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Advances in the treatment of diabetic retinopathy

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ABSTRACT

As the diabetes epidemic in the United States continues to worsen, so too does the prevalence of diabetic retinopathy (DR). DR is divided broadly into nonproliferative and proliferative stages, with or without vision-threatening macular edema. Progression to proliferative DR is associated with vision loss that is often irreparable, and a rapid decline in health-related quality of life. Vascular endothelial growth factor (VEGF)-A is upregulated in the diabetic eye, and has been identified as a key driver of DR pathogenesis. With this perspective, we review the published phase III clinical trial data of anti-VEGF therapies approved for the treatment of DR in the United States. Using the Early Treatment Diabetic Retinopathy Study Diabetic Retinopathy Severity Scale, in which an improvement of ≥2 steps is considered clinically significant, approximately one-third of patients with DR and macular edema experience this level of improvement after 1 year of treatment with either ranibizumab or aflibercept. The rates of clinically significant DR improvement with ranibizumab could be twice that in the subgroup of patients with moderately severe or severe nonproliferative DR and macular edema. These clinical trial data indicate that intraocular inhibition of VEGF is a rational approach for the management of DR.

Contents

1. Introduction

The burden of diabetes on patients, physicians, and health care sys` glycemic control. Diabetic retinopathy (DR) is the most common microvascular complication of diabetes, and a leading cause of legal blindness among working-age individuals in industrialized nations.[1–4] In earlier

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stages of nonproliferative DR (NPDR), chronic hyperglycemia damages the microvasculature that supply the retina, leading to ischemia, vascular leakage, and central vision loss due to diabetic macular edema (DME). As the disease progresses to proliferative DR (PDR), vision loss is associated with secondary neovascularization throughout the retina and subsequent hemorrhage and/or retinal detachment.[5]

Owing to an aging population and an increasing prevalence of diabetes, cases of DR in the United States rose from 4 million to 7.7 million between 2000 and 2010, and are projected to reach 14.6 million by 2050.[6] An analysis of the National Health and Nutrition Examination Survey 2005–2008 ($N = 1006$) estimated that 29% of people with diabetes aged ≥40 years had concurrent DR, while the prevalence of vision-threatening DR (defined as severe NPDR, PDR, or DME) in this population was 4%.[7] When stratified by age, sex, and race/ethnicity, DR prevalence estimates were higher in males than in females (32% vs. 26%, respectively; $p = 0.04$), and in non-Hispanic black individuals than in non-Hispanic white individuals (39% vs. 26% for DR and 9% vs. 3% for vision-threatening DR, respectively; both $p = 0.01$).[7]

Previous studies have shown that DR progression and vision loss are detrimental to patient quality of life. Conducted over a 10-year period, the Wisconsin Epidemiologic Study of Diabetic Retinopathy found that loss of visual acuity (VA) was the most important predictor of reduced vision-related quality of life in people with long-term type 1 diabetes, due to its negative impact on domains including mental health, role difficulties, social functioning, dependency, and driving.[8] Similarly, the Los Angeles Latino Eye Study showed that people with type 2 diabetes and concurrent DR had lower health-related quality of life scores than those without DR, and that progression to PDR was associated with a rapid decline in visual function and well-being.[9] The quality of life domains most significantly affected by progression to PDR included general health, driving difficulties, dependency, and mental health.[9]

Without appropriate intervention, approximately half of all patients with high-risk PDR will experience visual impairments due to DME, vitreous hemorrhage, and/or retinal detachment within 5 years of diagnosis.[10] Therefore, early detection and treatment are critical to delay DR progression, avoid vision loss, and alleviate the burden of advanced disease. To facilitate this, the American Academy of Ophthalmology (AAO) and American Diabetes Association (ADA) both advocate annual screening for DR in patients with diabetes.[5,11] In those with type 1 diabetes, annual dilated eye examinations should begin on or within 5 years of disease onset, while examinations are recommended from the time of diagnosis in patients with type 2 diabetes. According to ADA guidelines, less frequent examinations (every 2 years) may only be considered in patients with no evidence of DR following ≥1 annual eye exam; however, if any level of DR is detected, annual screening is required.[11] Furthermore, the AAO and ADA both advise that abnormal findings or evidence of progressive DR may necessitate more frequent follow-up examinations.[5,11]

Laser therapies were traditionally considered the standard of care for DR and DME; however, the identification of vascular endothelial growth factor (VEGF)-A as a key mediator in DR pathogenesis has led to a paradigm shift in the treatment of these conditions. On the basis of clinical trial evidence, the US Food and Drug Administration (FDA) has approved 2 anti-VEGF agents, ranibizumab and aflibercept, for all stages of DR with or without DME,[12,13] and AAO Preferred Practice Pattern® guidelines have been updated to recognize anti-VEGF therapy as an effective treatment option for DR in addition to DME.[5] In an effort to promote a collaborative approach to diabetes care among the medical community, this paper aims to review recent trial data that have informed the adoption of anti-VEGF therapies for DR management in US clinical practice.

2. Classification of diabetic retinopathy

Three scales are commonly used to assess the severity of DR and DME in research and clinical practice (Supplementary Table S1). Of these, the Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) is the most comprehensive, and often considered the "gold standard" for grading DR severity in clinical trial settings.[14] Scoring is based on the presence of anatomical markers of disease activity in retinal photographs, such as microaneurysms, macular edema, hemorrhages, and scars of prior laser photocoagulation. Disease progression is graded according to discrete, nonconsecutive "levels": from the absence of DR (ETDRS-DRSS levels 10 and 12), through NPDR and PDR stages (levels 35A–53E and 61A–71, respectively), to advanced PDR (levels 81 and 85).[14] Improvements of ≥2 ETDRS-DRSS steps are typically considered clinically significant; for example, a 2-step change from ETDRS-DRSS level 61 (mild PDR) to level 47 (moderately severe NPDR), as illustrated in Fig. 1.[14] A simplified variation of this grading system is the modified 9-step DRSS, where disease severity is evaluated on a consecutive scale of 1 through 9.[15] It is important to note that ETDRS-DRSS "levels" or "steps" refer to anatomical measures of DR severity, while "ETDRS letters" are a functional measure of VA. Anatomical and functional changes associated with DR progression may occur at different times; therefore, step-changes in ETDRS-DRSS level do not correlate with changes in vision.

The International Clinical DR and DME Disease Severity Scale is an alternative classification system that encourages communication and coordination between health care providers in routine clinical practice.[16] This scale utilizes a 5-stage disease severity classification for DR, featuring 3 stages of low risk, a fourth stage of severe NPDR, and a fifth stage of PDR.[16] DME is primarily classified as apparently present or apparently absent; however, if resources permit the assessment of the location of the edema, then DME may be further categorized as a function of its distance from the central macula.[16]

3. Risk factors for diabetic retinopathy

Duration of diabetes (type 1 or 2) is a significant nonmodifiable risk factor for the development of DR. In the Los Angeles Latino Eye Study, which recruited self-identified Latino participants from February 2000 to May 2003, 28% of patients with diabetes for 1–4 years developed retinopathy, increasing to ~60% in patients with diabetes for 5–14 years, and further increasing to 80% of patients with diabetes for ≥15 years.[17,18] Similarly, the Wisconsin Epidemiologic Study found that DR prevalence more than doubled among patients aged >30 years with type 2 diabetes for 19 years vs. 5 years; this result was irrespective of patient insulin status.[19] Approximately half of patients aged ≤30 years living with type 1 diabetes for 20 years had PDR,[20] whereas PDR

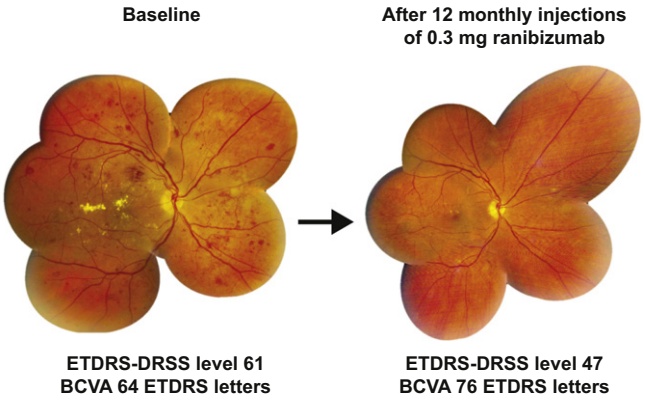

Fig. 1. Clinically significant improvement in DR severity, from mild PDR to moderately severe NPDR (2 ETDRS-DRSS steps). Retinal photographs show resolution of retinal hemorrhages, venous tortuosity, and reduction in microaneurysms; yellow patches are lipid exudate caused by diabetic macular edema, which were also resolved by Month 12. BCVA, best-corrected visual acuity; DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

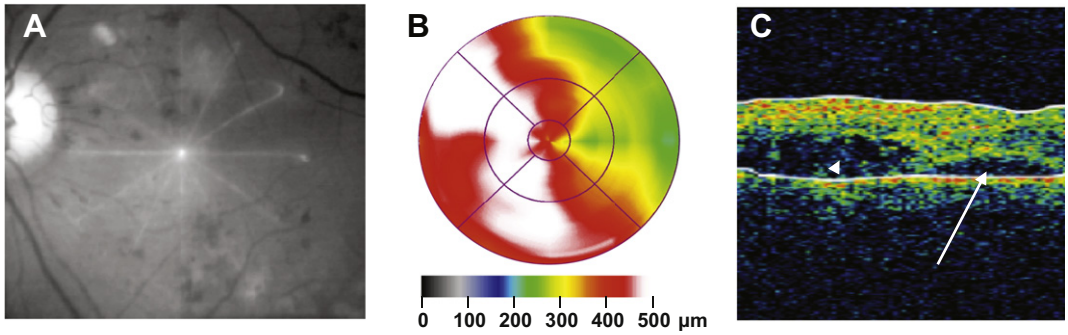

Fig. 2. Example of noninvasive ocular coherence tomography imaging of a patient with diabetic macular edema. (A) Retinal image showing sampled lines; (B) heat map showing thickened (red) vs. normal thickness macula (green); and (C) cross-sectional image revealing intra- (arrowhead) and subretinal fluid (arrow).

developed in 2% of patients with type 2 diabetes for <5 years, and in 25% of those with disease duration >25 years.[19]

Glycemic control is a modifiable risk factor for both the development and progression of DR, warranting treat-to-target glycated hemoglobin (HbA1c) goals of ≤7% in most patients and a lower goal of ≤6.5% in select patients.[5] Higher systolic blood pressure (BP) increased the risk for DR development and progression among patients with younger-onset disease participating in the Wisconsin Epidemiologic Study.[21] The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated the importance of managing hypertension in patients with type 2 diabetes to reduce the risk of developing retinopathy.[22] In UKPDS 38, a 37% reduction in microvascular disease risk was observed among hypertensive patients assigned to tight BP control (aiming for <150/85 mm Hg) vs. those assigned to less tight BP control (aiming for <180/105 mm Hg). Reduced microvascular risk in this study was primarily driven by lower odds of requiring retinal photocoagulation therapy, compared with patients assigned to less tight BP control. Once retinopathy has developed, the role of BP management in reducing the progression of DR remains uncertain.[23] Treating comorbid diabetic dyslipidemia may reduce progression of DR.[24–26]

4. Role of VEGF in the pathogenesis of diabetic retinopathy

Case-control data showed that median levels of VEGF in the vitreous were elevated in 8 patients with PDR, relative to 12 patients without PDR (29.1 vs. 8.1 pM, respectively; $p = 0.006$).[27] Case-control data also demonstrated that aqueous VEGF levels were elevated in patients with PDR (318.6 pg/mL) relative to normal eyes (63 pg/mL; $p < 0.001$), patients with diabetes without retinopathy (57 pg/mL; $p < 0.001$), or patients with diabetes with NPDR (133 pg/mL; $p < 0.001$).[28] Subgroup analysis revealed that aqueous VEGF levels were also markedly higher in patients with active PDR than in those with quiescent PDR (466 vs. 243 pg/mL, respectively; $p = 0.001$).[28] Data from animal models suggest that heightened intraocular VEGF levels may arise from chronic hyperglycemia, which induces subclinical inflammation that changes the endothelial surface and leads to leukostasis and capillary nonperfusion.[29,30] The resulting hypoxia is a powerful stimulus for the expression of VEGF and other chemokines.[31]

The biologic activity of VEGF includes direct effects on the integrity of the tight junctions maintaining the blood-retinal barrier, resulting in extravasation of proteins and fluid into the retinal extracellular space.[32] Because the retina does not have lymphatic vessels, it is poorly equipped to evacuate fluid from the extracellular space.[29] Edema then accumulates, resulting in increased retinal thickness. The aberrant morphology can be visualized with optical coherence tomography (OCT), a rapid and noninvasive imaging technique that allows 3-dimensional imaging of the retina in the office (Fig. 2). Central vision impairment can occur if the edema is located in the central region of the macula called the fovea, the area of the retina with the highest concentration of cone photoreceptors, and where the lens focuses images captured by the eye. The fovea is responsible for the type of sharp central vision required for reading or performing complex tasks such as operating machinery or driving. Foveal edema swells and disrupts the normally transparent retinal layers, causing optical scatter of light and reducing the quality of vision.

VEGF is an inducer of angiogenesis.[33] VEGF-induced vascular leakage of proteins into the perivascular space creates the matrix required for the formation of new immature vascular networks. Preretinal neovascularization derived from the venous portion of the capillary beds supplying the inner retina (the area close to the vitreous) can be seen in high-risk PDR. These immature vessels frequently climb into the vitreous and are prone to bleeding. Fibrotic changes following the resorption of the hemorrhages can cause adhesions in the vitroretinal interface with the potential for traction pull on the retina, resulting in traction retinal detachment and often irreparable vision loss.

5. Treatment modalities for diabetic retinopathy

Ranibizumab 0.3 mg (Lucentis®; Genentech, Inc., South San Francisco, CA) is indicated for the treatment of patients with DME and DR, and in April 2017, became the first anti-VEGF therapy approved for DR (NPDR or PDR) in the absence of DME.[12] In May 2019, the FDA expanded the indication of aflibercept 2.0 mg (Eylea®; Regeneron Pharmaceuticals, Inc., Tarrytown, NY) to similarly include the treatment of patients across all stages of DR, with and without DME.[13] Bevacizumab 1.25 mg (Avastin®; Genentech, Inc., South San Francisco, CA) was designed, studied, and approved as an antiangiogenic strategy to treat a variety of solid tumors in oncology, but is now also used off-label to treat various types of neovascular ophthalmic diseases.[34,35]

Ranibizumab, aflibercept, and bevacizumab differ in their molecular weights, structures, pharmacokinetics, and pharmacodynamics. Ranibizumab is a 48-kDa, monovalent, affinity-matured, humanized monoclonal antibody antigen-binding fragment (Fab) engineered to bind and inhibit all bioactive forms of VEGF.[36] Bevacizumab is a 149-kDa, full-length, bivalent, recombinant human monoclonal immunoglobulin G1 (IgG1) antibody directed against VEGF.[13] In contrast, aflibercept is a 115-kDa Fc recombinant fusion protein comprising portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1.[34] After leaving the intraocular compartment, full-length antibodies and fusion proteins persist in the systemic circulation, whereas Fabs are rapidly eliminated.[36,37]

Laser has been the mainstay in the treatment of diabetic eye disease for >40 years. For DME, precision photocoagulation is used to eliminate discrete vascular abnormalities in the retina such as microaneurysms, thereby eliminating sources of vascular leakage and alleviating retinal edema. Alternatively, light laser burns may be applied in a grid manner to ablate suspected areas of hypoxic tissue that are a source of

chemokines such as VEGF, which drive vascular leakage in DME. For PDR, panretinal photocoagulation (PRP) became the standard of care after the Diabetic Retinopathy Study demonstrated that photocoagulation could reduce the risk of severe vision loss by 50%.[10] The concept of the intervention is to eliminate peripheral retinal tissue that is not directly involved in supporting the central vision used for reading and other complex tasks. The procedure aims to eliminate areas of suspected hypoxic retina that may be the source of VEGF and other chemokines with angiogenic action. The tradeoffs are complications such as reduced peripheral and color vision, impaired night vision, visual field loss, pain during treatment, and increased risk of development of macular edema.[10,38] In addition, ~5% of eyes can still experience severe vision loss.[10,38] It should be noted that $1.5 billion are spent each year to prevent peripheral visual field loss in patients with glaucoma,[39] yet similar ocular damage is inflicted willingly in patients with PDR in order to preserve central vision.

6. Efficacy of anti-VEGF treatment for diabetic retinopathy

The efficacy of anti-VEGF therapy has been well established in several trials of patients with DR and DME,[40–42] and DR without DME.[43–45] Compelling evidence generated from these studies has led to the FDA approvals of ranibizumab[12] and aflibercept[13] for all stages of DR irrespective of DME status, and clinical guidance that recognizes anti-VEGF therapy as a viable treatment option for DR, both with and without DME.[5]

The pivotal, methodologically identical phase III trials of ranibizumab for DME (RIDE [NCT00473382] and RISE [NCT00473330]) offered the first opportunity to evaluate the effect of VEGF inhibition on DR.[40,41] In these studies, adults were randomized 1:1:1 to receive monthly intravitreal injections of 0.3 mg ranibizumab, 0.5 mg ranibizumab, or sham injections for 24 months.[40,41] During Months 24–36, patients originally randomized to receive sham injections were allowed to cross over to active treatment with 0.5 mg ranibizumab. All patients who completed Month 36 were eligible to enroll in an open-label extension phase wherein 0.5 mg ranibizumab injections were administered on an as-needed basis.[46] These trials met their prespecified endpoint (proportion of patients gaining ≥15 ETDRS letters in best-corrected visual acuity [BCVA] from baseline at 24 months) and informed the FDA approval of 0.3 mg ranibizumab for DME in 2012.[23]

In RIDE and RISE, DR severity was graded from baseline through Month 60 on prospectively collected color retinal photographs; significant improvements were found as early as Month 3, and 2-step ETDRS-DRSS improvements were found in 33% of the total population and in nearly 70% of the severe NPDR group at Month 12.[15,47] After 3 injections, a 2-step ETDRS-DRSS improvement from baseline was observed in ~18% of patients receiving the FDA-approved dose of 0.3 mg ranibizumab, compared with ~3% of sham patients ($p < 0.01$; Fig. 3).[12] With continued treatment, the percentage of patients achieving improvement of ≥2 ETDRS-DRSS levels continued to increase, reaching 35% and 33% after 1 year in RISE and RIDE, respectively.[12] Outcomes with 0.5 mg ranibizumab were similar. When considering these data from the overall patient population, it is important to appreciate the potential ceiling effect for improvement in patients with less severe disease, as well as the limiting effect of prior PRP in those with more severe disease (these patients cannot be graded below ETDRS-DRSS level 60 due to permanent laser scarring). For example, a recent post hoc analysis of pooled RIDE/RISE data found that rates of ≥2-step ETDRS-DRSS improvement at Month 24 increased to 78–81% among ranibizumab-treated patients with moderately severe or severe NPDR at baseline (ETDRS-DRSS level 47–53), a subgroup less susceptible to ceiling and floor effects, but at high risk of progression to PDR.[48]

Given the known role of VEGF in the pathogenesis of PDR and the positive effect of VEGF inhibition on DR severity in DME trials, the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S trial (NCT01489189) examined whether ranibizumab was as effective as PRP in preserving vision in patients with PDR (ETDRS-DRSS level ≥ 60) in ≥1 eye.[43] A total of 394 eyes in 305 adults were studied; the majority of eyes had PDR (343/394 [87%]) and no evidence of DME (306/394 [78%]) at baseline.[43] Individual eyes were randomized to receive PRP ($n = 203$) or 0.5 mg ranibizumab ($n = 191$ eyes). Importantly, eyes in both treatment groups could receive ranibizumab for DME. The primary outcome measure was mean VA change at 2 years in the intention-to-treat population. Mean VA letter improvement from baseline at 2 years was +2.8 in the ranibizumab group vs. +0.2 in the PRP group (difference: +2.2; 95% CI: −0.5 to +5.0; $p < 0.001$

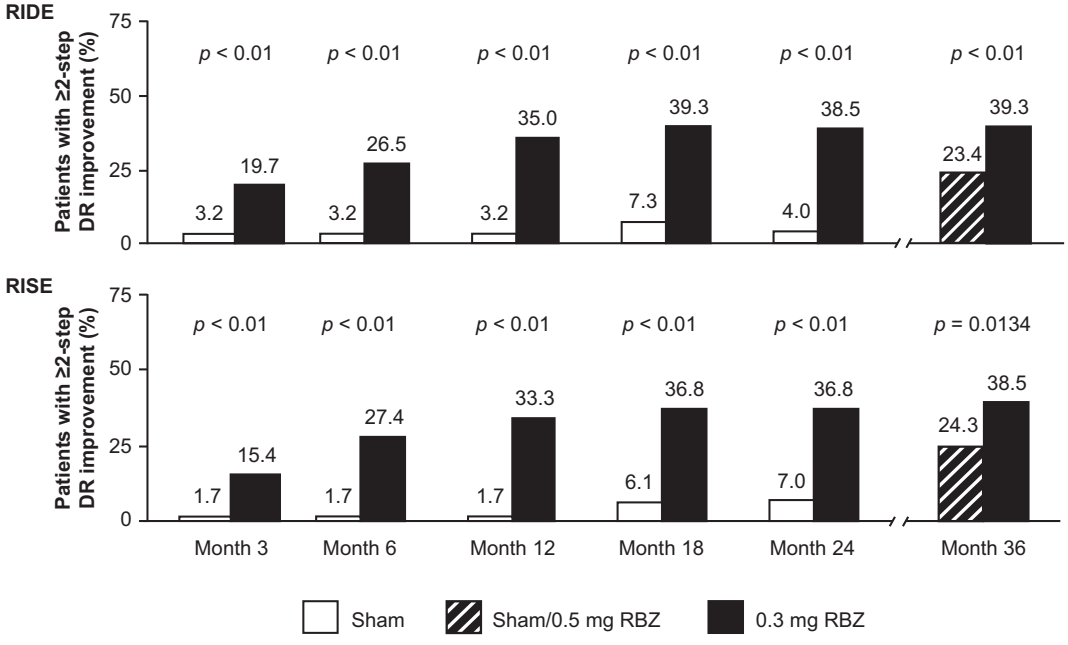

Fig. 3. Proportion of patients with ≥2-step ETDRS-DRSS improvement from baseline in the RIDE and RISE population. Importantly, sham patients who crossed over to treatment with 0.5 mg RBZ after 24 months had a significantly lower rate of ≥2-step ETDRS-DRSS improvement, indicating that such a delay in treatment initiation may limit efficacy. DR, diabetic retinopathy; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; RBZ, ranibizumab.

for noninferiority). When considering the vision outcomes, it is important to note that 53% of the patients in the PRP group received ranibizumab for DME either at baseline or during the trial, which was most likely critical for maintaining vision in the PRP group and may have narrowed the difference in central vision between the 2 groups. Regarding DR severity, 48% of eyes in the ranibizumab group achieved ≥2-step ETDRS-DRSS improvement from baseline at Year 2,[43] while 32% and 28% of ranibizumab-treated eyes with and without baseline DME, respectively, demonstrated ≥3-step ETDRS-DRSS improvement during the same period (Fig. 4).[12] Because progression to PDR is associated with a significant reduction in health-related quality of life,[9] the observation that ranibizumab therapy can promote DR regression in eyes with PDR is clinically meaningful.

Loss of peripheral vision is a complication of PRP therapy.[10,38] As expected, peripheral visual field loss was quite significant in the PRP group, but minimal in the ranibizumab group (−422 dB vs. −23 dB, respectively; $p < 0.001$).[43] Notably, ranibizumab decreased the chances of worsening and severe sight-threatening events.

Patients in Protocol S receiving ranibizumab were also less likely to require surgical removal of the vitreous (vitrectomy; 4% vs. 15%; $p < 0.001$) or to develop DME (9% vs. 28%; $p < 0.001$) than patients receiving PRP, respectively.[43] Furthermore, within 7 months, 45% of the patients in the PRP group required a second PRP procedure.[43] The findings of DRCR.net Protocol S demonstrated that ranibizumab offers a distinctly different treatment option for patients with PDR with significantly less peripheral vision loss, improved vision, and fewer sight-threatening events when compared with PRP laser.

Evidence also supports the use of aflibercept for the treatment of DR. In the pivotal, similarly designed, phase III trials of aflibercept for DME (VIVID [NCT01331681] and VISTA [NCT01363440]), 862 patients (1 eye per patient) received either intravitreal aflibercept injection 2 mg every 4 weeks, intravitreal aflibercept injection 2 mg every 8 weeks after 5 initial monthly doses, or macular laser photocoagulation.[42] Of these 862 patients, 709 (82%) had an ETDRS-DRSS level ≤51, and 153 (18%) had an ETDRS-DRSS level ≥61.[42] The proportions of patients with a ≥2-step ETDRS-DRSS improvement at 1 year in VIVID (33% for aflibercept every 4 weeks and 28% for aflibercept every 8 weeks) and VISTA (34% for aflibercept every 4 weeks and 29% for aflibercept every 8 weeks) were comparable with those observed in RISE and RIDE.[12,42]

Anti-VEGF therapy with aflibercept has been shown to improve outcomes at 1 year relative to control arms in patients with PDR without DME in the phase IIb, single-blind, noninferiority CLARITY trial,[44] and in patients with NPDR without DME in the phase III, double-masked, randomized PANORAMA trial.[45] In CLARITY (ISRCTN32207582), previously untreated or laser-treated patients with active PDR were randomly assigned to repeated intravitreal aflibercept (2 mg/0.05 mL at baseline, Week 4, Week 8, and as needed from Week 12; $n = 112$) or PRP ($n = 109$) for 52 weeks.[44] Aflibercept was non-inferior and superior to PRP with respect to mean BCVA difference at 1 year (3.9 ETDRS letters; 95% CI: 2.3–5.6; $p < 0.0001$), although it is noteworthy that this between-group difference was driven primarily by loss of vision in the PRP arm (BCVA change from baseline to year 1: −3.0), rather than clinically meaningful gain of vision in the aflibercept arm (BCVA change from baseline to year 1: +1.1).[44] Undertreatment may explain the lack of vision gain in the aflibercept arm, considering that treatment was administered when required beyond Week 12 on the basis of ocular changes occurring since screening or since the previous study visit.[44] The more stringent injection requirements adhered to in DRCR.net Protocol S, which did demonstrate a clinically meaningful VA improvement from baseline to Year 1 in the ranibizumab arm (gain of ~5 ETDRS letters in the comparable group of eyes without DME), mandated that a ranibizumab injection was required every 4 weeks unless neovascularization resolved or was stable (not improved or worsened) following 2 consecutive injections.[43]

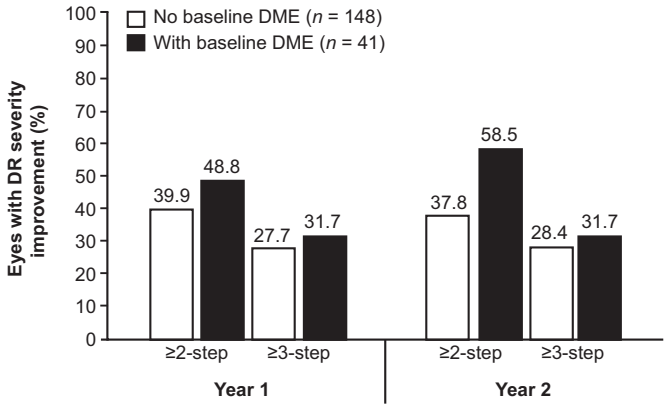

Fig. 4. Proportion of eyes in the 0.5 mg ranibizumab group with ≥2- and ≥3-step ETDRS-DRSS improvement from baseline at Years 1 and 2 of DRCR.net Protocol S. DME, diabetic macula edema; DR, diabetic retinopathy; DRCR.net, Diabetic Retinopathy Clinical Research Network; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study.

More recently, PANORAMA (NCT02718326) assessed the efficacy and safety of intravitreal aflibercept vs. sham injection in 402 patients with moderately severe to severe NPDR (ETDRS-DRSS level 47–53) without DME.[45] Patients were randomized to receive aflibercept 2.0 mg every 8 weeks after 5 monthly loading doses ($n = 134$), aflibercept 2.0 mg every 16 weeks after 3 monthly loading doses and one 8-week interval ($n = 135$), or matching sham injections ($n = 133$). At Week 24, 55% of the 8-week dosing group and 63% of the 16-week dosing group had met the primary endpoint of ≥2-step ETDRS-DRSS improvement, compared with only 6% of the sham group.[45] At Week 52, 65% and 80% of patients treated with 16-week or 8-week aflibercept, respectively, had achieved ≥2-step ETDRS-DRSS improvement, compared with only 15% of patients in the control arm ($p < 0.0001$).[45] Based on these data, the FDA expanded the label indication for aflibercept to include treatment of all stages of DR, with or without DME.[13]

A prespecified subgroup analysis of the DRCR.net Protocol T study[49] was performed to compare changes in DR severity during ranibizumab, aflibercept, or bevacizumab treatment for DME.[50] Of the 650 adults analyzed, 495 (76%) had NPDR and 155 (24%) had PDR. A significantly higher proportion of eyes with NPDR receiving ranibizumab (57/151 [38%]) or aflibercept (44/141 [31%]) had DR improvement at 1 year, compared with NPDR eyes receiving bevacizumab (29/131 [22%]). In a smaller sample analyzed at 2 years, 40 (31%) NPDR eyes in the ranibizumab group, 33 (25%) NPDR eyes in the aflibercept group, and 25 (22%) NPDR eyes in the bevacizumab group had DR improvement. For the smaller subgroup of patients ($n = 93$) with PDR at baseline, 1-year improvement rates were higher for aflibercept (76%) vs. ranibizumab (55%) and bevacizumab (31%), although the small sample size and between-group imbalances in patient characteristics at baseline must be considered when interpreting these data.[50]

7. Safety of anti-VEGF treatment for diabetic retinopathy

Given the essential role of angiogenesis in tumor growth and metastasis, several anti-VEGF therapies, including bevacizumab, have demonstrated efficacy and are approved for use in clinical oncology.[34,51] However, intravenous anti-VEGF therapy for some cancers has been associated with an increased risk of adverse cardiovascular events, including myocardial infarction, thromboembolism, hypertension, and proteinuria.[52] Despite this, current research indicates that intravitreal anti-VEGF treatment does not increase the risk of systemic adverse events in patients with ophthalmic diseases.[53] In RIDE/RISE[41] and Protocol S,[43] the incidence of systemic events were overall similar between ranibizumab and control groups, and although rates of death and cerebrovascular accident were numerically higher among ranibizumab-treated patients in RIDE/RISE, these were not observed in Protocol S or

other ranibizumab trials.[54,55] The systemic safety of aflibercept in DR has similarly been demonstrated in VISTA/VIVD[42] and PANORAMA,[45] which found that rates of cardiovascular and death events were overall low and balanced between treatment arms. Intravitreal anti-VEGF therapy has been associated with drug- and injection-related ocular events, including endophthalmitis, intraocular inflammation, vitreous hemorrhage, and retinal detachment[56]; however, pivotal phase III trials have shown that rates of serious ocular events were generally low among anti-VEGF–treated groups.[41–43,45] Ranibizumab was first approved for the treatment of neovascular age-related macular degeneration in 2006[12]; since this time, intraocular anti-VEGF therapies have demonstrated an acceptable safety profile in clinical practice, and have become the mainstay of treatment for DR and other retinal diseases.

8. Case presentation

This case study illustrates the utility of anti-VEGF treatment relative to the standard of care the patient had been receiving in prior months. A 47-year-old white Hispanic or Latino male, obese (body mass index: 31.4 kg/m^2), and diagnosed with diabetes 16 years earlier, presented for enrollment in a trial of ranibizumab for DME.[41] Approximately 6 months before evaluation for the trial, he received standard treatment with PRP, which is indicated for patients with advanced high-risk DR, and was also diagnosed with clinically significant macular edema.

The patient's baseline HbA1c level of 6.6% indicated good blood glucose control over the preceding 3 months, while his baseline BP was 165/80 mm Hg. Blood urea nitrogen of 23 mg/dL, serum creatinine of 1 mg/dL, and a glomerular filtration rate of 80.09 mL/min/1.73 m^2 (estimated using the Modification of Diet in Renal Disease Study equation[57]) were suggestive of mild renal impairment. At baseline, the patient was able to read only 54 letters on the ETDRS eye chart with his study eye. This corresponds to vision of 20/160 Snellen equivalent, which would not be sufficient for performing complex tasks such as driving, which is a significant handicap for a working-age individual. A vision of 20/40 or better (≥70 ETDRS letters) is one of the requirements for obtaining a driving license in most states. Retinal assessment of this patient included OCT (Fig. 5A). Despite receiving PRP 5 months earlier, OCT and retinal photographs of this patient revealed significant changes consistent with high-risk PDR (ETDRS-DRSS level 71) and macular edema.

The patient was randomized to receive monthly intravitreal injections of 0.3 mg ranibizumab. A retinal photograph and OCT after 3 monthly injections shows regression in the severity of DR as evidenced by resolution of the retinal hemorrhages (Fig. 5B), scored as a clinically significant 2-step improvement from high-risk PDR (ETDRS-DRSS level 71) to mild PDR (ETDRS-DRSS level 60–61). It should be noted that patients with prior PRP, such as this patient, cannot be scored below level 60 on the ETDRS-DRSS due to the presence of laser scars. The macular edema resolved with central foveal thickness, decreasing from 485 μm at baseline to 179 μm at Month 3. Retinal photographs and OCT from Month 6 showed further clearing of the fundus hemorrhages and no evidence of macular edema. At the end of the 36-month study period, this patient was able to read 85 letters on the ETDRS chart, which is equivalent to normal vision of 20/20 Snellen equivalent.

9. Future advances in diabetic retinopathy management

9.1. Advances in screening and diagnosis

Increased adoption of retinal imaging technologies in current clinical practice has given rise to large image databases that document the course of DR over time. These databases have in turn allowed the development of mathematical models, deep learning algorithms, and artificial intelligence (AI) that can diagnose DR,[58] grade DR severity,[59] assess risk of progression,[60,61] personalize screening intervals,[61–63] and predict response to treatment.[64] The first AI-based diagnostic system, the iDx-DR device, received FDA approval in 2018 for the automatic detection of DR.[65] The software device utilizes image quality and diagnostic algorithms to analyze retinal fundus images and detect the presence or absence of “more than mild” DR (defined as ETDRS-DRSS level ≥35 and/or DME).[65] A number of other automated retinal image analysis systems have also been developed to screen for DR and alleviate the burden of manual image grading.[66–68] A recent systematic review of deep learning–based screening algorithms found that they often have high rates of sensitivity and specificity; however, further real-world validation is required.[69] More recently, a pilot study using RIDE/RISE data found that a deep learning algorithm applied to baseline color fundus photographs was capable of predicting responses to ranibizumab with 81–87% sensitivity and 72–82% specificity.[64] Furthermore, the deep learning algorithm identified areas predictive of future improvement considered undetectable to human graders.[64]

9.2. Therapeutic agents in clinical development

Although anti-VEGF therapies are the most advanced agents currently approved for the treatment of DR, other agents in clinical development may feature prominently in the future of DR management. Faricimab

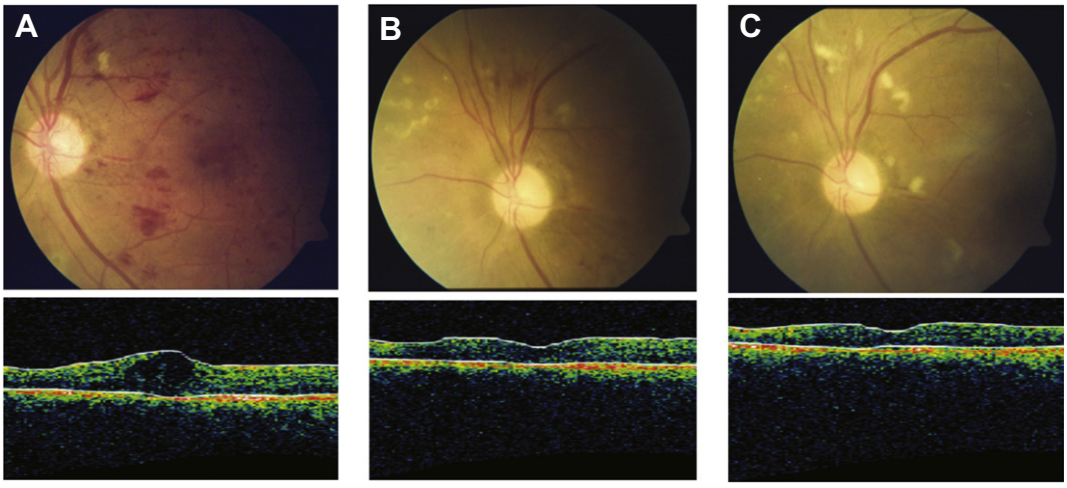

Fig. 5. Retinal photographs and OCT scans of patient receiving monthly intravitreal injections of 0.3 mg ranibizumab. Note resolution of retinal hemorrhages from: (A) screening; through (B) Month 3; and (C) resolution of macular edema on OCT at Month 6. White spots are cotton wool spots representing areas of retinal nerve fiber infarction from diabetic retinopathy. Fundus color differences (orange vs. yellow) are camera artefact. OCT, optical coherence tomography.

(Roche/Genentech, Inc.) is the first bispecific antibody designed for intraocular use, and neutralizes both angiopoietin-2 and VEGF-A with high potency and specificity.[70,71] In the phase II BOULEVARD trial of patients with DME (NCT02699450), those who received faricimab demonstrated superior VA gains compared with patients who received ranibizumab, irrespective of whether they were treatment naïve or had previously received anti-VEGF therapy.[72] Based on the strength of these data, 2 pivotal phase III trials, RHINE (NCT03622593) and YOSEMITE (NCT03622580), are ongoing to compare faricimab and aflibercept for the treatment of patients with DME.[73,74]

The safety and efficacy of brolucizumab (Novartis), a single-stranded VEGF-binding antibody fragment, is currently being studied in 2 phase III trials of patients with DME (KITE [NCT03481660] and KESTREL [NCT03481634]), which are expected to conclude in 2021.[75,76] KITE and KESTREL follow 2 recent phase III trials that compared brolucizumab and aflibercept in patients with untreated, active neovascular age-related macular degeneration (HAWK [NCT02307682] and HARRIER [NCT02434328]).[77] In HAWK and HARRIER, brolucizumab treatment demonstrated noninferiority to aflibercept in mean BCVA change from baseline, and was superior to aflibercept in key secondary endpoint measures.[77] Furthermore, >50% of eyes that received brolucizumab 6 mg were maintained with a 12-week dosing interval, suggesting a longer duration of action.[77]

Semaglutide (Novo Nordisk) is a glucagon-like peptide-1 analogue currently approved for glycemic control in patients with type 2 diabetes.[78] In the SUSTAIN clinical trial program, which informed the FDA approval of semaglutide for type 2 diabetes, subcutaneous semaglutide treatment led to significant and sustained improvements in HbA1c and body weight vs. placebo and active comparators.[79–83] In SUSTAIN 6 (NCT01720446), a 2-year preapproval cardiovascular outcomes trial, rates of DR complications (vitreous hemorrhage, blindness, or the need for treatment with an intravitreal agent or photocoagulation) were significantly higher in patients randomized to semaglutide vs. placebo.[84] However, post hoc analyses of SUSTAIN 6 attributed this observation to a known phenomenon of early DR worsening following rapid and marked HbA1c reductions in patients with pre-existing DR and poor glycemic control at baseline, and those treated with insulin.[85] A phase III clinical trial (FOCUS [NCT03811561]) has since been initiated to investigate the long-term effects of semaglutide in patients with any form of DR.[86]

10. Conclusions

The identification of VEGF as a key factor in the pathogenesis of DME and DR suggested that intravitreal anti-VEGF therapy had potential to arrest the disease process, and perhaps improve visual outcomes in affected individuals. The body of evidence reviewed here clearly demonstrates that intraocular inhibition of VEGF provides an effective treatment option for the management of DR. Anti-VEGF intraocular injections not only arrested the disease process, but additionally resulted in clinically significant improvements in DR severity. Furthermore, the need for PRP was significantly reduced, thus preserving peripheral vision in working-age individuals with DR. In light of such evidence, aflibercept and ranibizumab are now FDA approved for the treatment of DR in patients with and without DME, while bevacizumab is often used off label for DR management in current clinical practice.

As our understanding of modifiable risk factors and the array of therapeutic options for DR grow, the partnership between endocrinologists, primary care providers, and ophthalmologists is increasingly important. Communication is a fundamental component of this healthy partnership. While the AAO and ADA have published standards for diabetic eye screening, continued collaboration among these health care providers will reinforce the rationale and importance of complying with systemic and ocular care, thus supporting patients to take an active role in their health. Additional straightforward standards for communication, such as simple scales for DR, renal status, and peripheral neuropathy, will facilitate these communications.

The more that ophthalmologists can understand and reinforce updated standards of modifiable diabetic risk factors, such as HbA1c and BP, and the more that medical colleagues managing diabetes understand the mechanisms, administration, and interactions of DR therapies, the more likely it is that patients with diabetes can maintain quality vision and a productive life.

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Declaration of competing interest

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Roche data sharing statement

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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