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.
Review: Clinical Trial Outcomes

Golan & Lowenstein

New developments in the treatment of diabetic macular edema

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 [1]. Little untreated, 20–30% of patients with DME will experience a doubling of the visual angle within 3 years [2]. The pathogenesis of DME is multifactorial. It is predominantly due to generalized breakdown of the inner blood–retinal barrier, lead to accumulation of fluid and plasma constituents, such as lipoproteins, within the intraretinal layers of the macula [3]. Factors such as duration of diabetes, insulin dependence, glycosylated hemoglobin levels, proteinuria and hypertension have all been implicated in the development of DME [4]. 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: damage to tight junctions of capillary endothelial cells from vitreoretinal adhesion and traction on the macula, or from seepation into the vitreous of factors produced by the retina and other parts of the eye that increase vascular permeability, such as VEGF is the main factor whose expression is induced by hypoxia [5] and IL-6 [6]. The second mechanism is damage to the function of the retinal pigment epithelium by ischemia and disruption of the BRB tissues [7], and the third is disruption of the BRB by inflammation. The inflammatory mediators are prostaglandins, leukotrienes, histamine, bradykinin, platelet-activating factor and IL-1 [8]. It has long been postulated that focal DME is generally responsive to macular laser treatment [15]. It should be noted that focal photocoagulation was found to reduce 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 [9]. Treatment was applied to leaking microaneurysms and aneurysms and surgical oxygen pressure [10]. 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 50% demonstrating improved VA [11].

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 [12]. In order to minimize these complications a subthreshold diode micropulse laser photocoagulation protocol was developed, for treating DME [13–17] and PDR [18,19]. A randomized, controlled 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 [20]. In two other RCTs [21,22], 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 [21], than the newer technique [22].

Another new approach involved the application of a computer-driven pattern of short-duration laser burns (10–30 ms) [23]. 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 [24].

Therapeutic interventions

- Laser photocoagulation

Laser photocoagulation was the only established treatment for vision-threatening DR and DME until recently [25]. 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 [9]. Treatment was applied to leaking microaneurysms and aneurysms and surgical oxygen pressure [10]. 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 50% demonstrating improved VA [11].

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 [12]. In order to minimize these complications a subthreshold diode micropulse laser photocoagulation protocol was developed, for treating DME [13–17] and PDR [18,19]. A randomized, controlled 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 [20]. In two other RCTs [21,22], 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 [21], than the newer technique [22].

Another new approach involved the application of a computer-driven pattern of short-duration laser burns (10–30 ms) [23]. 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 [24].

- 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 [25–27]. The results of PPV for DME were first reported in patients with a thickened and taut posterior vitreous membrane [28] and subsequently studies evaluated vitrectomy results in patients with either a thickened posterior membrane or posterior vitreous detachment (PVD) [29] and those with both [23,30,31]. It was found that photocoagulation 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 dissection, most eyes with NPDR or severe nonproliferative DR as well as for resolving the condition without the need for surgery [24]. One small prospective case series investigating intravitreal injections of autologous plasma as a treatment for DME demonstrated improvements in both macular edema and retinal thickness compared with the noninjected control eyes [24].

- Corticosteroids

Intravitreal injections of corticosteroids have been studied extensively in the treatment 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 [30–32]. 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 leukocyte adhesion molecule-1 and CD18 [33–35]. Therefore, attenuation of the effects of VEGF and a reduction in inflammation may reduce macular edema associated with diabetes. Intravitreal corticosteroids have been demonstrated to both inhibit the expression of VEGF and the VEGF gene [36–39] and to have anti-inflammatory effects.
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 intraocularly for treatment of DME and other ocular neovascular diseases [64]. Intravitreal TA (IVTA) was found to inhibit ocular neovascularization [65] and the upregulation of inflammatory molecules [66] and VEGF in vitro [67]. A similar effect on VEGF levels in response to IVTA has been observed clinically [68]. 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 patients with eyes with refractive DMY 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 patients than in the controls (56 vs. 20%, 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 3% in the control group, IVTA 1 and 4 mg groups respectively and cataract surgery was required in 54% of the treated eyes compared with 0% in the placebo group and ocular hypertension required a laser or surgical procedure to control IOP 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 [73].

The results of the DRCR.net trial, evaluating ranibizumab plus prompt or deferred laser or triamcinolone acetonide 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. Despite this, IVTA was well tolerated and the incidence of adverse events was low with 1.8% at week 13. Only 2.1 mg 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 [75]. Results from a Phase III/III trial that evaluated the efficacy and safety of the 0.59 mg FA 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 [76].

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) [77], 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 compared with systemic therapy [78]. Complications associated with this drug-delivery system include rhematogenous retinal detachment, vitreous hemorrhage, device extrusion, endophthalmitis, raised IOP, cataract and suture exposure [79]. This drug is currently not US FDA-approved for DME due to its high side-effect profile.

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 [70]. The study recruited 693 patients with DME involving the fovea (840 eyes) and eyes were randomized to receive either IVTA or 4 mg of TA, respectively, in triplicate. 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 treated group (p = 0.002) compared with the 1 and 4 mg groups, respectively) [71]. Anatomical assessments by OCT were compatible with the VA results. Intraocular pressure was increased from baseline by ≥10 mmHg at 2 weeks, 4 weeks, 16 weeks, and 33% of eyes at 1 year. The mean VA was the same as that of patients treated with IVTA in a Phase II RCT for the treatment of DME [70]. 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 [71].

Sumiodic Avenue is a sustained delivery drug system with a helical design and contains 925 μg TA. It was evaluated in a Phase I study for DME (patients eyes 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 with ME was 70% in the fast-release group (≥15 letters gained) and 72% in the slow-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 [80].

Dexamethasone

Due to the limited efficacy of IVTA alone and its high side-effect profile, combination approaches using laser photocoagulation with TA administered either intravitreally [72] or by sub-Tenon’s capsule injection [73] have also been studied in small prospective series [74,75] and RCTs [76,77,81,82,83]. Results of these trials have been extremely variable, with some proving that combination treatment is superior to laser alone [77,78] and others finding benefits lasting only a few months [71] or not having found any additional benefit at all [74]. 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 [84]. 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 [71]. Sumiodic Avenue is a sustained delivery drug system with a helical design and contains 925 μg TA. It was evaluated in a Phase I study for DME (patients eyes 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 with ME was 70% in the fast-release group (≥15 letters gained) and 72% in the slow-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 [80].

Dexamethasone

Due to the limited efficacy of IVTA alone and its high side-effect profile, combination approaches using laser photocoagulation with TA administered either intravitreally [72] or by sub-Tenon’s capsule injection [73] have also been studied in small prospective series [74,75] and RCTs [76,77,81,82,83]. Results of these trials have been extremely variable, with some proving that combination treatment is superior to laser alone [77,78] and others finding benefits lasting only a few months [71] or not having found any additional benefit at all [74]. 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 [84]. 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 [71].

Sumiodic Avenue is a sustained delivery drug system with a helical design and contains 925 μg TA. It was evaluated in a Phase I study for DME (patients eyes 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 with ME was 70% in the fast-release group (≥15 letters gained) and 72% in the slow-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 [80].
levels of VEGF could induce pathology characteristic of DR [13-14], while agents that inhibit VEGF activity could inhibit DR pathology as well [15].

Several VEGF antagonists, administered intra- vitreally are currently being used and investigated for the treatment of DME. Pegaptanib, an RNA anti- sense therapeutic that selectively inhibits VEGF165 [16] and ranibizumab, a nonselective monoclonal anti- body antigen-binding fragment that binds all VEGF isoforms [17], are approved for the treatment of neo- vascular age-related macular degeneration. Bevacizumab, a full-length monoclonal antibody related to ranibizumab, is being used off-label for a variety of ocular neovascular diseases, including DR [18]. While these three agents have been extensively investigated, two other VEGF antagonists are also being evaluated in Phase II trials as intravitreal treat- ments for DME: one is the VEGF Trap-Eye (alibert- cim) [19], a fusion protein containing the binding site of VEGF receptor 1 [20] and the other is beva- siranib [21], a siRNA agent that targets VEGF. The results of these trials have yet to be reported. Siro- linus (rapacyn) is a drug principally used for its immuno- suppressive activity, has also been shown to act as a VEGF antagonist by inhibiting both VEGF expression [22] and VEGF-induced hyperpermeabil- ity [23] and it is being examined as a subconjunctival injection for the treatment of DME [24].

**Pegaptanib sodium (Macugen)**

The Macugen DR Study Group conducted a Phase II trial on its use for fovea-involving DME [25]. 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, 12 and 16. Additional injec- tions could be administered to subjects after week 12 at the discretion of the masked investigators. Simi- larly, 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 also seen in some 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 responded better to pegaptanib therapy [14,15].

The results of the Phase II/III, randomized, double blind, multicenter, 2-year trial [26] comparing pegap- tanib with sham injections in the treatment of DME were recently published. This 2011 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 13. In the sham arm, 39% of all macular injections were performed at 36 weeks, 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 sub- jects, 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 combination for the treatment of DME. In total, 126 patients with either Type 1 or 2 diabetes with a previous history of treat- ment 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 let- ters at month 24 and the percentage of patients who gained two or more lines of VA was 34, 21 and 19% 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. The mean foveal thick- ness at month 24 was 340, 286 and 258 µm for groups 1, 2, 3, respectively and the percentage of patients with center subfield thickness of 250 µm or less was 36, 36 and 68%, respectively [27]. This study showed that intravitreal 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.

The DRCR.net trial was a large-scale RCT that compared ranibizumab with TA as an adjunct to laser photocoagulation [28]. It randomized 854 eyes to four treatment arms: one group received IVTA with 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 the fourth group received ranibizumab with laser deferred for ≥24 weeks [29]. Determination was made by 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 ± 1, 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 thick- ness 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 psuedopho- kyes at baseline (n = 273), VA improvement in the TA plus prompt laser group was comparable to the ranibizumab groups. Overall, the ranibizumab groups had substantial improvement (210 letters), while approximately 30% gained ≥15 letters. Substantial VA loss (≥20 letters) was uncommon. The results were similar whether focal/grid laser was given at the first injection or if it was deferred to ≥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 ≥20 mmHg from baseline and 15% of eyes that were phakic at baseline had cata- ract 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-con- trolled, double-masked study (RESOLVE study) investigated the safety and efficacy of ranibizumab in DME involving the foveal center in patients with Type 1 and Type 2 diabetes, ≥73–79 ETDRS letters [30]. 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, in which each treat- ment could be stopped/reinitiated with an opportunity for rescue laser photocoagulation (protocol-defined...
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 the baseline group. This compares with 12.3% of the placebo group; the difference between each dose group and placebo was statistically significant (p < 0.001). At 24 months, 10.3 ± 9.1 letters of BCVA improved from baseline by 10.3 ± 9.1 letters.

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 of 122 patients who were randomized to receive monthly bevacizumab 1.25 mg at 0 and 6 weeks, two intravitreal injections of bevacizumab 2.5 mg at 0 and 6 weeks, bevacizumab 2.5 mg at week 0 followed by a sham injection at week 6, and bevacizumab 2.5 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 bevacizumab injections without laser had a statistically significant improvement in vision compared with the laser-only group; these improvements were maintained at 12 months. 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 toward better short-term VA outcomes than the eyes that received two bevacizumab injections.

In a noncomparative trial by Haritoglu et al., 1.25 mg bevacizumab was administered at baseline with subsequent repeat dosing based on the presence of a significant OCT or VA response after the initial injection. 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. The study SITA-R results were reported by the PACORES group [144] and by Lam et al. [145]. 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 [147]. Bonini-Filho et al. conducted a pilot study suggesting that the value of intravitreal bevacizumab for those eyes was 0.05 mg. All patients had a 1.5 mg injection at baseline and at follow-up visits based on the presence of intra- retinal or subretinal fluid on OCT. CRT and BCVA improved significantly throughout the 54-week study period. Follow-up fluorescein angiogram revealed no progression of capillary loss at study closure. Another study by Faghihi et al. also conducted intravitreal bevacizumab with IVTA in eyes with no history of treatment for DR [148]. They randomized 115 eyes of Type 2 diabetic patients to one of three trial arms: IVTA plus bevacizumab and macular photocoagulation injections of bevacizumab 1.25 mg and TA 2 mg.

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 treatments to treatment.

When comparing different dosing regimens, the DRCR.net study detected no difference between 1.25 and 2.5 mg bevacizumab. The study SITA-R results were reported by the PACORES group [144] and by Lam et al. [145]. 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 [147]. Bonini-Filho et al. conducted a pilot study suggesting that the value of intravitreal bevacizumab for those eyes was 0.05 mg. All patients had a 1.5 mg injection at baseline and at follow-up visits based on the presence of intra- retinal or subretinal fluid on OCT. CRT and BCVA improved significantly throughout the 54-week study period. Follow-up fluorescein angiogram revealed no progression of capillary loss at study closure. Another study by Faghihi et al. also conducted intravitreal bevacizumab with IVTA in eyes with no history of treatment for DR [148]. They randomized 115 eyes of Type 2 diabetic patients to one of three trial arms: 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 [151-153] 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 [214]. The DAVICII trial included 219 patients with DME and compared different doses of aflibercept with macular laser. The best result was observed for those monthly loading doses of 2.0 mg aflibercept followed by pre natal 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 (Bevasarumab, OPKO Health) for intravitreal injection for the treatment of DME [156] has been completed and the results are forthcoming.

Sirolimus

Sirolimus is an immunosuppressive agent that inhibits T-lymphocyte activation/proliferation occurring in response to antigen and cytokine (IL-2, -4 and -15) stimulation by a mechanism that is distinctly from that of other immunosuppressing agents. An interventional, nonrandomized open-label pilot study [157] 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 [158], as well as in processes central to DR pathology [159–163]. Clinical studies demonstrate reduced retinal microvascular damage, as well as inhibited ocular neovascularization [164,165]. The effects of TNF-α are attributed to its action in upregulating the synthesis of VEGF [166] and also independently of VEGF pathways [167]. 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, Shering-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 [168]. 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) [169]. Since intravenous administration of infliximab for the treatment of uveitis led to severe adverse effects [170], 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 [171].

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 [172]. Preclinical studies have demonstrated that PKC-β2 inhibitor ruboxistaurin (LY333531) can inhibit processes related to the pathophysiology of DR [173].

Intravitreal or oral administration of ruboxistaurin in rodents with diabetes blocked increases in vascular permeability [174,175]. Oral ruboxistaurin was examined in three placebo-controlled clinical trials as a treatment for DR and DME [176,177]. 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 but failed to meet 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 [178]. 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) [179]. A Phase III clinical trial is currently examining its efficacy in the treatment of DME [180].

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 being investigated extensively. In addition, studies are underway to evaluate potential

Investigational treatments

Aflibercept (VEGF Trap-Eye)

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.

Triamcinolone acetonide has been the principal agent of its class administered intravitreally for the treatment of DME. Sodium hyaluronate* 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 Duxtex®.

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, bevasaribin (Cand5) – OPIKO Health and AGN211745 (Sima-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.

TNFi

TNFi 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 specific molecular targets, including TNF-α and IL-6, and they also hold great promise. Multiple experimental strategies are ongoing, 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 pathology of DME. Further study is still much needed to establish the best treatment algorithm for DME.

Financial & competing interests dis-closure
A Lowenstein is a consultant to Allergan, Inc., Acorn, Inc., Lumenis, Ltd, Foveilabs, Natol Vision, Ltd and Orbus, Ltd. The authors have no other relevant affiliations or financial involve-ment with any organization or entity that could be perceived to influence the work reported in this manuscript apart from those disclosed above.

No writing assistance was utilized in the pro-duction of this manuscript.

References


858–865 (2007).


51, 1213–1225 (2010).


51, 1213–1225 (2010).
