Overview of Ocular Anti-Vascular Endothelial Growth Factor Therapy in the Management of Diabetic Eye Complications

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Diabetes has been increasing in prevalence over the years, and nearly 30 million Americans (9.3%) now have diabetes (1). This disease burden on the population also translates to increased prevalence rates of diabetes complications. Diabetes is associated with several eye complications, including cataracts and glaucoma (2). However, the most common eye disorder associated with diabetes is diabetic retinopathy (DR), which is the leading cause of blindness among U.S. adults (2,3). During the 2005–2008 time period, >4 million adults ≥40 years of age with diabetes had retinopathy, including diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR), which can lead to vision loss (1).

The management of systemic disorders is vital to preventing diabetic eye complications (4). Specifically, the management of diabetes, hypertension, and hyperlipidemia has been associated with reduced or delayed onset and progression of DR (5–11). However, even with adequate control of these metabolic conditions, people with diabetes may still be at risk for developing retinopathy. Adequate eye screening is therefore important for the early detection and treatment of visual complications (4). Screening recommendations call for a dilated, comprehensive eye examination within 5 years after diabetes diagnosis for people with type 1 diabetes and immediately after diagnosis for those with type 2 diabetes (12).

Laser therapy has been the mainstay of treatment for DR and DME. Primarily, laser photocoagulation treatment has been used to prevent vision loss and to delay progression of retinopathy (13). The associated adverse effects of laser therapy, including night and peripheral vision loss, are generally preferred to eventual blindness. When laser treatment is not feasible, vitreous surgery becomes an option and has been shown to be beneficial for PDR and DME (4).

Research has supported the intravitreal administration of steroids, whose anti-inflammatory and antiangiogenic effects are beneficial in the management of PDR and DME. However, steroid use is also associated with elevated rates of intraocular pressure, cataracts, glaucoma, and infection (13). In the past decade, elucidation of the role of vascular endothelial growth factor (VEGF) in the development of PDR and DME has facilitated the production of anti-VEGF pharmacological agents to reduce angiogenesis and blood-retinal barrier permeability (4,14). Intravitreal injection of these agents—namely, ranibizumab, aflibercept, bevacizumab, and pegaptanib—has been studied for the treatment of DR and DME. However, only ranibizumab and aflibercept are approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of DME and retinopathy in patients

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with DME. This article reviews the efficacy and safety of these four anti-VEGF agents. A summary of relevant efficacy and safety trials is provided in Table 1.

Ranibizumab

Approved in February 2015 for treatment of retinopathy in patients with DME, ranibizumab is also indicated for treatment of DME alone, neovascular age-related macular degeneration (AMD), and macular edema following retinal vein occlusion (RVO). It is a recombinant monoclonal antibody fragment that binds and inhibits VEGF-A (15). Of the four anti-VEGF agents discussed here, it has been the most thoroughly studied and was the first to be approved for the treatment of DME and DR.

Several clinical trials have been conducted to assess the safety and efficacy of ranibizumab in people with DME. In the phase 2 RESOLVE trial (16), 102 participants with type 1 or type 2 diabetes and DME were randomized to three monthly injections of a sham, 0.3 mg ranibizumab, or 0.5 mg ranibizumab followed by additional treatment as

TABLE 1. Clinical Efficacy and Safety Trials of Anti-VEGF Agents for DME and DR

Trial	Agent	Treatment Arms	Measurements	Outcomes (for treatment arms, respectively)
RESOLVE (16)	Ranibizumab	Pooled treatment (0.3 and 0.5 mg of ranibizumab), sham	Mean change in BCVA score from baseline to 12 months	+10.3 vs. –1 letters
RIDE (18)	Ranibizumab	0.3 mg of ranibizumab, 0.5 mg of ranibizumab, sham	Percentage of subjects gaining ≥15 letters in BCVA score	33.6, 45.7, and 12.3%
RISE (19)	Ranibizumab	0.3 mg of ranibizumab, 0.5 mg of ranibizumab, sham	Percentage of subjects gaining ≥15 letters in BCVA score	44.8, 39.2, and 18.1%
DA VINCI (23)	Aflibercept	Four aflibercept treatment arms (0.5 mg monthly, 2 mg monthly, 2 mg for three initial monthly doses and then every 2 months, 2 mg for three initial monthly doses), macular laser photocoagulation	Mean change in visual acuity and central retinal thickness at 24 weeks	Visual acuity: aflibercept arms ranged from +8.5 to +11.4 letters; macular laser photocoagulation +2.5 letters Central retinal thickness: aflibercept arms ranged from –127.3 to –194.5 μm, macular laser photocoagulation –67.9 μm
VISTA (25)	Aflibercept	2 mg aflibercept injection every 4 weeks or every 8 weeks subsequent to five monthly initial doses, macular laser treatment at baseline and as needed	Change in BCVA score from baseline to week 52	12.3, 10.6, and 0.1 letters
VIVID (26)	Aflibercept	2 mg aflibercept injection every 4 weeks or every 8 weeks subsequent to five monthly initial doses, macular laser treatment at baseline and as needed	Change in BCVA score from baseline to week 52	10.5, 10.7, and 1.2 letters
Yaseri et al. (randomized, double-masked, phase 3 trial) (29)	Bevacizumab	Intravitreal bevacizumab or in combination with intravitreal triamcinolone acetonide, macular laser photocoagulation	Percentage of eyes with visual acuity improvement ≥2 Snellen lines at 12 months	38, 9, and 18%
Mahajan et al. (randomized, prospective study) (30)	Bevacizumab	1.25 mg intravitreal bevacizumab injection, 4 mg intravitreal triamcinolone acetonide injection, macular grid augmentation	Change in BCVA from baseline to 6 months	Intravitreal bevacizumab from 20/160 at baseline to 20/80; intravitreal triamcinolone acetonide from 20/125 at baseline to 20/63; macular grid augmentation from 20/100 at baseline to 20/80

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TABLE 1. Clinical Efficacy and Safety Trials of Anti-VEGF Agents for DME and DR
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Trial	Agent	Treatment Arms	Measurements	Outcomes (for treatment arms, respectively)
BOLT (31)	Bevacizumab	Intravitreal bevacizumab (six weekly for maximum of nine injections in the first 12 months, macular laser therapy, four monthly with a maximum of four treatments in the first 12 months)	Percentage of subjects gaining ≥10 letters in BCVA as measured by letters in the ETDRS visual acuity test at 24 months	49 and 7%
Cunningham et al. (randomized, double-masked phase 2 study) (34)	Pegaptanib	Injections of pegaptanib (0.3, 1, or 3 mg), sham	BCVA at week 36	20/50 (0.3 mg pegaptanib) and 20/63 (sham)
Sultan et al. (multicenter, randomized, double-masked, phase 2 study) (35)	Pegaptanib	0.3 mg intravitreal pegaptanib, intravitreal sham injection	Percentage of subjects gaining ≥10 letters in BCVA score	36.8 and 19.7%
Pfizer, Inc. (randomized, double-masked, phase 3 study) (36)	Pegaptanib	0.3 mg intravitreal pegaptanib, intravitreal sham injection	Number of subjects gaining ≥10 letters in visual acuity from baseline to week 24	25/123 participants, 6/120 participants
Diabetes Retinopathy Clinical Research Network (aflibercept, bevacizumab, or ranibizumab for diabetic macular edema) (40)	Aflibercept, bevacizumab, ranibizumab	Intravitreal injection of aflibercept 2.0 mg, bevacizumab 1.25 mg, or ranibizumab 0.3 mg every 4 weeks	Mean BCVA change at 1 year	13.3, 9.7, and 11.2 letters

needed. Efficacy was measured using the visual acuity test from the Early Treatment Diabetic Retinopathy Study (ETDRS) starting at a test distance of 4 meters. The primary outcome was the mean average change in the best corrected visual acuity (BCVA) score from baseline (the change in BCVA score from month 1 to month 12). At 1 year, the pooled ranibizumab-treated group gained 10.3 letters, and the sham group lost 1 letter. Results from RESOLVE determined ranibizumab to be superior to the sham protocol in improving vision and found it to be safe, with adverse events comparable between treatment and sham groups.

In two randomized, double-masked, parallel phase 3 trials known as RIDE and RISE (A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema) (17), 382 and 377 participants, respectively, were randomized to monthly injections of a sham, 0.3 mg ranibizumab, or 0.5 mg ranibizumab. Results of RIDE and RISE demonstrated a significantly larger proportion of visual gain in the ranibizumab-treated groups compared to the sham groups. In RIDE, 33.6% and 45.7% of participants taking the 0.3- and 0.5-mg ranibizumab treatments, respectively, gained ≥15 letters in their BCVA score, compared to 12.3% of participants on the sham treatment at month 24 (P <0.0001) (18). Similarly, in RISE, 44.8% of those using the 0.3-mg ranibizumab treatment and 39.2% of those on the 0.5-mg treatment gained ≥15 letters in their BCVA score compared to 18.1% of those on the sham treatment (P <0.0001) (19).

Aflibercept

Approved in March 2015 for DR in patients with DME, aflibercept is also indicated for DME alone (approved in 2014), neovascular AMD, and macular edema following RVO (20,21). Aflibercept binds with high affinity to all isoforms of VEGF-A, VEGF-B, and placental growth factor. It was shown in animal studies to hold theoretical advantages over ranibizumab and bevacizumab (22).

In the DA VINCI (DME and VEGF Trap-Eye: Investigation of Clinical Impact) trial (23), a randomized, double-masked, phase 2 study, the efficacy of aflibercept was compared to focal coagulation in eyes with DME. The main outcome measures included mean change in visual acuity and central retinal thickness (CRT) at 24 weeks. Two hundred and twenty-one participants were assigned to one of five treatment arms: 0.5 mg aflibercept monthly, 2 mg aflibercept monthly, 2 mg aflibercept for three initial monthly doses

then every 2 months, 2 mg aflibercept for three initial monthly doses and then as needed, and macular laser photocoagulation. Patients in all four aflibercept treatment groups experienced visual acuity benefits ranging from gains of 8.5–11.4 letters compared to a gain of 2.5 letters in the laser therapy group at week 24 ($P \leq 0.0085$). Mean CRT reductions in the four aflibercept treatment groups ranged from –127.3 to –194.5 µm compared with –67.9 µm in the laser treatment group ($P = 0.0066$).

In two similarly designed, randomized, double-masked phase 3 trials known as the VISTA and VIVID studies (24–26), the safety and efficacy of two intravitreal aflibercept dosing regimens were compared to macular laser photocoagulation in people with DME. Four hundred and thirty-six participants were randomized to either 2-mg aflibercept injections every 4 weeks, 2-mg aflibercept injections every 8 weeks subsequent to five monthly initial doses, or macular laser treatment at baseline and as needed. The primary outcome measure was change from baseline in BCVA score at week 52. Mean BCVA gains for the two aflibercept injection regimens were 12.5 and 10.7 letters, respectively, compared to a gain of 0.2 letters with laser treatment ($P < 0.0001$). Thus, aflibercept was found to be more efficacious than laser photocoagulation in increasing BCVA scores at week 52.

Bevacizumab

Bevacizumab is a VEGF-specific angiogenesis inhibitor approved in 2004 for first-line treatment of metastatic colorectal cancer with 5-fluorouracil–based chemotherapy. In addition, it is indicated for several other cancer treatments such as metastatic renal cell carcinoma, cervical cancer, and metastatic HER2-negative breast cancer (27). As a recombinant antibody with VEGF-A blocking activity, it has been used off-label for DME treatment via compounding of an intravenous formulation (28).

In 2005, a randomized, double-masked, phase 3 trial (29) assessed the efficacy of bevacizumab by assigning 129 participants with significant DME to one of three treatment arms: intravitreal bevacizumab (IVB) alone, IVB in combination with intravitreal triamcinolone acetonide (IVB/IVTA), and macular laser photocoagulation (MPC). The study determined IVB treatment to be superior to MPC treatment for overall visual acuity, but only for up to 12 months ($P = 0.027$). The percentage of eyes with visual acuity improvement ≥2 Snellen lines at 12 months for IVB, IVB/IVTA, and MPC were 38, 9, and 18%, respectively.

In a similar randomized, prospective study (30) with 60 participants, 1.25 mg IVB injection, 4 mg IVTA, and macular grid augmentation treatments were compared with follow-up measurements at 1, 3, and 6 months. Results demonstrated clinical benefits and visual acuity improvements for both IVB and IVTA treatments. The mean BCVA change was from 20/160 at baseline to 20/80 for IVB and from 20/125 at baseline to 20/63 for IVTA ($P < 0.05$). Macular grid augmentation yielded little improvement, with a change from 20/100 at baseline to 20/80, which did not reach the level of statistical significance ($P = 1.0$).

In the BOLT (Bevacizumab or Laser Therapy study) (31), a randomized, prospective phase 3 trial, 80 people with clinically significant macular edema (CSME) were randomized to either bevacizumab or macular laser therapy (MLT). Bevacizumab-treated patients were given six weekly IVB treatments, and the MLT-treated group received four monthly treatments. The primary outcome measure was the difference in BCVA between arms based on the ETDRS visual acuity test. The mean BCVA for the bevacizumab group changed from 55.7 at baseline to 64.4 at 24 months. For the MLT group, the mean BCVA changed from 54.6 at baseline to 54.8 at 24 months ($P = 0.005$). The BOLT study demonstrated significant improvement in BCVA for CSME patients without advanced macular ischemia and the drug's efficacy for long-term use.

Pegaptanib

Pegaptanib, a pegylated oligoribonucleotide approved in 2004 for neovascular AMD, has high affinity and binding to VEGF-165 (32). It has been investigated and reviewed in several clinical trials for its efficacy and safety in DME, although it is not FDA-approved for any diabetic eye complications (33).

A randomized, double-masked phase 2 study (34) assessed the safety and efficacy of pegaptanib in DME patients. One hundred and seventy-two participants were given injections of either a sham or pegaptanib 0.3 mg, 1 mg, or 3 mg every 6 weeks for 48 weeks. The primary efficacy endpoints were maintenance of baseline visual acuity or loses of <15 letters of visual acuity from baseline to week 54. Results demonstrated that all three pegaptanib-treated groups had more favorable visual acuity change than the sham-treated group at week 36. Results also demonstrated an overall gain in visual acuity, as well as reduced risk of visual acuity loss, in DME patients receiving pegaptanib treatment. The 0.3-mg dose was found to be the most efficacious, and few serious adverse events were noted. A larger percentage of participants on the 0.3-mg treatment also gained ≥10 letters in visual acuity than of those receiving the sham treatment (34 vs. 10%, $P = 0.003$). However, the study was not powered to identify differences in outcomes with the different pegaptanib doses, and the safety and efficacy of pegaptanib administration to both eyes concurrently need further investigation.

The efficacy of pegaptanib for DME was evaluated in a randomized, controlled, double-masked phase 2/3 study (35). Two hundred and sixty participants with DME were randomized to receive either 0.3 mg

intravitreal pegaptanib or an intravitreal injection of a sham treatment. At week 54, the study determined a greater gain in visual acuity from subjects receiving the pegaptanib treatment compared to those receiving the sham. In the pegaptanib-treated group, 36.8% gained ≥10 letters of visual acuity compared to 19.7% in the sham-treated group ($P = 0.0047$). At week 102, the pegaptanib-treated group gained an average of 6.1 letters compared to 1.3 letters for the sham-treated group ($P < 0.01$).

Results from a randomized phase 3 study (36,37) determined pegaptanib to be superior to a sham therapy for improvement in visual acuity. Treatments were given every 6 weeks, and the primary outcome measure was the number of participants with an improvement from baseline of ≥10 letters in visual acuity at week 24. Twenty-five of 123 subjects on pegaptanib demonstrated the primary outcome compared to 6 of 120 subjects on the sham ($P = 0.003$). A secondary measured outcome of mean change from baseline in visual acuity was +3.1 and –1.2 for the pegaptanib and sham groups, respectively ($P = 0.0006$).

Discussion

The common side effects associated with anti-VEGF agents include eye pain, vitreous floaters, cataract, conjunctival hemorrhage, and increased intraocular pressure (15,21,33,38). Generally, there is increased risk for endophthalmitis and retinal detachment with intravitreal injections; thus, patients on these agents should be monitored soon after injection for blurred vision, eye pain or redness, photophobia, or vision changes (15,21,33,38,39). Serious but uncommon adverse effects observed with these agents include arterial thromboembolic events such as nonfatal stroke, nonfatal myocardial infarction, and vascular death. However, there appear to be no major differences among the four agents in terms of ocular and cardiovascular adverse effects (40–42). These agents are contraindicated in patients with ocular or periocular infection, active ocular inflammation, or hypersensitivity to any of the drug components. After receiving an injection, patients should expect to wait for ~60 minutes to be monitored for increased intraocular pressure and should have an alternate driver available after the procedure (15,21,33).

In contrast to the safety profiles, which are similar, the recently published 1-year results of a head-to-head clinical trial by the Diabetic Retinopathy Clinical Research Network (40) found that aflibercept was superior to ranibizumab and bevacizumab in DME patients with worse baseline visual acuity. However, aflibercept, ranibizumab, and bevacizumab were found to be equally efficacious in DME patients with mild baseline visual acuity loss. A systemic review (43) using an indirect comparison method also evaluated the effectiveness of aflibercept, ranibizumab, and dexamethasone implant and reported that aflibercept yielded the greatest improvement in visual acuity. Nevertheless, more long-term studies are needed to fully appreciate the comparative effectiveness of these agents. Pegaptanib has been shown to be efficacious in the treatment of DME. However, it is not widely used or studied because of its lower efficacy. It is important to note that both pegaptanib and bevacizumab are not FDA-approved to treat DME (44). Additionally, there is a cost differential between these agents that should be considered when selecting treatment. The costs per intravitreal injection for aflibercept, ranibizumab, pegaptanib, and bevacizumab are $1,850, $1,170, $995, and $60, respectively (41,45,46).

Conclusion

The standard of care for management of diabetic eye complications with laser photocoagulation is useful in slowing progression of DR and reducing vision loss. However, this type of therapy is limited by adverse side effects and a small effect in improving visual acuity (4,13). Availability and FDA approval of anti-VEGF agents will undoubtedly influence treatment approaches for DR and DME (37). The efficacy of anti-VEGF agents compared to laser therapy supports the likelihood that these agents will be considered more frequently. The availability of long-term efficacy and safety trials will provide further clarity on the exact roles these agents should play in the management of patients with DR and DME.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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