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NEW INSIGHTS IN RESISTANT DIABETIC MACULAR EDEMA

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Short Title: New Insights in Resistant Diabetic Macular Edema

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Abstract
Diabetic macular edema (DME) is the most common cause of vision loss in diabetic eyes and due to the rapid rise in number of diabetic patients the treatment burden has increased exponentially. The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy has been a major breakthrough in the management of center-involving DME, replacing laser photocoagulation as the first-line of treatment. Despite the improvement in DME treatment with anti-VEGF therapy, persistent DME remains a challenge due to the extremely complex pathogenesis and the involvement of several different biochemical pathways. This review focus on therapeutic options for persistent DME, which include corticosteroid, laser and surgery. Novel agents for DME control such as new anti-VEGF, interleukin inhibitor, Rho kinase inhibitor and neuroprotective agents that are being investigated are reviewed as well. Future treatment perspectives include an individualized DME management.
Introduction

Diabetes mellitus (DM) is a global epidemic of the 21st century. Currently, there are 382 million individuals with diabetes in the world and this number is projected to reach 592 million by the year 2035. [1] Diabetic macular edema (DME) is the most common cause of vision loss in diabetic eyes and due to the rapid rise in number of individuals with diabetes, the treatment burden has increased exponentially. [2-3]

The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy for DME has been a major breakthrough in the management of center-involving DME, replacing laser photocoagulation as the first-line of care. However, clinical response to anti-VEGF therapy may be highly variable and the prevalence of persistent DME is estimated to be up to 50% [3-4]. Other approaches such as therapy with intravitreal corticosteroids, subthreshold laser and surgery have been considered in DME treatment [1].

DME pathogenesis is multifactorial, but increased oxidative stress, inflammation, vascular dysfunction and neurodegeneration have been proposed as contributors to the development of DME. Persistent DME remains a challenge in the clinical practice, as it leads to chronic tissue stress and permanent disruption of retinal architecture, causing photoreceptor loss [4-5].

In this review, we describe the epidemiology and pathogenesis of DME, we define patterns of response to treatment and we report novel treatment agents for persistent DME that target different biochemical pathways. We highlight the importance of individualizing the treatment for each patient. Data from preclinical and early clinical trials have been considered and further trials will provide evidence for these agents in the future.

Epidemiology

The global prevalence of Diabetes Mellitus (DM) was 366 million in 2011 and it is expected to rise to 522 million by 2030 [4]. In recent decades, large increases in DM prevalence have been demonstrated in virtually all world regions [6]. DM describes a group of metabolic disorders characterized by increased blood glucose concentration [7] that leads to macrovascular complications, including coronary heart disease and stroke, and microvascular complications, such as end-stage renal disease and diabetic retinopathy, responsible for much of the burden associated with DM [6].

Diabetic retinopathy (RD) affects approximately one third of adults with DM and remains the leading cause of acquired vision loss worldwide in middle-aged, therefore, economically active people [6-7]. According to the World Health Organization (WHO) it is estimated that DR accounts for 4.8% of the number of cases of blindness [8]. The prevalence of RD in type 1 DM was reported to range from 10 to 50%. The overall prevalence of DR in type 2 DM was 25.2% [8].

Among the visually disabling conditions in patients with diabetic eye disease, diabetic macular edema (DME), left untreated, is a common cause of vision loss [9]. Among the population-based studies, prevalence of DME among patients with type 1 DM was between 4.2 and 7.9%. In patients with type 2 DM, it was between 1.4 and 12.8% [10]. Duration of diabetes, hyperglycemia and systemic hypertension are known risk factors for DR and DME [10].

Pathogenesis

DME is a multifactorial condition and it involves thickening of the macula due to leakage of fluid from retinal capillaries caused by loss of pericytes, thickening of basement membrane and loss of tight junctions of the retinal endothelium from chronic hyperglycemia [4]. Multiple biochemical pathways play an important role in the pathophysiology of DME [4]. These include upregulation of VEGF, placental growth factor (PGF), angiopoietin-2 (Ang2), intercellular adhesion molecule (ICAM-1), interleukins, pigment epithelium-derived factor (PEDF), matrix metalloproteinases, prostaglandins and other cytokines [4].

Increased VEGF has emerged as one of the key factors in DME development, especially in early stages of the disease [11]. Activation of VEGF induces retinal vascular permeability by direct effect on endothelial tight junctions and adherence junctions [11]. With persistent DME, chronic inflammation assumes a more important role and propagates the edema [12]. Inflammatory mediators such as monocyte chemoattractant protein-1, tumor necrosis factor-alpha (TNF-Alfa), interleukin-6 (IL-6) and
interleukin-8 (IL-8) become more relevant in chronic DME [12]. Many studies have shown that the aqueous humor of DME patients contains elevated levels of inflammatory cytokines. [12]. Some authors have described the association of aqueous IL-8, a well-known pro-inflammatory cytokine that acts as neutrophil chemoattractant and a T-cell activator, and the responsiveness to intravitreal bevacizumab. [12]

Although DME is considered a primarily vascular phenomenon with alteration of the blood-retinal barrier (BRB), recent works suggest that the pathology lies in alteration of the neurovascular unit that consists of Müller cells, astrocytes, ganglion cells, amacrine cells, retinal vascular endothelial cells and pericytes [1]. The intimate dynamic interaction of retinal neurons and glia that surround the retinal capillaries controls fluid transport and metabolite transfer in the neural tissue and abnormalities in these cells in DM affects this barrier property in the retinal vessels. [1]. DME pathogenesis is extremely complex and it is important to identify each contributing component to plan its management prudently [4].

Classification and Diagnosis
DME can occur in any stage of diabetic retinopathy, either non-proliferative or proliferative retinopathy [1]. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined “clinically significant macular edema” as (1) thickening of the retina within 500 μm of the center of the macular; (2) hard exudates at or within 500 μm of the center of the macula, if associated with thickening of the adjacent retina; or (3) a zone of retinal thickening ≥ 1disc area, any part of which lies within 1disc diameter of the center of the macula [13-14]. Although the clinical exam is still the gold standard for diagnosis of DME, optical coherence tomography (OCT) has now become a fast and convenient diagnostic tool for quantitative measurement and mapping of macular thickening. [1] Currently, diabetic eyes are generally classified by the International Council of Ophthalmology (ICO) as having no DME, noncentral-involved DME (retinal thickening in the macula that does not involve the central subfield zone that is 1mm in diameter) or central-involved DME (retinal thickening in the macula that does involve the central subfield zone that is 1mm in diameter).

Response to Treatment
Anti-VEGF agents have demonstrated remarkable efficacy in several pivotal clinical trials for control of center-involved diabetic macular edema (CI-DME) and have become the gold standard primary treatment, replacing laser photocoagulation [4]. Differences between anti-VEGF drugs have been explored in Protocol T, a comparative of effectiveness trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net), that compared 3 commonly used anti-VEGF agents (bevacizumab, ranibizumab and aflibercept) for eyes with CI-DME [23]. On average, each drug was found to improve vision and reduce central retinal thickness (CRT) [23]. Despite the efficacy of anti-VEGF agents in improving visual acuity and decreasing edema, approximately 40% of DME eyes experienced persistent DME after at least 6 monthly injections of anti-VEGF and 32% of them had a concomitant visual loss [5,23].

Characterization of responders to treatment of DME has been a challenge. A univocal definition of responsiveness to treatment has not been reached [23]. The DRCR.net proposed the definition of treatment as “success”, “improvement”, “no-improvement” after 6 monthly injections of anti-VEGF. “Success” was characterized by best-corrected visual acuity (BCVA) of 20/20 Snellen equivalent and CRT < 250 μm, “improvement” was defined by a visual gain of at least 5 letter and a decrease of CRT of at least 10%, “no-improvement” included a BCVA change less than 5 letters and CRT less than 10% since the baseline [23]. Persistent DME was defined by the DRCR.net as eyes with CRT of 250 μm or greater at 6 months of follow-up despite receipt of at least 4 of the potential 6 protocol-mandated intravitreal anti-VEGF during this period and chronic persistent DME was defined as eyes with persistent DME that have not achieved a CRT less than 250 μm and 10% or greater reduction relative to 6 months follow-up visit on at least 2 consecutive study visits [25]. Recent studies suggested that eyes with persistent DME might benefit from a switch to dexamethasone implant early (only 3 anti-VEGF injections before switch) in
the treatment course, providing a better visual and anatomical improvement in unresponsive patients, when compared with late switch (> 6 anti-VEGF injections before dexamethasone) [23-24].

**Biomarkers**

Intravitreal administration of anti-VEGF drugs is currently considered the first-line of treatment for DME. However, not all patients with DME show a good response to anti-VEGF agents. [15]. Approximately 32-66% of the eyes treated with intensive injection regimens over 6 months or beyond have persistent DME and 30-70% of eyes show minimal improvement best-corrected visual acuity [5].

In this context, many authors have described several biomarkers in DME to predict the response to anti-VEGF and corticosteroid therapy, and to determine functional outcomes. Several authors have described OCT biomarkers that help to predict poorer visual outcome in patients with DME at the baseline, such as ellipsoid zone disruption, disorganization of the inner retinal layers (DRIL) in 1mm foveal area and lower parafoveal vascular density in superficial layer on OCT Angiography (OCT-A) [16-18].

Some studies have suggested that the initial subfoveal choroidal thickness may help predict short-term anti-VEGF treatment outcomes [19]. Rayess et al reported that patients having a greater baseline choroidal thickness were more likely to attain better visual and anatomic results with anti-VEGF therapy. Many authors have described OCT biomarkers that may represent an inflammatory pattern of DME [20]. The presence of subretinal fluid (SRF) and hyperreflective spots (HRS) on OCT have been associated with major local inflammatory condition including higher levels of IL-6 in the vitreous [20]. HRS are described as small (<30 µm), sometimes punctiform, reflective lesions, located in the outer retina, without any back shadowing, that may correspond to activated and aggregated microglial cells [20]. The presence of SRF has been described as a biomarker that predicts better visual outcome in patients treated with dexamethasone implant [20-21].

Recently, aqueous humor cytokines levels have been used as biomarkers that could help anticipates response to anti-VEGF therapy [22]. Elevate ICAM-1 and reduced VEGF levels at baseline were associated with a favorable anatomic response to ranibizumab in DME [22]. Felfeti et al described that the VEGF concentration in aqueous humor was significantly lower in eyes with good response after two injections of aflibercept compared with eyes with a poor response to treatment.

**First-line treatment for DME**

Decades after the Early Treatment Diabetic Retinopathy Study (ETDRS) established macular photocoagulation (focal/grid laser) as standard care for DME, anti-VEGF injections have emerged as the first-line therapy for DME, with superior visual acuity outcomes and acceptable risks compared with focal/grid laser. [26]. There is a large body of evidence to support the anti-VEGF use for DME. The RISE and RIDE studies showed that ranibizumab rapidly and sustainably improved vision and reduced macular thickness in patients with DME. [27] In the VISTA and VIVID trials, eyes treated with intravitreal aflibercept achieved significantly greater improvements in functional and anatomical outcomes when compared to macular laser photocoagulation. [28]

The Protocol I from the DRCR.net has demonstrated that for eyes with baseline BCVA of 20/30 to 20/40, no significant differences in visual outcomes are identified among aflibercept, bevacizumab and ranibizumab. [26,28] For eyes with baseline BCVA of 20/50 or worse, aflibercept is associated with a superior visual acuity outcome up to 2 years follow up compared to bevacizumab, with a mean change in visual acuity of +18,1 letters score for the group treated with aflibercept and +13,3 letters score for the group treated with bevacizumab. [26,28] There was no significant difference between aflibercept and ranibizumab after 2 year in terms of visual acuity. Despite the minor difference on visual outcome, aflibercept is not cost-effective compared to bevacizumab. [26,28]

The combination of anti-VEGF with focal/grid photocoagulation could theoretically enhance the effect of laser photocoagulation because the retina would be less edematous if the laser treatment was administered sometime after the injection. [29] The Protocol I from the DRCR.net has demonstrated that intravitreal ranibizumab, either with prompt or deferred (24weeks) focal/grid laser, resulted in superior visual acuity and OCT outcomes compared with focal/grid laser treatment without ranibizumab at both 1 and 2 years of follow-up. (29)
Options for persistent DME

- **Switch of Anti-VEGF**

  The rationale for switching between anti-VEGF drugs lies in the molecular differences and the pharmacological targets for each of these agents [4]. Bevacizumab, ranibizumab and aflibercept each have different binding affinities for VEGF and different half-lives in the vitreous, and this could account for some of the differences noted between these drugs [30]. Ranibizumab is a small Fab fragment of the recombinant humanized monoclonal IgG1 antibody that binds and inhibits all isoforms of VEGF-A, and it lacks the Fc stem. Bevacizumab is a full-length recombinant humanized monoclonal IgG1 antibody that binds and inhibits all isoforms of VEGF-A [30]. Aflibercept is a recombinant fusion protein that is composed of the extracellular binding domains from VEGF receptors 1 and 2, fused to the Fc domain of a human IgG1 molecule, and it binds and inhibits all isoforms of VEGF-A, but in addition, also inhibits VEGF-B and placental growth factor, unlike ranibizumab and bevacizumab [4, 31]. Numerous authors have demonstrated that patients treated with repetitive ranibizumab or bevacizumab injections over the time may demonstrate tachyphylaxis, or a diminished therapeutic response, to those agents [32]. The mechanisms underlying this phenomenon are thought to be multifactorial, involving for example upregulation of VEGF from local macrophages, altered expression of surface receptors and humoral responses [32]. Some studies have demonstrated anatomical and visual improvement with the switch to ranibizumab or aflibercept in patients with persistent DME treated previously with bevacizumab [30-31, 33]. Ciulla et al. reported in their retrospective study that ranibizumab was useful in eyes with persistent DME treated previously with macular laser photocoagulation, bevacizumab and triamcinolone, with statistically significant improvement in CRT from 384 µm to 335 µm and visual acuity improvement from 20/100 to 20/90 after an average of 7 injection over 48 weeks [30-31, 33]. Lack of group control, small sample size and retrospective design limit interpretation from many of these studies.

- **Corticosteroids**

  Corticosteroids have several mechanisms of action that include decrease in VEGF synthesis, in leukocyte migration and in several proinflammatory cytokines such as IL-6 and IL-8, enhance of the barrier function of vascular endothelial cell tight junctions; and down-regulation of ICAM-1 expression [4, 34]. Currently, corticosteroid agents serve as the second-line drug for DME treatment, and specifically as the main therapy in control of persistent DME. Cataract formation and glaucoma are known side effects of intravitreal corticosteroid [4,34]. Intravitreal triamcinolone, fluocinolone insert and dexamethasone implant are agents available for DME treatment. Triamcinolone inhibits the arachidonic acid pathway, thereby inhibiting production of the prostaglandins that trigger the inflammatory response. The Protocol B from DRCR.net showed that over a 2 year-period, focal/grid photocoagulation is more effective and has fewer side effects than triamcinolone for patients with DME [35]. Jeon et al. have demonstrated that intravitreal triamcinolone had beneficial effects on DME unresponsive to anti-VEGF agents in improved visual acuity and reduced CRT. However, these effects were not sustained for more than 3 months [35]. Dexamethasone implant is a biodegradable polymer that gradually releases low-dose dexamethasone for several months after being injected into the vitreous cavity, maintaining drug concentration for 3-6 months. The peak concentration of the drug has been reached in the vitreous at the second month and the highest efficacy of the implant was shown to occur between the first and third month [34, 36-37]. The MEAD study showed robust long-term improvement in vision and macular thickness in patients with DME treated with dexamethasone implant, with a mean of only 4 to 5 injections over 3 years [37]. Jung et al. have demonstrated that vitrectomy combined with intraoperative dexamethasone implant may produce a clinically meaningful and statistically significant benefit in the treatment of persistent DME [38]. Some studies showed that the dexamethasone implant provides a more significant improvement in CRT compared with aflibercept in treatment-naïve DME with subretinal fluid, a marked inflammatory phenotype, with a low number of injections as an advantage [39].
Fluocinolone vitreal implant is a small, non-biodegradable implant, and applied as an injection using a 25-gauge injector via pars plana into the vitreous cavity, releasing an average of 0.2 microgram/day of fluocinolone acetonide for up to 36 months [40]. The FAME study showed a substantial visual benefit for up to 3 years in patients with persistent DME and fluocinolone provides an option for patients who do not respond to other therapy [40]. The multifactorial pathogenesis of DME provides rationale for the combination therapies [4]. Combining bevacizumab with dexamethasone implant was found to achieve a greater reduction on CRT, but achieved a similar visual acuity gain compared to bevacizumab alone in patients with persistent DME [4]. Maturi et al. have demonstrated that in eyes with persistent DME, after multiple anti-VEGF injection, the addition of dexamethasone implant with continued ranibizumab injections produced no better improvement of visual acuity at 6 months than the monotherapy with ranibizumab, even though there was a significantly greater reduction in CRT in the combination group [34, 41].

- **Laser**

Macular laser photocoagulation has been in use for the last several decades to treat DME since the ETDRS report was published in 1985 [42]. Currently, however, anti-VEGF therapy has replaced laser as the first-line treatment. The main disadvantage of anti-VEGF monotherapy are the high frequency of injections per year and the risk of injection-associated adverse events, such as endophthalmitis. Patients may require as many as eight injections per year, this high frequency placing a huge economic burden on patients and healthcare systems [43]. Macular laser photocoagulation may cause macular scars that result in central scotoma and it can also be complicated by choroidal neovascularization and subretinal fibrosis. To prevent these from occurring, subthreshold laser has been developed to deliver laser energy below the threshold of causing permanent tissue damage and it has shown to alter metabolic activity, RPE gene expression and enhance the expression of heat shock proteins [44]. Subthreshold laser uses longer wavelengths and delivers energy in a micropulse fashion [42-43, 45].

Micropulse laser has emerged as the main modality to achieve subthreshold treatment by decreasing the “duty cycle” of the laser. Instead of one single continuous pulse, the laser is divided into numerous short repetitive pulses, within 100 to 300 milliseconds “on” cycle and 1700 to 1900 millisecond “off” [46]. This effectively decreases the “duty cycle” of the laser as low as 5-10% of the conventional laser [42]. Micropulse laser has been shown in several randomized clinical trials to be as effective as conventional laser in the DME treatment [42]. Chen et al. have showed that the micropulse diode laser treatment resulted in better visual acuity compared to focal/grid macular laser. However, the two types of treatment seem to have similar anatomical outcome. Some authors have described the association between anti-VEGF therapy and micropulse laser with improvement of visual and anatomical outcome, with a significant decrease number of additional injections required. These studies have limitations such as a small sample size, retrospective design and short follow-up [43, 46]. Alternatively, in 2005, Topcon developed a pattern scanning laser system capable of applying multiple laser spots in a short period of time [44]. PASCAL streamline yellow with endpoint management (EPM) software allows grid pattern photocoagulation and the ability to calculate the level of subthreshold energy required [44]. Hamada et al. have demonstrated 10 cases of patients with DME treated with subthreshold laser using EPM with a significant decrease of the CRT, while there were no significant changes in BCVA. Further clinical trials are needed to corroborate these findings [44].

Microaneurysms are the hallmark of DR and DME, however the spectrum of microvascular abnormalities is far more complex, comprising large microvascular abnormalities, which can reach the diameter of several micra (150 µm or more) and receive the term of telangiectatic capillaries (TC). The TC are better seen by indocyanine green angiography (ICG) than by fluorescein angiography (FA), showing delayed and prolonged ICG staining. Some authors have reported anatomical and visual improvement of DME after target photocoagulation of the TC [47].

- **Surgery**
Pars plana vitrectomy (PPV) with or without internal limiting membrane (ILM) peeling has been described for persistent DME treatment [48]. Consistent with the guidelines for the management of DME by retinal specialists, PPV is currently recommended as a therapeutic option in cases of DME associated with tractional changes in the vitreomacular interface. In the absence of vitreomacular traction, there is no consensus on the role of PPV [48].

PPV is thought to play a role in non-tractional cases, allowing VEGF and other proinflammatory cytokines to diffuse away from the macula more easily and increasing the oxygen supply in ischemic areas. On the other hand, post-vitrectomy eyes have a decreased viscosity of the vitreous cavity, interfering with intraocular pharmacokinetics and reducing the half-life of intravitreal agents [4, 49]. Jackson et al. in their meta-analysis showed that PPV produced both structural and functional benefit in eyes with DME, but the functional benefit was not significantly better than that obtained using macular laser. Nakajima et al in their meta-analysis demonstrated similar visual acuity outcomes using PPV with ILM peeling versus no ILM peeling in patients with DME [50].

Future perspectives
Anti-VEGF therapy continues as the first-line treatment for center-involving DME. The main disadvantage of this therapy is the high frequency of injections. Patients may require as many as eight injections per year, and this focuses a huge economic burden on patients and healthcare systems [43]. Given the burden of frequent injections, agents with longer duration of action are being investigated intensively [4]. This review focuses on new anti-VEGF agents that are in advanced stage of clinical development: conbercept, brolucizumab, faricimab.

- **Conbercept**

  Conbercept is a recombinant fusion protein composed of the second Ig domain of VEGFR1 and the third and fourth Ig domain of VEGFR2 and the constant region (Fc) of human IgG [26, 51]. The structure of conbercept differs from aflibercept in that it incorporates the fourth extracellular domain of VEGFR-2, which was demonstrated to stabilize the receptor-ligand complex and further extend the half-life of conbercept [26, 51]. It is designed as a receptor decoy with high affinity for all VEGF isoforms and PIGF [26, 51]. The inhibitory effects of conbercept have been evaluated in vitro and in vivo, indicating that conbercept exerts potent anti-angiogenic effects [52]. The PHOENIX study evaluated the efficacy and safety of intravitreal injections of 0.5mg conbercept for the treatment of neovascular age-related macular degeneration (AMD) and showed significant visual and anatomic benefits with 3 initial monthly doses of conbercept (loading dose) followed by quarterly dosing of conbercept. [26, 51-52]

- **Brolucizumab**

  Brolucizumab is a low molecular weight humanized single-chain variable (scFc) antibody fragment VEGF inhibitor [53]. It binds and inhibits the three major isoforms of VEGF-A (VEGF110, VEGF121 and VEGF165) and prevents interaction with receptors VEGF-1 and VEGF-2 [53]. Brolucizumab is approved in the United States for the treatment of neovascular AMD based on the HAWK and HARRIER studies [53]. These studies have reported that brolucizumab provides comparable vision gains to aflibercept, with greater retinal fluid resolution [53]. The recommended regimen dosage is 6mg monthly for the first 3 months and then once every 8-12 weeks [54]. Baumal et al. have reported a case series of 15 eyes from 10 practices in the US that demonstrated retinal vasculitis and intraocular inflammation within the first 3 months of its availability [55].

- **Faricimab**

  DME is multifactorial and involves other angiogenic factor and inflammatory cytokines that are not addressed with anti-VEGF therapy [58-59]. Angiopoietin (Ang) pathway regulates the vascular homeostasis and vascular permeability [58-59]. Upregulation of angiopoietin 2 (Ang-2) was noted in conditions such as hypoxia, hyperglycaemia and oxidative stress [58-59]. Faricimab, a novel anti-Ang-2/anti-VEGF bispecific antibody designed for intraocular use, has been produced to inhibit these 2 pathways [58-59]. The phase 2 BOULEVARD study reported that 6mg intravitreal faricimab given monthly for 20 weeks had superior gains in visual acuity compared with ranibizumab in treatment-naïve patients with DME [58-59].

- **Port Delivery System**
The Port Delivery System with ranibizumab (PDS) is a novel, innovative, long-acting drug delivery system that enables continuous delivery of a customized formulation of ranibizumab into the vitreous [56-57]. The PDS includes a permanent, refillable implant that is surgically inserted through a small incision in the sclera and pars plana [56-57]. Ranibizumab moves by passive diffusion down a concentration gradient from implant reservoir, through a porous metal release control element specifically designed for ranibizumab, and into the vitreous cavity [56-57]. The PDS implantation procedure is well-tolerated, self-retaining, performed in a sutureless fashion, and the refill procedure is office-based [56-57]. The phase 2 LADDER clinical trial showed visual and anatomic outcomes comparable with monthly intravitreal ranibizumab. The mean refill time was 15 months, with 80% of the patients not requiring a refill per protocol for the first 6 months [56-57].

- **Abicipar Pegol**
  Ankyrin repeats are one of the most common protein patterns in nature and it forms ankyrin repeat proteins when stacked together. [2-4] Libraries of artificially stacked designed ankyrin repeat proteins (DARPins) is a novel flux of proteins that demonstrate high affinity and specificity for binding to specific proteins. Abicipar Pegol is a specifically designed DARPin that binds and inhibits VEGF and when administered at a dose of 0.4mg intravitreal, VEGF inhibition was observed for 8-12 weeks in the aqueous humor. [2-4] However, there are concerns regarding an increased incidence of intraocular inflammation in eyes treated with Abicipar Pegol. [2-4] The phase 2 PALM study was conducted on 151 patients with DME and reported visual acuity improvement with Abicipar Pegol. [2-4]

- **Interleukin inhibitors and chemokine inhibitors**
  DM is a systemic disease and it has been associated to higher serum levels of several cytokines, chemokines and angiogenic factors. In this context, novel systemically administered therapeutic agents are in development to treat DR and DME. [2-3, 60] Recent studies have shown that levels of insulin-like growth factor (IGF), inflammatory cytokines such as IL-1 and IL-6, and chemokines such as monocyte chemoattractant protein (MCP-1) are increased in the vitreous of patients with DME. [2-3, 60] Pharmacological inhibition of these factors appears to be a promising approach for treating DME. [2-3, 60] The use of IL-1 receptor antagonist has been shown to significantly reduce glucose induced abnormalities in bovine retina. R07200220, a recombinant fully humanized immunoglobulin G2 (IgG2) isotype monoclonal antibody that potently binds IL-6 and inhibits all forms of IL-6 signaling, is intended for the treatment of DME, uveitic macular edema and neovascular AMD. [2-3, 60] Further clinical studies involving inhibition of these pathways may elucidate whether there are beneficial effects for those therapeutic strategy for DME. [2-3, 60]

- **Rho-kinase inhibitors**
  Rho-associated protein kinase (ROCK) activity is upregulated in diabetic eyes and plays an important role in the pathogenesis of microvascular complication in DR/DME. [2-4, 61] ROCK inhibitors may be used to enhance the efficacy of anti-VEGF in treating persistent DME. [2-4, 61] AR-13403 (Aeri Pharmaceuticals) is a sustained release intravitreal implant designed to the treat neovascular AMD and DME that inhibits both Rho kinase and protein kinase C [2-4, 61]

- **Neuroprotective agents**
  Neurodegeneration is an early event in the pathogenesis of DR and DME, therefore, it is critical to develop agents that can target the disease process in early stages. [2-4, 62] Retinal neuroprotective drugs such as topical brimonidine and somatostatin have been assessed in the EUROCONDOR study. [2-4, 62] This study reported that topical treatment with these agents did not seem to be useful in preventing the development of neurodegeneration; however, these protective agents were reported to be effective in preventing the progression of neurodegeneration in patients that already had some degree of neurodegeneration. [2-4, 62]

**Conclusion**
Control de hyperglycemia is critical to minimizing the risk of onset and progression of DME. The American Diabetes Association recommends glycemic control targeting a hemoglobin A1C of 7.0% or lower for most people with DM. [2] Currently, the mainstay of the DME treatment include anti-VEGF agents, corticosteroids and laser therapy. The introduction of anti-VEGF has been a paradigm shift in
the DME management, with substantial improvement in visual outcome for patients with DME. However, this treatment implies in a high economic burden due to the need of multiple intravitreal injections.

Despite the improvement in DME treatment with anti-VEGF therapy, persistent DME remains a challenge due to the extremely complex pathogenesis and the involvement of several different biochemical pathways. Upregulation of VEGF, Ang-2, IL-6, IL-8, PGF, ICAM-1, PEDF and other cytokines have been described to play an important role in DME pathogenesis. Recently, there is emerging evidence suggesting that retinal neurodegeneration is an early event in DR/DME. Therefore, it is critical to identify each contributing component to plan a personalized treatment for DME.

Future treatment perspectives include an individualized management of DME, with the development of novel anti-VEGF agents with longer duration of action in the vitreous cavity, port delivery system for anti-VEGF, serum and aqueous humor measurement of inflammatory cytokines and evaluation of OCT biomarkers to guide therapy, agents targeting different biochemical pathways such as angiopoietin-2 and IL-6 and neuroprotective agents. These new targets may potentially serve as an alternative therapy or be used in combination with anti-VEGF. Multicenter randomized clinical trials may provide level 1 evidence for these novel agents in the future.
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Dante A K Kuroiwa: conceptualization; data acquisition; project administration; writing – original draft, review and editing
Fernando K Malerbi: conceptualization; data acquisition; project administration; writing – review and editing
Caio V S Regatieri: conceptualization; data acquisition; project administration; supervision; writing – review and editing
References


