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REVIEW

Diabetic Macular Edema: Therapeutic Options

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ABSTRACT

Treatment for diabetic macular edema (DME) is continuously evolving with the advent of pharmacologic therapies. Focal laser photocoagulation remains the historical standard of care; however, a new wave of studies is rapidly emerging that shows the benefit of intravitreal antivascular endothelial growth factor medications and corticosteroids. The goal of this review is to compare the various treatment options for DME, and include data from the most recent clinical trials of therapies for this complex condition.

Keywords: Antivascular endothelial growth factor; Corticosteroids; Diabetic macular edema; Intravitreal injection; Laser photocoagulation; Vitrectomy

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INTRODUCTION

Diabetic macular edema (DME) is a primary cause of visual loss in diabetic patients in the working age population of the US [1, 2]. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined macular edema as the thickening of the retina and/or hard exudates within 500 μm of the center of the macula [3]. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), the 10-year rate of developing DME was 20.1% in patients with type 1 diabetes and, in patients with type 2 diabetes, it was 25.4% for those treated with insulin, and 13.9% for those not treated with insulin [4]. The goal of this review is to compare the various treatment options for DME, and include data from the most recent clinical trials of therapies for this complex condition.

METHODS

The various treatment modalities for DME and the data from clinical trials were obtained by a PubMed search using the above keywords. Randomized, controlled trials that focused on treatment of DME from 1970 to 2011 were included in this review.

PATHOGENESIS

The pathogenesis of DME involves both systemic and local risk factors. These risk factors may alter the blood–retina barrier and allow the leakage of proteins and fluid into the macula [5]. Systemic risk factors associated with DME include age, male gender, systolic blood pressure, hyperlipidemia, proteinuria, insulin use, diuretic use, a longer duration of diabetes, higher glycosylated hemoglobin, and pan-retinal photocoagulation (PRP) [5–8]. Local factors that may influence DME include angiogenic factors, such as vascular endothelial growth factor (VEGF), protein kinase C (PKC), prostaglandins, growth hormone, and the anatomy of the posterior hyaloid face [9–11].

DIAGNOSIS

Clinically-significant macular edema (CSME) [3] is defined as one or more of the following: retinal thickening at or within 500 μm of the center of the macula; hard exudates at or within 500 μm of the center of the macula, if associated with adjacent retinal thickening; or a zone or zones of retinal thickening one disc area in size, at least part of which is within one disc diameter of the center of the macula (Fig. 1). This definition primarily refers to eyes eligible for laser photocoagulation. With the advent of pharmacotherapy (anti-VEGF agents or corticosteroids) DME is more appropriately defined as center-involved versus non-center involved, with most cases of center-involved macular edema appropriately eligible for treatment with pharmacotherapy [12]. Intravenous fluorescein angiography (FA) and optical coherence tomography (OCT) can assist in the evaluation of DME [13]. Angiographic findings reflect changes in vessel permeability and patency [14]. FA assists in identifying areas of macular edema, leakage, neovascularization, and nonperfusion [15]. OCT is a useful tool for the detection and monitoring of DME [16]. There exists a weak-to-modest correlation between OCT-measured center-point thickness and visual acuity [17, 18].

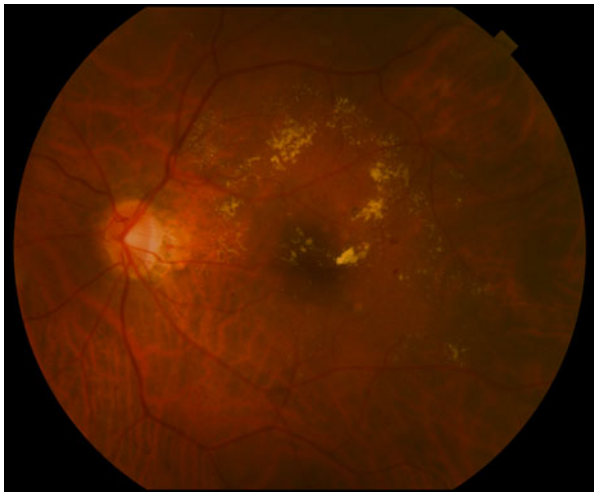

Fig. 1 Fundus photo of CSME. *CSME* clinically significant macular edema

MANAGEMENT

The treatment of DME is focused on optimizing systemic risk factors and use of laser, pharmacologic, or surgical modalities to

reduce leakage into the macula and subsequent macular edema [19].

Systemic Therapies

The United Kingdom Prospective Diabetes Study (UKPDS) of type 2 diabetics [20], the Diabetes Control and Complications Trial (DCCT) [21, 22] of type 1 diabetics, and the WESDR [23] established that a higher level of glycosylated hemoglobin is a risk factor for DME. The DCCT and UKPDS established that intensive control of blood glucose should be a goal for almost all patients with diabetes [20, 22]. The intensive control group of the DCCT had a trend toward less DME that did not reach statistical significance. The UKPDS showed that superior control of blood glucose and systemic hypertension led to a lower rate of micro-vascular complications [20, 24]. One study showed that treatment of hyperlipidemia in patients with macular edema and hard exudates resulted in improvement or stability of visual acuity [25]. Treatment of renal dysfunction or smoking cessation has not been proven to have a direct benefit on DME; however, they are still encouraged for diabetic patients.

PKC

The effect of VEGF on retinal vascular permeability appears to be mediated predominantly by the beta-isoform of PKC [9]. Ruboxistaurin (RBX) is an orally administered, isoform-selective inhibitor of PKC-beta. Animal models of diabetic retinopathy (DR) and patients with diabetes-induced retinal hemodynamic abnormalities have achieved beneficial effects from the use of RBX [26]. In a study by Aiello et al. [27] in treatment naive DME patients, fewer eyes in the RBX group (26.7%) required initial focal/grid photocoagulation versus the placebo group (35.6%; $P = 0.008$).

Cyclooxygenase Isozyme-2 Inhibitors

Inflammation plays a role in DME and chronic inflammation has been shown to be mediated, in part, by the cyclooxygenase (COX) isozymes localized in the retina [28, 29]. Immunohistochemistry studies and animal models of retinopathy have shown the efficacy of COX-2 inhibitors [30–32]. In a prospective, randomized, multicenter trial, celecoxib did not show evidence of benefit as compared to laser treatment. However, participants assigned to the celecoxib group were more likely to have a reduction in fluorescein leakage [33]. Potential side effects of COX-2 inhibitors include allergic reactions, gastrointestinal discomfort, and gastrointestinal bleeding.

Ocular Therapies

Laser Photocoagulation

The mechanism of action of laser photocoagulation is unknown. The possible explanations include laser-induced destruction of the oxygen-consuming peripheral retina and increased diffusion of oxygen through the laser scars to the inner retina [34]. The ETDRS was carried out, in part, to help understand the effectiveness of photocoagulation in the management of DME. The ETDRS used FA to help direct laser photocoagulation treatment of DME [35]. Treatable lesions were defined as discrete angiographic points of retinal hyperfluorescence or clinical points of focal leakage between 500 and 3,000 μm from the center of the fovea center considered to produce retinal thickening or hard exudates; focal areas of leakage between 300 and 500 μm from the center of the macula causing retinal thickening and hard exudates that persisted after a first

treatment, and visual acuity of 20/40 or worse; areas of diffuse leakage within the retina, including microaneurysms, intraretinal microvascular abnormalities (IRMA), and a diffusely-leaking macular capillary bed; and thickened avascular zones (except for the foveal avascular zone). The ETDRS has described two methods of treatment with laser photocoagulation: focal or grid-pattern [35]. Focal photocoagulation consisted of whitening or darkening of microaneurysms and areas of focal fluorescein leakage with 50–200 μm laser spots. Grid-pattern photocoagulation consisted of light burns with a spot size of 50–200 μm, spaced at least one spot size apart in an area more than 500 μm from the foveal center and the optic disc. Retreatment was carried out if CSME was present at the 4-month follow-up visit. FA was performed to detect new or residual areas of focal or diffuse leakage. Focal leaks within 500 μm from the center were treated if the visual acuity was worse than 20/40, and if such treatment could be performed without significant risk to the center of the fovea [35].

Benefits of Laser Photocoagulation

The beneficial effect of immediate focal photocoagulation was most pronounced for patients with CSME (Fig. 2). The benefit of treatment was present regardless of initial visual acuity. Eyes with better visual acuity had a better prognosis. In eyes with an initial visual acuity of 20/40 or worse, an improvement of one or more lines occurred more frequently in treated than deferral eyes [3]. Improvements of three or more lines of visual acuity occurred infrequently. Patients with macular edema and mild-to-moderate nonproliferative DR (NPDR) benefited most from immediate focal treatment and PRP

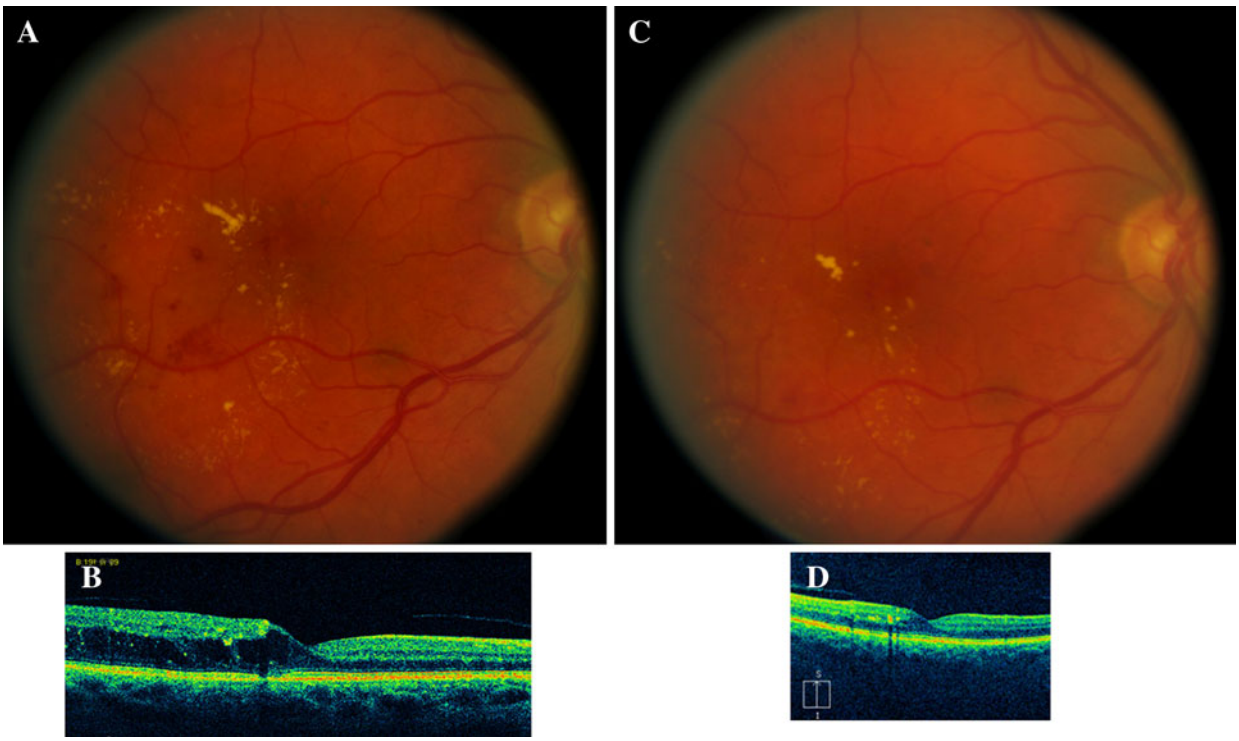

Fig. 2 Fundus photo (**a**) and baseline OCT scan (**b**) of patient with CSME. The patient underwent laser photocoagulation and there was partial resolution of macular edema as noted in follow-up fundus photo (**c**) and OCT (**d**). *CSME* clinically significant macular edema, *OCT* optical coherence tomography

could be deferred until the development of more severe retinopathy [3]. This treatment strategy decreased the risk of a loss of 15 letters on the ETDRS chart (defined as a moderate visual loss) by 50% compared with eyes that did not receive laser treatment [3]. The incidence of moderate visual loss at 2 years was 7% in the immediate laser treatment subgroup compared to 16% in the deferral of photocoagulation subgroup.

Adverse Effects of Laser Photocoagulation

Laser photocoagulation of the macula can cause chorioretinal scars to expand up to 300% and produce dense focal scotomas [36]. Other potential adverse effects include reduced color vision, choroidal neovascularization, retinal pigment epithelium (RPE) fibrous metaplasia, and inadvertent photocoagulation of the center of the macula [34].

Alternative Laser Delivery Systems

Alternative laser delivery systems are being developed to reduce complications of focal photocoagulation. The micro-pulsed laser system is able to achieve the desired benefits by delivering energy as a train of short bursts to the RPE with sufficient time between bursts to allow the heated tissue temperature to return to normal. This technique reduces collateral damage significantly and decreases the risk of expansion of retinal scars [37]. Moorman and Hamilton [38], using a grid of sub-threshold burns with a micro-pulsed diode laser (100 μs in 200 ms, or 5% duty cycle), demonstrated resolution of macular edema in 57% of diabetic eyes followed for 6 months. Solid-state green pattern-scanning laser (PASCAL) with a short-duration (0.01 s) has also shown comparable results with standard focal laser treatment for DME after a 4-month follow-up [39]. Furthermore, to improve the treatment accuracy and localization of retinal lesions, a navigated laser (NAVILAS®; OD-OS GmbH, Teltow, Germany) photocoagulator has been developed [40]. It consists of a retinal eye-tracking laser delivery system with integrated digital fundus imaging that allows overlay of a treatment plan, based on either fundus photography or FA, onto a real-time image of the patient's retina. This system uses a diode-pumped solid-state laser (532 nm) and automatically advances the aiming beam from the marked site to the next after each photocoagulation spot until the treatment plan is completed. The other advantages are: a larger area of the retina can be visualized than with a slit lamp, images are reflex free, infrared fundus illumination, no requirement for contact lens use or topical anesthesia during the procedure, and the availability of an immediate detailed report.

Pharmacologic Treatments

Although focal laser photocoagulation per ETDRS was successful in reducing the rates of visual loss due to DME, many patients did not recover lost vision and there was a subset of patients who were unresponsive to this therapy [41]. This led to the use of intraocular pharmacologic agents for management of DME [41]. Pharmacologic treatments are typically administered in an outpatient setting with topical anesthesia and a 27 or 30 G needle is introduced into the vitreous cavity of the eye, via the pars plana, to deliver the medication.

Corticosteroids

Corticosteroids decrease the release of prostaglandins and inhibit the expression of the VEGF gene [42, 43]. These antiinflammatory and anti-VEGF properties may be able to reduce breakdown of the blood–retina barrier.

The various routes used for corticosteroids delivery in the treatment of DME include periocular injection, intravitreal injection, or via the implantation of a bioerodable or nonbioerodable sustained-release device [41].

Intravitreal Injection

Initial reports by Jonas et al. [44] and Martidis et al. [45] showed promising results using intravitreal steroids for the management of refractory DME. Subsequent studies by Massin et al. [46] and Gillies et al. [47] demonstrated an improvement in visual acuity, a reduction in macular thickness, and a decreased necessity for laser treatment in eyes treated with 4 mg of intravitreal triamcinolone (IVT). The Diabetic Retinopathy Clinical Research (DRCR) Network initiated a trial that evaluated IVT in 1 and 4 mg doses, compared with focal laser treatment over 2 years [48]. The study consisted of 840 eyes randomized to these three arms. At 4 months, both triamcinolone groups had a greater improvement in visual acuity and macular thickness than the focal laser group; however, by 1 year, there was no difference between groups. At 2 years, the focal laser group demonstrated better visual acuity and macular thickness results compared to the corticosteroid groups. Furthermore, there was a fourfold elevation in the intraocular pressure and rate of cataract formation in the steroid groups compared with the focal laser group [48]. Several other studies have attempted to evaluate the benefit of IVT as an adjunct to focal/grid laser treatment [49–51]. The DRCR Network group, in a recent phase 3 study, showed no overall difference in visual acuity between IVT plus laser treatment ($n = 203$) and laser treatment alone ($n = 186$) after 1 year; however, a subgroup of pseudophakic eyes treated with combined IVT/laser had better visual acuity results compared with laser alone [52].

Extended-Release Delivery Systems

One potential drawback of intravitreal injection is that the treatment effect typically wanes, and patients that are initially responsive to treatment may require repeated injections. An extended-release product could reduce the risks associated with repeated injections. Retisert® (Bausch & Lomb, Rochester, NY, USA) is FDA-approved for the treatment of uveitis and is designed to release 0.59 μg/day fluocinolone acetonide [53]. It has been evaluated for the treatment of DME and showed some promise in reducing macular thickness in DME; however, after 2 years, 80–90% of phakic patients required cataract extraction and 15–20% of patients required incisional glaucoma surgery [53]. Hence, a polymer insert positioned in the eye by intravitreal injection was developed that releases 0.2 μg/day (low dose) or 0.5 μg/day (high dose) fluocinolone acetonide [54]. A randomized phase 3 trial, Fluocinolone Acetonide in Diabetic Macular Edema (FAME), was conducted in eyes with persistent DME despite laser treatment [55]. It showed a 15-letter improvement from baseline at 2 years in 28.7% of low-dose, 28.6% of high-dose, and 16.2% of sham injection patients [55].

An intravitreous drug delivery system (DDS) that delivers dexamethasone directly to the posterior segment for 35 days is also being developed [56]. A phase 2 clinical trial was conducted which included patients with DR retinal vascular occlusive disease, Irvine-Gass syndrome, or uveitis. Patients receiving the 700-μg implant had a statistically significant improvement in visual acuity of two or more lines, and significant improvements in retinal thickness and fluorescein leakage in comparison to patients who did not receive the implant [57]. An intraocular pressure elevation to 25 mmHg or more was noted at some point in 32 of 306 study eyes. All eyes with intraocular

pressure elevation were controlled with the use of topical antiglaucoma medications [57].

Adverse Effects of Corticosteroids

Cataracts and elevation of intraocular pressure are the principal adverse effects from use of ocular steroids [58]. Intravitreal injection and implantable devices carry additional risks associated with the injection and implantation procedure, respectively [56, 59].

Anti-VEGF Therapies

Increased vascular permeability is a hallmark of DME. In human eyes with DR, hypoxia causes upregulation of VEGF production, and leads to retinal capillary hyperpermeability [60]. The anti-VEGF therapies available at this time include: pegaptanib sodium, ranibizumab, bevacizumab, and aflibercept [19].

Pegaptanib

Pegaptanib binds to the VEGF-165 isomer [61]. In a phase 2, double-masked, randomized, controlled trial evaluating patients with DME, the intravitreal pegaptanib (0.3 mg dose) group had a statistically higher proportion of patients with a gain of 10 or more letters in visual acuity (34 vs. 10%) as well as a reduction in macular thickness (−68 vs. +4 μm) as compared to the sham group at 9 months follow-up [62]. The patients treated with pegaptanib were also less likely to need repeat focal laser treatment at follow-up.

Bevacizumab

Bevacizumab is a FDA-approved intravenous chemotherapy for various cancers and consists of recombinant humanized antibody directed at all isoforms of VEGF-A [63]. The DRCR Network group conducted a phase 2 study comparing various treatment arms of bevacizumab intravitreal injections (1.25 mg), with or without focal photocoagulation, over 3 months in 121 eyes [64]. Compared with laser treatment alone, eyes in the bevacizumab groups had an improvement in visual acuity after 3 months (−1 letter vs. +5 and +7 letters, respectively). Several other studies [65–67] have examined the effect of bevacizumab therapy on DME in a noncomparative fashion (Fig. 3). The Bevacizumab Or Laser Therapy (BOLT) was designed to compare bevacizumab therapy head-to-head with laser treatment for DME [68]. The BOLT study consisted of 80 patients who had previously received focal laser treatment for DME. Patients were randomly assigned to the bevacizumab arm, receiving injections every 6 weeks for the first 3 months and every 6 weeks as needed thereafter, and the laser arm, receiving laser treatment as needed every 4 months. The bevacizumab arm showed a superior gain in visual acuity at 12 months (+8 letters vs. −0.5 letters), and a greater decrease in macular thickness (130 vs. 68 μm, $P = 0.06$) [68].

Ranibizumab

Ranibizumab is a humanized antibody fragment directed at all isoforms of VEGF-A [69]. It is an FDA-approved intravitreal therapy for the treatment of age-related macular degeneration [70] and macular edema associated with retinal vein occlusion [71]. In the Ranibizumab for Edema of the mAcula in Diabetes-2 (READ-2) study, intravitreal ranibizumab 0.5 mg alone, or laser treatment alone, or a combination of ranibizumab and focal laser treatment was compared in 126 eyes. The ranibizumab group had the superior visual outcome (a gain of 7.2 letters), while the laser group lost ETDRS 0.43 letters and the combination group gained 3.8 letters [72]. Another phase 2, randomized, clinical trial, Ranibizumab in Diabetic Macular

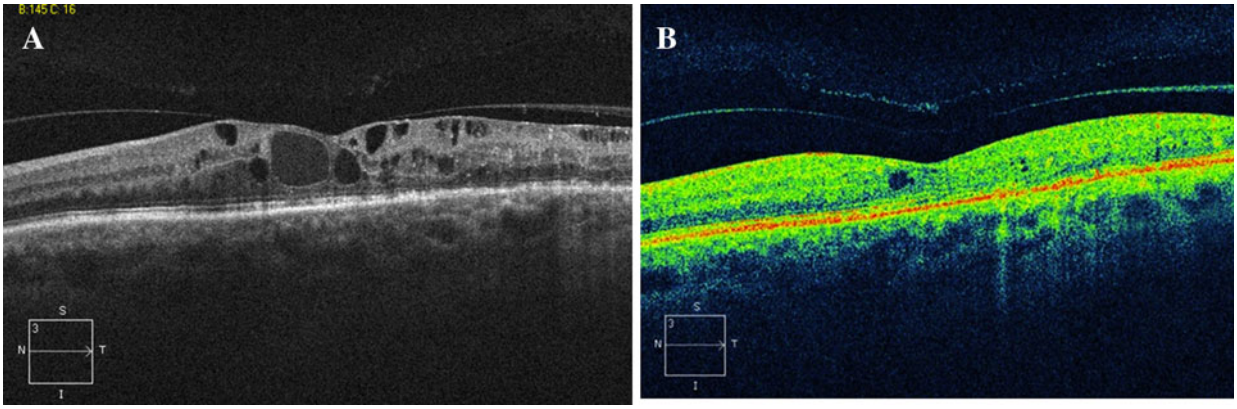

Fig. 3 Baseline OCT scan (**a**) of patient with persistent DME in spite of laser photocoagulation. The patient underwent five intravitreal injections of bevacizumab at 6 weeks interval. There was a considerable resolution of macular edema as noted in follow up OCT scan (**b**). *DME* diabetic macular edema, *OCT* optical coherence tomography

Edema Study (RESOLVE), compared 0.3 and 0.5 mg ranibizumab with sham injections for the treatment of DME in 151 eyes [73]. Patients received monthly injections for an initial 3 months, followed by a continuation of monthly injections on an as-needed basis with the opportunity for rescue focal laser treatment. At 12 months, there was an improvement in visual acuity in the ranibizumab group (+10.3 letters) and reduction in macular thickness (−194 μm) versus the sham group (−1.4 letters and −48 μm, respectively). The percentage of patients who gained at least 10 letters was significantly greater in the ranibizumab group (60.8%) versus the sham group (18.4%). The DRCR Network group has also reported 1-year results of a phase 3, randomized, controlled trial showing visual acuity improvement was greater in ranibizumab groups (+9 letters) versus the laser-only treatment (+3 letters) and the triamcinolone group (+4 letters) [52]. Recently, Genentech announced the 24-month results from two phase 3, multicenter, randomized, double-masked studies (RISE $n = 377$; RIDE $n = 382$) designed to assess the safety and efficacy of ranibizumab in patients with DME [74]. In these studies, patients were randomized to receive monthly injections of ranibizumab or sham injections with macular laser rescue-treatment available to all patients at 3 months. The results revealed a significant percentage of patients in the ranibizumab group (40%) had an improvement of at least 15 additional letters (3 lines) from baseline as compared to the sham group (15%). These studies also show that the benefit from ranibizumab was as early as 7 days post first injection, and 60% of the patients achieved visual acuity greater than or equal to 20/40. Furthermore, approximately 4% of the patients in the ranibizumab group progressed to proliferative DR as compared to 13% in the sham group.

Aflibercept

Aflibercept is a fusion protein that binds to VEGF-A and placental growth factor [75]. It has a tighter binding affinity to VEGF compared with the current anti-VEGF therapies [75]. The DME and VEGF Trap-Eye: Investigation of Clinical Impact (DAVINCI) trial investigated the role of aflibercept in DME. In this trial, aflibercept was given in 3 monthly loading doses followed by either as-needed dosing or

dosing every 8 weeks, and compared to macular laser photocoagulation [76]. This phase 2 trial showed aflibercept had superior visual outcomes (+8.5 to +11.4 letters) as compared to laser photocoagulation (+2.5 letters; $P = 0.0085$) at 6 months. A phase 3 trial of Intravitreal Administration of VEGF Trap-Eye in Patients With Diabetic Macular Edema (VISTA DME) is currently underway [75].

Vitrectomy

There are several reports of an association between DME and the anatomy of the vitreoretinal interface [77, 78]. In one study, the prevalence of posterior vitreous detachment (PVD) was observed among 20% of the eyes with CSME as compared to 55% of the non-CSME group [77]. Furthermore, vitreomacular separation was associated with an increased rate of spontaneous resolution of macular edema [11]. Thus, an attached posterior hyaloid predisposes to the development of DME (Fig. 4) and, hence, pars plana vitrectomy may have a role in the treatment of DME [79–82]. Harbour et al. [83] reported a case series of seven eyes with DME attributed to a thickened and taut posterior hyaloid that underwent pars plana vitrectomy. Visual acuity improved by two or more lines in four eyes, and macular edema resolved in four eyes and diminished in two eyes. The DRCR Network group has also reported the 6-month primary outcome and 1-year final follow-up results on visual and anatomic outcomes after vitrectomy performed without concomitant cataract surgery in eyes with DME [84]. This prospective, observational study consisted of 87 eyes with DME and vitreomacular traction that underwent standard pars plana vitrectomy with peeling of posterior hyaloid/epiretinal membrane, and additional maneuvers based on the investigator's evaluation. At 6 months, visual acuity improved by ≥10 letters in 38% of eyes and the median OCT central subfield thickness decreased by 160 μm (43% having central subfield thickness <250 μm and 68%

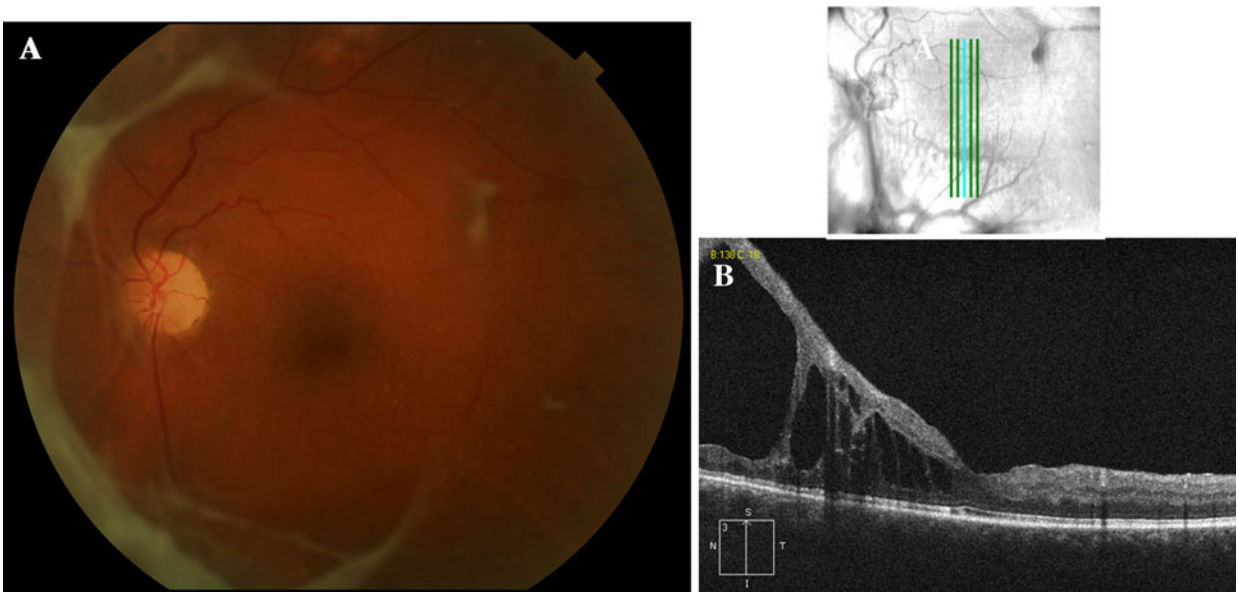

Fig. 4 Fundus photo (**a**) and OCT scan (**b**) of patient with DME secondary to vitreoretinal interface disease. *DME* diabetic macular edema, *OCT* optical coherence tomography

having at least a 50% reduction in thickening), as compared to baseline median visual acuity of 20/100 and median OCT thickness of 491 μm [84]. Postoperative complications during the 6 months included retinal detachment (3 eyes), endophthalmitis (1 eye), vitreous hemorrhage (5 eyes), and elevated intraocular pressure requiring treatment (7 eyes). Thus, vitrectomy performed in eyes with DME reduces macular thickening with a visual acuity improvement in 28–49% patients, and worsening in 13–31%. Patients with macular ischemia, RPE atrophy, subfoveal lipid, and a baseline visual acuity of 20/200 or less tended to respond less favorably to surgery [85]. The expected complications of vitrectomy include cataract progression, vitreous hemorrhage, and retinal tear or detachment [84, 86].

CONCLUSION

There has been considerable progress in understanding the pathophysiology of DME and the development of new therapies. Based on various clinical and epidemiologic studies, it is recommended for all patients with diabetes to maintain good control of blood sugars, blood pressure, and hyperlipidemia as determined by their primary care physician. Focal or grid photocoagulation remains the first-line treatment in the majority of patients with non-center-involved DME. In many patients with center-involved DME, intravitreal injection of anti-VEGF therapies is becoming commonly used. Patients unresponsive to anti-VEGF therapies may benefit from intravitreal injection of triamcinolone or possibly an extended-release steroid delivery system to deliver corticosteroids to the posterior segment. However, patients need to understand the risks of these treatments, especially with regards to cataract and glaucoma. In patients with vitreoretinal interface disease, vitrectomy with removal of the posterior vitreous may be a viable option. As new and improved therapies are continuously developed, treatment paradigms will also change, with DME patients being the ultimate beneficiaries of these exciting developments.

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The authors declare that they have no conflicts of interest. M. S. I. is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

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