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New developments in the treatment of diabetic macular edema: latest clinical evidence

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Shani Golan* & Anat Lowenstein

Department of Ophthalmology, Tel Aviv Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel
*Author for correspondence:
Tel.: +972 3697 3408
Fax: +972 3697 3867
E-mail: shanigol2@walla.com

Diabetic retinopathy is a major cause of blindness in the western world and its incidence is expected to increase with the incidence of the diabetes. Macular edema is a major cause of visual impairment in the diabetic population. Laser therapy and tighter control of metabolic factors are the cornerstone of treatment. However, it recently became evident that other treatments, particularly pharmacological ones, can provide good results and should be considered for these patients. Medical therapies consist of two major classes of agents: anti-inflammatory drugs, such as intravitreal corticosteroids, some of which are delivered by means of extended-release technologies, and anti-VEGF agents. Agents targeting TNF-α and PKC-β2 are also implicated in the pathogenesis of diabetic retinopathy and are currently under investigation. Surgical therapies are usually implicated in the treatment of diabetic macular edema that is resistant to other treatment strategies, especially in cases that have specific anatomic characteristics. Surgical options include pars plana vitrectomy with or without internal limiting membrane peeling, combination therapy of pars plana vitrectomy plus intravitreal steroid or anti-VEGF, or the use of intravitreally administered pharmacological agents such as microplasmin prior to or during vitrectomy. This article reviews the current developments in treatment for diabetic macular edema.

Keywords: anti-VEGF • corticosteroid • diabetic macular edema

Diabetic retinopathy (DR), is the third major cause of blindness in western developed countries [1]. The prevalence of DR increases with the duration of diabetes and nearly all individuals with Type 1 diabetes and >60% of those with Type 2 diabetes, have some retinopathy after 20 years [2]. The two most important causes of visual impairment secondary to DR are diabetic macular edema (DME) and proliferative DR (PDR). Laser photocoagulation has been the mainstay of DME treatment for more than a quarter of a century, based on the findings of the ETDRS study [3], with vitrectomy being an option for patients not responding to photocoagulation.

More recent approaches currently under investigation include newer medical and surgical therapies. Among the medical treatment options are anti-inflammatory agents (mostly corticosteroids) and agents targeting VEGF, TNF-α and PKC-β2. Many experimental treatment strategies are under investigation, but the benefits of most have yet to be established in Phase III clinical trials [4]. This article provides a thorough overview of the latest clinical evidence in the medical and surgical treatment of DME.

DME

DME is defined as a retinal thickening involving or approaching the center of

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the macula. It plays a major role in the loss of vision associated with DR. The prevalence of DME is 3% in mild nonproliferative retinopathy and rises to 38% in eyes with moderate-to-severe nonproliferative retinopathy, eventually reaching 71% in eyes with proliferative retinopathy [5]. If left untreated, 20–30% of patients with DME will experience a doubling of the visual angle within 3 years [6]. The pathogenesis of DME is multifactorial. It is predominantly due to generalized breakdown of the inner blood–retinal barrier (BRB), leading to accumulation of fluid and plasma constituents, such as lipoproteins, within the intraretinal layers of the macula [7,8]. Factors such as duration of diabetes, insulin dependence, glycosylated hemoglobin levels, proteinuria and hypertension have all been implicated in the development of DME [6]. The factors that underlie the pathogenesis of DME are of great importance in order to better understand the various treatment modalities that are currently available.

The BRB operates fundamentally in two ways:

- The inner barrier is the endothelial membrane of the retinal vessels;
- The outer barrier is the retinal pigment epithelium.

Breakdown of the BRB may result from several mechanisms. One is damage to the tight junctions of capillary endothelial cells from vitreoretinal adhesion and traction on the macula, or from secretion into the vitreous of factors produced by the retina and other parts of the eye that increase vascular permeability [9]. VEGF is the main factor whose expression is induced by hypoxia [10] and IL-6 [11]. The second mechanism is damage to the function of the retinal pigment epithelium by ischemia and disruption of the BRB tissues [12]; and the third is disruption of the BRB by inflammation. The inflammatory mediators are prostaglandins, leukotrienes, histamine, bradykinin, platelet-activating factor and IL-1 [13]. It has long been postulated that focal DME is generally responsive to focal argon laser photocoagulation, based on the findings from the ETDRS [14]. Eyes with diffuse DME or with refractory DME are, however, much less responsive to macular laser treatment [15]. It should be noted that the distinction between focal and diffuse DME has been recently challenged [16].

Therapeutic interventions

Laser photocoagulation

Laser photocoagulation had been the only established treatment for vision-threatening DR and DME until recent years [17,18]. Most of the clinical evidence for the benefits of laser treatment of clinically significant DME is derived from the findings of the ETDRS trial. This trial defined clinically significant DME as either any retinal thickening within 500 µm of the center of the macula, hard exudates within 500 µm of the center of the macula with adjacent retinal thickening, or retinal thickening at least 1 disc area in size, any part of which is within 1 disc diameter of the center of the macula. It was found that focal photocoagulation reduced the risk of a 15-letter loss in visual acuity (VA) from 8 to 5% at 1 year and from 24 to 12% at 3 years [3]. Treatment was applied to leaking microaneurysms and areas of retinal thickening, not closer than 500 µm from the center of the macula, with spot sizes of 50–100 µm [18]. Grid laser may be used for a more diffuse presentation of DME [18], although the results are generally not as promising as those for focal laser [17].

Potential adverse effects of laser treatment for DME include VA loss, altered color perception, night blindness, choroidal neovascularization, metaplasia of the retinal pigment epithelium and accidental burns in the fovea [19]. In order to minimize these complications a subthreshold diode micropulse laser photocoagulation protocol was developed, for treating DME [20–22] and PDR [21,23]. A randomized, controled trial (RCT) involving 263 patients with DME, evaluated this technique and focused the laser on thickened retinal areas, zones of nonperfusion and leaking microaneurysms. This micropulse laser was compared with a mild macular grid approach, which used lighter but more widespread burns (200–300 in all) to both thickened and unthickened retinas throughout the macular area. Results demonstrated similar VA outcomes at 12 months in both methods, but reduced retinal thickness in the subthreshold diode micropulse laser group [24]. In two other RCTs [25,26], both treatment modalities resulted in similar outcomes in terms of both VA and retinal thickness. In one of those studies, retinal sensitivity as measured by microperimetry, was better following the micropulse technique [26], than the newer technique [25].

Another new approach involved the application of a computer-driven pattern of short-duration laser burns (10–30 ms) [27]. Nagpal *et al.* compared this approach to standard laser in 60 patients with PDR or severe nonproliferative DR (NPDR). They found that VA did not change from baseline at 6 months in either group, although the patterned laser led to less spreading of laser spots and was associated with less patient discomfort during treatment [28].

Pars plana vitrectomy

Pars plana vitrectomy (PPV) in the treatment of DR was usually preserved for managing severe, complicated proliferative DR or for treating DME when other modalities failed [29,30]. The results of PPV for DME were first reported in patients with a thickened and taut posterior vitreous membrane [29]. Subsequent studies evaluated vitrectomy results in patients with neither a thickened posterior membrane nor posterior vitreous detachment (PVD) [30] and in those with PVD [31,32]. The mechanism underlying the effectiveness of vitreous surgery for DME involves relief of the posterior hyaloid membrane traction [29,30], removal of inflammatory cytokines [31] such as VEGF [33] and an increase in preretinal oxygen pressure [34]. Surgical approaches are most commonly used for diffuse and nonresolving DME. Christoforidis *et al.* analyzed multiple studies involving a variety of inclusion criteria and surgical techniques and found that PPV led to the resolution of DME in 83% of cases, with 56% demonstrating improved VA [35].

A prospective cohort study recently examined the utility of PPV in treating DME with vitreomacular traction in 87 eyes with at least moderate VA loss and central subfield thickening on ocular computerized tomography (OCT) of ≥300 µm. Additional surgical techniques employed were epiretinal membrane peeling (61%), internal limited membrane peeling (54%) and injection of corticosteroids at the end of surgery (64%). All patients were followed for 6 months. At the end of this period all eyes experienced a median reduction of retinal thickness of 160 µm and a mean VA gain of three letters [36].

Further support to the effectiveness of PPV has also been reported for diffuse nontractional DME. In a retrospective consecutive case series involving 332 patients (496 eyes) followed for a mean of 74 months (range: 12 to 170 months), results showed that the final VA improved in 53% of eyes, remained unchanged in 31% and worsened in 16% [37]. There have not yet been any publications on randomized placebo-controlled trials for evaluating PPV for DME. Improvements in the PPV technique include the use of smaller gauge vitrectors (23 and 25 gauge), which offer the advantages of less trauma and postoperative discomfort as well as quicker healing [38–42].

Combination treatment was suggested to enhance the beneficial effects of PPV and to obviate the limitations of the above-mentioned treatment methods [43–45]. Kang *et al.* reported a prospective, interventional case series involving 24 eyes from 24 subjects who were diagnosed with intractable DME of nontractional origin and who underwent PPV [44]. Intravitreal triamcinolone acetonide (TA) injection and macular laser photocoagulation were conducted sequentially at 1 and 14 days after PPV. The changes in both best-corrected VA (BCVA) and central macular thickness (CMT) at 3, 6 and 12 months from baseline were statistically significant ($p < 0.003$). The major adverse events after triple therapy were the development of nuclear sclerotic cataracts (eight out of 12 phakic eyes) and elevation of intraocular pressure (IOP; eight out of 24 eyes). Other reports suggested that eyes that received TA-assisted PPV showed significantly less breakdown of the blood–ocular barrier than those who underwent routine PPV [45]. Complications of PPV include cataract formation (11%), vitreous hemorrhage (7%), retinal tear (9%), retinal detachment (2%), reproliferation of diabetic fibrovascular membranes, iris rubeosis and neovascular glaucoma (2%), epiretinal membrane and macular hole formation (7 and 1%, respectively) [35,46].

Intravitreally administered pharmacological agents

Pharmacological agents administered intravitreally during PPV are also being investigated as possible options creating PVD or for the clearance of vitreous hemorrhage [47]. Vitreosolve® (a carbamide derivative) is currently being evaluated in a Phase III RCT [201] in patients with NPDR. Another agent is microplasmin, a fragment of plasmin. It is being studied in a placebo-controlled Phase II trial [202] as a treatment for DME. When evaluated for nonproliferative vitreoretinal disease [203], it proved superior to a placebo for inducing PVD as well as for resolving the condition without the need for surgery [48]. One small prospective case series investigating intravitreal injections of autologous plasmin as a treatment for DME demonstrated improvements in both macular edema and retinal thickness compared with the noninjected control eyes [49].

Corticosteroids

Inflammatory processes have been strongly implicated in the etiology of DME. The rationale for the use of corticosteroids to treat DME derives from the observation that the increase in retinal capillary permeability leading to the formation of macular edema is caused by the breakdown of the BRB, mediated in part by VEGF [50–52]. The pathogenesis of retinal vascular permeability has also been attributed to inflammation, particularly via leukostasis within retinal capillaries. The attraction and adhesion of leukocytes to the vascular wall in the setting of diabetes may be due to an increased expression of leukocyte adhesion molecules, such as retinal endothelial cell intercellular adhesion molecule-1 and CD18 [53–55]. Therefore, attenuation of the effects of VEGF and a reduction in inflammation may reduce macular edema associated with DR. Since corticosteroids have been demonstrated to both inhibit the expression of VEGF and the VEGF gene [56,57] and to have anti-inflammatory

properties, there is a strong rationale for their use in the treatment of DME.

Triamcinolone acetonide

For nearly a decade, TA, a synthetic corticosteroid, has been the principal agent of its class administered intravitreally for the treatment of DME [58–60] and other ocular neovascular diseases [61]. Intravitreal TA (IVTA) was found to inhibit ocular neovascularization [62] and the upregulation of inflammatory molecules [63] and VEGF *in vitro* [64]. A similar effect on VEGF levels in response to IVTA has been observed clinically [65]. Most of the clinical trials investigating IVTA for DME showed improvement in edema and BCVA [66–69], but the majority have included small numbers of patients or have had relatively limited follow-up and adverse effects of cataract formation and IOP elevations were common [69]. The effect of a single injection IVTA is dose-dependent, ranging from 6–9 months for a 20 mg dose and 2–4 months for a 4-mg dose [70].

In a 2-year, randomized, placebo-controlled trial that randomized 69 eyes with refractory DME to IVTA (4 mg) or sham injection, the IVTA group (mean 2.6 injections) produced VA improvements of five or more letters in a significantly greater number of eyes than those observed in the controls (56 vs 26%, respectively; $p = 0.006$) [71]. At the end of the 5-year open-label extension, these improvements were maintained with TA [72]. Among the side effects commonly observed were cataract and ocular hypertension. Cataract surgery was required in 54% of the treated eyes compared with 0% in the placebo group and ocular antihypertensive therapy was required in 44% of the TA-treated patients compared with 3% in the control arm [71]

The DRCR.net trial was a Phase III randomized, multicenter clinical trial, evaluating the efficacy and safety of 1 and 4 mg doses of preservative-free IVTA in comparison with focal/grid photocoagulation for the treatment of DME [73]. The study recruited 693 patients with DME involving the fovea (840 eyes) and eyes were randomized to receive either IVTA 1 or 4 mg or focal/grid photocoagulation. At 4 months, the mean VA was better ($p = 0.001$) in the 4 mg TA-treated eyes than in the other two groups. At 2 years, however, the mean VA was greater in the laser-treated group ($p = 0.02$ and 0.002 compared with the 1 and 4 mg groups, respectively) [74]. Anatomical assessments by OCT were compatible with the VA results. Intraocular pressure was increased from baseline by ≥10 mmHg at any visit in 4, 16 and 33% of eyes in the control group, IVTA 1 and 4 mg groups respectively and cataract surgery was performed in 13, 23 and 51% of eyes in the three treatment groups, respectively [74]. The VA results were similar after a 3-year follow-up [75], although a further exploratory analysis suggested that risk of progression of retinopathy was significantly lower with TA 4 mg but not TA 1 mg, compared with laser treatment [76]. The results of this study support that focal/grid photocoagulation should currently be the benchmark against which other treatments are compared in clinical trials of DME.

It is noteworthy that the DRCR.net study did not classify DME into focal or diffuse with regard to IVTA. However, IVTA may still have a therapeutic role in eyes that have previously failed to benefit from laser treatment: those patients were specifically excluded from the DRCR.net [73] and these patients would be most likely to be considered for TA in clinical practice [60].

IVTA should also be considered an effective treatment option in pseudophakic eyes with DME according to the DRCR.net trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser [74]. Visual acuity results were substantially better than for phakic eyes, such that the degree of improvement appeared comparable to that of the pseudophakic eyes in the ranibizumab groups and superior to that of the pseudophakic eyes in the sham plus prompt laser group at 1 year and 2 years.

Due to the limited efficacy of IVTA alone and its safety profile, combination approaches using laser photocoagulation with TA administered either intravitreally [71,77–81] or by sub-Tenon's capsule injection [81–83] have also been studied in small prospective case series [77,82] and RCTs [71,78–81,83,84]. Results of these trials have been extremely variable, with some proving that combination treatment is superior to laser alone [78,79,82,84] and others finding benefits lasting only a few months [83] or not having found any additional benefit at all [81]. In addition, IVTA is currently being evaluated in combination with topical nepafenac versus TA alone in a Phase III RCT for the treatment of DME [204]. In recent years many RCTs involving TA alone, as a sustained-release formulation or in combination with other agents, were included in the ClinicalTrials.gov registry [59,85,205].

Sumodics I-vation™ is a TA sustained-delivery drug system with a helical design and contains 925 µg TA. It was evaluated in a Phase I study for DME (patients were randomized to either a slow- or fast-release formulation) and showed reduction in macular edema (ME) and stabilization of VA after 24 months of follow-up for both formulations. At 24 months, the proportion of patients demonstrating improved VA (>0 ETDRS letter gain from baseline) was 64% in the slow-release group and 72% in the fast-release group and 28.6% of patients in the fast-release group gained >15 letters. The reported adverse events were cataract formation, rise in IOP and one culture-positive endophthalmitis [86,87].

Dexamethasone

Due to the short half-life of intravitreal dexamethasone (DEX) [88], it played a limited role in the management of chronic and/or recurrent DME. However, biodegradable sustained-release intravitreal implants containing DEX were shown to increase the duration of the drug's action [89,90]. Ozurdex® (Allergan Inc., CA, USA) is a sustained-release DEX implant that is injected intravitreally. The DEX is embedded in a biodegradable polymer filament. The polymer undergoes slow, consistent hydrolysis and gradually releases the steroid into the vitreous cavity, allowing sustained release for up to 4 months. The polymer breaks down into lactic acid and glycolic acid, which are then metabolized into carbon dioxide and water and the device breaks down completely over a period of 6 weeks.

A Phase II, multicenter trial evaluated the safety and efficacy of the use of Ozurdex in the treatment of persistent ME secondary to DR, retinal vein occlusion, post-cataract surgery and uveitic cystoid macular edema. It showed that the 700 µg implant resulted in a significant increase in the percentage of patients achieving at least two lines of improvement in VA with no increased risk of raised IOP or cataract [90].

In an open-label Phase II study of a 0.7 mg DEX implant for the treatment of DME in vitrectomized patients (the INTERIM study) [91], improvement in DME was seen as early as 1 week after injection and persisted to week 13. The BCVA also improved: at weeks 1 and 13, 18.5 and 30.9% of patients, respectively, achieved ≥10 letter gain and no patient lost ten letters after 13 weeks. The most common adverse events in the treated eyes were conjunctival hemorrhage (24%), eye pain (13%) and conjunctival hyperemia (7%). A total of 7.5% of all patients had an IOP increase ≥10mmHg from baseline at week 4, which decreased to 1.8% at week 13.

In a larger open-label, Phase IIIb study of DEX 700 µg intravitreal implants for the treatment of DME in vitrectomized patients (the CHAMPLAIN study) [92], the mean change from baseline central retinal thickness was -156 µm at week 8 ($p < 0.001$) and -39 µm at week 26 ($p = 0.004$). The mean increase in BCVA from baseline was six letters at week 8 ($p < 0.001$) and three letters at week 26 ($p = 0.046$). At week 8, 30.4% of patients had gained ≥10 letters in BCVA. Conjunctival hemorrhage, conjunctival hyperemia, eye pain and increased IOP were the most common adverse events. Specifically, 16.7% of patients (eight out of 48) initiated IOP medication during the study, no patient required a laser or surgical procedure to control IOP and no patient discontinued from the study due to elevated IOP. Phase III RCTs of a novel DEX intravitreal delivery system [206,207] are underway to confirm the benefits of DEX implant for the treatment of ME in general [93], and specifically DME [94,95].

Fluocinolone acetonide

Two slow-release devices containing fluocinolone acetonide (FA) were tested in Phase III clinical trials for the treatment of DME: one was the 0.59 mg implant of Retisert® (Bausch & Lomb, Rochester, NY, USA) and the other was Alimera Iluvien®.

Retisert

Retisert is a nonbiodegradable FA implant [96,97]. The pharmacokinetics study of this implant revealed that the drug delivery is linear and that it releases corticosteroid for up to 3 years [98]. Two Phase IIb/III, multicenter, randomized, double-blind, clinical studies in eyes with severe, noninfectious posterior uveitis evaluated two implant dosages: 0.59 mg FA that releases 0.5 µg of the drug per day and 2.1 mg that releases 2 µg per day. Efficacy and safety results were similar for both doses at 34 weeks. Favorable effects included reduction of inflammation, reduction of the number of anti-inflammatory medications and preservation or improvement of VA [97]. Results from a Phase IIb/III trial that evaluated the efficacy and safety of the 0.59 mg FA intravitreal implant for patients with uveitis compared with standard of care showed that the FA intravitreal implant provided better control of inflammation in patients with uveitis compared with systemic therapy [99]. Complications associated with this drug-delivery system include rhegmatogenous retinal detachment, vitreous hemorrhage, device extrusion, endophthalmitis, raised IOP, cataract and suture exposure [85,97,99]. This drug is currently not US FDA-approved for DME due to its high side-effect profile.

Alimera iluvien

Alimera Iluvien is another reservoir implant and contains one-half the amount of FA as Retisert. It has two release rates (0.5 or 0.2 µg/day) designed to last approximately 1.5 or 3 years, respectively. Results from the FAMOUS trial that assessed the pharmacokinetics and pharmacodynamics of 0.2 or 0.5 µg/day Iluvien showed that this intravitreal insert provided excellent sustained intraocular release of FA for more than 1 year [100]. Results from the FAME trial (which consists of two 36-month, double-blind, randomized,

multicenter trials, involving patients with persistent DME despite at least one macular laser) were recently published [101]. According to the combined analysis, 28.7% of patients treated with the low-dose (0.23 µg/day) and 28.6% of patients treated with the high-dose (0.45 µg/day) gained at least 15 letters, compared with 16.2% of the control patients (p = 0.002 for high vs low dose). Over 50% of the Iluvien low-dose patients gained at least five letters at 24 months. Furthermore, over 75% of the Iluvien low-dose patients received only a single administration of Iluvien. Over one-third of the one-time administration patients for whom there were 24 months of data, gained >15 letters at 24 months. Patients receiving low-dose Iluvien were also less likely to require additional treatments for their DME. IOP increases of ≥30 mmHg at any time point were seen in 16.3% of the low-dose patients compared with 21.6% of the high-dose patients. Over the 24-month study period, 3.7% of the low-dose patients and 7.6% of the high-dose patients had undergone a filtration procedure to reduce their IOP compared with 0.5% in the sham group. Low-dose Iluvien patients also experienced slightly lower rates of retinal detachment (0.5 compared with 1.6% for controls) and vitreous hemorrhage (2.1 compared with 2.7% for controls) that were deemed serious by the reporting physician. The authors concluded that both low- and high-dose inserts significantly improved BCVA, but that the risk:benefit ratio was superior for the low-dose type.

Anti-VEGF agents

VEGF is a potent promoter of angiogenesis and vascular permeability, both are directly associated with the pathophysiology of DR [102–105]. VEGF promotes angiogenesis by acting as an endothelial cell mitogen [106], chemoattractant [107] and survival factor [108] and induces vascular permeability [109] by acting directly on endothelial cells, forming fenestrations [110] and dissolution of tight junctions [51,111].

VEGF also acts as an inflammatory cytokine [112] causing leukostasis. This process is of major importance to capillary blockage and dropout [53,113] and to endothelial cell apoptosis, both are characteristic of retinal vascular damage found in DR [114]. VEGF also acts as a chemoattractant for monocytes [115,116] – the migration of which to the site of ischemic neovascularization is essential for its full manifestation [117]. Furthermore, VEGF synthesis is upregulated by hypoxia [118] and its levels are elevated in regions of focal ischemia [53].

Early clinical studies demonstrated elevated levels of VEGF in eyes of patients with DR [10,103,105,119,120]. Preclinical studies also demonstrated that elevated levels of VEGF could induce pathology characteristic of DR [121,122], while agents that inhibit VEGF activity could inhibit DR pathology [112,117].

Several VEGF antagonists, administered intravitreally are currently being used and investigated for the treatment of DME. Pegaptanib, an RNA anti-VEGF aptamer that selectively binds VEGF165 [123] and ranibizumab, a nonselective monoclonal antibody antigen-binding fragment that binds all VEGF isoforms [124], are approved for the treatment of neovascular age-related macular degeneration [125–127]. Bevacizumab, a full-length monoclonal antibody related to ranibizumab, is being used off-label for a variety of ocular neovascular diseases, including DR [128]. While these three agents have been extensively investigated, two other VEGF antagonists are also being evaluated in Phase II trials as intravitreal treatments for DME: one is the VEGF Trap-Eye (aflibercept) [208], a fusion protein containing the binding site of VEGF receptor 1 [129,130] and the other is bevasiranib [209], a siRNA agent that targets VEGF. The results of these trials have yet to be reported. Sirolimus (rapamycin), a drug principally used for its immunosuppressive activity, has also been shown to act as a VEGF antagonist by inhibiting both VEGF expression [131] and VEGF-induced hyperpermeability [132] and it is being examined as a subconjunctival injection for the treatment of DME [210].

Pegaptanib sodium (Macugen®)

The Macugen DR Study Group conducted a Phase II trial on its use for fovea-involving DME [133]. 172 patients who had no previous history of treatment for DME were randomized to four study arms: 0.3, 1 or 3 mg intravitreal pegaptanib or sham injections that were given at weeks 0, 6 and 12. Additional injections could be administered to subjects after week 12 at the discretion of the masked investigators. Similarly, investigators could choose to treat with focal laser beginning at week 13. Results demonstrated that eyes treated with pegaptanib did better than the ones in the sham arm, especially those in the 0.3 mg group. After 36 weeks of follow-up, the pegaptanib-treated eyes had better VA (p = 0.04 for the 0.3 mg group vs sham), more reduced central retinal thickness (CRT) (p < 0.01 for the 0.3 mg group vs sham) and less need for macular laser photocoagulation (p = 0.042 for the 0.3 mg group vs sham).

It is worth mentioning that these results were seen despite the fact that 23% more sham-treated eyes received focal or grid laser treatment between weeks 12 and 36. Visual improvement was detected in 73% of patients in the pegaptanib 0.3 mg group versus 51% in the sham group. The mean improvement in the 0.3 mg group was 4.7 letters and 18% gained ≥3 Snellen lines. Other trials have concluded that treatment-naive eyes respond better to anti-VEGF therapy [134–136].

The results of the Phase II/III, randomized, double blind, multicenter, 2-year trial [137] comparing pegaptanib with sham injections in the treatment of DME were recently published. This study randomized 260 patients to receive pegaptanib 0.3 mg or sham injections every 6 weeks for 1 year. Patients could receive focal/grid photocoagulation beginning at week 18. During year 2, subjects received injections as often as every 6 weeks per prespecified criteria. In total, 36.8% subjects from the pegaptanib group experienced a VA improvement of ≥10 letters at week 54 compared with baseline versus 19.7% from the sham group (p = 0.0047). For pegaptanib-treated subjects, change in mean VA from baseline by visit was superior (p < 0.05) to sham at weeks 6, 24, 30, 36, 42, 54, 78, 84, 90, 96 and 102. At week 102, pegaptanib-treated subjects gained, on average, 6.1 letters versus 1.3 letters for sham (p < 0.01). Fewer pegaptanib- than sham-treated subjects received focal/grid laser treatment (p = 0.002). Pegaptanib was well tolerated; the frequencies of discontinuations, adverse events, treatment-related adverse events and serious adverse events were comparable in the pegaptanib and sham groups.

Ranibizumab

The READ-2 trial was a Phase II trial that compared ranibizumab to focal/grid laser photocoagulation or their combination. In total, 126 patients with either Type 1 or 2 diabeties with a previous history of treatment for DME were randomized to three groups; the first received ranibizumab 0.5 mg alone at baseline and at months 1, 3 and 5. The remaining groups received focal/grid laser or combined ranibizumab plus laser at baseline and at 3 months. After 6 months, if retreatment criteria were met, all subjects could be treated with ranibizumab. The mean improvement in BCVA was 7.4, 0.5 and 3.8 letters at the 6-month primary end point, compared with 7.7, 5.1 and 6.8 letters at month 24 and the percentage of patients who gained three lines or more of BCVA was 21, 0 and 6% at month 6, compared with 24, 18 and 26% at month 24. The percentage of patients with 20/40 or better Snellen equivalent at month 24 was 45, 44 and 35% for groups 1, 2 and 3, respectively. Mean foveal thickness at month 24 was 340, 286 and 258 µm for groups 1, 2 and 3, respectively and the percentage of patients with center subfield thickness of 250 µm or less was 36, 47 and 68%, respectively [138]. This study showed that intraocular injections of ranibizumab provided benefit for patients with DME for at least 2 years, and when combined with focal or grid laser treatments, the amount of residual edema was reduced, as were the frequency of injections needed to control edema.

The DRCR.net trial was a large-scale RCT that compared ranibizumab with TA as an adjunct to laser photocoagulation [74]. It randomized 854 eyes to four treatment arms: one group received IVTA and focal/grid photocoagulation within 3–10 days of injection, the other received ranibizumab 0.5 mg with focal/grid photocoagulation within 3–10 days of injection, the third received sham injection and laser treatment and the fourth group received ranibizumab with laser deferred for ≥24 weeks [74]. Retreatment was determined by an algorithm at monthly visits. The 1-year mean change in the VA letter score from baseline was significantly greater in the ranibizumab plus prompt laser group (+9 ± 11, p < 0.001) and ranibizumab plus deferred laser group (+9 ± 12, p < 0.001) but not in the TA plus prompt laser group (+4 ± 13, p < 0.31) compared with the sham plus prompt laser group (+3 ± 13). Reduction in mean central subfield thickness in the TA plus prompt laser group was similar to both ranibizumab groups and greater than the sham plus prompt laser group. In the subset of pseudophakic eyes at baseline (n = 273), VA improvement in the TA plus prompt laser group was comparable to the ranibizumab groups. Overall, 50% of the eyes in the ranibizumab arms had substantial improvement (≥10 letters), while approximately 30% gained ≥15 letters. Substantial VA loss (≥10 letters) was uncommon. The results were similar whether focal/grid laser was given starting with the first injection or if it was deferred by >24 weeks. 2-year VA outcomes were similar to the 1-year outcomes. There was no evidence of any systemic events attributable to any given treatment. There were three cases of endophthalmitis in the ranibizumab groups, while 38% of the eyes in the TA arm had increases in IOP of ≥10 mmHg from baseline and 15% of eyes that were phakic at baseline had cataract surgery. This study concluded that ranibizumab is superior to IVTA or laser treatment alone and should be considered for patients with DME and characteristics similar to those in this clinical trial.

Another 12-month, multicenter, placebo-controlled, double-masked study (RESOLVE study) investigated the safety and efficacy of ranibizumab in DME involving the foveal center in patients with Type 1 or 2 diabetes, a CRT ≥ 300 µm and a BCVA of 73–39 ETDRS letters [139]. The patients were randomly assigned to intravitreal ranibizumab (0.3 or 0.5 mg; n = 51 each) or sham (n = 49). The treatment schedule comprised three monthly injections, after which treatment could be stopped/reinitiated with an opportunity for rescue laser photocoagulation (protocol-defined

criteria). Dose-doubling was permitted after month 1 (protocol-defined criteria according to which the injection volume increased from 0.05–0.1 ml and remained at 0.1 ml thereafter). At month 12, the mean BCVA improved from baseline by 10.3 ± 9.1 letters in the ranibizumab group and declined by 1.4 ± 14.2 letters in the sham group ($p < 0.0001$). The mean CRT reduction was 194.2 ± 135.1 µm for ranibizumab and 48.4 ± 153.4 µm for sham ($p < 0.0001$). There was a gain of ≥10 letters BCVA from baseline in 60.8% of the ranibizumab-treated eyes and 18.4% of sham eyes ($p < 0.0001$). Safety data were consistent with previous studies of intravitreal ranibizumab.

In a recent publication by Mitchell *et al.* that evaluated ranibizumab monotherapy or combined with laser versus laser monotherapy for DME, 345 patients aged ≥18 years with Type 1 or 2 diabetes mellitus and visual impairment due to DME were randomized to ranibizumab plus sham laser (n = 116), ranibizumab plus laser (n = 118), or sham injections plus laser (n = 111) [140]. Ranibizumab/sham was given for 3 months and then *pro re nata* and laser/sham laser was given at baseline and then *pro re nata* (the patients had scheduled monthly visits). The results demonstrated that ranibizumab alone and combined with laser were superior to laser monotherapy in improving mean average change in BCVA letter score from baseline to month 1 through 12 (+6.1 and +5.9 vs +0.8; both $p < 0.0001$). At month 12, a significantly greater proportion of patients had a BCVA letter score ≥15 and a BCVA letter score level >73 (20/40 Snellen equivalent) with ranibizumab (22.6 and 53%, respectively) and ranibizumab plus laser (22.9 and 44.9%) versus laser alone (8.2 and 23.6%). The mean CRT was significantly reduced from baseline with ranibizumab (-118.7 µm) and ranibizumab plus laser (-128.3 µm) versus laser alone (-61.3 µm; both $p < 0.001$). Health-related quality of life, assessed through National Eye Institute Visual Function Questionnaire (NEI VFQ-25), improved significantly from baseline with ranibizumab alone and combined with laser ($p < 0.05$ for the composite score and vision-related subscales) versus laser alone. Patients received approximately seven (mean) ranibizumab/sham injections over 12 months. There were no cases of endophthalmitis. Increased IOP was reported for 1 patient in each of the ranibizumab arms. Ranibizumab monotherapy or combined with laser was not associated with an increased risk of cardiovascular or cerebrovascular events in that study.

In another two Phase III RCTs (the RISE and RIDE studies), a significantly higher percentage of patients receiving monthly Lucentis® achieved an improvement in BCVA of at least 15 letters at 24 months, compared with those in sham injection group. The Phase III RIDE study randomized 382 patients with DME to double-blind monthly injections of ranibizumab 0.3 (n = 125) or 0.5 mg (n = 127) or placebo (n = 130) [211]. After month 24, patients in the placebo group were eligible to receive monthly injections of 0.5 mg ranibizumab.

At 24 months, 33.6% of patients who received ranibizumab 0.3 mg and 45.7% of those who received ranibizumab 0.5 mg were able to read at least 15 more letters on the eye chart than they were at baseline. This compares with 12.3% of the placebo group; the difference between each dose group and placebo was statistically significant (no p-values are stated in the report). A preliminary safety analysis showed an ocular and systemic safety profile consistent with previous Phase III trials of ranibizumab.

The Phase III RISE study randomized 377 patients with DME to receive monthly injections of either Lucentis 0.3 (n = 125) or 0.5 mg (n=125), or monthly sham injections (n = 127) [212]. At 24 months, 44.8% of patients who received Lucentis 0.3 mg and 39.2% of patients who received Lucentis 0.5 mg were able to read at least 15 more letters on the eye chart than they were at the start of the study, compared with 18.1% of patients who received sham injections. The difference between each Lucentis dose group and the sham injection group was statistically significant.

■ Bevacizumab

For reasons of cost and availability, bevacizumab is currently the best-studied anti-VEGF medication for DME. The DRCR.net conducted a randomized study of 121 eyes over a 12-week period (safety data are reported for 24 weeks) [141]. There were five treatment arms in the study: focal photocoagulation, two intravitreal injections of bevacizumab 1.25 mg at 0 and 6 weeks, two intravitreal injections of bevacizumab 2.5 mg at 0 and 6 weeks, bevacizumab 1.25 mg at week 0 followed by a sham injection at week 6 and bevacizumab 1.25 mg at 0 and 6 weeks combined with focal photocoagulation at 3 weeks. 69% of eyes in this study have had previous treatment for DME. Results showed that the two groups that received only two bevacizumab injections without laser had a statistically significant improvement in vision compared with the laser-only group; these improvements were maintained at the 12-week study period. The median gain in vision at week 9 was seven letters for the 1.25 mg group and eight for the 2.5 mg group. OCT results were also better in these groups at the 3-week visit, with a trend suggesting a similar finding at subsequent visits, with no detectable differences between the 1.25 and 2.5 mg doses. The single injection group had no advantage over the photocoagulation group in this study. Interestingly, the combination of laser and bevacizumab yielded comparable results to the laser-only group, with a trend toward worse short-term VA outcomes than the eyes that received two bevacizumab injections.

The study reports that previously untreated eyes and eyes with subretinal fluid had a greater improvement in VA ($p = 0.04$ and $p = 0.06$ respectively) after bevacizumab treatment, it also demonstrated a trend toward a better response in terms of OCT after bevacizumab treatment.

In a noncomparative trial by Haritoglou *et al.*, 1.25 mg bevacizumab was administered at baseline with subsequent repeat dosing based on the presence of a improved OCT or VA response after the initial injection [142]. All 126 eyes had diffuse and chronic DME that failed previous treatment. At 6 months, the mean CRT had decreased from 463–374 µm ($p < 0.001$). The improvement in mean VA was not significant at 6 months. Baseline retinal thickness, previous treatment and diameter of the foveal avascular zone did not correlate with responses to treatment.

When comparing different dosing regimens, the DRCR.net study detected no difference between 1.25 and 2.5 mg bevacizumab [141]. Similiar results are reported by the PACORES group [143] and by Lam *et al.* [144]. The latter study involved 52 eyes undergoing three monthly injections of 1.25 or 2.5 mg bevacizumab with a mean follow-up period of more than 6 months. Both dosage groups had significant reductions in central foveal thickness at all visits, which peaked at the 3- and 4-month visits. Significant improvements in BCVA at all visits, excluding the 1-week visit, was also observed in both groups. The two study groups had statistically similar results throughout the 6 months. Subgroup analyses suggested that the 17 eyes with histories of previous DME treatment had less improvement at 6 months.

ETDRS Report Number 19 suggests the possibility of a trend toward a lesser treatment effect for focal laser in eyes with DME and severe capillary loss [145]. Bonini-Filho *et al.* conducted a pilot study on the value of intravitreal bevacizumab for those eyes [146]. All patients have had a 1.5 mg injection at baseline and at follow-up visits based on the presence of intraretinal or subretinal fluid on OCT. CMT and BCVA improved significantly throughout the 54-week study period. Follow-up fluorescein angiogram revealed no progression of capillary loss at study closure.

Among the other published trials supporting the use of bevacizumab in patients with DME is the BOLT study [147]. This study randomized 80 eyes of 80 patients with center-involving clinically significant DME and at least one prior modified ETDRS macular laser therapy (MLT) to either intravitreal bevacizumab (ivB) (6 weekly; minimum of three injections and maximum of nine injections in the first 12 months) or MLT (4 monthly; minimum of one treatment and maximum of four treatments in the first 12 months). The baseline mean ETDRS BCVA was 55.7 ± 9.7 in the bevacizumab group and 54.6 ± 8.6 in the laser arm. The mean ETDRS BCVA at 12 months was 61.3 ± 10.4 in the bevacizumab group and 50.0 ± 16.6 in the laser arm ($p = 0.0006$). Furthermore, the bevacizumab group gained a median of eight ETDRS letters, whereas the laser group lost a median of 0.5 ETDRS letters ($p = 0.0002$). The odds of gaining ≥10 ETDRS letters over 12 months were 5.1-times greater in the bevacizumab group than in the laser group (adjusted odds ratio: 5.1; 95% CI: 1.3–19.7; $p = 0.019$). At 12 months, CMT decreased from 507 ± 145 µm at baseline to 378 ± 134 µm ($p < 0.001$) in the ivB group, whereas it decreased to a lesser extent in the laser group, from 481 ± 121 µm to 413 ± 135 µm ($p = 0.02$). The median number of injections was nine in the ivB group and the median number of laser treatments was three in the MLT group.

Three trials compared intravitreal bevacizumab and IVTA [148–150]. The study performed by Ahmadieh *et al.* had a longer follow-up (24 weeks) than the other two [148]. This study randomized 115 eyes to one of three study arms: a bevacizumab-only arm, an IVTA plus bevacizumab combination arm and a placebo arm. The two treatment arms received three 1.25 mg bevacizumab injections separated by 6 weeks, with the IVTA plus bevacizumab group receiving an additional injection of TA 2 mg at the baseline visit only. Results demonstrated better BCVA in the two treatment groups compared with the placebo group at all time points, with the exception of the bevacizumab-only group at the first 6-week follow-up. There was no difference in BCVA or CMT between the bevacizumab and IVTA plus bevacizumab groups. The effect of the injections lasted for 12 weeks after the final injection in their study, with no clear trend toward worsening acuity or edema throughout that period. At 24 weeks the mean CMT reductions were 96 µm ($p = 0.012$ compared with the control group) in the bevacizumab-only group and 92 µm ($p = 0.022$ compared with the control group) in the bevacizumab plus IVTA group.

Faghihi *et al.* also compared intravitreal bevacizumab with IVTA in eyes with no history of treatment for DR [149]. They randomized 130 eyes of Type 2 diabetic patients to one of three arms: bevacizumab, IVTA plus bevacizumab and macular photocoagulation. Injections of bevacizumab 1.25 mg and TA 2 mg

were given at the baseline visit only. Each of the three groups had significant improvements in CMT at both the 6- and 16-week visits compared with baseline and in BCVA at both visits, with the exception of the bevacizumab group at 16 weeks. The bevacizumab group outperformed the laser group in CMT and BCVA at week 6 but not at week 16. The bevacizumab plus IVTA group outperformed the laser group in CMT and BCVA at both weeks 6 and 16. The results of this study suggest that a single bevacizumab injection will generally not last 16 weeks.

Soheilian *et al.* conducted an investigation [150,151] using the same design as Faghihi *et al.* but, unfortunately, their photocoagulation group had a significantly better mean BCVA at baseline, which precludes direct comparison between the two works. They concluded that both bevacizumab groups had similar, significant improvements in VA only when compared with photocoagulation.

In conclusion, bevacizumab treatment is associated with improvements in both VA and CMT. The treatment usually requires repeat dosing in order to increase its beneficial effect. A repeat dosing interval of 3–6 weeks seems most likely to produce maximal benefit. A dose of 2.5 mg does not appear to have a benefit over one of 1.25 mg.

■ Aflibercept (VEGF Trap-Eye)

This 110 kDa soluble decoy receptor binds with high affinity to all VEGF members, except unprocessed VEGF-C and -D [152]. Its safety and efficacy was evaluated in the CLEAR-IT 1 study. It was well tolerated with no serious side effects and 95% of patients had stable or improved VA at 6 weeks [153]. The VIEW trial aims to compare aflibercept to ranibizumab [213,214]. The DAVINCI trial included 219 patients with DME and compared different doses of aflibercept with macular laser. The best result was observed for three monthly loading doses of 2.0 mg aflibercept followed by *pro re nata* injection (average gain of 10.3 letters after 4.4 injections) [154].

■ RNA interference

siRNA is a 21–23 nucleotide double-stranded RNA that binds specifically to mRNA and prevents translation at the ribosomal level [155]. A Phase II, pharmacokinetic, randomized, double-blind, controlled, dose-comparison study of Cand5 (Bevasiranib, OPKO Health) for intravitreal injection for the treatment of DME [214] has been completed and the results are forthcoming.

■ Sirolimus

Sirolimus is an immunosuppressive agent that inhibits T-lymphocyte activation/proliferation occuring in response to antigenic and cytokine (IL-2, -4 and -15) stimulation by a mechanism that is distinct from that of other immunosuppressing agents. An interventional, nonrandomized open-label pilot study [209] is investigating the effectiveness of two 20 ml (440 mg) subconjunctival injections of sirolimus for DME.

■ TNF-α

TNF-α is a proinflammatory cytokine that has been implicated in the development of a variety of inflammatory diseases [156], as well as in processes central to DR pathology [157–159]. Clinical studies demonstrated high levels of TNF-α in the vitreous [50,160] and serum [161–163] of patients with DR and preclinical models of either systemic [164] or intravitreal [165] TNF-α inhibitors for the treatment of DR have demonstrated reduced retinal microvascular damage, as well as inhibited ocular neovascularization [166,167]. The effects of TNF-α are attributed to its action in upregulating the synthesis of VEGF [168] and also independently of VEGF pathways [104].

Clinical evidence for the efficacy of TNF-α inhibitors in DME is limited to one case series and one RCT. Intravenous infliximab, a monoclonal antibody targeting TNF-α, was administered in two infusions of 5 mg/kg (Remicade®, Sherring-Plough, Greece) in 1-month intervals for severe DME and showed both anatomic and functional improvement in four of the six eyes in the case series [169]. In the RCT, intravenous infliximab treatment led to a mean VA gain of 6.9 letters after 16 weeks in 11 patients with DME, a benefit that was sustained after the crossover to placebo, whereas placebo-treated eyes initially lost a mean of 2.8 letters but regained a mean of 6.6 letters after switching to infliximab ($p = 0.017$) [170].

Since intravenous administration of infliximab for the treatment of uveitis led to severe adverse effects [171], intravitreal administration of this agent should involve much lower doses. However, it should be noted that a recent Phase I trial evaluating intravitreal infliximab for the treatment of DME (two patients) and neovascular age-related macular degeneration (two patients)found that three of the four patients, including both patients with DME, developed intraocular inflammation as well as systemic antibodies against infliximab [172].

■ PKC-β2

PKC-β2 is a member of a kinase family that is activated by diacylglycerol, a second messenger-signaling lipid. Diacylglycerol levels are elevated by hyperglycemia [173]. Preclinical studies have demonstrated that PKC-β2-inhibitor ruboxistaurin (LY333531) can inhibit processes related to the pathophysiology of DR [174].

Intravitreal or oral administration of ruboxistaurin in rodents with diabetes blocked increases in vascular permeability [175,176]. Oral ruboxistaurin was examined in three placebo-controlled clinical trials as a treatment for DR and DME [50,160,177]. In the first, involving 252 patients with moderately severe to very severe NPDR, the drug did not prevent the progression of DR, although the 32-mg dose did result in a significant reduction of the time to moderate VA loss [177]. In the second larger study involving 685 patients with NPDR, ruboxistaurin reduced the risk of moderate VA loss, the need for laser treatment and the progression of ME to within 100 μm from the center of the macula, as well as increased the likelihood of a ≥15-letter VA gain [160]. The third trial was a 30-month trial involving 686 patients with mild-to-moderate NPDR. In this trial ruboxistaurin did not delay the progression to sight-threatening DME or application of laser therapy ($p = 0.14$) [177]. A Phase III clinical trial is currently examining its efficacy in the treatment of DME [215].

Future perspective

The new availability of treatment options has opened new perspectives in the treatment of DME. Among these are intravitreal steroid-releasing implants that have been designed in an attempt to provide long-term drug delivery to the macular region. Agents targeting VEGF show great benefit and combination treatment of the two are investigated extensively. In addition, studies are underway to evaluate potential

Executive summary

Laser photocoagulation
- The findings of the ETDRS trial are the main source of clinical evidence for the benefits of laser treatment for clinically significant diabetic macular edema (DME).

Pars plana vitrectomy
- Surgical approaches, particularly pars plana vitrectomy (PPV) are most commonly used for diffuse and nonresolving DME.
- Pharmacological agents administered intravitreally during PPV are being investigated as possible options in treating DME.

Corticosteroids
- Anti-inflammatory drugs have been strongly implicated in the etiology of DME and several agents are studied as therapeutic options.
- Traimcinolone acetonide has been the principal agent of its class administered intravitreally for the treatment of DME. Sumodics I-vation™ is a triamcinolone acetonide sustained-delivery drug system.
- Biodegradable sustained-release intravitreal implants containing dexamethasone were shown to be an effective treatment of DME.
- Two slow-release devices containing fluocinolone acetonide (FA) have been tested in Phase III clinical trials for the treatment of DME: Retisert® and Alimera Iluvien®.

Anti-VEGF agents
- VEGF is a potent promoter of angiogenesis and vascular permeability, both are directly associated with the pathophysiology of diabetic retinopathy and DME.
- The Macugen Diabetic Retinopathy Study Group was the first study to investigate the efficacy of pegaptanib sodium. Further studies have confirmed their results.
- The effectiveness of ranibizumab in treating DME was demonstrated in the READ-2 trial as well as the DRCR.net, RESOLVE and RESTORE trials.
- For reasons of cost and availability, bevacizumab is currently the best-studied anti-VEGF medication for DME.
- The effect of aflibercept (VEGF Trap-Eye), a receptor that binds with high affinity to all VEGF members, is being investigated in the CLEAR-IT 1 study.
- Small interfering RNAs are being investigated in Phase II trials as therapeutic options for DME. For example, bevasiranib (Cand5) – OPKO Health and AGN211745 (Sirna-027) – Allergan.
- Sirolimus, an immunosuppressive agent that inhibits T-lymphocyte activation/proliferation occurring in response to antigenic and cytokine agents, is being investigated as a treatment option for DME.

TNFα
- TNFα is a proinflammatory cytokine that has been implicated in the development of a variety of inflammatory diseases, including DME.

PKC-β2
- PKC-β2 is a member of a kinase family that has been implicated in the pathogenesis of diabetes mellitus. Its inhibitor – ruboxistaurin (LY333531) – can inhibit processes related to the pathophysiology of diabetic retinopathy.

benefits from other novel drugs that are directed against other specific molecular targets, including TNF-α and PKC-β2, and they also hold great promise. Many experimental treatment strategies are under investigation, but the benefits of most have yet to be established in Phase III clinical trials.

Conclusion

DME is a major cause of blindness in patients with DR. Substantial progress has been made in understanding the complex pathophysiology of DME. Focal and grid photocoagulation, as described in the ETDRS trials, remain the gold standard of treatment, but new classes of pharmacologic agents, which include long-acting steroid formulations delivered as intravitreal injections and anti-VEGF agents, now provide even better alternative treatment. Multiple treatment approaches are often needed to resolve the persistence of fluid within the macular region and combination treatment plays an important role in the complex management of DME. Further study is still much needed to establish the best treatment algorithm for DME.

Financial & competing interests disclosure

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