

## Clinical use of Bevacizumab in treating refractory glaucoma

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### Abstract

Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). Though other VEGF inhibitors are being approved for the treatment of ophthalmological conditions, bevacizumab found its way into ophthalmology and clinical practice all around the world.

The objective of this review is to present the ophthalmic dosage and administration pathways of bevacizumab in treating refractory glaucoma patients.

**Keywords:** bevacizumab, glaucoma, trabeculectomy, vascular endothelial growth factor

**Abbreviations:** VEGF = vascular endothelial growth factor, FDA = Food and Drug Administration, AMD = age-related macular degeneration

### Introduction

Medications, such as ranibizumab, pegaptanib, aflibercept and bevacizumab, action by inhibiting vascular endothelial growth factor (VEGF). As a consequence, they inhibit angiogenesis. Although only pegaptanib and ranibizumab are approved for treatment of ophthalmological conditions, bevacizumab is also used in ophthalmology as an off-label drug since 2004 [1]. Bevacizumab is Food and Drug Administration (FDA) approved for the treatment of colorectal cancer [2,3]. Despite its off-label use, bevacizumab is the most widely used anti-VEGF factor in ophthalmology [4,5].

### Mechanism of Action and Pharmacokinetics

In 1971, Judah Folkman reported in the "New England Journal of Medicine" that all cancer tumors are angiogenesis-dependent [6]; he was the first to use the term "anti-angiogenic therapy" and bevacizumab became the first therapy approved by the US FDA designed to inhibit angiogenesis in tumors [7].

VEGF represents an angiogenic inducer in vivo and an endothelial cell-specific mitogen in vitro. 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 [8]. VEGF is a potent mitogen and survival factor for endothelial cells. (VEGF)-A seems to represent the primary target of recent anti-angiogenic strategies.

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 [8]. It is derived from the murine VEGF monoclonal antibody, combining over 90% human protein sequence with about 7% murine protein sequence [9]. Bevacizumab has a molecular weight of about 149kD, with structure of recombinant IgG antibody. Bevacizumab is preconditioned as a clear to slightly opalescent, colorless to pale brown, sterile solution with slightly acidic pH of 6.2. The product is formulated in alpha-trehalose dihydrate, sodium phosphate (monobasic, monohydrate), sodium phosphate (dibasic, anhydrous), polysorbate and water for injection.

Bevacizumab has a longer systemic half life, compared with other VEGF inhibitors (e.g. ranibizumab), due to its glycosylated structure [10]. Despite the fact that it is not approved for intravitreal use [11], it is often used as an off-label drug by ophthalmologists. This anti-cancer drug found its way in ophthalmology and clinical practice all around the world because the costs of the therapy with bevacizumab are much lower than with other similar VEGF inhibitors. Ranibizumab is a humanized antibody fragment (Fab) directed against VEGF-A produced in an E. coli expression system which was specifically designed for intravitreal use and which was approved for use in EU and USA. Although there are several ongoing trials that compare the two medications [12,13], the differences between the two drugs regarding safety and efficacy are still debatable.

**Clinical Use in Ophthalmology**

The mainstay treatment of exudative form of age-related macular degeneration (AMD), which is one of the most encountered ocular pathologies, is represented by intravitreal injection of anti-VEGF. Despite the fact that there are a couple of anti-VEGF types of drugs currently approved for intraocular use, off-label use of bevacizumab continues to be most widely spread among ophthalmologists.

Although the primary use of bevacizumab in ophthalmology remains the treatment of exudative AMD, a lot of other ocular entities are treated nowadays with this medication (Table 1).

**Table 1.** Ocular entities that can be treated with bevacizumab

<b>Ocular pathologies treated with Bevacizumab</b>	
<b>Retinal neovascularization</b>	Proliferative diabetic retinopathy Central retinal vein occlusion Branch retinal vein occlusion Central retinal artery occlusion Ocular ischemic syndrome Retinopathy of prematurity Sickle cell retinopathy
<b>Choroidal neovascularization</b>	Exudative age-related macular degeneration Angioid streaks Pathologic myopia Best disease Multifocal choroiditis Central serous chorioretinopathy Uveitis
<b>Pterygium</b>	
<b>Macular edema</b>	Diabetic retinopathy Pseudophakic Branch retinal vein occlusion Central retinal vein occlusion Uveitic

<b>Corneal neovascularization</b>	Corneal graft rejection neovascularization Herpetic corneal neovascularization Dry eye associated corneal neovascularization
<b>Glaucoma surgery</b>	Adjunct to glaucoma filtering surgery Bleb revision
<b>Neovascular glaucoma</b>	

**Ophthalmic dosage and administration**

Bevacizumab can be administered for refractory glaucoma using various pathways: intravitreal, topical, subconjunctival and intracameral.

1. Intravitreal administration

The use of anti-VEGF agents has expanded greatly over lasts years to include corneal neovascularization and neovascular glaucoma. Human clinical studies were performed because the key pathologies of neovascular glaucoma are iris neovascularization and fibrovascular membrane proliferation in the iridocorneal angle. A lot of studies reported a reduction of iris neovascularization and/or reduction of IOP after intravitreal bevacizumab injections in neovascular glaucoma [14]. Another study noted complete or partial reduction of leakage in iris fluorescein angiography after intravitreal or intracameral injections of bevacizumab [15-17]. Subsequently, larger case series reported the potential value of bevacizumab in the treatment of neovascular glaucoma [18]. Combined with panretinal photocoagulation, intravitreal bevacizumab produce a faster decrease in IOP [19]. Treatment regimen comprises of 1.25 mg/ 0.05 ml bevacizumab injected into vitreal cavity, in single or multiple administrations depending on the clinical response. Clinical trials compare various administration frequencies. Cornish et al. used for the first time bevacizumab as adjunct to trabeculectomy. After intravitreal injection post trabeculectomy with MMC, IOP was maximum 15mmHg without glaucoma medication at 6 month.

2. Topical administration

Topical administration is a potential treatment modality for corneal neovascularization and neovascular glaucoma. There are studies that confirm the efficacy of high dose 25 mg/ ml bevacizumab instillations administered twice daily [20,21], four or five times daily [22]. In eyes with a high risk of failure, topical application might favor normal bleb function, with a significantly lower proportion of bleb leaks. Corneal penetration of bevacizumab was demonstrated to be extremely low even at higher doses and following more prolonged treatment algorithms [23-26]. If corneal epithelium is intact, it should represent an effective barrier that cannot be penetrated by molecules larger than 1 nm [27]; bevacizumab size is approximately 12 nm, therefore it does not reach significant intraocular levels. When epithelial defects are

present, bevacizumab can penetrate cornea [28] and alters corneal healing process, also causing stromal melting after prolonged use [29-31].

Considering the above mentioned characteristics and despite several studies that reported safety profiles for topical administration, intraocular penetration may occur after prolonged topical administration of bevacizumab in patients with corneal neovascularization and epithelial defects [29,32-34]. While the median inhibitory concentration in vitro of bevacizumab was found to be 22 ng/ml, the minimal concentration effectively blocking endothelial cell proliferation induced by VEGF was 500 ng/ml [35]. This result shows that, by topical administration, therapeutic efficacy will be obtained with minimal risks for intraocular or systemic adverse effects [24].

### 3. Subconjunctival administration

Subconjunctival administration can be used for recurrent pterygium, for bleb failure modulation after glaucoma surgery, for corneal neovascularization etc. The dosage ranges between 1.25 mg and 2.5 mg. Nomoto et al demonstrated in his study on rabbit eyes that bevacizumab applied subconjunctivally had a longer half-life than intravitreal administration [36]. Grewal used subconjunctival bevacizumab in a pilot study of 12 patients with open and closed angle glaucoma at the end of glaucoma surgery. During surgery, no other fibrotic agent was used. Success, defined as IOP of 6-16 mm Hg without medication, was achieved by 11 patients (92%) at 6 months. Mean IOP decreased to 11.6 mm Hg with no additional medication. Another research team compared the effects of bevacizumab and 5-FU as adjunct to trabeculectomy. They found no significant differences of IOP between the two groups at the end of the study, but medical therapy was needed to obtain successful IOP for more patients in bevacizumab group. On the other hand, adjunctive bevacizumab caused minor reduction in corneal endothelial cell count.

In Choi et al. case series study, were included six eyes with refractory glaucoma which undergone laser or surgical treatment. They underwent trabeculectomy with MMC and received a subconjunctival injection of 1.25 mg bevacizumab at the end of the surgery.

Based on the favorable results of this study, this report suggests that bevacizumab administered subconjunctivally may be effective in improving glaucoma filtration surgery.

The largest prospective randomized double-masked study was realized by Vandewalle et al. This trial investigates the utility of anti-VEGF as adjunct to glaucoma surgery. Bevacizumab was administered as a single intracameral injection at the end of trabeculectomy. The absolute success was significantly higher in bevacizumab group. An important fact is that IOP at the

end of the study was similar in bevacizumab and placebo group, but at a cost of more frequent needlings in the placebo group.

### 4. Intracameral administration

The use of anti-VEGF drugs may be appealing for glaucoma patients because high levels of VEGF were found in their aqueous humor [37,38]. Intracameral administration (1.25 mg/ 0.05 ml) of bevacizumab is lately used as a replacement or as an adjunctive to antimetabolites for glaucoma filtration surgery. The largest prospective randomized double-masked study was realized by Vandewalle et al. Bevacizumab was administered as a single intracameral injection at the end of trabeculectomy. The absolute success was significantly higher in bevacizumab group. An important fact is that IOP at the end of the study was similar in bevacizumab and placebo group, but at a cost of more frequent needlings in the placebo group [39].

## Conclusion

The use of unlicensed treatments in medicine is currently under debate, with wide implications for patient safety and informed consent.

Bevacizumab use in ophthalmology targets a large number of ocular entities as an off-label drug, due to its low cost and good safety profile. Because its multiple ways of administration bevacizumab can be used for the treatment of more than 20 ophthalmic pathologies.

Anti-VEGF therapies may play a role in arresting or reversing the progression of glaucomatous disease, because of their potential inhibitory effect on postoperative new vessels growth and fibroblastic proliferation at the site of the bleb.

Over the past few years, many studies have investigated the utility of anti-VEGF agents in the treatment of NVG and filtering bleb survival and rescue. Investigators have tried different routes of bevacizumab administration with potential ocular effects, including intravitreal injection, intracameral injection, subconjunctival injection and topical administration. Through future research, the antiangiogenic and antifibroblastic properties of anti-VEGF agents may prove to be beneficial in patients being treated for various forms of the blinding condition of glaucoma.

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