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

Emerging Concepts in the Treatment of Diabetic Retinopathy

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Abstract

Purpose of Review Diabetic retinopathy (DR) is the leading cause of vision loss in working-age adults in the developed world. This review discusses the current approach to managing the disease, such as glycemic and blood pressure control, as well as laser photocoagulation, as well as emerging concepts and controversies on novel therapies.

Recent Findings In recent years, the rise of intraocular anti-angiogenesis treatments is changing the paradigm of classic laser photocoagulation in the management of DR, but its long-term benefits remain an area of controversy. We also discuss new targets including anti-inflammation, neuroprotection, and novel laser technologies. Finally, we discuss new advances in retinal imaging that has vastly improved the diagnosis and management of DR.

Summary Diagnosis and management of diabetic retinopathy is a rapidly progressing field. Emerging concepts in ophthalmic imaging, medical treatments, and surgical approaches provide insights into how DR management will evolve in the near future.

Keywords Diabetic retinopathy · Blood pressure · Glycemic control

Introduction

Diabetic retinopathy (DR) is the leading cause of blindness for those aged 20–74 in the USA, and rates are increasing globally [1]. Individuals with diabetes mellitus (DM) are expected to increase from 171 million to 366 million from 2000 to 2030, respectively (2.8% of the total world population to 4.4% of the world population) [2]. Epidemiologic studies recently estimated that the rate of diabetic retinopathy in the diabetic population is as high as 34.5% [3], and DR accounts for more than 8000 new cases of blindness annually [4]. The increasing rates of DR emphasize the importance of finding appropriate ways of treating DR and preventing the progression of vision changes. In this review, we present an overview of our current understanding, classification, and management of DR, as well as recent advances in laser and pharmacological therapies.

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

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Diabetic Macular Edema

Exudative extravasation from retinal capillaries in the macula may also result in diabetic macular edema (DME), which accounts for the majority of the vision impairment associated with DR. DME may occur in the setting of non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR), and historically was managed almost independently from the DR. Staging of DME was first reported in the Early Treatment Diabetic Retinopathy Study (ETDRS), and includes classification of "clinically-significant macular edema" (CSME) defined based on funduscopic examination of retinal thickening to define areas and location of edema with respect to the foveal center. However, since the advent of optical coherence tomography (OCT), which employs laser interferometry to provide near-histological cross-sectional visualization of

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retinal anatomy, the staging of DME primarily relies on imaging biomarkers such as the location and size of fluid and measured central macular thickness from OCT images (Fig. 1).

Management of Diabetic Retinopathy

Screening

Screening for DR is critical since many patients are asymptomatic, often resulting in delayed treatment. Therefore, it is strongly recommended that diabetic patients receive preventative screening exams to identify early signs of DR. Screening examinations generally include a complete ophthalmic exam with best corrected visual acuity, pupil dilation, and clinical ophthalmoscopy and/or retinal photography. Fluorescein angiography may also be employed to identify the presence of retinal ischemia or neovascularization. OCT may also be used to determine the presence of DME. Screening frequency varies by the severity of DR. For patients in high-resource settings, DR re-examination is recommended every 1–2 years if no DR is found on the prior examination. In mild, moderate, severe NPDR, and PDR, screening is recommended every 6–12 months, 3–6 months, less than 3 months, and less than 1 month, respectively. If resources are scarce, patients with mild and moderate NPDR can be evaluated less frequently (1–2 years and 6–12 months, respectively) [5].

Due to the growing population of patients who require diabetic screening, there has been significant progress made toward the use of tele-ophthalmology to provide DR screening to underserved communities or underdeveloped countries. Tele-ophthalmology involves the use of color fundus cameras deployed in locations lacking eye care providers to screen asymptomatic patients for possible DR. Fundus images are electronically transferred to a retinal specialist or reading center in a remote location to provide clinical feedback. The advent of artificial intelligence has further expanded the potential speed and accuracy of tele-ophthalmology programs, with the potential to provide instantaneous feedback to determine if patients need to be referred to an ophthalmologist for DR management.

Glucose Management

DR is associated with microvascular destruction due to chronic hyperglycemia. The severity and duration of a patient's hyperglycemia correlates with progression to DR. The Diabetes Control and Complications Trial (DCCT) evaluated the long-term complications of 1441 randomized subjects affected by type 1 diabetes, and whether intensive glycemic control could ameliorate these complications compared to controls. This cohort demonstrated a 35–76% decrease in early stages of microvascular disease (retinopathy, nephropathy, and neuropathy). Specifically, the progression to DR was reduced by 76% after glucose control compared to 54% by conventional treatments [6–8]. The United Kingdom Prospective Diabetes Study (UKPDS), a multicenter randomized trial of 3867 newly diagnosed individuals with type 2 diabetes, confirmed these results in type 2 diabetics showing intensive treatment improved microvascular morbidity by 25% and the need for photocoagulation laser therapy by 29% [9]. Mortality was not affected [10]. The UKPDS and the DCCT demonstrated the importance of tight glucose control and maintaining glycosylated hemoglobin (HbA1c) below 7% to prevent the progression of DR. Observational studies from the DCCT found that even when HbA1c levels were equalized after the DCCT study ended, the rate of DR in the intensive treatment group was significantly lower compared to conventional treatment. This highlights the importance of early glycemic control in preventing DR and its long-term benefits [7, 11].

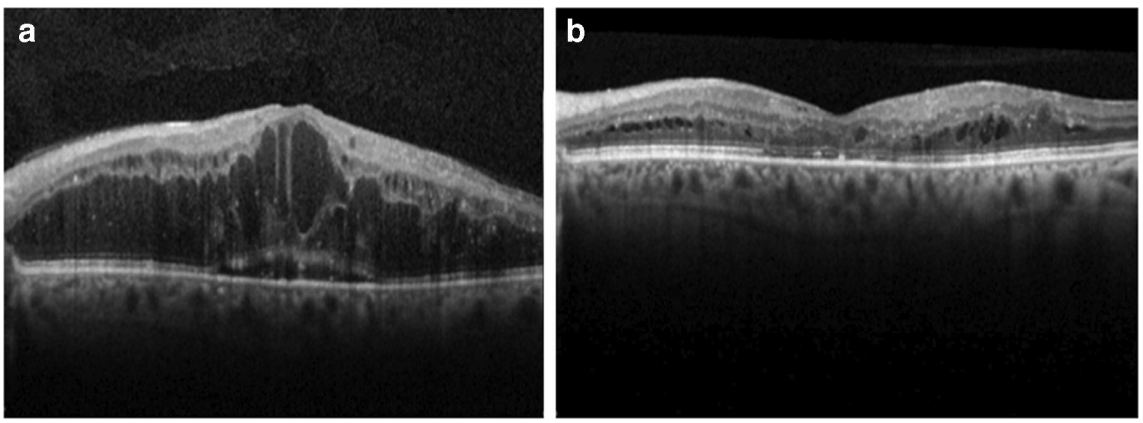

Fig. 1 Optical coherence tomography (OCT) image of an eye with DME prior to treatment (**a**), and after seven anti-vascular endothelial growth factor (anti-VEGF) treatments (**b**)

Dietary and Lipid Control

Lifestyle changes, including weight loss and regular exercise, are often first-line recommendations for newly diagnosed patients with DM. Lowering cholesterol is also strongly encouraged to prevent microvascular complications. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study showed that patients using long-term lipid lowering fibrate therapy (at a dose of 200 mg/day) decreased the rate of required laser treatments in 9795 patients with type 2 diabetes compared to the placebo group. However, there was no apparent reduction in progression of DR [12, 13]. There was no association between serum lipids and the onset of DR [13]. The large-scale randomized Control Cardiovascular Risk in Diabetes (ACCORD) Eye Subspecialty Study later found that patients with adequate glycemic control had reduced risk of DR, while those receiving fenofibrate and a statin had reduced progression [14]. It is unclear how these drugs affect DR or if they are critical for reduction of disease burden. Smoking and physical inactivity have also been identified as potential risk factors for DR, and therefore can also be potential targets for improving disease prevalence [15].

Blood Pressure Control

Hypertension is involved in retinopathy, due to the interplay of blood pressure-related vascular changes and diabetic vascular abnormalities occurring simultaneously [16]. The UKPDS randomized 1148 patients with hypertension to an intensive blood pressure (BP) control group (< 150/< 85 mmHg) vs. a conventional BP control group (< 180/< 105 mmHg). The study found that the intensive BP control group had a 34% reduction in DR progression, a 47% reduction in decline of visual acuity, and a 35% decrease in rates of laser photocoagulation compared to the traditional BP target group [17]. The UKPDS recommends maintaining hemoglobin A1c (HbA1c) below 7% and BP control of less than 140/80 mmHg [10]. The renin-angiotensin system (RAS) has also been targeted in DR, as it has a potential therapeutic role. Studies have found that the renin-angiotensin system is upregulated in DR, making it a valuable drug target [18]. Several trials using RAS inhibitors in DR have shown inconsistent results. In patients using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) monotherapy, studies have shown a reduced risk of progression and possible regression of the DR compared to normotensive patients [19]. However, data from the UKPDS did not show any superiority of a specific BP-lowering agent [20], further suggesting that more research is necessary to evaluate what hypertensive therapy is best for patients with DR.

Laser Photocoagulation

Panretinal photocoagulation (PRP) is often used in PDR to decrease oxygen demand and reduce neovascularization. The mechanism of action is unclear, but some hypothesize that PRP ablates hypoxic retina or increase oxygen diffusion from the choroid to supplement the compromised retinal circulation. The laser treatment results in decreased production of vaso-proliferative factors and inhibition of neovascularization. The technique involves the application of scattered 200–500 μm laser "spots" over the entire peripheral retina, but sparing the central macula (Fig. 2). A typical PRP treatment includes approximately 1200–1600 spots applied over 2–3 sessions. In the DRS, PRP resulted in a 50% reduction in severe vision loss (visual acuity of < 5/200) [21], with the greatest benefit found in the eyes of high-risk patients [22, 23]. The ETDRS randomized 3711 patients to early PRP vs. deferred laser treatment and observed that early PRP decreased the risk of progression to high-risk PDR by half compared to treatment deferral [24]. Early PRP was not beneficial for mild and moderate NPDR. ETDRS also demonstrated the benefits of focal laser treatments for DME [23, 25], which involves a lighter application of laser spots to areas of microaneurysms in the macular region to reduce exudation. Side effects from PDR include moderate vision loss, macular edema, diminished visual field, reduced color vision, reduced night vision, and decreased contrast sensitivity [26]. Together, these studies support the use of PRP in preventing progression of high-risk PDR with minimal risk of damaging the macula and a low side-effect profile.

Anti-VEGF and Diabetic Retinopathy

The advent of anti-VEGF therapy revolutionized the management of DME (Fig. 1), but until recently had not been used for the treatment of DR without DME. The most common anti-VEGF agents used in the treatment of DME are ranibizumab (Lucentis, Genentech, South San Francisco, CA, USA), bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), and aflibercept (Eylea, Regeneron Pharmaceuticals, Tarrytown, NY, USA) [27].

Ranibizumab

Ranibizumab is a 48-kDa antibody fragment that targets all isoforms of human VEGF-A, and exhibits both greater binding affinity and reduced systemic half-life compared to the full-length recombinant humanized anti-VEGF antibody bevacizumab initially employed for the treatment of colon cancer. The landmark studies for employing ranibizumab for DME were the RISE/RIDE, which compared monthly ranibizumab 0.3 or 0.5 mg to sham treatment [28]. At month 36, up to 51.2% of eyes that received ranibizumab gained 15-

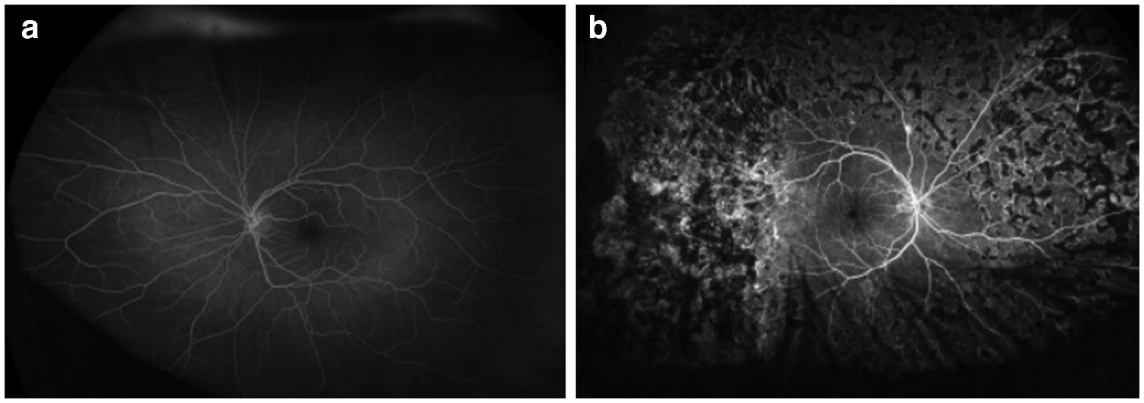

Fig. 2 Ultrawide-field angiography (UWFA) of a normal eye (**a**), and an eye with proliferative diabetic retinopathy (PDR) that has undergone panretinal photocoagulation (**b**)

letters or more, compared to 22% of sham-treated controls. Due to the similar efficacy seen across both doses, and slight but non-statistically significant increase in arterial thromboembolic events in the higher dose, the Food & Drug Administration (FDA) approved the lower dose for DME management in 2012. A secondary analysis of the RISE/RIDE trials examined the groups for improvement on the Diabetic Retinopathy Severity Scale (DRSS) and showed that among the sham/ranibizumab crossover, 0.3 and 0.5 mg ranibizumab groups 3.3, 15.0, and 13.2%, respectively, improved by ≥ 3 steps through 36 months [29]. It was also noted that 39.1% of the sham/ranibizumab group developed PDR whereas 18.3% developed PDR in the 0.3 mg group and 17.1% in the 0.5 mg group. An additional secondary analysis showed that retinal nonperfusion in the sham group was halted with the addition of ranibizumab [30].

The Diabetic Retinopathy Clinical Research (DRCR) network was established in 2002 and funded by the National Eye Institute to conduct high-quality research to improve visual outcomes primarily in the area of diabetic retinopathy. It has since expanded its scope beyond diabetic retinopathy and changed its name to the DRCR Retina Network [31]. With the advent of ranibizumab for DME management, the DRCR Protocol I compared anti-VEGF, laser and steroid therapy for DME management, with randomization to 4 groups: sham injection + prompt laser (L), triamcinolone injection + prompt Laser (TL), ranibizumab with prompt Laser (RpL), and ranibizumab with deferred laser (RdL) [32]. The study showed a significant improvement in visual acuity in the RpL and RdL group ($P < 0.001$) but not in the TL compared to L group (($P = 0.031$) at 1 year. Secondary analysis showed for those without PDR at baseline (P values compared to sham group), 3 year cumulative incidence of PDR was 23% L, 18% in the RpL group ($P = 0.25$), 7% in the RdL group ($P = 0.001$), and 37% in the TL group ($P = 0.10$). For those with PDR at baseline, the 3 year cumulative probability of DR worsening was 40%, 21% ($P = 0.05$), 18% ($P = 0.02$), and 12% ($P < 0.001$) [33]. Together, these secondary analyses of RISE/RIDE and DRCR Protocol I helped lead to the expanded label of ranibizumab 0.3 mg for the management of NPDR or PDR in patients with DME.

The more recent DRCR Protocol S explored the use of ranibizumab for PDR compared with PRP at 2 years [34]. The study enrolled 305 adults with PDR and aimed to show non-inferiority of ranibizumab vs. PRP. Non-inferiority was defined as less than five letters worse. The study showed that eyes in the PRP group gained 0.2 letters and eyes in the ranibizumab group gained 2.8 letters. Percentage of eyes that gained or lost ≥ 15 letters was also similar between the 2 groups. Vitrectomy and DME were noted to be more frequent in the PRP group but the rate of endophthalmitis was higher in the injection group. Eyes in the injection group without baseline DME received a median of 7 injections by the end of year 1 and 10 injections by the end of year 2. Eyes with baseline DME that received injections received a median of 9 injections in year 1 and 14 injections through year 2. Patients in the PRP group required subsequent sessions of PRP. Thirty-five percent of eyes in the PRP group had baseline DME and required injections. An additional 18% of eyes required additional ranibizumab prior to 2 years. These findings helped lead to the approval in 2017 of expanding ranbizumab's indication for all forms of DR, even in eyes with DME.

Bevacizumab

There is limited evidence for the use of bevacizumab for the management of DR without DME. The BOLT study compared bevacizumab to macular laser (MLT) for the treatment of CSME [35]. The study included 80 patients and compared bevacizumab vs. MLT given based on retreatment criteria. At 12 months, the bevacizumab group received a median of 9 injections compared to the MLT group which received a median of 3 treatments. The bevacizumab group gained 8 ETDRS letters whereas the laser group lost an average of 0.5 ETDRS letters ($P = 0.0002$). Patients in the bevacizumab group trended toward lower DR levels but the results were not statistically significant, likely due to the low number of patients in the study.

Aflibercept

Aflibercept was approved for the treatment of DME through the VIVID/VISTA trials [36]. These trials evaluated aflibercept 2 mg given every 4 weeks, aflibercept 2 mg every 8 weeks after 5 monthly doses and focal/grid laser. Baseline vision from baseline to 3 years improved by 10.5 letter, 10.4 letters, and 1.4 letters, respectively ($P < 0.0001$). Cataract was the most common serious ocular adverse event reported. Patients in both aflibercept groups were three times more likely to achieve at least a two-step improvement in the DRSS [36].

The Clarity Study was a phase 2b study done in the UK for 1 year that showed that aflibercept was non-inferior and superior to PRP for the treatment of PDR without foveal-involving DME with a difference of 3.9 letters $P < 0.0001$ [37]. The study analyzed 232 patients either with type 1 or 2 diabetes mellitus, 116 in the PRP group and 116 in the aflibercept group. It should be noted that no patients in the PRP group that developed DME during the 1-year follow-up were given anti-VEGF. Patients in the aflibercept group received a mean of 4.4 ± 1.7 injections including the 3 loading doses. Incidence of vitreous hemorrhage was 2 times higher in the PRP group (18%) compared to the aflibercept group (9%) ($P = 0.034$).

The 1-year result of the phase 3 PANORAMA study was reported recently comparing aflibercept with sham treatment for moderately severe to severe NPDR [38]. Aflibercept was given to 135 patients as 4 monthly loading treatments followed by every 16 weeks versus 5 loading doses followed by injections every 8 weeks (134 patients) vs. sham (133 patients). At 1 year, 40% of sham developed a complication such as DME vs. 9% in the 16-week aflibercept group vs. 11% in the 8-week aflibercept group. Sixty-five percent of patients receiving aflibercept every 16 weeks experienced a 2-step improvement in the DRSS vs. 79% in those that received aflibercept every 8 weeks and 15% of the sham group.

Comparison of Different Agents

Given the repertoire of different anti-VEGF agents, physicians naturally questioned the relative efficacy of these different agents. In clinical practice, providers often consider switching between different treatments if a clinical response is not seen after 3–6 injections [39], although most notice an improved response when switching therapies 59% of the time [27]. The 6-month results of the SWAP-2 study [40] showed that switching to Eylea from other anti-VEGF agents still shows benefit at 6 months in those with persistent DME as defined of CMT ≥ 250 μm described in the DRCR Protocol I [41]. However, the sequence by which these different agents were approved and adopted into clinical use affects the interpretability of switch studies, as relatively few physicians start with a newer agent, and then switch to an older treatment.

The DRCR Protocol T compared all 3 anti-VEGF agents for the management of DME in a prospective, randomized study of 660 patients. While all three agents improved vision in eyes with center-involving DME, aflibercept was superior to ranibizumab and bevacizumab in eyes with presenting visual acuity of 20/50 or worse at 1 year [42], although the three agents performed similarly at 2 years [43]. A secondary analysis of protocol T was also performed to compare the impact on DRSS, and while all three agents improved DR severity at 1 and 2 years of follow-up, bevacizumab showed less improvement. Among eyes with NPDR, 31.2% of eyes with aflibercept, 22.1% with bevacizumab, and 37.1% with ranibizumab had an improvement in their DRSS. For eyes with PDR, 1-year improvement rates were 75.9% for aflibercept, 31.4% for bevacizumab, and 55.2% for ranibizumab, with $P = 0.02$ for aflibercept vs. ranibizumab [44••]. Currently, the DRCR Protocol W is exploring whether anti-VEGF agents are effective in preventing PDR in eyes with NPDR [45]. A table of relevant DRCR trials is shown in Table 1 [48].

Although all three anti-VEGF agents have the ability to treat DME and DR [50], the relative efficacy in different patient populations remain unclear and is an active area of investigation. Some studies suggest that eyes that respond within the first 3 months may have the greatest benefit [51]. Patients that have more ischemia in the deep capillary plexus may not respond as well to anti-VEGF therapy [52]. Although these drugs clearly provide benefit, patients are frequently lost to follow-up in clinical practice whereas PRP is still a more permanent solution as these drugs require chronic treatment [53]. In a study of eyes with PDR in patients who were lost to follow-up for more than 6 months, those that received only anti-VEGF therapy had significantly worse outcomes than those that received PRP. [54] In addition, it is difficult to ascertain an endpoint with anti-VEGF injections, as few prospective studies to date employed well-defined retreatment criteria. In addition, anti-VEGF injections have been associated with decreased central choroidal thickness in patients with DME but its significance remains unknown [55].

Advantages of PRP for PDR include lower cost (can be done usually in one–four sessions) and fewer patient visits. Disadvantages include peripheral vision or night vision impairment and inability to treat concurrent DME if present. In fact, PRP treatment often leads to short-term worsening of DME, so concurrent anti-VEGF cannot be avoided altogether. At the same time, intravitreal injections are also susceptible to endophthalmitis, vitreous floaters, and transient intraocular pressure increases [42, 49, 56].

Intraocular Steroids

The pathogenesis of DME and DR includes both neovascular and inflammatory pathways that may also benefit from steroid therapy [57–59]. Intravitreal dexamethasone implants (Ozurdex, Allergan, Dublin, Ireland), for example, have been postulated to

Table 1 Relevant DRCR clinical trials regarding treatment of DR

DRCR study	Study endpoints	Study arms	Main outcomes
Protocol I [33]	Effects of ranibizumab or triamcinolone in patients with DME with worsening DR	1) L group: sham injection and prompt laser 2) TL group: triamcinolone injection and prompt laser 3) RpL group: ranibizumab with prompt laser 4) RdL group: ranibizumab with deferred laser	1) RpL and RdL groups: improved visual acuity letter score (+ 9 $P < 0.001$)) at 1 year but not in the TL group compared to the L group 2) Eyes without PDR at baseline, 3-year cumulative incidence of PDR was: a) 23% in the L group b) 18% in the RpL group c) 7% in the RdL group d) 37% in the TL group
Protocol S [46]	Visual acuity changes at 2 years (5 letter noninferiority margin) in patients with PDR	1) Ranibizumab for PDR 2) PRP treatment for PDR	1) The PRP group gained 0.2 letters and the ranibizumab group gained 2.8 letters on visual acuity testing 2) The PRP group without baseline DME received 7 injections by the end of year 1 and 10 injections by the end of year 2 3) Eyes without baseline DME that received injections received a median of 9 injections in year 1 and 14 injections through year 2 4) 45% of patient in the PRP group required subsequent sessions of PRP
Protocol T [47]	Percentages with retinopathy improvement at 1 and 2 years	1) Aflibercept 2) Ranibizumab 3) Bevacizumab	1) Aflibercept superior to ranibizumab and bevacizumab in eyes with visual acuity of 20/50 or worse at 1 year. 2) Improvement of DRSS for patients with NPDR: a) Aflibercept (31.2%) b) Bevacizumab (22.1%) c) Ranibizumab (37.1%) 2) DRSS improvement for patients with PDR: a) Aflibercept (75.9%) b) Bevacizumab (31.4%) c) Ranibizumab (55.2%)
Protocol V [48]	Visual acuity (5-letter or more decrease) changes at 2 years	1) Aflibercept 2) Laser 3) Observation	1) Visual acuity at 2 years was not significantly different between groups: a) Aflibercept (16% decrease), b) Laser photocoagulation (17% decrease) c) Observation (19% decrease)
Protocol W [49]	Evaluating if anti-VEGF agents are effective in preventing PDR in eyes with NPDR	1) Intravitreous aflibercept injections 2) Sham injection	Study in progress (expected completion in 2020)

modulate the release of VEGF, enhance tight junction function, and inhibit leukostasis over a 6-month period [60]. The Macular Edema: Assessment of Implantable Dexamethasone in Diabetes (MEAD) study investigated the dexamethasone implant vs. sham for DME over 3 years, and found superior proportion of 3-line gainers in the 0.7 and 0.35 mg implant groups over sham control (22.2, 18.4, and 12.0%, respectively, $P \leq 0.018$), respectively. A pooled analysis showed that both 0.35 and 0.7 mg implant doses delayed 2-step DR worsening by 12 months [61]. The fluocinolone acetonide implant (Iluvien, Alimera Sciences, Alpharetta, GA, USA) is another intravitreal steroid that may be effective for at least 3 years. A study compared 0.2 μg/d (low dose) or 0.5 μg/d (high dose) to sham in DME over 36 months, and found at least a 2-step improvement in DRSS in 13.7% of low-dose and 10.1% of high-dose patients compared with 8.9% of sham patients [62]. Hence, intraocular steroids may be just as efficacious as anti-VEGF therapy in modulating DR progression.

Beyond intravitreal steroids, suprachoroidal delivery of triamcinolone acetonide has also been employed for treatment of DME. The suprachoroidal space is a potential space between the scleral wall of the eye and the choroidal vasculature, which can be accessed using transscleral microneedles [63]. Although efficacy for DME treatment appears unclear, [64] advances with OCT using enhanced depth imaging (EDI) allows visualization of the suprachoroidal space [65, 66], and real-time visualization of the injected agent [67]. Future studies may enable clinical use of suprachoroidal pharmacotherapies for DR management.

Other Emerging Treatments

Beyond targeting retinal angiogenesis and inflammation, neuroprotective agents may also play a role in reducing retinal damage in DR [68, 69]. The EUROCONDOR trial

evaluated if topical brimonidine and somatostatin could halt retinal neurodegeneration in patients with type 2 diabetes mellitus [70•]. Although they did not find any benefit on the study population as a whole, they did find a statistically significant improvement in implicit time on multifocal ERG in patients with pre-existing retinal neuro-dysfunction. Brimonidine and somatostatin may also have an impact on arteriolar and venular dilation [71]. Although these therapies are not used yet clinically and further research is required, future management of DR will likely require multiple pathways to be targeted.

Specific blockade of the renin-angiotensin system with enalapril and losartan has been shown to slow the progression and onset of diabetic retinopathy [72]. The candesartan for Diabetic Retinopathy Trials suggested that targeting this pathway may also be effective in reducing the incidence, but not the progression, of DR [73]. Further studies are needed to clarify angiotensin converting enzyme inhibitor and angiotensin receptor blockers role in the treatment of DR.

Tetracyclines in addition to their antimicrobial action have been shown to possess neuromodulatory and anti-inflammatory properties [74, 75]. In a proof of concept clinical trial oral doxycycline was tested in patients with NPDR. Thirty patients with NPDR or PDR (less than high risk as defined by ETDRS) were given 50 mg of doxycycline vs. placebo daily for 24 months. Foveal sensitivity was − 1.9 dB at 24 months in placebo and + 1.8 dB in the doxycycline group ($P = 0.02$), suggesting possible efficacy [76].

Soluble epoxide hydrolases (sEH) have recently been identified as a potential target in treating several retinal vascular diseases including diabetic retinopathy although further studies are needed [77]. Photobiomodulation (PBM) is a therapy consisting of infrared light from 600 to 1000 nm through brief illumination periods to decrease superoxide production, leukostasis and ICAM-1 expression to reduce ganglion cell death and improve ERG b waves in rats, and may be beneficial in early DR [78, 79].

Emerging Laser Therapy

PRP has been the standard for PDR management for many years, and historically had been delivered either by slit lamp or indirect biomicroscopy. However, performing PRP can be labor-intensive for the clinician, and application of the laser spots can be variable in distribution and intensity. Navigated laser systems integrates laser delivery with infrared retinal imaging to provide more accurate macular laser treatments and more high-speed pattern laser delivery to the peripheral retina. [80–82] Chhablani et al. [83] recently compared navigated patterns to conventional patterns of PRP for PDR among 74 eyes, including comparison of short duration (30 ms) vs. long duration (100 ms) applications, and showed no significant visual acuity change among the groups. Short-pulse groups required more additional treatments compared to long-pulse treatments ($P < 0.05$). Pain scores were lower in the navigated long-pulse group compared to conventional laser ($P < 0.001$) and the treatment time was shorter ($P = 0.05$), although the study was limited due to a small sample size.

Subthreshold micropulse laser differs from conventional continuous-wave laser by delivering short pulses to minimize thermal damage. While the mechanism of action is unclear, subthreshold micropulse laser is believed to exert its effects by upregulating heat shock proteins (HSPs) rather than directly photocoagulating microaneurysms, and therefore can be applied confluently across the macular region for DME management. Various studies have demonstrated possible efficacy and superior visual outcomes for the DME treatment, although few prospective studies have been performed [84]. A retrospective study suggests that eyes treated with micropulse laser may require fewer ant-VEGF injections for DME [85]. However, subthreshold micropulse laser has been used extensively for the management of DR alone.

Advances in Imaging

Management of DR requires clinical ophthalmoscopy and/or color fundus photography to document and diagnose DR severity. However, conventional color fundus photography provide only up to 45° viewing angle, and requires capturing images from different peripheral quadrants of the retina to be comparable to clinical examination. Other modalities such as OCT and fluorescein angiography are also limited to visualization of the same posterior region [86–90]. Ultra-widefield fundus imaging (UWFI) technology (Optos PLC, Dunfermline, Scotland) provides up to 200° view of the retina, allowing peripheral pathologies such as capillary nonperfusion or retinal neovascularization to be visualized over a much larger portion of the retina in a single image (Fig. 2). The DAVE study evaluated ultra-widefield FA (UWFA) images to demonstrate non-perfused areas in eyes of patients with treatment-naïve DME [91]. They found that ischemic index increases with distance away from the fovea, but that the ischemia did not correlate with severity of DME. In a study by Wessel et al. [92], UWFI imaging was found to show 1.9 times more neovascularization and 3.9 times more nonperfusion compared to the ETDRS 7 standard field method [24].

Optical coherence tomography angiography (OCT-A) is another emerging non-invasive, diagnostic tool for diabetic retinopathy which allows for 3-D reconstruction of the

retina and vasculature by using variations in phase and light intensity, rather than injection of contrast dye [93, 94]. Compared to conventional FA, OCTA is not only faster and less invasive, avoiding complications related to drug allergies and venipuncture, but also provides exquisite vascular detail including the superficial, intermediate, and deep retinal capillary plexuses [95]. Some studies suggest that OCT-A may be better at detecting up some forms of retinal edema compared to OCT and FA [96]. Clinically, it does have value when combined with OCT but critics cite its limited ability to detect microaneurysms and its relatively limited field of view [97]. OCT-A may also provide a more accurate measurement of the foveal avascular zone (FAZ), an area in the central macula devoid of retinal capillaries which may be enlarged and lead to vision loss in eyes with DR. While the application of OCT-A to clinical ophthalmic practice remains limited, automated assessment of vascular density and FAZ size may provide some prognostic value to the management of NPDR and PDR.

Conclusion

Despite the progress and advances for the treatment of diabetic retinopathy, glycemic control, blood pressure management, and diet and lifestyle modifications still constitute the core of DR management. Advances in intravitreal pharmacotherapies have revolutionized the management of DR, but the benefits must be weighed against the burden and cost of frequent intraocular injections, compared to more conventional laser therapies. New drug targets are under investigation, although anti-VEGF and steroids remain the most important tools for DR and DME treatments. The widening range of diagnostic and treatment modalities will require a greater understanding of different DR manifestations, and tailoring management approaches to individual patients. Future studies in understanding the genetic or molecular basis of DR could help enable more individualized treatment paradigms.

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Compliance with Ethical Standards

Conflict of Interest Michael Patrick Ellis, Daniella Lent-Schochet, and Therlinder Lo declare that they have no conflict of interest.

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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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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