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REVIEW ARTICLE

DME Management – Current Perspective and Therapeutic Strategies

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ABSTRACT

Diabetic Retinopathy (DR) is the premier cause of blindness world over and is the leading ocular complication of diabetes. Visual morbidity in diabetic retinopathy is largely because of Diabetic Macular Edema (DME), although the tractional and hemorrhagic issues of proliferative diabetic retinopathy (PDR) are the more debilitating. There has been a paradigm shift in the gold standard of therapy from macular laser photocoagulation to the current era of anti-Vascular endothelial growth factor therapy (anti-VEGF). The three anti-VEGF injections in vogue are ranibizumab, bevacizumab and aflibercept. Several trials have provided critical information on their safety, efficacy and their dosage as well as dosing regimens. Steroid injections and depot formulations remain in the therapeutic armamentarium, despite their cataractogenic and intraocular pressure elevating side effects. The repetitive nature of the injections and the fact that there still remains a significant quanta of patients that are non-responsive or refractory in time to the anti-VEGF injections, has fuelled continued research for newer therapeutic alternatives.

Keywords: diabetes, macular edema, ranibizumab, bevacizumab, aflibercept, steroids

Introduction

Diabetic Retinopathy, today, has emerged as the leading cause of blindness globally. Diabetic macular edema (DME) is responsible for significant proportion of the visual morbidity associated with diabetic retinopathy. There are various treatment options available nowadays but managing cases of DME not responding to the time tested and proven management strategies is a challenging and uphill task. Despite possessing a greater understanding of the pathophysiology of disease, breakthroughs in molecular genetics research, newer investigation modalities, there continues to be a significant proportion of DME cases that remains refractory to treatment. Refractory DME, has been diagnosed if the patients showed persistent DME for at least 6 months duration despite at least 2 prior treatments, including any combination of macular laser photocoagulation, or pharmacotherapy [1,2].

Laser Photocoagulation

Laser photocoagulation has since long been the gold standard in the management of DME [3,4]. Early Treatment Diabetic Retinopathy Study (ETDRS) study clearly showed that in patients with visual impairment caused by DME, laser therapy reduced the relative risk of loss of 15 letters by 50% compared to deferred treatment [3]. Focal/grid photocoagulation was found to be more effective and had fewer side effects compared to 2 doses of IVTA in a multicentre randomized clinical trial by the Diabetic Retinopathy Clinical Research Network at both 2- and 3-year follow-ups [4,5]. However, the conventional laser photocoagulation (CL) is tissue-destructive and is thus naturally associated with visual acuity and field loss [6-10].

Subthreshold micropulse diode laser (SDM) treatment and selective retina therapy (SRT), have been found to be more safe and effective both in terms of reducing foveal thickness and improving long term visual outcomes [11,12]. Therapeutic success with subthreshold

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micropulse yellow laser (577 nm) has also been reported [13].

Despite the inferior efficacy of laser monotherapy, it remains the only one-time event treatment option. Hence in patients who either refuse intravitreal injections or have poor compliance to the relatively strict treatment regimen of intravitreal injections, and in terms of affordability, laser still retains its value [14]. However, focal or grid laser therapy simply stabilises and does not improve vision.

With newer research, the era of laser therapy has been replaced by the newer pharmacotherapeutic era with rapid improvement in visual acuity. Though combination therapy with lasers has been found to be effective by providing the synergistic benefits of both the treatments.

Managing DME – Current Era

Anti VEGF agents

The pathophysiological mechanisms causing DME are complex and multifactorial with VEGF playing the pivotal role in the initiation and propagation of edema and exudation. There is increased vitreous fluid concentration of VEGF levels in DME patients as compared to nondiabetic patients [15]. Pharmacologic inhibition of VEGF was found to provide significant benefits and has now has become the standard treatment of centre involving diabetic macular edema.

Ranibizumab (Lucentis, Genentech, San Francisco, CA) consists of a humanized monoclonal antibody fragment that binds to all isoforms of VEGF-A. Ranibizumab was the first anti-VEGF to be approved by the United States Food and Drug Administration (FDA) in 2012, based on Genentech's Phase III trials, RISE and RIDE for the treatment of diabetic macular edema [16,17].

RISE and RIDE were 2 major phase 3, randomized controlled trials that compared monthly ranibizumab with sham injections. The percentage of patients with a greater than 15 letter gain in visual acuity from baseline at both 2- and 3-year end points was approximately double in patients receiving ranibizumab compared with those receiving sham, i.e. 44.8 % (0.3 mg ranibizumab group) and 39.2% (0.5-mg ranibizumab group) compared with 18.1% sham group.

RESTORE study [18] demonstrated that treatment with ranibizumab alone is superior to laser treatment in improving BCVA in patients with visual impairment due to DME and that laser does not add any benefit in terms of improving BCVA and treatment exposure, at the end of 1 year [18].

The RESTORE Extension study [19,20] followed the RESTORE patients until year 3 and found that patients with prior ranibizumab or combined therapy could maintain their prior CRT decreases and BCVA gains with a mean of only 3.7/2.7 retreatments per year. Thus, early therapy induction with ranibizumab is important in DME to minimize the risk of significant BCVA loss.

The Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol I was a large randomised control trial on 854 eyes, comparing sham injection with laser photocoagulation, with intravitreal ranibizumab with either prompt or deferred focal laser, and intravitreal triamcinolone with prompt laser photocoagulation [21]. The results were similar to those in RISE and RIDE study - visual acuity gains in patients treated with ranibizumab were higher versus sham injection and intravitreal triamcinolone. At 5-years, the initial visual acuity gains were maintained, with reduced frequency of injections.

The READ 2 study in 126 eyes with DME proved superiority of ranibizumab monotherapy till 6 months of treatment [22]. Later in follow-up studies it was found that intraocular injections of RBZ provided benefit for at least 2 and 3 years in DME patients, and when combined with focal or grid laser treatments, reduced the amount of residual edema, as well as the frequency of injections needed [23,24].

In Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema (REVEAL Study) study, 396 Asian diabetic patients were randomized to 0.5 mg ranibizumab, 0.5 mg ranibizumab plus laser, or sham injections plus laser. Though not statistically significant, combination therapy was found to have better outcomes in terms of anatomical resolution of edema, requiring less injections but similar visual gains compared to ranibizumab monotherapy [25].

Ranibizumab 0.5 mg Treat-and-Extend Regimen for Diabetic Macular Edema (RETAIN Study) aimed to demonstrate non-inferiority of ranibizumab treat-and-extend (T&E) with or without laser to ranibizumab pro re nata (PRN) for best-corrected visual acuity (BCVA) in patients with DME. Treat-and-extend (T&E) approach progressively increases visits and intravitreal injections intervals when BCVA stability is achieved. The second-year results showed better visual outcomes with T&E regimen when associated with laser instead of ranibizumab [26].

Aflibercept (Eylea, Regeneron, New York, NY) is a soluble fusion protein composed of key domains from human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin G1. It has a greater binding affinity to VEGF-A than either bevacizumab or ranibizumab [27]. Intravitreal aflibercept injection (VEGF Trap-Eye or IVT-AFL) was approved by FDA for treatment in DME based on results of the VIVID and VISTA studies [28,29].

The VIVID and VISTA studies consisted of 2 identical, parallel, phase 3 randomized controlled trials comprising of 3 groups, first to whom aflibercept was given every 4 weeks, second of aflibercept given every 8 weeks after 5 initial monthly doses, and third of focal/grid laser photocoagulation. Aflibercept groups had better

improvement in visual acuity versus laser control with VISTA showing gains of +10.4 letters with monthly aflibercept compared with +1.4 letters in laser and VIVID with similar gains +10.3 letters versus +1.6 letters. 42.9% of patients in VISTA and 41.2% in VIVID had greater than 15 letter gain from baseline on treatment with monthly aflibercept, compared with 13.6% and 18.9% with laser photocoagulation alone [28].

VEGF-Trap-Eye in Patients with Diabetic Macular Edema (DA VINCI Study) was a phase II clinical trial having 221 diabetic patients, randomised to receive either 0.5 mg aflibercept every 4 weeks, 2 mg aflibercept every 4 weeks, 3 monthly injections of 2 mg aflibercept and then every 8 weeks, 3 monthly injections of 2 mg aflibercept and then on a PRN protocol, or macular laser photocoagulation alone. Patients who received aflibercept gained VA ranging from a mean of +9.7 to +13.1 letters, while patients in the group who received only laser lost a mean of 1.3 letters at 1-year follow-up. The 4 aflibercept groups had a significant reduction in CMT ranging from −165 to −227 μm compared with only −58 μm in the laser group (aflibercept arms versus laser) [29,30].

Bevacizumab (Avastin, Genentech, San Francisco, CA), is a full-length humanized monoclonal antibody that binds to all subtypes of VEGF. Bevacizumab, initially developed as a chemotherapy, is not FDA approved for treatment of diabetic macular edema but has found significant, widespread off-label use in view of its low cost and easy availability.

The DRCR.net conducted a randomized phase 2 control trial on 121 eyes to study short term effects of bevacizumab over a 12-wk period [31]. It suggested that bevacizumab was an effective drug for the management of DME as both primary treatment and also for refractory eyes. No significant difference was found in using single dose (1.25 mg) or double dose (2.5 mg) bevacizumab. Safety data were reported for 24 weeks without any safety concerns.

The BOLT study was another randomized control trial which compared treatment with intravitreal bevacizumab with laser therapy [32]. This study showed that the bevacizumab arm had a mean gain of +8.6 letters at 2 years, compared with a mean loss of −0.5 letters in the laser arm. 32% patients also gained at least 15 letters from baseline compared with 4% in the laser group. Studies have found similar benefits in treatment with bevacizumab compared with focal laser [33,34].

Comparing anti-vegf agents

DRCR.net protocol T study helped compare safety and efficacy of different anti-VEGF agents for their effects on diabetic macular edema [35]. This study done on 660 patients evaluated visual outcomes in patients with macular edema treated with ranibizumab, bevacizumab, or aflibercept up to every 4 weeks, with additional focal laser if indicated at or after 6 months. When initial visual acuities were 20/40 or better, there was found to be no statistically significant differences among the agents. While in patients with visual acuities of 20/50 or worse, after 1 year of treatment, aflibercept was found to have statistically significantly greater gains in visual acuity compared with ranibizumab and bevacizumab (+18.9, +14.2, and +11.8, respectively). After 2 years of followup, aflibercept and ranibizumab didn't show any difference but maintained greater outcomes than bevacizumab in this group. Based on this study it can be concluded that aflibercept may be considered the drug of choice in patients with poorer baseline visual acuity.

Corticosteroids

The first class of intravitreal drugs that were evaluated for the treatment of DME were intravitreal steroids [36]. They still are a promising treatment modality for people with DME owing to both its anti-inflammatory and antivascular permeability effects. Recent evidence has highlighted the role of inflammation in DME formation, in addition to VEGF-mediated breakdown of the blood-retinal barrier [37]. Hence, in cases not responding to anti VEGF therapy and lasers, steroids have emerged as a potential therapeutic option [38].

The DRCR.net protocol I study, a 5-year, independent, multicentre, RCT was another important milestone study for triamcinolone acetonide. A total of 854 eyes of 691 participants with BCVA of 20/32 to 20/320 and DME involving the fovea were randomized to sham injection + prompt laser, 0.5 mg ranibizumab + prompt laser, 0.5 mg ranibizumab + deferred (≥24 weeks) laser, or 4 mg triamcinolone acetonide + prompt laser. At 1 year, treatment with triamcinolone and laser resulted in a gain of 4 letters from baseline compared with a 3-letter gain in the laser group, and a 9-letter gain in both the ranibizumab and laser groups. In a subgroup of pseudophakic patients treated with triamcinolone and laser, BCVA gain was comparable to that of pseudophakic eyes treated with ranibizumab and superior to that of pseudophakic eyes treated with laser only. More eyes in the TA group required cataract surgery and IOP elevation, with 2 eyes requiring glaucoma surgery [39].

Gillies et al showed that treatment with IVTA plus macular laser in eyes with DME resulted in a doubling of improvement in vision compared with laser only over 2 years, but is associated with cataract and raised intraocular pressure [40].

Dexamethasone

The dexamethasone intravitreal implant 0.7 mg (DEX implant, Ozurdex®, Allergan Inc., Irvine, CA, USA) is a long-acting sustained-release, biodegradable corticosteroid. The PLACID trial was the first study that evaluated dexamethasone for DME. It was seen that in the initial months of therapy (1 month, 9 month) percentage of gain in mean BCVA was more in the group receiving ozurdex compared to that receiving laser therapy [41].

The most important trial evaluating Ozurdex for DME

were the MEAD trials. MEAD study found that at the end of 3 years, the percentage of patients with a ≥15-letter gain of BCVA from baseline was more in the Ozurdex 0.7/0.35 mg group compared to the sham group [42]. The CHAMPLAIN study evaluated the role of a single intravitreal injection of 0.7 mg Ozurdex in fifty-five patients with treatment-refractory DME and a history of previous pars plana vitrectomy (PPV) in the study eye. The mean BCVA gain was ≥10 letters at 8 weeks, in approximately 30% patients [43].

The ozurdex implant releases the corticosteroid into the vitreous over a period of ≤6 months [44]. The CHROME study included patients with DME, retinal vein occlusion, and uveitis. The mean reinjection interval was 2.3-4.9 months [45].

Fluocinolone Acetonide

Iluvien® (Alimera Sciences Inc., Alpharetta, GA, USA) is an intravitreal, nonbiodegradable microimplant containing the corticosteroid 0.19 mg fluocinolone acetonide. Pharmacokinetic studies showed that it provides sustained delivery in the eye for at least one year [46,47].

The FAME trials were 2 parallel, prospective, randomized, phase III, multicenter trials. Patients were randomized to receive an intravitreal insert releasing 0.2 or 0.5 µg fluocinolone acetonide per day or sham injection. The percentage of patients with a BCVA gain of ≥15 letters after 2 years was 28% in the fluocinolone groups versus 16% in the sham group [48]. A subgroup analysis found that while comparing chronic (≥3 years from diagnosis) with acute DME, higher percentage of patients with chronic DME gained ≥15 letters (34 vs. 13.4% in the sham group) compared to acute DME (22.3 vs 27.8% in the sham group [49].

Recommendation for Steroids in DME

Despite the documented ocular side effects of corticosteroids like cataract and glaucoma, corticosteroids are one of the effective adjunct modalities for the treatment of DME especially for refractory and persistent cases that failed to respond to standard conventional laser photocoagulation or anti-vegf agents. Hence for pseudophakic patients having no previous history of glaucoma, steroids can be given as the first choice.

They may be used as first line treatment in patients who have a history of a major cardiovascular event, cerebrovascular accidents or stroke or in those who are not willing to come for monthly injections (and/or monitoring) in the first 6 months of therapy. Dexamethasone shall be used first; fluocinolone may be appropriate for non-steroid responders with chronic macular edema that is not responsive to other treatments.

Surgery

Posterior vitreous detachment (PVD) leads to spontaneous resolution of DME [50]. There is lower incidence of PVD in eyes with DME compared to eyes without DME [51]. Vitrectomy, with or without membrane removal, may help improve DME via multiple mechanisms that include the release of abnormal vitreomacular adhesions, elimination of free and bound VEGF loads and improved oxygenation of the retina from the vitreous cavity [52,53].

Evaluation of the vitreomacular interface helps in selecting potential surgical candidates of DME and is best accomplished by funduscopic examination and OCT imaging.

Surgical Classification of DME

1. DME with abnormal vitreomacular adhesions and/or proliferation

   a. Taut hyaloid

   b. Vitreomacular and/or vitreofoveal traction

   c. Epiretinal membrane (avascular and/or vascular)

2. Post vitrectomy taut ILM syndrome

3. Recalcitrant DME without abnormal vitreomacular adhesions.

Lewis et al. introduced the term “taut hyaloid” to describe a subset of eyes with DME related to the thickened and taut premacular posterior hyaloid [54]. OCT was not available then and the funduscopic features included a glistening sheen and posterior hyaloid striae. Vitrectomy with posterior hyaloid removal had complete resolution of DME in 80% of eyes and improvement in DME and BCVA in 90% of patients.

A larger study with 55 eyes, by Pendergast et al, had similar anatomic outcomes, with DME completely resolving in 81% of eyes after a mean follow-up of 4.5 months [55]. Varying, although largely positive results of vitrectomy in DME were noted in other series [55–60]. Recently several authors have suggested a positive effect of ILM peeling in vitrectomy for DME [59,61]. Nakajima et al, however, found that the visual acuity outcomes using pars plana vitrectomy with ILM peeling versus no ILM peeling were not significantly different [62].

New Therapeutic Targets

Refractory DME has been proposed to be multifactorial in origin and several molecules such as prostaglandins, leukotrienes, protein kinase C, nitric oxide, vascular endothelial growth factor, and tumor necrosis factor (TNF) have been implicated in the development of DME [63]. Hence to combat edema resistant to anti VEGFs, newer agents targeting the molecules involved, pathophysiologic pathways or signalling agents for diabetic macular edema have been recently introduced [64].

Tumor necrosis factor-α is a proinflammatory cytokine implicated in the breakdown of the blood–retinal barrier in diabetic animal models [65,66]. In experimental models

of diabetic retinopathy, inhibition of TNF-α has resulted in suppressing the breakdown of the blood–retinal barrier [67]. In humans, Infliximab, the TNF-α inhibitor, resulted in a decrease in central macular thickness (CMT) with visual improvement in four of six eyes with DME refractory to macular laser photocoagulation after two systemic infusions infliximab [68].

Vascular Adhesion Protein-1 (VAP-1) is an adhesion molecule expressed and located on the surface of endothelial cells involved in leucocyte transmigration during inflammation. ASP8232 (Astellas Pharma Europe BV, Netherlands) is an orally administered VAP-1 inhibitor currently in the phase 2 VIDI trial, comparing ASP8232 versus ranibizumab versus combination therapy with both agents [69].

The Designed Ankyrin Repeat Proteins (DARPins) are genetically engineered mimetic proteins that target VEGF based on naturally occurring proteins in the human genome. Abicipar pegol (Molecular Partners, Zurich, Switzerland) is a DARPin antagonist to VEGF-A which on intravitreal injection, suppresses aqueous levels of VEGF and reduces retinal thickness for up to 8 to 12 weeks in individuals with diabetic macular edema [70]. The PALM study is a phase 2 clinical trial comparing abicipar with monthly ranibizumab for treatment in diabetic macular edema. All 3 of the abicipar treatment arms showed efficacy and improvements in visual acuity and retinal thickness comparable to monthly ranibizumab with fewer injections needed [71].

Angiopoietins are a family of growth factors that interact with tyrosine kinase receptors also known as Tie2 receptors located primarily on endothelial cells. AKP-9778 (Aerpio Therapeutics, Cincinnati, OH), in combination with ranibizumab has shown relative reduction in diabetic macular edema compared with ranibizumab alone in a few studies [72,73].

The monoclonal antibody RO6867461 (Roche, Basel, Switzerland), is a biphasic immunoglobulin with one arm binding VEGF and the other Ang-2. The BOULEVARD study is a phase 2 trial comparing RO6867461 with ranibizumab. However, disappointing results have been seen in investigations of the use of another monoclonal antibody to Ang-2, Nesvacumab (Regeneron, New York, NY), which was being coadministered with aflibercept in the RUBY study and hence further development is suspended [74,75].

Integrins are cell surface transmembrane receptors involved with attachments and interactions between cells and between cells and the extracellular matrix. ALG-1001 (Allegro Ophthalmics, San Juan Capistrano, CA) is an integrin antagonist designed to inhibit interaction between integrins and the extracellular matrix. Integrins can induce vitreolysis, similar to ocriplasmin, and can cause induction of PVD. Thus, VEGF levels are lowered and also the vitreous scaffold for neovascularization and subsequent tractional detachment. DEL MAR phase 2 trial for DME, found ALG-1001 noninferior compared with monthly bevacizumab in terms of visual acuity gains and retinal thickness reductions, with less frequent need for injections with ALG-1001 [76].

Plasma kallikrein, a serum protease, is the primary proinflammatory mediator of the KKS. Intravitreal injection with kallikrein or bradykinin increases retinal vascular permeability. KVD001 (Kalvista Pharmaceutical, Cambridge, MA), an intravitreally administered plasma kallikrein inhibitor, has shown promising results in a phase 1 trial in patients with DME with improvements in visual acuity and decreased retinal thickness [74]. Squalamine is a small molecule antiangiogenic drug delivered as 0.2% eye drops (OHR-102; Ohr Pharmaceutical, New York, NY). It binds phospholipid membranes that blocks many, but not all, downstream effects of the VEGF pathway. A phase II trial (IMPACT) study combined with ranibizumab for age-related macular degeneration has found some improvement compared with ranibizumab alone [69]. The phase 3 MAKO study showed contradictory results where co-treatment with topical squalamine did not have visual acuity gains compared with ranibizumab alone [77].

Conclusion

Diabetic macular edema is a complex disease and is recognised as a major cause of blindness in our world today. Although various novel treatments have been developed, refractory cases of DME still abound and a definitive solution to this remains elusive. Multiple treatment approaches and combination of therapies would be needed to manage DME. Further studies and research efforts are thus warranted to determine newer pathophysiological pathways and consequently novel therapies and management algorithms to tackle the growing menace of DME.

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