Although of differing etiologies, both diabetic retinopathy (DR) and branch retinal vein occlusion (BRVO) are associated with vision loss resulting from retinal ischemia, edema, hemorrhage, and possibly retinal neovascularization.\(^1,2\) The ischemia of BRVO commonly results from narrowing of arteriovenous crossings and consequent venous compression,\(^2\) while in DR retinal vascular leukostasis, leading to capillary blockage and damage to the retinal vasculature, is believed to be a major contributing factor.\(^1\) Until recently, the principal therapeutic option for BRVO has involved laser photocoagulation to reduce the associated macular edema;\(^2\) similarly, laser approaches have been central in treating both the retinal neovascularization that may accompany DR, as well as the associated diabetic macular edema (DME) that is a major contributor to vision loss.\(^1\)

Over the past 15 years, however, investigations into the underlying molecular and cellular mechanisms of ischemia-related vision loss have clarified the essential role of vascular endothelial growth factor (VEGF) in promoting both edema and retinal neovascularization.\(^1\) In addition to its importance in angiogenesis, VEGF is a potent promoter of vascular permeability and is especially important for the leukostasis that is key to the vascular damage associated with DR.\(^1\) Moreover, VEGF synthesis is upregulated by the hypoxia that accompanies retinal ischemia, and numerous retinal cell types

**Figure 1.** Mean center point thickness in pegaptanib vs control groups (A). Mean center point thickness in patients with baseline thickness greater than 250 µm (B).
have been found to accelerate their production of VEGF in hypoxic conditions.\(^3\) As a result, ocular levels of VEGF are significantly increased in patients with BRVO\(^4\) and DR.\(^1\) It should be noted, however, that VEGF exerts a wide range of essential physiological functions in addition to its pathological effects on retinal neovascularization and vascular permeability; for example, it is now well established that VEGF serves as a survival factor for a wide range of neuronal cell types.\(^5\) This protective function has been especially well characterized for retinal neurons in conditions of ischemia, a context in which only the VEGF\(_{121}\) isoform is required.\(^6\)

To date, two clinically approved intravitreal agents targeting VEGF are available, pegaptanib, an RNA aptamer that binds VEGF\(_{165}\) and larger isoforms while sparing smaller isoforms such as VEGF\(_{121}\),\(^7\) and ranibizumab, a monoclonal antibody fragment that binds all VEGF isoforms.\(^8\) Both are indicated for the treatment of neovascular age-related macular degeneration but have also been studied with promising results in conditions such as DME\(^9\)\(^10\) and BRVO.\(^11\)\(^12\) In addition, bevacizumab, a full-length antibody related to ranibizumab that also binds all VEGF isoforms, has also been used in DME and BRVO.\(^13\)\(^14\)

Given that pegaptanib targets the VEGF\(_{165}\) isoform that exerts most of the pathological effects of VEGF,\(^1\) while sparing the VEGF\(_{121}\) isoform that is protective of retinal neurons stressed by ischemia,\(^6\) we have employed it to treat the vision loss characteristic of two ischemic conditions, DR\(^15\) and BRVO.\(^16\)

**PEGAPTANIB FOR DR AND BRVO: STUDY DESIGN**

This is an open-label study in a private retina specialty practice that assessed the efficacy of pegaptanib treatment of ischemic DR or BRVO. Patient inclusion criteria were younger than 75 years of age; baseline visual acuity of at least 20/800; angiographically documented capillary nonperfusion and/or neovascularization; and ischemia less than or equal to 20 total disc areas. Informed consent was obtained from all patients.

Patients with DR were randomly assigned to receive intravitreal pegaptanib 0.3 mg or usual care. The pegaptanib protocol included pretreatment with topical antibiotics 3 days prior to injection; aseptic/sterile technique with surgical drape and lid speculum for every injection; topical antibiotics prescribed for 5 days postinjection; and intravitreal pegaptanib injections administered at 6-weekly intervals for a minimum of three and a maximum of five injections. Patients receiving usual care were treated clinically according to the “standard of care.”

Patients with BRVO were treated with pegaptanib 0.3 mg according to the administration protocol detailed above.

All patients underwent a full ophthalmic exam (eg, Early Treatment for Diabetic Retinopathy Study visual acuity, intraocular pressure, anterior/posterior segment) and optical coherence tomography (OCT3, Carl Zeiss Meditec, Dublin, CA) at every visit. As clinically indicated, fundus photography and fluorescein angiography were

---

**Figure 2.** Case experiencing resolution of DME.  
**Figure 3.** Case experiencing resolution of neovascularization.  
**Figure 4.** An example of microperimetry improvement.  

---
performed every 4 to 6 weeks and microperimetry (MP1, Nidek, Gamagori, Japan) every 2 to 3 months. Follow-up continued for 3 to 6 months.

**VISUAL OUTCOMES WITH PEGAPTANIB IN DR AND BRVO**

*Diabetic Retinopathy.* In all, 13 DR patients were randomized to treatment with pegaptanib 0.3 mg and six patients were randomized to usual care. Mean center point thickness decreased 5 µm between baseline and week 24 in patients receiving pegaptanib and increased 24 µm in controls (Figure 1A). During the same period, the seven pegaptanib-treated patients with a mean baseline center point thickness greater than 250 µm had a 17 µm reduction (Figure 1B).

Illustrative cases showing resolution of DME and neovascularization are presented in Figures 2 and 3, respectively. Note that dark areas of ischemia appeared to improve (Figure 3). An example of microperimetry improvement is seen in Figure 4.

Accordingly, from baseline to week 24, mean visual acuity increased 0.9 letters in the pegaptanib group and decreased 5.9 letters among controls (Figure 5A). The increase in mean visual acuity was most striking—6.3 letters—among the six pegaptanib-treated patients with baseline visual acuity of fewer than 80 letters (Figure 5B). In this subgroup, visual acuity improved in six of six (100%) patients from baseline to week 6 and was stable or increased in five of six (83%) patients from baseline to week 24.

*Branch Retinal Vein Occlusion.* Mean center point thickness decreased by 82 µm between baseline and week 24 in seven patients treated with pegaptanib 0.3 mg (Figure 6). Decreases in center point thickness were observed in all seven patients between baseline and both weeks 6 and 24.

An illustrative case showing partial resolution of macular edema is presented in BRVO Figure 7. A case suggesting improvement in retinal perfusion is presented in Figure 8. Six subjects had microperimetry examinations at baseline and week 24, and all demonstrated some improvement (example in Figure 9).

Figure 10 provides the mean number of points with different sensitivities showing, from baseline to week 24, a shift toward more
points with higher sensitivities.

Accordingly, from baseline to week 24, mean visual acuity increased by 11.6 letters (Figure 11). Visual acuity improved in all seven patients between baseline and both weeks 6 and 24.

CONCLUSIONS

Anti-VEGF therapy with pegaptanib appears to provide clinical benefit in ischemic retinopathies. When administered over a 6-month period, pegaptanib appeared to improve microperimetry results in the majority of patients with ischemic retinopathies while also improving retinal perfusion in some cases. In general, vision improved or stabilized in patients with DR or BRVO treated with pegaptanib. In contrast, no improvement was observed in DR control patients. These results are encouraging and merit further investigation in larger scale studies.

Michael D. Bennett, MD, is a vitreoretinal surgeon at the Retina Institute of Hawaii in Honolulu and an Associate Professor in the Department of Surgery at the University of Hawaii, John A. Burns School of Medicine. Dr. Bennett is a Retina Today Editorial Board member. Funding for this study was provided as an independent research grant by Eyetech, Inc. Dr. Bennett can be reached at +1 808 955 0255; or fax: +1 808 955 4155.