Current Diabetes Reports (2019) 19: 68
https://doi.org/10.1007/s11892-019-1188-4

MICROVASCULAR COMPLICATIONS—RETINOPATHY (DL CHAO AND G YIU, SECTION EDITORS)

Treatment of Diabetic Macular Edema

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Published online: 29 July 2019

Abstract

Purpose of Review Diabetes mellitus is a global epidemic which is growing in prevalence, and diabetic macular edema (DME) is a leading cause of visual impairment among patients affected by this disease. Our objective is to review current and upcoming therapeutic approaches to DME.

Recent Findings Once considered the gold standard in treatment of DME, focal/grid laser is now reserved mostly for non-center-involving DME, while anti-vascular endothelial growth factor (anti-VEGF) therapy has become the first-line treatment. However, suboptimal responders to anti-VEGF and the burden of frequent injections have stimulated the development of novel approaches. Corticosteroids can be effective in treating DME, but adverse effects such as intraocular pressure elevation and cataract formation must be considered. Emerging therapeutics and drug delivery systems in the pipeline offer exciting potential solutions to this vision-threatening disease.

Summary Multiple types of therapeutics targeting various pathways implicated in the pathogenesis of DME may help lessen the global burden of vision loss from diabetes.

Keywords Diabetic macular edema · Diabetic retinopathy · Anti-VEGF · Intravitreal injection · Laser photocoagulation · Diabetes mellitus

Introduction

Over 30 million people, or 9.4% of the population, have diabetes mellitus in the USA [1]. Ophthalmic complications of diabetes are a leading cause of blindness among those aged 20 to 74 years [2]. Diabetic macular edema (DME) affects approximately 746,000 or 4% of all Americans with diabetes aged 40 years or older [3]. The prevalence of DME increases with duration of disease and stage of diabetic retinopathy [4], approaching 30% in adults who have had diabetes for ≥ 20 years and 71% of those with proliferative diabetic retinopathy (PDR) [5]. Associated risk factors include elevated blood glucose, lipid, and triglyceride levels, hypertension, advanced diabetic nephropathy, and pregnancy.

DME generally refers to retinal thickening within two disc diameters of the fovea and can be either focal or diffuse. Focal edema is generally caused by leakage from retinal capillary microaneurysms and often associated with surrounding rings of lipoprotein deposits in the retina known as "hard exudates." In contrast, diffuse edema usually involves widespread

This article is part of the Topical Collection on *Microvascular Complications—Retinopathy*

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breakdown of the inner blood-retinal barrier (BRB) due to basement membrane thickening and pericyte loss, often forming a flower-like or petaloid pattern of edema in the perifoveal macula. Vascular endothelial growth factor (VEGF), which is upregulated by the resultant hypoxia, and other inflammatory cytokines are believed to play a role in DME [6, 7].

Diagnosis

The presenting symptoms of DME can include blurry central vision, metamorphopsia, changes in color perception, and difficulty with reading. Diagnosis is made by observation of macular retinal thickening on slit-lamp biomicroscopy or optical coherence tomography (OCT). Fluorescein angiography (FA) can also be used as an adjunct diagnostic tool to demonstrate breakdown of the BRB. However, FA leakage can occur in the absence of macular retinal thickening, so definitive diagnosis must still be made via slit lamp or OCT.

Historically, DME was classified according to the Early Treatment Diabetic Retinopathy Study (ETDRS) as clinically significant macular edema (CSME) if it met any of the following criteria: (1) retinal thickening within 500 μm of the foveal center; (2) hard exudates within 500 μm of the foveal center if associated with adjacent retinal thickening; (3) zone of retinal thickening > 1 disc area if located within 1 disc diameter of the foveal center [8]. Now, the term center-involving DME (CI-DME) is used if the central macula is thickened on OCT, typically based on a threshold value for central subfield thickness (CST) measured from the central 1-mm-diameter circular region centered on the fovea which varies depending on specific OCT device and patient sex (Fig. 1).

Treatment

Medical Treatment

Primary prevention is the ideal management of DME. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found a direct association between the duration of diabetes and the prevalence of retinopathy in both insulin-dependent (type 1) and non-insulin-dependent (type 2) forms. Nearly 99% of people with type 1 diabetes and 60% of people with type 2 diabetes developed retinopathy after 20 years of disease duration [9, 10]. The Diabetes Control and Complications Trial (DCCT) studied 726 participants with type 1 diabetes without retinopathy and found that intensive glycemic control decreased the risk of developing retinopathy by 76% compared to less-intensive control [11, 12]. Analogously, in 715 participants with type 1 diabetes and mild to moderate diabetic retinopathy, the DCCT found that intensive glycemic control decreased the rate of retinopathy progression by 54%.

The United Kingdom Prospective Diabetes Study (UKPDS) randomized 4209 participants with newly diagnosed type 2 diabetes to either conventional management with diet and exercise, using medications only if blood glucose levels exceeded 15 mmol/L, versus intensive therapy involving treatment to maintain blood glucose levels below 6 mmol/L. The intensive treatment group had lower levels of hemoglobin A1c compared to the conventional treatment group (7.0% versus 7.9%), as well as a 25% reduction in microvascular endpoints and 12% fewer serious endpoints, including kidney failure, limb amputation, blindness, and death [13]. The UKPDS also found that among participants with diabetes and hypertension, tight blood pressure control reduced the rate of retinopathy progression and risk of other vascular complications [14]. Given that prevention of DME is closely linked with prevention of DR, patients should be advised to optimize their glucose and cardiovascular risk factor control; smoking cessation should be recommended to active smokers.

Laser Photocoagulation

The ETDRS was the first prospective, randomized clinical trial to investigate the use of laser photocoagulation in patients with diabetes and mild non-proliferative diabetic retinopathy (NPDR) through early PDR, with and without macular edema, and played a major role in standardizing DME treatment [8, 15]. Over 3700 patients had 1 eye randomly assigned to scatter and/or focal laser photocoagulation and 1 eye assigned to no photocoagulation. Focal photocoagulation involved targeting focal lesions, such as leaking microaneurysms or ischemic areas on FA, and was applied in either direct or grid pattern [16]. Scatter photocoagulation was applied either in mild (400–650 burns; usually 1 episode) or full (1200–1600 burns; ≥ 2 episodes) scatter amounts [16].

The risk of progression to high-risk PDR at 5 years was reduced by 50% in eyes receiving full scatter and 25% with mild scatter compared to the deferral group [17]. The rate of moderate visual loss (MVL), defined as a loss of ≥ 15 letters on the ETDRS VA charts, was decreased from 24% in the deferral group to 12% in eyes receiving immediate focal photocoagulation at 3 years [8, 17].

The ETDRS concluded that scatter laser photocoagulation is not recommended for mild to moderate NPDR in the setting of proper follow-up. However, for high-risk PDR, it stated that scatter photocoagulation should be considered and generally administered without delay. It also suggested that focal

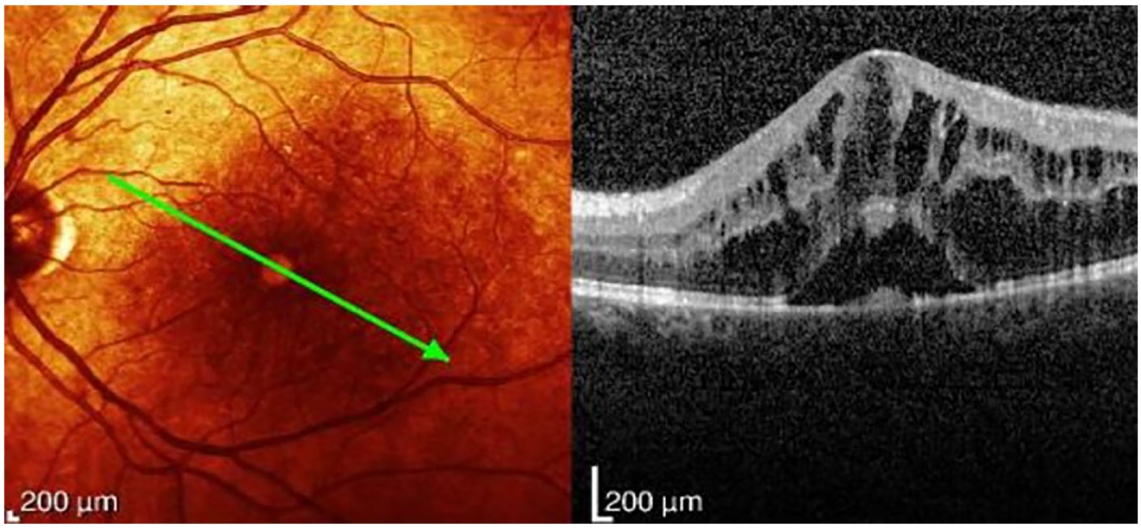

Fig. 1 Center-involving diabetic macular edema (CI-DME) illustrated by optical coherence tomography (OCT). Green line with arrowhead in the *left panel* represents the line scan being illustrated in the *right panel* (image courtesy of Christina Y. Weng, MD, MBA)

photocoagulation should be considered in eyes with DME involving or threatening the central macula.

The modified ETDRS (mETDRS) treatment approach has been studied in non-CI-DME. As in the original ETDRS technique, focal/grid laser photocoagulation is directly applied to all leaking microaneurysms within areas of retinal thickening 500–3000 μm from the macula center (and not within 500 μm of the disc) with a duration of 0.05–0.1 s. However, it uses a less intense laser, greater spacing, and a spot size of 50 μm rather than 50–100 μm [18]. Regardless of which laser treatment approach is used, the potential complications of macular laser photocoagulation must be considered, including transient increase of DME, paracentral scotomas, accidental foveal burns or scar expansion, subretinal fibrosis, and disruption of Bruch's membrane causing choroidal neovascularization (CNV) [19, 20].

Anti-VEGF

VEGF is upregulated in diabetic retinopathy and causes breakdown of the BRB and increased vascular permeability, resulting in DME. Currently available intravitreal anti-VEGF agents include pegaptanib sodium (Macugen, Eyetech Pharmaceuticals, Melville, NY/Pfizer, New York, NY), bevacizumab (Avastin, Genentech, San Francisco, CA), ranibizumab (Lucentis, Genentech, San Francisco, CA), and aflibercept (Eylea, Regeneron Pharmaceuticals, Inc., Tarrytown, NY).

Pegaptanib, an aptamer that inhibits the $VEGF_{165}$ isoform, was the first FDA-approved anti-VEGF drug to treat CNV from age-related macular degeneration (ARMD). A phase II prospective randomized controlled trial (RCT) randomized 172 patients with DME to receive 3 intravitreal injections of pegaptanib (initially, then every 6 weeks) of 3 different doses, with a sham control and follow-up at 36 weeks [21]. At 36 weeks, mean VA improved to 20/50 in the pegaptanib 0.3 mg group compared to 20/63 in the sham group ($P = 0.04$). Mean CST was reduced by 68 μm in the pegaptanib group and increased by 4 μm in the sham group ($P = 0.02$). The use of pegaptanib has been largely overtaken by bevacizumab, ranibizumab, and aflibercept because its selective binding to the $VEGF_{165}$ isoform is presumed to render it less efficacious than the other anti-VEGF agents available.

Ranibizumab is a recombinant humanized monoclonal antibody fragment that inhibits all VEGF-A isoforms. RISE and RIDE were landmark studies designed as parallel RCTs that randomized 759 patients 1:1:1 to monthly injections of ranibizumab 0.3 mg or 0.5 mg or placebo [22••]. The ranibizumab 0.3 mg group had more patients gaining ≥ 3 lines of VA compared to placebo at 24 months (34% vs. 12% in RIDE; 45% vs. 18% in RISE), as well as greater average VA improvement (10.9 letters vs. 2.3 letters in RIDE; 12.5 letters vs. 2.6 letters in RISE). Based on the results of the RIDE and RISE trials, the FDA approved ranibizumab for DME in 2012.

Bevacizumab, a full-length monoclonal antibody that inhibits all VEGF-A isoforms, has been used off-label to treat DME and is available at a much lower cost than its anti-VEGF counterparts.

Aflibercept is a soluble decoy receptor that inhibits VEGF with greater affinity than its natural receptors and binds to both sides of the VEGF dimer to form an inert 1:1 complex also known as a VEGF trap. The VISTA and VIVID studies, two similarly designed phase III RCTs, randomized 872 eyes with CI-DME to aflibercept 2 mg every 4 weeks (q4), 2 mg every 8 weeks (q8) after 5 monthly doses, or laser control [23]. The increase in BCVA from baseline to week 148 in the q4, q8, and laser groups was 10.4, 10.5, and 1.4 letters in VISTA ($P < 0.0001$) and 10.3, 11.7, and 1.6 letters in VIVID

Table 1 Summary of intravitreal corticosteroid treatment of DME

Generic name	Triamcinolone acetonide	Dexamethasone	Fluocinolone acetonide
Commercial name	Triesence	Ozurdex	Iluvien
FDA-approved indications	Vitrectomy visualization Sympathetic ophthalmia	DME Macular edema due to retinal vein occlusion	DME (after steroid trial)
	Temporal arteritis Uveitis	Uveitis	
Dosage/route	1 mg intravitreal injection	0.7 mg implant via single-use preloaded 22-G injector	0.19 mg implant via preloaded 25-G injector
Duration of action	3 months	3–6 months	3 years
Efficacy	BCVA improvement − 0.1 logMAR at 3 months but not at 6 months Inferior to focal/grid laser	BCVA improvement ≥ 15 letters in 22.2% (12.2% in sham)	BCVA improvement ≥ 15 letters in 28.7% (16.2% in sham)
	With photocoagulation, inferior to ranibizumab with photocoagulation		
Adverse effects	Cataract-related events in 46% (31% in focal/grid laser)	Cataract-related events in 67.9% (20.4% in sham)	Cataract-related events in 81.7% (50.4% in sham)
	Incidence of IOP elevation ≥ 10 of 18% (4% with focal/grid laser)	41.5% required IOP-lowering drops (9.1% in sham)	38.4% required IOP-lowering drops (14.1% in sham)
		0.6% required incisional glaucoma surgery (0% in sham)	4.8% required incisional glaucoma surgery (0.5% in sham)

BCVA best-corrected visual acuity, *DME* diabetic macular edema, *FDA* Food and Drug Administration, *G* gauge, *logMAR* logarithm of the minimum angle of resolution

($P < 0.0001$), respectively. There was also a greater proportion of eyes improving ≥ 2 steps in the Diabetic Retinopathy Severity Scale score in the q4 and q8 groups, compared to the laser group (in VISTA: 29.9% (q4) vs. 34.4% (q8) vs. 20.1% (laser control); in VIVID: 44.3% (q4) vs. 47.8% (q8) vs. 17.4% (laser control)) [24]. Similar overall efficacy was observed between the q4 and q8 groups.

The DRCR.net Protocol T RCT compared three anti-VEGF agents for CI-DME [25••]. Six hundred sixty patients were randomized to intravitreal aflibercept 2 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg administered up to monthly according to the study protocol. At 2 years, mean VA improved by 12.8, 10.0, and 12.3 letters in the aflibercept, bevacizumab, and ranibizumab groups, respectively. With worse baseline VA (20/50–20/320), mean improvement was 18.1, 13.3, and 16.1 letters, respectively. With better baseline VA (20/32–20/40), mean improvement was 7.8, 6.8, and 8.6 letters, respectively. All 3 anti-VEGF agents improved VA from baseline at 2 years, with similar outcomes among eyes with better baseline VA, and superiority of aflibercept over bevacizumab in those with worse baseline VA. Earlier this year, Protocol V results were reported. This DRCR.net study randomized 702 patients to aflibercept, laser photocoagulation, or observation for initial management, and found no significant difference in vision loss at 2 years. Reported rates of a ≥ 5-letter visual acuity decrease were similar among groups treated with aflibercept, laser photocoagulation, or observation: 16%, 17%, and 19%, respectively [26••].

Corticosteroids

Triamcinolone acetonide can treat DME by suppressing inflammation, downregulating VEGF, and decreasing fluid extravasation from leaking retinal vasculature [27, 28]. It is currently administered via intravitreal injection, sub-Tenon injection, periocular injection, and intravitreal sustained-release implant (Table 1) [29, 30]. Effect peaks at 1 week following intravitreal injection and lasts for up to 3 months [31]. Larson et al. conducted a systematic review comparing intravitreal triamcinolone acetonide (IVTA) injection to sub-Tenon triamcinolone acetonide (STTA) injection or no treatment [32]. The pooled results from 6 RCTs showed that at 3 months, IVTA significantly improved VA compared with no treatment (weighted mean difference [WMD] = − 0.10, $P = 0.05$) or STTA (WMD = − 0.09, $P = 0.02$). However, at 6 months, there was no significant difference in VA among the groups. STTA was associated with increased intraocular pressure (IOP), but there was no significant difference in VA observed at 6 months. The authors concluded that IVTA improves VA in patients with refractory DME in the short term, but not in the long term. IVTA can also be associated with potential complications, including increased IOP and cataract progression [32–34].

A single-dose preparation of preservative-free triamcinolone (Triesence, Alcon Laboratories, Inc., Fort Worth, TX) has received FDA approval for treatment of select posterior segment inflammatory diseases and visualization during pars

plana vitrectomy, but not for DME [35]. The DRCR.net Protocol B study compared focal/grid laser photocoagulation to intravitreal injections of Triesence 1 mg or 4 mg, and found that the vision gain of +5 letters in the laser group was superior to 0 letters in the triamcinolone groups at 3 years [36, 37]. A significantly greater number of patients (83%) in the Triesence 4 mg group required cataract surgery compared to those in the laser or Triesence 1 mg groups. One third of patients in the higher-dose Triesence group experienced a ≥ 10 mmHg IOP elevation, consistent with the known adverse effect profile of ocular corticosteroids.

The DRCR.net Protocol I RCT compared ranibizumab with prompt or deferred photocoagulation versus preservative-free triamcinolone 4 mg (Trivaris, Allergan, Inc., Irvine, CA) with prompt photocoagulation versus sham injection with prompt photocoagulation [38]. Significantly greater mean BCVA improvement was seen in the ranibizumab with either prompt or deferred photocoagulation groups (+9 letters in both) compared to sham injection with prompt photocoagulation (+3 letters) and triamcinolone with prompt photocoagulation (+4 letters). In pseudophakic eyes, similar mean BCVA improvements were seen in the triamcinolone with prompt photocoagulation group (+8 letters) and the ranibizumab with prompt (+8 letters) or deferred (+7 letters) photocoagulation groups, suggesting that cataract formation may have negatively confounded the triamcinolone groups' outcomes. The ranibizumab groups continued to have better BCVA outcomes compared to the triamcinolone groups at both 2 and 5 years [39, 40].

An extended-release, biodegradable, dexamethasone intravitreal implant (Ozurdex, Allergan, Inc., Irvine, CA) has received FDA approval for treating DME, noninfectious intermediate or posterior uveitis, or retinal vein occlusion-associated macular edema [41, 42]. Two multicenter phase III RCTs with identical protocols randomized 1046 patients 1:1:1 to 0.7 mg or 0.35 mg dexamethasone implant or sham injection [43]. At 3 years, BCVA improvement of ≥ 15 letters was found in 22.2%, 18.4%, and 12.0% in the 0.7 mg implant, 0.35 mg implant, and sham groups, respectively ($P \leq 0.018$). The rates of cataract-related adverse events in phakic eyes were 67.9%, 64.1%, and 20.4% in the 0.7 mg implant, 0.35 mg implant, and sham groups, respectively. In the 0.7 mg dexamethasone implant group, the dose that received FDA approval, 41.5% of patients required IOP-lowering drops, but only 0.6% required incisional surgery. Other rare potential complications include anterior chamber implant migration in pseudophakic or aphakic eyes and retinal or vitreous hemorrhage secondary to impact during injection [44–46]. The duration of efficacy is approximately 3–6 months [47]. Protocol U was an RCT conducted by DRCR.net which showed that for patients with persistent DME following multiple anti-VEGF injections, treatment with a combination of ranibizumab and dexamethasone implant led to better anatomic outcomes than ranibizumab monotherapy did; however, no significant difference in VA was seen at the 6-month endpoint between the two treatment approaches [48].

An extended-release, non-biodegradable, intravitreal fluocinolone acetonide implant (Iluvien, Alimera, Alpharetta, GA) that lasts up to 3 years received FDA approval in 2014 for DME in patients previously treated with corticosteroids without clinically significant IOP elevation [49, 50]. Two multicenter, parallel RCTs randomized 953 patients 1:2:2 to sham injection or 0.2 μg/day (low dose) or 0.5 μg/day (high dose) fluocinolone implants. At 2 years, BCVA improvement ≥ 15 letters was found in 16.2%, 28.7%, and 28.6% in the sham, low-dose, and high-dose groups, respectively ($P = 0.002$) [51]. Overall, the low-dose group was found to have a superior risk-to-benefit ratio, with 38.4% receiving IOP-lowering drops (14.1% in sham) and 4.8% requiring incisional glaucoma surgery (0.5% in sham) within 3 years [52]. However, this latter figure was 0% in a post hoc analysis of those patients who had received corticosteroids in the past without an induced IOP elevation. This observation led to the label including the requirement of a prior steroid challenge [53]. The fluocinolone implant can have complications similar to the dexamethasone implant, including cataract formation and anterior chamber implant migration [54].

Surgery

A higher rate of posterior vitreous detachment (PVD)—a separation between the vitreous body from the retinal surface—has been found in patients with diabetic retinopathy without DME (55%) than with DME (20%), suggesting that the vitreous may play a role in DME pathogenesis [55]. Pars plana vitrectomy (PPV) to induce a PVD can be used to treat DME, especially when concurrent vitreomacular traction (VMT) may mechanically contribute to the macular edema. The DRCR.net Protocol D, a prospective cohort study of 87 eyes with DME and VMT, found that PPV reduced retinal thickening in most eyes, with 68% experiencing ≥ 50% reduction [56]. However, the median VA did not change over 6 months, with VA improving by ≥ 10 letters in 38% and decreasing by ≥ 10 letters in 22%.

Jackson et al. conducted a systematic review of PPV for DME with 5 studies (127 eyes) in the efficacy meta-analysis and 40 studies (1562 eyes) in the safety analysis [57]. Combining follow-up intervals from 6 to 12 months, vitrectomy was associated with a non-significant VA increase of 2 letters and a significant reduction of CST of 102 μm; however, post hoc subgroup analysis found that the anatomic benefits observed at 6 months did not persist through 12 months. Overall, PPV led to improvements in structure and function in select eyes with DME, but there was no significant difference compared to laser or observation for VA improvement. The most common complications included cataract (68.6% in

121 phakic eyes), retinal break (7.1%), IOP elevation (5.2%), epiretinal membrane (ERM) (3.3%), and vitreous hemorrhage (2.4%). A meta-analysis of 14 studies (857 eyes) of PPV with internal limiting membrane (ILM) peeling for DME found that compared to PPV alone, PPV with ILM peeling improved BCVA (OR = 1.66, $P = 0.01$) and reduced CST (OR = 3.89, $P = 0.01$) [58]. However, several other meta-analyses found no significant difference in postoperative BCVA and CST with PPV plus ILM versus PPV alone [59–61]. Hence, the use of PPV for the sole indication of DME requires further investigation.

Future Treatments

Research efforts in the arena of diabetic macular edema are abundant. In this section, we will summarize several of the most promising therapies being studied for DME (Table 2).

Anti-VEGF

Brolucizumab is a single-chain antibody fragment that binds VEGF-A. It is smaller in size at 26 kilodaltons (kDa) than ranibizumab (48 kDa) or aflibercept (115 kDa), enabling it to potentially achieve a higher molar concentration, more effective tissue penetration, and quicker systemic clearance than larger drugs [62, 63]. HAWK and HARRIER, two similarly designed phase III RCTs, randomized 1817 patients with untreated neovascular ARMD (NVAMD) to intravitreal brolucizumab 3 mg or 6 mg or aflibercept 2 mg [64]. Brolucizumab was noninferior to aflibercept in BCVA at 48 weeks, and > 50% of the brolucizumab 6 mg group was maintained on a 12-week dosing interval. Phase III trials comparing brolucizumab to aflibercept in DME are ongoing [65].

Designed ankyrin repeat proteins (DARPins) are small antibody mimetic proteins genetically engineered to have high specificity, affinity, potency, and intravitreal half-life, and thus may allow for less frequent injections. A phase I/II study of the anti-VEGF DARPin abicipar pegol (Allergan Inc., Irvine, CA) in DME found that a single intravitreal injection produced levels above the half-maximal inhibitory concentration and VEGF neutralization in aqueous humor for 8–12 weeks [66]. CEDAR and SEQUOIA were two similarly designed phase III studies that found noninferiority of abicipar compared to monthly ranibizumab in terms of visual stability at 52 weeks despite a less frequent dosing schedule. However, there was a reported 15% incidence of ocular inflammation among patients treated with abicipar; even with a modified manufacturing process, the incidence remained relatively elevated at 9% compared to the ranibizumab group [67]. Phase III trials studying this novel drug for DME will likely commence in the next year.

Corticosteroids

The suprachoroid is a potential space between the sclera and the choroidal vasculature of the eye that can be visualized on OCT [68, 69]. Suprachoroidal delivery of corticosteroids using microneedles has the potential to increase drug concentrations at the retina while reducing cataract formation or IOP elevation by minimizing exposure to anterior segment structures. TYBEE was a phase II RCT conducted by Clearside Biomedical (Alpharetta, GA) evaluating the use of intravitreal aflibercept combined with a suprachoroidal injection of triamcinolone acetonide (CLS-TA) versus intravitreal aflibercept alone. The primary outcome evaluated was mean change from baseline in BCVA at 24 weeks. While only topline data is available at time of publication, the trial met its primary endpoint of mean improvement in BCVA from baseline, with patients in the combination arm gaining an average of 12.3 ETDRS letters compared to 13.5 ETDRS letters in the monotherapy arm ($P = 0.664$) [70].

Table 2 Future DME treatments

Drug	Route	Clinical development
Anti-VEGF		
Brolucizumab	IVT	Phase III
Abicipar pegol (anti-VEGF DARPin)	IVT	Phase III anticipated
Corticosteroids		
CLS-TA	SCh	Phase II/III
Danazol	PO	Phase III
Ang-2 inhibitors		
Faricimab	IVT	Phase III
AKB-9778	SC	Phase II endpoint not met
Integrin inhibitors		
Risuteganib	IVT	Phase III anticipated

Ang-2 angiopoietin-2, *DARPin* designed ankyrin repeat protein, *DME* diabetic macular edema, *IVT* intravitreal, *PO* oral, *SC* subcutaneous, *SCh* suprachoroidal, *VEGF* vascular endothelial growth factor

Danazol is a synthetic testosterone analog that can strengthen intercellular junctions and decrease capillary permeability when given at very low doses [71]. A phase II RCT compared ultra-low-dose oral danazol (Optina, Ampio Pharmaceuticals, Englewood, CO) to placebo in 425 eyes with DME, finding a significant 5.8 letter increase in BCVA from baseline at 12 weeks in those also on a concomitant renin-angiotensin system inhibitor [72]. Results from a completed phase III trial are pending [73].

Angiopoietin-2 Inhibitors

Angiopoietin (Ang)-1 and Ang-2 are growth factors that competitively interact with the transmembrane receptor tyrosine kinase (Tie-2) expressed in vascular endothelium to regulate permeability, inflammation, and angiogenesis [74–78]. Ang-2 is upregulated in hyperglycemia and increases retinal vascular permeability [79]. The BOULEVARD phase II RCT compared faricimab (Roche, Basel, Switzerland), a new bispecific antibody that binds both Ang-2 and VEGF-A, to ranibizumab in DME [80••]. The study randomized 229 patients 1:1:1 to intravitreal ranibizumab 0.3 mg or faricimab 6.0 or 1.5 mg. Faricimab 6.0 mg produced a significantly greater BCVA improvement compared to ranibizumab at 24 weeks in treatment-naive patients (13.9 versus 10.3 ETDRS letters from baseline, $P = 0.03$).

AKB-9778 (Aerpio Pharmaceuticals, Cincinnati, OH) is an inhibitor of vascular endothelial protein tyrosine phosphatase (VE-PTP) that activates Tie-2 receptors to decrease retinal vascular permeability [81]. The TIME-2 phase II sham-controlled RCT randomized 144 patients with DME to AKB-9778 subcutaneous injection monotherapy versus ranibizumab monotherapy versus combination therapy, and found a greater reduction from baseline CST at 12 weeks in the combination group than the ranibizumab monotherapy group [82]. While the phase IIb study failed to meet its primary endpoint, the company plans to advance a topical formulation into clinical development [83].

Integrin Inhibitors

Risuteganib (Luminate, Allegro Ophthalmics, LLC, San Juan Capistrano, CA) is an integrin antagonist that downregulates oxidative stress by inhibiting the $\alpha v\beta 3$, $\alpha v\beta 5$, and $\alpha 5\beta 1$ integrin receptors [84]. The DEL MAR phase IIb RCT met the primary endpoint of BCVA noninferiority with sequential dosing of a single bevacizumab injection followed by 3 doses of risuteganib 1 mg compared to 6 bevacizumab injections at 20 weeks [85, 86]. Plans for a phase III trial are underway.

Conclusion

The treatment of DME has evolved markedly in recent years. Formerly the standard of care, focal/grid laser is now utilized mainly for non-center-involving DME, as anti-VEGF therapy has emerged as the first-line therapy. Corticosteroids and even vitreoretinal surgery can also be helpful agents in DME management. However, there are several unmet needs such as suboptimal response, treatment burden, and socioeconomic costs. Development of therapeutics with better efficacy, longer duration, and greater cost-effectiveness is critical in light of the growing global burden.

Compliance with Ethical Standards

Conflict of Interest Eric J. Kim, Weijie V. Lin, Sean M. Rodriguez, Ariel Chen, and Asad Loya declare that they have no conflicts of interest.

Christina Y. Weng has received consulting fees from Allergan, Inc., Alcon, Inc., and Alimera Sciences, Inc.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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