The Review of DIABETIC STUDIES

REVIEW

New Therapeutic Approaches in Diabetic Retinopathy

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■ Abstract

Diabetic retinopathy is a common microvascular complication of diabetes mellitus. It affects a substantial proportion of US adults over age 40. The condition is a leading cause of visual loss. Much attention has been given to expanding the role of current treatments along with investigating various novel therapies and drug delivery methods. In the treatment of diabetic macular edema (DME), intravitreal pharmacotherapies, especially anti-vascular endothelial growth factor (anti-VEGF) agents, have gained popularity. Currently, anti-VEGF agents are often used as first-line agents in center-involved DME, with recent data suggesting that among these agents, aflibercept leads to better visual outcomes in patients with worse baseline visual acuities. While photocoagulation remains the standard treatment for proliferative diabetic retinopathy (PDR), recent FDA approvals of ranibizumab and aflibercept in the management of diabetic retinopathy associated with DME may suggest a potential for pharmacologic treatments of PDR as well. Novel therapies, including small interfering RNAs, chemokines, kallikrein-kinin inhibitors, and various anti-angiogenic agents, are currently being evaluated for the management of diabetic retinopathy and DME. In addition to these strategies, novel drug delivery methods such as sustained-release implants and refillable reservoir implants are either under active evaluation or have recently gained FDA approval. This review provides an update on the novel developments in the treatment of diabetic retinopathy.

Keywords: diabetic retinopathy · macular edema · proliferative diabetic retinopathy · vascular endothelial growth factor

1. Background

1.1 Epidemiology

Over 29 million people in the US, or 9.3% of the population, had diabetes mellitus in 2012 [1]. An estimated prevalence of 28.5% among US adults with diabetes, or 3.8% of all US adults aged 40 years or older, had diabetic retinopathy between 2005 and 2008 [2]. In the US population, 1.5% of diabetic adults aged 40 and older are affected by proliferative diabetic retinopathy (PDR) and 2.7% by clinically significant macular edema (CSME) [3]. Globally, it is estimated that there were approximately 93 million people, or 35% of diabetic adults aged 20-76 years, with any diabetic retinopathy, 17 million people with PDR, and 21 million people with diabetic macular edema (DME) in 2010 [3].

Diabetic retinopathy seems to be more common in men than in women in the US [2], although there are no reported significant gender differences worldwide [3]. Diabetic retinopathy can affect individuals from all racial and ethnic backgrounds. However, it has been reported that African-Americans and Hispanics in the US have higher rates of both diabetic retinopathy and sight-threatening diabetic retinopathy than non-

Hispanic whites [2, 4, 5]. Data from other regions of the world suggest that African/Afro-Caribbean, South Asian, Latin American, and indigenous tribal populations tend to have a higher prevalence of diabetic retinopathy [4, 6].

Diabetic retinopathy has been reported more commonly associated with type 1 than with type 2 diabetes mellitus. A recent study utilizing the data from the Diabetic Retinopathy Screening Service for Wales (DRSSW) reported a prevalence of diabetic retinopathy of 56% in type 1 diabetes patients and 30% in type 2 diabetes patients. Similarly, the prevalence of sight-threatening diabetic retinopathy was higher in type 1 (11%) than in type 2 diabetes patients (3%) [7].

1.2 Risk factors

Numerous risk factors have been associated with diabetic retinopathy, including duration of diabetes, high HbA1c levels (chronic hyperglycemia), hypertension, and ethnicity [3, 8-12]. Potential risk factors such as dyslipidemia and body mass index (or obesity) have been less consistently linked with diabetic retinopathy; some studies have reported these as risk factors [13-16], while others have not [5, 17-19].

1.3 Diabetic retinopathy projections and need for treatment

It is estimated that by 2035, 592 million people worldwide will have diabetes [20]. In the US, the number of individuals with diabetic retinopathy is projected to approximately double by 2050 to over 15 million, from over 7 million people in 2010 [21]. The number of individuals with vision-threatening diabetic retinopathy is projected to increase from 1.2 million in 2005 to close to 2.2 million people in 2020 [21]. After 10 years of follow-up, a reported 53% of patients with non-proliferative diabetic retinopathy (NPDR) at baseline developed pre-proliferative diabetic retinopathy and 11% developed PDR. Among diabetic patients with no retinopathy at baseline, 66% developed NPDR at 10 years and 1.5% developed PDR at 10 years [22].

Abbreviations:

ACCORD – Action to Control Cardiovascular Risk in Diabetes
CCL-2 – chemokine ligand 2
CSME – clinically significant macular edema
DA VINCI – DME and VEGF Trap-Eye: Investigation of Clinical Impact
DCCT – Diabetes Control and Complications Trial
DEGAS – Dose-Ranging Evaluation of Intravitreal siRNA PF-04523655 for DME
DME – diabetic macular edema
DRCR – Diabetic Retinopathy Clinical Research Network
DRS – Diabetic Retinopathy Study
DRSSW – Diabetic Retinopathy Screening Service for Wales
ECT – encapsulated cell technology
ETDRS – Early Treatment Diabetic Retinopathy Study
FAME – Fluocinolone Acetonide for Diabetic Macular Edema
FDA – Food and Drug Administration
FIELD – Fenofibrate Intervention and Event Lowering in Diabetes
GAG – glycosaminoglycan
HbA1c – glycosylated hemoglobin
HDL – high-density lipoprotein
IOP – intraocular pressure
IVTA – intravitreal triamcinolone acetonide
LDL – low-density lipoprotein
MEAD – Macular Edema: Assessment of Implantable Dexamethasone in Diabetes
mTOR – mammalian target of rapamycin
NPDR – non-proliferative diabetic retinopathy
OCT – optical coherence tomography
PAI – platelet aggregation inhibitor
PDR – proliferative diabetic retinopathy
PRP – panretinal photocoagulation
RIDE – Ranibizumab Injection in Subjects With Center Involvement Secondary to Diabetes Mellitus
RISE – Ranibizumab Injection in Subjects With Clinically Significant Macular Edema
siRNA – small interfering RNA
TIE2 – tunica internal endothelial cell kinase 2
VEGF – vascular endothelial growth factor
VIVID-DME – Intravitreal Alfibercept Injection in Vision Impairment Due to DME
VISTA-DME – Study of Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema
UKPDS – UK Prospective Diabetes Study

2. Current treatment

2.1 Control of modifiable risk factors

The Diabetes Control and Complications Trial (DCCT) reported that patients with insulin-dependent diabetes mellitus receiving 'intensive' treatments aimed at tight glycemic control had a 74% reduction in the risk of developing diabetic retinopathy at a mean of 6.5 years of follow-up when compared with patients receiving conventional therapy [12]. In a follow-up study of the same DCCT participants with type 1 diabetes, the 'intensive' therapy group maintained a reduced risk of developing diabetic retinopathy after 15-18 years, but the relative difference was smaller than in the original study [23].

Hypertension is another modifiable risk factor that has been shown to influence the development and progression of diabetic retinopathy. The UK

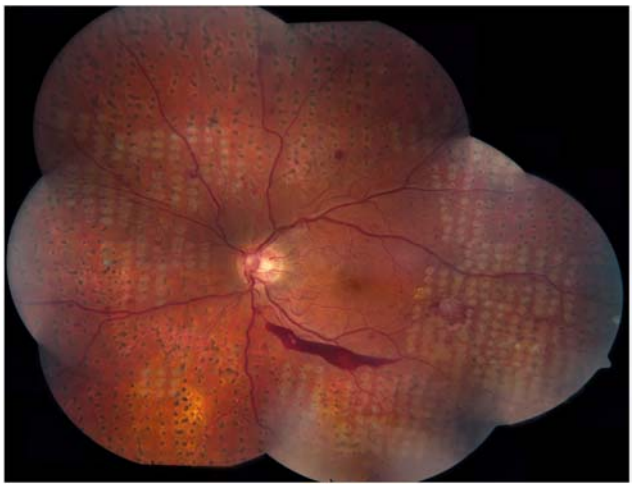

Figure 1. Montage fundus photography of left eye, demonstrating proliferative diabetic retinopathy and panretinal photocoagulation burns. The white burns are fresh (placed approximately one hour prior to obtaining the photograph). The pigmented burns are several weeks older.

Prospective Diabetes Study (UKPDS) reported that, among type 2 patients with diabetic retinopathy, tight control of blood pressure resulted in a 47% reduction in the risk of visual acuity loss of 3 or more lines [11]. A 2015 review of qualifying randomized clinical trials on the effect of blood pressure on diabetic retinopathy reported that overall, intensive blood pressure control reduced the 4- to 5-year odds of developing diabetic retinopathy (estimated risk ratio = 0.78) [24]. However, a consistent benefit of blood pressure control in progression to PDR or development of CSME was not shown.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study reported its 4-year results on the effect of intensive blood pressure control (target systolic blood pressure <120) or intensive glycemic control (target HbA1c <6.0%) on diabetic retinopathy. Among diabetic patients with no diabetic retinopathy at baseline, neither intensive glycemic control nor intensive blood pressure control had a significant effect on the development of any diabetic retinopathy stage. Among patients with diabetic retinopathy at baseline, however, intensive glycemic control significantly reduced the odds of ≥1-, ≥2- or ≥3-step worsening of diabetic retinopathy on the Early Treatment Diabetic Retinopathy Study (ETDRS) scale, with the strongest effect among eyes with microaneurysms only or mild NPDR. In this study, intensive blood pressure control did not show any benefits in the development or progression of diabetic retinopathy [25].

Fenofibrate is a medication sometimes prescribed to reduce low-density lipoprotein (LDL) and increase high-density lipoprotein (HDL) levels. In addition to its role in the management of lipids, fenofibrate is reported to have anti-inflammatory, anti-angiogenic, anti-apoptotic, and antioxidant properties [26]. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study including 1,012 patients with type 2 diabetes reported that a significantly smaller proportion of patients in the fenofibrate treatment group received photocoagulation when compared with the group not receiving fenofibrate. Furthermore, the proportion of participants in the treatment group with diabetic retinopathy at baseline, who had a 2-step progression based on ETDRS scale, was significantly smaller than the proportion of those participants in the group without fenofibrate treatment (3.1% vs. 14.6% respectively; p = 0.004) [27]. More recent results from the ACCORD study reported that patients receiving this medication were less likely to have ≥3- and ≥4-step diabetic retinopathy progression [25]. Despite these clinical results, fenofibrate is not commonly used for the purpose of reducing the progression of diabetic retinopathy.

2.2 Photocoagulation

Panretinal photocoagulation (PRP) involves the placement of photocoagulation treatment in the peripheral retina in order to induce regression of abnormal neovascular tissue. The Diabetic Retinopathy Study (DRS) was a randomized controlled trial evaluating the effects of PRP versus observation on more than 1,700 participants with severe NPDR (in both eyes) or PDR (in at least one eye) (**Figure 1**). Compared to the untreated study eyes, the DRS reported an approximate 50% reduction in the incidence of severe visual loss in the PRP-treated eyes throughout the 5-year study period. This reduced incidence rate at 5 years was apparent in both NDPR and PDR groups, with the "high-risk" PDR group benefiting the most (57% reduction in severe visual loss) [28].

The ETDRS evaluated the benefit of early treatment with PRP among 3,711 participants with mild to severe NPDR or early PDR. The reported 5-year rates of severe visual loss were small in both the treatment (2.6%) and control (deferred treatment) groups (3.7%), therefore PRP was not recommended for these patients [29]. A follow-up study evaluating the visual acuity of the remaining ETDRS participants after a median of 16.7

years after the initial PRP showed that most of those patients retained good vision with 84% having at least 20/40 visual acuity in the better eye [25].

A review of qualifying randomized controlled trials evaluated the overall effect of PRP in PDR (including 9,503 eyes) and reported that photocoagulation appeared to reduce the risk of severe visual loss by 50%, and reduced the risk of both retinopathy progression and vitreous hemorrhage, also by approximately 50% [30].

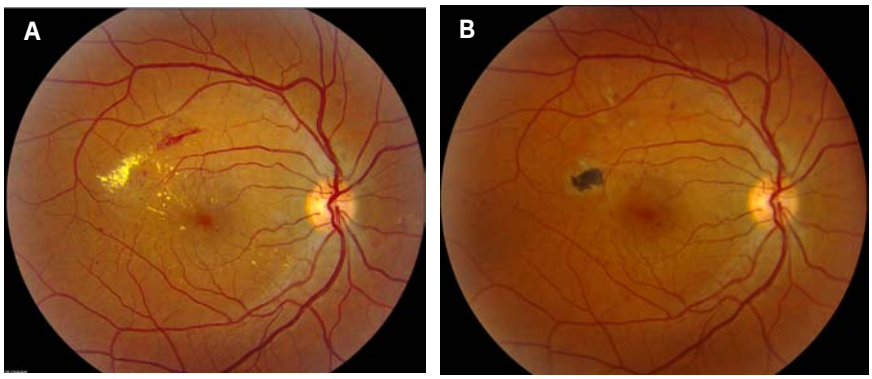

Figure 2. Fundus photography of diabetic macular edema. A. Fundus photography of right eye, demonstrating diabetic macular edema. **B**. Fundus photography of the same eye several months later following focal/grid photocoagulation. The diabetic macular edema has improved.

The ETDRS studied the benefits of focal/grid photocoagulation versus observation in 2,244 participants with CSME and mild to moderate NPDR. It was reported that the treatment group experienced a 50% reduction in the risk of moderate vision loss, whereby eyes with center-involved macular edema benefitted most [31] (**Figure 2**). However, in this study, fewer than 3% of eyes with CSME experienced a visual gain of 15 letters of more. Since two-thirds of the eyes in the ETDRS study had 20/25 or better at baseline, the ability to improve visual acuity was necessarily limited.

2.3 Corticosteroids

Intravitreal injections of corticosteroids for the treatment of DME have been extensively studied. Three synthetic corticosteroids (triamcinolone acetonide, dexamethasone, and fluocinolone) have been evaluated. All intravitreal injections of corticosteroids were associated with risks of endophthalmitis, retinal tear/detachment, vitreous hemorrhage, elevated intraocular pressure (IOP), and cataract [32, 33].

Triamcinolone acetonide. In 2008, the Diabetic Retinopathy Clinical Research Network (DRCR) conducted a randomized controlled trial comparing focal/grid photocoagulation with 1 mg and 4 mg intravitreal triamcinolone acetonide (IVTA), an off-label therapy (DRCR protocol B). At 4 months, the 4 mg treatment group showed better mean visual acuity than the other 2 groups, but at 12 months, there were no significant differences among the three groups. At 16 months, both the 1 mg and 4 mg IVTA group had significantly worse mean visual acuities than the photocoagulation group. Furthermore, the IVTA groups had much higher rates of increased IOP and cataract [35]. In 2010, the DRCR-reported protocol I, a randomized controlled trial comparing focal/grid photocoagulation alone or with combined intravitreal injection of ranibizumab (Lucentis, Genentech, South San Francisco, CA) or IVTA in patients with center-involved DME [35]. At 1 year, combined IVTA and photocoagulation significantly reduced the central subfield thickness evaluated by optical coherence tomography (OCT), but there were no significant improvements in visual acuity in comparison with photocoagulation alone. In the pseudophakic subgroups, however, combined IVTA and photocoagulation was associated with significantly better visual acuities than photocoagulation alone. In summary, the results of combined IVTA and photocoagulation remained inferior to ranibizumab with or without photocoagulation.

A 1-year study, comparing IVTA combined with PRP versus PRP alone in eyes with both PDR and DME, reported significantly better visual gains along with significant improvement in OCT parameters in the combined PRP/IVTA treatment group [36]. Similar positive results with combination of IVTA and PRP in eyes with PDR and DME have been reported by other studies [37, 38]. An exploratory analysis of the DRCR study on DME management showed that patients with PDR at baseline had a significantly reduced risk of worsening retinopathy when treated with both IVTA and PRP when compared with the PRP alone [39]. This study reported similar reductions in retinopa-

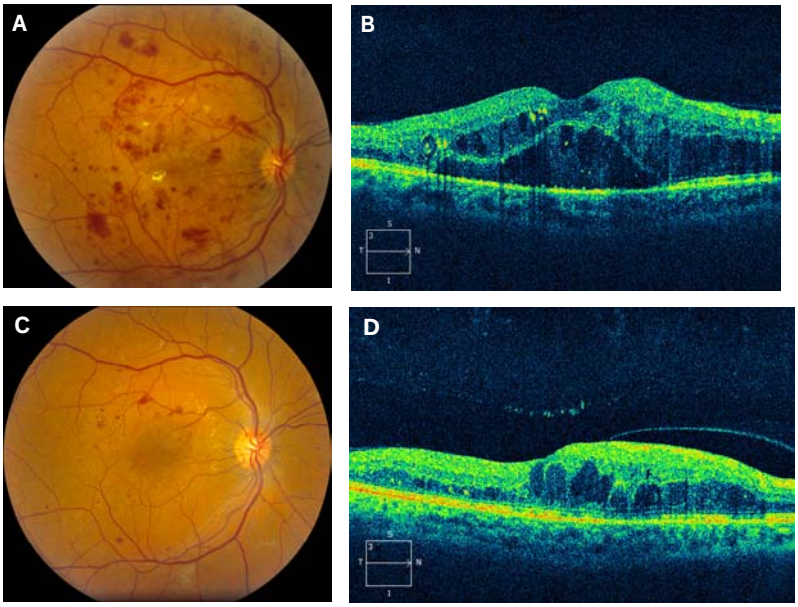

Figure 3. Fundus photography of diffuse diabetic macular edema. A. Fundus photography of right eye, demonstrating diffuse diabetic macular edema. **B**. Optical coherence tomography of the same eye, demonstrating cystoid macular edema. **C**. Fundus photography of the same eye following three years of treatment with anti-vascular endothelial growth factor agents. The diabetic macular edema has improved. **D**. Optical coherence tomography of the same eye, demonstrating improvement of cystoid macular edema.

thy progression with ranibizumab and either prompt or deferred photocoagulation. However, despite these positive clinical trial results, IVTA is not FDA-approved for the treatment of DME or PDR in the US.

Dexamethasone. A bioerodable intravitreal dexamethasone implant (Ozurdex, Allergan, Irvine, CA) has been approved for the treatment of DME. In two randomized controlled trials, this implant was associated with improved visual acuity. In one study, a significantly greater proportion of patients receiving focal/grid photocoagulation combined with the dexamethasone implant achieved improvements in visual acuity of at least 10 letters at 9 months than that of patients receiving photocoagulation alone. However, the visual acuities of the two groups were not significantly different after 12 months [40].

The Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) study reported that treatment with the dexamethasone implant was associated with a higher proportion of eyes achieving at least 15 letters of visual acuity improvement at 3 years compared with sham injections [41]. Increased IOP and cataract rates were the most commonly reported side effects in the treatment groups.

Fluocinolone acetonide has also been studied in the treatment of DME. A surgically implanted non-bioerodable fluocinolone-eluting device, Retisert (Bausch and Lomb, Madison, NJ), is FDA-approved for the treatment of chronic non-infectious posterior segment uveitis. In a 3-year clinical trial, the proportion of subjects gaining ≥3 lines of visual acuity was significantly higher in patients treated with this implant after 6, 9, and 24 months, but not after 3 years, compared with the "standard of care" control group. Furthermore, the implant group had high rates of cataract (>90%) and elevated IOP (61.4%) at 4 years, with more than 30% of the implanted eyes undergoing incisional surgery because of uncontrolled IOP [42].

A smaller, non-bioerodable fluocinolone acetonide insert that may be injected in a clinical setting (Iluvien, Alimera, Alpharetta, GA) is FDA-approved for the treatment of DME in eyes that previously have been treated with corticosteroids and that did not have a clinically significant rise in IOP. The Fluocinolone Acetonide for Diabetic Macular Edema (FAME) trials reported that the inserts were associated with a greater proportion of eyes achieving 15 or more letters of visual acuity improvement at 24 months compared with sham treatment [43]. An extension of the FAME studies reported that after 3 years, the beneficial effects of the implant persisted [44]. In these trials, almost all treated phakic eyes developed cataract and 4.8% - 8.1% of treated eyes ultimately required incisional glaucoma surgery to control IOP [44].

2.4 Anti-VEGF agents

Increased levels of vascular endothelial growth factor (VEGF) in diabetic retinopathy were first

reported in the 1990s [45, 46]. Four anti-VEGF agents have been studied in the treatment of diabetic retinopathy (**Figure 3**): bevacizumab (Avastin, Genentech, South San Francisco, CA), ranibizumab (Lucentis, Genentech, South San Francisco, CA), aflibercept (Eylea, Regeneron, Tarrytown, NY), and pegaptanib (Macugen, Valeant, Madison, NJ).

Bevacizumab. Off-label use of intravitreal bevacizumab has been used widely in the treatment of DME. Several clinical trials have reported that intravitreal bevacizumab was associated with more favorable outcomes than focal/grid photocoagulation in the treatment of DME [47-49].

Intravitreal injection of bevacizumab has been reported to reduce the regression of neovascularization in eyes treated with PDR [50-53]. It has been applied as an adjunct therapy with PRP [54, 55], and as a pre-operative adjunct therapy with pars plana vitrectomy [56-58].

Ranibizumab. Ranibizumab is FDA-approved for the treatment of DME and diabetic retinopathy associated with DME. The second indication emerged as a result of the phase III randomized controlled trials of ranibizumab for diabetic macular edema (RISE and RIDE). These two industry-sponsored randomized controlled trials evaluated the benefits of 0.3 mg or 0.5 mg monthly intravitreal ranibizumab injections in patients with DME [59]. While the main outcome measure was the proportion of participants gaining ≥15 letters at 2 years, an analysis of patients with both DME and diabetic retinopathy at baseline showed that the groups treated with ranibizumab had lower rates of retinopathy deterioration and higher rates of retinopathy improvement. Also, the ranibizumab treatment groups were less likely to develop PDR. Ranibizumab 0.3 mg monthly injections for DME were approved by the FDA, based on similar efficacy and fewer systemic side effects in the 0.3 mg vs. the 0.5 mg study group.

In multiple randomized controlled trials, ranibizumab has been reported beneficial in the treatment of DME as a monotherapy or as an adjuvant to focal/grid photocoagulation [59-66]. In the RIDE/RISE and DRCR protocol I studies, favorable outcomes were sustained for up to 5 years respectively with continued therapy [67, 68]. Recently, the DRCR (protocol S) found that ranibizumab was non-inferior to PRP in patients with PDR, suggesting that pharmacologic therapy alone may be a reasonable option in some patients with PDR [69].

Pegaptanib. A phase II/III randomized controlled trial reported that a significantly greater proportion of DME patients who received pegaptanib had improvements in visual acuity than of those DME patients receiving sham injections only [70]. A prospective exploratory study compared intravitreal injection of pegaptanib alone with panretinal photocoagulation alone in patients with PDR. It was reported that 100% of eyes treated with pegaptanib showed complete regression of neovascularization at week 36, while only 25% of eyes treated with panretinal photocoagulation showed this benefit [71]. Regression of neovascularization associated with PDR after intravitreal pegaptanib has also been reported by other studies [72, 73]. Nevertheless, pegaptanib is not FDA-approved for the treatment of DME or diabetic retinopathy.

Aflibercept. Aflibercept is FDA-approved for the treatment of DME and diabetic retinopathy associated with DME. The DME and VEGF Trap-Eye: Investigation of Clinical Impact (DA VINCI) phase II randomized controlled trial reported that aflibercept was associated with better visual outcomes than focal/grid photocoagulation [74]. Two phase III randomized controlled trials, Study of Intravitreal Administration of VEGF Trap-Eye in Patients with Diabetic Macular Edema (VISTA-DME) and Intravitreal Alfibercept Injection in Vision Impairment Due to DME (VIVID-DME), reported that intravitreal aflibercept was associated with better visual outcomes than focal/grid photocoagulation at 53 weeks [75].

In 2015, the DRCR published the results from protocol T [76]. In this randomized controlled trial, involving 89 participating centers, a total of 660 participants with center-involved DME were randomized to receive aflibercept, bevacizumab, or ranibizumab as frequently as every 4 weeks. Patients would additionally receive focal/grid photocoagulation at or after 6 months if DME persisted or declined. The main outcome measure was mean change in visual acuity at 1 year compared with baseline. Among eyes with baseline visual acuity of 20/40 or better, all three treatment groups showed similar improvements in visual acuity. However, in eyes with baseline visual acuity of 20/50 or worse, 1-year visual acuity improvements in the group treated with aflibercept were significantly better than in both the bevacizumab and ranibizumab groups. There were no statistically significant visual differences between bevacizumab and ranibizumab. Furthermore, aflibercept reduced central subfield thickness on OCT significantly more than both bevacizumab and ranibizu-

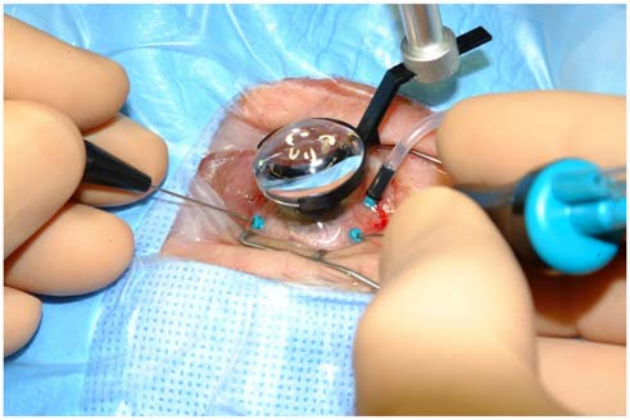

Figure 4. Pars plana vitrectomy. Demonstration of pars plana vitrectomy for complications of proliferative diabetic retinopathy (right eye).

mab, while ranibizumab showed significantly better OCT outcomes than bevacizumab.

The protocol T subgroup analysis reported that in eyes with visual acuity of 20/40 or better, aflibercept and ranibizumab showed similar OCT benefits, and they both outperformed bevacizumab. The same trend was observed in eyes with baseline visual acuity of 20/50 or worse. Overall, all three treatments had similar safety profiles. However, *post hoc* analysis revealed that there were more adverse cardiovascular events in the ranibizumab treatment group. It was concluded that all three anti-VEGF agents substantially improved visual acuity at 1 year, with aflibercept providing significantly better visual acuity results in eyes with poor baseline visual acuity.

2.5 Pars plana vitrectomy

For decades, pars plana vitrectomy has been utilized in the treatment of DME, especially in eyes with concurrent vitreomacular interface abnormalities, but results have been mixed (**Figure 4**). A meta-analysis of clinical trials evaluated pars plana vitrectomy for DME. While pars plana vitrectomy can provide anatomical and visual acuity improvements at 6 months, functional improvements were minimal when compared with focal/grid photocoagulation. Furthermore, at 12 months, there were minimal overall advantages of pars plana vitrectomy for DME over focal/grid photocoagulation [77]. In a prospective cohort study by the DRCR (protocol D), the effect of pars plana vitrectomy in 87 eyes with DME and vitreomacular traction was evaluated. After 6 months, 68% of eyes had at least a 50% reduction in OCT thickness. Approximately 38% of eyes had a visual improvement of 10 letters or more, but 22% experienced visual impairment of 10 letters or more [78].

Pars plana vitrectomy is generally more beneficial in the treatment of patients with various manifestations of PDR, including non-clearing vitreous hemorrhage and traction retinal detachment (**Figure 5**). The Diabetic Retinopathy Vitrectomy Study (DRVS) evaluated the benefits of "early" pars plana vitrectomy (within 6 months) in eyes with severe diabetic vitreous hemorrhage. At 2 years follow-up, a significantly higher proportion of vitrectomized eyes had final visual acuity of at least 10/20 than of eyes managed by other treatments [79]. A follow-up study reported similar results after 4 years [80]. In another study, 87% of eyes with non-clearing diabetic vitreous hemorrhage improved by at least 3 lines of visual acuity at 1 year [81].

In a randomized controlled trial by the DRCR (protocol N), the effect of intravitreal ranibizumab versus intravitreal saline was compared among 261 eyes with PDR and vitreous hemorrhage. The main outcome measure was the cumulative probability of pars plana vitrectomy after 16 weeks. The cumulative probability of pars plana vitrectomy did not differ significantly between the two groups [82], although a probable biologic effect was seen in improved rates of vitreous hemorrhage clearing and improved visual acuity outcomes in the ranibizumab-treated eyes.

Traction retinal detachment secondary to PDR is another common indication for pars plana vitrectomy (**Figure 6**). While anatomic success rates of more than 90% have been reported [83, 84], visual outcomes have been mixed. In a representative study, only 50% of eyes with diabetic traction retinal detachment had visual acuity improvement of 3 lines or more after pars plana vitrectomy [81]. Other studies have reported similar results with less than 40% of eyes achieving final visual acuity of at least 20/100 [85, 86].

3. Emerging new treatments for diabetic retinopathy and diabetic macular edema

Both photocoagulation and intravitreal pharmacotherapies (anti-VEGF and corticosteroids) are associated with potentially serious adverse effects. Furthermore, a percentage of patients do not show a favorable response with either of these treatment modalities.

3.1 Proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR)

Inflammatory processes and neurodegeneration have been implicated in the early stages of diabetic retinopathy [87, 88]. It has also been reported that the levels of the neuroprotective substance, somatostatin, were significantly lower in diabetic donor eyes without clinical signs of diabetic retinopathy [89] and in living eyes with PDR or DME compared with non-diabetic eyes [90].

The role of neuroprotective agents in preventing the progression of diabetic retinopathy has been evaluated. Two pilot studies have reported that patients with severe NPDR or early PDR receiving intramuscular administration of somatostatin analogs were less likely to require panretinal photocoagulation [91, 92]. Currently, a European phase II/III study is evaluating the effects of topically administrated neuroprotective substances somatostatin and brimonidine in patients with NPDR [93].

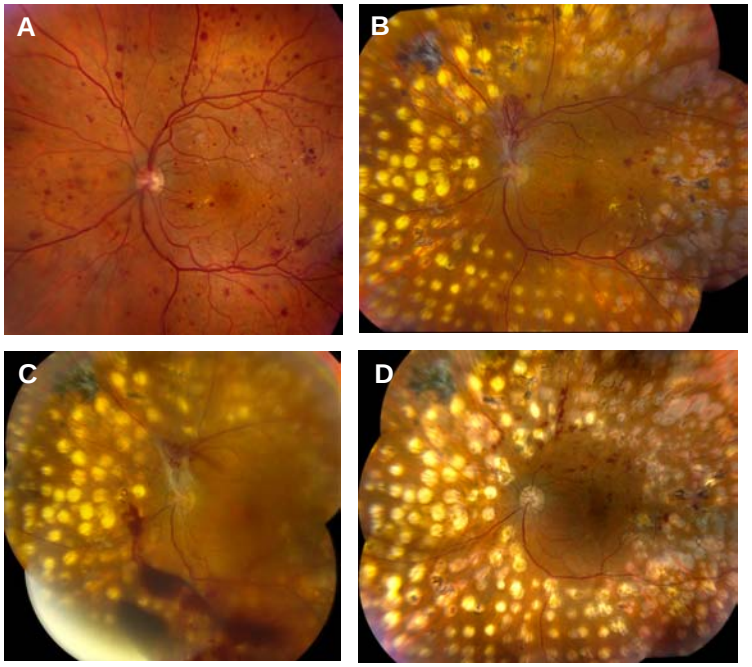

Figure 5. Treatment of diabetic retinopathy using panretinal photocoagulation and pars plana vitrectomy. A. Montage fundus photography of left eye, showing early proliferative diabetic retinopathy. **B**. Montage fundus photography of the same eye several months after treatment with panretinal photocoagulation. There is persistent proliferative diabetic retinopathy. **C**. Montage fundus photography of the same eye. There is now vitreous hemorrhage (obscuring the view) plus early traction retinal detachment. **D**. Montage fundus photography of the same eye following pars plana vitrectomy. The vitreous hemorrhage and traction retinal detachment have resolved.

A proof-of-concept randomized controlled trial was set out to evaluate the effects of 50 mg daily doxycycline given for 24 months versus placebo in eyes with severe NPDR and eyes with mild or moderate PDR. The 2-year results showed that foveal sensitivity (measured by photopic visual field) decreased among the placebo group, while it increased in the group receiving doxycycline, when compared with baseline. However, all other anatomical and functional outcomes were not significantly different between the two groups [94].

A phase II randomized controlled trial evaluated the effects of oral therapy with a glycosaminoglycan (GAG), sulodexide (Vessel Due F, Aju Pharm, Seoul, South Korea, under license from Alfa Wassermann, Bologna, Italy), on hard exudates in patients with NPDR, and reported a significant reduction in these exudates compared with placebo [95]. The premise for this clinical trial was that in diabetic retinopathy, similar to diabetic nephropathy, GAGs are replaced by collagen in the retinal capillary basement membrane, leading to changes in the permeability of these capillaries [95, 96]. Currently, the role of dietary supplements such as alpha-lipoic acid and multicomponent nutritional capsules in the management of NPDR are also being evaluated in a number of clinical trials [97, 98].

3.2 Diabetic macular edema (DME)

Novel agents are being evaluated in the treatment of DME. Angiopoietin 2 is a protein that acts as an antagonist of the tunica internal endothelial cell kinase 2 (TIE2) receptor, which promotes increased vascular permeability and angiogenesis, and which has been reported to be increased in eyes with DME. A novel substance, AKB-9778 (Aerpio Therapeutics Inc., Cincinnati, OH), has been developed to activate TIE2 with the aim of reducing vascular permeability [99]. This phase II

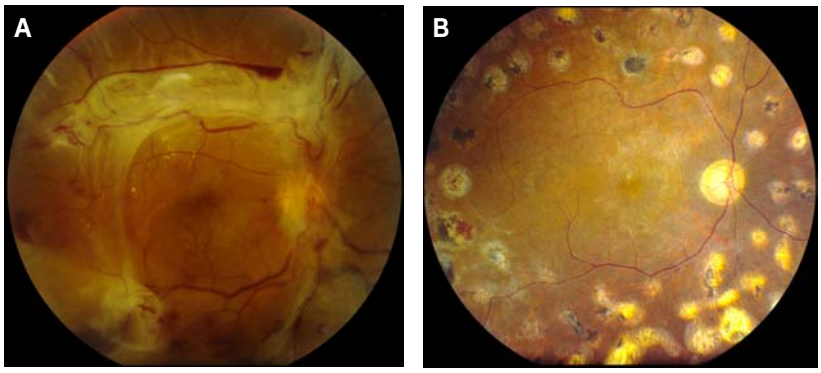

Figure 6. Traction retinal detachment. A. Fundus photography of right eye, demonstrating traction retinal detachment. **B**. Fundus photography of the same eye following pars plana vitrectomy. The traction retinal detachment has resolved.

randomized controlled trial included patients with DME receiving subcutaneous injections (5 mg, 15 mg, 22.5 mg, or 30 mg) of AKB-9778 twice a day for 4 weeks. The drug was well tolerated with no safety concerns, and showed improvements in visual acuity and reduction of OCT thickness in approximately 40% of patients receiving 15 mg or more [100].

Among other chemokines, CCL-2 (chemokine ligand 2) is a proinflammatory ligand. Its levels are significantly increased in rats with diabetic retinopathy. CCL-2 knockout diabetic rats had significantly less retinal vascular leakage [101]. PF-04634817 (Pfizer, New York, NY, USA), an antagonist of two chemokine receptors CCR2 and CCR5, is currently being evaluated in a phase II randomized controlled trial for the treatment of DME [102].

Components of the plasma kallikrein-kinin system are increased in the vitreous fluid of patients with advanced DR [103]. Activation of this system has been reported to increase retinal vascular leakage in rats [104]. A recently initiated phase I study aims to evaluate intravitreal injection of a plasma kallikrein-inhibiting agent, KVD001, in patients with DME [105].

Small interfering RNAs (siRNAs) can be designed to bind to their target genes and prevent their expression. One such siRNA, bevasiranib (Cand5, Opko Health Inc., Miami, FL, USA), was made to inhibit the expression of VEGF. Preliminary results from the RNA interference (RNAi) Assessment of Bevasiranib in DME (RACE) study, evaluating three different doses of this novel substance, showed a reduction of OCT thickness [106]. However, the official results from the phase II study have not yet been published [107].

Another siRNA, PF-04523655 (Quark, Fremont, CA, USA and/ Pfizer, New York, NY, USA), aims to inhibit the expression of the RTP801 gene, which is upregulated during hypoxia. The Dose-Ranging Evaluation of Intravitreal siRNA PF-04523655 for DME (DEGAS) study evaluated the safety and efficacy of this novel drug (as an intravitreal injection) versus focal/grid photocoagulation. Preliminary results showed improved visual acuity in all treatment groups [108]. Currently, a new dose-escalation phase II randomized controlled trial is underway evaluating the dosing and efficacy of PF-04523655 alone and in combination with ranibizumab versus ranibizumab alone [109].

Sirolimus, also known as rapamycin, has both antifungal and immunosuppressive properties, and leads to inhibition of the mammalian target of rapamycin (mTOR), which is involved in angiogenic pathways [110]. A phase I/II study involving subconjunctival sirolimus in patients with DME reported no safety concerns at 1 year. However, efficacy was not adequately demonstrated because of the small number of participants (n = 5) and the non-randomized nature of the study [111].

Luminate (formerly ALG-1001, Allegro Ophthalmics, LLC, San Juan Capistrano, CA) is an engineered oligopeptide that targets integrin receptors involved in retinal angiogenesis. The preliminary safety and efficacy data from intravitreal injection of this drug in patients with DME showed that about 50% of the participants had visual improvements of 3 or more letters after 3 monthly injections, and among these patients, there was an 83% reduction in OCT thickness. No patients had worsening of visual acuity or worsening of OCT thickness over 5 months [112]. A phase II randomized controlled trial was initiated, evaluating 3 different doses of luminate versus bevacizumab or photocoagulation [113]. Other integrin inhibiting agents such as ATN-161 (an integrin$\alpha 5\beta 1$ inhibitor) [114] and an anti-integrin platelet aggregation inhibitor (PAI) protein-derived snake venom [115] have been reported to have anti-angiogenic effects in animal models.

4. Novel drug delivery methods

Novel drug delivery methods to the posterior segment of the eye could prove promising for the treatment of diabetic retinopathy. Encapsulated cell technology (ECT) allows a genetically modified group of cell lines expressing the gene of interest to be encapsulated in synthetic semi-permeable capsules, which allows diffusion of nutrients to these cells while protecting them from the host's defense mechanisms [116]. These capsules can be surgically implanted in target areas including the posterior segment of the eye. This technology has already been tested in a number of neurodegenerative diseases. Proof-of-concept and phase I/II studies are currently underway to evaluate the efficacy of capsules with anti-VEGF activity [117].

Another treatment strategy under investigation is the surgically implanted small intraocular pump that releases a predetermined amount of drugs at scheduled intervals. One potential advantage of these implantable reservoir pumps is that they can be easily refilled without the need to remove or insert a whole new pump apparatus. One such example of this technology is the Replenish Micro-Pump (Replenish, Pasadena, California, USA). This small refillable pump is implanted in a similar way as a glaucoma drainage device (placed in the subconjunctival space), with its cannula extending into the vitreous. Initially, the implant was successfully tested in dogs [118]. The feasibility and safety of this implant filled with ranibizumab was evaluated in a prospective non-randomized study using human participants with DME [119]. No serious adverse effects were reported at 3 months.

Another newly developed reservoir implant is the Port Shunt Delivery (ForSight; Menlo Park, CA, USA). This is also a refillable drug delivery system, which is currently being investigated in age-related macular degeneration [120].

5. Novel utilizations of diagnosis and testing modalities in diabetic retinopathy

Advances in imaging modalities such as fundus photography, fluorescein angiography, OCT, and other testing tools provide valuable means of evaluating, characterizing, and managing different stages of diabetic retinopathy. A prospective study of 109 diabetic eyes without PDR at baseline included patients with at least 1 predominantly peripheral diabetic retinopathy lesion (defined as a lesion of which 50% lies outside of the ETDRS 7 standard photographic fields). The lesions were identified using 200° ultrawide field imaging. The patients were 3.2 times more likely to have a ≥2-step diabetic retinopathy progression and 4.7 times more likely to develop PDR when compared with eyes without predominantly peripheral lesions [121]. The investigators concluded that these peripheral lesions could provide additional important information on the risk of diabetic retinopathy progression.

In a cross-sectional study, 45 patients (15 with PDR treated with PRP, 15 with untreated PDR, and 15 age-matched controls) underwent multiple testing modalities, including contrast sensitivity, frequency doubling perimetry, Humphrey visual fields, photo-stress recovery, and dark adaptation. Compared with controls, both PRP-treated PDR patients and untreated PDR patients had significant changes in retinal structure and function using multiple modalities, with untreated patients exhibiting more changes in inner and PRP-treated patients in outer retinal structure [122].

6. Conclusions

Diabetic retinopathy, including DME and PDR, remains one of the most critical causes of visual loss worldwide. For decades, there were only surgical treatment options, using either photocoagulation or pars plana vitrectomy. More recently, pharmacological therapies have become more widely accepted. In particular, intravitreal pharmacotherapies have become popular in the management of DME. Although PRP is still standard treatment for PDR, the recent FDA approvals of ranibizumab and aflibercept for patients with diabetic retinopathy associated with DME, and the promising results of these agents in diabetic retinopathy suggest a potential role in pharmacologic treatment of PDR. The recent DRCR finding (protocol S) that ranibizumab was non-inferior to PRP in patients with PDR supports a role for pharmacologic treatment of proliferative eye disease.

Currently, intravitreal anti-VEGF agents are frequently used as first-line therapies in the management of center-involved DME. Focal/grid photocoagulation remains beneficial for patients with non-center-involved DME, and may reduce the burden of frequent intravitreal injections. Intravitreal corticosteroids do also have a role in the management of DME, but they are frequently used as second-line agents. Ongoing clinical trials and other investigations will determine the role of novel agents in the treatment of diabetic retinopathy.

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