Anti-VEGF Agents and Glaucoma Filtering Surgery

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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.[1] It is a rather unique surgical procedure in medicine, because prevention of wound healing is crucial for surgical success.[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.[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;[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.[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.[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.[9] It is hypothesized that VEGF may be a survival factor for certain non-angiogenic blood vessels in adults.[10]

VEGF has three high affinity receptors, among which, VEGF-R2 mediates most of its biologically relevant responses, including cell migration and proliferation.[11] Various isoforms of VEGF, such as $VEGF_{121}$, $VEGF_{165}$ and $VEGF_{189}$, 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.[12,13] While various isoforms have the same affinity for VEGF-R2 receptor,[14,15] they significantly differ in their affinity to VEGF co-receptors, such as neurophilin-1 (NRP-1) and heparin sulphate proteoglycans (HSPGs). Because of this variation, differential tissue effects have been demonstrated for various isoforms: $VEGF_{165}$ and $VEGF_{121}$ predominantly affect blood vessel growth and angiogenesis, while $VEGF_{189}$ has a more prominent role in fibrosis and wound healing processes.[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.[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.[9,19,20] At the filtering site, VEGF could modify fibroblast activity and stimulate collagen cross-linking and contraction, resulting in scar formation.[9] Moreover, higher VEGF levels in Tenon's tissue preoperatively are associated with a worse outcome following trabeculectomy surgery.[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	Timing / route of administration	Type of glaucoma	Sample size	Follow-up duration (months)	Success Criteria, IOP (mmHg)	Success rate	IOP reduction
1	Grewal et al[21]	2008	Case series	Bevacizumab	IntraOp/ SC	POAG PACG	12	6	<16 and >6 or ≥30%	Complete: 92%	52%
2	Cornish et al[22]	2009	Case series	Bevacizumab	IntraOp/ IVi	NVG	2	6	<16	100%	67%
3	de Moraes et al[23]	2009	Case series	Bevacizumab	IntraOp/ IC	NVG	4	12.75	<16 and > 6	100%	77.5%
4	Alkawas et al[24]	2010	Case series	Bevacizumab	PreOp/ IVi	NVG	17	6	≤21	Complete: 52.9% Qualified: 35.3%	54%
5	Choi et al[25]	2010	Case series	Bevacizumab	IntraOp/ SC	NVG UG PostPPV	6	6	<16	100%	67.5%
6	Fakhraie et al[26]	2010	Case series	Bevacizumab	PreOp/ IVi	NVG	23	6	<21 and >6	Complete: 22% Qualified: 39%	52.4%
7	Saito et al[27]	2010	Case series	Bevacizumab	PreOp/ IVi	NVG	52	12	<21	95%	65%
8	Marey[28]	2011	Case series	Bevacizumab	PreOp/ IVi	NVG	9	12	<21	77.8%	57%
9	Miki et al[29]	2011	Case series	Bevacizumab	PreOp/ IVi	NVG (PostPPV)	15	12	<21	73%	62.7%
10	Sedghipour et al[30]	2011	RCT	Bevacizumab	IntraOp/ SC	OAG	17	3	-	-	45.8%
11	Takihara et al[31]	2011	Comparative, Case series	Bevacizumab	PreOp/ IVi	NVG	24	12	≤21	65.2%	54%
12	Jurkowska-Dudzińska et al[32]	2012	Comparative, Case series	Bevacizumab	Pre-, Intra- and Post-Op, SC	POAG PEXG	21	12	30%	78.1%	49.8%
13	Nilforushan et al[33]	2012	RCT	Bevacizumab	IntraOp/ SC	POAG	18	7.4	≤21 or 20%	100%	30.2%
14	Sengupta et al[34]	2012	RCT	Bevacizumab	Pre-, Intra- and Post-Op, SC	POAG PACG (Combined Phacotrabx)	10	6	<18 or 20%	Complete 90% Total: 100%	46.3%
					SS	POAG PACG (Combined Phacotrabx)	10	6	<18 or 20%	Complete: 60% Total: 80%	45.8%
15	Akkan et al[35]	2013	RCT	Bevacizumab	IntraOp/ SC	POAG	21	12	<12	Complete: 33%	41.8%
16	Kahook[36]	2010	RCT, Pilot	Ranibizumab	IntraOp/ IVi	POAG	10	6	<22 and >5 and 30%	100%	36.5%
17	Elmekawey et al[37]	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, pseudoexfoliative glaucoma; POAG, primary open angle glaucoma; PostOp, postoperative; PostPPV, postvitrectomy Phacotrabx, 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[38] 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.[39] 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.[33,35] There are several explanations for this phenomenon. First, the role of antiproliferative agents on prevention of bleb-encapsulation is not proven and controversial.[2,40-42] 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[34] and intravitreal ranibizumab[43] 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 $VEGF_{189}$ 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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