Diabetic retinopathy is the most common complication of diabetes mellitus and a major cause of visual morbidity throughout the world. It is the leading cause of blindness among people 20-64 years old in the United States,[1] and based on a large cross-sectional study, 28.5 percent of American adults over 40 years of age with diabetes had diabetic retinopathy in 2005-2008.[2] Globally, diabetic retinopathy affects approximately 150 million people, and the World Health Organization projects that this number will double by the year 2025.[3]

Diabetic retinopathy is characterized by increased vascular permeability, retinal ischemia, edema and the formation of neovascularization. Diabetic retinopathy may lead to significant permanent visual loss via macular edema, macular ischemia, vitreous hemorrhage, retinal detachment and neovascular glaucoma. The Early Treatment Diabetic Retinopathy Study (ETDRS) classified diabetic retinopathy into two main categories based on severity of clinical features: non-proliferative and proliferative.[4] Non-proliferative diabetic retinopathy (NPDR) refers to the presence of intraretinal vascular changes without extraretinal fibrovascular tissue, or neovascularization. It is further subdivided into mild, moderate and severe categories. Proliferative diabetic retinopathy (PDR) is characterized by the presence of neovascularization secondary to retinal ischemia. It was further described as early, high-risk or advanced based on the extent of proliferation. These subdivisions constitute the ETDRS diabetic retinopathy severity scale (DRSS).

One specific complication of diabetic retinopathy is diabetic macular edema (DME), which is diagnosed clinically by the presence of retinal thickening on slit-lamp biomicroscopy or optical coherence tomography (OCT). DME may manifest as focal or diffuse retinal thickening, with or without exudates. Historically, DME was treated with focal laser
photocoagulation if it met the criteria for clinically-significant macular edema (CSME) as defined by the early ETDRS reports.

Now, with the advent of OCT, a more relevant description of DME is fovea-involving and non-foveal involving to help guide treatment.

The mainstay for treatment of diabetic retinopathy is pan-retinal laser photocoagulation (PRP). The Diabetic Retinopathy Study recommended initiating PRP in cases of high-risk PDR. It has been suggested that earlier PRP in cases of severe NPDR or early PDR may also be expedient, but the current evidence is insufficient to determine this conclusively. In addition to PRP, strict glycemic control has been found to reduce the incidence and progression of diabetic retinopathy. The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive blood glucose control was associated with a reduced risk of newly diagnosed diabetic retinopathy as well as decreased progression of existing retinopathy in individuals with diabetes mellitus types 1 and 2, respectively. In addition, poorly-controlled hypertension is associated with a higher risk of progression of diabetic retinopathy and DME, as well as loss of vision. Other systemic conditions associated with exacerbated diabetic retinopathy include hyperlipidemia, pregnancy and severe carotid artery occlusive disease.

PRP works to induce regression of neovascularization by destroying ischemic peripheral retina and increase oxygen tension in the eye by decreasing oxygen consumption by the peripheral retina and enhancing oxygen diffusion from the choroid beneath the chorioretinal PRP scars. It is known that ischemic retina produces growth factors, such as vascular endothelial growth factor (VEGF), which promote retinal neovascularization. Based on this observation, it is reasonable to assume that anti-VEGF agents may be useful in treating diabetic retinopathy. While intravitreal anti-VEGF injections are commonly used in DME, its specific use in modifying the severity of diabetic retinopathy is still being investigated. The present article aims to summarize the existing knowledge on the use of anti-VEGF agents in diabetic retinopathy.

VEGF is known to be a potent regulator of pathologic ocular neovascularization and an important cause of increased retinal vascular hyperpermeability, leakage and macular edema development. With respect to diabetic retinopathy specifically, Aiello, et al. demonstrated that VEGF levels were elevated in vitreous samples of patients with PDR and venous occlusive disorders.

Numerous publications have shown that anti-VEGF therapy is effective against DME specifically, the most common cause of vision loss in diabetic patients. While focal/grid laser photocoagulation was once the
recommended treatment strategy for DME, the new standard of care for foveal-involving DME has quickly become intravitreal anti-VEGF injections. There are three agents that comprise the overwhelming market share of intravitreal anti-VEGF therapies for DME: bevacizumab, ranibizumab and aflibercept.

Bevacizumab (Avastin, Genentech Inc., San Francisco, CA) is a full-length recombinant humanized monoclonal antibody that binds all isoforms of VEGF-A and works by inhibiting receptor binding. It is approved by the US Food and Drug Administration (FDA) for intravenous use in metastatic colon cancer but is not FDA approved for use in any ocular diseases. However, it is the least expensive anti-VEGF therapy available and has been used extensively off-label for various retinal proliferative vascular diseases, including neovascular glaucoma, DME, CNV and neovascular AMD. Several studies have demonstrated improved outcomes with bevacizumab over laser photocoagulation in managing DME.[13, 14]

Ranibizumab (Lucentis, Genentech Inc., San Francisco, CA), is an affinity-enhanced humanized monoclonal antibody fragment developed from the parent molecule of bevacizumab against all isoforms of VEGF-A. Ranibizumab is one-third the molecular weight of bevacizumab, and its smaller size was designed for enhanced intraretinal penetration. It was the first anti-VEGF agent FDA-approved for intravitreal use in DME in the United States and Europe, and is also approved for use in exudative AMD. In several phase II/III trials, ranibizumab was superior to sham or focal/grid laser photocoagulation in improved best-corrected visual acuity and reducing macular thickness in patients with visually significant DME.[15]

Aflibercept (Eylea or VEGF-Trap, Regeneron, Tarrytown, NY) is a recombinant fusion protein that binds all forms of VEGF-A, VEGF-B and PIGF. Aflibercept was found to bind VEGF with a markedly greater affinity than bevacizumab or ranibizumab, with approximately a 100-fold greater binding affinity for the VEGF 165 isoform.[16] Studies suggest that this difference may allow for significantly longer binding to VEGF and subsequently more prolonged clinical effects with extended intervals between intravitreal injections.[17] Aflibercept was FDA-approved for use in neovascular AMD in 2011, and was recently approved for use in DME in March of 2015.

While the uses of anti-VEGF therapy are well established for DME, the effects of anti-VEGF agents on the severity of diabetic retinopathy aside from DME are more incompletely established. PRP remains the treatment of
choice for PDR, but in the face of adverse effects of and clinical barriers to PRP, anti-VEGF agents are being explored as an alternative and adjunctive therapeutic strategy in the treatment of diabetic retinopathy.

Multiple studies have explored the use of intravitreal bevacizumab or ranibizumab with PRP for the treatment of PDR. Studies have found reduced leakage on fluorescein angiography with the use of intravitreal bevacizumab adjunctively compared with PRP alone.[18, 19] In addition to fluorescein angiography findings, it has been demonstrated that intravitreal bevacizumab in conjunction with PRP induced clinical regression of neovascularization greater than PRP alone.[20] Furthermore, it has been suggested that combined intravitreal bevacizumab and PRP allows for rapid clearance of vitreous hemorrhage, regression of retinal neovascularization and visual improvement in the treatment of high-risk PDR in the short-term.[20-22]

It has also been shown that the adjunctive use of ranibizumab mitigates the transient macular thickening and associated visual acuity loss seen in eyes treated with PRP alone.[23, 24] In a prospective study that included 29 eyes in 29 patients with high-risk PDR and no prior laser treatment, Filho, et al. found that intravitreal ranibizumab (0.5mg) after PRP was associated with a larger reduction in fluorescein leakage at week 48 compared with PRP alone.[23] Moreover, while BCVA worsened after PRP at weeks 16, 32 and 48 in the PRP alone group, no significant BCVA changes were observed in the PRP plus ranibizumab group.

In the latest prospective randomized controlled studies, the metric of “2-step improvements” in the DRSS score serves as the gold standard for measuring the effectiveness of an intervention on diabetic retinopathy. Each step is based on the original subdivisions of diabetic retinopathy delineated in the original ETDRS publications of the early 1990s. Most recently, two double-masked, randomized, controlled, clinical trials VISTA and VIVID aimed to compare the efficacy and safety of two dosing regimens of intravitreal aflibercept injections (2mg given every 4 or 8 weeks) with macular laser photocoagulation in eyes with DME over 52 [25] and 100 weeks [26]. In addition to significant gains in visual acuity compared with baseline, treated eyes appeared to benefit in their underlying diabetic retinopathy. A significantly higher proportion of eyes treated with either dosing regimen of intravitreal aflibercept had a ≥2 step improvement in the DRSS score than the laser control group in both VISTA (37.0 percent and 37.1 percent versus 15.6 percent, respectively; p < 0.0001) and VIVID (29.3 percent and 32.6 percent versus 8.2 percent, respectively; p ≤ 0.0004).[26]
The largest prospective randomized controlled trials to date specifically aimed at assessing the effects of intravitreal ranibizumab on diabetic retinopathy severity are based on data from the RISE and RIDE trials.[27, 28] In the first published study, eyes with DME were assigned to monthly ranibizumab (0.3mg or 0.5mg) for 24 months.[27] In the follow-up report, eyes were treated for 36 months, with those initially randomized to sham treatments eligible for crossover to monthly 0.5mg ranibizumab beginning at month 25.[28] The authors found that monthly intravitreal ranibizumab injections over 24 months prevented worsening of and led to improvements in diabetic retinopathy as measured by DRSS scores. Moreover, sham-treated patients were 3-fold more likely to develop PDR than patients treated with ranibizumab (33.8 versus 11.2-11.5 percent, respectively).

At month 36, a significantly greater proportion of eyes had ≥3 steps of improvement in the 0.3mg and 0.5mg ranibizumab-treated eyes compared with the sham group (15.0 percent and 13.2 percent versus 3.3 percent, respectively, p<0.0001). Moreover, a greater proportion of ranibizumab-treated eyes had ≥2- or ≥3-step improvements in the DRSS score compared with sham-crossover eyes, suggesting that delayed initiation of anti-VEGF therapy is beneficial in preventing further disease progression, but administering treatment early in the course of DME maximizes treatment benefits. Approximately 39 percent of eyes in the sham group developed PDR, compared with 18.3 percent and 17.1 percent of eyes treated with 0.3mg or 0.5mg ranibizumab, respectively. No systemic factors were significantly associated with the development of PDR, but the presence of macular capillary non-perfusion at baseline appeared to be associated with PDR progression in ranibizumab-treated eyes.

Currently, the Diabetic Retinopathy Clinical Research (DRCR) Network Protocol S is underway to compare the effects of prompt PRP versus ranibizumab plus deferred PRP in the treatment of PDR.[29] This study aims to determine if visual acuity outcomes at two years in PDR eyes receiving intravitreal ranibizumab injections with deferred PRP are non-inferior to eyes that receive standard prompt PRP therapy. Secondary objectives include other measures of visual function, including Humphrey visual field testing, determining the percentage of eyes not requiring PRP when anti-VEGF is given in the absence of prompt PRP, comparing safety outcomes between treatment groups and comparing associated costs between treatment groups.

As most of the existing studies highlight the potential utility of intravitreal anti-VEGF injections as an adjunct to PRP by inducing further regression of neovascularization as seen on fluorescein angiography or clinical exam, reducing PRP-induced macular thickening, potentially improving visual outcomes, and reducing the duration of vitreous
hemorrhages, they are all limited by their small sizes and the fact that PRP was always administered in conjunction with an anti-VEGF agent. Additional large randomized controlled studies will be required to compare PRP with anti-VEGF agents administered individually, as well as independent of the presence of DME, in order to observe the unique effects of anti-VEGF agents on diabetic retinopathy specifically.

Anti-VEGF agents may be especially useful in cases resistant to standard PRP treatment. Schmidinger, et al. evaluated 11 eyes in 10 patients with persistent neovascularization after previous complete PRP for a six-month follow-up period. Intravitreal bevacizumab (1.0mg) led to a significant reduction in retinal neovascularization for a mean 2.9 ±1.0 months. Seventy-three percent of treated eyes revealed complete regression of retinal neovascularization at one-week follow-up, with 73 percent of eyes showing signs of recurrent neovascularization requiring reinjection at three-months follow-up. The authors concluded that injecting bevacizumab every three months might be a valid method to control neovascularization in patients with recalcitrant PDR.

Erdol, et al. also performed intravitreal bevacizumab (1.25mg) injections in 33 eyes of 24 patients with persistent PDR in spite of prior PRP. The authors found that after a single dose of bevacizumab, complete resolution of neovascularization was seen in 78.8 percent at one month post-injection, 63.6 percent at three months and 45.4 percent at six months. In nine eyes that had a second injection at three months, the complete resolution rate was 60.6 percent at five months. Even at six months after injection, there was a statistically significant improvement in visual acuity compared to before treatment. Thus, the authors recommended bevacizumab injections in patients with PDR with poor response to or recurrence with PRP.

One current limitation to using anti-VEGF therapy for PDR is the unknown duration of its anti-neovascular effects. It appears that intravitreal anti-VEGF agents induce regression of neovascularization as soon as six days post-injection to up to nine months and one year. However, the exact longevity of effects appears to vary significantly among patients based on as yet unknown factors.

In a prospective study by Mirshahi, et al. involving 80 eyes in 40 patients with high-risk PDR, all eyes received PRP and were subsequently randomized to receive either intravitreal sham or bevacizumab (1.25mg) injections after PRP. Follow-up was performed at weeks six and 16. At six-weeks follow-up, 87.5 percent of bevacizumab-injected eyes and 25 percent of the sham group showed complete regression of neovascularization. By week 16, the complete
PDR regression rate was equal between the two groups. In a subgroup analysis of bevacizumab-treated eyes, hemoglobin A1c was the strongest predictor of PDR recurrence.

In addition, the optimal dosage of anti-VEGF agents is debatable. Studies involving bevacizumab have used between 1 and 2.5mg for patients with diabetic retinopathy. It is unclear what effect this dosing variation may have on the response rates to treatment in PDR.

Thus, the literature suggests that the duration of intravitreal anti-VEGF therapy on PDR varies considerably depending on undetermined factors, which may include hemoglobin A1c levels. The wide range of reported activity underscores the importance of further studies to explore the duration and effects of anti-VEGF agents used as primary treatments for PDR. Long-term, randomized controlled trials centered on the use of anti-VEGF therapy alone for PDR will be needed to delineate potential treatment algorithms with recommended dosing based on the average longevity of their effects.

Administration of intravitreal anti-VEGF injections is associated with several rare, potential complications. In general, intravitreal anti-VEGF injections may lead to retinal detachment, endophthalmitis, transient IOP elevation, uveitis, retinal hemorrhages, lens injury, retinal pigment epithelial tear, and acute vision loss. Macular hole has been reported after intravitreal injections of bevacizumab [36] and aflibercept.[37] There is also concern that anti-VEGF agents may cause geographic atrophy in patients receiving monthly injections for AMD.

Particularly in PDR, it is thought that anti-VEGF agents may cause rapid contraction of retinal neovascularization, replacing them with fibrous membranes. Contraction of these membranes may lead to tractional retinal detachments and vitreous hemorrhages.

Finally, given that all the intravitreal anti-VEGF agents have been found in detectable levels in the systemic circulation, there may be a possibility of increased thromboembolic events and non-ocular hemorrhages. However, the rates of any causes of deaths were not significantly increased.[38]

In conclusion, the preponderance of studies to date suggest that anti-VEGF agents play an important role in the treatment of PDR in the following ways: inducing rapid and moderately sustained regression of neovascularization, reducing the macular edema and transient drop in visual acuity following PRP treatment, reducing neovascularization in
eyes with PDR recalcitrant to PRP, expediting the resolution of vitreous hemorrhages, reducing the incidence of immediate post-operative vitreous hemorrhages after PDR-related vitrectomies, and reducing DME.

In spite of these suggestive findings, the evidence level of these studies for proliferative diabetic retinopathy as long-term monotherapy is low. Large-scale, randomized controlled trials will need to be performed in the future to conclusively determine the effects of anti-VEGF therapy on the severity of diabetic retinopathy in the absence of DME, as well as its role as an adjunctive or alternative therapy to PRP, which remains the gold standard treatment for PDR and its complications.
REFERENCES


1. Which of the following is NOT true about the role of VEGF in diabetic retinopathy?
   A. It promotes vascular hyperpermeability.
   B. It creates a stimulus for the growth of abnormal new blood vessels.
   C. It is decreased in patients with proliferative diabetic retinopathy.
   D. It leads to the development of diabetic macular edema.
   E. There is more than one drug available to block its effects in this condition.

2. Which of the following is NOT true about diabetic macular edema?
   A. It is the result of vascular hyperpermeability brought about by VEGF.
   B. It can occur at any level of diabetic retinopathy.
   C. It is the most common cause of vision loss in diabetic patients.
   D. It rarely causes vision loss in diabetic patients.
   E. It is commonly treated with intravitreal injections of anti-VEGF agents.

3. Which of the following is NOT an anti-VEGF agent?
   A. Bevacizumab (Avastin)
   B. Ranibizumab (Lucentis)
   C. Aflibercept (Eylea)
   D. Triamcinolone acetonide (Triesence)
   E. All of the above are anti-VEGF agents

4. Which of the following is true about anti-VEGF agents and their role in the management of diabetic retinopathy?
   A. Aflibercept (Eylea), ranibizumab (Lucentis), and bevacizumab (Avastin) all have positive impacts on diabetic retinopathy severity scores.
   B. Only aflibercept (Eylea) has a positive impact on diabetic retinopathy severity scores.
   C. Only ranibizumab (Lucentis) has a positive impact on diabetic retinopathy severity scores.
   D. Only bevacizumab (Avastin) has a positive impact on diabetic retinopathy severity scores.
   E. None of the above statements are true.

5. Which of the following anti-VEGF agents are FDA approved to treat diabetic retinopathy in the setting of diabetic macular edema?
   A. Only Bevacizumab (Avastin)
   B. Only Ranibizumab (Lucentis)
   C. Only Aflibercept (Eylea)
   D. Ranibizumab (Lucentis) and Aflibercept (Eylea)
   E. Ranibizumab (Lucentis) and Bevacizumab (Avastin)

6. Which of the statements regarding the use of anti-VEGF agents in the management of proliferative diabetic retinopathy is true?
   A. Anti-VEGF agents are the gold standard treatment of PDR.
   B. Anti-VEGF agents are superior to pan-retinal laser photocoagulation (PRP laser) in the treatment of PDR.
   C. Pan-retinal laser photocoagulation (PRP laser) remains the gold standard treatment of PDR.

7. Which of the statements regarding the management of proliferative diabetic retinopathy is true?
   A. Anti-VEGF agents cause peripheral visual field defects similar to pan-retinal laser photocoagulation (PRP laser).
   B. Anti-VEGF agents cause peripheral visual field defects worse than pan-retinal laser photocoagulation (PRP laser).
   C. Anti-VEGF agents do NOT cause peripheral visual field defects.
   D. Pan-retinal laser photocoagulation (PRP laser) causes no significant peripheral visual field defects.
   E. Pan-retinal laser photocoagulation (PRP laser) is also the treatment of choice for diabetic macular edema.

8. Which of the following statements about ant-VEGF agents and laser in the management of diabetic retinopathy is true?
   A. Anti-VEGF agents also have a role in the improvement of diabetic retinopathy severity for patients with all levels of diabetic retinopathy, including non-proliferative diabetic retinopathy.
   B. Anti-VEGF agents only have a role in the improvement of diabetic retinopathy severity for patients with proliferative diabetic retinopathy.
   C. Pan-retinal laser photocoagulation (PRP laser) is never used for non-proliferative diabetic retinopathy.
   D. Pan-retinal laser photocoagulation (PRP laser) is only used for PDR management if anti-VEGF monotherapy fails.
   E. None of the above statements are true.

9. Which of the following statements about bevacizumab (Avastin) in the management of diabetic eye disease is true?
   A. It is FDA-approved for the management of diabetic retinopathy.
   B. It is FDA-approved for the management of diabetic macular edema.
   C. It is not FDA-approved for the management of diabetic macular edema or diabetic retinopathy.
   D. It is FDA-approved for the management of other eye diseases.
   E. It is considered an off-label treatment that is in widespread use in the management of diabetic macular edema or diabetic retinopathy.

10. Which of the following statements about anti-VEGF agents is true?
    A. Bevacizumab (Avastin) is much more expensive than aflibercept (Eylea).
    B. Aflibercept (Eylea) and ranibizumab (Lucentis) are much more expensive than bevacizumab (Avastin).
    C. Bevacizumab (Avastin) is much more expensive than aflibercept (Eylea) or ranibizumab (Lucentis).
    D. Bevacizumab (Avastin), aflibercept (Eylea) and ranibizumab (Lucentis) are approximately the same price.