In addition to the automated measurements being accurate, i.e., interchangeable with top human reader measurements, they were also reproducible. Lam described how human readers can only pick one or two frames of a full echo study to perform the measurements on. "We cannot possibly measure every frame of every video in one patient study, it's just humanly impossible. But the software does. And in measuring everything all the time it is completely reproducible. In other words, as long as the algorithm hasn't been updated and you give us the same study it will produce the same results 100% of the time. Whereas, you cannot say that about a human being. If you give me the same study twice, I will for sure have some variability in my manual measurements; it depends which frame of which cardiac cycle I choose, for instance."

Improving Outcomes for Patients

Lam highlighted that the combination of automated AI and a handheld device has the potential to facilitate the early diagnosis of patients with heart failure, both by enabling GPs to perform imaging and by increasing the efficiency of echo labs so that patients are not waiting for months for a test. "The sad fact is that one in six elderly patients with heart failure have their diagnoses missed at a GP's, the reason being they tend to be elderly, and the symptoms are non-specific (breathlessness, swollen ankles), and GPs don't have access to echo now since it's restricted to cardiology centres. On the flipside, 80% of patients get their first diagnosis of heart failure with an unplanned hospitalisation, despite the fact that many of them have had symptoms for up to 5 years before presenting. Those months when they have had symptoms and the diagnosis was missed really represent opportunities lost to treat the condition, prevent hospitalisation, and change the disease trajectory with effective medications and devices that we already have."

She also envisages nurses performing echo in patients' homes, which will save time travelling and waiting for their appointment. "COVID has taught us that patients don't want to be in hospital and, humbly, they don't even need to be in hospital. Tools like the Kosmos and Us2.ai combination are essential for home-based care of heart failure."

Li-Ming Gan

Path into Using Artificial Intelligence Tools

As a clinical specialist in non-invasive cardiology with a special focus on ultrasound-based cardiovascular imaging, Gan has been doing clinical diagnostics and research using ultrasound

for more than 20 years. He was introduced to the Us2.ai AI tool through a longstanding collaboration with Lam on non-invasively assessing heart failure with preserved ejection fraction (HFpEF) and microvascular function. In the pioneering PROMIS-HFpEF study, they demonstrated that microvascular impairment is the main feature of HFpEF.[4] "Despite their very different clinical presentation, the heterogeneity in clinical features is not reflected in the phenotype as the majority of these patients suffer from microvascular disease," he said.

Multiple different cardiac features in ultrasound imaging can reflect microvascular disease but non-invasive coronary flow measurements require a challenge test, high-end machinery, and skilled staff. The idea then arose to use AI to automatically predict microvascular function based on ordinary echo images. The PROMIS-HFpEF study also revealed the key features that are highly associated with impaired microvascular function of the heart, for example right ventricular motion and left atrial motility, and these can be readily measured using conventional echo.[4]

The ultimate aim is to describe a more specific phenotype in each patient so that treatment can be personalised. "HFpEF is a syndrome meaning diagnosis can be difficult," said Gan. "With AI-based assessment you automatically get all these echo measures which helps with diagnosis. Going forward that should also make recruitment into clinical trials much easier."

A Comprehensive and Reproducible Tool That Saves Time

It may take up to 1 hour to measure all relevant cardiac parameters after image acquisition, which in itself is a labour-intense session and requires a skilled and well-trained operator, noted Gan. With the EchoNous AI-assisted acquisition, he has noticed a dramatic improvement regarding how quickly he can teach beginners to perform echo examinations with impressive image quality. Also, with the Us2.ai cloud-based analysis tool, the 1-hour measurement time is down to less than 1 minute for image upload. AI performs the measurement with extremely good reproducibility and accuracy.

Gan admits he was hesitant in the beginning because of previous experience with other AI algorithms that were in-built into commercial machines but never performed like an experienced operator. That meant adjustments were always needed afterwards. "I have worked with this Us2.ai cloud-based AI tool for a while now, and I do see the performance is excellent," he said. "Just by uploading nine images you get 23 FDA-endorsed cardiac parameters, meaning they are of very high quality. And when I look back at how the software measures the original images, I very seldom have anything extra to add. That means it's in agreement with how a well-trained operator would do it in real life."

Gan pointed out that because most of the measures, including cardiac output and left ventricular outflow tract velocity, are done automatically, they can be performed over multiple heartbeats, which is too time-consuming for manual acquisition. The AI software then calculates an average of all the signals. "I do believe the final value from AI is much more robust compared with manual measurement," he said. "And even more fascinating, if we do measurements on a conventional set of data, it takes usually half an hour to an hour depending on the number of variables. But the software can provide the full list of measures instantaneously after the images have been uploaded."

The reproducibility has also been impressive, added Gan. In a pilot validation study, his team trained medical students who had no experience with echocardiography. Over 2 days, these beginners were shown the basic images they needed to acquire and how to use the Kosmos AI-guided tool, which shows where to place the probe to get the best image. After the newly trained medical students acquired the images from 20 patients, two experienced operators repeated the measurements manually on the same day using a gold standard high-end machine. The question was, could a beginner, after brief training with AI-guided acquisition and with fully automated AI measurements, mimic or predict what could be acquired by an experienced operator? "The coefficient of variation was less than 3% for ejection fraction which is amazing," said Gan. "I never expected that. It was almost better than my own intra-observer variability. This was a real eye opener because we all know echo is highly variable and user dependent. And now an AI-powered machine could do that so reproducibly and in so great agreement with expert operators. The AI-guided tool is useful for

standardising images and can be used by both beginners and experienced operators. We need to figure out whether this tool can bring down variability even further."

The pilot study provided evidence that echo-beginners can acquire accurate measurements of ejection fraction using AI-powered software. Gan is also interested to know whether AI can reduce inter-day variability among skilled operators. And on top of that, can it lower variability of more challenging measures such as left artrial motility, left ventricular strain, and right ventricular motility.

Implementation of Artificial Intelligence Tools

Gan sees numerous uses of AI-based echocardiography analysis. One, which can be put into practice now, is to diagnose cardiac conditions. "I will most likely use this machine in everyday clinical practice instead of a stethoscope because you see all the cardiac parameters you want to know instantaneously," he said. "Instead of guessing who is having aortic murmur, insufficiency, etc, you see it directly with such a machine."

A second use is as a screening tool for clinical studies, where a research nurse could be trained to measure ejection fraction and diastolic parameters and thereby recruit patients instead of waiting for an experienced sonographer. Third is to assess changes in cardiovascular parameters, both in a clinical setting to follow progression of disease and to capture clinical trial endpoints. "Trial endpoints are the highest end of validity," noted Gan. "In these studies, we care about a few percentage points improvement of ejection fraction and are keen to keep the variability as low as possible, whereas in the clinic we are happy with 5% as a clinically meaningful change."

This precision would help trialists recruit the desired patient population, which could improve the likelihood of detecting any effect of a new therapy. "This is particularly relevant for Phase 2 trials that require a substantial number of subjects to address questions such as would a drug improve any of these cardiac parameters," he added. "Some of the inclusion criteria for HFpEF studies are highly variable and many are cumbersome to measure. One of the reasons for the variability of the measures is that the sites use different machines, some of them high-end, some of them low-end, and it is not standardised. So even if the analysis is done by a core lab the acquisition itself implies a lot of variability. With this package of EchoNous and the AI-powered software you can standardise the acquisition across all sites and take an average value from multiple measures. I think this approach will most likely dramatically improve accuracy and inter-site variability."

The reduction in variability could have a huge impact because when studies are designed, the calculations to determine the patient population required to demonstrate efficacy are dependent on the variability inherent in having multiple centres, different skills and operators, and different machines. Gan said, "It's an obvious mathematical equation that if you reduce the standard deviation by half, you need only half the number of patients which is a dramatic saving for the clinical trial and a dramatic improvement in trial quality. It could be the case that in the past we threw out a drug because we were not able to detect any efficacy just due to the noise of the method."

Closing Remarks

While Gan believes that automated echocardiography will become invaluable in clinical practice and in research, he also envisages it being used to increase heart failure awareness in the community. "We know heart failure is dramatically underdiagnosed with some patients struggling with their symptoms for years before being hospitalised, diagnosed, and treated," he said. "The problem is that it takes a very long time before patients get an echo of the heart. That means GPs and others measure a lot of circumstantial surrogate markers for a potential heart problem. Imagine this AI tool being implemented in a GP clinic." Early access to automated echo is being piloted in the AstraZeneca Heart Bus project in the Gothenburg region, which screens people in the community with dyspnoea. "This type of point of care in our diagnostics to exclude heart failure and other conditions will probably become a successful approach in the future," he said.

Both Gan and Lam noted that some level of caution is needed in the early stages of introducing this technique. "There is no question

that this can dramatically improve the workflow of physicians, especially cardiologists," said Gan. "But we still need to explore how the level of the beginner and their willingness to learn may or may not influence the outcome."

"AI in general will always struggle with the very rare cases because it needs to learn from something and datasets are not infinite, so I think that we should recognise those limitations," said Lam. "We should embrace the advantages in automating highly manual tasks, but then never see it as replacing doctors who are still needed for that human touch and ability to manage the complex cases. Another crucial point is that we should always hold AI up to the same bar that we do for therapeutics: it should be validated and tested with the same rigour."

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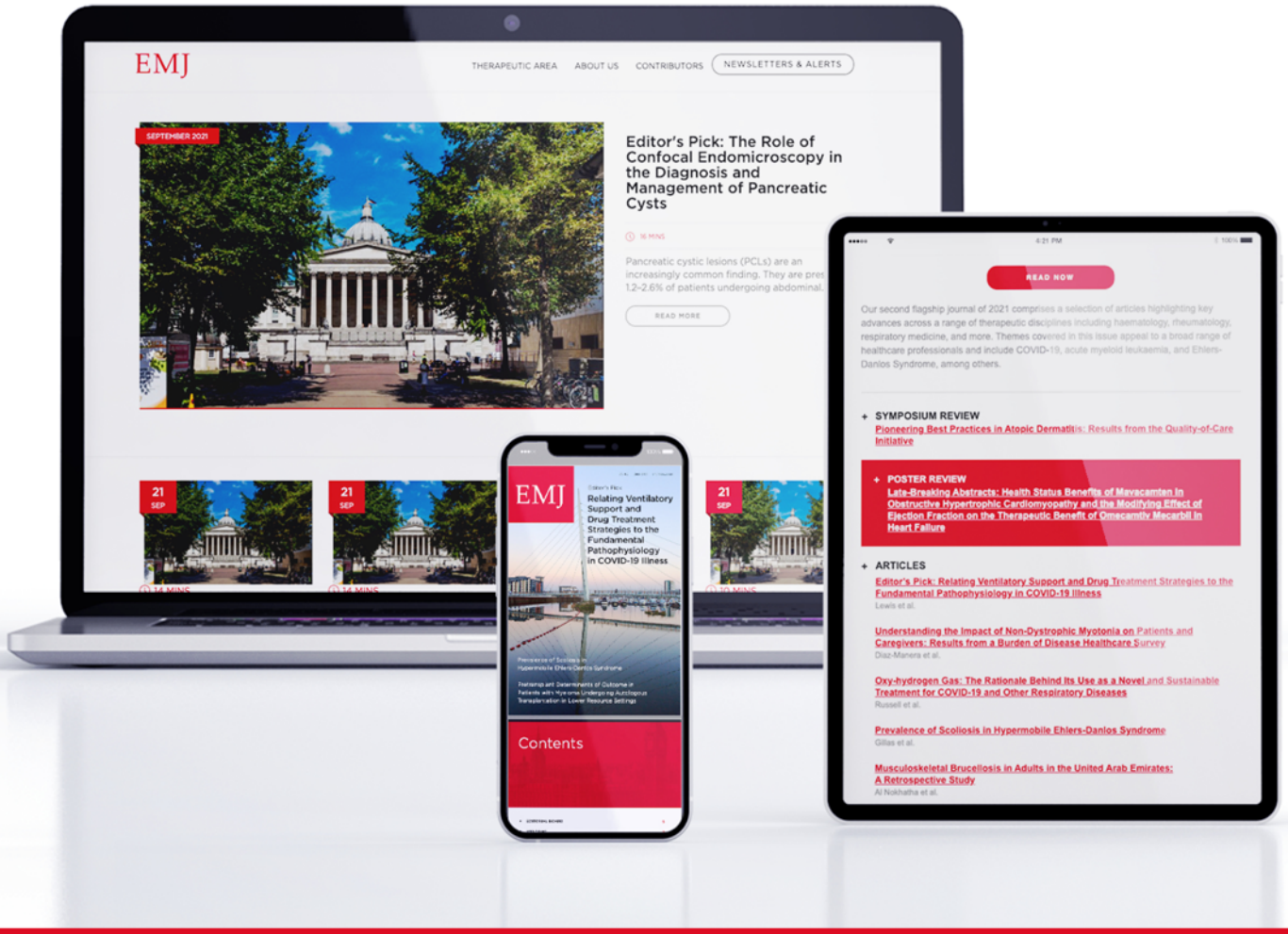

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A Case of Severe COVID-19 Infection in a Patient with Acute Myeloid Leukaemia: Critical Care Management and a Review of the Literature

EDITOR'S PICK

Acute myeloid leukaemia (AML) is a debilitating disorder with the lowest survival rate of all leukaemias. Patients with AML are more susceptible to developing severe COVID-19, and it increases the risk of adverse effects and mortality. This fascinating paper explores the case of a patient with AML who was infected with COVID-19 and the critical treatment strategies carried out, as well as reviewing current literature and the epidemiology of the disease. This article sheds valuable light on the risks and management of coronavirus infection in susceptible patients such as those with AML.

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Abstract

Acute myeloid leukaemia (AML) is a highly heterogeneous disorder and is characterised by the proliferation of poorly differentiated myeloid cells due to underlying mutation, eventually causing bone marrow failure. Accounting for approximately 25% of cases, AML is the most frequent form of leukaemia in the world yet has the lowest survival rate among all leukaemias. Patients with haematological malignancy are more susceptible to severe acute respiratory syndrome coronavirus-2 infection and further development of severe infection, including pneumonia with poor blood oxygenation. The management of such patients is more challenging than expected. Successful management of one such case is discussed in this report. COVID-19 infection can cause great harm to a patient with underlying leukaemia and increase the mortality risk. It has a major impact on the physical and psychological health of the patient. Therefore, these patients need special care and attention. The authors emphasise the importance of supportive management (oxygen with bilevel positive airway pressure, prone positioning, and physiotherapy) to prevent complications.

INTRODUCTION

The COVID-19 outbreak, first identified in the Wuhan district of China in December 2019, was declared a pandemic by the World Health Organization (WHO) in March 2020.[1] The virus predominantly targets the respiratory system, causing symptoms of varying severity, with

acute respiratory distress syndrome (ARDS) representing the most severe form and requiring intensive care. Patients who are of an advanced age or with comorbidities such as diabetes, heart disease, and an immunocompromised state are at the highest risk of death.[2] Patients with cancer constitute a significant caseload of the diseased population. The current pandemic has further increased the susceptibility of such patients to infections.[3] One such risk group of patients who have a high mortality rate with COVID-19 infection are patients with haematological malignancies.[4] However, patients with benign disorders like sickle cell disease are also prone.[5]

Acute myeloid leukaemia (AML), which makes up 80% of leukaemias in the adult population, is a highly heterogeneous disorder characterised by the proliferation of poorly differentiated myeloid cells due to an underlying mutation, eventually resulting in bone marrow failure.[6] Incidence of AML increases with age, with the majority occurring in those over 65 years. Despite the improvement in outcomes with recent advances in treatment, the prognosis in older patients is still lacking.[7] This article hereby reports a case of a patient with known AML who presented with a severe COVID-19 infection. There is a paucity of literature regarding the management of severe COVID-19 infection in a known case of AML malignancy, and hence the authors found it worthwhile to share the successful management of one such case with a review of the literature.

CASE

A 45-year-old male patient was diagnosed with AML in January 2020 in a tertiary care hospital where he was admitted for drainage of perianal abscess. The patient was of average build, recently diagnosed with Type 2 diabetes mellitus, and had no other associated illness. His initial workup revealed pancytopenia, with atypical white blood cells in the peripheral smear. Bone marrow aspiration and biopsy showed the presence of 20% blast cells. Further morphological and flow cytometric analysis of the bone marrow specimen was completed, and the patient was diagnosed with AML-M4. Treatment was induced with cytarabine and daunorubicin; in total, three cycles of chemotherapy were given within 6 months, with the last cycle administered in June 2020. After the second cycle of chemotherapy, the patient developed febrile neutropenia and was managed with intravenous antibiotics and granulocyte colony-stimulating factor.

Six months later, during the COVID-19 pandemic, he developed a mild-to-moderate fever on 20th June 2020, with a dry cough and shortness of breath. He denied any history of chest pain, anosmia, and diarrhoea. He consulted elsewhere for this complaint, where he was diagnosed with COVID-19 before being referred to his tertiary care institute.

At presentation in the authors' emergency department, he had progressive difficulty in

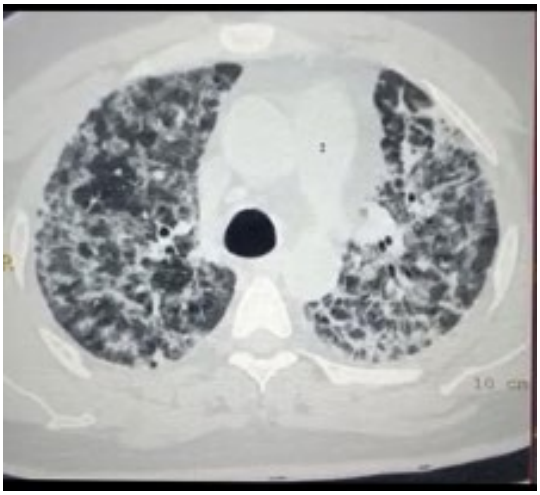

Figure 1: High-resolution CT of the patient's thorax on Day 4.

breathing on 24th June 2020, with a respiratory rate of 34 breaths/min and oxygen saturation (SpO_2) of 94% on 12 L oxygen through a non-rebreathing mask (NRBM). Other vital parameters included a heart rate of 102 beats/min, non-invasive blood pressure of 130/90 mmHg, and an axillary temperature of 98.5 °F. A real-time PCR (RT-PCR) on his nasopharyngeal swab repeated at the authors' institute confirmed COVID-19. His chest X-ray revealed bilateral lung infiltrates with a patch of consolidation in the right lower zone.

The patient was shifted to the COVID-19 intensive care unit for further management. A high-resolution CT (HRCT) chest done in the first week of admission (on 27th June 2020) revealed extensive bilateral ground-glass opacities with sub-pleural, inter-lobular septal thickening, which is consistent with a diagnosis of COVID-19 (Figure 1). The laboratory tests revealed an elevated white blood cell count and C-reactive protein.

All investigations performed over a period in the intensive care unit are summarised in Table 1.

The patient met the criteria of severe ARDS with a partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio of <100. He was kept on a NRBM initially at 12 L/min. However, due to persistent hypoxia

Table 1: Routine investigations of a patient with diagnosed acute myeloid leukaemia who tested positive for COVID-19 in the intensive care unit.

Date Day of hospitalisation		24/06 1st	27/06 4th	30/06 7th	2/07 9th	5/07 12th	7/07 14th	11/07 18th	13/07 20th	17/07 24th	19/07 26th
Blood tests											
Hb (g/dL)		8.10	7.59	8.30	8.37	8.89	9.10	9.60	9.40	9.30	N/A
TLC (×10^9/L)		14.50	18.23	22.59	20.90	22.12	22.77	9.80	6.53	9.58	N/A
Neutrophils (%)		83.28	85.90	89.80	89.00	91.70	87.00	82.00	75.72	83.68	N/A
Lymphocytes (%)		5.37	5.30	7.70	2.40	2.90	3.30	7.70	7.70	7.90	N/A
Platelets (×10^9/L)		90.0	94.0	150.0	156.0	143.6	123.0	121.0	90.0	107.0	N/A
CRP		N/A	N/A	N/A	80.4	N/A	41.3	N/A	N/A	35.9	N/A
Procalcitonin (ng/mL)		N/A	0.24	0.11	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Creatinine (µmol/l)		0.76	N/A	0.70	0.60	N/A	0.70	0.70	N/A	0.70	N/A
Albumin		4.40	4.27	3.90	3.85	N/A	3.80	N/A	N/A	3.90	N/A
Pre-meal RBS		156	167	182	132	162	112	99	105	120	117
ABG											
pH		7.42	7.43	7.41	7.45	7.42	7.41	7.43	7.42	7.44	7.42
PaO_2 (mmHg)		63.0	69.6	80.0	82.7	86.0	90.4	122.7	114.0	147.0	N/A
$PaCO_2$ (mmHg)		28.2	31.5	29.4	29.8	30.2	36.9	42.4	42.0	39.2	44.0
Oxygen support											
	Type	NRBM	NRBM NIV	NRBM NIV	NRBM NIV	NRBM NIV	NRBM NIV	NRBM HM	HM	HM	Nasal prongs
	FiO_2		0.6	0.6	0.5	0.4	0.4				
	Flow	12.0	10.0	10.0	10.0	10.0	8.0	8/6	4	3	2
	PEEP		8.0		6.0	6.0	6.0				

ABG: arterial blood gas; CRP: C-reactive protein; FiO_2: fraction of inspired oxygen; Hb: haemoglobin; HM: Hudson mask; N/A: not applicable; NIV: non-invasive ventilation; NRBM: non-rebreathing mask; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; PEEP; positive end-expiratory pressure; RBS: random blood glucose; TLC: total leukocyte count.

(SpO_2: 85–90%), non-invasive ventilation (NIV) was applied intermittently, with continuous positive airway pressure and settings of FiO_2 of 60%, positive end-expiratory pressure of 8 cmH_20, and pressure support of 6 cmH_2O for 2 hours. The patient was advised to maintain a prone position for at least 10–12 hours daily, with regular chest physiotherapy with an incentive spirometer. He was also encouraged to change his position every 2 hours to left lateral or right lateral if he found the prone positioning challenging to maintain for prolonged hours.

Simultaneously, he was started on parenteral antibiotics (meropenem 1 gm three times a day and vancomycin 1 gm twice a day) and parenteral antifungal (voriconazole 200 mg twice a day). In addition, 6 mg of dexamethasone was given once daily as per the RECOVERY trial. Supportive treatment in the form of intravenous fluids, paracetamol, and pantoprazole was instituted.

Thrombo-prophylaxis was ensured mechanically with an intermittent pneumatic compression device, and pharmacologically with low-molecular-weight heparin, ensuring adequate platelet counts. The patient was kept nil per oral initially for a couple of days, while contemplating high chances of endotracheal intubation if required, and was gradually shifted to an oral liquid diet. The patient's high blood glucose levels (pre-meal random blood glucose: 140–200 mg/dL) were managed with insulin therapy.

NIV settings were revised to FiO_2 of 40% on the ninth day, positive end-expiratory pressure to 6 cmH_2O, and pressure support to 5 cmH_2O. After the second week, there was a significant clinical and radiological improvement, with reduction in oxygen requirement, maintaining adequate oxygen saturation on an alternate Hudson mask (4–6 L/min) and non-rebreathing mask (10 L/min) for 2 hours and 4 hours, respectively.

By the third week, he maintained a good SpO_2 on a Hudson mask alone, and PaO_2 levels in arterial blood gas had also improved. However, another chest HRCT in the third week (13th July 2020) suggested severe disease, with a CT severity score of 37/40 and features of early fibrosis (Figure 2).

In the third week (9th July 2020), antibiotics were de-escalated to piperacillin and tazobactam injection, which was stopped after 7 days as he remained afebrile with decreasing white blood cell counts and a sterile blood culture report. IL-6 levels were within the normal range (18.4 pg/mL; 20.4 pg/mL).

In the fourth week, he was shifted to a high dependency unit on nasal prongs at 2–4 L/min on account of improved blood oxygenation levels and no new findings in his chest X-ray.

Throughout his hospital stay, COVID-19 nasopharyngeal swab RT-PCR testing was repeated, weekly; once for the initial 3 weeks and then every fourth day as per the hospital protocol.

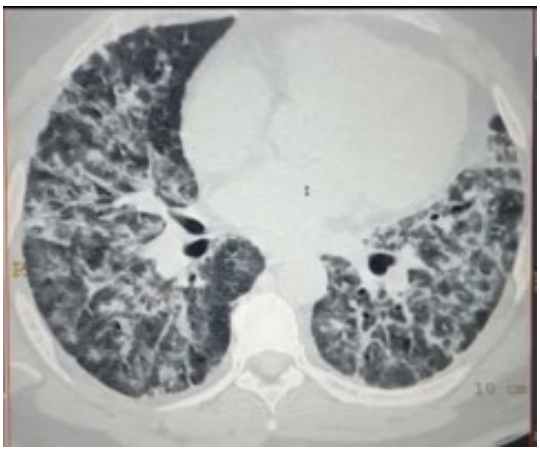

Figure 2: High-resolution CT of the patient's thorax on Day 19.

After 1 month, his COVID-19 RT-PCR report came negative, and he was discharged with a home isolation protocol and advised follow up after 2 weeks.

REVIEW OF LITERATURE AND DISCUSSION

Search Strategy

The paucity of literature on patients with leukaemia infected with COVID-19 prompted the authors to highlight one such rare case, admitted and managed at their institute with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The search was limited to human studies published in the English language in PubMed, Embase, Google Scholar, and Cochrane, from 1995 to February 2021.

Bibliographies and references of selected publications on critical care management of patients positive for COVID-19 diagnosed with AML were manually screened. The full text of each article was studied once the abstract was analysed by the reviewer and being found appropriate. The decision to include a study in the final analysis was based on an independent assessment performed by another reviewer. The authors conducted the literature search themselves. The initial electronic search using medical subject headings (such as "critical care," "acute myeloid leukemia," "AML," "COVID-19," and "Coronavirus") and PubMed searches were emphasised the most.

Acute Myeloid Leukaemia

Definition and epidemiology

Leukaemia comprises <3% of all cancers and is the leading cause of death in children and young adults. AML is defined as cancer involving blood and bone marrow, arising from clonal expansion of malignant haematopoietic precursor cells, which, if left untreated, can be lethal. It is also known as acute myelogenous, myeloblastic, granulocytic, or non-lymphocytic leukaemia. Accounting for approximately 25% of leukaemias, AML is the most frequent form of leukaemia globally, with the lowest survival rate. It has a slight male predominance in adults in most countries.[8]

Pathogenesis and risk factors

In AML, the myeloid stem cells undergo malignant transformation, becoming myeloblasts, which are types of immature white blood cells that can proliferate and not differentiate into mature blood cells.[9] These myeloblasts accumulate and result in ineffective erythropoiesis and bone marrow failure. AML is categorised, according to the WHO classification system, based on morphology, immunophenotype, karyotype, molecular features, and clinical features. The WHO system has superseded the French–American–British (FAB) classification scheme.[10] Several congenital disorders like Down syndrome and Bloom syndrome also predispose to AML. Besides these, environmental exposures like radiation, tobacco smoke, benzene, and exposure to chemotherapeutic agents are also risk factors for AML. However, most AML cases develop *de novo* in an otherwise previously healthy individual.[11]

Clinical features and overlap with COVID-19

A patient with AML usually presents with signs of ineffective erythropoiesis and bone marrow failure, like anaemia and thrombocytopenia, including fatigue, anorexia, and excessive bleeding. Besides this, patients can also have recurrent infections, headaches, and bone pains, as well as bruise easily. Depending on the degree of anaemia, they can experience generalised weakness, fatigue, shortness of breath, and chest tightness. Disseminated intravascular coagulation is also common in a subset of patients with AML. Lymphadenopathy and organomegaly are not very common in these patients. If not intervened, death occurs within a few months of diagnosis due to infection and bleeding.[6]

COVID-19 is an ongoing pandemic caused by SARS-Cov-2, a zoonotic β-coronavirus, like Middle East respiratory syndrome and SARS.[12] Most of the cases are mild, with symptoms such as fever, fatigue, and a dry cough; some are severe, complicated by ARDS. Unlike the otherwise healthy population, patients with advanced age and an immunocompromised status are at a higher risk of fatal infections. This raises concern for patients with haematological malignancies like myeloid neoplasms, including AML, myelodysplastic syndromes,

myeloproliferative neoplasms, and overlap disorders with features of both myelodysplastic syndromes and myeloproliferative neoplasms.[8] Recipients of haematopoietic cell transplantation and cellular therapy are also at risk.[13,14]

Patients with AML infected with COVID-19 impose a tremendous diagnostic and treatment challenge. There are various points of concern. The striking similarity in the symptoms like fever, cough, and malaise creates confusion in diagnosis.[15]

The diagnosis of AML is confirmed by the presence of 20% or more blasts in bone marrow or peripheral blood. Besides this, the presence of Auer rods, and immune-phenotyping and documenting myeloperoxidase activity in cells further help establish the diagnosis.[7]

Treatment

Treatment consists of two phases. The first is induction therapy, which aims to kill leukaemia cells in the blood and bone marrow. The second is post-remission therapy, which kills remaining leukaemia cells, preventing relapse. Four types of treatment include chemotherapy, radiotherapy, stem cell transplant, and targeted therapy.

Complications

AML treatment is usually complicated by infections, which are important causes of morbidity and mortality. This is because of immunosuppressive state, polypharmacy, and complex epidemiology of the resistant organisms[16] and can lead to treatment withdrawal. Infections are mainly haematogenous, which can be Gram-negative or Gram-positive, pulmonary, and fungal. The infection can be either documented clinically, microbiologically, or sometimes may just present as fever of unknown origin.[17] Kebudi et al.[18] conducted a study in children and concluded that haematologic malignancies and mixed infections (other bacterial and fungal infections) are prognostic factors for critical disease, as in this patient.

Challenges during the pandemic

Due to rapidly rising cases of COVID-19, hospitals are overburdened, leading to a shortage of isolation beds and blood products that are needed by patients with leukaemia. Prognosis in young, low-risk patients may be affected due to delays in the initiation of chemotherapy. Patients with leukaemia undergoing haematopoietic stem cell transplantation can face life-threatening complications if infected with COVID-19 and if the disease is severe. Also, giving chemotherapy in the background of COVID-19 infection looks like it could be relatively high-risk as well.

Case management

The case reported here was diagnosed with AML in January 2020 and underwent chemotherapy. He was started on induction therapy with daunorubicin and cytarabine, which have been cornerstones of remission therapy in patients with AML.[19] However, due to the increasing demand for inpatient beds during the pandemic, lower intensity regimens have been developed that can be given in outpatient settings.[20] Consolidation or post-remission therapy with high-dose cytarabine should continue to be offered to patients in complete remission, preferably with fewer cycles (three instead of four) and lowering the dose of cytarabine to 1.5 g/m^2 instead of 3.0 g/m^2.

Clinical management

The patient presented with a respiratory infection and the diagnosis of COVID-19 was confirmed by a RT-PCR test.[21] The patient was initially hypoxic, with a peripheral SpO_2 of 85–88% and PaO_2 of 58 mmHg, which improved to 93% on 15 L/min oxygen after using a NRBM. An initial chest X-ray revealed diffuse bilateral infiltrates without cardiomegaly, consistent with ARDS, likely secondary to viral pneumonia. Due to the high infectivity rate and associated leukaemia, the patient was kept in isolation in the intensive care unit. Patients with severe COVID-19 symptoms are prone to infections, so a necessary workup was done. The authors did a complete blood count every third to fourth day. Although the procalcitonin was normal and blood cultures were negative, raised C-reactive protein and leucocytes count initially suggested underlying sepsis.

Patients with leukaemia are reported to have a higher risk of invasive fungal infections due to immunocompromised state, chemotherapeutic drugs, unfavourable cytogenetics, relapsed or refractory disease, and prolonged myelosuppression.[22] Among all haematological studies, AML has the highest risk of fungal

infections.[23] In this patient, an underlying pulmonary infection is further predisposed to this risk. Therefore, a prophylactic antifungal, voriconazole, was added to the treatment as the best available option for the patient and cost-effectiveness.[24] As per the RECOVERY trial, dexamethasone at 6 mg once daily, given intravenously, decreases mortality in patients with COVID-19 on oxygen support.[25]

Defer intubation

Although this patient met the criteria of severe ARDS with a PaO_2/FiO_2 ratio <100,[26] intubation was avoided as airway reflexes were preserved, and his PaO_2 was maintained at >90% on NIV and NRBM. Intubation and mechanical ventilation can cause a high risk of viral transmission to healthcare workers; besides this, there are high chances of procedure-related complications and cross-infection.[27] There is also high mortality in intubated patients. Monitoring of serial arterial blood gases for pH, PaO_2, and partial pressure of carbon dioxide levels was also done.

Prone positioning

Regular prone positioning was ensured in the patient for 12–16 hours daily. Prone positioning ventilation is generally used for patients with ARDS to prevent ventilator-induced lung injury. The basic mechanism involves decreasing the heart's compressive force by acting on the lung's dependent region, thus increasing aeration in the dorsal lung regions. There is an overall improvement in lung ventilation from dorsal to ventral areas, which are more homogeneous in the prone position than supine, thus improving oxygenation. However, perfusion remains almost constant in both postures. This physiological basis behind a prone position in ventilated patients should also apply to spontaneously breathing patients. Unfortunately, not much literature is available for prone positioning of awake patients.[28]

In the authors' case, the patient was awake and spontaneously breathing but was in severe hypoxaemic respiratory failure, and prone positioning improved oxygenation, which was assessed by blood gas analysis and oxygen saturation. Early prone positioning in patients with raised inflammatory markers (increased serum C-reactive protein) is beneficial since the lungs in the initial phase of ARDS are potentially recruitable unlike in the later phase.[29] Also in recent studies, it has been shown that prone ventilation combined with a non-invasive ventilator support has better effects on a ventilation–perfusion mismatch and better lung drainage in infection-induced ARDS.[30]

Intensive monitoring

The patient was strictly monitored for emergency signs like obstructed or absent breathing, central cyanosis, shock, coma, or convulsions. He was kept on NIV and NRBM alternatively and titrated flow rates for FiO_2 levels to reach the target SpO_2 of ≥93%. Once the patient maintained the target saturation with no further deterioration, the reservoir bag (at 10–15 L/min) was combined with a face mask at 4–6L/min.

Lung imaging: the new gold standard

Lung imaging is an important tool in COVID-19, for diagnosis as well as monitoring and discharge assessment. In the reported patient, a chest HRCT revealed bilateral extensive ground-glass opacities and a high CT severity score, consistent with typical findings of COVID-19 infection. COVID-19 pneumonia generally manifests on lung CT scans as bilateral, sub-pleural, ground-glass opacities with air bronchograms, ill-defined margins, and a slight predominance in the right lower lobe.[31] The CT severity score is an important tool to detect the severity of COVID-19 and it provides details about the extent of lung opacities and disease burden.[32]

Immunosuppression and COVID-19

Minotti Chiara et al.[33] published a systematic review that studied the current data on SARS-Cov-2 cases in children and adults with immunosuppression. They concluded that patients with COVID-19 who are immunosuppressed are few as compared with the overall figures, and have a favourable outcome as compared with other comorbidities. But this study drew conclusions based only on the systematic review, without a meta-analysis.[33] Therefore, Gao et al.[34] conducted a systematic review and meta-analysis, concluding that immunosuppression and immunodeficiency are associated with increased risk of severe disease and mortality in patients with COVID-19.

Thrombo-prophylaxis

COVID-19 is a state of profound inflammation due to the high surge of cytokines and macrophages, leading to an increased risk of thromboembolism.[35] As per the recommendations, it is important to add appropriate thrombo-prophylaxis for a severe COVID-19 infection for a better outcome.[36] Mechanical prophylaxis along with low-molecular-weight heparin was added while keeping a regular check on platelet count, considering the background haematological malignancy.[37]

Blood sugars

The authors reported inadvertently high blood glucose levels in the patient, who was recently diagnosed with Type 2 diabetes mellitus. As per the literature, there is increased risk and severity of infection in patients with diabetes who are infected with COVID-19, probably due to overexpression of angiotensin-converting enzyme receptors, increased IL-6 levels, and impaired T cell function.[38] The exact mechanism is not known.

Viral clearance

Factors like advanced age, being male, and diabetes may adversely affect viral clearance.[39] This may explain the repeatedly positive RT-PCR test in the authors' patient, which came negative in the fifth sample. In addition to this, previous studies also suggest that in patients with AML, glycaemic variability is associated with poor outcomes and lower remission rates.[40] Hence, these patients need more attention for adequate control and management of hyperglycaemia.

Mental health

COVID-19 has a major impact on patients' mental health, who face a lot of emotional adjustment, partly due to the disease itself and partly because of the isolation accompanying it.[41] Along with clinical management, the psychological health of patients' needs attention. Patients need help to maintain a positive attitude to overcome stress, anxiety, and panic associated with the disease. The authors regularly counselled and motivated their patient regarding the prognosis and outcome of the illness. The family was allowed to contact the patient on phone through video calling while maintaining all standard precautions. Music therapy was also provided.

Home isolation

After approximately 1 month, the patient was discharged as per the criteria and was advised to strict home isolation and pulse oximeter monitoring for domiciliary oxygen therapy. A chest CT scan, nasopharyngeal swab, and clinical examination were repeated 15 days after the patient was discharged. He was advised to continue oral voriconazole 200 mg twice daily for 2 weeks.

LIMITATION

A limitation of the study was the non-availability of the galactomannan test in the authors' hospital. However, follow-up radiological imaging did not suggest any findings of invasive fungal infection.

CONCLUSION

To conclude, the authors reported a case of COVID-19 occurring in a patient with AML with a good outcome. Patients with haematological malignancies are more susceptible to SARS-CoV-2 infection and further development of severe infection, including pneumonia with poor blood oxygenation. COVID-19 infection can cause significant harm to a patient with underlying leukaemia, increasing mortality risk. The management of such patients is more challenging than expected, especially in patients with superimposed bacterial infections. The importance of supportive management (oxygen with a bilevel positive airway pressure, prone positioning, and physiotherapy) to prevent complications is emphasised. It also has a significant impact on the physical and psychological health of the patient, necessitating special care and attention. Due to a lack of sufficient literature, more research is needed on the treatment and management strategies for patients with leukaemia during the COVID-19 pandemic.

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Epidermal Growth Factor Receptor Inhibitor-Induced Hypomagnesaemia: Is There a Best Replacement Strategy?

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Abstract

Monoclonal antibodies targeting the epidermal growth factor receptor (EGFRI), such as cetuximab and panitumumab, are commonly used systemic therapies for advanced colorectal and head and neck cancers. Hypomagnesaemia is a common side effect of these therapies and occurs in up to 30% of patients. Interruption of EGFR signalling in the distal convoluted tubule leads to inactivation of the transcellular transporter transient receptor potential channel melastatin member 6 and increased renal magnesium excretion. This paper describes the incidence, risk factors, and the emerging management options for EGFRI-induced hypomagnesaemia.

INTRODUCTION

Over the past few decades, there have been important advances in cancer therapeutics, including a shift from traditional cytotoxic chemotherapy to targeting specific intra-cellular pathways and harnessing the immune system through immunotherapies. One important target is the epidermal growth factor receptor (EGFR), which is a member of the ErbB receptor kinase family. Activation of EGFR can occur through amplification, point mutations, or ligand excess and leads to a signalling cascade through mitogen-activated protein kinase, with downstream effects on the Ras/Raf/MEK/ERK and PI3K-AKT- (PTEN)-mTOR pathways. This overstimulation results in tumour invasion, growth, and metastasis and has been shown to be of oncogenic importance in glioblastomas, lung cancer, head and neck cancer, and colorectal cancer (CRC).[1-3]

Approximately 15% of non-small cell lung cancers harbour mutations in EGFR tyrosine kinase and tyrosine kinase inhibitors such as erlotinib, gefitinib, afatinib, and osimertinib have significantly improved survival for patients with EGFR-mutated advanced non-small cell lung cancers with life expectancies measured in years.[4] In CRC and head and neck cancers, monoclonal antibodies that block ligand binding to EGFR, such as cetuximab (CTX) and panitumumab (PMAB), have been shown to improve survival in advanced disease.[5,6]

Although targeting the same pathway and sharing a similar toxicity profile (diarrhoea, rash, paronychia), EGFR tyrosine kinase inhibitors have rarely been associated with hypomagnesaemia (hMG), in contrast to EGFR inhibitors (EGFRIs), which may lead to hMG in up to 30% of patients. Often referred to as the 'forgotten ion', magnesium (MG) plays a pivotal role in many bodily processes through its role as a cofactor for many enzymatic reactions and serving as a structural component of proteins and nucleic acids. Manifestations of hMG can be quite variable, ranging from asymptomatic to non-specific symptoms such as fatigue and nausea. Lethal manifestations may include arrhythmias, seizures, and tetany.[7]

In this review, the authors will explore the mechanism, risk factors, and current management strategies for hMG induced by EGFRIs.

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS IN ONCOLOGY

The original Phase I studies of EGFRIs investigated CTX as a single agent or in combination with cisplatin in patients with EGFR expressing tumours (mainly head and neck and lung cancers).[8] CTX is a chimeric IgG1 monoclonal antibody targeting the EGFR pathway by competitively inhibiting the extracellular domain of the EGFR, as well as leading to dimerisation and downregulation of EGFR.

In advanced CRCs (ACRC), expression or upregulation of the *EGFR* gene is present in 60–80% of tumours, making EGFR an attractive target.[6] In patients with EGFR expressing irinotecan refractory metastatic colon cancer, the addition of CTX to irinotecan resulted in improved response rates and progression-free survival (PFS) compared with CTX monotherapy alone.[6,4] Acne-like rash occurred in 80% of patients on this trial; however, since MG was not collected as part of the study procedures, information about the frequency of hMG was not reported. In the landmark National Cancer Institute (NCI) of Canada trial CO.17, CTX was compared with best supportive care (BSC) in patients with EGFR expressing refractory ACRC and showed an improved overall survival (OS) benefit.[9] A follow-up biomarker analysis of mutation of the *KRAS* gene identified *KRAS* as an important predictive biomarker, as those with a gene mutation did not derive benefit from CTX, while those with wild-type *KRAS* had significant OS benefit from the EGFRI (hazard ratio: 0.55; 95% confidence interval [CI]: 0.41–0.74).[10] The CO.17 trial also collected MG as part of the study procedures and found that 53% of those treated with CTX developed hMG versus 15% on BSC.

PMAB is a humanised IgG2 monoclonal antibody against EGFR and has also been found to improve response rates and PFS in *KRAS* wild-type tumours compared to BSC in refractory ACRC.[11] In this trial, hMG was observed in 36% of patients receiving PMAB compared with 1% in the BSC arm.[12] Interestingly, in the non-inferiority trial of PMAB compared with CTX in ACRC, any grade hMG (27.6% versus 18.1%) and Grade 3/4 hMG (7.0% versus 2.8%) was higher with the use of PMAB.[13]

Advances in the knowledge of the predictive impact of *RAS* and primary tumour location in the selection of initial therapy for untreated ACRC has led to EGFRIs (PMAB or CTX) being combined with a chemotherapy backbone (FOLFOX/CAPOX or FOLFIRI) in patients with *RAS/BRAF* wild-type and left-sided primary tumours.[14,15] These combinations have resulted in a median OS approaching 3 years in this population, but have also been associated with high rates of any grade hMG (>63%), including Grade 3/4 hMG (4–8%).[16-18]

EGFRIs have also played a role in the treatment of head and neck cancer, where the combination of CTX and radiation for localised disease was shown to improve survival when compared with radiation alone.[19] In the recurrent or metastatic disease setting, CTX and platinum plus 5-fluorouracil resulted in improved OS compared with chemotherapy alone.[5] The incidence of Grade 3/4 hMG in CTX plus chemotherapy arm was significantly greater than the chemotherapy alone arm, occurring in 5% and 1% of cases, respectively. Multiple other studies have established the role of EGFRIs in the world of oncology.

PHYSIOLOGY OF MAGNESIUM HOMEOSTASIS

MG is the fourth most commonly abundant cation in the body and is the second most common intracellular cation after potassium.[20] It is the cofactor for over 300 enzymatic reactions and is involved in stabilising enzymes including many adenosine triphosphate-generating reactions. It plays an essential role in cellular processes, as it is involved in important physiologic functions such as nucleic acid metabolism, protein synthesis, and energy production.[21,22] MG is also crucial for muscle contraction and relaxation, nerve function, heart rhythm, vascular tone, and bone formation.[20,21]

Distribution, Absorption, and Excretion

MG is located intracellularly in 99% percent of the total body, which includes bones, skeletal muscles, and non-muscular soft tissues, leaving only 1% in the extracellular space (serum and red blood cells).[21] The kidneys easily filter 70% of the total body MG, either as complex anions (oxalate, phosphate, citrate) or ionised MG.[21,23] The remaining 30% of the total body plasma MG is bound to proteins, mainly albumin.[21,23]

MG's homeostasis is mainly regulated by the intestines, kidneys, and bones. MG is absorbed in the gut and stored in bones, and the excess is excreted by the kidneys and intestines.[23] The majority of MG (90%) is absorbed in the ileum, with some absorption in the colon via a paracellular mechanism, which is driven by an electrochemical gradient and solvent drag.[20] The second transport system for MG occurs in the cecum and colon, using the transcellular transporter transient receptor potential channel melastatin member (TRPM) 6 and TRPM7.[20,23] The latter is an active process and accounts for about 10% of MG reabsorption.[23] About 30–50% of the dietary MG intake is absorbed in the gut. The amount of MG absorbed is related to the MG status: the lower the MG level, the more the mineral will be absorbed.[21]

The Kidney's Role in Handling Magnesium

The kidneys play an important role in MG homeostasis, as non-protein bound MG is freely filtered across the glomerulus to maintain proper serum MG concentration.[20,21] MG excretion follows the circadian rhythm as the majority of excretion occurs at night.[20] Under physiological conditions, 95% of filtered MG is reabsorbed by the kidneys and 3–5% is excreted in the urine.[20,21] Reabsorption sites include the proximal tube and more commonly (60–70%) the thick ascending limb of the loop of Henle via a passive paracellular transport process.[20] A small percentage (10%) is reabsorbed at the distal convoluted tubules (DCT) for the fine-tuning of MG excretion via an active transcellular transport process.[20] The entry of MG into the DCT cells is facilitated by TRPM6.[22] The mechanism of activation of this transport channel has been linked to binding of EGF to the EGFR on the DCT cells.[24] EGFRIs bind to EGFR and inhibit the influence of EGF, which leads to decreased activation of the TRPM6 channels and a decrease in MG reabsorption in the body[24] (Figure 1).

ASSESSMENT OF MAGNESIUM STATUS

Several methods are utilised to measure MG levels; however, the most common method used is testing the serum MG concentration.[21] Unfortunately, this is a poor predictor of the MG concentration in the body, as serum MG only accounts for 0.3% of the total body MG.[21] In oncology, the degree of hMG is assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, with Grade 1 defined as <lower limit normal–0.5 mmol/L (1.2 mg/dL); Grade 2 as <0.5–0.4 mmol/L (<1.2–0.9 mg/dL); Grade 3 as <0.4–0.3 mmol/L (<0.9–0.7 mg/dL); and Grade 4 as <0.3 mmol/L (<0.7 mg/dL [Table 1]).[25] Other than EGFRIs, which lead to hMG by reducing kidney reabsorption, other causes of hMG include poor dietary intake, gastrointestinal losses, kidney losses, and endocrine diseases (Table 2).[20,21] It is important to assess for hMG in patients on EGFRIs as symptoms are often non-specific and may overlap with symptoms of cancer therapy and/or cancer progression. Clinical manifestations include neuromuscular signs (tremor, spasticity, weakness, ataxia, tetany, and cramps), cardiovascular symptoms (prolonged QT interval and ventricular arrhythmia), and neurocognitive dysfunction (depression, cognitive impairment, agitation, psychosis, and seizures).[20,21,26] In addition, MG is involved in the regulation of the parathyroid hormone and, therefore, hMG can lead to hypocalcaemia (hCA).[26]

Table 1: Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 hypomagnesaemia grading.[2]

Grade 1	Grade 2	Grade 3	Grade 4
0.5 mmol/L–less than the lower limit of normal	0.4–0.49 mmol/L	0.30–0.39 mmol/L	<0.3 mmol/L

Table 2: Various aetiologies of hypomagnesaemia.

Decreased dietary intake	> Malnutrition > Parenteral infusions without magnesium
Gastrointestinal losses	> Malabsorption > Severe or prolonged chronic diarrhoea
Increase kidney losses	Congenital or acquired tubular defects: > Gitelman syndrome > Bartter syndrome Drugs: > Loop and thiazide diuretics > Aminoglycosides > Amphotericin > Cyclosporine > Tacrolimus > Cisplatin > Pentamidine > Foscarnet > Anti-EGFR antibodies
Endocrine causes	> Primary and secondary hyperaldosteronism > Hungry bone syndrome, e.g., after surgery of primary hyperparathyroidism > Syndrome of inappropriate anti-diuretic hormone hypersecretion > Diabetes mellitus
Other causes	> Stress > Chronic alcoholism > Excessive lactation > Heat > Prolonged exercise > Severe burns > Cardiopulmonary bypass surgery > Iatrogenic

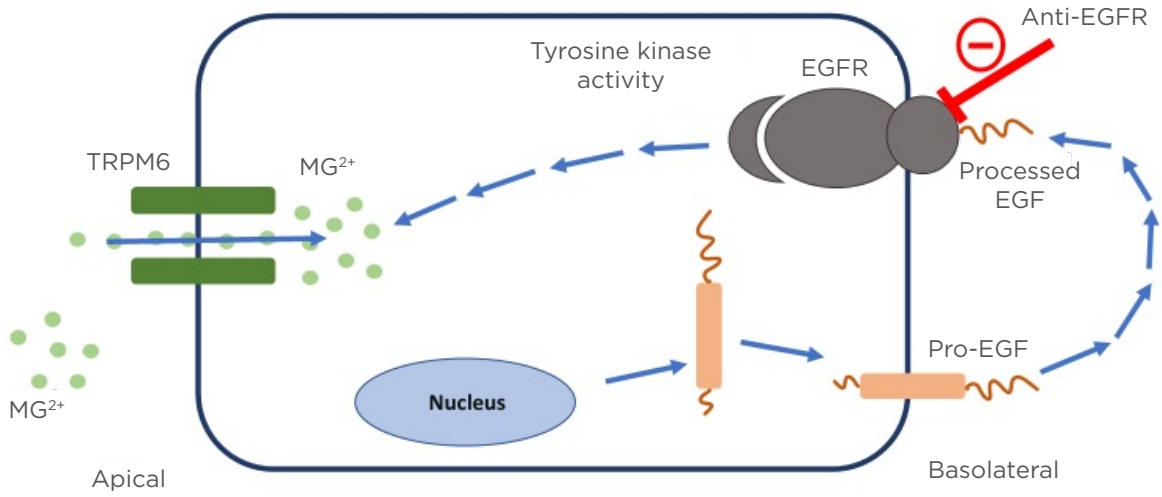

Figure 1: The role of the epidermal growth factor receptor pathway interruption in causing hypomagnesaemia.

Pro-EGF mutation leads to impaired stimulation of EGFR, as shown above. EGFR activation is necessary for TRPM6 channel activation to prevent renal magnesium wasting. EGFRIs work by interrupting this pathway resulting in renal MG wasting.

EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; MG: magnesium; TRPM6: transcellular transporter transient receptor potential channel melastatin member 6.

Adapted from Costa et al.[23]

CHARACTERISTICS OF EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITOR-INDUCED HYPOMAGNESAEMIA

The first report of EGFRI-induced hMG was in a 34-year-old male patient with metastatic CRC receiving irinotecan and CTX, where symptoms manifested as profound fatigue, paraesthesia, muscular fasciculations, and symptomatic hCA.[27] Investigations revealed inappropriately high levels of urinary MG consistent with renal wasting. The patient's symptoms resolved with intravenous (IV) repletion only to recur within 48 hours of oral supplementation with MG oxide and calcium carbonate. Ultimately, the patient required nightly infusions of 10 g MG sulfate to maintain his MG levels and allow ongoing CTX based therapy.

A further prospective study by Tejpar et al.[28] evaluated 98 patients with CRC being treated with CTX, with or without chemotherapy, and used 16 patients on treatment with chemotherapy alone as a control group. This study showed that 97% of patients treated with CTX developed progressive hMG. The mean serum MG slope during EGFRI treatment (with or without combined chemotherapy) was significantly lower compared with chemotherapy alone (-0.00157 mmol/L/day; standard deviation: 0.00162 [95% CI: -0.00191–-0.00123] versus 0.00014 mmol/L/day; standard deviation: –00076 [95% CI: -0.00026–0.00055]; t-test p<0.0001). The degree of hMG was correlated with the duration of treatment and patients treated for under 12 weeks who did not develop Grade 3/4 hMG. Higher baseline serum MG concentration and increasing age were identified as factors that inversely correlated with hMG development. An IV MG load test (N=5) confirmed a defect in renal MG reabsorption as the underlying mechanism of hMG, and nicely illustrated why intermittent boluses of IV MG are an ineffective strategy for the management of EGFRI-induced hMG.

Similarly, retrospective studies have showed direct relationships between older age and duration of EGFRI therapy on risk of developing hMG.[29,30] A systematic review by Jiang et al.[26] also found that length of EGFRI treatment, concomitant platinum chemotherapy, increasing age, and baseline MG concentration correlated with severity of hMG. The effects of EGFRIs on MG typically resolve within weeks to a few months

after discontinuation of EGFRI therapy.[26,31] In addition, a meta-analysis of prospective clinical trials involving CTX and PMAB revealed all-grade incidence to be 34.0%, 14.5%, and 16.8% for the development of hMG, hypokalaemia, and hCA, respectively.[32] PMAB had a similar incidence of all grade hMG to CTX (31.8% versus 34.9%), but possibly a higher risk of Grade 3/4 hMG (5.4% versus 4.4%). For CRC specifically, Grade 3/4 hMG was higher for PMAB at 4.6% versus 2.9% for CTX. Likewise, the ASPECCT trial, which compared the efficacy of CTX with PMAB in chemotherapy-refractory ACRC, found that PMAB was associated with more severe hMG (Grade 3/4: 7.0% versus 2.8%).[13]

Since off-target EGFRI side effects such as acneiform rash have been associated with improved response rates and survival,[9,33] there has been interest in EGFRI-induced hMG as a surrogate predictive biomarker for improved outcomes. In an initial study involving 68 patients treated with CTX plus irinotecan, a 20% (and subsequently 50%) MG reduction from baseline was associated with improved response rates, time to progression, and OS.[34,35] In contrast, an analysis of the CO.17 clinical trial (CTX versus BSC) found that Grade ≥1 and ≥20% reduction in hMG from baseline was associated with worse OS.[36] Subsequent secondary analyses and meta-analyses have suggested that EGFRI-induced hMG is associated with improved clinical benefits (PFS and OS).[13,37] It is important to note that studies showing a positive correlation with worse hMG and improved survival are subject to bias, since patients have a higher chance of developing hMG if they have disease control (and longer survival) on EGFRIs because they are receiving EGFRIs for a greater duration, in contrast to those that have early disease progression and cease EGFRIs earlier.[38] This guaranteed time bias (also known as immortal time bias) can be overcome by using a landmark approach as was used in the CO.17 hMG analysis.[36] As a result, it is unclear at present if the development of hMG can be used to predict for improved outcomes with EGRIs.

MANAGEMENT OF EPIDERMAL GROWTH FACTOR RECEPTOR-INDUCED HYPOMAGNESAEMIA

While hMG is generally easily correctable, when it is EGFRI-induced, it can be very challenging to manage. This is a result of ongoing renal losses due to EGFRI effects on the TRPM6 MG channel in the DCT and also due to impaired transcellular intestinal MG absorption from similar inhibition of TRPM6 in the gut.[24,39] These effects on absorption and excretion make oral and IV supplementation problematic.

Early institutional practices favoured 4 g of IV MG sulfate starting at Grade 2 hMG and increasing to 6–10 g IV MG daily or twice weekly for Grade 3/4; however, it was noted that neither IV or oral magnesium replacement sustained magnesium repletion beyond 72 hours.[20,40] Oral MG supplementation may cause diarrhoea, while frequent IV administrations are very inconvenient and time consuming for patients, and may exacerbate renal MG leak as a result of altered TRPM6 signalling.[28,40,41] Recent opinion-based guidelines suggest consideration of oral MG for Grade 1/2 and adding regular IV MG infusions at Grade 2/3 hMG.[42] With the development of Grade 4 hMG, discontinuation of EGFRIs is suggested until MG improves to Grade 2 or less.

A survey of Canadian medical oncologists found that most physicians (>90%) regularly monitor MG prior to each EGFRI infusion, and most employ a reactive MG replacement strategy (as opposed to prophylactic).[43] Forty percent of respondents (N=40) favoured IV supplementation alone, while 45% used both oral and IV, and 70% introduced supplementation at Grade 1 hMG and the remainder at Grade 2. Importantly, 30% of oncologists were withholding EGFRIs at Grade 3 hMG and 45% at Grade 4. The vast majority felt that a consensus guideline on the management of EGFRI-induced hMG was necessary given the confusion about the significance of this side-effect and the best replacement strategy. In an attempt to explore the availability of evidence-based management practices for EGFRI-induced hMG, Jiang et al.[26] performed a systematic review and found a lack of high-quality management strategies and the available reports suggested refractoriness to IV and oral replacement. As a result, prospective comparative trials were recommended.

EGFRIs inihibition of EGFR and resultant downstream effects on the TRPM6 channel in the kidney and intestine is analagous to an inherited syndrome called familial hMG with secondary hCA. This rare autosomal, recessive

condition is due to a defect in the *TRMP6* gene on chromosome *9q22*, which encodes the magnesium-permeable ion channel.[44] Patients with this condition have severe hMG and hCA as neonates, which can lead to intractable seizures, cerebral damage, and death. If recognised early, patients may be spared morbidity as long as they are maintained on a high dose of oral MG supplementation. Other evidence supporting an oral supplementation approach to EGFRI-induced hMG comes from Pietropaolo et al.[39] and studies on the effects of CTX on intestinal MG absorption. They showed that CTX does indeed affect active transcellular transport through intestinal TRPM6 and, that by increasing oral MG supplementation and thus intestinal MG concentrations, paracellular transport may be the most effective strategy to combat EGFRI-induced hMG.

Recently, the results of the randomised multicentre MAGNET trial became available, which focused on early oral MG supplementation.[45] Eighty-nine patients were randomised to a reactive strategy of oral MG gluconate 3 g twice daily (BID) at the occurrence of Grade 1 hMG, while 84 patients were randomised to a prophylactic strategy of oral MG gluconate 3 g BID at initiation of EGFRI and increasing to 6 g six times a day at Grade 1 hMG. The slope of decline of MG was significantly steeper with the reactive strategy, and 13% developed hMG in the reactive arm compared with only 4% in the prophylactic arm. Importantly, oral supplementation was well tolerated, with no significant adverse events and no difference in bowel movements between the two arms. This study suggests that a prophylactic oral MG strategy may be effective in preventing significant hMG. Another prospective trial[46] assessed the feasibility of using reactive oral MG replacement strategies, initiated at the initial development of Grade 1–3 hMG for patients receiving platinum-based chemotherapy or EGFRIs. Patients were randomised 1:1 to MG oxide 420 mg *per os* BID or MG citrate 150mg *per os* BID (and titrated up depending on the grading of hMG). The trial failed to accrue sufficient numbers, but of the 15 randomised patients MG levels stabilised with positive slopes of change in MG from the baseline. Few patients required IV MG replacement and only 20% developed Grade 1 diarrhoea (Vickers, personal communication, 2021).

Given the increasing use of EGFRIs in earlier lines of therapy for ACRC, managing hMG will be a common challenge for oncologists. In combination with cytotoxic chemotherapy, EGFRI-induced hMG may occur in over 50% of patients and up to 30% on monotherapy EGFRIs. Routine monitoring of MG levels is required, and recognition of risk factors such as advancing age, longer duration of EGFRI therapy, and concomitant platinum chemotherapy is important.[26] In addition, comorbidities such as diabetes, renal tubular disorders, hyperthyroidism, hyperaldosteronism, refeeding syndrome, and the postoperative setting should be taken into account.[21,26] Physicians should also consider electrocardiograms for baseline QTc assessments, as hMG could exacerbate the risk of cardiac arrhythmias. From a management perspective, physiologic studies and prospective trials support the use prophylactic oral MG supplementation at initiation of EGFRIs, or early after hMG develops.[39,45] These studies also show that oral supplements appear to be well tolerated and the requirement for IV MG may be avoided or delayed until more severe hMG develops. Due to the variable availability of MG supplements across the world, a specific MG supplement cannot be universally recommended; however, a diet high in MG and upward titration of oral MG supplementation is suggested to saturate intestinal MG concentrations for paracellular absorption. IV MG supplementation should mainly be administered in patients requiring immediate correction such as for ventricular arrhythmias, or those at risk of other complications related to moderate or severe hMG.[20] Future trials focusing on efficacy, tolerability, and quality of life of patients receiving different oral MG supplements are required.

CONCLUSION

hMG is a common side effect of treatment with EGFRIs, with some patients more susceptible to EGFRI-induced hMG than others. Recent investigations have provided insights that support the use of early oral MG supplementation. Clinicians should closely monitor for this side effect and consider early implementation of an oral MG replacement to avoid serious complications and achieve the best therapeutic results from EGFRIs.

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Identifying Common Biomarkers Between COVID-19 and Commonly Associated Comorbidities

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Abstract

Background: Severe COVID-19 has been associated with certain pre-existing health conditions and can cause respiratory failure along with other multi-organ injuries. However, the mechanism of these relationships is unclear and prognostic biomarkers for the disease and its systemic complications are lacking. This study aimed to examine the plasma protein profile of patients with COVID-19 and evaluate overlapping protein modules with biomarkers of common comorbidities.

Method: Blood samples were collected from COVID-19 cases (n=306) and negative controls (n=78) among patients with acute respiratory distress. Proteins were measured by proximity extension assay utilising next-generation sequencing technology. Its associations to COVID-19 disease characteristics were compared to that of pre-existing conditions and established biomarkers for myocardial infarction, stroke, hypertension, diabetes, smoking, and chronic kidney disease.

Results: Several proteins were differentially expressed in COVID-19, including multiple pro-inflammatory cytokines such as interferon-γ, CXCL10, and CCL7/MCP-3. Elevated IL-6 was associated with increased severity, while baseline IL1RL1/ST2 levels were likely associated with a worse prognosis ($p<5x10^{-5}$). Network analysis identified several protein modules associated with COVID-19 disease characteristics overlapping with processes of pre-existing hypertension and impaired kidney function. B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide,

markers for myocardial infarction and stroke, increased with disease progression and were positively associated with severity. MMP12 was similarly elevated and has been previously linked to smoking and inflammation in emphysema, along with increased cardiovascular disease risk.

Conclusion: This study provides an overview of the systemic effects of COVID-19 and candidate biomarkers for clinical assessment of disease progression and the risk of systemic complications.

INTRODUCTION

The recent COVID-19 pandemic is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and, since its identification in late 2019, the virus has spread worldwide with >30 million reported cases.[1] Clinical presentation can range from mild flu-like symptoms, including fever, cough, and shortness of breath, to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation.[2-4] Disease severity and mortality rate have been associated with certain pre-existing conditions such as a history of cardiovascular disease, hypertension, diabetes, and obesity, which correspond with a worse prognosis.[4-7] These conditions often accompany older age and likely explain the higher mortality rate observed among the elderly population.[4] Recent genetic studies indicate the potential protective effect of specific blood antigens and possibly polymorphisms within the angiotensin-converting enzyme 2 (*ACE2*) gene,[8,9] the primary cell entry receptor for SARS-CoV-2.[10]

Although clinical manifestations are mainly respiratory, early clinical reports and extrapolation from similar coronaviruses[11] (e.g., SARS-CoV-1 and Middle East respiratory syndrome coronavirus) have detailed the systemic effects of COVID-19, including acute cardiac injury, heart failure, arrhythmia, gastrointestinal distress, impaired liver function, and acute kidney injury.[4,7,11-13] Thromboembolic complications are common among patients with pre-existing cardiac and cerebrovascular diseases, which is likely related to the systemic inflammation and pro-coagulatory conditions from COVID-19 infection.[14,15] Early surveillance studies have also reported neurological manifestations, including altered mental status and impaired consciousness along with fatigue, pain, and sensory disturbances (e.g., anosmia, dysgeusia) post-recovery;[16,17] however, the long-term complications of COVID-19 remain unclear.

While the clinical characteristics of COVID-19 are continually refined in real-time, more efficient tools, particularly prognostic markers, are needed to evaluate disease progression for targeted intervention strategies and to better understand the overlapping systemic pathology between SARS-CoV-2 infection and comorbidities. Using high-sensitivity proximity extension technology, this study examined the blood proteome of patients with COVID-19 for protein markers associated with early infection and disease prognosis, and compared them with known biomarkers of common pre-existing conditions and related complications.

METHODS

Adult patients (n=384) presenting with acute respiratory distress were investigated at Massachusetts General Hospital, Boston, USA, of which 306 patients tested positive for COVID-19 while 78 remained as negative controls.[18] The descriptive statistics of the cohort are provided in Table 1. Longitudinal blood sampling was conducted for cases at 3, 7, and 28 days from baseline, if possible. Pre-existing conditions, including heart (e.g., coronary artery disease, congestive heart failure, valvular disease), lung (e.g., asthma, chronic obstructive pulmonary disease, regular oxygen use), and kidney (e.g., chronic kidney disease, baseline creatinine >1.5 mg/dL) diseases, were recorded along with any history of diabetes, hypertension, and any immunocompromising conditions. Characterisation of obesity was defined as a BMI of ≥30 kg/m^2. Each patient's condition was assessed using a 6-point ordinal scale (1: death; 2: intubation and mechanical ventilation; 3: non-invasive ventilation or high-flow oxygen; 4: hospitalised with supplementary oxygen; 5: hospitalised

without supplementary oxygen; and 6: not hospitalised) based on World Health Organization (WHO) guidelines.[19]

Proteins were measured in plasma using a proximity extension assay, a high-sensitivity multiplex immunoassay that utilises paired oligonucleotide antibody probes for protein identification, followed by quantification using quantitative polymerase chain reaction or next-generation sequencing (NGS) technology.[20] In this study, samples were analysed with the NGS-based Olink® Explore (Olink, Uppsala, Sweden) product, consisting of four 384-plex panels of 1,536 assay probes, including 48 controls and three inter-panel quality control markers (IL-6, IL-8, and TNF).[21] The relative concentration for each protein was quantified as log base-two normalised protein expression levels. Internal assay controls were used to quality check each step of the assay (i.e., incubation, extension, and amplification), and sample measures with high variability were excluded. Additional details regarding the method have been described elsewhere.[20,21]

In summary, 1,420 unique proteins were analysed, with the majority having a call rate (i.e., measurable levels above the limit of detection) >80%. Measures <25% (x=160) were excluded, while those between 25% and 80% (x=229) remained in the analysis but were interpreted with precaution. In total, 1,260 proteins passed quality control for the analysis.

Table 1: Descriptive statistics of the cohort.

	Patients with COVID-19 (n=306 [%])	Controls (n=78)	p
Age			
20–34 years	32 (10%)	4 (5%)	0.221
35–49 years	66 (22%)	7 (9%)	0.0178
50–64 years	89 (29%)	22 (28%)	0.99
65–79 years	65 (21%)	34 (44%)	0.000103
≥80 years	54 (18%)	11 (14%)	0.565
BMI (kg/m²)			
Underweight; <18.5	2 (1%)	5 (7%)	0.00416
Normal; 18.5–24.9	44 (15%)	29 (39%)	$1.66x10^{-5}$
Overweight; 25.0–29.9	110 (38%)	12 (16%)	0.000426
Obese; 30.0–39.9	95 (33%)	21 (28%)	0.47
Severely obese; ≥40	35 (12%)	8 (11%)	0.862
Pre-existing disease			
Heart disease	48 (16%)	23 (29%)	0.00831
Lung disease	66 (22%)	40 (51%)	$3.43x10^{-7}$
Kidney disease	41 (13%)	20 (26%)	0.0136
Hypertension	111 (36%)	28 (36%)	1
Diabetes	146 (48%)	53 (68%)	0.00217
Immunocompromised	25 (8%)	17 (22%)	0.0012
WHO score: Day 0			
1: Death	0 (0%)	0 (0%)	N/A
2: Intubated/ventilation	79 (26%)	19 (24%)	0.906
3: Non-invasive ventilation	0 (0%)	0 (0%)	N/A
4: Hospitalised, O_2	152 (50%)	35 (45%)	0.528
5: Hospitalised, no O_2	46 (15%)	15 (19%)	0.464
6: Not hospitalised	29 (9%)	9 (12%)	0.74

Severe condition (WHO score: 1 or 2)			
Day 0; baseline	79 (26%)	19 (24%)	0.906
Day 3	92 (30%)	10 (13%)	0.00334
Day 7	94 (31%)	7 (9%)	0.000177
Day 28	83 (27%)	9 (12%)	0.00633
Max. within 28 days	109 (36%)	23 (29%)	0.376

Frequency and proportion are reported. Differences between cases and controls were assessed using a chi-square test. WHO-based 6-point ordinal scale was used to categorise severity of patient condition: 1=death, 2=intubation and mechanical ventilation, 3=non-invasive ventilation or high-flow oxygen, 4=hospitalised with supplementary oxygen, 5=hospitalized without supplementary oxygen, and 6=not hospitalised. Severe condition was categorised as WHO score of ≥2.

O_2: oxygen; Max.: maximum; N/A: not applicable; WHO: World Health Organization.

Differences in protein levels between patients who tested positive for COVID-19 and negative controls were analysed using a multivariable linear regression model, adjusting for age and pre-existing conditions (Table 1). Longitudinal changes in protein concentrations were analysed using a paired Student t-test. Pre-analytical variation associated with sample quality was assessed and corrected using previously defined markers of sample handling (e.g., CD40L).[22] Association with severity and prognosis was assessed using the baseline severity score or maximum-reached severity score within the 28-day period, respectively. Scores for severity and prognosis were dichotomised based on the usage of mechanical ventilation or death (severe: 1-2, non-severe: 3-6; WHO score). Significance after Bonferroni correction for multiple testing was set at conservative cut-off of $p<10^{-5}$, although suggestive associations of $p<5x10^{-4}$ were considered. All statistical analyses were conducted using R v.4.0.2 (R Core Team, Vienna, Austria).

Modules or clusters of proteins were identified by weighted correlation network analysis using a Pearson-based weighted adjacency matrix (signed, β=14) and average linkage hierarchical clustering.[23] Modules were evaluated for enriched biological processes[24] and used to compare study associations with the differential protein profiles of other diseases including myocardial infarction,[25-27] cardiovascular-related death/heart failure,[27] stroke,[27,28] hypertension,[29] atherosclerosis,[30] diabetes,[31] smoking,[32] kidney function,[33] and chronic kidney disease.[33]

RESULTS

Many proteins were differentially expressed among patients with COVID-19 compared to negative controls, as shown in Figure 1. Inflammatory cytokines such as CXCL10, CXCL11, and interferon-γ increased four-fold at initial sampling but then decreased during the follow-up period. In contrast, lower levels were detected for CDON, ROR1, and BOC but likewise stabilised and regressed within the first week. However, several proteins, including ITGA11, continued to decrease over time. A delayed effect was observed with SDC1, PTN, and SFRP1, which were not initially associated with the disease but increased gradually as the disease progressed. Similarly, levels of ACE2 increased over two-fold within the first week but were not elevated at baseline (β=-0.06, p=0.65).

Findings were not significantly affected after correcting for sample handling, although there was a minor improvement in the variability. The majority remained significant after correcting for pre-existing conditions and obesity. However, a few proteins, including IL1R2, a protein upregulated in the adipose tissue of patients with obesity,[34] were only associated after stratification by BMI (normal: β<0.001; p=0.99; obese: $\beta=-0.54$, $p=3.3x10^{-7}$).

Biomarkers associated with disease severity, as defined by mechanical ventilator use, are illustrated in Figure 1B and compared to the disease-associated markers identified in Figure 1A. Overlapping markers, including *EZR*, nicotinamide adenine dinucleotide kinase,

and *KRT19*, may be useful biomarkers for diagnosing infection and monitoring disease severity. IL-6, which was only slightly elevated among cases (β=0.60; p=0.02), was significantly correlated with severity. However, the majority of proteins associated with severity were different from those associated with disease development. Measures such as *DDAH1* and *NPM1* were also associated with severity among COVID-19-negative controls, indicating a lack of specificity for certain proteins.

Baseline levels of DCN, S100P*, and the cardiac biomarker* IL1RL1*/*ST2 were suggestively associated with maximum-observed severity (i.e., death or requiring ventilation) within the 28 days ($p=1.2x10^{-6}$, $1.8x10^{-4}$, $1.3x10^{-12}$, respectively), even after correcting for baseline severity ($p<5x10^{-5}$). Plasma levels of S100P were lower among cases compared to controls (β=-0.48; p=0.0004), but levels of DCN and IL1RL1 *were not affected at baseline. However,* IL1RL1 was associated with baseline severity (β=0.83; $p=1.2x10^{-8}$). Chemokine CXCL10 was also correlated with baseline severity and prognosis (β=0.63; p=0.0003; β=0.89; p=0.0005).

As most cases were >50 years old, many had pre-existing conditions such as diabetes and hypertension (Table 1). Patients with COVID-19 were more likely to be obese but had unexpectedly lower rates of lung disease and diabetes, although this may be due to selection bias among controls. Association between baseline protein levels and pre-existing conditions among cases was examined in Figure 1C. Leptin, a metabolism-regulating hormone primarily secreted by adipose tissue,[34] was the primary protein associated with obesity but was only slightly increased among cases (β=0.681; p=0.0007). Cardiac biomarkers B-type natriuretic peptide (BNP) and its N-terminal pro-hormone (NT-proBNP) were negatively associated with obesity but positively associated with pre-existing heart disease. Both were under-expressed in COVID-19 at baseline ($β<-1.19$, $p<2x10^{-7}$) but increased significantly during follow-up ($β>1.1$; $p<3x10^{-5}$). BMI significantly modified baseline association for both cardiac biomarkers (normal: $β>-0.71$, $p>0.20$; obese: $β<-1.82$, $p<2x10^{-8}$). Fibroblast growth factor 19 was elevated in patients with hypertension and possibly those with pre-existing kidney disease (unadjusted: $β=0.73$, $p=2x10^{-5}$; adjusted: β=0.77, p=0.08).

To determine if specific biological processes overlap between COVID-19 disease and related comorbidities, modules of intercorrelated proteins were identified and used to cross-examine associations between disease characteristics, pre-existing conditions, and relevant biomarkers established in previous studies. As illustrated in Figure 2, several identified modules correspond to over- (green) and under- (turquoise/black) expressed proteins among patients with COVID-19. As previously illustrated, these tend to differ from proteins associated with disease progression (red/turquoise) and severity (yellow).

There was a significant overlap in markers associated with pre-existing kidney disease and hypertension (turquoise), which were responsive to COVID-19 infection and increased with disease progression. Many have been previously established as markers of reduced kidney function, based on estimated glomerular filtration rate, and increased risk of developing chronic kidney disease.

BNP and NT-proBNP (left-end turquoise) were associated with myocardial infarction, heart failure, and ischaemic stroke. Its moderately correlated protein matrix metallopeptidase 12 (MMP12) was similarly elevated in both myocardial infarction and stroke. MMP12 was also higher among smokers, being associated with inflammation in emphysema; therefore, it may be a shared pro-inflammatory mediator between COVID-19 and severity-related comorbidities. The protein module associated with disease severity (yellow) overlapped with biomarkerAs for increased myocardial infarction risk such as AGER, CTSL, PARP1, and SOD2. Many severity-related measures were also associated with pre-existing lung disease, although in the opposite direction. Proteins of the last module (black), which include *ITGA11*, continued to decrease throughout the 28-day observation period. Considering its moderate overlap with

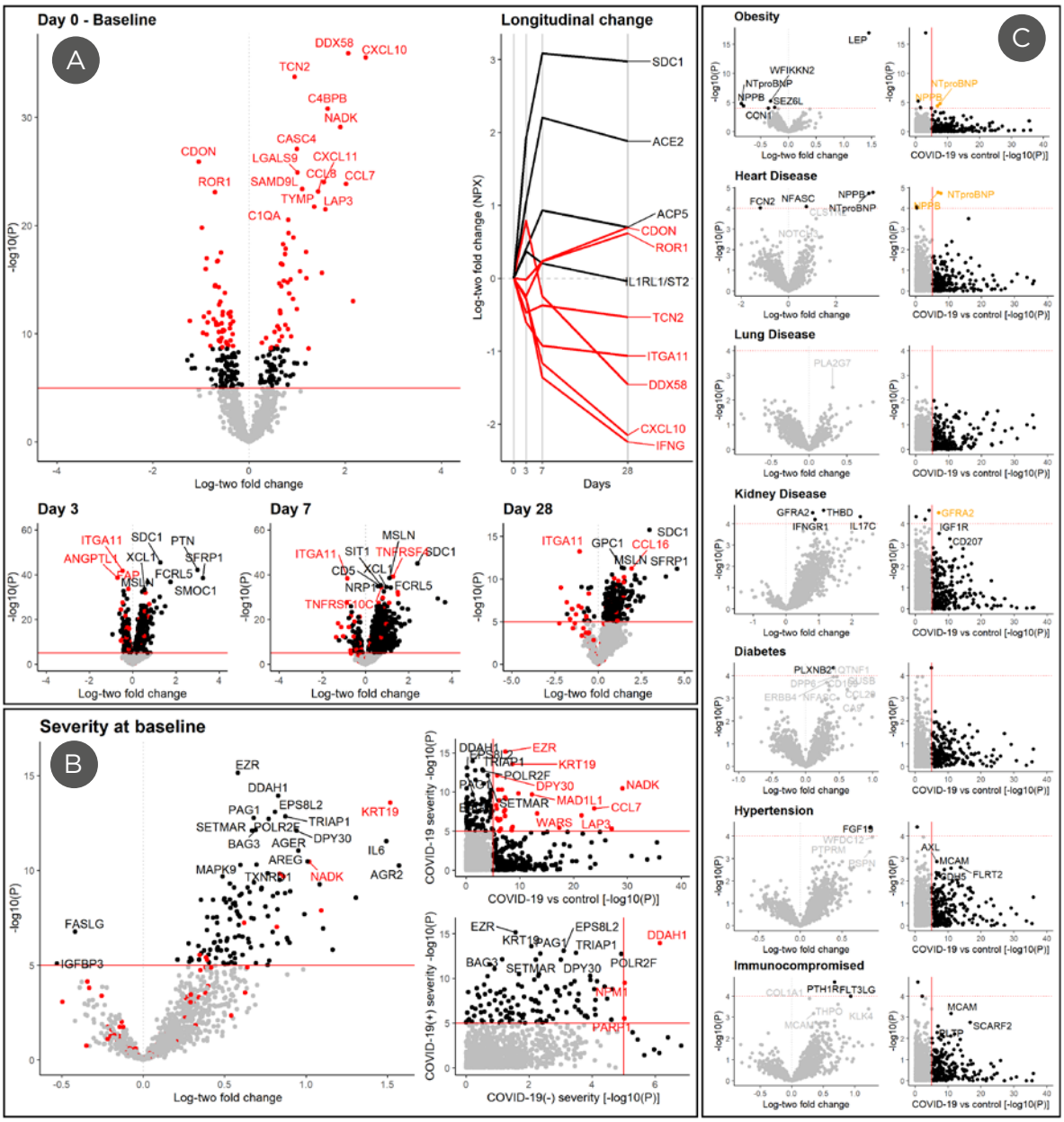

Figure 1: Proteins associated with COVID-19 disease onset, severity, and pre-existing conditions at baseline.

A) Differences in log base-two protein levels (NPX) between COVID-19-positive cases (n=305) and -negative controls (n=78) were analysed using a multivariable linear regression model adjusting for age, pre-existing conditions (Table 1), and sample handling. The top 100 COVID-19-associated markers are labelled in red for all plots. Changes in protein levels at 3, 7, and 28 days compared to baseline among cases were analysed using a paired Student t-test (n=211, 131, and 40, respectively). Levels relative to baseline are also plotted longitudinally for those followed till Day 28 (n=40) to limit potential survivorship bias. B) Association between protein levels and severity at baseline was determined using a multivariable linear regression model adjusting for age, pre-existing conditions, and sample handling. Only DCN, S100P, and IL1RL1 was suggestively associated with prognosis ($p<5x10^{-5}$) after adjusting for baseline severity (not shown). Both severity and prognosis were defined as a WHO score of ≥2 (i.e., death or use of mechanical ventilation) at baseline or within 28 days, respectively. C) Association to pre-existing conditions including obesity (≥30kg/m²), heart/lung/kidney disease, diabetes, hypertension, and any immunocompromising conditions are illustrated above (left) in comparison to their association with COVID-19 (right). Cases with pre-existing conditions were compared to those with no pre-existing condition (n=89) using a multivariable linear regression model, adjusting for age and other pre-existing conditions.

NPX: normalised protein expression; vs: versus; WHO: World Health Organization.

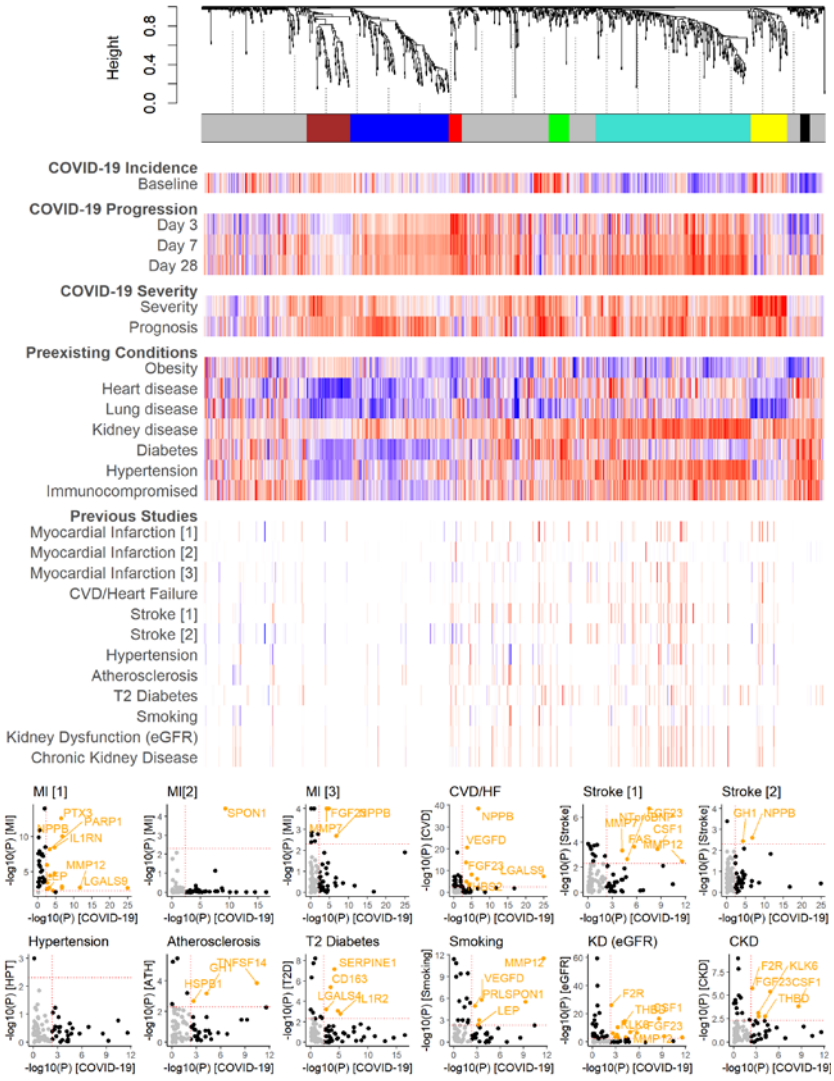

Figure 2: Comparison of protein modules associated with COVID-19 and disease-related pre-existing conditions and complications.

Dendrogram and coloured bars illustrate intercorrelated protein modules among patients who tested positive for COVID-19, determined by weighted correlation network analysis. Colours indicate a normalised score (-1: blue; +1: red) of the effect estimate divided by standard error, with colour and intensity corresponding to the direction and strength of the association, respectively. Scores were normalised within each study by the 95th percentile of the absolute scores to allow inter-study comparability and minimise outlier effects. Studies are referenced in the methods by order.

CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HPT: hypertension; KD: kidney dysfunction; MI: myocardial infarction; log10: logarithm with base 10; T2: Type 2.

obesity and diabetes, the module may be related to long-term metabolic dysfunctions.

DISCUSSION

This study provides a broad overview of the systemic effects of COVID-19 measured through blood, a natural sink for multiple organ systems and an easily accessible medium for clinical investigation. Findings indicate a significant disruption in the circulating proteome of infected patients, impacting multiple biological processes relating to pulmonary inflammation along with cardiac injury and renal dysfunction. These findings support the observation of multi-organ complications reported in previous clinical studies.[4,7,35]

As expected, many pro-inflammatory cytokines were elevated during the early stages of the disease and may influence overall severity, as shown in the previous studies.[3,4] The hyperactive immune response against SARS-CoV-2 infection, often referred to as a 'cytokine storm', has been hypothesised to be a cause of disease mortality.[36,37] Interferon-γ-induced chemoattractant CXCL10 was one of the primary cytokines elevated in cases and was a suggestive marker for disease severity. Previous studies have also shown increased levels of CXCL10 along with CCL7 (MCP-3) in COVID-19, and CXCL10 was a suggested biomarker for ARDS with protein DDX58.[38,39] As IL-6 blockade has been effective for managing cytokine release syndrome, IL-6 has also been investigated as a therapeutic target for COVID-19.[36] Although not notably elevated among cases in this study, higher levels of IL-6 were associated with increased severity. Findings further support the potential benefits of such treatment. As IL-6 is also a marker with myocardial infarction and smoking, treatment efficacy may be modulated by active cigarette smoking or pre-existing cardiovascular disease targeting related disease complications.[25,27]

Several cardiac biomarkers were influenced by COVID-19, including the hormone BNP and its inactivated-form, NT-proBNP. Both are known predictors of acute cardiac injury and heart failure[27,40] and have been proposed as prognostic measures for increased mortality among patients with COVID-19.[41] A retrospective examination of deceased patients with COVID-19 has also shown elevated levels of circulating NT-proBNP during hospitalisation.[4] Therefore, BNP-related measures may be useful for monitoring cardiac stress and the risk of thromboembolic complications, particularly among those who are obese or with pre-existing heart conditions. Another biomarker, IL1RL1, also known as ST2, is associated with cardiac remodelling, and soluble ST2 has been a marker of acute myocardial infarction.[42-44] Elevated levels of ST2 were associated with increased mortality rate and may be an additional complementing marker of cardiac complications for COVID-19.[45]

Other proteins may also indicate cardiac-related injury, including *CDON*, which, along with its co-expressed partner *BOC*, were lower among cases. *CDON* deficiency in mice has been associated with cardiac remodelling and fibrosis through hyperactivation of the Wnt/β-catenin pathway and may indicate an increased risk of cardiac injury and heart failure in patients.[46] CDON levels were also negatively correlated with severity and, to a lesser extent, disease prognosis. On the other hand, MMP12, an increased measure associated with cigarette smoking, may be a mediator of pulmonary inflammation[32,47] in COVID-19 and pre-existing lung conditions and cardiovascular-related comorbidities.

As the primary entry receptor for SARS-CoV-2, *ACE2* is an essential moderator of blood pressure and has often been examined in the relationship between COVID-19 and cardiovascular complications. Studies have suggested that SARS-CoV-2 infection can affect the expression of *ACE2* pathways in the heart and increase cardiac complication risk associated with localised inflammation.[48] ACE inhibitors frequently used to manage hypertension have been associated with increased risk of kidney injury among patients with COVID-19.[49] Furthermore, increased levels of soluble *ACE2*, as seen among cases in this study, may offer some protection against SARS-CoV-2 infection by inhibiting receptor-binding activity, although this requires further clinical investigation.[50]

Studies have also shown *ACE2* expression in kidneys, which may indicate a direct relationship between SARS-CoV-2 infection and renal complications.[51] Systematic release of pro-inflammatory cytokines in ARDS may increase the risk of acute kidney injury, while its resulting accumulation from reduced renal function may, in turn, exacerbate ARDS.[52] In this study, several proteins were associated with both COVID-19 and kidney dysfunction, and may be possible biomarkers for monitoring acute injury, particularly among those with hypertension.

The long-term complications of COVID-19 could not be directly assessed in this study due to the limited follow-up time. However, previous studies have reported lasting changes in metabolic and sensory functions, particularly among severe cases.[17,53] Although levels of proteins like *ILTGA11* seemed to show long-term disruptions from disease, proper longitudinal studies will be required to investigate its trajectory. Although this study focused on circulating proteins, other media such as sputum may provide more localised measures for

COVID-19.[47] Similarly, urine and cerebrospinal fluid may be better for assessing renal and neurological complications. However, blood remains the single most comprehensive source for assessing systemic effects, and the sensitivity of proximity extension technology allows the detection of trace proteins from multiple organ systems. Unfortunately, previous studies have been limited to targeting specific aspects of the blood proteome, which significantly limits the resolution for comparing overlapping biological processes. However, the recent incorporation of NGS readout in a proximity extension assay will likely provide a more comprehensive disease proteomic profile in future studies.

In summary, this study provides an initial assessment of the overlapping biological processes associated with COVID-19 and related comorbidities. Cardiac biomarkers NT-proBNP, BNP, and ST2 may be useful for monitoring and assessing the risk of cardiac and cerebrovascular complications, while specific measures of inflammation such as CXCL10, IL-6, and MMP12 may be useful for identifying patient groups responsive to immunosuppressive treatments. However, further investigations are required to validate the efficacy of these potential biomarkers in clinical settings.

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Current Therapy for Homozygous Familial Hypercholesterolaemia

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Abstract

Homozygous familial hypercholesterolaemia is a rare and severe genetic disorder affecting one in 300,000 people. Due to the very high cholesterol levels since birth, compromise of the aortic valve and atherosclerotic cardiovascular disease can develop during the first decade of life. An early diagnosis and aggressive treatment before vascular damage occurs is critical for the evolution of the disorder. In this review, the authors discuss current lipid-lowering therapies for the management of patients with homozygous familial hypercholesterolaemia, with special focus on safety, efficacy, and potential cardiovascular benefits.

INTRODUCTION

Homozygous familial hypercholesterolaemia (HoFH) is a rare and aggressive disorder, resulting from the inheritance of mutations in the two alleles of genes regulating the low-density lipoprotein receptor (LDL-R) function. In >90% of cases, familial hypercholesterolaemia (FH) is caused by variants in the *LDLR* gene, and less frequently in *APOB*, *PCSK9,* or *LDLRAP1* genes.[1] Prevalence of HoFH is one in 300,000 people.[1,2] The diagnosis is based on extremely high LDL-cholesterol (LDL-C) levels, usually >500 mg/dL. In addition, cutaneous and tendon xanthomas can be detected before the age of 10 years, and both parents should have high cholesterol levels suggesting heterozygous FH (HeFH).[3] This population is characterised by high frequency and very early onset of cardiovascular disease

(CVD).[4] In children, cardiovascular (CV) events, including aortic and supra-aortic valve disease and coronary heart disease, are found in almost 50% of cases around age 11 years.[5] Usually, if individuals with HoFH are not treated, they may not survive beyond the third decade of life.[3,4,6]

The major determinant of survival in this population is on-treatment total cholesterol (TC) levels, which are 6.2-times higher in cases with TC >15.1 mmol/L (585 mg/dL) than those with TC <8.1 mmol/L (314 mg/dL).[4] On the other hand, there is evidence suggesting great phenotype heterogeneity depending, in part, on the molecular defect. LDL-C levels may overlap those observed in HeFH, and CVD may occur later in life in patients with defective mutations with certain LDL-R activity.[7,8]

This review summarises the advantages and disadvantages of available treatments approved for patients with HoFH. For this purpose, the Medline/PubMed databases were systematically searched for literature published between 1982 and May 2021 to focus on more relevant data applicable to the current scenario of the management of HoFH. No restriction on publication type was applied. Due to the rarity of the disorder, consensus statements, guidelines, randomised controlled trials, open-label trials, and case reports were analysed. The databases were searched with the terms "homozygous familial hypercholesterolemia," "lipid-lowering therapies," "statins," "ezetimibe," "PCSK9 inhibitors," "lomitapide," "evinacumab," "mipomersen," "LDL-apheresis," and "liver transplantation," related to efficacy and safety in this specific population. All literature in English were included. The literature revision was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020.[9]

TREATMENT GOALS

The main objective of LDL-C reduction in treating HoFH is to delay or prevent the development of atherosclerotic coronary artery disease and the compromise of the aortic valve. As HoFH is a rare disorder, it can be assumed that goals proposed for HeFH in different national and international guidelines could be applicable to this condition.[3,10-12] The 2014 European statement recommended an LDL-C target of <2.5 mmol/L (<100 mg/dL) in adults, <1.8 mmol/L (<70 mg/dL) in adults with atherosclerotic cardiovascular disease (ASCVD) or diabetes, and <3.5 mmol/L (<135 mg/dL) in children.[3] The same LDL-C goals were considered in the Spanish statement, but a 50% reduction in LDL-C was also added.[12] This percent reduction in LDL-C is also recommended by the National Lipid Association (NLA)[11] and National Institute for Health and Care Excellence (NICE) in the UK.[10] However, there is general agreement that these targets are very difficult to achieve with standard lipid-lowering therapies (LLT) in most patients with homozygous FH.

CURRENTLY AVAILABLE LIPID-LOWERING TREATMENTS FOR PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLAEMIA

The mechanisms of action and efficacies of discussed approved LLT for HoFH are outlined in Table 1.

Statins and Ezetimibe

Statins are the mainstay of treatment and should always be prescribed in patients with HoFH together with a healthy lifestyle, ideally starting at the age of 2 years. Statins upregulate LDL-R; therefore, the response is very modest in HoFH, depending on the severity of the causative mutation. LDL-C reduction with statins varies between 6% in those patients with null mutations and 28% in those carrying defective mutations.[13] Randomised trials comparing efficacy and safety of statins in treating HoFH have included children aged from 6 years, and have shown that statins are well tolerated, with isolated cases of myalgia, no significant increases in transaminases, and no patient discontinuation of medication due to an adverse event (AE).[13,14] Reduction in mortality has been shown retrospectively in a cohort of patients with HoFH in South Africa.[6] Despite a mean reduction of 26% in LDL-C levels, mainly with statins, a 66% risk reduction in mortality and a significant delay in the age of first CV event or death were observed.[6]

Due to the severe hypercholesterolaemia, patients with HoFH require other LLT to further reduce LDL-C levels and reduce the residual cholesterol risk.

Table 1: The mechanisms of action and efficacies of approved lipid-lowering therapies for homozygous familial hypercholesterolaemia.

LLT	Mechanism of action	Upregulation of LDL-R	LDL-C reduction (%)
Statins	Reduce intra-hepatocyte cholesterol synthesis by inhibiting the limiting enzyme HMG-CoA reductase	Yes	<6.0% in null mutations. Up to 28.0% in defective mutations
Ezetimibe	Reduce GI cholesterol absorption by inhibiting NPCL1 receptor	No	10.0–15.0%
PCSK9i	Monoclonal antibodies that inhibit the PCSK9 serum, thereby increasing the recycling of LDL-R in hepatocytes	Yes	In null/null mutations: mostly absent 35.6–40.8% in patients with defective mutations in one or both alleles
Lomitapide	Inhibits the MTP in hepatocytes and enterocytes, affecting lipoprotein assembly and reducing apoB, containing lipoprotein production	No	40.0% intention-to-treat analysis; 50.0% in patients who completed efficacy phase; and 45.5% long-term follow-up
Mipomersen	Antisense oligonucleotide against messenger RNA of *APOB*, reducing apoB synthesis	No	24.70%
Evinacumab	Monoclonal antibody against ANGPTL3 with effects on the lipoprotein lipase and endothelial lipase	No	49.0% Up to 79.0% in those with null mutations
LDL-apheresis	Extracorporeal removal of apoB, containing lipoprotein	No	63–71% per session, according to the type of apheresis

ApoB: apolipoprotein B; GI: gastrointestinal; HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein-cholesterol; LDL-R: low-density lipoprotein-receptor; LLT: lipid-lowering therapy; MTP: microsomal triglyceride transfer protein; NPCL1: Niemann-Pick C1-Like 1; PCSK9i: PCSK9 inhibitors.

Ezetimibe targets the intestinal Niemann-Pick C1-Like 1 (NPC1L1) protein, selectively inhibiting cholesterol absorption without affecting the absorption of fat-soluble vitamins. It is commonly used in combination with statins, providing approximately 15–20% further reduction in LDL-C in the primary hypercholesterolaemia or high-risk population.[15,16] There are few studies addressing the efficacy and safety of ezetimibe in treating individuals with HoFH aged 12 years and older.[17,18] When ezetimibe is added to a high-intensity statin, with or without LDL-apheresis, there can be a further reduction of at least 20.5% in LDL-C levels.[17] In general, the safety profile of ezetimibe co-administered with statins is similar to that observed with statins in monotherapy.

A recent systematic review including 26 randomised clinical trials showed that ezetimibe with statins reduced the risk of major adverse CV events by 6% compared with statins in monotherapy; however, the combination did not show benefit in reducing total mortality.[19] In terms of safety, ezetimibe is well tolerated, and there are no differences in the risk of hepatopathy or myopathy and no risk of new-onset diabetes.[20]

PCSK9 Inhibitors

Alirocumab and evolocumab are monoclonal antibodies that lower plasma LDL-C levels by binding *PCSK9* and upregulating LDL-R expression on hepatocytes. Several studies have shown that proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) reduce LDL-C levels in up to 60% of patients with HeFH and other high-risk populations.[21-24] Moreover, two randomised controlled clinical trials in secondary prevention populations demonstrated that PCSK9i reduced ASCVD by 15% on top of a maximum-tolerated statin therapy compared with statins alone.[21] Both agents were approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to be used in patients with HeFH and in patients with ASCVD. Evolocumab was also approved for the treatment of patients with HoFH over age 12 years. The safety and efficacy of both PCSK9i in patients with HoFH were evaluated in Phase III trials[25,26] and, in the long term, the open-label TAUSSIG study with evolocumab.[27]

In the TESLA trial,[25] 49 patients with HoFH aged >12 years and not on LDL-apheresis, were randomised to evolocumab 420 mg every 4 weeks (n=33) or placebo (n=16) for 12 weeks. A significant 30.9% LDL-C reduction was obtained with evolocumab compared with placebo. The response to evolocumab was related to the severity of the causal mutation. In those patients with one or two defective mutations, LDL-C reduction ranged from 40.8% to 46.9%. On the other hand, no response was observed in one patient with null/null mutations.

In the ODYSSEY HoFH study,[26] 69 patients were randomised to alirocumab 150 mg every 2 weeks (n=45) or placebo (n=24) for 12 weeks. A 26.9% reduction in LDL-C from baseline was observed with alirocumab at Week 12, and the difference with placebo was 35.6% (primary efficacy endpoint). In cases (n=5) with null/null mutations, the response was variable but mostly absent.

The TAUSSIG trial[27] was an open-label, single-arm, non-randomised study that examined the long-term efficacy and safety of evolocumab in patients with HoFH and those with severe HeFH receiving stable LLT including LDL-apheresis (34 cases in HoFH). A 21% reduction in LDL-C levels from baseline was observed at Week 12 and remained constant until Week 216 (24% reduction). There was no difference in the response among patients with or without LDL-apheresis, and three HoFH cases on apheresis discontinued this procedure in the follow-up. Like in Phase III trials, patients with null/null mutations had variable responses that were lower compared to those with defective mutations.

In all trials, the safety and tolerability of PCSK9i were confirmed. No neutralising anti-PCSK9i antibodies have been detected with both evolocumab and alirocumab.

Lomitapide

Lomitapide has been approved by the FDA and the EMA for the treatment of adult patients with HoFH along with a low-fat diet and other LLT or LDL-apheresis. Lomitapide binds to and inhibits the microsomal triglyceride transfer protein (MTP), an enzyme with a key role in the assembly of very-low-density lipoprotein (VLDL) in hepatocytes and chylomicrons in enterocytes. By inhibiting MTP, lomitapide reduces plasma levels of VLDL, LDL, and chylomicrons.[28] Therefore, the effect on lowering LDL-C levels is independent of LDL-R activity. On the other hand, its mechanism of action explains some AEs of lomitapide such as liver steatosis and steatorrhoea.[29]

Lipid-lowering efficacy and safety of lomitapide in treating HoFH has been demonstrated in Phase II and Phase III trials, in registries, and real-world experience reports.[30-34] Patients receiving lomitapide are required to follow a very-low-fat diet (<20%). In the Phase II proof-of-concept trial,[30] six patients without LLT received lomitapide at four different doses every 4 weeks. A dose-dependent reduction in LDL-C levels was observed, reaching 51% with the highest dose of 1 mg/kg. Also, triglycerides and apolipoprotein B (apoB) levels were significantly reduced by 65% and 55%, respectively. The most frequent AEs were gastrointestinal symptoms that were transient, dose-related, and explained mostly by low adherence to diet. An increase in transaminases was observed in four patients and fat accumulation in the liver was highly variable ranging from <10% to >30%. Transaminase and hepatic fat levels returned to baseline levels after the discontinuation of the drug in all patients. No patient withdrew from lomitapide due to an AE.[30]

The Phase III pivotal trial[31] was a long-term, single-arm, open-label trial including 29 patients with HoFH >18 years old with molecular diagnosis. This trial had two phases: Phase I lasted 26 weeks to evaluate the efficacy; while Phase II lasted 52 weeks to evaluate long-term safety. In the efficacy phase, lomitapide was up-titrated every 4 weeks, from 5 mg to 60 mg every day or the maximum tolerated dose. Unlike the Phase II trial, all LLT including LDL-apheresis were maintained during the efficacy phase of this study and could be modified in the safety phase, while keeping the dose of lomitapide, reached in Phase I, stable. The median dose during the trial was 40 mg/day. Intention-to-treat analysis showed a mean 40% reduction in LDL-C levels, which rose to 50% in patients who completed the efficacy phase. LDL-apheresis did not affect efficacy. Four patients discontinued the treatment in Phase I due to AEs.[31] The extension trial showed a mean 45.5% reduction in LDL-C in 17 patients who completed Week 126, which remained constant for a median of 5.1 years (range: 2.1–5.7 years).[32] During this Phase, 74% patients achieved LDL-C levels below 100 mg/dL and 58% patients achieved LDL-C levels below 70 mg/dL.

The Lomitapide Observational Worldwide Evaluation Registry (LOWER),[34] a prospective, non-interventional, multicentre and observational registry, reported data of 187 patients with HoFH with an exposure to treatment for up to 5.9 years. The results of efficacy and safety were consistent with the Phase III study, despite using a lower median dose of lomitapide than in the Phase III trial (10 mg/day). LDL-C reduction was 45.3% at Month 6 and 29.2% at Month 48 in those cases who remained on lomitapide. At any time after initiating treatment, 65.4% patients achieved LDL-C <100 mg/dL and 41.1% patients achieved LDL-C <70 mg/dL. Regarding AEs, no new safety issues were identified in comparison with the Phase III trial. Eighty-six patients (46.5%) experienced AEs leading to a dose reduction, and 43 (23.2%) discontinued treatment because of AEs, with gastrointestinal symptoms (13.5%) and an increase in transaminases (8%) being the most frequent causes. Temporary interruption or dose reduction of lomitapide resulted in the normalisation of transaminase levels and allowed treatment to continue. No patient experienced liver injury that was clinically overt or as assessed on laboratory findings by Hy's law.

The benefit of lomitapide on CV events has not been evaluated. However, a modelling analysis showed a 23% risk reduction in mortality and 15% in major CV events for every 1 mmol/L in LDL-C reduction. Also, a delay of almost 6 years in the time to first event was determined,[35] suggesting that an increase in life expectancy may be expected in these patients if treatment is started at age 18 years. Another post hoc analysis of the Phase III trial showed that almost half of patients with lomitapide reached a LDL-C level below 70 mg/dL after 2 years and fewer major CV events per 1,000 patients during the months of treatment was observed.[36]

Lomitapide has not yet been approved for use in the paediatric population. However, some reports of its use in children (aged 3–16 years), considered 'urgent to treat' because of early ASCVD or insufficient response to conventional treatment, have been recently published.[37] After a median exposure time of 18.2 months and a median dose of 20 mg/day, a median 63.7% reduction in LDL-C levels from baseline to nadir was shown.

Mipomersen

Mipomersen is a second-generation antisense oligonucleotide inhibitor of apoB-100 synthesis. It binds to a target and specific mRNA sequence encoding apoB-100 and activating endoribonuclease H, which reduces apoB-100 synthesis and atherogenic lipoprotein concentration.[38] Mipomersen was approved by the FDA for the management of patients with HoFH based on a HoFH Phase III trial.[39] In this trial, 51 patients aged >12 years on maximum statin dose were allocated to mipomersen (n=34) or placebo (n=17). Mipomersen 200 mg once weekly reduced LDL-C by 24.7% (interquartile range: -31.6–-17.7%) compared to a 3.3% reduction with placebo at Week 26. Other atherogenic lipoproteins such as lipoprotein(a) and triglycerides were also reduced by 31% and 18%, respectively. The most common AEs were injection site reactions, resolving spontaneously in most patients; flu-like symptoms (FLS); and an increase in alanine aminotransferase, which was not always accompanied by an increase in hepatic fat accumulation.[39]

The long-term efficacy and safety of mipomersen in treating HoFH (n=38), with maximally tolerated

LLT, was evaluated after 2 years of follow-up in an open-label trial.[40] The reduction of LDL-C and apoB levels and AEs were consistent with those observed in the Phase III trial. FLS were the principal cause of discontinuation in almost half of the patients. Transaminase elevations and the increase in liver fat occurred in the first year of treatment but trended to return to baseline values during the second year.[40]

Paediatric experience is scarce. A post hoc analysis of seven patients with HoFH aged 12–18 years included in the Phase III trial and in the extension study[41] showed LDL-C reduction of 30.8–62.0% in the three cases with mipomersen, and no changes with the placebo. In the extension trial, three of four patients who were initially on the placebo responded well to mipomersen, with a reduction in LDL-C of 26.5–42.0%. The safety profile was consistent with those seen in other Phase III trials.

Evinacumab

Angiopoietin-like 3 (ANGPTL3) plays a key role in the regulation of lipid metabolism by inhibiting lipoprotein lipase and endothelial lipase. Human genetic studies have shown that patients with loss-of-function variants in the *ANGPTL3* gene have lower levels of LDL-C, triglycerides, and high-density lipoprotein (HDL) cholesterol, and have a lower risk for coronary artery disease (41%) than the general population.[42] Evinacumab is a fully human, monoclonal antibody that works by binding to and blocking the function of this protein. The FDA has recently approved evinacumab-dgnb in patients with HoFH aged 12 years or older as an adjunct to other LLT.

The efficacy and safety of evanicumab in treating patients with HoFH have been evaluated in Phase II and III trials.[43,44] In the Phase II proof-of-concept trial,[43] nine patients with HoFH with stable and intensive LLT, including statins, ezetimibe, LDL-apheresis, PCSK9i, or lomitapide, received 250 mg of evinacumab subcutaneously and then 15 mg/kg through intravenous infusion at Week 2. LDL-C reduction at Week 4 (primary endpoint) was 49% (range: 25–90%). No patient discontinued treatment.

In the Phase III ELIPSE trial,[44] 65 patients receiving the maximum tolerated LLT were randomised to intravenous infusion of 15 mg/kg of evinacumab or a placebo every 4 weeks. A rapid drop in LDL-C was observed at Week 2, which was sustained until Week 24. At this point, patients randomised to evinacumab had a 47.1% reduction in LDL-C compared with an increase in 1.9% in the placebo group. Results were not affected by the type of mutation in *LDLR* gene. No patient discontinued the treatment because of an AE and no deaths occurred. The most frequent AE was FLS. The long-term safety and the effect of evinacumab on CV events have not been established.

NON-PHARMACOLOGICAL LIPID-LOWERING THERAPIES

Liver Transplantation

More than 70% of LDL-R are in the liver; therefore, liver transplantation (LT) is a therapeutic option in patients with HoFH because dysfunctional receptors are replaced by normal receptors from the donor. The first case of a heart–liver transplant was reported in 1984 in a 6-year-old girl with HoFH and recurrent angina pectoris.[45] Her total cholesterol fell from 1,225 mg/dL to 268 mg/dL and the regression of xanthomas occurred early after surgery. A report 2 years after the transplant showed a restoration of LDL-R activity of 60% and LDL-C was reduced by 81%, reaching levels of 184 mg/dL. In this scenario, the addition of lovastatin normalised LDL-C levels.[46] Since then, other cases of patients with HoFH, who underwent liver or heart–liver transplantations, have been reported.[47] The important and significant reduction of LDL-C levels and the regression of xanthomas has been constant; however, the CV benefit is still unclear.[47] Some cases have shown no development or no progression of coronary artery disease, while others have shown a slow regression. On the other hand, aortic valve stenosis may develop despite normalisation of lipoproteins with the transplantation.[48]

Several guidelines consider LT as an exceptional therapeutic option when patients do not respond to other treatments, or when these are contraindicated or are not tolerated.[10,49] The European statement on HoFH[3] recognises that LT is a successful therapeutic strategy for these patients; however, the risks associated with liver transplantation are considerable, and patients require long-term immunosuppressant therapy, thereby replacing one medical condition with

another. Either way, if the possibility of a LT is considered, the decision should be made with the patient and parents or guardians, explaining benefits and potential harms.

Low-Density Lipoprotein-Apheresis

Lipoprotein-apheresis (LA) is a very effective therapeutic option for children and adults with HoFH, especially in severe cases where patients do not respond to conventional lipid-lowering drugs and during pregnancy.[3] The ideal age for starting LA is before aortic root involvement starts, which occurs when an individual is approximately 5–6 years old, and always before age 10 years.[3,12] Ideally, this procedure should be performed every week.

The use of plasmapheresis to treat HoFH was introduced in 1975 and an improvement in survival was demonstrated in the few patients who have undergone this procedure for approximately 8.5 years compared to their siblings who died untreated.[50] The major limitation of plasmapheresis is its non-specificity, removing all proteins from the plasma and reducing HDL. Apheresis was improved to a more selective removal of apoB-containing lipoproteins, with minimal impact on other proteins and HDL. There are several techniques to remove lipoproteins; some separate blood cells, while others use the whole blood. All methods lower LDL-C by approximately 60% in a single procedure. The LA also removes oxidised LDL, inflammatory cytokines, fibrinogen, coagulation factors, and improves endothelial function, to prevent progression of atherosclerosis.[51]

A recent systematic review of 209 patients with HoFH showed a mean LDL-C reduction of 63–71% per session, according to the type of apheresis.[52] This reduction was accompanied by the disappearance or regression of xanthomata in 83% of cases. Surrogate markers of CVD such as coronary artery disease or aortic stenosis showed less progression and, in a few cases, regression of the abnormalities after a median follow-up of 3.8 and 5.4 years, respectively. In patients with no CV events before starting apheresis, 14% developed a clinical event in the follow-up (14%), compared with 48% in patients who had previous CV events.

Recent data from an international registry showed that LA is effective and safe in children.[53] The median percentage of LDL-C reduction per session was 71%, and the LDL-C level was lower in children who were treated with LA twice per week; however, few patients reached an LDL-C of <130 mg/dL. Xanthomas completely disappeared with LA in 45% of cases, and persistent xanthomatosis was inversely correlated with the duration of apheresis.[53] The main AEs reported were hypotension due to bradykinin release, iron deficiency, nausea, abdominal pain, and vascular access problems.[51-53]

Some problems with LA are the need for specialised centres to perform the treatment, often far from patient's home; cost; time consumption; and a worse quality-of-life, affecting long-term adherence and potential CV benefits.

THE AUTHORS´ PERSPECTIVES

HoFH is a serious and devastating genetic condition resulting from mutations in the *LDLR* gene, which produces extremely high plasma LDL-C levels from birth and is associated with an elevated risk of premature CV mortality and morbidity, especially as a result of aortic valve damage and atherosclerotic coronary disease. If left untreated, survival is not expected beyond the third decade of life. Making an early diagnosis and reducing cholesterol levels and the burden of atherosclerosis in the first years of life is critical to reduce the risk of developing coronary events and aortic stenosis.

Patients should be monitored and followed by specialists with experience in the management of this severe and rare disorder. Despite being a monogenic disease, the phenotypic expression is highly variable, according to the molecular defect. In this sense, null allele mutations are associated with a more severe phenotype than defective mutations, although patients still have a high CV risk. Statin and ezetimibe remain the basis of treatment together with a healthy lifestyle; in some countries, without access to new lipid-lowering drugs and LDL-apheresis, they are the only options of treatment. They should be started as early as the second year of life. Nonetheless, the response is limited to the degree of LDL-R activity. PCSK9i, which are available in Europe and the USA, are effective only in cases with defective mutations and are approved for use in treating HoFH in patients aged 12 years and

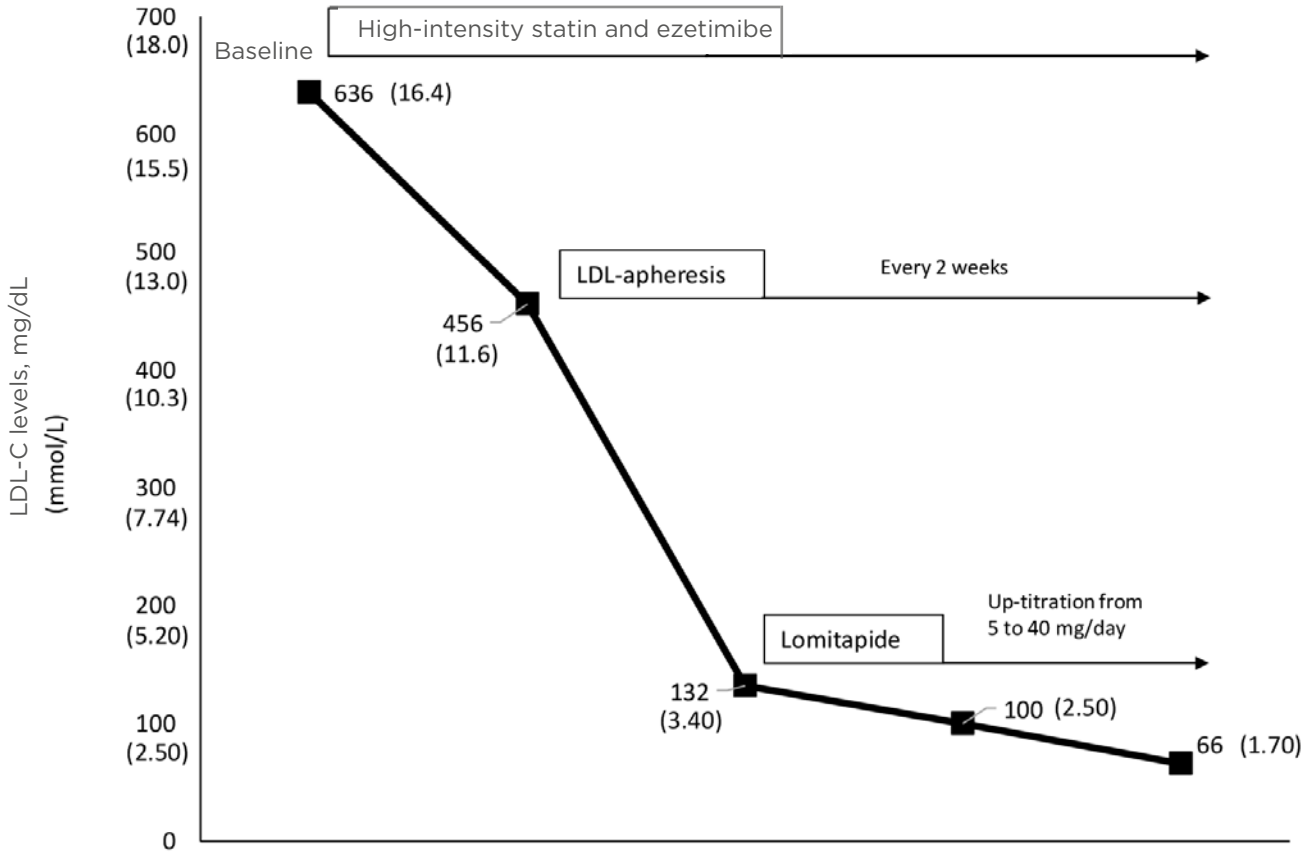

Figure 1: Response to different lipid-lowering therapies in a patient with homozygous familial hypercholesterolaemia carrying a severe mutation (null/null), showing a 90% reduction using high-intensity statin, ezetimibe, lomitapide, and low-density lipoprotein-apheresis.

LDL: low-density lipoprotein; LDL-C: low-density lipoprotein-cholesterol.

older. Lomitapide, mipomersen, and evinacumab significantly reduce LDL-C levels through mechanisms independent of LDL-R and have shown to be effective in patients with HoFH. Experience with these drugs in children is scarce, and some concerns arise regarding long-term safety. Selective LDL-apheresis is a good option to treat children and adults who are refractory to LLT (Figure 1). The procedure should start before age 6 years to avoid aortic valve damage; however, it is a high-cost procedure that requires specialised centres and can compromise the quality-of-life of patients, affecting long-term adherence and CV outcomes.

Despite the availability of different treatments, most patients with HoFH do not reach the LDL-C goals proposed by the guidelines. All efforts should be made to reduce LDL-C levels and the burden of atherosclerosis with available treatments (Figure 2), in combination with the management of other CV risk factors that can be present in patients.

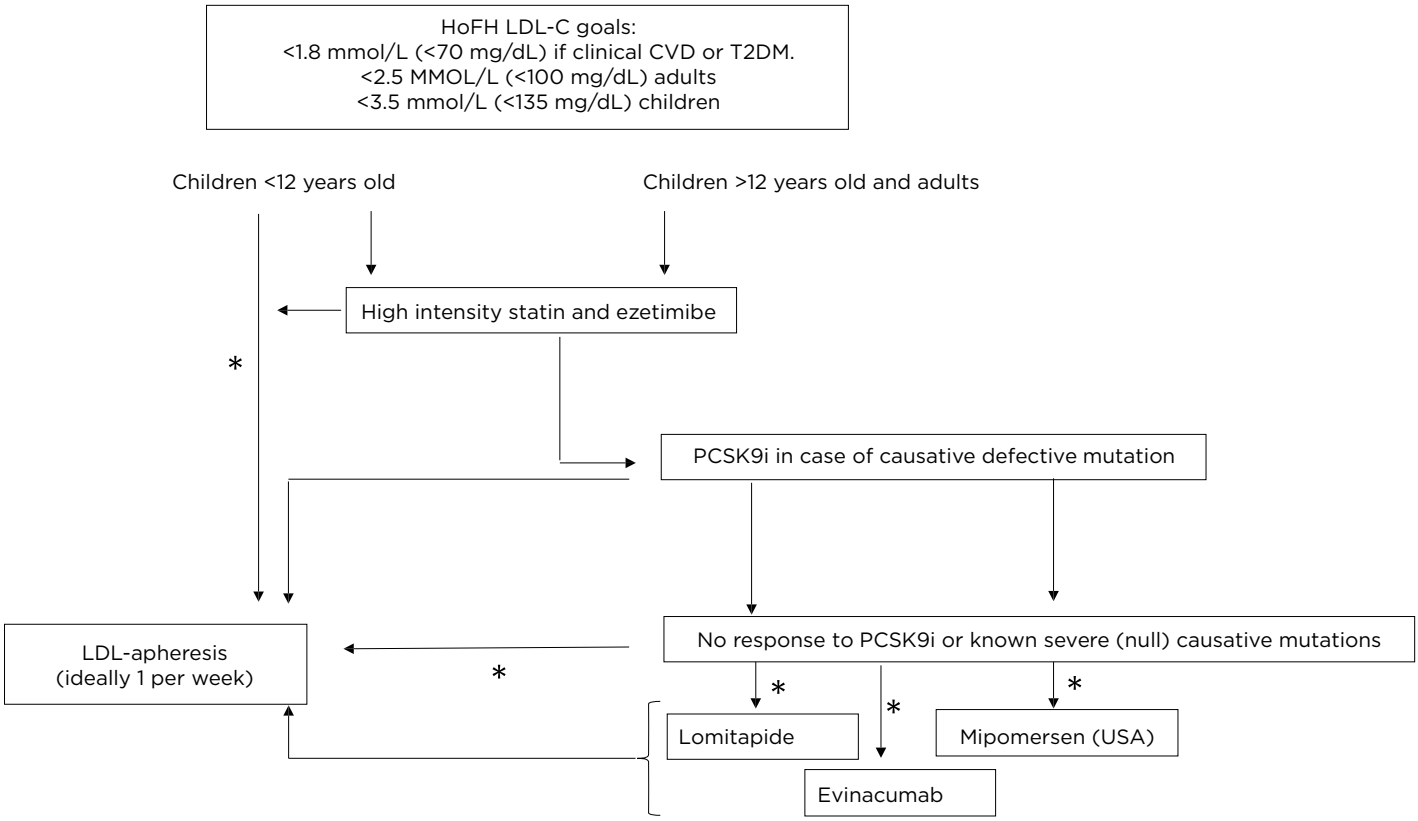

Figure 2: Clinical algorithm for the management of low-density lipoprotein-cholesterol in patients with homozygous familial hypercholesterolaemia.

*Evaluate availability, affordability, accessibility, benefits, and risks.

HoFH: homozygous familial hypercholesterolaemia; LDL: low-density lipoprotein; LDL-C: low-density lipoprotein-cholesterol; PCSK9i: PCSK9 inhibitors.

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Pasteurella multocida Endocarditis with Septic Arthritis: Case Report and Review of the Literature

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Abstract

Background: There is a paucity of evidence regarding optimal management of *Pasteurella* spp. endocarditis. The authors report the first case of *Pasteurella* spp. endocarditis with septic arthritis and review the literature.

Case Description: A 79-year-old patient with significant comorbidities, including prosthetic aortic valve, was admitted with left knee swelling, fever, and confusion, having been scratched by a cat 2-weeks prior. At presentation, there was a metallic click, a Grade 3 pan-systolic murmur and Grade 1 flow murmur audible on auscultation. Blood and synovial fluid cultures both isolated *Pasteurella multocida*, identified by matrix-assisted laser desorption ionisation–time of flight, which was sensitive to penicillin according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST); minimum inhibitory concentration: 0.094). The patient underwent joint washout and received intravenous piperacillin/tazobactam for 3 days before switching to benzylpenicillin once sensitivities were known. Due to continued pyrexia, a transthoracic echocardiogram was obtained, which revealed a small mobile mass on a thickened mitral valve suspicious for a vegetation. On review by the Infective Endocarditis team, conservative management was deemed best, given the presence of comorbidities. Despite requiring further joint washout due to persistent knee pain, the patient was successfully treated with 8 weeks of antibiotic therapy (24 days of benzylpenicillin monotherapy, 2 weeks of benzylpenicillin and ciprofloxacin, and 15 days ciprofloxacin monotherapy).

Discussion: Previous literature reviews report a higher mortality of *Pasteurella* spp. endocarditis when managed without cardiac surgery, thus recommending surgery in all cases. The authors found these to have confounding factors, including inadequate duration of antimicrobials, aortic root abscess, and rapid progression to death. The authors' case of *Pasteurella* spp. endocarditis, complicated by septic arthritis, showed successful therapy without cardiac surgery.

BACKGROUND

Pasteurella multocida (formerly *Pasteurella septica*) is a gram-negative aerobic and facultatively anaerobic coccobacillus. It is non-motile, non-sporing, capsulated, and acts as a commensal or opportunistic pathogen in a variety of animal species. Animal to human transmission occurs occasionally, following a break in tissue leading to transmission of the bacteria from the animal to the human. This can be in the form of bites or scratches. Human infections commonly present as a localised abscess or cellulitis and in severe cases, osteomyelitis. Rare manifestations include meningitis, pericarditis, blood stream infection or infective endocarditis.[1]

P. multocida infections usually respond to penicillin, with tetracyclines, macrolides, and cotrimoxazole as possible alternatives with patients who are allergic to penicillin. Treatment of invasive infections such as infective endocarditis is challenging because of the rarity of the condition and a lack of evidence to inform treatment, especially in patients where a surgical approach is not suitable.

In this report, the authors describe a case of prosthetic valve *P. multocida* infective endocarditis, which was treated conservatively.

CASE PRESENTATION

A 79-year-old patient presented to hospital with history of left knee swelling, pain, increased confusion, poor appetite, and pyrexia. Collateral history obtained from their spouse revealed a cat scratch 2 weeks prior to presentation. Past medical history included metallic aortic valve replacement, tissue mitral valve replacement, a pacemaker, Type 2 diabetes, Alzheimer's dementia, anxiety, breast cancer, and endometrial cancer with hysterectomy (2001). At initial presentation, clinical examination showed an alert and mildly confused patient with a temperature of 37.9°C. There were no peripheral stigmata of infective endocarditis; however, a metallic click, consistent with the replaced aortic valve, a Grade 3 mitral pan-systolic murmur, and Grade 1 aortic flow murmurs were both audible on auscultation. There were no signs of pulmonary oedema or aortic regurgitation. The left knee was swollen, warm to touch with limited flexion and extension of the joint, and a working diagnosis of septic arthritis was made.

Blood cultures were taken, and a gram-negative bacillus was identified on the initial blood culture gram stain. Input from the microbiology team advised that the patient be switched from empirical intravenous (IV) flucloxacillin to IV piperacillin-tazobactam to provide adequate gram-negative cover. On matrix-assisted laser desorption ionisation–time of flight (MALDI-TOF) testing, *P. multocida* was identified from the blood cultures. The patient was taken to theatre for aspiration and washout of the knee joint. The knee joint aspiration produced purulent synovial fluid and *P. multocida* was cultured from synovial and tissue samples sent from the knee (identified using MALDI-TOF). The isolate was found to be susceptible to penicillin on to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) disc sensitivities and subsequent penicillin minimum inhibitory concentration of 0.094 mg/L; therefore, the patient was switched to IV of benzylpenicillin of 1.2 g every 6 hours.

The patient remained pyrexial, despite being on the appropriate antibiotics and joint washout, prompting the arrangement of a transthoracic echocardiogram to look for other sources of deep-seated infection. This showed a small mobile mass on the mitral valve, consistent with a vegetation (Figure 1). The non-microbiology investigations for this case and timeline to diagnosis of suspected endocarditis are summarised in Table 1.

The case was reviewed by the infective endocarditis team and discussed thereafter at the cardiac multidisciplinary team meeting. Due to significant comorbidities, transoesophageal echocardiography and cardiac surgery were deemed not to be suitable in this case. It was agreed that management should be conservative with transthoracic echocardiograms for imaging follow-up.

The patient was treated with benzylpenicillin monotherapy for 24 days, but dosing frequency was increased from 1.2 g every 6 hours to 1.2 g every 4 hours on Day 30 because of persisting pyrexia. Oral ciprofloxacin, 500 mg every

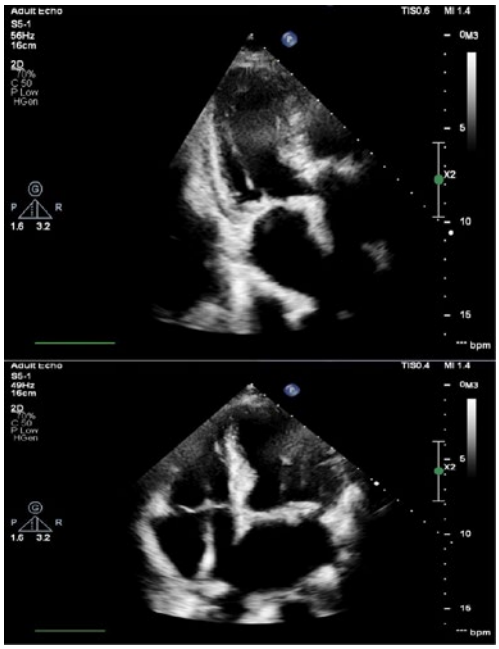

Figure 1: Echocardiogram images showing mitral valve with small mobile mass suspicious of vegetation.

Table 1: Non-microbiology investigations in a patient presenting with *Pasteurella multocida* septic arthritis and infective endocarditis.

Days from time of clinical presentation	Investigation	Results and findings
1	Knee X-ray	Moderate volume joint effusion, several medial tibiofemoral and patellofemoral compartment osteoarthritis with bony remodelling, sclerosis, and osteophytosis No acute fracture
2	Arthroscopic washout of knee	Copious purulent fluid from the joint Washed out and sent to microbiology
3	TTE	Metallic AVR *in situ* Tissue MVR *in situ* Small, mobile mass on MV, consistent with vegetation Preserved LV systolic function Moderate RV systolic impairment. Severe TR Pulmonary hypertension and moderate bi-atrial dilation

AVR: aortic valve replacement; LV: left ventricle; MV: mitral valve; MVR: mitral valve replacement; RV: right ventricle; TR: tricuspid regurgitation; TTE: transthoracic echocardiography.

12 hours, was then added as a second agent based on static raised C-reactive protein and ongoing knee pain (*P. multocida* isolate was susceptible to ciprofloxacin). The patient had a further joint washout 35 days after commencement of IV benzylpenicillin. On Day 40, IV benzylpenicillin was stopped, ciprofloxacin monotherapy continued, and the indwelling vascular long line was replaced with a peripheral cannula. Repeat blood cultures and synovial fluid cultures from this point onwards were negative. The patient continued to make a good recovery following this and was discharged to a nursing home following a 60-day inpatient stay, without need for further orthopaedic or cardiology follow-up. The total duration of effective antibiotics was 56 days (8 weeks). This included 3 days on IV piperacillin-tazobactam, 24 days of IV benzylpenicillin monotherapy, 2 weeks on dual agent therapy of benzylpenicillin and oral ciprofloxacin and 15 days on ciprofloxacin monotherapy.

LITERATURE REVIEW

Method

A local database of all infective endocarditis cases at Leeds Teaching Hospital Trust, UK, was searched for cases involving *Pasteurella* spp. and this case was the only one identified since 1998. A literature search was conducted via PubMed using the search terms '*Pasteurella*' AND 'endocarditis'. Further references were then identified from the references used in these papers. Only case reports written in English, French, or Spanish were included in the analysis, due to the availability of interpretation services. The modified Duke's criteria[2] were applied to these case reports and papers were included if they met the criteria for definite or possible infective endocarditis caused by *Pasteurella* spp.

Results of the Literature Search

The search identified 28 papers and searching by citation identified a further six papers (Table 2). Of these, 32 papers met the authors' inclusion criteria (including case in this article), 31 described cases that met Duke's criteria for a definite diagnosis and one met the criteria for possible diagnosis of *Pasteurella* endocarditis.[11] Of these there were 24 cases of *P. multocida* endocarditis,[3-10,14-19,21-23,31-33] seven cases of non-multocida *Pasteurella* endocarditis,[9,21,26-28,30,31] and one case of undifferentiated Pasteurella endocarditis.[7] Seven cases (21%) had prosthetic valve endocarditis,[6,18-21,27] while 17 patients (53%) had a predisposing cardiac condition[3,6,7,10,13,14,18,19,20,21,23,25,27] and 17 (53%) had other underlying comorbidities reported.[3,5,6,10,14,-16,19,22,26,27,29-31] Twenty-one patients (66%) had documented animal exposure,[3,4,6,8,10,11,13,14,16-20,22,25-29] of which 10 (31%) reported a bite, scratch, or contact of saliva with broken skin.

Fever was the most common presenting symptom, afffecting 31 patients (97%), and 18 patients (56%) presented with systemic upset. Only 16 (50%) had a cardiac murmur on initial presentation but 24 (75%) developed complications, including 5 (16%) with aortic root abscess and 13 (41%) with septic emboli.

The diagnosis of infective endocarditis was missed in seven patients (22%) and diagnosed on representation. Although the majority of patients presented within 7 days of symptom onset, nine patients (28%) presented with a more prolonged history of general malaise, the longest being 3 months.[10]

Of the *Pasteurella* isolates, 19 patients (59%) had susceptibility testing results reported and, of these, only one case reported penicillin resistance.[5] Antibiotic therapy included a β-lactam antibiotic in the majority of cases (24 patients, 75%). Of the four patients who received penicillin or aminopenicillin monotherapy for the duration of treatment, three underwent valve surgery. Only one case had a reported allergy to penicillin and was treated successfully with 6 weeks of IV ceftriaxone.[22]

One patient with *Pasteurella pneumotropica* endocarditis of a native tricuspid valve was successfully treated with 6 weeks of ciprofloxacin monotherapy without surgery.[27] Duration of treatment was reported in 25 cases (78%). Of these cases, 20 patients (80%) received at least 4 weeks of antibiotic therapy, with a median duration of 6 weeks (range: 1 day–20 weeks). Median duration of antibiotic therapy in patients who did not have surgery and survived was 5.8 weeks. Of the patients who did not survive, all apart from one were still on antimicrobial therapy when they died.[5]

Fourteen patients (44%) underwent valve replacement surgery, and one was awaiting surgery. Indications for surgery included aortic root abscess in four patients (33%), severe valvular regurgitation in seven (42%), and persistent fever in three (17%). Five out of seven (71%) cases of prosthetic valve endocarditis were treated successfully, with three achieving cure on antibiotics alone, whilst the other two cases underwent surgical intervention.

Overall mortality rate from these cases was 19% (6/32). The mortality rate with surgery was 7% (1/14) and without surgery was 28% (5/18). Of the cases who died without surgery, two died within 24 hours of presentation and infective endocarditis was diagnosed at post-mortem examination;[13,19] one had an aortic root abscess, a concurrent bacteraemia with *Burkholderia cepacia* and a candidaemia;[6] one received only 2 weeks of antibiotics and then died later from heart failure;[6] and one of the patients died 9 days prior to an operation being performed from severe heart failure.[31] The patient who died after surgery presented with recurrence of infective endocarditis 6 weeks after his initial operation. The patient then represented after 4 months with a pseudomonal mitral and aortic valve endocarditis and died shortly after a further operation.[20] Of the cases who did not have surgery, 14 (88%) had underlying comorbidities compared with eight of the cases (57%) who did have surgery.

DISCUSSION

A literature search found *P. multocida* to be a very rarely reported cause of infective endocarditis, with only 31 cases in the English language literature. The patient the authors' described was the first to be seen in their institution for over 20 years. This patient was also the first to suffer from septic arthritis as a complication. Although the authors' patient was successfully treated without surgery, they needed 8 weeks of antibiotics and the septic arthritis did not respond well to penicillin, requiring the addition of ciprofloxacin.

A recent analysis of *Pasteurella* spp. infective endocarditis cases concluded that all patients should be offered surgical intervention, unless an absolute contraindication exists given the difference in mortality rate.[19] However, they did not include a patient who died 4 months post-valve replacement from early prosthetic valve endocarditis caused by *Pseudomonas aeruginosa*.[20] The analysis was also limited by a lack of consideration of confounding factors such as comorbidity, which would skew the outcome in favour of surgery as surgical cases had a lower incidence of comorbidities. Furthermore, they did not adjust for severity of illness at presentation, nor whether existing guidelines were followed when considering surgical intervention. Therefore, the authors would suggest, as with other bacterial causes of infective endocarditis, that surgical intervention is not indicated in all cases, and should be decided on a case-by-case basis.

It is difficult to draw conclusions from the available literature as to the optimal choice and duration of antimicrobial therapy due to the significant variation in practice and the lack of reporting of antimicrobial susceptibility data or duration of antimicrobials. The authors' patient received an initial 24 days of penicillin monotherapy; however, due to persistent pyrexia and knee pain, the dose frequency of penicillin was increased, and oral ciprofloxacin was added. The patient improved clinically after this, but this could be attributed to a further joint washout. Although the patients required 8 weeks of therapy, this prolonged duration was likely required due to the infected joint. Based on the average duration of antibiotic therapy of 5.8 weeks in patients who survived without surgery, the authors would recommend 6 weeks of antibiotic therapy, depending on clinical response.

In summary, the authors have reported a patient who, despite significant comorbidities, including a pre-disposing cardiac condition, was successfully treated for *P. multocida* endocarditis and concurrent septic arthritis with an 8-week course of single and dual agent therapy of both penicillin and ciprofloxacin, without the need for cardiac surgery. It would be useful for future case reports to clearly document treatment duration as well as the indication for surgery or rationale for not performing surgery in order to build an evidence-base for treatment. The authors suggest that patients with *Pasteurella* spp. endocarditis can be managed according to

Table 2: Summary of case reports with *Pasteurella* spp. endocarditis.

Reference	Age	Sex	Duke's criteria	Valve type	Valve location	Cardiac risk factors	Other comorbiditie	Exposure Hx.	Organism	Isolated from	Resistance	Antibiotic therapy	Surgery	Outcome
Ahlsson et al. (2016)[3]	70	M	D	N	A	AS	Yes	Cat bite	*P. multocida*	BC	Nil	GEN, CTA, CIP, PTA	Yes	S
Al-Ghonaim et al. (2006)[4]	50	M	D	N	A	Nil	No	Sheep contact	*P. multocida*	BC	Nil	PEN, GEN	Yes	S
Branch et al. (2015)[5]	50	M	D	N	M	Nil	Yes	Nil	*P. multocida*	BC	PTA	PTA, CTR, APS	Yes	S
Camou et al. (2005)[6]	79	F	D	N	M	Nil	Yes	Cat bite	*P. multocida*	BC	ND	COA, CIP	No	D
Camou et al. (2005)[6]	81	F	D	Pr	A	mAVr	Yes	Nil	*P. multocida*	BC	ND	CTR, CIP, RIF	No	D
Carter et al. (2021)	79	F	D	N	M	mAVr, MS	Yes	Cat scratch	*P. multocida*	BC, synovial fluid	Nil	PEN, CIP	No	S
Fayad et al. (2003)[7]	48	M	D	N	A	Nil	Yes	Dog contact	*P. multocida*	BC	ND	CXA, GEN	Yes	S
Fayad et al. (2012)[8]	62	M	Po	N	A	Nil	No	Pet dog	*P. haemolytica*	BC	ND	AMOX	Yes	S
Fukumoto et al. (2002)[9]	48	M	D	N	M	MS	No	Pet dog	*P. multocida*	BC	Nil	PEN, CAZ	Yes	S
Genne et al. (1996)[10]	38	F	D	N	A	Nil	Yes	Nil	*P. multocida*	BC	ND	PEN, CTR	No	S
Graf et al. (2007)[11]	36	F	D	N	Pu	Tricuspid morphology to PV	Yes	No	*P. multocida*	BC	Nil	AMP	Yes	S
Gump et al. (1972)[12]	48	M	D	N	?	Heart murmur since childhood	No	Cat bite	*Pasteurella* spp.	BC	Nil	PEN	No	S

Table 2 contined.

Reference	Age	Sex	Duke's criteria	Valve type	Valve location	Cardiac risk factors	Other comorbiditie	Exposure Hx.	Organism	Isolated from	Resistance	Antibiotic therapy	Surgery	Outcome
Hombal et al. (1991)[13]	61	M	D	N	A	Bicuspid AV	Yes	Dog licked leg ulcers	*P. multocida*	BC	ND	GEN, VAN	No	D
Khan et al. (2012)[14]	82	M	D	N	A	Calcification AV	Yes	Pet cat	*P. multocida*	BC	ND	AMP, GEN	No	S
Lehmann et al. (1977)[15]	51	M	D	N	A	Nil	No	Nil	*P. multocida*	BC	Sulphonamides, cephalosporins	PEN G, STREP	Yes	S
Mikaberidz et al. (2013)[16]	60	F	D	N	A	Nil	No	Pet dog and cat	*P. multocida*	BC	Nil	APS	Yes	S
Naba et al. (2008)[17]	88	F	D	N	T	Nil	Yes	Cat bite	*P. multocida*	BC and pus	Nil	PEN CIP	No	S
Nettles et al. (1997)[18]	72	F	D	Pr	A	tAVr	No	Pet cat	*P. multocida*	BC	Nil	PEN, APS	No	S
Porter et al. (2020)[19]	66	F	D	Pr	A	mAVr, ICD, thoracic pseudo-aneurysm	Yes	Pet cat	*P. multocida*	BC	ND	PTA	Yes	S
Reinsch et al. (2008)[20]	66	M	D	Pr	A	AVR for IE	No	Cat bite	*P. multocida*	BC	Nil	AMP	Yes	D
Rosenbach et al. (2001)[21]	78	M	D	Pr	A	tAVr	No	Nil	*P. dagmatis*	BC	ND	CTR	No	S
Salmon et al. (1989)[22]	63	F	D	N	A	Nil	No	Dog contact	*P. multocida*	BC	Nil	DOTE GEN CTR	Yes	S
Satta et al. (2012)[23]	38	M	D	?	RA	Marfan syndrome, mAVr	Yes	Nil	*P. multocida*	BC	ND	CTR	No	S

Table 2 contined.

Reference	Age	Sex	Duke's criteria	Valve type	Valve location	Cardiac risk factors	Other comorbiditie	Exposure Hx.	Organism	Isolated from	Resistance	Antibiotic therapy	Surgery	Outcome
Sauvet et al. (2004)[24]	78	F	D	N	A	Nil	Yes	Nil	*P. multocida*	BC	Nil	AMOX, GEN	?	?
Singh et al. (1983)[25]	50	M	D	N	M	Nil	Yes	Pet dog, sheep	*P. multocida*	BC	Nil	AMP, GEN, PEN	No	S
Sorbello et al. (1993)[26]	55	F	D	N	M	Nil	Yes	Bites from stray cats	*P. dogmatis*	BC	Nil	CTR	No	S
Strahm et al. (2012)[27]	77	M	D	Pr	A	tAVr, previous endocarditis	No	Cat licked broken skin	*Pasturella* (dogmatis-like)	BC	Nil	CTR PEN	Yes	S
Tirmizi et al. (2012)[28]	34	M	D	N	T	VSD	No	Owns fish aquarium	*P. pneumotropica*	BC	ND	CIP	No	S
Vasquez et al. (1998)[29]	65	M	D	N	A	AS	Yes	Dog licked leg ulcers	*P. multocida*	BC	ND	ND	No	D
Yamamoto et al. (1993)[30]	59	M	D	N	M	Previous endocarditis, MR	No	Nil	*P. ureae*	BC	Nil	PTA, GEN, CFH	No	S
Yaneza et al. (1991)[31]	40	M	D	N	A	Nil	No	Nil	*P. haemolytica*	BC	Nil	AMP, GEN, CXA	No	D
Yuji et al. (2015)[32]	50	M	D	N	M	Nil	No	Nil	*P. multocida*	BC	ND	PEN, GEN	Yes	S

A: aortic; AMP: ampicillin; AMOX: amoxicillin; APS: ampicillin/sulbactam; AS: aortic stenosis; BC: blood culture; CAZ: ceftazidime; CFH: cefotiam hexetil hydrochloride; CIP: ciprofloxacin; COA: co-amoxiclav; CTR: ceftriaxone; CXA: cefotaxime; D: definite; DOTE: doxycycline; GEN: gentamicin; M: mitral; mAVR: metallic aortic valve replacement; MS: mitral stenosis; N: native; *P.*: *Pasteurella*; Po: possible; Pr: prosthetic; Pu: pulmonary; PEN: penicillin; PTA: piperacillin/tazobactam; RIF: rifampicin; T: tricuspid; VSD: ventricular septal defect.

available infective endocarditis guidelines, which include the involvement of a dedicated infective endocarditis team, who assess the need for surgical intervention on a case-by-case basis. This adds to the small number of case reports in the literature that describe successful management of *Pasteurella* spp. endocarditis and may help inform other clinicians when they encounter similar cases.

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Risk Factors and Prevention of Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis: An Update

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a diagnostic modality to a therapeutic tool for various biliary and pancreatic diseases. The major reason for this evolution is the risk of post-ERCP pancreatitis (PEP) and the availability of safer non-invasive imaging modalities. PEP is the most common and dreaded complication after ERCP, with significant morbidity and mortality. Several pharmacological therapies and modifications to endoscopic techniques have been evaluated in different clinical settings to prevent PEP; however, except for few, evidence to support the practice of most is poor. Rectal non-steroidal anti-inflammatory drugs, aggressive hydration with lactated Ringer's solution, and prophylactic pancreatic duct stenting are some of the preventive measures strongly recommended by endoscopic societies, although the quality of evidence is low to moderate. Evidence in support of a combination of rectal non-steroidal anti-inflammatory drugs and aggressive hydration is emerging. Despite the recent developments in the prevention strategies, the risk of PEP remains substantial. Therefore, proper risk stratification of patients and the development of better risk mitigation strategies are the need of the hour.

INTRODUCTION

The therapeutic technique of endoscopic retrograde cholangiopancreatography (ERCP) has evolved as a therapeutic endoscopic technique for various benign and malignant conditions of the pancreato-biliary system. Post-ERCP pancreatitis (PEP) is the most common and dreaded complication after ERCP, with significant morbidity and mortality. For the same reason, the use of ERCP for diagnostic indications has virtually diminished with the emergence of safer, non-invasive imaging modalities such as magnetic resonance cholangiopancreatography and endoscopic ultrasound. The incidence of PEP ranges widely between 3.5% and 9.5%, and mortality between 0.1% and 0.7%.[1,2] A recent nationwide study suggested an increasing rate of hospital admission and mortality in the USA (mortality: 2.8% in 2011 and 4.4% in 2017).[3] Since Freeman et al. studied the risk factors of PEP prospectively for the first time in 1996, there have been a plethora of publications over the

past two decades in this field.[4] Risk stratification of patients, based on the number and nature of risk factors, is crucial for proper patient selection before ERCP and for the initiation of appropriate preventive measures in a timely fashion. Although PEP is mild in the majority of the cases, mortalities have been reported and, therefore, prevention is the best strategy to save these patients.[5]

In this review, the authors discuss the definition, severity assessment, risk factors, and prevention of PEP.

DEFINITION AND SEVERITY ASSESSMENT

PEP is defined by the 1991 consensus criteria as new-onset or worsened abdominal pain, with more than three-fold elevation in serum amylase or lipase at more than 24 hours after ERCP, requiring hospital admission or prolongation of a planned admission.[6] Although, this definition is widely accepted, minor variations in the minimum duration of hospital stay have been proposed.[7] Cross-sectional imaging of the pancreas is generally not required to make a diagnosis of PEP; however, imaging is required to grade the severity of pancreatitis, according to the revised Atlanta classification.[8]

The consensus criteria and the lexicon of adverse events proposed by the American Society of Gastrointestinal Endoscopy (ASGE) grade the severity of PEP based on the length of hospital stay.[6,7] In addition, the ASGE lexicon also considers the requirement of intensive care unit admission, radiological or surgical intervention, permanent disability, and death. The revised Atlanta classification appears to be more specific for PEP and stratifies the patients according to the presence of local complications and the duration of organ failure.[8] A recent multicentre study of 387 patients with PEP found that the revised Atlanta criteria, compared with the consensus criteria, had a superior sensitivity, specificity, and positive predictive value in predicting mortality.[9] The length of hospital stay is dependent on multiple factors and may not reflect the severity of the disease, and is often influenced by concomitant diseases or comorbidities.

RISK FACTORS FOR POST-ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY PANCREATITIS

The stratification of patients undergoing ERCP is paramount for implementing appropriate preventive strategies against PEP. Risk factors for PEP may be classified as definite or likely based on the level of evidence in the published literature (Table 1).[5] A patient is considered to be at high-risk for PEP if one definite or two likely patient- or procedure-related risk factors are present. Among the patient-related definite risk factors, including female gender, sphincter of Oddi dysfunction (SOD), previous pancreatitis, and previous PEP, have been shown to be consistently associated with PEP.[12-14] In addition, younger age (<60 years), normal serum bilirubin, and non-dilated common bile duct have been confirmed to be independent risk factors for PEP in prospective multicentre studies.[4,11,15-17]

Table 1: Risk factors for post-endoscopic retrograde cholangiopancreatography pancreatitis.[5,10,11]

Definite	Likely
Patient-related	
Suspected SOD, female sex, previous pancreatitis, previous PEP	Younger age, non-dilated bile duct, normal bilirubin, absence of chronic pancreatitis, end-stage renal disease
Procedure-related	
Difficult cannulation, >1 pancreatic guidewire passages, pancreatic injection	Precut sphincterotomy, pancreatic sphincterotomy, balloon sphincteroplasty, failure to clear bile duct stones, intraductal ultrasound

PEP: post-endoscopic retrograde cholangiopancreatography pancreatitis; SOD: sphincter of Oddi dysfunction.

Difficult cannulation of Vater's papilla and major pancreatic duct (PD) injection are the major procedure-related definite risk factors for PEP.[13,14] Other procedure related risk factors include multiple attempts at cannulation and pancreatic guidewire passage.[18]

Contrast to the popular belief, needle knife precut sphincterotomy is not associated with increased risk of PEP. On the contrary, early precut appears to be protective against PEP in difficult biliary access. Two recent meta-analyses have shown that early precut, compared with persistent cannulation attempts, can significantly decrease the incidence of PEP (relative risk [RR]: 0.29–0.57) in difficult biliary access.[19,20] In selected high-risk cases, primary needle knife fistulotomy appears to reduce the risk of PEP when compared with conventional cannulation methods.[21]

Alternatively, in difficult biliary access, the double guidewire (DGW) technique has been proposed to increase biliary cannulation rates. This technique involves placement of a guidewire deep into the PD, followed by attempts to cannulate the common bile duct using a second guidewire. However, the DGW technique increased the risk of PEP in a recent meta-analysis (RR: 1.98; 95% confidence interval [CI]: 1.14–3.42) and the risk was reduced by concomitant PD stenting.[22]

Although biliary balloon sphincter dilation is a risk factor for PEP,[14] large-balloon dilation and dilation for a longer duration (>3 minutes) could reduce the incidence of PEP as insufficient dilation increases the use of mechanical lithotripsy and puts stress on the papilla during stone removal.[23,24] On the contrary, a recent multicentre, randomised trial concluded that the incidence of PEP increased significantly after dilatating for 300 seconds when compared with dilatating for shorter durations, i.e., 30, 60, and 180 seconds (15% versus 7%, 8%, and 9%).[25] The authors concluded that 30 seconds dilatation time was optimal with regard to the incidence of PEP.

With regard to hospital volume and the experience of the endoscopist, a recent study showed that PEP was more common when the procedure was performed by less experienced endoscopists (<200 procedures) (odds ratio [OR]: 1.630; 95% CI: 1.050–2.531).[26] However, a recent meta-analysis failed to demonstrate a significant difference in the risk of PEP between high- and low-volume endoscopists (<40 /year and >40 /year procedures) or centres (<200 /year and >200 /year procedures), although only three studies included in the analysis reported PEP specifically.[27]

PATHOPHYSIOLOGY

The aetiopathogenesis of PEP is multi-factorial and includes an increase in pancreatic ductal pressure and spasm of the SO, causing mechanical obstruction. A SO spasm may directly result from mechanical trauma or indirectly due to hypersensitive sphincter as in SOD. Irrespective of the underlying cause, these inciting factors ultimately initiate an inappropriate activation of proteolytic enzymes and cytokine release, leading to a vicious inflammatory cycle.

PREVENTION OF POST-ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY PANCREATITIS

Prevention of PEP includes pharmacological, endoscopic, and combined approaches. Since rectal non-steroidal anti-inflammatory drugs (NSAIDs) have opened a new era in this field, the authors discuss the current available preventive strategies pertinent to advances in the last decade.

Wire-Guided Cannulation

There are two main techniques of cannulation: contrast-assisted and wire-guided. Inadvertent contrast injection into the PD is a well-known risk factor for PEP. On the other hand, guidewire-assisted cannulation has been shown to increase the success rates of cannulation and reduce the risk of PEP when compared with the contrast-assisted cannulation technique.[28] In addition, inadvertent guidewire cannulation into the PD may facilitate biliary cannulation by the DGW technique. A prophylactic PD stent should be placed to mitigate the risk of PEP associated with this technique.[29] In expert hands, early use of alternate cannulation techniques like PD stenting and precut sphincterotomy are equally effective in achieving cannulation, as well as reducing

the risk of PEP. In practice, a hybrid technique (guidewire plus contrast) is often utilised where a small volume of contrast guides the path of the guidewire. Although the hybrid technique may facilitate biliary cannulation, the risk of PEP appears to be unchanged when compared with exclusive wire guided cannulation.[30]

The ASGE guidelines recommend that physicians who perform ERCP be facile with procedural techniques that reduce the risk of pancreatitis (i.e., wire-guided cannulation, prophylactic pancreatic duct stenting).[31]

Pharmacological Prevention

Non-steroidal anti-inflammatory drugs

NSAIDs exert their anti-inflammatory action by inhibition of cyclo-oxygenase (COX), especially an inducible form of COX-2. The hypothetical mechanisms of COX-2 inhibition in ameliorating pancreatitis include reduction in prostaglandin synthesis and pancreatic oedema, and suppression of proinflammatory nuclear transcription factor κB.[32] The effectiveness of NSAIDs in preventing PEP is affected by the route and timing of administration.

Among the non-selective COX inhibitors, indomethacin and diclofenac have been extensively studied in recent trials (Table 2). Oral and intramuscular routes of administration have been shown to be ineffective in the prevention of PEP for unclear reasons.[44] In a randomised study including 207 patients, there was no difference in the incidence of PEP between oral diclofenac and placebo groups (16.2% versus 16.7%).[45] In another multicentre, randomised study including 216 patients, the combination of udenafil and aceclofenac failed to reduce the incidence of PEP over placebo.[46] Similar to oral route, prophylactic intramuscular diclofenac has been found to have no preventive effect on PEP.[47] Although, the bioavailability (80–100%) is excellent with both the routes (oral and rectal) and their plasma concentrations peaking at 60–90 minutes, peak plasma concentration is more sustained (>2 hours) and declines slowly after rectal administration compared with oral and intramuscular administration.[48] Sustained plasma concentration after rectal NSAIDs may play a key role in preventing PEP.[49]

In contrast to diclofenac, oral indomethacin is not subject to significant first pass metabolism. Therefore, indomethacin may be effective by oral route, theoretically. However, this hypothesis needs to be substantiated by quality studies. Two meta-analyses that evaluated the optimal timing of administration of rectal NSAIDs (before or after ERCP) have given conflicting results.[50,51]

In a large multicentre trial, rectal indomethacin administration before ERCP, compared with after ERCP, was more effective in reducing the incidence of PEP (6% versus 12% [RR: 0.47; 95% CI: 0.27–0.82]) in high-risk patients.[39] Since the plasma concentration peaks at 90 minutes after rectal administration, the optimal timing of rectal NSAIDs administration may be 90 minutes before ERCP. Nevertheless, the timing of rectal NSAIDs remains an active area for research. In a recent meta-analysis (21 randomised clinical trials [RCT], 6,854 patients), rectal NSAIDs were more effective than placebo in reducing the overall incidence of PEP (risk difference: -0.07; 95% CI: -0.10–-0.04; number needed to be treated [NnT]: 20; p<0.001).[52] Although rectal NSAIDs effectively prevented mild PEP, the effect on moderate-to-severe PEP has not been consistent.[35,39] A recent meta-analysis (19 RCTs, 5,031 patients) confirmed that rectal NSAIDs were associated with significant reduction in the risk of moderate-to-severe PEP.[53] In regard to PEP risk stratification, prophylactic effect of rectal NSAIDs was consistent in the group of patients who are at high-risk;[33,35,36] however, results were not reproducible in those at average (not fulfilling the high-risk criteria) and low-risk.[34,37,41]

Universal prophylaxis using rectal NSAIDs for PEP across all risk groups has been a matter of debate. In a recent multicentre, randomised trial, preprocedural administration of rectal indomethacin in unselected patients reduced the overall occurrence of PEP.[39] In addition, considering the relatively low cost, safety profile, and ease of administration of rectal NSAIDs, it is reasonable to administer rectal NSAIDs in all patients undergoing ERCP. The optimal dose of rectal indomethacin or diclofenac is 100 mg. While increasing the dose does not appear to confer additional benefit,[42] lower doses are ineffective in preventing PEP.[43] Administration of NSAIDs is contraindicated in pregnant women >30 weeks of gestation, in patients with history

Table 2: Randomised controlled trials of rectal non-steroidal anti-inflammatory drugs, conducted between 2010 and 2020 for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis.

Author	NSAID type, dosage, timing at ERCP	Intervention groups (N)	PEP risk population studied	PEP incidence	Incidence of moderate-to-severe PEP	NnT* (p)
Elmunzer, 2012[33]	I: 100 mg, post	I: 295 versus PLA: 307	High (82% SOD)	9.2% versus 16.9%	4.4% versus 8.8%	13.0
Dobronte, 2014[34]	I: 100 mg, pre	I: 347 versus PLA: 318	Unselected	5.8% versus 6.9%	N/A	NS
Patai, 2015[35]	I: 100 mg, pre	I: 270 versus PLA: 269	High (precut)	6.7% versus 13.8%	1.1% versus 1.5%	14.0
Choksi, 2015[36]	I: 100 mg, post	I: 283 versus PLA: 294	High (failed pancreatic stenting)	5.3% versus 34.7%	N/A	3.4
Levenick, 2016[37]	I: 100 mg, during	I: 223 versus PLA: 226	Average (70%)	7.2% versus 4.9%	0.0% versus 0.8%	NS
Mansour, 2016[38]	N: 500 mg, pre	N: 162 versus PLA: 162	Unselected	7.4% versus 17.0%	10.0% versus 25.0%	10.4
Luo, 2016[39]	I: 100 mg, pre in unselected and post in high-risk group	I (unselected): 1,297 versus I (high-risk): 1,303	Unselected	4.0% versus 8.0%	1.0% versus 2.0%	25.0
			High	6.0% versus 12.0%	1.0% versus 2.0%	16.6
Mohammad Alizadeh, 2017[40]	D: 100 mg, pre; I: 100 mg, pre; N: 500 mg, pre	D: 124 versus I: 122 versus N: 126	Unselected	4.0% versus 5.8% versus 15.9%	2.4% versus 3.4% versus 10.3%	D: 8.4; I: 10
Hauser, 2017[41]	D: 100 mg, pre	D: 129 versus ceftazidime: 143	Unselected	8.5% versus 14.7%	1.5% versus 3.5%	NS
Fogel, 2020[42]	I: 100 mg and 200 mg, post	I (100 mg): 515 versus I (200 mg): 522	High	15.0% versus 12.0%	5.0% versus 5.0%	NS
Katoh, 2020[43]	D: 50 mg, pre	D: 147 versus PLA: 150	Unselected	5.4% versus 3.3%	0.7% versus 0.6%	NS

Only trials with >200 patients were included.

*Value reported only when p<0.05.

D: diclofenac; ERCP: endoscopic retrograde cholangiopancreatography; I: indomethacin; N: naproxen; NSAID: non-steroidal anti-inflammatory drug; PEP: post-ERCP pancreatitis; PLA, placebo; post: after ERCP; pre: before ERCP; N/A: not available; NnT: number needed to be treated; NS: non-significant: SOD: sphincter of Oddi dysfunction.

of Stevens–Johnson syndrome, and in those with impaired renal function, particularly taking antihypertensive drugs.[5]

The European Society of Gastrointestinal Endoscopy (ESGE) guideline recommends routine rectal administration of 100 mg of diclofenac or indomethacin immediately before ERCP in all patients without contraindications to NSAID administration (strong recommendation, moderate quality evidence).[5] The ASGE guidelines recommend rectal NSAIDs in high-risk individuals (moderate evidence).[31] In average-risk individuals, rectal indomethacin may reduce the risk and severity of PEP (low quality evidence).

Sublingual nitrates

Nitrate is a smooth muscle relaxant and is believed to prevent PEP by inhibiting SO spasm

and increasing pancreatic parenchymal blood flow. The prophylactic role of nitrates was confirmed in a meta-analysis (12 RCTs, 2,649 patients). Although, glyceryl trinitrate (GTN) significantly reduced the overall incidence of PEP (RR: 0.70; 95% CI: 0.52–0.87) the incidence of moderate-to-severe PEP was not affected. Subgroup analysis revealed that sublingual route of GTN administration was more effective than transdermal and topical routes in preventing PEP, particularly in those who are at high-risk.[54] More recently, the effect of combination of rectal NSAIDs (indomethacin or diclofenac) and sublingual isosorbide dinitrate (5 mg) was evaluated in two RCTs that largely involved patients who were at high-risk (70–80%). The combination therapy administered before ERCP was superior to rectal NSAIDs alone in preventing PEP (NnT: 12–26).[55,56] Transient hypotension was observed in up to 8% of patients in the combination group.[56] Sublingual nitrates for the prevention of PEP should be considered before ERCP in patients who are at high-risk, in whom rectal NSAIDs and aggressive hydration are contraindicated.

The ESGE suggests the administration of 5 mg sublingual GNT before ERCP in patients with a contraindication to NSAIDs or to aggressive hydration for the prevention of PEP (weak recommendation, moderate evidence).[5]

Somatostatin and protease inhibitors

Somatostatin and protease inhibitors theoretically prevent PEP by inhibiting the activation of pancreatic proteolytic enzymes. Somatostatin, when administered as a long-term infusion (0.25 mg/hour, intravenous injection for ≥10 hours), initiated 30 minutes–1 hour before ERCP, was found to be superior to short-term (≤4 hours), or bolus injection in reducing the overall incidence of PEP. However, in a recent meta-analysis (15 RCT, 4,943 patients), the risk reduction was marginal (OR: 0.68; 95% CI: 0.47–0.98) compared with placebo, and the effect was largely limited to patients who are at high-risk (OR: 0.54; 95% CI: 0.34–0.86).[57]

Nafamostat, a potent protease inhibitor, is widely used in the Eastern countries for the prevention of PEP. Although nafamostat reduced the overall risk of PEP in two meta-analyses, requirement of intravenous infusion (for at least 6 hours), high cost, and the lack of benefit in patients who are at high-risk preclude its routine application in clinical practice.[58,59] In a recent multicentre, randomised trial, nafamostat was not effective in preventing PEP, regardless of the timing of administration.[60] Octreotide (somatostatin analogue) and less potent protease inhibitors such as gabexate and ulinastatin were found to be ineffective in preventing PEP.[58,61]

The ESGE has no recommendation about the use of somatostatin and does not recommend protease inhibitors for PEP prophylaxis (strong recommendation, moderate evidence).[5]

Aggressive Intravenous Hydration

Intravenous fluid resuscitation using lactated Ringer's (LR) solution is the mainstay of treatment in the initial phases of acute pancreatitis, irrespective of the aetiology. Aggressive peri-ERCP hydration prevents haemoconcentration and restores pancreatic microcirculation, thereby minimising the risk of pancreatitis and its subsequent complications. Aggressive hydration with LR solution, compared with standard hydration, has been associated with lower incidence of PEP and moderate-to-severe PEP (NNT: 6–18) in groups of patients who are average- to high-risk[62-64] (Table 3). A recent RCT (395 patients) reported that aggressive hydration with LR solution, but not with normal saline, significantly reduced the incidence of PEP compared with standard hydration.[65] Henceforth, the protective effect of hydration against PEP may be specific to type and volume of the fluid. The total periprocedural fluid volume administered in aggressive hydration regimens is 35–45 mL/kg over 8 hours in contrast to 12–15 ml/kg in standard regimens. Adverse events due to fluid overload is observed in 1–2% of patients receiving aggressive hydration and the risk increases in older patients due to undiagnosed cardiac or renal comorbidities.[65] The effect of combining aggressive hydration with rectal NSAIDs is not clear. Two out of three RCTs that evaluated the combination of aggressive hydration and rectal NSAIDs found that the combination was superior to rectal NSAIDs or hydration alone in reducing the overall incidence of PEP.[66,68,69] Aggressive hydration with a LR solution should be considered in patients who are at high-risk in combination with rectal

Table 3: Randomised controlled trials of aggressive hydration, with or without rectal non-steroidal anti-inflammatory drugs for the prevention of post- endoscopic retrograde cholangiopancreatography pancreatitis.

Author	Intervention groups (N)	PEP risk population studied	PEP incidence	Incidence of moderate-to-severe PEP	NnT* (p)	Incidence of fluid overload
Buxbaum, 2014[62]	LR_1: 39 versus LR_{SD}: 23	Unselected	0.0% versus 17.0%	N/A	5.9	0% versus 0%
Shaygan-Nejad, 2015[64]	LR_1: 75 versus LR_{SD}: 75	Unselected	5.3% versus 22.7%	N/A	5.7	0% versus 0%
Choi, 2017[63]	LR_2: 255 versus LR_{SD}: 255	Unselected	4.3% versus 9.8%	0.4% versus 2%	18	0.4% versus 0.0%
Park, 2018[65]	LR_1: 132 versus NS_1: 134 versus LR_{SD}: 129	Average to high	3.0% versus 6.7% versus 11.6%	1.5% versus 0.7% versus 0.8%	LR_1: 11.6; NS_1: 20.4	0.7% versus 2.2% versus 0.0%
Mok, 2017[66]	LR_3 plus I: 48 versus LR_3 plus PLA: 48 versus NS_2 plus I: 48 versus NS_2 plus PLA: 48	High	6.0% versus 19.0% versus 13.0% versus 21.0%	2.0% versus 0.0% versus 2.0% versus 0.0%	LR_3 plus I: 6.6	N/A
Masjedizadeh, 2017[67]	LR_4: 62 versus I: 62 versus PLA: 62	Unselected	12.9% versus 25.8% versus 32.3%	N/A	5.1	N/A
Hosseini, 2016[68]	NS_2 and I: 100 versus NS_2: 100 versus I: 101 versus PLA: 105	Unselected	0.0% versus 10.0% versus 11.0% versus 16.2%	N/A	NS_2: 6.2	N/A
Hajalikhani, 2018[69]	LR_1 and D: 107 versus LR_{SD} plus D: 112	Unselected	0.9% versus 2.7%	N/A	NS	N/A

*Value reported only when the p=<0.05.

LR_1: 3 ml/kg/hour during ERCP, 20 ml/kg bolus, and 3 ml/kg/hour for 8 hours after.

LR_2: 10 ml/kg bolus before ERCP, 3 ml/kg/hour during and for 8 hours after, and 10 ml/kg bolus after ERCP.

LR_3: 1 litre bolus over 30 minutes before ERCP.

LR_4: 20 ml/kg bolus and 3 ml/kg/hour for 8 hours after ERCP.

LR_{SD}: 1.5 ml/kg/hour during ERCP and for 8 hours after.

NS_1: 3 ml/kg/hour during ERCP, 20 ml/kg bolus, and 3 ml/kg/hour for 8 hours after.

NS_2: 1 litre before ERCP, 2 litres during, 16 litres after ERCP.

D: rectal diclofenac; ERCP: endoscopic retrograde cholangiopancreatography; I: rectal indomethacin; LR_{SD}: lactated Ringer's solution, standard hydration regimen; LR_{1-4}: lactated Ringer's solution, aggressive hydrogen regimens; N/A: not available; NnT: number needed to be treated; NS: non-significant; $NS_{1,2}$: normal saline solution, aggressive hydration regimens; PEP: post-ERCP pancreatitis; PLA: placebo.

NSAIDs, or in those with contraindications to NSAIDs for prevention of PEP.

The ESGE recommends aggressive hydration with a LR solution (3 mL/kg/hour during ERCP, 20 mL/kg bolus after ERCP, and 3 mL/kg/hour for 8 hours after ERCP) in patients with contraindication to NSAIDs provided that they are not at risk of fluid overload and a prophylactic PD stent is not placed (strong recommendation, moderate evidence).[5] The ASGE guidelines suggest periprocedural intravenous hydration with lactated ringers, when feasible, to decrease the risk of PEP (very low quality of evidence).[31]

Prophylactic Pancreatic Duct Stenting

PD stenting using small calibre plastic stents reduces the risk of PEP by relieving the obstruction at the level of ampulla of Vater. Recent meta-analyses reported a significant reduction in the overall incidence of PEP in patient groups who are unselected (OR: 0.21–0.25) and at high-risk (OR: 0.27–0.41), undergoing prophylactic pancreatic stenting compared with no stenting (NNT: 5–14).[70,71]

In addition, prophylactic pancreatic stenting markedly decreased the occurrence of moderate-to-severe PEP.[72,73] The majority of trials of prophylactic pancreatic stenting in the rectal NSAIDs era (after 2010) have been carried out in patients who are at high-risk (Table 4). Given the high efficacy rate of rectal NSAIDs in preventing PEP, prophylactic pancreatic stenting should be limited to patients who become high-risk for PEP during ERCP, particularly in instances such as repeated inadvertent guidewire insertion into the PD and during the DGW technique of biliary cannulation.[74] On the contrary, the risk of PEP increases after failed attempts of pancreatic stenting.[80] The combination of rectal NSAIDs and pancreatic stenting have not been shown to be superior to either approach alone.[79,81]

In regard to the diameter and length of pancreatic stents, larger (5 Fr) and shorter (3 cm) stents are more efficacious than smaller (3 Fr) and longer (5 cm) stents in preventing PEP.[75,78] Besides, stents with pigtail on the duodenal side and unflanged stents are preferred to prevent intraductal migration and to facilitate spontaneous elimination, respectively. A pancreatic stent should stay in place for at least 24 hours, since immediate removal of the stent after ERCP provides no protection against PEP.[77] The majority of the small calibre pancreatic stents pass spontaneously within 4 weeks.

The position of the stent should be evaluated at 5–10 days of placement, using an abdominal X-ray, and should be removed endoscopically if retained. It is important to remove retained pancreatic stents in a timely fashion in order to reduce stent-induced ductal changes, including strictures.

The ESGE recommends prophylactic PD stenting in selected patients who are at high-risk for PEP (inadvertent guidewire insertion, opacification of the PD, or DGW calculation [strong recommendation, moderate evidence]).[5] The ASGE recommend PD stenting to reduce the incidence and severity of PEP in individuals who are at high-risk.[31]

Topical Epinephrine Spray

Topical epinephrine spray over the papilla has been proposed to prevent PEP by reducing papillary oedema and PD outflow obstruction. Although initial reports were encouraging,[82,83] two recent multicentre RCTs found that the combination of rectal indomethacin and topical spraying of epinephrine, compared with rectal indomethacin alone, did not reduce the incidence of PEP;[84,85] indeed, one of the trials was prematurely terminated as the combination strategy increased the risk of PEP.[85]

The ESGE does not recommend topically administered epinephrine onto the papilla for PEP prophylaxis (strong recommendation, moderate evidence).[5]

Combined Prophylaxis

Several preventive strategies have been conclusively proven to be useful in the prevention of PEP. Nevertheless, the incidence of PEP refuses to reach an absolute zero. Since the mechanism of PEP prevention may be different among various methods, it seems prudent to combine different preventive strategies to optimise the outcomes. In this regard, the combination of rectal indomethacin and topical epinephrine have not been found to further reduce the risk of PEP when compared with rectal indomethacin alone.[86] On the contrary, the combination was found to increase the risk of PEP over indomethacin alone in one randomised study.[85] The proposed hypothesis for this paradox is reduction in the local concentration of indomethacin due to vasoconstriction induced by epinephrine, and possible activation of phospholipase A2, thereby antagonising the effect of indomethacin.

Another multicentre, randomised trial compared the effect of combined prophylaxis with aggressive hydration and rectal NSAIDs versus NSAIDs alone.[87] There was no difference in the incidence of PEP between both the groups (8% combined versus 9% rectal NSAIDs). In tune with these studies, the combination of rectal NSAIDs and a PD stent was not superior to

Table 4: Randomised controlled trials of prophylactic pancreatic duct stenting, with or without rectal non-steroidal anti-inflammatory drugs, conducted between 2010 and 2020 for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis.

Author	Pancreatic stent size	Intervention groups (N)	PEP risk population studied	PEP incidence	Incidence of moderate-to-severe PEP	NnT* (p)
Ito, 2010[74]	5 Fr, 4 cm, SPT, unflanged	PS: 35 versus no PS: 35	High (pancreatic guidewire for biliary cannulation)	2.9% versus 23.0%	N/A	5.0
Zolotarevsky, 2011[75]	3 Fr, 6 cm; 5 Fr, 5 cm	3 Fr stent: 40 versus 5 Fr stent: 38	High	17.5% versus 10.5%	12.5% versus 7.9%	NS
Sofuni, 2011[73]	5 Fr, 3 cm, straight, unflanged	PS: 213 versus no PS: 213	High	7.9% versus 15.2%	1.9% versus 4.2%	13.7
Kawaguchi, 2012[76]	5 Fr, 3 cm, straight, unflanged	PS: 60 versus no PS: 60	High	1.7% versus 13.3%	0.0% versus 0.0%	8.6
Lee, 2012[72]	3 Fr, 4, 6, or 8 cm, SPT, unflanged	PS: 50 versus no PS: 51	High (difficult biliary access)	12.0% versus 29.4%	2.0% versus 5.9%	5.7
Cha, 2013[77]	5 or 7 Fr straight; or SPT, flanged	PS for 10 days: 46 versus immediate PS removal: 47	High (precut)	4.3% versus 21.3%	0.0% versus 12.7%	5.9
Fujisawa, 2016[78]	5 Fr, 3 cm; or 5 cm, unflanged, straight	PS 3 cm: 98 versus PS 5 cm: 102	Unselected	2.0% versus 8.8%	0.0% versus 1.0%	14.7
Sotoudehmanesh, 2019[79]	5 Fr, 4 cm, SPT	PP and PS: 207 versus PP only: 207	High	12.6% versus 15.9%	1.9% versus 2.9%	NS

*Value reported only when the p=<0.05.

Rectal indomethacin: 100 mg.

Sublingual isosorbide dinitrate: 5 mg.

Lactated Ringer's solution: 6 ml/kg/hour during ERCP, 20 ml/kg bolus, and 3 ml/kg/hour for 8 hours after.

ERCP: endoscopic retrograde cholangiopancreatography; N/A: not available; NnT: number needed to be treated; NS: non-significant; PEP: post-ERCP pancreatitis; PP: pharmacological prophylaxis; PS: pancreatic stent; SPT: single pigtail stent.

either approach alone in a systematic review and network meta-analysis.[81]

In contrast to the non-superior results of combined prophylaxis in the aforementioned studies, the combination of rectal diclofenac and sublingual isosorbide dinitrate was found to be superior to rectal diclofenac alone in preventing PEP in a recent multicentre study (5.6% combined versus 9.5% rectal diclofenac).[54] Barring this study, there is limited data to support the role of combined prophylaxis in preventing PEP.

PUTTING IT ALL TOGETHER

The risk stratification of patients into low- and high-risk types enables the physician to plan and implement preventive strategies for PEP. However, the absence of risk factors does not guarantee the complete avoidance of PEP.

Therefore, universal prophylaxis is recommended by most experts.

The cornerstone of PEP prophylaxis includes rectal NSAIDs, prophylactic PD stenting, and aggressive hydration using LR. These preventive modalities have stood the test of time and the evidence of their efficacy has been reproduced in multiple quality studies. The evidence of combination strategies (stent plus NSAIDs or LR) appear appealing due to different mechanisms of action. However, quality evidence is lacking regarding the superiority of the combination approach versus rectal NSAIDs alone. Nevertheless, planned or unplanned use of combination strategies is not uncommon in routine clinical practice.

In the authors' unit, rectal NSAIDs are administered in unselected patients who undergo ERCP. Aggressive hydration is initiated in high-risk patients unless contraindicated. In selected patients who are at high-risk, especially those with repeated (>1) inadvertent insertion of a guidewire into the PD and those with contraindications to aggressive hydration and rectal NSAIDs, a prophylactic pancreatic stent is placed to prevent PEP as well as facilitate biliary cannulation. It is important to note that overzealous attempts at cannulation and deep access of the PD with a guidewire may be counterproductive and should be avoided. Once the guidewire is in the PD, the authors perform no more than two gentle attempts for deep PD access.

Post-ERCP, the authors continue with intravenous hydration with RL. Finally, preventive strategies for PEP are not fool-proof and, therefore, vigilance is required after ERCP as well. In cases with clinical suspicion of PEP, the authors prefer to restart aggressive hydration, pending the results of pancreatic enzyme assays.

SUMMARY

ERCP has been the cornerstone of treatment for multiple biliary and pancreatic diseases. The risk of PEP has pushed the utilisation of ERCP predominantly for therapeutic purposes. Despite the recent advances in this field, it may be difficult to predict the severity of pancreatitis. Consequently, it may be best to prevent PEP by using one or more preventive strategies.

Several preventive methods have been rigorously evaluated over the last decade and appear to be effective in preventing PEP. The frontrunners among these include rectal NSAIDs, prophylactic pancreatic stenting, and aggressive hydration using a LR solution.

The strategy of combining two preventive strategies appears logical, but lacks quality evidence. So far, combining rectal NSAIDs with topical epinephrine spray or aggressive hydration has not been found to be superior to NSAIDs alone.

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The Safety of Medications During Pregnancy and Lactation in Patients with Inflammatory Rheumatic Diseases

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Abstract

The advances in treatments, including disease-modifying anti-rheumatic drugs and biologic agents, have significantly improved the management of inflammatory rheumatic diseases, allowing females with severe disease to become pregnant and lactate, previously considered as prohibited. Maintaining low disease activity with medications known to be safe from pre-conception to post-partum is a key point in reducing adverse pregnancy outcomes. Numerous observational and case studies have provided a growing amount of evidence on the use of safe anti-rheumatic medications in patients during pregnancy and lactation. Based on this information, this review discusses the safety of medications for patients with inflammatory rheumatic diseases during pregnancy and lactation. Among these, hydroxychloroquine, sulfasalazine, azathioprine, low-dose glucocorticoids, and low-dose aspirin are considered compatible with pregnancy, while methotrexate, cyclophosphamide, mycophenolate mofetil, and leflunomide are contraindicated. Non-steroidal anti-inflammatory drugs are only recommended for use early in pregnancy, as they are reported to cause rare but serious kidney problems in the fetus after 20 weeks or later. Cyclosporin, tacrolimus, and anti-TNF agents can be continued throughout pregnancy if the benefit is greater than the potential risk for the individual patient. Physicians should carefully weigh the risks and benefits of medications in patients with inflammatory rheumatic diseases considering pregnancy.

INTRODUCTION

The majority of inflammatory rheumatic diseases (IRDs) affect females more frequently and many have peaks in their childbearing age.[1] Pregnancy can influence underlying disease activity by inducing a variety of changes in the hormone levels, type of immune responses, inflammatory cytokine signals, and interactions of molecular pathways.[2] These changes may lead to an increased risk of disease flare during pregnancy and post-partum periods in IRDs.[3] Females with IRDs hoping to conceive may have to consider

the combination of worsening pregnancy by disease, disease flare by pregnancy, and the safety of medications during pregnancy and lactation.[3] Therefore, pregnancy and lactation in fertile females with IRDs are always challenging.

Notably, over the past decades, significant improvements in the management of pregnancy have made it possible to maintain pregnant females with quiescent disease through safe medications. However, the actual adherence is known to be low, as previous studies in pregnant females with chronic diseases reported that approximately 40% of females do not adhere to their medications because of negative beliefs.[4] In this regard, educational intervention by physicians is needed to reinforce the positive beliefs that appropriate medications can reduce adverse maternal and fetal outcomes. Physicians should be aware of professional and accurate information to determine the optimal timing of pregnancy, considering the potential benefits and risks of medications. In this article, the authors discuss the effects of commonly used anti-rheumatic medications on pregnancy and lactation and provide guidelines for the safe use of these medications (Table 1).

ANTI-RHEUMATIC MEDICATIONS IN PREGNANCY AND LACTATION

Non-steroidal Anti-inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly prescribed medication and are often used to treat fever, pain, and inflammation and can be easily available over the counter. Most experts agree that the traditional NSAIDs are probably safe to use in small to medium doses during the first trimester.[5] While the majority believed that safety would be maintained throughout the second trimester, a warning recently issued by the U.S. Food and Drug Administration (FDA) added to the risk of NSAIDs in the second trimester. In October 2020, the FDA announced that the use of NSAIDs after 20 weeks of pregnancy increases the potential risk of fetal renal dysfunction, oligohydramnios, and neonatal renal impairment.[6] In the third trimester, all NSAIDs are contraindicated as they have been linked with an increased risk of a premature closure of the ductus arteriosus and inhibition of labour.[7,8] Moreover, the patients planning for pregnancy also need to avoid or reduce the use of NSAIDs, as they have been shown to significantly reduce fertility rates by inhibiting ovulation and reducing progesterone levels.[9] While cyclogenase-2 (COX-2) inhibitors may potentially have the same side effects as other NSAIDs, they can be considered higher risk for pregnant females because one study showed that COX-2 inhibitor exposure increases musculoskeletal malformations.[10]

The majority of the NSAIDs are proven safe during lactation because they are poorly transferred to milk, and safety in children has been well studied; however, there are some reports of increased risk of jaundice and kernicterus.[11,12] It is recommended to use relatively proven safe medications (i.e., ibuprofen) with extremely low levels in breastmilk and a short half-life.[13] The data on the lactation of COX-2 inhibitors are limited.

Corticosteroids

Corticosteroids are used to treat a wide range of IRDs, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory myopathy, and other connective tissue diseases, and are often necessary to control the activity of the disease during pregnancy. They are considered the first-line therapy for acute flares throughout pregnancy because of a rapid onset of action. Important to recognise is that the types of corticosteroids vary depending on whether the treatment target is the mother or the fetus. Corticosteroid treatment for mothers requires short-acting agents (prednisone, prednisolone, and methylprednisolone), and 90% is metabolised by the placental enzyme 11β-dehydrogenase.[14] If corticosteroid treatment is needed for the fetus, dexamethasone and betamethasone, which have the ability to cross the placenta from the mother to fetus, should be chosen. Corticosteroids need to be delivered to the fetus to prevent complete congenital heart block in neonatal lupus syndrome and induce lung maturity in preterm labour.[15,16]

Although corticosteroids are generally considered as safe medications during pregnancy, side effects can occur in both the mother and fetus. In terms of maternal complications of corticosteroids, pregnancy-specific complications such as pre-eclampsia, gestational diabetes, and premature rupture of membranes may occur.[17]

Table 1: Recommendations of anti-rheumatic medications in females during pregnancy and lactation.

Medication	Pre-conception	Pregnancy	Lactation
NSAIDs	Low risk (discontinue in females who are having difficulty with conceiving)	Discontinue before 20 weeks	Low risk (ibuprofen is preferred)
Corticosteroids	Low risk	Low risk	Low risk (breastfeeding recommended 4 hours after taking doses of >20 mg)
LMWH	Low risk	Low risk	Low risk
Low-dose aspirin	Low risk	Low risk (discontinue at 36 weeks)	Low risk
Hydroxychloroquine	Low risk	Low risk	Low risk
Sulfasalazine	Low risk	Low risk	Low risk
Azathioprine	Low risk	Low risk	Low risk
Methotrexate	High risk (stop 3 months prior to conception)	High risk	High risk
Tacrolimus/cyclosporin	Low risk	Low risk	Low risk
Cyclophosphamide	High risk	High risk	High risk
Mycophenolate mofetil	High risk (stop 6 weeks prior to conception)	High risk	High risk
Leflunomide	High risk (cholestyramine wash-out until plasma levels of LEF are undetectable)	High risk	High risk
Anti-TNF agents			
Certolizumab pegol	Low risk	Low risk	Low risk
Etanercept Infliximab Adalimumab Golimumab	Low risk	Low risk (may be safe to stop in the late second or early third trimester in stable disease)	Low risk
Rituximab	High risk	High risk (can use in life-threatening disease)	Low risk
Other biologic agents			
Abatacept Tocilizumab Belimumab Secukinumab Ustekinumab Tofacitinib Baricitinib	Inadequate information		

LEF: Leflunomide; LMWH: low-molecular-weight heparin; NSAIDs: non-steroidal anti-inflammatory drugs.

Several studies have shown an increased incidence of cleft palate and intrauterine growth retardation following corticosteroid therapy.[18] Given the potential risk of complications, it is preferable to keep the corticosteroid dose below 5–10 mg/day.[19]

Prednisone and prednisolone pass into breastmilk in small quantities and are safe medications during lactation. Up to 20 mg of maternal prednisolone is not expected to cause any adverse effects on breastfed infants. For mothers taking high-dose corticosteroids, it is advised to breastfeed 4 hours after taking them to minimise drug exposure.[20] There are no data available on the use of dexamethasone or betamethasone during lactation.

Antiplatelet and Anticoagulant Agents

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterised by recurrent vascular thrombosis or fetal loss in the presence of antiphospholipid antibodies (aPL). Without treatment, pregnancy complications increase to 90%; however, it is widely accepted that the miscarriage rate can be greatly improved through anticoagulation treatment.[21] The standard anticoagulation treatment for APS is lifelong anticoagulation with warfarin or an alternative vitamin K antagonist. In particular, since pregnancy is related to a hypercoagulable state, females with APS need careful attention throughout the pregnancy and post-partum period. Notably, warfarin is a teratogen that can cross the placenta and should be avoided between 6 and 12 weeks of gestation.[22] Patients with APS undergoing warfarin treatment are recommended to confirm pregnancy 6 weeks before the conversion of anticoagulation from warfarin to a combination of low-molecular-weight heparin (LMWH) and low-dose aspirin (LDA). LMWH and LDA have not been detected to exert any specific adverse fetal side effects or teratogenicity.[23] It is suggested that the same dose of LMWH should be continued for 6 weeks after delivery, as the risk of post-partum thrombosis may increase. In the case of asymptomatic aPL carriers (those with positive aPL but no vascular thrombosis or pregnancy complications), LDA helped protect pregnant females from thrombosis.[24] Both LMWH and LDA are not well excreted into breastmilk; therefore, breastfeeding is safe in mothers who are treated with both drugs.[23]

Despite the widespread use of direct-acting oral anticoagulants for the prevention of secondary thrombosis in the general population, it is not recommended to be used in patients with definite APS.[24] No clinical trials have been performed on direct-acting oral anticoagulants during pregnancy and lactation, and safety has not been demonstrated during this period.[25]

Conventional Disease-Modifying Anti-rheumatic Drugs

Hydroxychloroquine

Hydroxychloroquine (HCQ), an antimalarial drug, has been widely used, either alone or in combination with other agents, in the treatment of SLE, RA, and other IRDs. Above all, in patients with SLE, HCQ should be continued during pregnancy in order to prevent a disease flare and reduce adverse pregnancy outcomes. Despite the theoretical concerns of retinal toxicity and ototoxicity, generally known as HCQ toxicity from long-term use, no visual, auditory, or congenital abnormalities have been reported in children in previous studies.[26] One study suggested that the continuation of HCQ during pregnancy has a possible protective effect against the occurrence and recurrence of neonatal lupus and congenital heart block.[27]

HCQ also appeared to be compatible with breastfeeding. Low concentrations of HCQ can be found in breastmilk and exposed to infants; however, there are no data on the adverse effects of breastfeeding from mothers taking HCQ till date.[28]

Sulfasalazine

Sulfasalazine (SSZ) is a compound of 5-aminosalicylic acid and sulphapyridine developed for the treatment of RA more than 60 years ago. Aside from its use as a treatment for RA, ankylosing spondylitis, psoriatic arthritis, juvenile arthritis, and ulcerative colitis are also indications for treatment. Significant information about the risk of SSZ during pregnancy was obtained from patients with inflammatory bowel disease, and most studies have demonstrated safety during pregnancy.[29] Although SSZ and its metabolite sulphapyridine pass through the placenta, current studies have shown that these concentrations do not cause significant displacement of bilirubin from albumin.[30] The

risk of kernicterus does not appear to increase in infants exposed to SSZ. It should be noted that folate supplementation is necessary during pre-conception and pregnancy, as SSZ is a potential inhibitor of folate carrier.[31]

There is a general consensus that SSZ is safe during lactation. However, there has been one reported case of bloody stool and diarrhoea in an infant receiving breastmilk from mothers taking SSZ; thus, it should be explained to patients to observe the symptoms and signs of infants treated with SSZ throughout this period.[32]

Azathioprine

Azathioprine (AZA) is a purine analogue, an immunosuppressive agent that prevents T- and B-cell proliferation by inhibiting nucleic acid synthesis.[33] Teratogenicity has been found in animals due to DNA damage caused by the active metabolites of AZA, but it has not been identified as a human teratogen because there is no enzyme that converts into active metabolites in the fetal liver.[34] In the past, numerous case series have been reported for adverse outcomes of pregnancies, including intrauterine growth retardation, chromosomal anomalies, and immunosuppression; however, there are limitations in the analysis of results, given that a small number of patients were included and that the investigators did not consider the severity of the disease.[35] Based on the safety data during pregnancy, proven primarily from observational studies of inflammatory bowel disease and organ transplantation patients, AZA has recently been recognised as a safe immunosuppressant and steroid-sparing agent in pregnant females with various IRDs.[36] Breastfeeding is compatible with AZA as the drug transfer into maternal milk is minimal.[37]

Methotrexate

Methotrexate (MTX) is a folate antagonist that inhibits dihydrofolate reductase and causes the termination of cell growth and division. Although it is commonly used for autoimmune diseases such as RA and psoriasis because of its anti-inflammatory effects, MTX is a teratogen and abortifacient by inhibiting folic acid, which is essential for the development of fetal neural tubes.[38] The major congenital malformations induced by MTX include microcephaly, hydrocephalus, cleft palate, congenital cardiopathy, and delayed ossification.[39] The critical period of malformation production by MTX is regarded as 6–8 weeks after conception.[40] Since MTX can persist in the maternal liver up to 4 months after exposure, females who wish to conceive should stop taking the medication for at least 3 months before attempting pregnancy.[17] Considering the widespread use of MTX in rheumatic diseases, physicians should inform females of childbearing age regarding the risks of taking this medication and continue to recommend folic acid supplementation. Most expert guidelines suggest that breastfeeding is contraindicated during maternal MTX treatment.[41] Although the levels found in breast milk are very low, they can accumulate in neonatal tissues.[42]

Tacrolimus and cyclosporine

Tacrolimus (TAC) and cyclosporine (CSA) are calcineurin inhibitors that interfere with the transcription of IL-2 and several other cytokines in T lymphocytes.[43] Both medications belong to a family of immunosuppressive agents and are widely used in the prevention of transplant rejection and in the treatment of autoimmune disorders. The current available data indicate favourable pregnancy outcomes without any evidence of increased risk of congenital anomalies following intrauterine exposure to TAC.[44] CSA is also classified as a relatively safe medication during pregnancy, although the incidence of maternal diseases such as pre-eclampsia, gestational diabetes, and maternal hypertension may increase.[45] The medical literature concerning the effects of TAC and CSA on lactation is not known precisely as it mainly includes case reports and registry data. TAC and CSA are considered safe as the detectable concentration in breast milk is extremely low and there are no cases of increased malformations in pregnant females exposed to these medications.[46]

Cyclophosphamide

Cyclophosphamide (CYC) is an alkylating agent that is toxic to cancer cells and proliferating lymphocytes and is known as a treatment for various rheumatic diseases such as SLE and vasculitis as well as malignancies.[47] This medication is generally avoided in females of reproductive age because of its impact on embryofetal toxicity and fertility. CYC administration to pregnant females not only produced deformities

of the skeleton, limbs, eyes, and palate, but has been observed to result in severe bone marrow hypoplasia, gastroenteritis, and fetal resorption. The risk seems to increase among the fetuses exposed during the first trimester.[48] For this reason, during pregnancy planning, CYC should be discontinued before conception and switched to pregnancy-compatible medications to avoid fetal exposure to medication. Considering the risk of ovarian failure, other immunosuppressive agents should be preferred as first-line therapy for young females instead of CYC. Nevertheless, if the benefits of CYC outweigh the clinical risks, the use of gonadotropin-releasing hormone agonists during CYC therapy will help preserve ovarian function.[49]

Patients taking CYC should avoid breastfeeding, as it appears in maternal milk in potentially toxic amounts. There are reports that breastfeeding by females exposed to CYC caused neutropenia and bone marrow suppression in the infant.[24]

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive agent that selectively inhibits the proliferation of lymphocytes by blocking purine synthesis in B and T lymphocytes.[50] It has become a major treatment for lupus nephritis and other IRDs, with fewer side effects on fertility, bladder toxicity, cancer, and infection compared to CYC. Apart from the evidence that MMF is not related to the risk of infertility, this medication is widely known to increase the risk of congenital malformations and miscarriage during pregnancy if the fetus is exposed *in utero*.[51] Toxic effects include facial cleft; anomalies of the external ear, vertebra, rib, eye, and intestine; congenital heart disease; and 2–3 times higher rates of miscarriage than non-exposed groups.[51] Since there have been many cases of malformation occurring, especially when exposed to MMF during the critical organogenesis period, the manufacturer recommends effective contraception for at least 6 weeks after last treatment.[52] There is a paucity of information regarding the transmission of MMF into breast milk; therefore, breastfeeding should be discouraged during treatment with MMF.

Leflunomide

Leflunomide (LEF) is a potent inhibitor of pyrimidine nucleotide synthesis and protein tyrosine kinase, which is mainly used as a treatment for RA. Embryonic cells require a large amount of nucleotides for DNA and RNA synthesis to proliferate and, in this respect, LEF may be embryotoxic.[53] In animal studies, LEF reduced the fetal viability and increased the incidence of exencephaly, cleft palate, and deformities of the skeleton, heart, and vessels at therapeutic doses, similar to those used in humans.[54] Hence, LEF is contraindicated during pregnancy and lactation. LEF has a long half-life and enterohepatic circulation that can be sequestered in the bile circulation for up to 2 years after drug cessation. In the event of unintended pregnancy, the drug should be eliminated for 11 days with 8 g cholestyramine three times daily; afterward, plasma levels <0.02 mg/mL should be verified twice at least 2 weeks apart.[53]

Biologic Disease-Modifying Anti-rheumatic Drugs

Anti-TNF therapy

Anti-TNF agents have been developed as treatments for autoimmune diseases, as TNF is deemed a master pro-inflammatory cytokine that is a major cause of autoimmune inflammation.[55] To date, five agents have been approved for IRDs, including etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. Most studies generally suggest that anti-TNF therapy has a lower risk in pregnancy, especially in the first two trimesters.[56] It is necessary to weigh the benefits and potential risks of maintaining anti-TNF agents in consideration of disease activity. Although slightly different depending on the drug, it may be safe to stop treatment in the late second or early third trimester in stable disease, as anti-TNF agents can pass through the placenta after 20 weeks. On the other hand, treatment with an anti-TNF agent is an appropriate option for females with severe active diseases to have a successful pregnancy. Breastfeeding is also compatible with anti-TNF therapy. Among them, certolizumab pegol is known to be the safest during pregnancy and lactation. It is notable that neonates exposed to anti-TNF agents should avoid live vaccinations during the first 6 months of life.[57]

Rituximab

Rituximab (RTX) is a chimeric monoclonal B-cell depleting anti-CD20 antibody indicated

for RA, SLE, systemic sclerosis, anti-neutrophil cytoplasmic antibody-associated vasculitis, and inflammatory myopathy.[58] According to the analysis of neonates who were exposed to RTX, few congenital malformations or neonatal infections were observed.[59] Nevertheless, the routine use of RTX in females who plan to conceive or become pregnant is discouraged. Although the offspring of pregnant animals exposed to RTX had no teratogenicity, lymphoid B cells were depleted in the newborn, and in humans RTX was detected in the serum of infants after intrauterine exposure.[60] Except for potentially life-threatening diseases occurring during pregnancy, all females of childbearing age should continue to be counselled to avoid pregnancy for ≥12 months after RTX exposure.

There are no data on whether RTX is transmitted to maternal milk and its effect on breastfed children. The European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) argue that this medication is considered safe because of its large molecular weight and poor absorption into breast milk.[41,56]

Other biologic agents

Scant data are available regarding the compatibility of other biologics with pregnancy and lactation. CTLA-4 inhibitors (i.e., abatacept), IL-6 inhibitors (i.e., tocilizumab), B-cell activating factor inhibitors (i.e., belimumab), IL-17 inhibitors (i.e., secukinumab), and IL-12/23 inhibitors (i.e., ustekinumab) are included in this group. They are conditionally recommended before conception, in that these agents do not cross the placenta until the second trimester, but should be stopped during pregnancy. Further investigation is expected, given that there are little data on the effects of these biologic agents during pregnancy and lactation.

Targeted Synthetic Disease-Modifying Anti-rheumatic Drugs

JAK inhibitors, a 'target' therapy that acts on the immune response like other biologic agents, are the latest approved medication for use as a treatment for RA.[61] Currently, these agents include two JAK inhibitors, tofacitinib and baricitinib, which block one or more JAK enzymes and prevent the signalling of pro-inflammatory cytokines.

Table 2: Safety of anti-rheumatic medications in males during pregnancy planning.

Low risk	High risk	Limited safety data
NSAIDs	Cyclophosphamide†	Rituximab
Corticosteroids		Abatacept
LMWH		Tocilizumab
Low-dose aspirin		Belimumab
Hydroxychloroquine		Secukinumab
Sulfasalazine*		Ustekinumab
Azathioprine		Tofacitinib
Methotrexate		Baricitinib
Tacrolimus/cyclosporin		
Mycophenolate mofetil		
Leflunomide		
Anti-TNF agents		

*Sulfasalazine can reduce the counts and motility of sperm, causing reversible azoospermia at doses >2 g/day.

†Cyclophosphamide has a high risk of irreversible infertility at doses >7.5 g.

LMWH: low-molecular-weight heparin; NSAIDs: non-steroidal anti-inflammatory drugs.

As they are a small molecule that can cross the placenta and are known to decrease the fertility and increase embryo lethality in animal models, the randomised controlled trial protocols excluded pregnant females.[62] Case reports with no adverse outcomes of pregnancy in females exposed to JAK inhibitors are extremely rare; however, there is little information on the safety of these medications during pregnancy so far.[63] Therefore, the present recommendation is that the use of JAK inhibitors should be discontinued during pregnancy and lactation.

MALE FERTILITY AND RISK OF CONCEPTION WITH ANTI-RHEUMATIC THERAPY

Assessment of the safety of paternal exposure to medications during pregnancy planning considers whether the medication causes infertility or can lead to adverse pregnancy outcomes. Except for CYC and SSZ, most medications are not teratogenic and do not affect fertility.[64] CYC is reported to lead to irreversible azoospermia and potential teratogenicity and should be discontinued for 3 months prior to conception. SSZ causes reversible azoospermia; thus, it is recommended that males who take this medication and have difficulty conceiving are advised to stop this medication for 3 months. Table 2 summarises the safety of paternal exposure to anti-rheumatic medications.

CONCLUSION

The authors have discussed the safety of medications during pregnancy and lactation in patients with IRDs. Prior to the initiation of treatment for females with rheumatic diseases of childbearing age, extensive counselling should be provided on the possible toxicity of exposure to medications and the potential risks should be emphasised in the case of an unplanned pregnancy. Physicians should carefully weigh the risks and benefits of adverse outcomes during pregnancy from exposure to the medication against disease flare when withholding maternal treatment.

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Cannabinoids in the Treatment of Epilepsy: A Review

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Abstract

Cannabinoids have been studied for their role in the treatment of epilepsy for many years. The U.S. Food and Drug Administration (FDA) approved them for the treatment of some refractory syndromes in 2018. Cannabidiol and tetrahydrocannabinol are the most commonly studied cannabinoids and have been studied in great depth vis-à-vis their pharmacokinetics and pharmacodynamics. Studies have shown the efficacy of cannabinoids in the treatment of refractory epilepsy. A substantial amount of research has been performed exploring the interactions between cannabinoids and other conventional antiseizure medications. The exact mechanisms by which cannabinoids exert their effects on seizure control remain unclear and research into these mechanisms continues in great earnest. Cognitive changes from cannabinoids are constantly being studied and add to potential benefits from the use of these compounds. Cultural and social misconceptions and roadblocks about the use of cannabinoids persist and represent an ongoing obstacle to increasing research and therapeutic use of these compounds. This review focuses on all these aspects and of the use of these cannabinoids in the treatment of epilepsy and seeks to offer a fairly comprehensive description of the facets of cannabinoid therapy for refractory epilepsy.

INTRODUCTION

Cannabidiol (CBD) comes from *Cannabis sativa*, which is a medicinal plant known to have several properties. Several types of extracts from cannabis can be broadly classified into psychotropic and non-psychotropic compounds, and CBD falls within the non-psychotropic compounds. In recent years, it has been found to be useful in several diseases such as Huntington's disease, amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease.[1-4]

Cannabis has been in medicinal use for a long time, but it was first described in the United States Pharmacopoeia in 1850.[5] However, on 25th June 2018, Epidiolex® (cannabidiol) was the very first cannabis-derived drug that was approved for use.[6] Sativex, which is also a derivative and is known as nabiximols, is approved as an adjunctive treatment in multiple sclerosis in several countries.[7]

People with epilepsy constitute 1% of the global disease burden of disease, affecting over 50

million people worldwide.[8] While there are several types of epilepsy, drug treatment-resistant epilepsy is defined as having failed at least 2 antiepileptic drugs (AEDs), which were tolerated and appropriately chosen to achieve sustained seizure freedom.[9] Most types of epilepsy are managed with antiepileptic drugs but for severe drug-resistant epilepsy, other treatments are being explored; one being the use of CBD.

Initially, as the medicinal use of cannabis started being explored, there were hardly any trials and evidence of efficacy was unclear. Due to the abuse potential of cannabis, many states were hesitant to approve the cannabis containing CBD. Now, with more trials and evidence, the use of CBD is being medically prescribed and distributed. Therefore, now more than ever, there is a need to increase awareness around appropriate use of CBD in various diseases, especially epilepsy.

The objectives of this review article are to describe the science behind the properties of CBD and tetrahydrocannabinol (THC), summarise the clinical trials and adverse effects to date and explore the future directions of treatment using CBD and THC.

BASIC SCIENCE

THC and CBD act via the endocannabinoid system. The endocannabinoid system is composed of G protein-coupled receptors, endogenous cannabinoid (CB) receptor ligands such as N-arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol, and ligand metabolic enzymes such as fatty acid amide hydrolase and monoacylglycerol lipase.[10] CB receptors are part of the GPCR family. CB1 receptors are located primarily in central and peripheral neurons, and CB2 receptors predominantly in immune cells.[10] The activation of the CB1 receptors prevents excessive neuronal excitation in the central nervous system by modulation of neurotransmitter release.[10] They modulate release of various inhibitory as well as excitatory molecules (transmitters) such as γ-aminobutyric acid (GABA), noradrenaline, acetylcholine, dopamine, serotonin, and glutamate.[10] Endocannabinoids also act as retrograde synaptic messengers. Certain neurotransmitters can cause increase in postsynaptic calcium, which can trigger synthesis and the release of endocannabinoid molecules into synapses, which then act on presynaptic CB1 to inhibit the release of neurotransmitters such as glutamate and GABA.[10] THC has equal or higher affinity towards CB1 and CB2 receptors but has lower efficacy than the other phytocannabinoids.[10]

While the psychotropic agent THC acts on CB1 and CB2 receptors, CBD does not. However, its actions include inhibitory action on the orphan G protein-coupled receptor 55, equilibrative nucleoside transporter, and the transient receptor potential of melastatin type 8 channel.[11] On the contrary, it enhances action of the 5 hydroxytryptamine receptor 1A on the glycine receptors α3 and α1, and the transient receptor potential ankyrin type 1 channel.[11] It has a bidirectional action on intracellular calcium.[10]

At higher concentrations, CBD exerts its excitatory effects on transient action potentials vanilloid Type 1 and Type 2 and on the nuclear peroxisome proliferator-activated receptor γ and inhibits cellular uptake and fatty acid amide hydrolase–catalysed degradation of anandamide.[12]

The complex combination of these receptor-ligand interactions has helped CBD emerge with antiepileptic, neuroprotective, and anti-inflammatory properties.

Pharmacokinetics

Absorption

Inhaled cannabinoids exhibit similar pharmacokinetics to intravenous (IV) cannabinoid. After inhalation, peak plasma concentrations of both THC and CBD are attained rapidly (within 3–10 min).[13]

Bioavailability

The bioavailability of THC has been found between 10–35%. This could be attributed to inhalational characteristics, size of inhaled particles, and inter- and intra-subject variability.[13] The inhaled version of CBD has 35% bioavailability.[13] The sublingual route is also noted to have much higher bioavailability than the oral form.[14] Although less frequently used, the intravenous version of THC has found to have a higher bioavailability.[13]

Half-life

The mean half-life of CBD was reported as 1.1- and 2.4-hours, following nebuliser and aerosol administration (20 mg).[15,16]

Distribution

THC is highly lipophilic. Upon delivery, it gets distributed in highly perfused regions first including the lung, heart, brain, and liver.[13] Mean volume of distribution was 2,520 L following IV administration.[17] Apparent volume of distribution after oromucosal spray was 26,298, 31,994, and 28,312 L.[18] Volume of distribution of CBD via the IV route has been found to be 32.7 (8.6) L/kg.[16]

Metabolism

Hydroxylation of THC at C9 by the hepatic Cytochrome P450 enzyme system leads to production of the equipotent metabolite 11 hydroxy-Δ^9-THC. Cytochrome P450 2C9, 2C19, and 3A4 are involved in the oxidation of THC.[19] Phase II metabolism of the 11-Nor-9-carboxy-Δ^9-THC involves the addition of glucuronic acid and, less commonly, of sulfate, glutathione, amino acids, and fatty acids via the 11-carboxylic acids group.[13]

Although similar to THC, CBD undergoes oxidation of C9 to the alcohol and carboxylic acid and side-chain oxidation.[13] Both THC and CBD are subjected to a significant first-pass effect; however, unlike THC, a large proportion of CBD is excreted, unchanged in the faeces.[13]

Elimination

Of the THC that gets excreted, 80–90% is excreted as hydroxylated and carboxylated metabolites within 5 days.[20] More than 65% is excreted in the faeces, approximately 20% being eliminated in the urine.[21]

Ujváry et al. also reported that 16% of CBD administered IV was excreted in urine as unchanged and conjugated CBD in 72 hours.[22] It was also observed that 33% of the initial CBD was mostly excreted as unchanged CBD, with metabolites such as mono- and di-hydroxylated and monocarboxylic derivatives of CBD in the faeces within 72 hours.[22]

Keeping the above properties in mind, it was found that cannabinoids have variable properties depending on the type of formulations that could be effective. To counter hurdles of first pass metabolism and poor water solubility or absorption, several synthetic compounds have been designed such as water-soluble CBD powders, self-emulsifying delivery systems, and encapsulation of CBD within gelatine matrix pellets.[23]

CLINICAL STUDIES

Clinical Efficacy in Current Use

To date, there have been five major Phase III randomised controlled trials (RCTs) and several open label, expanded access studies that evaluated the efficacy and safety of CBD (Tables 1 and 2).

Of the RCTs, two of them studied the safety and efficacy of CBD on Dravet syndrome (DS), two on Lennox-Gastaut syndrome (LGS), and one on epilepsy associated with tuberous sclerosis (TS).[24-28] All RCTs were double-blind and placebo-controlled and took place in multiple centres in the USA and Europe, with the TS trial also including patients from Australia. They all demonstrated a significant difference in percentage reduction of monthly seizure frequencies over the course of at least 3 months compared to the placebo. Two of the studies assessed efficacy, comparing doses of CBD at 10 mg/kg/day and 20 mg/kg/day for DS and LGS and found that both dosing groups demonstrated significantly increased efficacy in reducing seizures compared to the placebo but otherwise produced similar results compared to each other.[25,27] Adverse effects were noted to be more frequent in the higher dose group.[25,27] One study similarly compared doses of CBD at 25 mg/kg/day and 50 mg/kg/day for patients with TS, both of which reduced seizure frequency compared to the placebo but otherwise produced similar results compared to each other.[28]

Multiple open label and expanded access trials were also identified from the literature review that demonstrated reduction in seizures in patients with various treatment-resistant epilepsies (Table 2). Six of the studies evaluated add-on treatment of CBD for treatment-resistant epilepsy (TRE) in general, one for LGS, one for epilepsy associated with TS, and one for epileptic spasms.[29-37]

Table 1: Randomised controlled trials.

Study	Epilepsy syndrome	Treatment group	n	Study period	Efficacy variable	Outcome	Estimated median differences (from placebo)
Devinsky et al., (2017)[24]	DS	CBD, up to 20 mg/kg/day after 2 weeks	61	14 weeks	Median % change in monthly seizures	-38.9% (range: -100–337)	-22.8% (95% CI: -41.1–-5.4; p=0.010)
		Placebo	59	14 weeks	Median % change in monthly seizures	-13.3% (range: -91.5–230)	N/A
Miller et al., (2020)[25]	DS	CBD, up to 20 mg/kg/day after 2 weeks	67	14 weeks	Median % reduction in monthly seizures	45.7%	25.7% (95% CI: 2.9–43.2%; p=0.030)
		CBD, up to 10 mg/kg/day after 2 weeks	66	14 weeks	Median % reduction in monthly seizures	48.7%	29.8% (95% CI: 8.4–46.2; p=0.010)
		Placebo	65	14 weeks	Median % reduction in monthly seizures	26.9%	N/A
Thiele et al., (2018)[26]	LGS	CBD, up to 20 mg/kg/day after 2 weeks	86	14 weeks	Median % reduction in monthly drop seizures	43.9% (IQR: 1.9–69.6)	17.2% (95% CI: 4.1–30.3; p=0.010)
		Placebo	85	14 weeks	Median % reduction in monthly drop seizures	21.8% (IQR: 1.7–45.7)	N/A
Devinsky et al., (2018)[27]	LGS	CBD, up to 20 mg/kg/day after 2 weeks	76	14 weeks	Median % reduction in monthly drop seizures	41.9%	21.6% (95% CI: 6.7–34.8; p=0.005)
		CBD, up to 10 mg/kg/day after 2 weeks	73	14 weeks	Median % reduction in monthly drop seizures	37.2%	19.2% (95% CI: 7.7–31.2; p=0.002)
		Placebo	76	14 weeks	Median % reduction in monthly drop seizures	17.2%	N/A
Thiele et al., (2021)[28]	Epilepsy with TS	CBD, up to 50 mg/kg/day after 4 weeks	73	16 weeks	Median % reduction in monthly seizures	47.5% (95% CI: 39.0–54.8)	28.5% (95% CI: 11.9–42.0; p=0.002)
		CBD, up to 25 mg/kg/day after 4 weeks	75	16 weeks	Median % reduction in monthly seizures	48.6% (95% CI: 40.4–55.8)	30.1% (95% CI: 13.9–43.3; p<0.001)
		Placebo	76	16 weeks	Median % reduction in monthly seizures	26.5% (95% CI: 14.9–36.5)	N/A

CBD: cannabidiol; CI: confidence interval; DS: Dravet syndrome; IQR: interquartile range; LGS: Lennox-Gastaut syndrome; TS: tuberous sclerosis.

Table 2: Open-label studies.

Study	Epilepsy syndrome or aetiology	Treatment group	n	Study period	Efficacy variable	Primary outcome
Devinsky et al., (2016)[29]	TRE	CBD, variable dosing, up to 50 mg/kg/day	137	12 weeks	Median % reduction in monthly motor seizures	36.5% (IQR: 0–64.7)
Klotz et al., (2019)[30]	TRE	CBD, titrated up to 18 mg/kg/day	35	3 months	Median % reduction in monthly motor seizures	40.0% (IQR: 18.2–58.5)
Gaston et al., (2021)[31]	TRE	CBD, variable dosing, up to 50 mg/kg/day	169	6 months	% of patients who had ≥50% reduction in seizures	56.0%
Szaflarski et al., (2018)[32]	TRE	CBD, variable dosing, up to 50 mg/kg/day	132	12 weeks	Mean % reduction per participant per 2-week period	63.6%
D'Onofrio et al., (2020)[33]	TRE	CBD, titrated up slowly to 10 mg/kg/day after 4 weeks	125	6 months	Total monthly seizure frequency change	-41%±37.5% (SD)
Sands et al., (2019)[34]	TRE	CBD, titrated up to 25 mg/kg/day	26	3 months	% of patients who had ≥50% reduction in motor seizures	26.9%
Thiele et al., (2019)[35]	LGS	CBD, variable dosing up to 30 mg/kg/day	366	12 weeks	Median % reduction in monthly drop seizures	48.2%
Hess et al., (2016)[36]	TS	CBD, variable dosing, up to 50 mg/kg/day	18	3 months	Median % reduction in weekly motor seizures	40.0% (IQR: 0–77.0)
Herlopian et al., (2020)[37]	Epileptic spasms	CBD, titrated up to 25 mg/kg/day	9	3 months	Mean % reduction in weekly epileptic spasms	0.59%
Devinsky et al., (2018)[38]	Aicardi syndrome	CBD, variable dosing, up to 50 mg/kg/day	14	48 weeks	Median % reduction in monthly convulsive seizures	59.2% (IQR: 45–86)
	CDKL5	CBD, variable dosing, up to 50 mg/kg/day	17	48 weeks	Median % reduction in monthly convulsive seizures	59.7% (IQR: 5–75)
	Doose	CBD, variable dosing, up to 50 mg/kg/day	7	48 weeks	Median % reduction in monthly convulsive seizures	28.8% (IQR: -8–92)
	Dup15Q	CBD, variable dosing, up to 50 mg/kg/day	8	48 weeks	Median % reduction in monthly convulsive seizures	38.4% (IQR: -13–88)

CBD: cannabidiol;CDKL5: cyclin-dependent kinase-like 5; IQR: interquartile range; LGS: Lennox-Gastaut syndrome SD: standard deviation; TRE: treatment-resistant epilepsy; TS: tuberous sclerosis.

One study was specific to epilepsies associated with Aicardi syndrome, cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder, Doose syndrome, and Dup15Q syndrome.[38] These studies took place in the USA and/or Europe. In Asia, one study retrospectively evaluated the use of CBD in 42 patients with DS or LGS in South Korea and found that 33.3% of patients who received CBD at a dose of 10 mg/kg/day had at least a 50% reduction in seizure frequency after 3 months.[39]

Combined Effects with Clobazam

Additional studies have been performed to investigate the potential additive effects of CBD and clobazam (CLB). Using a mouse model, Anderson et al. showed that CBD and CLB can modulate the $GABA_A$ receptors to a greater extent when combined, providing a potential additive effect to their therapies, but did not act in a synergistic manner.[40] In a Phase II clinical trial, VanLandingham et al. evaluated the levels of drug metabolites in blood samples of patients receiving concomitant CBD and CLB and reported that there was no evidence of any drug-drug interaction between CBD and CLB, but CBD did increase one of the metabolites of CLB.[41] This study determined that CBD at a dose of 20 mg/kg/day had an acceptable safety profile while co-administered with CLB.

Gunning et al. performed a meta-analysis of the four RCTs that investigated CBD as add-on therapy for LGS or DS and calculated that patients who received the CBD add-on therapy had a significant reduction in frequency of drop seizures in LGS (treatment ratio: 0.70; 95% confidence interval (CI): 0.62–0.80; p<0.0001) and convulsive seizures in DS (treatment ratio: 0.71; 95% CI: 0.60–0.83; p<0.0001) compared to placebo.[42] They then performed a subgroup analysis of patients on CLB, demonstrating a similar reduction in frequency of drop seizures in LGS (treatment ratio: 0.56; 95% CI: 0.47–0.67; p<0.0001) and convulsive seizures in DS (treatment ration: 0.63; 95% CI: 0.52–0.77; p<0.0001) compared to placebo.[42]

Devinsky et al., as part of the project team that carried out the RCTs, also performed a meta-analysis of the same four RCTs and found that the CBD treatment groups with (treatment ratio: 0.51; 95% CI: 0.52-0.68: p<0.0001) and without CLB (treatment ratio: 0.85; 95% CI: 0.73–0.98; p=0.0226) were more efficacious than the placebo group in average reduction in seizure frequency.[43] Furthermore, they reported via logistic regression analysis that the odds ratio of patients yielding a >50% reduction in seizures from baseline was 2.51 (95% CI: 1.69–3.71; p<0.0001) in the CBD group without CLB and 2.40 (95% CI: 1.38–4.16; p=0.0020).[43] The treatment ratio appeared to numerically favour the CBD group with CLB versus without CLB, but the odds ratios of achieving >50% reduction in seizures were similar.

In a separate study, Savage et al. retrospectively analysed data from 47 patients with refractory epilepsy who received CBD therapy and compared the outcomes between those who had concomitant CLB (n=32) and those who did not (n=15), finding no significant difference in reduction of mean weekly seizure frequency between the two groups.[44]

Investigations of CBD and Other Epilepsies

Infantile spasms

There are some clinical data available for the use of CBD in infantile spasms. In a multicentre Phase II clinical study, Hussain et al. reported that, of the 9 patients with infantile spasms refractory to vigabatrin and adrenocorticotropic hormone, after 2 weeks of receiving CBD titrated up to 20 mg/kg/day, one of the patients achieved complete response to treatment.[45] This was defined as freedom from infantile spasms or hypsarrhythmia on 24-hour video EEG monitoring on Day 14 of the treatment. Similarly, in an open-label study, Herlopian et al. reported that, of the 9 patients with epileptic spasms (as classified per the 2001 International League Against Epilepsy [ILAE] at the time) who received CBD titrated up to 25 mg/kg/day, 3 of the patients were seizure-free and had resolution of the hypsarrhythmia pattern on video EEG after 2 months of treatment.[37]

Genetic and developmental epilepsies

Multiple preliminary clinical studies have been performed evaluating the use of CBD in other genetic and developmental treatment-resistant epilepsies as well. Devinsky et al. reported results of an open-label study using CBD for treatment-resistant epilepsy in patients with Aicardi

syndrome, CDKL5 deficiency disorder, Doose syndrome, and Dup15q syndrome, reporting a 48-week median monthly convulsive seizure reduction of 59.2%, 59.7%, 28.8%, and 38.8%, respectively.[38] Kuchenbuch et al. reported that 3 patients with SYNGAP1 epileptic encephalopathy had an average 85% monthly seizure reduction by Month 9 after receiving maximum doses of 10, 17, or 23 mg/kg/day.[46] Poisson et al. studied the use of CBD titrated up to 30 mg/kg/day as add-on therapy in 4 patients with migrating focal seizures associated with KCNT1 mutations and found, while none of the patients following 12 weeks of treatment did not have a reduction in seizures, one of the patients had a reduced intensity of seizures.[47] Kaplan et al. studied 4 paediatric patients with refractory seizures in Sturge–Weber syndrome who, at Week 14 reported an average 65% monthly reduction in seizures.[48] Sands et al. reported results of an expanded access program using CBD in 26 children with various treatment-resistant epilepsies, mostly presumed to be genetic, of whom 26.9% had a ≥50% reduction in motor seizures following 3 months of treatment.[34]

Adverse Effects

The safety of CBD has also been extensively studied. In the five Phase III RCTs, there was a higher percentage of adverse events in the CBD groups compared to placebo groups.[24-28] The most common adverse events attributed to CBD reported in these trials included somnolence, pyrexia, upper respiratory tract infection, vomiting, decreased appetite, and diarrhoea.[24-28] Three of the RCTs mentioned that 3.5–12.0% of patients in the CBD treatment group who had liver transaminase levels 3 times greater than the upper limit of normal, resulting in withdrawal from the trial.[24,25,27] The other two RCTs noted 13.4–18.9% of patients with elevated liver transaminase levels, most of whom were also taking valproic acid.[26,28] Despite these adverse events, most patients in the CBD treatment group were able to continue receiving CBD in at least the 14–16 week treatment periods of the study. The three RCTs that compared different doses of CBD also demonstrated a higher prevalence of adverse events with higher dose groups (around 90% of patients with at least 20 mg/kg/day and 100% of patients in the 50 mg/kg/day groups) without improved clinical efficacy.[25,27,28]

Beyond RCTs for epilepsy, Dos Santos et al. reported a review of 18 clinical trials that included CBD as a treatment group, reiterating the common adverse effects, as mentioned above.[49] They also noted that the presence of elevated transaminases, pyrexia, and upper respiratory tract infections appeared to be more frequent in patients receiving CBD as add-on therapy for seizures.[49] This could be related to certain comorbidities involved or drug interactions with other antiseizure drugs. Indeed, multiple studies have demonstrated that CBD affects serum levels of multiple antiseizure drugs due to shared metabolic pathways.[50-52]

Given CBD's close relationship with marijuana, some studies have also investigated its cognitive effects. In one study, Gaston et al. evaluated 20 patients with TRE who received functional MRI (fMRI) before and >2 weeks after receiving CBD with titration up to 25 mg/kg/day, while testing immediate and delayed memory, and found that treatment in CBD resulted in no significant changes in working memory performance and significant increases in neural activity on functional MRI in regions associated with verbal memory and attention compared with healthy controls.[53] The same study group also explored cognitive functioning after long-term use of CBD in both children and adults with TRE and, by using the National Institute of Health (NIH) Toolbox Cognition Batter test before and after 1 year of CBD use, there was no significant change in cognitive test performance.[54, 55]

DIFFICULTIES IN DEVELOPMENT AND USE

Adverse Effects and Drug-drug Interactions

As discussed above, adverse effects and drug-drug interactions are a limiting factor in the initiation and continuation of CBD in some situations. Elevation in liver enzymes was the most common reason for discontinuation in the four RCTs for LGS and DS. Most, if not all, of these patients were on concurrent valproate, and there were no cases of drug induced-liver injury.[42,49] Additionally, concomitant use of CBD and CLB has been associated with increased somnolence. This combination has also resulted in rare cases of pneumonia and respiratory failure, thought

to be secondary to the CBD-induced increase in plasma CLB levels as opposed to CBD alone.[43,49] Special attention should be paid to these interactions, especially in European populations where the use of CBD has only been approved as an adjunctive treatment with CLB. This regulatory caveat may yield to potential harm in this regard and does not allow for minimising AED burden in patients who could potentially respond to CBD independent of CLB. Studies have shown mixed results on the effects of CBD on other AEDs, specifically having either no effect on or increasing levels of valproate and topiramate.[49] There have also been some reported increases in the drug levels of rufinamide, zonisamide, eslicarbazepine, and brivaracetam.[49,52,56] All of this must be taken into consideration when prescribing CBD to patients with TRE who, by definition, are already on multiple other AEDs. Further studies are needed to explore potential interactions between CBD and other AEDs in order to identify potential limitations on dose escalation, minimise adverse effects, and optimise seizure control and ultimately quality of life.[57]

Stigmatisation

In general, stigmatisation stemming from social, political, and legal factors has been a barrier to the investigation and prescribing of medical cannabis over the years.[58] While CBD is not psychoactive, given its derivation from Cannabis sativa, this stigma still carries over and raises theoretical concerns, particularly regarding abuse potential. A single dose, randomised, crossover trial demonstrated that CBD had a significantly low abuse potential at both therapeutic and supratherapeutic doses as compared to alprazolam and dronabinol in a population of recreational polydrug users.[59] This study also showed that CBD had no observable cognitive or psychomotor impairment in contrast to alprazolam.[59] The growing body of evidence demonstrating the efficacy and safety of CBD in the treatment of epilepsy has effectively reduced this stigma among the medical community, though some reservations may remain among patients based on cultural, political, and religious ideals. For instance, as recreational use of marijuana is forbidden in Islam, despite religious scholars considering medical use of cannabis and its derivatives acceptable, cultural barriers to patients who are Muslims accepting this as a treatment option persist.[60] A survey on patient experiences with stigmatisation related to the use of medical cannabis found negative views of cannabis as a recreational drug, associated criminal sanctions, and using cannabis in the context of vulnerability (i.e., illness, disability) to be contributory to their sentiments.[61] Ideally, the increasing legalisation and normalisation of medical and recreational cannabis products throughout the world will help break down some of these barriers going forward.

FUTURE DIRECTIONS

Further Understanding of Mechanism and Predicting Treatment Response

As discussed above, the complete mechanism of action of CBD in the treatment of epilepsy is not fully understood. Some studies have examined the relationship between CBD and patterns of neural synchronisation, and how these can be used to predict treatment response. Anderson et al. demonstrated that CBD treatment responders, as evidenced by >70% seizure reduction, had stronger network integration and segregation in β frequencies compared with non-responders.[62] This study also showed that higher CBD dosage was associated with stronger network integration and segregation in Δ, θ, and α frequencies. Larger studies are needed to identify whether these findings suggest that CBD is causing these stronger brain network dynamics, or rather if stronger network dynamics predispose to treatment response. More clarification on this may identify which patients would benefit most from treatment with CBD. Additionally, further study of pharmacogenomics could help distinguish which patients are most likely to respond to CBD and identify optimal CBD and AED combinations on a tailored, individualised basis.[57]

Use in Other Types of Epilepsy

Given the limited U.S. Food and Drug Administration (FDA) indications for use of pharmaceutical-grade CBD, it is not currently available for the majority of epilepsy disorders. More evidence is needed to elucidate the efficacy of CBD in these other types of epilepsy beyond LGS, DS, and TS. There are a few ongoing clinical trials further examining CBD in these groups, in

addition to one more novel study examining use in electrical status epilepticus of sleep.[63,64] A recent systematic review of open-label studies and reports of experimental off-label use of purified, plant-based CBD suggested effectiveness in multiple other epilepsy syndromes including CDKL5 deficiency disorder, Aicardi syndrome, Dup15q syndrome, Doose syndrome, SYNGAP1 encephalopathy, Sturge–Weber syndrome, and epilepsy with myoclonic absences.[65] There is also anecdotal evidence supporting efficacy beyond epileptic encephalopathies as some patients successfully supplement their prescribed anti-epileptic regimen with cannabis for improved seizure control. For example, a survey of patients at an Oregon tertiary care centre found a majority of these patients reported successful seizure reduction with use of both high-CBD strains and varied THC:CBD combination strains of cannabis.[66] Given the risks associated with these products including psychoactive effects of THC and the method of ingestion, specifically smoking and vaping, these patients may benefit from a safer, regulated pharmaceutical-grade CBD option for the maximisation of their epilepsy treatment.

Antiepileptic Potential of Other Cannabinoids

The therapeutic potential of other cannabinoids in epilepsy requires further evaluation. Cannabidivarin has anticonvulsant properties in animal models, specifically in acute seizure and status epilepticus and was recently evaluated in a Phase II clinical trial for focal seizures; however, it did not meet primary endpoint of percentage change in focal seizure frequency.[56,67,68] Cannabigerol did not demonstrate anticonvulsant properties in a mouse model, despite voltage-gated sodium channel blockade.[69] Tetrahydrocannabivarin has been shown to suppress seizure activity in rats.[70] Cannabichromene and its related phytocannabinoids were recently demonstrated to have anticonvulsant properties in a DS mouse model.[71] Other cannabinoids including cannabinol, cannabidiolic acid, and tetrahydrocannabinolic acid that have been researched for neuroprotective and therapeutic potential in other neurologic conditions have yet to be studied in epilepsy.[72]

There is also evidence to suggest benefit from combinations of cannabinoids. A recent observational meta-analysis showed that CBD-rich cannabis extracts were over 4 times more potent as compared to purified CBD, such that the same therapeutic effect could be achieved with significantly lower doses.[73] Mild and severe adverse effects were significantly lower with CBD-rich extracts as compared with purified CBD as well. These observations support hypotheses of a synergistic or 'entourage effect' of CBD, with other minor phytocannabinoids and suggest that plant-based CBD extracts could potentially be more efficacious and better tolerated than the currently approved purified CBD in the treatment of seizures.

CONCLUSIONS

CBD exhibits antiepileptic effects through complex actions at multiple receptors in the brain. Previously there was a deficiency of evidence to support its use in the treatment of epilepsy due to legal barriers. Now, there have been 5 RCTs and several other open-label trials demonstrating the efficacy of CBD in the treatment of LGS, DS, TS, and TRE. While these studies have yielded promising results, there were some doubts about whether this data suggested a synergistic effect of CBD and CLB, or truly represented CBD efficacy independently. Several additional meta-analyses of the major RCTs have shown similar efficacy of CBD both concomitantly and independent of CLB, though this combination does cause increased adverse effects, particularly sedation. Going forward, as use of CBD in the treatment of TRE increases, there is much more to be discovered regarding the complete mechanism of action, how to predict treatment responders, use in other forms of epilepsy, and possibly increased therapeutic potential when combined with other cannabinoids.

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The Association Between Hypermobility Ehlers–Danlos Syndrome and Other Rheumatologic Diseases

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Abstract

Research has shown hypermobility Ehlers–Danlos syndrome (hEDS) to be associated with some complicated rheumatologic disease. In this feature paper, the authors discuss the prevalence and pathophysiology of rheumatologic conditions, specifically ankylosing spondylitis and rheumatoid arthritis, in patients with hEDS. Furthermore, the authors discuss possible reasons for the association of hEDS with these rheumatologic diseases.

INTRODUCTION

Research has shown that hypermobility Ehlers–Danlos syndrome (hEDS) is associated with rheumatologic disease.[1] In this article, the authors first discuss the clinical features and pathogenesis of hEDS, rheumatoid arthritis (RA), and ankylosing spondylitis (AS). They examine the association between hEDS and rheumatological disease closely by discussing the prevalence of RA and AS in patients with hEDS as compared to the general population of the USA. In addition, they explore possible causes for this association.

CLINICAL FEATURES AND PATHOGENESIS OF HYPERMOBILITY EHLERS–DANLOS SYNDROME

A heritable connective tissue disorder, hEDS is characterised by joint hypermobility, musculoskeletal, skin, and soft tissue symptoms.[2] The clinical course of hEDS follows three distinct phases: a 'hypermobility phase', a 'pain phase', and a 'stiffness phase'. The 'hypermobile phase' occurs early in life and increases risk for joint sprains and dislocations.[2] Patients in this phase often experience pain predominantly in the lower limbs and easy fatigability. Patients begin to experience the 'pain phase' in their 20s–40s. In this phase, patients experience worsening musculoskeletal pain, paresthesias, and

gastrointestinal disorders.[2] The 'stiffness phase' is characterised by pain and reduction of joint mobility to a debilitating degree.[2] hEDS is also multisystemic in nature. Patients often struggle with a plethora of non-musculoskeletal symptoms such as dysautonomia, chronic fatigue, abnormal proprioception, gastrointestinal dysmotility, and mood disorders.[3]

Pathogenesis

There is no conclusive evidence confirming the aetiology of hEDS. However, transcriptome profiling of hEDS cells revealed a transcriptional change leading to "fibroblast-to-myofibroblast transition."[4] This transition results in cells with an increased ability for contraction, which can explain some systemic manifestations of hEDS such as gastrointestinal dysfunction, chronic musculoskeletal pain, and soft tissue inflammation.[4] Furthermore, continuous activation of myofibroblasts leads to impaired wound healing, thus explaining the soft tissue lesions patients with hEDS experience.[4] Transcriptome profiling of hEDS cells also revealed a dysfunctional signalling pathway between TGF-β and Wnt, resulting in continuous post-inflammatory fibrosis and myofibroblast formation.[4] Though the specific molecular mechanism causing chronic pain in patients with hEDS is not known, it is presumed that "inflammation-related genes" such as spondin-2 are upregulated.[4] Spondin-2 codes for many functions of the innate immune system, and is also involved in inflammatory cell recruitment.[4] This dysregulation is believed to increase painful sensations in patients with hEDS.[4]

CLINICAL FEATURES AND PATHOGENESIS OF RHEUMATOID ARTHRITIS

RA is an inflammatory disease that attacks the joints.[5] Continuous inflammation in the synovium leads to damage in the affected joints, causing pain and functional deterioration in patients.[5] RA typically starts off insidiously with fatigue and generalised muscle pain, and progresses within weeks to months to involve the joints in a symmetric pattern.[6] The most commonly affected joints are in the hands, feet, wrists, ankles, elbows, and knees.[6] These joints tend to appear swollen, warm, and are particularly stiff and painful in the morning or following a period of inactivity.[6] As RA can lead to inflammation of surrounding tendons, ligaments, and skeletal muscle, patients can experience radial deviation of the wrist, ulnar deviation of the fingers, swan-neck, and boutonniere deformities of the fingers.[6] Joints affected with RA will have a minimal range of movement in a waxing and waning course.[6]

Pathogenesis

A combination of genetic and environmental factors lead to a loss of self-tolerance to a native protein that contains a citrullinated residue.[5] Due to this lack of tolerance, the body then develops antibodies against these citrullinated residues, called anti-citrullinated peptide antibodies.[5] Both the adaptive and innate immune system are involved in an inflammatory reaction causing leukocytes to enter into the synovium and cause joint destruction.[5] The inflammatory response is persistently activated in patients with RA, causing continuous progression of the disease.

CLINICAL FEATURES AND PATHOGENESIS OF ANKYLOSING SPONDYLITIS

AS is an inflammatory disease that causes the destruction of articular cartilage of the sacroiliac and apophyseal joints, resulting in bony ankylosis.[6] The classic symptoms of AS include inflammatory back pain that is worse in the morning or during periods of inactivity, which persists for longer than 3 months and improves with movement.[7] Additionally, patients with AS experience reduced spinal mobility later in the advanced stage of the disease.[7] The progression of the disease can be followed and distinguished in radiologic imaging. Early imaging results will reveal reactive sclerosis and syndesmophyte formation at the edges of the vertebral bodies.[7] Late imaging results will show a "bamboo spine" resulting from bony bridging.[7]

Pathogenesis

The pathogenesis of AS is poorly understood. It is predicted that enthesitis, which is defined as "the insertion of a tendon, ligament, capsule, or fascia into bone," is the major hallmark of AS.[8] Recent studies show that the immune system attacks the enthesis of the intervertebral

discs and the annulus fibrosus, which contains fibrocartilage as well.[8] Patients with AS were found to have a higher concentration of cluster of differentiation-8+ T-cells, leading to the possible theory that T-cells from the bone marrow invade the fibrocartilage.[8] Some studies have shown that antigens from fibrocartilage presented by human leukocyte antigen-B27 (HLA-B27) to cluster of differentiation-8+ T-cells is the pathologic basis for AS.[8]

PREVALENCE OF RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS IN HYPERMOBILITY EHLERS–DANLOS SYNDROME

A study conducted in 2017 showed that hEDS is associated with rheumatologic conditions.[1] This study examined the number of patients with hEDS who tested positive for HLA-B27, a characteristic feature heavily correlated with AS.[1,8] Of the patients with hEDS who received a complete serological and radiographic workup, 24% tested positive for HLA-B27.[1] In comparison, the prevalence of HLA-B27 in the general population of the USA is 6.1%.[1] Additionally, in this study, 6.8% of patients with hEDs were also diagnosed with RA.[1] Comparatively, the prevalence of RA between 2004–2014 in adults in the USA ranged from 0.41–0.54%.[9] As shown in the studies conducted by Rodgers et al.[1] and Hunter et al.,[9] patients with hEDS have a higher prevalence of RA and characteristic genetic marker for AS.

Compared to HLA-B27, 3.4% of hEDS patients who received a complete serological and radiographic workup tested positive for anti-citrullinated protein antibody.[1] In comparison, a cohort study showed that the percentage of anti-citrullinated protein antibody positivity in the general population is 1.0%.[10]

PLAUSIBLE REASONS FOR ASSOCIATION

Rheumatological conditions such as RA and AS are associated with hEDS.[1] However, because the aetiology of hEDS is largely unknown, the understanding for this association remains limited.[1,4] The pathogenesis of hEDS is thought to include an increased fibroblast-to-myofibroblast transition, along with a dysfunctional signalling pathway leading to post-inflammatory fibrosis.[4] In comparison, RA contains an autoimmune response to a decreased self-tolerance capability of T-cells.[5] In addition, studies have predicted that the pathogenesis of AS is related to the dysfunction between HLA-B27 signalling to T-cells, causing an inflammatory response in fibrocartilage.[8] Due to the apparent differences in mechanisms of pathogenesis in RA and AS when compared to hEDS, it is difficult to specify the cause of association.[1] However, the authors think since the basis of hEDS lies in a dysregulation of the "inflammation-related genes,"[4] patients with hEDS are more susceptible to developing autoimmune conditions, such as RA and AS.

LIMITATIONS

In order to fully understand the association between hEDS, RA, and AS the genetic basis of hEDS is an important factor; however, it is beyond the scope of this review. Although clinically these conditions may present similarly, further studies have to be conducted in order to establish a concrete reasoning for the association between hEDS and rheumatological conditions. In particular, the authors suggest the need for future research to explore the molecular mechanisms of hEDS, which may lead to its association with other rheumatologic diseases. There has been limited qualitative research done to support the association between hEDS, RA, and AS and, therefore, a concrete connection between these conditions is difficult to establish. Additionally, it should be noted the pathophysiology of RA and AS are more comprehensive than what is included. Only the pathophysiology that is relevant for comparing RA and AS to hEDS has been presented.

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Cefixime-Induced Hepatitis: A Case Report and Review of Literature

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Abstract

Cefixime is a well-tolerated third-generation cephalosporin with severe side effects that are infrequently encountered. Herein, the authors report a clinical case of a 79-year-old female diagnosed with cefixime-induced hepatitis. To the best of the authors' knowledge, a single reported case was documented in the medical literature but has not been supported by liver biopsy. This case highlights the need to suspect drug-induced liver injury with cefixime use.

INTRODUCTION

Cephalosporins, a family of bactericidal antibiotics, have side effects like penicillin due to the similarity in their basic structure. Hypersensitivity and drug allergy are often reported but hepatotoxicity and drug-induced liver injury (DILI) due to these agents have rarely been encountered. A special exception is ceftriaxone, which belongs to the third generation and, when given parenterally, can cause biliary sludge with symptoms of cholestatic jaundice and even cholecystitis.[1]

Cefixime is one of the widely used cephalosporins in the treatment of urinary tract and abdominal infections caused by Gram-negative bacteria. It belongs to the third generation and is usually a safe and well-tolerated drug. Like all β-lactam antibiotics, cefixime binds to specific penicillin-binding proteins located inside the bacterial cell wall but with higher stability in the presence of β-lactamase enzymes, causing the inhibition of bacterial cell wall synthesis. It is metabolised by the liver and approximately 50% of the absorbed dose is excreted, unchanged, in the urine in 24 hours. Its known side effects are disturbances in bowel habits, mainly diarrhoea; dyspepsia; headache; fatigue; dizziness; and myalgias.[2] To the best of the authors' knowledge, only one previous case of cefixime-related hepatitis has been reported in medical literature but no liver biopsy was completed to support the causality.[3] Herein, the

authors document a case of cholestatic hepatitis caused by cefixime, after ruling out all other causes. The diagnosis was supported by liver biopsy and confirmed by a positive challenge test in the second admission. This case highlights the need to suspect DILI with cefixime use.

CASE REPORT

The patient was a 79-year-old female non-smoker with a history of Type 2 diabetes mellitus and recurrent urinary tract infections, who presented at the authors' hospital with jaundice. Three days prior to presentation, the patient started experiencing dysuria associated with chills and was consequently started on cefixime 400 mg once daily. Two days later, she started to have non-radiating epigastric pain, along with nausea, multiple episodes of vomiting, pruritis, and progressive jaundice. She also reported clay-coloured stools and dark urine. She denied any alcohol intake. She had no recent history of travelling. Her only current medication was repaglinide 2 mg twice daily, without herbal products or any other drug intake.

On presentation, the patient was haemodynamically stable, afebrile, not in distress, and had an icteric sclera with right upper quadrant and epigastric tenderness on abdominal examination. Her blood test results were as follows: white blood cells: $5.2x10^9$/L, with neutrophilic shift; haemoglobin: 11.9 g/dL; creatinine (Cr): 0.91 mg/dL; urea: 53.0 mg/dL; aspartate aminotransferase: 266.0 U/L (normal: <40.0 U/L); alanine aminotransferase (ALT): 205.0 U/L (normal <40.0 U/L), γ-glutamyl transpeptidase: 178.0 U/L (normal: <55.0 U/L); total bilirubin: 7.4 mg/dL; direct bilirubin: 6.8 mg/dL; alkaline phosphatase (ALP): 276.0 U/L (normal: <140.0 U/L); total protein: 6.8 g/dL; albumin (Alb): 3 g/dL; prothrombin: 1.1 sec.

One month prior to admission, the patient's liver enzymes were at normal levels at a routine check-up. Furthermore, viral serologies for hepatitis A, B, C, cytomegalovirus, and Epstein–Barr virus were all negative, as well as markers for autoimmune hepatitis (e.g., γ-globulin, smooth muscle actin antibody, antinuclear antibodies, and antimitochondrial antibodies) and iron profile was normal. An abdominal ultrasound showed that the gallbladder was distended, no calculi, no wall thickening, no biliary ductal dilatation, a slightly enlarged liver with homogeneous echotexture, no focal solid or cystic lesions, and normal pancreas and kidneys.

During hospitalisation, there was a persistent increase in liver enzymes as shown in Table 1, so a liver biopsy was scheduled and completed on the eighth day of admission. A liver biopsy showed a preserved hepatic lobular architecture, with no evidence of portal tract fibrosis, fibrous septa, or portal to portal bridging fibrosis and cirrhosis. Within the portal tracts sampled was a lymphocytic inflammatory cell infiltrate and few eosinophils (Figure 1). A focal area of necrosis (Figure 2) was seen, but no bile duct inflammation or damage, lymphoid aggregates, and plasma cell infiltrate was seen. Canalicular and hepatocyte cholestasis was prominent, with no evidence of steatosis, iron, or copper overload, granulomas, viral inclusions, or ground glass cytoplasm; however, Mallory bodies were noted. Consequently, intravenous methylprednisolone 80 mg was started daily due to the persistent increase in cholestasis and international normalised ratio (INR). A very good response, with gradual decrease in cholestasis and INR, is shown in Table 1. The patient was discharged on Day 18, with gradual steroid tapering over a period of 2 months. After 2 months her liver enzymes were back to normal values.

Five months later, she presented again with jaundice, pruritis, dark urine, and clay-coloured stools, one day after taking cefixime for a urinary tract infection prescribed by another physician. Her laboratory test results were as follows: white blood cells: $7.2x10^9$/L; haemoglobin: 11.5 g/dL, Cr: 0.8 mg/dL; urea: 43.0 mg/dL; aspartate aminotransferase: 184.0 U/L; ALT: 240.0 U/L; γ-glutamyl transpeptidase: 273.0 U/L; ALP: 488.0 U/L; total bilirubin: 8.9 mg/dL; direct bilirubin: 7.8 mg/dL; total protein: 6.8 g/dL; Alb: 3.5 g/dL; prothrombin: 1.1 sec. Cefixime was stopped and her liver enzymes showed a gradual amelioration without starting steroids, and the patient was discharged on Day 3 of admission. At a 1-month follow-up her liver enzymes were back to normal values. According to the Roussel Uclaf Causality Assessment Method (RUCAM) score, it was "highly probable" that cefixime was the cause of the liver injury in this case.[4]

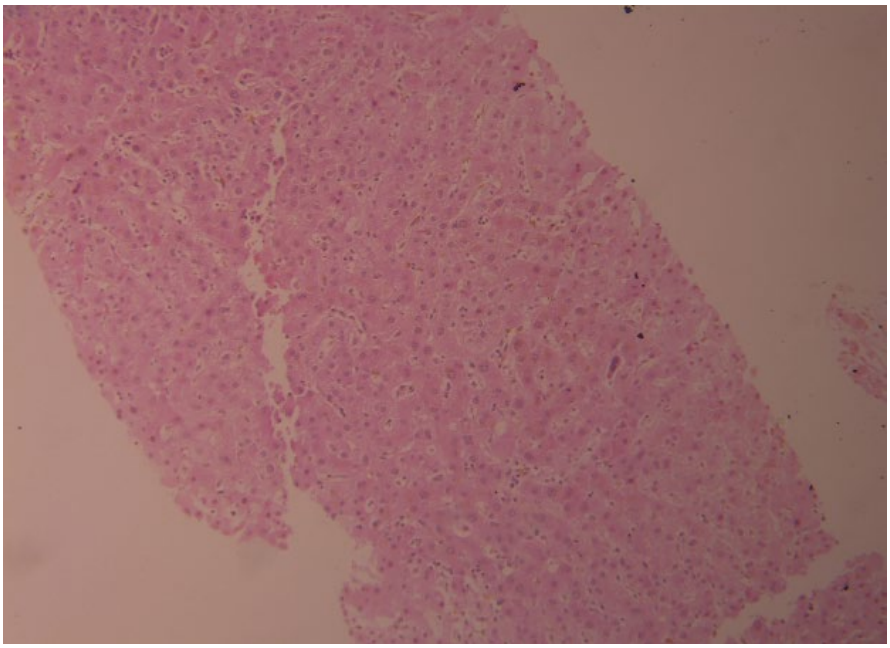

Figure 1: Acute and eosinophilic cell infiltrate.

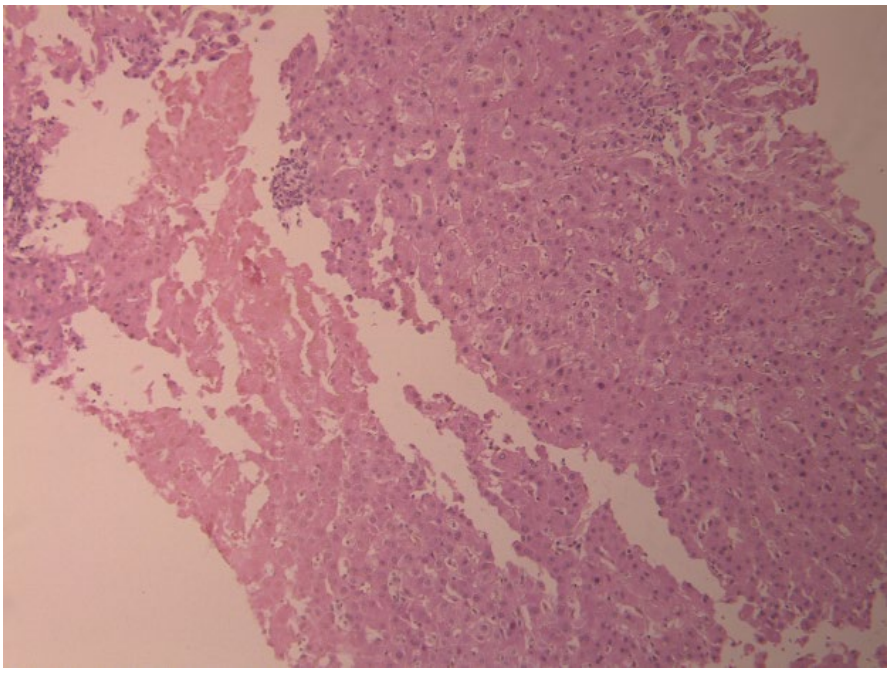

Figure 2: Portal tract inflammation, with focal area of necrosis, but with preserved architecture.

DISCUSSION

The authors' patient presented with jaundice and her laboratory results showed cholestatic hepatitis. She had no history of liver disease and there was no encephalopathy or an increase in INR >1.5 during her hospitalisation. Therefore, acute liver failure and acute-on-chronic liver failure were ruled out. All causes of hepatitis and perturbation of liver function tests, including viral serologies, autoimmune hepatitis, haemochromatosis, choledocholithiasis, and tumours, were ruled out.

Table 1: Follow-up on liver enzyme tests, as documented during the admission.

Days from presentation	1	2	4	6	10 (started on steroids)	12	13	17	18
SGOT (IU/L)	266	215	136	50	45	40	32	23	19
SGPT (IU/L)	205	190	121	40	43	20	17	18	19
ALP (IU/L)	276	289	427	354	578	519	425	324	249
GGT (IU/L)	175	158	210	202	382	278	311	300	207
Total bilirubin (mg/dL)	6.8	7.1	9.9	11	12.3	8.5	5.7	2.7	2.7
Direct bilirubin (mg/dL)	7.4	7.3	11	13.2	13.7	10.1	6.8	3.3	3.3
INR	1.12	1.09	1.12	1.23	1.46	1.21	1.14	1.08	1.02

ALP: alkaline phosphatase; GGT: γ-glutamyl transpeptidase; INR: international normalised ratio; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamate pyruvate transaminase.

DILI usually occurs 5–90 days following drug ingestion. In this case, the injury occurred 3 days after the intake of cefixime in the first presentation and 1 day after in the second presentation.

It is noteworthy that DILI is traditionally classified as intrinsic (or direct) versus idiosyncratic. Direct DILI is typically dose-related. Its onset is within a short time span (hours to days), and it occurs in a large number of individuals exposed to the drug (predictable). Whereas idiosyncratic DILI is not usually dose-related, it requires a dose threshold of 50–100 mg/day and exhibits a variable latency to onset, ranging from days to weeks. It occurs in only a small proportion of exposed individuals (unpredictable).[5]

The mechanism of DILI related to cefixime needs to be elucidated but it is, most probably, idiosyncratic. The diagnosis is usually difficult due to the lack of specific symptoms, signs, and tests and is, in part, a diagnosis of exclusion. The clinical spectrum of drug-induced hepatotoxicity is widely variable, ranging from asymptomatic elevation of liver enzymes to fulminant hepatic failure. Thus, comprehensive clinical assessment is a must to establish the diagnosis. Typically, history indicates a suspect drug, with reasonable temporal association to the illness. A pattern of liver injury, characterising the effect of the drug, is also helpful in diagnosis.[6]

According to the Councils for International Organizations of Medical Sciences (CIOMS), DILI may present as hepatocellular, cholestatic, and mixed.[7,8] Hepatocellular injury is characterised by an elevation of liver enzymes by ALT ≥3 times the upper limit of normal (ULN), and ALT/alkaline phosphatase (R ratio) ≥5 times the ULN. Cholestatic injury consists of an ALP elevation of ≥2 times the ULN and an ALT/ALP ratio of ≤2 times the ULN. Mixed type is established when ALT is ≥3 times the ULN, ALP is ≥2 times the ULN, and the ALT/ALP ratio is <5 but >2 times ULN.[9] During the first days, the type of injury in the authors' case seemed to be classified as a mixed pattern, and became a cholestatic pattern in the following days. However, in the other case reported in the literature it was classified as hepatocellular pattern on diagnosis.[3]

Drug-induced hepatitis is a diagnosis of exclusion but should be suspected[10] when a new drug has been started in the past 3 months; there is mixed-type liver injury; the presence of a rash or eosinophilia; cholestasis, with no biliary obstruction on imaging; hepatitis without hypergammaglobulinemia or autoantibodies.

The liver biopsy helps in identifying alternative aetiologies. In addition to the fact that it raises or lowers the likelihood of a particular drug injury based on reported patterns,[11] especially when there is persistent deterioration of liver enzymes, as in the authors' patient.

In most cases, the histologic findings of DILI are as follows: demarcated perivenular necrosis; canalicular cholestasis with minimal hepatitis; poorly developed portal inflammatory reaction; neutrophilic infiltration; eosinophilic infiltration; and granulomatous with epithelioid cells.[12] The authors' patient's liver biopsy showed that cholestasis excluded all other aetiologies of liver injury and supported the diagnosis, but the positive challenge test that was completed by mistake in the second presentation confirmed it. The only new drug started was cefixime, and because the symptoms started 2 days after starting it in the first presentation and 1 day after starting it in the second presentation, cefixime was responsible of this liver injury and cholestasis.

Management of DILI consists of rapid discontinuation of the offending suspected drug.[13,14] In fact, no beneficial therapies were reported except the use of N-acetyl cysteine for acetaminophen hepatotoxicity,[15,16] and the use of ursodeoxycholic acid and steroids in cholestatic DILI,[17] with circumstantial success;[18] however, a targeted treatment for idiosyncratic injury remains to be found.[19]

Given the anti-inflammatory effects of corticosteroids, they have been widely used for the treatment of DILI. Although multiple studies and case reports have shown a beneficial effect of corticosteroids in DILI,[20] a recent observational study of 90 patients refuted this hypothesis in patients with severe DILI.[21] Therefore, the efficacy of corticosteroids in DILI remains controversial and a prospective controlled trial will be needed to confirm or refute their beneficial effect in DILI. Whereas, in the authors' patient, the persistent increase in cholestasis lead to steroids treatment with a very good outcome in the first presentation; however, in the second presentation, the cholestasis resolved by stopping the offending drug without steroid treatment.

CONCLUSION

The liver is responsible for metabolising a majority of medications, which make this organ a prime target for drug-induced damage, which can manifest in abnormal liver tests without any symptoms suggestive of liver disease. The authors' case is the second case in the medical literature reporting cefixime-induced hepatitis and the first one supported by liver biopsy and confirmed by a positive challenge test. Treatment with steroids was of benefit in the first presentation, whereas stopping the offending drug led to the normalisation of liver enzymes in the second presentation. This case of hepatotoxicity highlights the importance of considering cefixime as potential cause of liver injury in the future.

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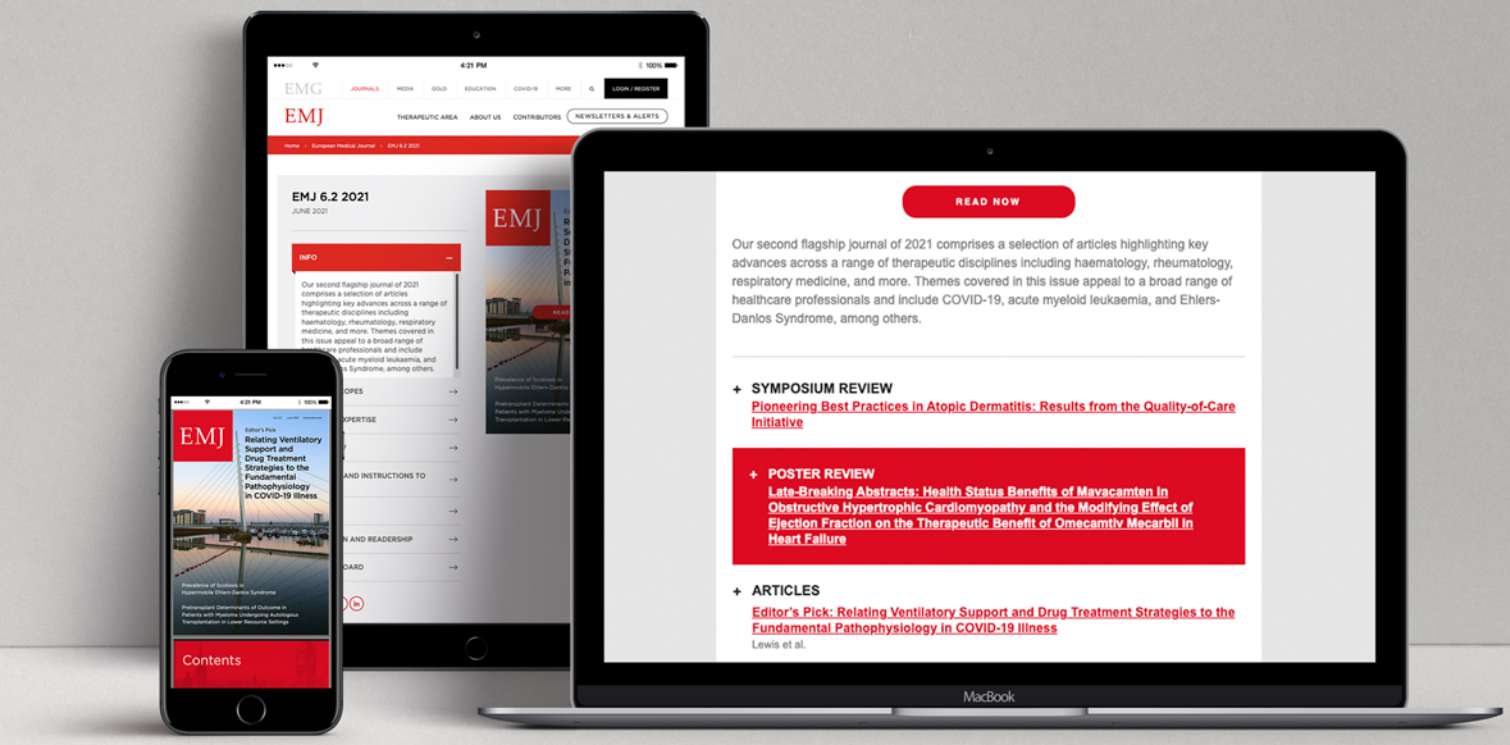

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