



Role of Anti-VEGF (Bevacizumab) in Management of Neovascular Glaucoma: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i40A32237

Editor(s):

(1) Dr. R. Deveswaran, M.S. Ramaiah University of Applied Sciences, India.

Reviewers:

(1) Partha Chakraborty, Univeristy Hospitals Sussex NHS Foundation Trust, England.

(2) Fatemeh Tabatabaie, Iran University of Medical Sciences, Iran.

Complete Peer review History: <https://www.sdiarticle4.com/review-history/70921>

Review Article

**Received 25 May 2021
Accepted 31 July 2021
Published 06 August 2021**

ABSTRACT

Neovascular glaucoma (NVG) is an aggressive type of glaucoma, which often results in poor visual outcomes. Antivascular endothelial growth factor is frequently used for various conditions in which VEGF release is induced in response to retinal ischemia. Bevacizumab is a humanized anti-VEGF monoclonal IgG1 antibody. The potential of antivascular endothelial growth factor (anti-VEGF) agents to modify the disease course of neovascular glaucoma (NVG) was recognized shortly after their use in the treatment of age-related macular degeneration was reported. These medications were noted to induce rapid regression of the anterior segment neovascularization that characterizes NVG. Several studies as well as extensive clinical experience have demonstrated a rapid regression of anterior segment neovascularization following the injection of anti-VEGF agents. This review aims to summarize current evidences regarding effectiveness of Bevacizumab in management of neovascular glaucoma.

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Keywords: Anti-VEGF; Bevacizumab; neovascular glaucoma.

1. INTRODUCTION

Neovascular glaucoma (NVG) is an aggressive type of glaucoma that often causes poor visual results. It is known as hemorrhagic glaucoma, thrombotic glaucoma, congestive glaucoma, rubeotic glaucoma and diabetic hemorrhagic glaucoma [1]. Based on the number of investigations and experimental studies, the pathophysiological basis of neovascularization (NV) or NVG is retinal capillary non-perfusion, retinal ischemia or uveal capillary insufficiency due to primary or secondary diseases. , such as proliferative diabetic retinopathy (PDR), retinal venous obstruction (VOR),occlusive ischemic syndrome (OIS) and some uncommon eye causes such as uveitis, eye tumors and other retinopathies. Unlike the initial compensation, neovascularization brings more pathological catastrophe than an improvement in circulation in the eye [2].

Although the prevalence of NVG is generally low, it contributes to significant vision loss and morbidity. The rate of NVG in the population is as low as 0.12% [3]. In hospital studies, the percentage of eyes with NVG among secondary glaucoma was 9 to 17.4% [4]. Antivascular endothelial growth factor is frequently used for various conditions in which VEGF release is induced in response to retinal ischemia. Anti-VEGFs such as bevacizumab (Avastin), pegaptanib sodium (Macugen), and ranibizumab (Lucentis) block angiogenic factors that promote the formation of new vessels, reversing the neovascularization process [5]. The potential of antivascular endothelial growth factor (anti-VEGF) agents to modify the disease course of neovascular glaucoma (NVG) was recognized shortly after their use in the treatment of age-related macular degeneration was reported. These medications were noted to induce rapid regression of the anterior segment neovascularization that characterizes NVG [6,7]. The amount of growth factors in aqueous solution decreased after intravitreal injection of antiVEGF, reducing the progression of angular damage following an increase in IOP [8]. Inhibition of VEGF in the ocular vasodilator trial (VISION) demonstrated that 70% of patients treated with pegaptanib had less than three lines of vision loss compared to 55% of controls ($p < 0.001$). Unfortunately, a small number of patients have achieved vision with this therapy [8]. However, other investigators have reported

the lack of efficacy of oral bevacizumab in the treatment of iris neovascularization and arterial angle [9]. This review aims to summarize the current evidence regarding the efficacy of bevacizumab in the treatment of neovascular glaucoma.

1.1 Mode of Action of Anti-VEGFs (Bevacizumab)

The pathogenesis of NVG involves the promotion of neovascularization in the anterior chamber angle and specifically the iris. Neovascularization is mediated by pro-angiogenic factors produced in the retina as a result of ischemia; these factors eventually diffuse into the anterior chamber. As a result, a fibrovascular membrane forms in the iris, the anterior chamber angle, or both. The subsequent contraction of the membrane pulls peripheral iris into the angle leading to the development of secondary angle-closure glaucoma. The successful management of NVG requires adequate control of IOP as well as a targeted therapy directed at the ischemic condition causing the neovascularization [2].

Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) is a humanized anti-VEGF monoclonal IgG1 antibody (molecular weight, 149 kDa) [10]. It is derived from the murine VEGF monoclonal antibody, combining over 90% human protein sequence with about 7% murine protein sequence. The product is formulated in alpha-trehalose dihydrate, sodium phosphate (monobasic, monohydrate), sodium phosphate (dibasic, anhydrous), polysorbate and water for injection [11].

VEGF is a dimeric glycoprotein of 36-46 kD which binds on the surface of endothelial cells and initiates endothelial proliferation and the formation of new blood vessels (angiogenesis). This growth factor plays a key role in developmental angiogenesis, being one of the most potent positive regulators, and also demonstrated to act as a mediator of pathological angiogenesis. VEGF is a potent mitogen and survival factor for endothelial cells. (VEGF)-A seems to represent the primary target of recent anti-angiogenic strategies [11]. Bevacizumab (Avastin, Roche) acts by inhibiting the binding of VEGF to its receptors, thus preventing the angiogenesis. Bevacizumab is humanized monoclonal antibody designed against the biologically active isoforms of VEGF-A [12].

In the eye, VEGF is mainly produced by vascular endothelial cells or pericytes and also by retinal neurons and astrocytes, Müller cells, retinal pigment epithelium, and non-pigmented ciliary epithelium [13]. Low-oxygen conditions cause upregulation of VEGF through the induction of HIF-1 and the consequent transcriptional activation of target genes [14]. Increased VEGF transcription and upregulation of angiogenesis serve to restore oxygen and nutrition supply for tissues affected by hypoxia [15]. VEGF may also contribute to the inflammatory process by inducing the expression of vascular cell adhesion molecule 1 (VCAM-1) enhancing leukocyte recruitment and endothelial cell adhesion and increasing blood-retinal blood barrier breakdown [16]. Beside angiogenesis, inflammation may also be involved in the development and progression of eye diseases such as retinal vein occlusion (RVO), diabetic retinopathy, neovascular age-related macular degeneration (AMD), or neovascular glaucoma [15].

Several studies as well as extensive clinical experience have demonstrated a rapid regression of anterior segment neovascularization following the injection of anti-VEGF agents.

A prospective, interventional case series included 50 patients (51 eyes) with NVG divided into central retinal vein occlusion (CRVO) and proliferative diabetic retinopathy (PDR) followed up for 6–30 months reported that; 39 eyes displayed controlled IOP (≤ 21 mmHg) after treatment. Visual acuity was relatively improved in 32 eyes (72.9 %), and 12 eyes (27.3 %) had a visual acuity better than 0.1. No significant difference in IOP between the PDR and CRVO groups at the end of follow-up was reported but the visual acuity in the PDR group was much better than that in the CRVO group [17].

Wakabayashi et al evaluated the clinical outcomes of intravitreal bevacizumab (IVB; Avastin, Genentech) injection in NVG secondary to ischemic retinal disease and presented results based on this continuum. They found that, when NVI was present without elevated IOP, injections resulted in regression of the neovessels, and the IOP remained normal. Some patients in the NVI-only group required repeat injections. When NVI or NVA was present with open angles and elevated IOP, 40% of patients eventually required surgery to lower their IOP. When NVA and angle closure were present, more than 90% of patients needed glaucoma surgery and IVB to

control the IOP.6 A randomized controlled study by Yazdani et al showed that, when compared with sham injections, three monthly IVB injections for NVG resulted in a lower IOP and a greater regression of NVI, but the researchers did not observe a difference in rates of surgery or final visual acuity [18].

Ishibashi et al found that, although NVI disappeared clinically 4 to 6 days Anti-VEGF Therapy and Neovascular Glaucoma Intravitreal injections improve visual outcomes, but the careful monitoring of patients after treatment is necessary [19]. Waisbourd et al. [20] the efficacy of topically applied bevacizumab for the treatment of NVG was evaluated. Eight patients were treated with topical bevacizumab (25 mg/mL) four times daily for 2 weeks. The authors observed a mean IOP reduction of 6.1 mmHg and noted that three patients had clinical regression of iris neovascularization. Wasik, Alyon et al. [21] conducted a case study and reported possible beneficial effects of bevacizumab in conjunction with panretinal photocoagulation as a treatment option for neovascular glaucoma.

Grover et al. [22] reported a considerable reduction in aqueous humor VEGF concentrations following an intracameral injection of bevacizumab. Yazdani et al. [23] investigated the effect of intravitreal bevacizumab on NVG in a randomized controlled trial with 26 eyes from 26 patients. All eyes received conventional treatment for NVG and were randomly allocated to three 2.5 mg intravitreal bevacizumab injections at 4-week intervals or a sham procedure. Authors concluded that intravitreal injections of bevacizumab reduced iris neovascularization and IOP in NVG and may be considered as an adjunct to more definitive surgical procedures for NVG. In the same context, a 12-month prospective clinical series published by Lüke et al. [24], 10 cases with NVG received intraocular injections of RBZ (0.5 mg/0.05 mL). According to the authors, RBZ appeared to be beneficial owing to its anti-angiogenic properties and its ability to prevent or halt anterior chamber angle occlusion.

Wittstrom et al. [25] investigated the effect of a single intravitreal injection of bevacizumab for NVG after ischemic central retinal vein occlusion. Alkawas, Ayman A et al. [26] conducted a study to evaluate the safety and efficacy of using intravitreal bevacizumab, panretinal photocoagulation, and trabeculectomy with

mitomycin C in the management of neovascular glaucoma. The study included 17 eyes of 15 patients with neovascular glaucoma and concluded that trabeculectomy with intraoperative mitomycin C after an adjunctive treatment with intravitreal bevacizumab and panretinal photocoagulation is a good treatment modality in the management of eyes with neovascular glaucoma.

A systematic review and meta-analysis conducted by Simha, Arathi et al. to assess the effectiveness of intraocular anti-VEGF medications, alone or with one or more type of conventional therapy, compared with no anti-VEGF medications for the treatment of NVG included four RCTs (263 participants) and identified one ongoing RCT reported that available evidence is uncertain regarding the long-term effectiveness of anti-VEGF medications such as bevacizumab as an adjunct to conventional treatment in lowering IOP in NVG [27].

Costagliola, Ciro et al. conducted a prospective pilot trial with clinical data of 26 eyes from 23 patients and reported that; regression of corneal oedema together with significant pain reduction was achieved in all eyes already after the first IVB, without any noteworthy improvement of visual acuity. At the end of the scheduled protocol (three IVB), regression of iris neovascularization was documented in all patients, together with significant improvement of visual acuity. The IOP reduction from baseline ranged from 30 to 0 mmHg (12.1 ± 8 mmHg) [28].

Zhou et al. [29] conducted a systematic review to evaluate the efficacy and tolerability of Ahmed glaucoma valve implantation with intravitreal bevacizumab injection pretreatment in the treatment of NVG and found that the intravitreal bevacizumab group was associated with significant greater complete success rates compared with the control group. However, it did not show a significant difference for the qualified success rate between them. In addition, the intravitreal bevacizumab group was associated with a significantly lower frequency of hyphema than the control group. However, in a recent retrospective, comparative, case series conducted by Olmos et al. [30] intravitreal injection of bevacizumab was not superior than panretinal photocoagulation. The study included 163 eyes of 151 patients with NVG, including 99 treated without and 64 treated with intravitreal

bevacizumab. They found that IOP decreased to 18.3 ± 13.8 mmHg in the non-bevacizumab group and 15.3 ± 8.0 mmHg in the bevacizumab group. Panretinal photocoagulation substantially reduced the need for glaucoma surgery ($P < 0.001$) in bevacizumab treated NVG eyes. Therefore, although bevacizumab delayed the need for glaucoma surgery, panretinal photocoagulation was the most important factor that reduced the need for surgery. Vision and IOP in eyes with NVG treated with bevacizumab showed no long-term differences when compared with eyes that were not treated with bevacizumab. Thus, intravitreal bevacizumab serves as an effective temporizing treatment, but is not a replacement for close monitoring and definitive treatment of NVG.

Another prospective, noncomparative interventional case series was conducted to assess the efficacy of preoperative intravitreal bevacizumab with guarded filtration surgery and mitomycin C in neovascular glaucoma where patients received 1.25 mg of intravitreal bevacizumab and repeated if needed. The intraocular pressure in 3 cases was controlled after receiving bevacizumab. In 23 cases that underwent filtering surgery and completed at least 6 months of follow-up, the mean preoperative and last visit intraocular pressure was 43.3 ± 10.0 mmHg and 20.6 ± 5.4 mmHg, respectively ($P < 0.001$). The qualified success rate was 61% at final visit. Neither the significant intraoperative nor postoperative complications were noted. Authors concluded that preoperative intravitreal bevacizumab combined with guarded filtration surgery with mitomycin C is a safe and effective method of controlling intraocular pressure in neovascular glaucoma [31].

Regarding Subconjunctival injections; Grewal administered subconjunctival bevacizumab in a pilot study involving 12 patients with open-angle and closed-angle glaucoma at the end of glaucoma surgery. During surgery, no other fibrous agents were used. Success, defined as a drug-free IOP of < 16 mmHg, was achieved by 11 patients (92%) at 6 months. Mean IOP decreased to 11.6 mmHg without additional medication [32].

In Choi et al. Six eyes with refractory glaucoma that had received laser treatment or surgery were included. They underwent orbitectomy with MMC and received an injection of 1.25 mg of bevacizumab at the end of the surgery [33].

Another study group compared the effects of bevacizumab and 5FU in addition to cervical spine surgery. They found no significant difference in IOP between the two groups at the end of the study, but medical treatment was needed to achieve successful IOP for more patients in the bevacizumab group. In contrast, adjuvant bevacizumab resulted in a slight decrease in the number of corneal endothelial cells [34].

Regarding adverse events; Higashide, Tomomi et al. [35] retrospectively reviewed the histograms of 84 eyes of 70 patients with neovascular glaucoma who received intravitreal bevacizumab for first-line segmental neovascularization to study the occurrence of adverse events associated with intravitreal injection of bevacizumab in patients with neovascular glaucoma. The total number of intraocular bevacizumab injections was 116 (1.4 ± 0.8 injections/eye, range, 1-5 injections/eye). Most are intravitreal injections (1.25 mg/0.05 ml; 115 injections, 99%). There were no cases of marked inflammation, vitreous injury, obvious vitreous hemorrhage, retinal detachment or endophthalmitis. However, two eyes (2%) out of two cases (3%) developed central retinal artery occlusion 3 or 4 days after bevacizumab injection. Both were among the four eyes (ie, 50%) with ocular ischemic syndrome. One of them had received bevacizumab (0.75 mg / 0.03 ml) by mouth before the onset of side effects. There have been no cases of systemic side effects, including myocardial infarction and stroke, within 3 months of being injected with bevacizumab. Poku, Edith et al. conducted a systematic review to assess the safety of Intravitreal bevacizumab (IVB) as monotherapy and to assess the relationship between treatment quality and adverse events.

22 RCTs and 67 observational studies were included. Only two RCTs reported valid safety data. The rate of serious adverse events after treatment is low [36]. Kotecha et al reported a case of temporary central artery occlusion immediately after IVB that was associated with an IOP of 57 mm Hg and resolved after an anterior chamber paracentesis was performed. They also found that, compared with the angle's configuration at baseline, 6 months after IVB, 35% of patients had progressive angle closure which could be due to recurrent neovascularization or the progressive contraction of the preexisting vascular tissue in the angle [37].

2. CONCLUSION AND FUTURE RECOMMENDATIONS

Bevacizumab appears to be effective in the managing of neovascular glaucoma. Researchers have attempted various routes of bevacizumab administration with potential ocular effects, including intravitreal injection, intracameral injection, sub conjunctival injection and topical administration. Future research with larger sample sizes is needed to investigate the long-term effect of these medications compared with, or in addition to, conventional surgical or medical treatment in lowering IOP in NVG.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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