YOU SAY YOU WANT A REVOLUTION

Antivascular endothelial growth factor agents have dramatically changed the early management of neovascular glaucoma.

BY MARK SLABAUGH, MD, AND MATTHEW OHR, MD

Neovascular glaucoma (NVG) is a potentially blinding disease associated with retinal ischemia. The release of vasoproliferative factors and the subsequent formation and contraction of fibrovascular membranes result in progressive synechial closure of the drainage angle and IOP elevation.

Antivascular endothelial growth factor (anti-VEGF) therapy has revolutionized the initial management of NVG, and it serves as a bridge to panretinal photocoagulation and glaucoma surgery. Several studies have reported the regression of neovascularization and a reduction of ocular pain, IOP, and surgical complications when anti-VEGF agents are used in conjunction with glaucoma surgery.

In this article, Drs. Slabaugh and Ohr discuss currently available anti-VEGF agents in terms of their mechanisms of action and potential side effects, and they review surgical outcomes when these agents are combined with different types of glaucoma surgery.

—Sarwat Salim, MD, section editor

NVG has historically been difficult to manage. This secondary angle-closure glaucoma results from the formation, proliferation, and contraction of a fibrovascular membrane over the iris and trabecular meshwork in the anterior chamber angle. Patients often present with marked pain in the affected eye and acutely elevated IOP. The examination may be difficult, but it typically shows the characteristic iris and angle neovascularization, corneal edema and hyphema, and the inciting posterior segment pathology (Figure 1).

There are several reasons why traditional glaucoma therapies and surgeries are consistently less successful for NVG than in most other types of glaucoma. First, eyes that develop NVG generally have an underlying condition that directly threatens the patient's sight in addition to affecting IOP. The most common predisposing conditions include proliferative diabetic retinopathy, retinal vein occlusion, and ocular ischemic syndrome, all of which require aggressive management directed at the underlying disease that tends to complicate IOP control. Second, the proinflammatory and proliferative cytokines that are released in NVG worsen the outcomes of traditional glaucoma surgeries. Finally, by distorting the iris, lens, and corneal anatomy, anterior segment scarring decreases the effectiveness of glaucoma drainage devices and cycloablative procedures. Fibrovascular membrane contraction may mechanically displace the iris and ciliary body, leading to tube occlusion and insufficient ciliary body energy absorption when laser energy is applied through the sclera.

ANTI-VEGF AGENTS

In the past decade, the use of anti-VEGF agents has dramatically altered the initial management of the underlying conditions that lead to NVG (Figure 2).

AT A GLANCE

- Antivascular endothelial growth factor (anti-VEGF) therapy has revolutionized the initial management of neovascular glaucoma (NVG), and it serves as a bridge to panretinal photocoagulation and glaucoma surgery.
- In the initial management of NVG, anti-VEGF agents are generally delivered via intravitreal injection. After the first dose, neovascularization should visibly decrease within 24 to 48 hours.
- Anti-VEGF therapy alone is not usually sufficient for the long-term control of NVG. The extent of residual angle closure and ciliary body perfusion will determine the IOP and the timing of further intervention.

(Courtesy of Paul Weber, MD.)

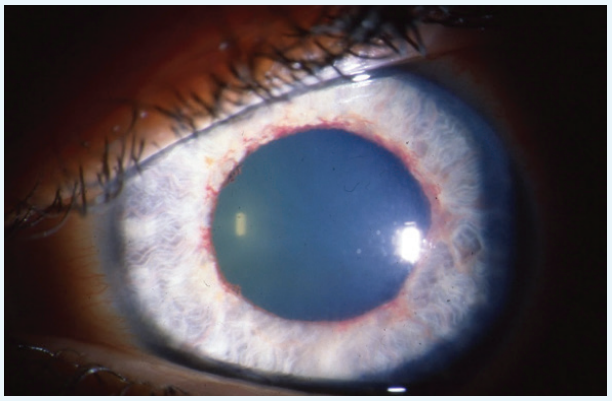

Figure 1. Typical anterior segment findings of rubeosis iridis and early ectropion uveae.

The direct impact of these medications on NVG was initially described with bevacizumab. In subsequent studies, other agents have produced a similar, rapid resolution of the anterior segment neovascularization.[1,2]

In the initial management of NVG, the delivery of the anti-VEGF agents is generally via intravitreal injection, although other methods may be used. Several investigators have reported regression of neovascularization after either the topical or intracameral administration of bevacizumab.[3,4] A complicating factor to the standard intravitreal injection is that patients who present with a new diagnosis of NVG often have a very high IOP, and the additional intraocular volume may further elevate it. These patients are frequently managed medically in the clinic until their IOP decreases to a more acceptable level before the anti-VEGF agents are adminstered. Alternatively, an anterior chamber paracentesis can be performed at the time of the intravitreal injection. In this scenario, there may also be a role for other anti-VEGF delivery methods.

Neovascularization should visibly decrease within 24 to 48 hours after the first dose of the anti-VEGF medication, but that therapy alone is not usually sufficient for long-term control. The extent of residual angle closure and ciliary body perfusion will determine the IOP and the timing of further intervention. Several studies have demonstrated that anti-VEGF injections are also useful adjuncts to standard laser therapy for retinal disease.[5] Panretinal photocoagulation (PRP) should still be performed, if possible, to address the underlying retinal disease and to reduce retinal oxygen demand and the release of VEGF prior to surgical intervention for NVG.

LONG-TERM MANAGEMENT

It is difficult to predict, based on initial presentation, which patients with NVG will eventually require glaucoma surgery. In general, there is a link between more severe retinal ischemia and increased anterior segment neovascularization. However, if the ciliary body is also ischemic, as in ocular ischemic syndrome, the IOP may not be as elevated as expected based solely on the amount of iris and angle involvement.

Once the diagnosis of NVG has been made, the patient's response to medical therapy will dictate the timing of any surgical intervention, and the constellation of pathologic findings will determine the surgical approach. Trabeculectomy or a glaucoma drainage device can provide IOP control, while lens status, vitreous hemorrhage, or tractional retinal detachment will determine what other surgery may be required simultaneously or consecutively.

Historically, glaucoma filtration surgery for NVG had a high rate of failure, and even with adequate control of the underlying condition, visual outcomes were poor. The advent of anti-VEGF agents has greatly enhanced success in controlling active neovascularization. With adequate initial control of the neovascularization, glaucoma surgery for NVG has become possible, although its overall success depends on the long-term management of the underlying condition. Injecting bevacizumab at the time of surgery has not been definitively shown to improve the success of trabeculectomy in NVG compared to the use of mitomycin C alone, although changes in bleb vascularity have been reported.[6] Several investigators have reported similar results with glaucoma drainage devices.[7]

Anti-VEGF agents offer significant benefits in the management of NVG, including less anterior segment bleeding and rapid control

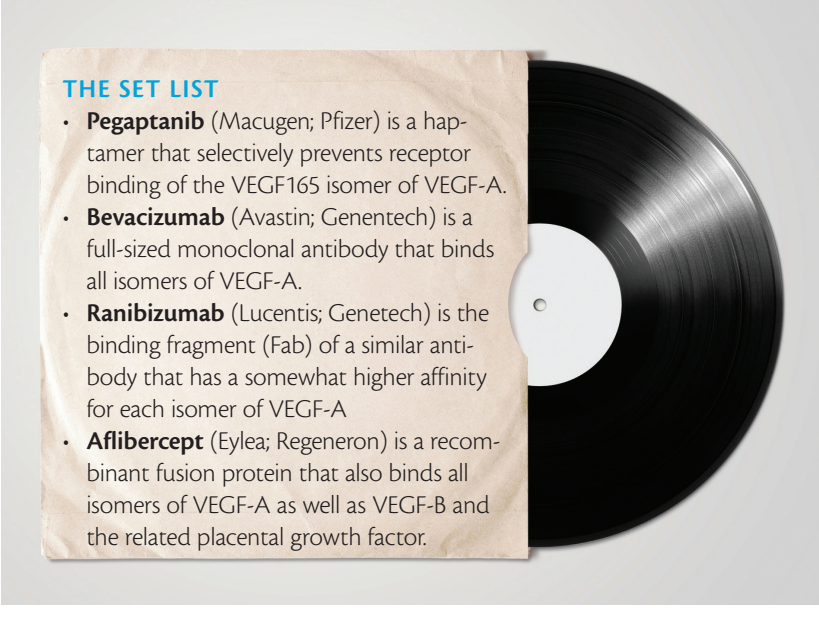

Figure 2. Currently available anti-VEGF drugs.

WATCH IT NOW

Usha Chakravarthy, MD, FRCS, FRCOphth, PhD, shares her thoughts on recent research into the systemic effects of antivascular endothelial growth agents.

of neovascularization, even when the posterior view does not allow for immediate PRP. That said, the long-term visual acuity and IOP outcomes depend more on definitive control of the underlying condition than on perioperative anti-VEGF injections.[8] Unfortunately, visual outcomes remain poor in the presence of severe underlying ocular ischemia. In eyes with limited visual potential, cycloablation may be the initial intervention.[9] Cycloablation can also be used after the placement of a glaucoma drainage device if episodes of neovascularization reoccur.

Some patients who undergo full PRP may have recurrent episodes of anterior segment neovascularization and additional scarring, making their observation and management more challenging. These patients may also have recurrent vitreous hemorrhages or hyphemas in the absence of an identifiable source of bleeding. In this setting, more regularly scheduled anti-VEGF injections seem to decrease the frequency of such episodes.

SIDE EFFECTS

Acute IOP elevation from anti-VEGF injection occurs in all eyes, but with a normally functioning outflow pathway, the IOP of most patients undergoing injections will rapidly return to a normal level. Persistent IOP elevation occurs in a small subset of patients. A number of recent reports document that serial injections carry an increased risk of this problem regardless of the agent used.[10] Some investigators have proposed that elevated IOP is caused by direct trabecular damage, either from the injection or from contaminants, or by a low-lying inflammatory reaction.[11]

Sustained IOP rise is observed with an increased number of injections, although the vast majority of patients undergoing serial injections do so without experiencing an adverse effect on IOP. Closer monitoring of IOP is recommended as the accumulated number of injections increases.

Unexpected conjunctival dehiscence or necrosis has been observed with subconjunctival or intravitreal injections of bevacizumab or ranibizumab. There are reports of blebs that underwent necrosis after injections for age-related macular degeneration despite having been stable for many years.[12] There are also reports of severe conjunctival dehiscence after the placement of glaucoma drainage devices with an intraoperative subconjunctival injection of bevacizumab.[13]

Although most studies document a safer profile with the anti-VEGF agents compared to mitomycin C or 5-fluorouracil, anti-VEGF agents are not without risk, and complications may still occur in a subset of patients.

SUMMARY

The initial management of NVG has been improved with the widespread use of anti-VEGF agents. These drugs effectively induce regression of neovascularization and facilitate the surgical management of NVG, but their impact on long-term visual outcomes remains unclear. Control of NVG requires definitive management of the underlying condition and close follow-up in case additional laser treatment or injections are indicated by the clinical course. A subset of patients may require multiple injections over time despite adequate laser treatment. ■

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