Despite the introduction of various modern and minimally invasive glaucoma procedures, trabeculectomy is still considered to be the most effective treatment for glaucoma and the cornerstone of management for this potentially blinding condition.\textsuperscript{1} It is a rather unique surgical procedure in medicine, because prevention of wound healing is crucial for surgical success.\textsuperscript{2} Indeed, progressive fibroblast proliferation and collagen deposition at the site of the filtration bleb, and development of fibrosis in the conjunctiva and episclera are the most common causes of trabeculectomy failure.\textsuperscript{2,3} Thus targeting the healing process is highly important for success in trabeculectomy. In current practice, perioperative anti-mitotic agents such as mitomycin C (MMC) and 5-fluorouracil (5-FU) are administered to improve surgical success;\textsuperscript{4} however, these agents carry a significant risk of vision-threatening complications such as toxicity to the corneal endothelium, scleral thinning, hypotony, bleb leakage, blebitis and endophthalmitis.\textsuperscript{1,5-7} Because of these, there is a need for more targeted and effective antiscarring interventions.

Wound healing involves a complex interaction between humoral and cellular responses, and occurs through four interconnected processes: clot formation, angiogenesis, inflammation and collagen deposition. Among these components, angiogenesis plays a key role because it provides the substrate for wound healing at the site of injury.\textsuperscript{8} Vascular endothelial growth factor (VEGF), as an endothelial and permeability factor, has a prominent role in physiological and pathological angiogenesis. However, beside angiogenesis it can stimulate many non-vascular cells, such as Tenon’s fibroblasts.\textsuperscript{9} It is hypothesized that VEGF may be a survival factor for certain non-angiogenic blood vessels in adults.\textsuperscript{10}

VEGF has three high affinity receptors, among which, VEGF-R2 mediates most of its biologically relevant responses, including cell migration and proliferation.\textsuperscript{11} Various isoforms of VEGF, such as VEGF\textsubscript{121}, VEGF\textsubscript{165} and VEGF\textsubscript{189}, result from alternate splicing of a single VEGF-gene; these isoforms differ in the number of amino acids, molecular weight, and co-receptor binding properties.\textsuperscript{12,13} While various isoforms have the same affinity for VEGF-R2 receptor,\textsuperscript{14,15} they significantly differ in their affinity to VEGF co-receptors, such as neuropilin-1 (NRP-1) and heparin sulphate proteoglycans (HSPGs). Because of this variation, differential tissue effects have been demonstrated for various isoforms: VEGF\textsubscript{165} and VEGF\textsubscript{121} predominantly affect blood vessel growth and angiogenesis, while VEGF\textsubscript{189} has a more prominent role in fibrosis and wound healing processes.\textsuperscript{16}

As mentioned above, VEGF has potential direct and indirect roles in wound healing and there are reports of delayed wound healing and an increased incidence of wound dehiscence following systemic use of bevacizumab.\textsuperscript{17,18} Several investigators demonstrated that VEGF is present in aqueous humor samples of glaucoma patients undergoing filtering surgery and its receptors are expressed on Tenon’s fibroblasts.\textsuperscript{9,19,20} At the filtering site, VEGF could modify fibroblast activity and stimulate collagen cross-linking and contraction, resulting in scar formation.\textsuperscript{9} Moreover, higher VEGF levels in Tenon’s tissue preoperatively are associated with a worse outcome following trabeculectomy surgery.\textsuperscript{20}

Based on these evidences, targeting VEGF to modulate wound healing following...
trabeculectomy surgery has been a hot topic of research over the past few years. Several investigators have tried various anti-VEGF drugs and different administration routes to increase the success of trabeculectomy with variable results (Table 1). 21-37 Most of these studies used bevacizumab (Avastin; Genetech Inc., San Francisco, CA, USA) as the anti-VEGF agent.

Bevacizumab is a full-length recombinant humanized monoclonal antibody against all isoforms of VEGF. It has obtained FDA approval

Table 1. Summary of studies on the use of anti-VEGF agents for filtering surgery*

| N  | Authors Year Design | Anti-VEGF Type of glaucoma | Sample size | Follow-up duration (months) | Success Criteria, IOP (mmHg) | Success rate | IOP reduction |
|----|---------------------|---------------------------|-------------|-----------------------------|--------------------------------|--------------|--------------|
|    | Grewal et al21 2008 Case series Bevacizumab IntraOp/SC POAG PACG 12 6 <16 and >6 or ≥30% Complete: 92% 52% |
| 2  | Cornish et al22 2009 Case series Bevacizumab IntraOp/IVi NVG 2 6 <16 100% 67% |
| 3  | de Moraes et al23 2009 Case series Bevacizumab IntraOp/IC NVG 4 12.75 <16 and >6 100% 77.5% |
| 4  | Alkawas et al24 2010 Case series Bevacizumab PreOp/IVi NVG 17 6 ≤21 Complete: 52.9% Qualified: 35.3% 54% |
| 5  | Choi et al25 2010 Case series Bevacizumab IntraOp/SC NVG UG PostPPV 6 6 <16 100% 67.5% |
| 6  | Fakhraie et al26 2010 Case series Bevacizumab PreOp/IVi NVG 23 6 <21 and >6 Complete: 52.4% |
| 7  | Saito et al27 2010 Case series Bevacizumab PreOp/IVi NVG 52 12 <21 95% 65% |
| 8  | Marey28 2011 Case series Bevacizumab PreOp/IVi NVG 9 12 <21 77.8% 57% |
| 9  | Miki et al29 2011 Case series Bevacizumab PreOp/IVi NVG (PostPPV) 15 12 <21 73% 62.7% |
| 10 | Sedghipour et al30 2011 RCT Bevacizumab IntraOp/SC OAG 17 3 - - 45.8% |
| 11 | Takihara et al31 2011 Comparative, Case series Bevacizumab PreOp/IVi NVG 24 12 ≤21 65.2% 54% |
| 12 | Jurkowska-Dudzińska et al32 2012 Comparative, Case series Bevacizumab Pre-, Intra- and Post-Op, SC POAG PEXG 21 12 30% 78.1% 49.8% |
| 13 | Nilforoushan et al33 2012 RCT Bevacizumab IntraOp/SC POAG 18 7.4 ≤21 or 20% 100% 30.2% |
| 14 | Sengupta et al34 2012 RCT Bevacizumab Pre-, Intra- and Post-Op, SC POAG PACC (Combined Phacoetrax) 10 6 <18 or 20% Complete: 90% Total: 100% 46.3% |
|    |                     SS POAG PACC (Combined Phacoetrax) 10 6 <18 or 20% Complete: 60% Total: 80% 45.8% |
| 15 | Akkan et al35 2013 RCT Bevacizumab IntraOp/SC POAG 21 12 ≤12 Complete: 33% 41.8% |
| 16 | Kahook36 2010 RCT, Pilot Ranibizumab PreOp/IVi POAG 10 6 <22 and >5 or 30% 100% 36.5% |
| 17 | Elmekawy et al37 2013 Case series Ranibizumab PreOp/IC NVG 15 6 ≤21 and >10 Complete: 53.3% Qualified: 40% 56% |

*For the sake of brevity, in comparative studies, only the anti-VEGF arm has been reported.

IC, intracameral; IntraOp, intraoperative; IVi, intravitreal; NVG, neovascular glaucoma; PACG, primary angle closure glaucoma; PEXG, pseudoxefoliative glaucoma; POAG, primary open angle glaucoma; PostOp, postoperative; PostPPV, postvitrectomy Phacotrabs, phacoemulsiﬁcation and trabeculectomy; PreOp, preoperative; SC, subconjunctival; SS, Sponge Soaked; UG, Uveitic Glaucoma; VEGF, vascular endothelial growth factor; N, number; IOP, intraocular pressure
for treatment of colorectal and breast cancers and is used off-label in many ocular conditions. There are different routes of bevacizumab administration with potential ocular effects, including subconjunctival injection, intravitreal injection, and topical administration in the form of eye drops or soaked sponges. While intravitreal administration is the most effective route for intraocular tissue, the longest biologic half-life is achieved by subconjunctival injection because of bevacizumab binding to scleral matrix and its storage-effect. With respect to filtering surgery, subconjunctival injection seems to be the most appropriate route.

When using bevacizumab in filtering surgery, one should consider that in several studies it has been shown that there is more bleb encapsulation with bevacizumab as compared to MMC and several studies suggest that MMC is more effective than bevacizumab in achieving a diffuse filtering bleb in primary trabeculectomy. There are several explanations for this phenomenon. First, the role of antiproliferative agents on prevention of bleb-encapsulation is not proven and controversial. Moreover, bevacizumab may have limited sensitivity to different subtypes of fibroblasts active in encapsulation or it could have insufficient effect on inflammatory mediators. Direct toxicity of MMC to the ciliary epithelium and decreased aqueous humor secretion is another explanation.

Considering bevacizumab as an adjuvant for trabeculectomy, one should also consider the contraindications for bevacizumab use, including pregnancy, breast feeding, uncontrolled systemic hypertension, and cerebrovascular accidents or transient ischemic attacks one month prior to injection. Moreover, complications such as conjunctival necrosis have been reported following subconjunctival bevacizumab and intravitreal ranibizumab injection.

In summary, while anti-VEGF agents seem to offer valuable augmentation of trabeculectomy surgery, sufficient evidence on their long-term safety and efficacy are lacking. More specific anti-VEGF agents, perhaps targeting VEGF could improve their potency and decrease the complications. In addition, increasing their duration of effect would be necessary for long-term success of filtering surgery.

**Conflicts of Interest**

None.

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