Intravitreal Bevacizumab (Avastin) Injection for Neovascular Glaucoma

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Purpose: To report two cases with neovascular glaucoma secondary to ischemic central retinal vein occlusion (CRVO) who were treated with intravitreal bevacizumab.

Case Report: Two patients were referred for neovascular glaucoma following CRVO. Visual acuity was light perception. Both eyes had extensive iris neovascularization (NVI), synechial angle closure and high intraocular pressure (IOP) in spite of anti-glaucoma medications. After obtaining informed consent, both eye received an intravitreal injection of 2.5 mg (0.1 ml) bevacizumab (Avastin). Both eyes demonstrated dramatic IOP reduction together with decreased severity and extent of NVI during 4 weeks of follow up. Visual acuity remained unchanged.

Conclusion: Despite the dramatic short-term response in terms of IOP reduction and regression of neovascularization, due to limited clinical experience, one should consider this novel indication for bevacizumab cautiously.

INTRODUCTION
Neovascular glaucoma (NVG) is a form of secondary glaucoma in which pathologic fibrovascular tissue grows on the iris and angle structures including the trabecular meshwork. Contraction of this tissue leads to progressive angle closure and elevation of intraocular pressure (IOP) eventually leading to a glaucoma which is poorly responsive to conventional treatment with poor visual prognosis. Ischemic retinal disorders are the most prevalent conditions leading to NVG, however other pathophysiologic mechanisms such as inflammation, retinal detachment, tumors and irradiation may also lead to this condition. Currently, management of NVG is directed toward the underlying disease process, mostly by some form of retinal ablation to reduce the neovascular stimuli, and IOP reduction by means of various forms of medical and surgical therapy.

It is now evident that several mediators are involved in the process of neovascularization, the most important and well studied of which is the vascular endothelial growth factor (VEGF). Regarding the pivotal role of VEGF in ocular neovascularization, inhibition of this mediator seems to have a strong biologic basis for treatment of NVG. Herein we report two patients with NVG who were treated with intravitreal bevacizumab (Avastin), a monoclonal nonselective antibody against VEGF.
CASE REPORT

Case 1

A 49 year-old male patient was referred for pain and visual loss in the right eye following ischemic central retinal vein occlusion (CRVO). The eye had previously undergone full scatter panretinal photocoagulation. Vision was as poor as light perception (LP). Slitlamp examination revealed 360 degree iris neovascularization (Fig. 1) and gonioscopy disclosed near total synechial angle closure. IOP was 44 mmHg on timolol drops Bd and acetazolamide 250 mg every 6 hours. Fundus examination was not possible due to media haziness. The patient was informed of the grave visual prognosis and the course of the disorder and was offered off-label treatment with intravitreal bevacizumab to which he consented. The right eye received a 2.5 mg (0.1 ml) intravitreal injection of bevacizumab (Avastin 100 mg/4 ml, made for Roche, Switzerland by Genentech Inc. USA). One week after the injection, IOP decreased to 30 mmHg which further decreased to 16 mmHg after 2 weeks. At the 4 week follow up examination vision was LP, IOP dropped to 8 mmHg and dramatic reduction in severity and extent of iris neovascularization was evident (Fig. 2).

Case 2

This 51 year-old male patient was also referred for neovascular glaucoma following CRVO in the right eye. Full scatter panretinal photocoagulation had been performed previously and an Ahmed glaucoma valve had been implanted 3 months before referral. Vision was LP. Slitlamp examination revealed extensive iris neovascularization and gonioscopy disclosed total synechial angle closure. IOP was 42 mmHg on timolol Bd. On fundus examination, the optic nerve head had near total cupping. This patient was also offered off-label treatment with intravitreal bevacizumab after obtaining informed consent. This eye also received 2.5 mg (0.1 ml) intravitreal bevacizumab. IOP decreased to 34, 22 and 10 mmHg after one, two and four weeks respectively, the caliber of iris new vessels also decreased markedly and vision was unchanged at LP.

DISCUSSION

This report demonstrated the efficacy of intravitreal bevacizumab in regression of new vessels and reduction of IOP in the setting of NVG which is in accordance with two other recently published case reports. However the dose...
used in our patients was higher than the two previous reports and also higher than studies on intravitreal bevacizumab injection for other retinal disorders such as age related macular degeneration (ARMD), CRVO and diabetic retinopathy. The higher dosage we selected was based on the assumption that the target tissue and extent of pathologic neovascularization in NVG is much greater than limited conditions such as choroidal neovascular membrane or macular edema. Furthermore, this 2.5 mg dose has not been shown to be associated with retinal toxicity in animal models and other experimental studies utilizing up to 5 mg of intravitreal bevacizumab.

Ocular ischemic disorders account for 97% of cases with NVG. The most common disorders leading to NVG are diabetes mellitus, CRVO and the ocular ischemic syndrome. There is adequate evidence supporting the role of VEGF in the pathogenesis of ocular neovascularization and studies have confirmed the increased levels of VEGF in glaucoma and NVG in particular. However other mediators such as insulin like growth factors I and II, insulin like growth factor binding proteins 2 and 3, basic fibroblast growth factor, platelet derived growth factor, interleukin 6, pigment epithelium-derived growth factor, angiopoietins and extracellular matrix factors have also been implicated in pathological angiogenesis.

VEGF, a member of the platelet derived growth factors, was isolated in the 1980's. It was recognized initially as a tumor derived factor leading to increased vascular permeability and subsequently as an endothelial cell mitogen. VEGF levels are increased in ischemic-hypoxic conditions. Alternate splicing of the VEGF gene leads to 4 major human isoforms with 121, 165, 189 and 208 amino acids. The VEGF165 isoform is the most important subtype in the eye responsible for pathologic ocular neovascularization. VEGF also exhibits pro-inflammatory and neuroprotective properties under physiologic conditions. Under conditions of retinal ischemia, Muller1 and RPE3 cells play key roles in production of VEGF. On the other hand the lens and the vitreous seem to possess vasoinhibitory properties which may explain the higher incidence of pathological neovascularization after cataract surgery and vitrectomy. Experimental elevation of VEGF levels induces typical neovascularization and several studies have shown that specific inhibition of VEGF inhibits pathological neovascularization in the iris, choroid, cornea and retina. Inflammation also seems to facilitate the neovascularization process which explains the basis for management of neovascular disorders with anti-inflammatory steroids such as triamcinolone and cortisone and angiotastic steroids like anecortave acetate.

The two anti-VEGF agents available for clinical use are bevacizumab (Avastin) and pegaptanib. Bevacizumab is a humanized murine antibody which binds all isoforms of VEGF. It is approved by the Food and Drug Administration (FDA) for treatment of metastatic colorectal cancer and in phase III studies for advanced breast and renal cancer. Ranibizumab which is an antibody fragment of bevacizumab (currently in phase III clinical trial for neovascular ARMD) also nonspecifically binds to all VEGF isoforms. Pegaptanib is an aptamer, a synthetic oligonucleotide with three-dimensional conformation capable of binding to a wide range of molecular targets. Pegaptanib is capable of selective binding to VEGF165, the isoform responsible for pathologic ocular neovascularization. Potential advantages of this agent include less interference with physiologic functions of other isoforms of VEGF such as neuroprotection. Pegaptanib has been FDA approved for all types of neovascular ARMD.

This report demonstrates the potential for intravitreal bevacizumab (Avastin) as a treatment option for NVG. Intravitreal injection of this agent bypasses the blood ocular barrier and provides high local concentrations without exposing the patient to serious events associated with systemic administration such as thromboembolism, hypertension, epistaxis, hemoptysis, proteinuria, gastrointestinal hemorrhage and wound healing complications. Despite the dramatic short-term effect on regression of iris neovascularization and IOP reduction, due to
limited clinical experience one should consider this novel indication for bevacizumab cautiously. Larger studies and randomized trials are needed to verify the outcomes thus far observed, and determine the duration of effect, need for multiple injections and possible adverse effects.

REFERENCES

4- Avery RL. Regression of retinal and iris neovascularization after intravitreal bevacizumab (Avastin) treatment. Retina 2006;26:352-354.