INVITED REVIEW

The Expanding Role of Anti-VEGF Therapy in Glaucoma Surgery: A Narrative Review

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ABSTRACT

The use of anti-vascular endothelial growth factor (anti-VEGF) agents in glaucoma surgery has emerged as a promising adjunctive strategy to improve surgical outcomes by modulating postoperative wound healing. Current data suggest that anti-VEGF therapy effectively reduces angiogenesis, bleb vascularity, and fibroblast proliferation, resulting in more widespread and avascular blebs and potentially providing better short-term intraocular pressure control. While studies are primarily focused on neovascular glaucoma, anti- VEGF agents also have the potential to modulate fibrosis in other glaucoma subtypes. Anti-VEGF agents such as bevacizumab, ranibizumab, aflibercept, and conbercept have been investigated as adjuvants to mitomycin-C (MMC) in the treatment of glaucoma filtration surgeries (GFS) and microinvasive bleb-forming surgery (MIBS). However, there is currently no established consensus regarding the optimal route and timing of anti-VEGF administration, and these remain active areas of ongoing research. This review summarizes the current evidence and clinical outcomes of anti-VEGF agents used in glaucoma surgery and provides an overview of their role in postoperative modulation of wound healing, routes of administration, and optimal timing.

Keywords: Anti-VEGF, Glaucoma surgery, Wound healing, Fibrosis modulation

INTRODUCTION

Wound-healing modulation is a critical determinant of success in many glaucoma surgical modalities, including glaucoma filtration surgery (GFS) and microinvasive bleb-forming surgery (MIBS). Despite the expansion of surgical options, bleb scarring remains the leading cause of surgical failure. The introduction of anti-fibrotic agents, such as mitomycin C (MMC) and 5-fluorouracil (5-FU), has significantly prolonged bleb survival; however, these agents are associated with an increased risk of postoperative complications. Recent research has focused on identifying alternative adjunctive agents to improve glaucoma surgery outcomes. Among these, vascular endothelial growth factor (VEGF) has received particular attention due to its importance in modulating angiogenesis, wound healing, and fibrosis. Targeting VEGF has shown promise in managing intraocular pressure (IOP), improving surgical outcomes, and reducing potential risks in glaucoma patients. Analyses indicate that anti-VEGF therapy may serve as a valuable adjunct to existing surgical approaches, offering an avenue to enhance both efficacy and safety in glaucoma management.

WOUND HEALING AND FIBROSIS: THE VEGF PATHWAY

Angiogenesis and fibrosis, while conceptually distinct, share overlapping molecular and cellular pathways. Vascular endothelial growth factor is upregulated in response to tissue hypoxia or injury, stimulating angiogenesis. This process can progress to a fibrotic phase characterized by fibroblast activation, extracellular matrix (ECM) deposition, and scar formation, which accompanies angiogenic activity.[1] For instance, as seen in neovascular age-related mac-

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ular degeneration, even when neovascularization is treated with anti-VEGF therapy, subretinal fibrosis remains a significant concern because VEGF/VEGF receptor-2 (VEGFR-2) signaling can contribute to both angiogenesis and fibrosis.[2] Following anti-VEGF therapy, a significant proportion of patients develop fibrotic scars beneath the retina, suggesting that VEGF-induced vessels and subsequent fibrovascular tissue are precursors to permanent scarring.

VEGF-A and its receptors are expressed in many anterior segment tissues, such as the iris stroma, ciliary body, and trabecular meshwork.[3] Under ischemic conditions, hypoxia-inducible factor-1α upregulates VEGF transcription, leading to pathological neovascularization of the iris and anterior chamber angle, a characteristic feature of neovascular glaucoma.[4] In addition to classical neovascularization, low-grade VEGF-A/VEGFR-2 signaling can modulate aqueous humor dynamics by affecting trabecular endothelial integrity and modifying the composition of the ECM.

Similarly, a recent ophthalmological review suggested that VEGF plays a central role in the epithelial-mesenchymal transition and fibro-myofibroblast transformation that underlie ocular fibrotic disease. Mechanistically, VEGF binds to the kinase insert domain containing receptor (KDR), alternatively referred to as VEGFR-2, which is primarily expressed in the endothelium, and activates a cascade of intracellular signaling pathways that promote cell survival, proliferation, and increased vascular permeability.[5] Vascular endothelial growth factor signaling can also affect non-endothelial cells: For example, it may increase ECM modulators (e.g., fibronectin, matrix metalloproteinase inhibitors) and indirectly contribute to fibroblast recruitment or activation. In particular, fibrogenic growth factors, such as connective tissue growth factor, can activate VEGF signaling, promoting a switch from vascular repair to scar formation.[6] This suggests that in ocular tissues, while VEGF initially directs vessel formation, persistent or dysregulated VEGF signaling may predispose to fibrotic tissue accumulation, particularly in settings of chronic injury or inflammation. In summary, the VEGF pathway in ocular tissues acts as a double-edged sword: It is essential for vascular repair but can also promote fibrotic remodeling. This duality is vital in the context of surgical wound healing and eye diseases.

Immediately following surgical trauma to the conjunctiva, episclera, and iris, local blood vessels constrict, and plasma proteins like fibrinogen, fibronectin, and plasminogen, together with blood cells, leak into the surrounding tissues. Exposure to tissue factors triggers coagulation, resulting in the formation of a provisional fibrin–fibronectin matrix. Furthermore, after GFS, the wound site becomes a rich environment for VEGF release from platelets, macrophages, and stressed epithelial cells, promoting angiogenesis and fibroblast activation. These events underlie the excessive subconjunctival scarring that leads to bleb failure. Experimental studies in rabbits have shown that fibroblast proliferation and migration begin on approximately the fifth postoperative day.[7] Fibroblast activity is a key determinant of wound-healing outcomes after GFS. While the precise molecular triggers for fibroblast activation remain unclear, multiple factors are known to exert chemotactic or mitogenic effects. These include lymphokines, complement components, native and fragmented collagens, fibronectin, and platelet-derived growth factor (PDGF), with the last being particularly potent.[8]

Transforming growth factor β1 (TGF-β1) is another key molecule affecting subconjunctival fibrosis at the surgical site that has been reported to promote myofibroblast differentiation through VEGF-dependent mechanisms. In a rabbit trabeculectomy model, either VEGF stimulation or VEGF inhibition was applied during surgery. VEGF stimulation increased TGF-β1 expression, which was accompanied by a loss of epithelial markers (E-cadherin, β-catenin) and upregulation of mesenchymal and contractile markers (α-smooth muscle actin) within the subconjunctival tissues following trabeculectomy. Upregulation of Smad and Snail markers, which play a central role in myofibroblast transformation, was observed in the conjunctival and subconjunctival layers at the trabeculectomy site. Electron microscopy findings supported myofibroblast transformation, which was promoted by VEGF stimulation and suppressed by VEGF inhibition. These findings suggest that VEGF potentially triggers myofibroblast transformation by affecting the TGF-β1/Smad/Snail pathway. Among these mediators, VEGF has gained increasing attention as a key link among angiogenesis, inflammation, and fibrosis in ocular wound healing.

CLINICAL RELEVANCE AND IMPLICATIONS

Although glaucoma is known as a neurodegenerative optic neuropathy, research increasingly recognizes that vascular and fibrotic mechanisms contribute significantly to its

pathophysiology. VEGF is also thought to play an active role, acting as both an angiogenic mediator and a regulator of fibrotic tissue remodeling. In glaucomatous eyes, chronic oxidative stress, mechanical stretch, and ischemia induce persistent upregulation of VEGF and its receptors, which contribute to vascular dysregulation and abnormal wound healing.[9] As evidence, elevated VEGF levels have been reported in the aqueous humor of patients with various types of glaucoma, suggesting that elevated VEGF levels play an active role in anterior segment homeostasis and disease progression.[10,11]

Wound healing following glaucoma surgery is a complex, multifactorial, and not yet fully elucidated process. Moreover, the search for reliable protective factors against bleb fibrosis represents a critical unmet need in glaucoma surgery. Numerous attempts to modulate postoperative wound healing using antimetabolites and antifibrotic agents have been made; however, excessive fibrosis still compromises long-term surgical outcomes.

Anti-VEGF as an Adjuvant to Glaucoma Surgery

Among all glaucoma subtypes, the use of anti-VEGF therapy is best established in neovascular glaucoma (NVG). Anti-VEGF agents, such as bevacizumab (Avastin, Genentech Inc., San Francisco, CA), ranibizumab (Lucentis, Genetech Inc., San Francisco, CA), aflibercept (Eylea, Regeneron, New York), and conbercept (KH902; Lumitin, Chengdu Kanghong Biotech Co., Chengdu, China), play a significant role in reducing anterior segment inflammation and improving the surgical environment by effectively reducing iris and angle neovascularization. By rapidly regressing iris and angle neovascularization, these agents facilitate panretinal photocoagulation and improve the safety and success of subsequent glaucoma surgeries. A recent meta-analysis of 17 randomized controlled trials involving 1,311 eyes, including both glaucoma surgery and no antiglaucoma surgery groups, evaluated different anti-VEGF agents and delivery routes in NVG management. The analysis compared intravitreal, intracameral, and combined regimens of bevacizumab, ranibizumab, and conbercept. At one month postoperative, all anti-VEGF treatments significantly reduced IOP compared with control groups. The greatest IOP reduction was achieved with simultaneous intravitreal and intracameral conbercept, followed by intravitreal conbercept, ranibizumab, and bevacizumab. However, anti-VEGF monotherapy is temporary, and the need for repeat therapy, its timing, and its long-term effects remain uncertain.[12]

In addition to examining their role in suppressing inflammation and neovascularization in NVG, research has also studied anti-VEGF agents in other glaucoma subtypes, mainly for their potential to modulate fibrosis during wound healing. In common forms of glaucoma, such as primary open-angle glaucoma and pseudoexfoliation glaucoma, anti-VEGF therapy does not directly reduce intraocular pressure; rather, its benefit is limited to improving the wound-healing response after filtration surgery.[13,14] When administered intraoperatively or in the early postoperative period, bevacizumab acts as a complementary agent to MMC, reducing bleb vascularity and promoting a more diffuse, avascular bleb morphology.[14]

Recent studies show that adding anti-VEGF agents to trabeculectomy, especially in combination with MMC, significantly increases complete surgical success rates and reduces the need for IOP-lowering medications, with notable benefits for intracameral and intravitreal bevacizumab.[15] In trabeculectomy, excessive vascularity around the scleral flap and bleb surface is strongly associated with early failure. Grewal et al. conducted one of the first prospective pilot studies assessing subconjunctival bevacizumab (1.25 mg) administered three to seven days preoperatively. They observed reduced conjunctival hyperemia, a clearer operative field, and lower early vascular activity compared with controls, supporting VEGF inhibition as a perioperative adjunct to antimetabolite therapy.[16] Similarly, a prospective randomized pilot trial compared trabeculectomy outcomes using intraoperative intravitreal ranibizumab (0.5 mg) combined with topical MMC versus using MMC alone. Though all participants achieved surgical success, the combination group developed more diffuse blebs with significantly lower vascularity in both the peripheral bleb area and adjacent conjunctiva.[17] Thus, while anti-VEGF agents show promise, evidence suggests they are not as effective as MMC for long-term IOP control in trabeculectomy. However, they may offer a safer profile and better bleb morphology.[18]

In glaucoma drainage device surgery, particularly Ahmed Glaucoma Valve (AGV) implantation, fibrovascular encapsulation of the endplate remains the primary cause of late pressure elevation. Recent systematic reviews and meta-analyses indicate that combining AGV with anti-VEGF

implantation yields reduced IOP across multiple time intervals (from one week to 12 months), higher surgical success rates, less postoperative medication, and a lower incidence of hyphema compared with AGV alone.[19,20] However, the long-term benefits for IOP control and visual acuity are not yet definitive, with some studies reporting no significant differences in mid- or long-term outcomes.[21] Although comparative studies by Tang et al. and Ma et al. reported that intravitreal intraoperative anti-VEGF medications did not affect the final outcome of AGV implantation, a study comparing a combination of AGV implantation and anti-VEGF therapy to AGV implantation alone demonstrated reduced postoperative antiglaucoma medication requirements, superior IOP-lowering effects at various time points, lower incidence of postoperative hyphema, and reduced aqueous humor VEGF levels.[19,21,22]

Interest in anti-VEGF timing has also extended to newer MIBS (subconjunctival microshunts, such as the XEN Gel Stent (Allergan Inc., Dublin, Ireland) and PRESERFLO™ MicroShunt (Santen, Osaka, Japan)), in which subconjunctival fibrosis remains a major cause of failure. A recent study compared PRESERFLO™ MicroShunt implantation with MMC alone versus MMC combined with intracameral bevacizumab. Though both groups achieved similar reductions in intraocular pressure at six months, the group receiving adjunctive bevacizumab required significantly fewer postoperative interventions, such as needling and 5-FU injections, suggesting that bevacizumab may reduce early complications and postoperative wound modulation needs without compromising efficacy.[23] Similarly, Tai et al. reported comparative six-month outcomes in patients with failed trabeculectomy and ExPRESS shunts between those treated with needling with bevacizumab and MMC and those treated with needling with MMC alone. All patients received a subconjunctival injection of MMC (0.04 mg/mL) at the start of the procedure and were then randomized to receive either subconjunctival bevacizumab (0.04 mL of 25 mg/mL) or balanced salin solution as a control. At 6 months postoperatively, no significant differences in success rates or intraocular pressure (IOP) were found between the treatment and control groups. Postoperative blebs in the treatment group were less vascular and larger.[24]

Routes of Anti-VEGF Administration in Glaucoma Surgery

Comparative and combination studies have further clarified the adjuvant role of anti-VEGF agents and have evaluated local tissue exposure and pharmacokinetics alongside established antifibrotics.[16,25]

Subconjunctival injection of anti-VEGF agents is one of the most studied routes in the GFS context. The subconjunctival route directly reduces conjunctival and episcleral vessel density at the surgical site. Because the half-life of bevacizumab in the subconjunctival space is relatively short (approximately five to seven days), injections administered too far in advance may lose pharmacologic efficacy by the time of surgery. For this reason, precise preoperative timing is critical to ensure adequate VEGF suppression during surgical wound creation. In addition, anti-VEGF agents have been investigated as an alternative adjunct to traditional antifibrotics. In a randomized controlled pilot study comparing subconjunctival bevacizumab with MMC during single-site phacotrabeculectomy, short-term outcomes showed that subconjunctival bevacizumab achieved a comparable reduction in intraocular pressure and a more favorable safety profile at the tested dosing schedule. In contrast, the use of bevacizumab-soaked sponges offered no additional benefit over MMC. These findings indicate that subconjunctival bevacizumab may be a safer and potentially effective adjunct for enhancing surgical success and reducing postoperative fibrosis in combined cataract–glaucoma surgery.[26]

Intracameral injection refers to the delivery of the anti-VEGF agent into the anterior chamber, often at the time of or just prior to surgery. This route allows higher local concentration in the anterior chamber, iris, and angle structures. Bai et al. conducted a study comparing intracameral and intravitreal conbercept injections in 81 cases of NVG and found that, compared to intravitreal administration, intracameral administration resulted in faster IOP reduction (within two days) and greater regression of iris neovascularization.

Intravitreal injection suppresses VEGF activity originating from the ischemic retina and may indirectly reduce anterior segment neovascularization by reducing the overall VEGF load. Slabaugh et al. have used intravitreal anti-VEGF injection, a widely used procedure, to regress iris and angle neovascularization in NVG.[27] Wang et al.'s systematic review comparing routes found that combined intravitreal and intracameral anti-VEGF injection was more effective and safe than other regimens for NVG. However, their

work emphasized that purely intravitreal administration may be less directly effective at the conjunctival-subtenon interface and may not optimally affect filtration bleb morphology.[12]

A recent systematic review and meta-analysis provided more substantial evidence supporting the adjunctive use of anti-VEGF agents in trabeculectomy. Sixteen randomized controlled trials involving 1,002 adult patients were evaluated to compare trabeculectomy with and without anti-VEGF supplementation. When combined with mitomycin-C, anti-VEGF agents (specifically intracameral or intravitreal bevacizumab [1.25 mg]) demonstrated a significantly higher likelihood of complete surgical success at 12 months and a significantly reduced need for IOP-lowering medications. Meta-analytic data have shown that adjunctive anti-VEGF therapy improves outcomes, particularly at 12-month follow-ups. These results highlight that anti-VEGF treatment enhances the efficacy of trabeculectomy beyond the traditional use of MMC and improves bleb survival by modulating postoperative wound healing.[28]

A new and evolving approach in glaucoma surgery involves the local delivery of anti-VEGF agents at the subconjunctival interface to modulate wound healing and prevent postoperative fibrosis. This strategy aims to achieve targeted inhibition of angiogenesis and fibroblast activation while minimizing the systemic and intraocular risks associated with repeated intravitreal injections. By leveraging the transscleral route, subconjunctival administration provides direct access to both anterior and posterior ocular tissues, ensuring higher local drug concentrations at the surgical site. Recent innovations—including biodegradable hydrogels, microporous matrices, and nanoparticle-based carriers, such as poly(lactic-co-gylcolic acid), chitosan-coated, and cubosome systems—enable sustained anti-VEGF release over extended periods, thereby enhancing bioavailability and reducing dosing frequency. These sustained-release platforms have already demonstrated promise in other neovascular ocular diseases, such as age-related macular degeneration, diabetic retinopathy, corneal neovascularization, and postoperative scarring.[29,30] In glaucoma surgery, early studies suggest that subconjunctival anti-VEGF delivery may reduce vascularization and fibrosis; however, its efficacy relative to MMC remains uncertain. Overall, the approach appears well tolerated, with a low incidence of local complications. As research progresses, sustained-release formulations may be found to further improve safety and consistency by minimizing the need for repeated interventions, although optimal dosing, long-term biocompatibility, and comparative effectiveness versus standard antifibrotic agents still require rigorous evaluation.[31]

Timing of Anti-VEGF Administration in Glaucoma Surgery

Building on their expanding role in ophthalmic surgery, the application of anti-VEGF agents in glaucoma filtration procedures has attracted growing attention, particularly regarding timing and sequence. While traditional wound-healing modulators, such as MMC and 5-FU, remain the mainstays for enhancing surgical success, postoperative fibrosis and bleb failure continue to limit long-term outcomes. In this context, anti-VEGF therapy has been explored as an adjunctive approach to modulate early postoperative angiogenesis and fibrotic remodeling. The timing of anti-VEGF administration, preoperative, intraoperative, or postoperative, plays a crucial role in determining surgical outcomes. However, the optimal timing for anti-VEGF administration remains one of the most debated aspects of its clinical use.

The goal of preoperative anti-VEGF use is to reduce conjunctival vascularity and intraoperative bleeding, particularly in eyes with severe inflammation or neovascularization. Grewal et al. evaluated subconjunctival bevacizumab administered three to seven days before trabeculectomy and reported a clearer surgical field and less early hyperemia compared with controls.[16] Similarly, Satoshi et al. demonstrated that preoperative intravitreal bevacizumab in vascularized glaucoma minimizes intraoperative bleeding and improves the early postoperative course.[32] These findings are particularly important for secondary glaucomas, such as the uveitic or neovascular subtypes, in which intense vascular activity may compromise surgical safety.

Intraoperative administration represents another critical opportunity to interfere with the initial wound-healing cascade. In a prospective randomized clinical trial (the Bevacizumab in Trabeculectomy Study), intravitreal bevacizumab administered at the time of trabeculectomy was associated with improved surgical success and bleb survival at 12 months compared with standard trabeculectomy, suggesting that adjunctive intraoperative anti-VEGF may enhance

long-term filtration outcomes through modulation of early wound healing responses.[13] Furthermore, Nilforushan et al. reported that intraoperative or immediately postoperative bevacizumab administered with low-dose MMC produced thinner, less vascular blebs and similar IOP results at one year compared with MMC alone.[33] However, the long-term persistence of intraoperative anti-VEGF remains controversial, and variability in dosing and technique across studies makes consensus recommendations difficult to achieve.

The early postoperative period, particularly within the first two weeks after surgery, represents a biologically dynamic phase characterized by angiogenesis and fibroblast migration. Postoperative use of anti-VEGF agents has also been explored as a means of modulating wound healing following filtration surgery. In a prospective, single-center, randomized placebo-controlled study, 59 patients with uncontrolled glaucoma despite maximal tolerated medical therapy underwent primary trabeculectomy with MMC and were randomized to receive postoperative subconjunctival injections of bevacizumab (1.25 mg/0.05 mL) or a balanced salt solution. Forty-seven patients completed one year of follow-up. At 12 months, no statistically significant differences were observed between the two groups regarding intraocular pressure, bleb morphology, or the need for glaucoma medications and 5-FU needling. Nonetheless, the bevacizumab-treated group exhibited a trend toward higher surgical success rates, reduced postoperative medication use, and more favorable bleb appearance, albeit with a slightly increased need for needling procedures. Although the differences did not reach statistical significance, these findings suggest that adjunctive postoperative subconjunctival bevacizumab may improve bleb function and IOP control.[34] Similarly, early postoperative intravitreal bevacizumab (IVB) has been shown to significantly reduce the incidence of NVG following phacovitrectomy for proliferative diabetic retinopathy, with only 3.44% of IVB-treated eyes developing NVG compared with 16.67% of controls. These findings collectively indicate that postoperative anti-VEGF administration, whether subconjunctival or intravitreal, can modulate fibrovascular responses, improve bleb morphology, and prevent secondary neovascular complications after ocular surgery.[35]

In addition to early phase, late postoperative or rescue anti-VEGF injections have also been explored to manage bleb encapsulation or revascularization. The combination of anti-VEGF therapy with conventional antifibrotic approaches, such as 5-FU, has been particularly well described, with Freiberg et al. reporting a reduced number of requisite 5-FU when bevacizumab was used concurrently.[36] Nevertheless, these interventions appear most effective when fibrosis is at an early or intermediate stage; once dense collagen remodeling has occurred, VEGF inhibition alone offers limited benefit.[37]

Taken together, these findings indicate that there is no consensus regarding the optimal timing of anti-VEGF therapy in glaucoma surgery. Preoperative administration may help create a less vascular surgical field; intraoperative dosing can suppress the early inflammatory and angiogenic surge; and early postoperative application may modulate fibroblast and endothelial activation during wound healing. In later stages, rescue interventions can be valuable in eyes developing bleb vascularization or encapsulation. Despite encouraging clinical outcomes, the absence of standardized timing protocols reflects the ongoing variability in dosage, delivery route, and concomitant antimetabolite use.

SAFETY, UNSOLVED QUESTIONS, AND GAPS

Animal studies indicate that the intracameral administration of anti-VEGF agents, such as aflibercept and ranibizumab, may cause apoptosis of corneal endothelial cells through the modulation of nerve growth factor-related pathways. Aflibercept appears to have a stronger cytotoxic effect than ranibizumab, likely due to its broader binding profile for both VEGF and placental growth factor. These findings raise concerns that repeated intracameral exposure could compromise corneal transparency.[38] Bevacizumab interrupts the fibroproliferative phase of wound healing, resulting in less thickening and, thus, less resistance to aqueous diffusion at the level of the tenon's capsule and the conjunctiva. Previous work has raised concerns that bevacizumab might lead to a higher prevalence of avascular blebs or tenon's cysts.[39]

Regarding the conducted studies, many issues remain unclear. First, the optimal timing, dose, and repeat intervals for anti-VEGF when used as an adjunct in glaucoma surgery are undefined. Existing studies have not been standardized to isolate these variables, and outcomes are generally predicted based on posterior segment paradigms. Second, it is

unclear whether anti-VEGF should be used as an add-on therapy or an alternative to antifibrotics, such as MMC. Although anti-VEGF alone has been shown to be biologically ineffective in suppressing fibroblast-derived scarring, the individual and synergistic effects of the two agents have not yet been prospectively tested. Third, the long-term effect of VEGF suppression on bleb fibrosis is unknown. Even if early angiostasis delays vascular-induced fibroplasia, compensatory activation of non-VEGF scar pathways (E.g., TGF-β, CTGF, PDGF, YAP/TAZ, hypoxia-induced cascades) may neutralize the initial gain. However, while this "fibrotic escape" phenomenon has been hypothesized, it has not been studied. Another important limitation is the lack of assessment of glaucoma subtype-specific differences. It is unlikely that the post-GFS wound response in primary open-angle glaucoma will be equivalent to those in uveitic, pseudophakic, postvitrectomized, or neovascular phenotypes.

CONCLUSION

The use of anti-VEGF agents in glaucoma surgery is being investigated to address one of the field's most critical challenges: postoperative fibrosis and bleb failure. Current research indicates that the role of anti-VEGF agents extends beyond neovascular glaucoma, including modulation of fibrosis in primary open-angle and secondary glaucoma. While studies demonstrate the short-term efficacy of anti-VEGF agents, particularly when combined with MMC, research on long-term intraocular pressure control and bleb survival is ongoing. Variability in the timing of administration (preoperative, intraoperative, and postoperative) and the route of administration (subconjunctival, intraocular, or intravitreal) highlights the need for standardized protocols and controlled, comparative studies. Furthermore, while integrating anti-VEGF therapy with novel biomaterials, sustained-release drug delivery systems, or next-generation wound-healing modulators represents a promising research direction, the long-term efficacy and safety of these approaches must be determined through prospective clinical trials.

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