Modulation of Fibrosis After Ahmed Glaucoma Valve Implantation: Comparing Ologen and Anti-VEGF Therapy in Refractory Glaucoma

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Abstract

Background: Refractory glaucoma represents a major therapeutic challenge in ophthalmology because of the high risk of progressive optic neuropathy and failure of conventional filtration procedures. Ahmed glaucoma valve (AGV) implantation has become one of the most widely used surgical options for refractory glaucoma owing to its efficacy in lowering intraocular pressure (IOP) and its relatively favorable safety profile. However, postoperative fibrosis and encapsulation around the valve plate remain the principal causes of surgical failure and hypertensive phase development. Excessive subconjunctival wound healing, fibroblast proliferation, angiogenesis, and extracellular matrix deposition significantly compromise long-term surgical success. Consequently, various adjunctive strategies have been investigated to modulate postoperative fibrosis and improve AGV outcomes.

Aim :This review aims to critically evaluate the current evidence regarding the role of Ologen collagen matrix and anti-vascular endothelial growth factor (anti-VEGF) therapy, particularly ranibizumab, as adjuvant modalities for fibrosis modulation following AGV implantation in adult refractory glaucoma. The review further explores the underlying mechanisms of wound healing, hypertensive phase development, clinical outcomes, safety profiles, and future perspectives for biologic and biomaterial-based modulation of postoperative scarring.

Ologen is a biodegradable porous collagen-glycosaminoglycan matrix designed to guide randomized fibroblast proliferation and reduce dense scar formation by promoting physiologic tissue remodeling. In contrast, ranibizumab acts through inhibition of VEGF-mediated angiogenesis, vascular permeability, and inflammatory signaling pathways that contribute to fibrosis and bleb encapsulation. Experimental and clinical studies have demonstrated that both approaches may reduce postoperative fibrosis, improve bleb morphology, and enhance IOP control after AGV surgery. Ologen augmentation has been associated with reduced encapsulation and improved subconjunctival architecture, whereas ranibizumab may decrease postoperative neovascularization, vascular congestion, and inflammatory fibrosis, particularly in neovascular glaucoma. Nevertheless, currently available studies remain heterogeneous regarding study design, patient selection, surgical techniques, administration protocols, and follow-up duration.

Conclusion: Both Ologen collagen matrix and anti-VEGF therapy represent promising adjunctive strategies for improving AGV outcomes through modulation of postoperative fibrosis. While Ologen primarily acts as a structural scaffold for physiologic wound healing, ranibizumab targets molecular pathways involved in angiogenesis and scar formation. Current evidence suggests potential benefits for both modalities; however, the absence of large randomized comparative studies limits definitive conclusions regarding superiority. Further well-designed prospective trials are required to establish optimal indications, administration protocols, long-term efficacy, and safety of these adjunctive therapies in refractory glaucoma surgery.

Keywords: Ahmed Glaucoma Valve Implantation, Ologen , Anti-VEGF Therapy ,Refractory Glaucoma

Introduction

Glaucoma is a chronic progressive optic neuropathy characterized by irreversible retinal ganglion cell damage, retinal nerve fiber layer loss, and progressive visual field deterioration. Elevated intraocular pressure (IOP) remains the only modifiable risk factor associated with disease progression, making adequate pressure reduction the principal target of glaucoma management. Despite major advances in medical and surgical therapies, a significant proportion of patients continue to experience progressive visual impairment because of inadequate IOP control or surgical failure. Refractory glaucoma represents one of the most challenging forms of glaucoma due to its resistance to conventional medical therapy and poor outcomes following standard filtration surgery. Conditions commonly associated with refractory glaucoma include neovascular glaucoma, uveitic glaucoma, post-vitrectomy glaucoma, aphakic and pseudophakic glaucoma, and glaucoma associated with previous ocular surgeries or severe ocular inflammation. [1-3]

Trabeculectomy has long been considered the gold standard filtration surgery for glaucoma management; however, its success is markedly reduced in refractory glaucoma because of aggressive postoperative fibrosis and subconjunctival scar formation. Excessive fibroblast proliferation, inflammatory cytokine release, and extracellular matrix deposition frequently result in bleb failure and inadequate aqueous humor drainage. Although antimetabolites such as mitomycin-C and 5-fluorouracil have improved filtration surgery outcomes, their use may be associated with serious complications including hypotony, avascular blebs, bleb leakage, and endophthalmitis. Consequently, increasing attention has been directed toward safer biologic and biomaterial-based strategies capable of modulating wound healing while preserving physiologic tissue remodeling. [4,5]

Glaucoma drainage devices (GDDs) have become increasingly preferred in refractory glaucoma because they bypass compromised conventional outflow pathways and provide an alternative route for aqueous humor drainage. Among available GDDs, the Ahmed glaucoma valve (AGV) is one of the most commonly used implants because of its valved mechanism, which reduces the risk of postoperative hypotony while achieving effective IOP reduction. Since its introduction, AGV implantation has shown favorable outcomes in various forms of refractory glaucoma. Nevertheless, long-term surgical success remains limited by postoperative fibrosis and encapsulation around the valve plate, leading to increased outflow resistance and development of the hypertensive phase. Fibrosis surrounding the implant remains the principal cause of late AGV failure. [6-8]

Postoperative wound healing after AGV implantation is a complex biologic process involving inflammation, angiogenesis, fibroblast activation, and extracellular matrix remodeling. Vascular endothelial growth factor (VEGF) plays a critical role in this process through promotion of vascular permeability, inflammatory cell recruitment, and fibroblast proliferation. Excessive VEGF expression and subconjunctival fibrosis contribute to formation of dense encapsulated blebs that impair aqueous outflow and compromise long-term pressure control. Therefore, modulation of fibrosis and angiogenesis has emerged as an important therapeutic target for improving AGV outcomes. [4,9]

Recently, adjunctive approaches such as Ologen collagen matrix and anti-VEGF therapy have gained increasing interest in glaucoma surgery. Ologen is a biodegradable porous collagen-glycosaminoglycan scaffold designed to promote organized fibroblast growth and reduce dense scar formation through physiologic tissue remodeling. In contrast, anti-VEGF agents such as ranibizumab inhibit VEGF-mediated angiogenesis and inflammatory fibrosis. Both strategies have shown promising potential in reducing postoperative scarring and improving surgical success after AGV implantation. However, currently available evidence remains heterogeneous, and direct comparative data are still limited. [10-13]

The aim of this review is to evaluate the current evidence regarding fibrosis modulation after Ahmed glaucoma valve implantation using Ologen collagen matrix and anti-VEGF therapy, with particular emphasis on ranibizumab. The review further discusses the mechanisms of postoperative wound healing, hypertensive phase development, clinical outcomes, and future perspectives for optimizing surgical

success in adult refractory glaucoma.

Refractory Glaucoma and Surgical Failure

Refractory glaucoma represents a heterogeneous group of glaucomatous disorders characterized by persistently elevated intraocular pressure (IOP) despite maximal tolerated medical therapy and/or previous failed glaucoma surgery. These eyes are generally associated with severe conjunctival scarring, excessive postoperative inflammation, altered aqueous outflow pathways, and aggressive wound healing responses that significantly reduce the success of conventional filtration procedures. Common causes of refractory glaucoma include neovascular glaucoma (NVG), uveitic glaucoma, post-vitrectomy glaucoma, aphakic and pseudophakic glaucoma, traumatic glaucoma, and glaucoma associated with keratoplasty or previous ocular surgery. Because of the complex pathophysiology and high risk of surgical failure, management of refractory glaucoma remains one of the greatest challenges in glaucoma surgery. [14,15]

The principal cause of filtration surgery failure in refractory glaucoma is excessive subconjunctival fibrosis. Following surgical intervention, tissue injury initiates a cascade of inflammatory and wound healing responses involving cytokine release, fibroblast migration, angiogenesis, and extracellular matrix deposition. Although these mechanisms are essential for normal tissue repair, exaggerated wound healing leads to scar formation around the filtration site or drainage implant, resulting in increased resistance to aqueous humor outflow and progressive surgical failure. Eyes with refractory glaucoma frequently exhibit enhanced inflammatory activity and vascular proliferation, which further accelerate postoperative fibrosis. [16]

Among the various forms of refractory glaucoma, neovascular glaucoma is considered one of the most aggressive and surgically challenging subtypes. Retinal ischemia secondary to proliferative diabetic retinopathy or central retinal vein occlusion stimulates the release of vascular endothelial growth factor (VEGF), leading to neovascularization of the iris and anterior chamber angle. These fragile neovessels are associated with severe inflammation, fibrovascular membrane formation, synechial angle closure, and markedly elevated IOP. In addition to its angiogenic effect, VEGF contributes significantly to postoperative fibrosis through stimulation of fibroblast proliferation and vascular permeability, making wound healing modulation particularly important in these eyes. [17,18]

Uveitic glaucoma also demonstrates high rates of surgical failure because of persistent intraocular inflammation and recurrent breakdown of the blood-aqueous barrier. Chronic inflammatory cell infiltration and cytokine activation induce subconjunctival fibrosis and scarring, which compromise filtration surgery outcomes. Similarly, post-vitrectomy glaucoma and glaucoma associated with previous ocular surgeries often exhibit conjunctival alterations, disturbed ocular anatomy, and excessive cicatrization, further reducing the long-term efficacy of conventional filtration procedures. These factors have contributed to the increasing preference for glaucoma drainage devices in refractory glaucoma management. [14,15]

Trabeculectomy augmented with antimetabolites such as mitomycin-C and 5-fluorouracil has historically been utilized to suppress fibroblast proliferation and improve surgical success. However, despite improved short-term outcomes, antimetabolites may produce thin avascular blebs and serious complications including hypotony, bleb leakage, infection, and endophthalmitis. Therefore, interest has shifted toward newer biologic and biomaterial-based strategies capable of modulating wound healing in a more physiologic manner while minimizing tissue toxicity. Such approaches include biodegradable collagen matrix implants and anti-VEGF therapy, both of which aim to regulate postoperative fibrosis and improve long-term aqueous filtration. [16,19]

Understanding the mechanisms underlying fibrosis and surgical failure is critical for optimizing outcomes after glaucoma drainage device implantation. Excessive fibroblast activation, angiogenesis, and extracellular matrix remodeling remain central factors in encapsulated bleb formation and hypertensive phase development after Ahmed glaucoma valve surgery. Consequently, modulation of these biologic pathways has become an important focus of contemporary glaucoma research and forms the basis for the use of adjunctive therapies such as Ologen collagen matrix and anti-VEGF agents. [16,18,19]

Ahmed Glaucoma Valve in Refractory Glaucoma

Glaucoma drainage devices (GDDs) have become increasingly important in the management of refractory glaucoma because they provide an alternative pathway for aqueous humor drainage while bypassing compromised trabecular and subconjunctival outflow pathways. Their use has expanded significantly in recent years, particularly in eyes with previous failed filtration surgery, extensive conjunctival scarring, severe inflammation, or neovascularization where trabeculectomy demonstrates limited long-term success. Among currently available GDDs, the Ahmed glaucoma valve (AGV) is one of the most commonly implanted devices because of its valved mechanism, which was specifically designed to reduce the risk of postoperative hypotony while maintaining effective intraocular pressure (IOP) reduction. [20,21]

The Ahmed glaucoma valve was developed by Mateen Ahmed and approved by the Food and Drug Administration in 1993. The implant consists of three principal components including a silicone drainage tube, a plate positioned in the posterior subconjunctival space, and a valve mechanism formed of thin silicone elastomer membranes. The valve operates according to pressure-sensitive mechanics that permit aqueous humor outflow when IOP rises above approximately 8–12 mmHg. This design allows gradual filtration of aqueous humor while minimizing excessive postoperative drainage and shallow anterior chamber formation that are commonly associated with non-valved implants. [21,22]

Several AGV models have been developed, including adult and pediatric variants as well as silicone and polypropylene plate designs. The silicone FP7 model remains the most widely used because of its favorable tissue biocompatibility and lower inflammatory response. Following implantation, aqueous humor drains through the tube toward the episcleral plate where a fibrous capsule gradually forms around the implant. Long-term surgical success therefore depends largely on the permeability and thickness of this capsule, as excessive fibrosis may significantly increase outflow resistance and compromise IOP control. [21]

The surgical technique of AGV implantation typically involves conjunctival dissection in the superotemporal quadrant followed by fixation of the plate approximately 8–10 mm posterior to the limbus. After priming the valve mechanism with balanced salt solution, the drainage tube is inserted into the anterior chamber through a scleral needle tract and covered using a scleral or pericardial patch graft to reduce the risk of tube erosion. Alternative approaches including pars plana tube insertion may be utilized in vitrectomized eyes or eyes with compromised anterior segment anatomy. Proper tube positioning is essential to minimize complications such as corneal endothelial damage, tube occlusion, and iris touch. [21,23]

Ahmed glaucoma valve implantation has demonstrated favorable outcomes in various forms of refractory glaucoma including neovascular glaucoma, uveitic glaucoma, post-vitrectomy glaucoma, traumatic glaucoma, and pediatric glaucoma. Several studies have reported significant postoperative IOP reduction together with decreased dependence on topical antiglaucoma medications. Nevertheless, despite satisfactory short-term outcomes, long-term surgical efficacy may progressively decline over time due to fibrous encapsulation around the valve plate. Previous reports have shown that the success rate of AGV surgery decreases gradually during long-term follow-up, highlighting the major role of postoperative fibrosis in surgical failure. [15,20,24]

One of the most characteristic postoperative phenomena following AGV implantation is the hypertensive phase, which is generally defined as elevation of IOP during the early postoperative period after initial successful pressure reduction. This phase is believed to result primarily from active fibrovascular proliferation and encapsulation around the implant plate, leading to increased resistance to aqueous filtration. Histopathologic studies have demonstrated dense collagen deposition, fibroblast proliferation, and inflammatory cell infiltration within encapsulated blebs. The hypertensive phase has been associated with poorer long-term surgical outcomes and increased need for additional medications or surgical interventions. Consequently, prevention of excessive postoperative fibrosis has become a major target for improving AGV success rates. [25,26]

Traditional antifibrotic agents such as mitomycin-C have been utilized to suppress wound healing

following glaucoma surgery; however, concerns regarding tissue toxicity and long-term complications have encouraged investigation of safer biologic alternatives. More recently, adjunctive approaches such as Ologen collagen matrix and anti-vascular endothelial growth factor (anti-VEGF) therapy have emerged as promising modalities for modulation of postoperative fibrosis after AGV implantation. These therapies aim to improve bleb morphology, reduce fibrovascular encapsulation, and enhance long-term aqueous outflow while minimizing complications associated with excessive wound inhibition. [16,19]

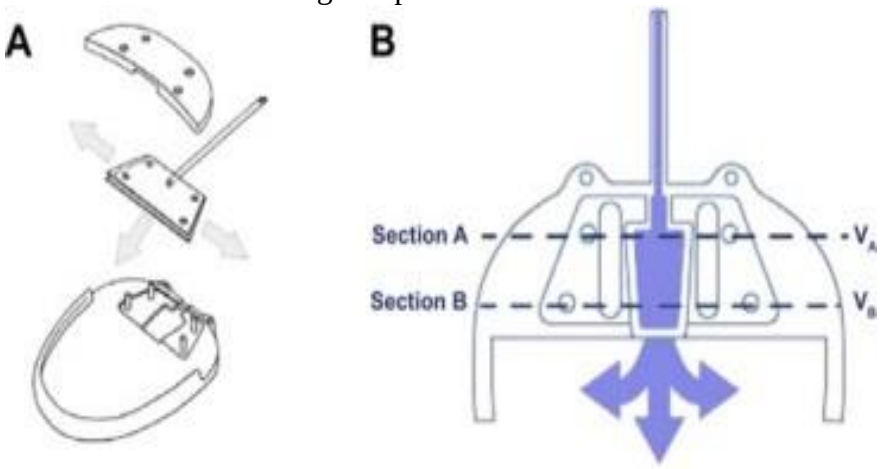


Figure (1) A) Ahmed glaucoma valve implant components; **B**) Ahmed glaucoma valve mechanism. V_A presented as velocity of fluid flowing in section A. V_B presented as velocity of fluid flowing in section B [7]

Wound Healing and Fibrosis After Ahmed Glaucoma Valve Implantation

Postoperative wound healing following Ahmed glaucoma valve (AGV) implantation is a highly dynamic and complex biologic process that plays a decisive role in determining long-term surgical success. Although controlled tissue repair is essential for maintaining implant stability and preventing aqueous leakage, excessive healing responses frequently result in fibrosis and encapsulated bleb formation, which remain the principal causes of AGV failure. The balance between physiologic healing and exaggerated subconjunctival scarring is therefore critical for maintaining adequate aqueous humor filtration and long-term intraocular pressure (IOP) control. [27,28]

The wound healing process after glaucoma surgery classically occurs through overlapping inflammatory, proliferative, and remodeling phases. Immediately after surgical trauma, inflammatory mediators and cytokines are released from injured tissues, leading to recruitment of macrophages, neutrophils, fibroblasts, and vascular endothelial cells. This early inflammatory cascade stimulates fibroblast migration and activation, initiating extracellular matrix production and collagen deposition. Although these processes are necessary for tissue repair, excessive fibroblast proliferation may lead to dense fibrous capsule formation around the AGV plate, resulting in increased resistance to aqueous outflow. [16,27]

Fibroblasts are considered the principal effector cells in postoperative subconjunctival fibrosis. Following activation, fibroblasts differentiate into myofibroblasts capable of producing large amounts of collagen and extracellular matrix proteins. These myofibroblasts also exhibit contractile properties that contribute to tissue contraction and reduction of filtration space surrounding the implant. Histopathologic studies of encapsulated blebs have demonstrated dense collagen bundles, activated fibroblasts, inflammatory cell infiltration, and vascular proliferation, all of which compromise permeability of the filtering capsule and reduce long-term surgical efficacy. [16,29]

Angiogenesis also plays a major role in postoperative fibrosis after AGV implantation. Vascular endothelial growth factor (VEGF) is one of the most important mediators involved in wound healing modulation because it stimulates endothelial cell proliferation, vascular permeability, inflammatory cell recruitment, and fibroblast activation. Elevated VEGF expression has been strongly associated with excessive subconjunctival scarring and failure of glaucoma filtration procedures. In experimental studies, inhibition of VEGF signaling has been shown to reduce fibroblast proliferation and decrease scar

formation following glaucoma surgery, highlighting the important relationship between angiogenesis and fibrosis. [18,30]

One of the most characteristic manifestations of postoperative fibrosis after AGV implantation is the hypertensive phase. This phenomenon is generally observed within the first few postoperative months after an initial period of satisfactory IOP reduction and is characterized by transient elevation of IOP secondary to fibrovascular encapsulation around the valve plate. The encapsulated bleb formed during this phase tends to be thick, tense, and poorly permeable, thereby increasing resistance to aqueous humor drainage. Several studies have demonstrated that development of the hypertensive phase is associated with poorer long-term surgical outcomes and increased dependence on topical antiglaucoma medications. [25,26]

The degree of postoperative fibrosis varies according to several factors including patient age, glaucoma subtype, inflammatory activity, previous ocular surgeries, and presence of neovascularization. Eyes with neovascular glaucoma and uveitic glaucoma are particularly prone to excessive fibrosis because of elevated inflammatory cytokines and VEGF levels. In addition, surgical manipulation itself may stimulate conjunctival inflammation and fibroblast activation, further aggravating postoperative scar formation. Consequently, modulation of wound healing has become a major therapeutic objective in modern glaucoma surgery. [17,27]

Traditional antimetabolites such as mitomycin-C and 5-fluorouracil suppress fibroblast proliferation by inducing cellular toxicity and inhibiting DNA synthesis. Although these agents improve short-term surgical outcomes, they may interfere with normal tissue healing and lead to complications including thin avascular blebs, hypotony, bleb leakage, and infection. Therefore, recent research has focused on development of safer biologic and biomaterial-based alternatives capable of regulating fibrosis in a more physiologic manner. Ologen collagen matrix aims to guide organized tissue remodeling through mechanical scaffold modulation, whereas anti-VEGF therapy suppresses angiogenesis and VEGF-mediated fibrosis at the molecular level. Both approaches represent promising strategies for improving long-term AGV outcomes by reducing excessive postoperative scar formation. [4,10,12]

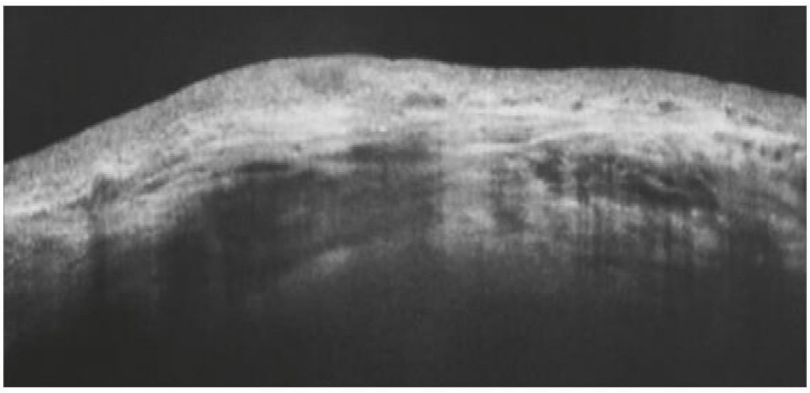


Figure:(2) encapsulated bleb with dense hyperreflective bleb wall mono-cystic fluid-filled bleb cavity, maximal bleb wall thickness of 375 μm with high reflectivity [20]

Ologen Collagen Matrix

Ologen collagen matrix is a biodegradable porous scaffold developed as a biologic alternative to conventional antimetabolites for modulation of wound healing after glaucoma surgery. Unlike cytotoxic agents such as mitomycin-C, which suppress fibroblast proliferation through nonspecific cellular inhibition, Ologen aims to regulate subconjunctival healing in a more physiologic manner by guiding organized tissue remodeling and reducing dense scar formation. Because postoperative fibrosis remains the principal cause of Ahmed glaucoma valve (AGV) failure, increasing attention has been directed toward the potential role of Ologen in improving long-term surgical outcomes. [31,32]

Ologen is composed primarily of cross-linked porcine atelocollagen combined with glycosaminoglycans, forming a three-dimensional porous matrix with interconnected pores of variable diameter. This porous

architecture acts as a temporary scaffold that promotes random fibroblast migration and prevents the linear alignment of fibroblasts responsible for dense collagen scar formation. Instead of forming compact fibrotic tissue, fibroblasts proliferate in a loosely organized manner that facilitates formation of a more diffuse and permeable subconjunctival filtration space. The implant gradually biodegrades over several months while being replaced by remodeled connective tissue. [31]

The biologic rationale behind Ologen implantation is based on modification of the wound healing microenvironment. Following glaucoma surgery, activated fibroblasts tend to produce parallel collagen bundles and excessive extracellular matrix deposition that lead to encapsulation and filtration failure. Ologen mechanically separates subconjunctival tissues and distributes fibroblasts within its porous framework, thereby reducing myofibroblast transformation and limiting dense fibrotic capsule formation. This process promotes development of a healthier bleb architecture with improved aqueous humor diffusion and lower outflow resistance. [16,31]

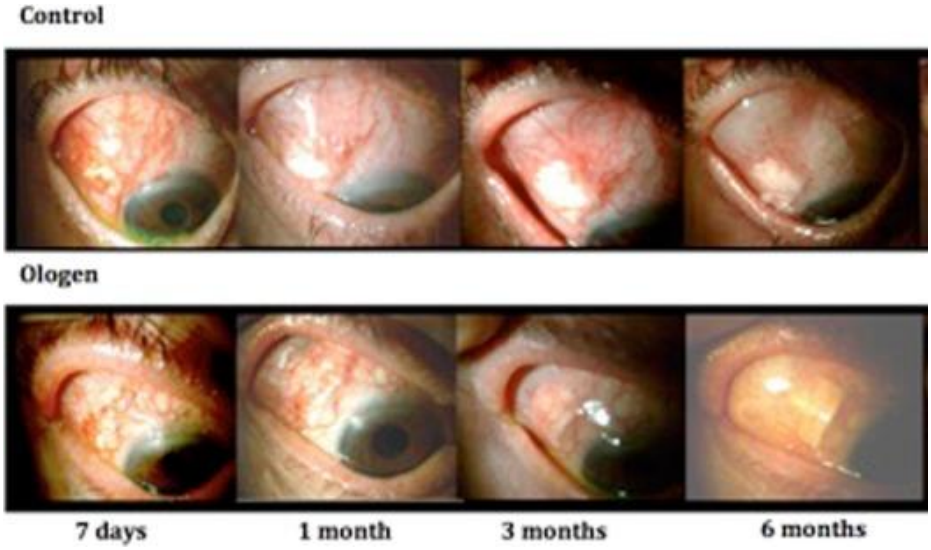
Initially, Ologen was primarily investigated as an adjunctive implant in trabeculectomy procedures. Several studies demonstrated that collagen matrix augmentation may achieve IOP reduction comparable to mitomycin-C while potentially reducing complications related to excessive wound inhibition. Favorable bleb morphology characterized by diffuse vascularized blebs and reduced avascular scarring has also been reported following Ologen implantation. These encouraging findings stimulated interest in extending its application to glaucoma drainage device surgery, particularly in eyes at high risk of postoperative fibrosis. [10,32]

More recently, Ologen has been evaluated as an adjunctive material in Ahmed glaucoma valve implantation. The implant is generally positioned over or around the valve plate to reduce fibrovascular encapsulation and improve permeability of the filtering capsule. Clinical studies have suggested that Ologen augmentation may reduce incidence of the hypertensive phase and improve postoperative IOP control by limiting excessive scar formation around the implant. Additionally, imaging studies demonstrated more diffuse bleb morphology and reduced capsular thickness in eyes receiving Ologen-assisted AGV implantation compared with conventional surgery alone. [11,33]

Kim and colleagues compared one-year outcomes after AGV implantation with and without Ologen augmentation and observed favorable postoperative IOP reduction and decreased encapsulation rates in the Ologen group. Similarly, Harizman et al. reported that adjunctive Ologen implantation may improve bleb characteristics and reduce postoperative fibrosis following Ahmed valve surgery. Pediatric studies have also demonstrated promising outcomes regarding reduction of subconjunctival scarring and maintenance of aqueous drainage function in refractory childhood glaucomas. These findings support the concept that collagen matrix implantation may serve as an effective biologic modulator of wound healing after glaucoma drainage device surgery. [11,17,34]

Despite these promising results, the currently available literature remains heterogeneous with respect to patient selection, surgical techniques, implant positioning, and follow-up duration. Some studies demonstrated significant improvement in surgical outcomes, whereas others reported limited differences compared with conventional AGV implantation. Furthermore, long-term evidence remains relatively limited, and direct comparisons with other antifibrotic strategies such as anti-VEGF therapy are still insufficient. Nevertheless, Ologen represents an attractive therapeutic option because it modulates fibrosis through tissue engineering principles rather than direct cytotoxic suppression of healing responses. [31,32]

The growing interest in biomaterial-based wound healing modulation reflects an important shift in glaucoma surgery toward more physiologic control of postoperative fibrosis. By promoting organized subconjunctival remodeling and reducing dense collagen deposition, Ologen collagen matrix may enhance long-term success of Ahmed glaucoma valve implantation while potentially minimizing complications associated with excessive inhibition of tissue repair. Further prospective randomized studies are still needed to determine optimal implantation techniques, patient selection criteria, and long-term efficacy in refractory glaucoma management. [11,31]



figure(3): bleb in ologen Vs. control group. [30]

Anti-VEGF Therapy in Ahmed Glaucoma Valve Surgery

Vascular endothelial growth factor (VEGF) is a pivotal mediator in ocular angiogenesis, inflammation, and postoperative fibrosis. Beyond its well-established role in neovascular ocular diseases, VEGF has increasingly been recognized as a critical contributor to wound healing responses following glaucoma surgery. Elevated VEGF expression enhances vascular permeability, inflammatory cell recruitment, fibroblast proliferation, and extracellular matrix deposition, all of which contribute to subconjunctival fibrosis and encapsulated bleb formation after Ahmed glaucoma valve (AGV) implantation. Consequently, inhibition of VEGF signaling has emerged as a promising strategy for modulation of postoperative wound healing and improvement of long-term glaucoma drainage device outcomes. [35,36]

VEGF is produced by multiple ocular tissues including retinal pigment epithelium, vascular endothelial cells, macrophages, fibroblasts, and inflammatory cells in response to tissue hypoxia, ischemia, and surgical trauma. In refractory glaucomas, particularly neovascular glaucoma (NVG), VEGF levels become markedly elevated because of retinal ischemia associated with proliferative diabetic retinopathy or retinal vein occlusion. VEGF stimulates proliferation of fragile neovessels over the iris and anterior chamber angle while simultaneously promoting fibrovascular membrane formation and inflammatory fibrosis. These biologic processes significantly increase the risk of surgical failure following filtration procedures and glaucoma drainage device implantation. [17,37]

Experimental studies have demonstrated that VEGF is not solely an angiogenic mediator but also an important regulator of fibrosis. VEGF enhances fibroblast migration, promotes transformation into myofibroblasts, and increases collagen synthesis through activation of multiple intracellular signaling pathways. Additionally, increased vascular permeability induced by VEGF facilitates leakage of plasma proteins and inflammatory mediators into subconjunctival tissues, thereby intensifying postoperative scar formation. Li et al. demonstrated that VEGF inhibition significantly reduced fibroblast proliferation and subconjunctival fibrosis after glaucoma filtration surgery, supporting the concept that anti-VEGF therapy may serve as an effective adjunctive antifibrotic strategy in glaucoma surgery. [18]

Ranibizumab is a recombinant humanized monoclonal antibody fragment designed to bind and neutralize all biologically active isoforms of VEGF-A. Because of its smaller molecular size compared with full-

length antibodies, ranibizumab demonstrates enhanced tissue penetration and rapid biologic activity. Although originally developed for retinal vascular diseases, its potential role in glaucoma surgery has gained increasing attention due to its combined antiangiogenic and antifibrotic properties. By suppressing VEGF-mediated vascular proliferation and inflammatory fibrosis, ranibizumab may reduce postoperative subconjunctival scarring and improve aqueous humor filtration following AGV implantation. [38]

Anti-VEGF therapy may be administered through several routes during glaucoma surgery, including subconjunctival, intracameral, intravitreal, or topical application. Subconjunctival administration directly targets fibrovascular tissues surrounding the implant and may provide localized inhibition of postoperative scarring. Intravitreal injection is particularly valuable in neovascular glaucoma because it simultaneously suppresses retinal ischemia-driven neovascularization and reduces iris and angle neovessels before surgery. Preoperative anti-VEGF administration has also been associated with reduced intraoperative and postoperative hyphema by inducing regression of fragile neovascular vessels. This is clinically important because postoperative hyphema itself may aggravate inflammation and fibrosis around the drainage implant. [39,40]

Several clinical studies have investigated the role of anti-VEGF therapy as an adjunct to Ahmed glaucoma valve implantation. Miraftabi et al. evaluated the effect of subconjunctival bevacizumab injection during AGV surgery and reported improved postoperative IOP control together with reduced incidence of encapsulated bleb formation. Other reports similarly demonstrated that anti-VEGF therapy may decrease postoperative vascularity, inflammation, and hypertensive phase severity following AGV implantation. In neovascular glaucoma, combined AGV implantation and anti-VEGF therapy has shown particular benefit because VEGF suppression targets both the primary ischemic pathology and postoperative fibrotic response. [13,41]

Despite these favorable findings, anti-VEGF therapy alone may not completely prevent postoperative fibrosis because wound healing involves multiple cytokines and cellular pathways beyond VEGF signaling. Some studies demonstrated that the antifibrotic effect of anti-VEGF agents may be temporary, with recurrence of neovascularization and fibrovascular activity occurring several months after treatment. Additionally, variability in administration timing, dosage, injection route, and patient selection contributes to heterogeneity among published studies. Consequently, the long-term superiority of anti-VEGF therapy over other wound modulation strategies remains uncertain. [39,41]

Compared with conventional antimetabolites, anti-VEGF therapy offers the theoretical advantage of more selective biologic modulation without inducing excessive tissue toxicity or avascular bleb formation. Unlike mitomycin-C, which indiscriminately suppresses cellular proliferation, VEGF inhibition primarily targets angiogenesis-associated fibrosis and inflammatory vascular responses. This distinction may be particularly important in eyes with severe ischemia and active neovascularization, where VEGF-driven pathology plays a dominant role in surgical failure. [35,36]

The integration of anti-VEGF agents into glaucoma drainage surgery reflects the evolving understanding of fibrosis as a multifactorial biologic process involving angiogenesis, inflammation, and extracellular matrix remodeling. Current evidence suggests that ranibizumab and other anti-VEGF agents may improve AGV outcomes through suppression of fibrovascular proliferation and modulation of postoperative wound healing. However, further prospective randomized studies with standardized protocols and long-term follow-up are required to define the optimal therapeutic regimen, timing of administration, and patient populations most likely to benefit from adjunctive anti-VEGF therapy in refractory glaucoma surgery. [13,35]

Comparative Clinical Outcomes of Ologen and Anti-VEGF Therapy in Ahmed Glaucoma Valve Surgery

Optimization of long-term Ahmed glaucoma valve (AGV) success depends primarily on controlling postoperative fibrosis and maintaining adequate permeability of the filtering capsule surrounding the implant plate. Both Ologen collagen matrix and anti-vascular endothelial growth factor (anti-VEGF) therapy were introduced as adjunctive strategies aiming to improve wound healing modulation after AGV implantation. Although these modalities act through fundamentally different mechanisms, both have

demonstrated potential benefits regarding intraocular pressure (IOP) control, reduction of encapsulation, and modulation of the hypertensive phase. Nevertheless, currently available evidence remains heterogeneous, with considerable variability in surgical techniques, patient populations, glaucoma subtypes, and follow-up duration. [42,43]

One of the principal parameters used to evaluate postoperative efficacy is the degree of IOP reduction achieved after surgery. Studies evaluating Ologen augmentation in AGV implantation have generally demonstrated favorable postoperative pressure control with reduced incidence of excessive capsular fibrosis. Kim et al. reported significant IOP reduction after AGV implantation with Ologen augmentation, together with lower encapsulation rates compared with conventional surgery alone. Similarly, Harizman et al. observed improved bleb morphology and more stable postoperative pressure control in eyes receiving Ologen-assisted AGV implantation. The proposed explanation for these findings is that the collagen matrix promotes diffuse subconjunctival remodeling and reduces formation of dense fibrotic tissue around the plate. [11,34]

Anti-VEGF therapy has likewise demonstrated promising effects on postoperative IOP control, particularly in eyes with neovascular glaucoma where VEGF-mediated inflammation and angiogenesis are highly active. Miraftabi et al. showed that subconjunctival bevacizumab administration during AGV surgery was associated with improved IOP reduction and decreased encapsulated bleb formation. Reduction of postoperative vascular permeability and fibrovascular proliferation likely contributes to improved aqueous humor filtration during the early healing period. Additionally, suppression of iris and angle neovascularization may decrease postoperative inflammation and reduce the incidence of hyphema, which is considered an important risk factor for surgical failure. [41,44]

The hypertensive phase remains one of the most important determinants of long-term AGV success. This phase typically develops within the early postoperative months and is characterized by elevation of IOP secondary to fibrovascular encapsulation around the implant plate. Several studies suggest that Ologen may reduce the incidence or severity of the hypertensive phase by mechanically modulating fibroblast proliferation and maintaining a more permeable filtration capsule. Anti-VEGF therapy may also attenuate hypertensive phase development through suppression of angiogenesis and inflammatory fibrosis during the critical early healing period. However, the duration of anti-VEGF biologic activity may be limited, and recurrence of fibrovascular proliferation may occur after drug clearance. [25,26,43]

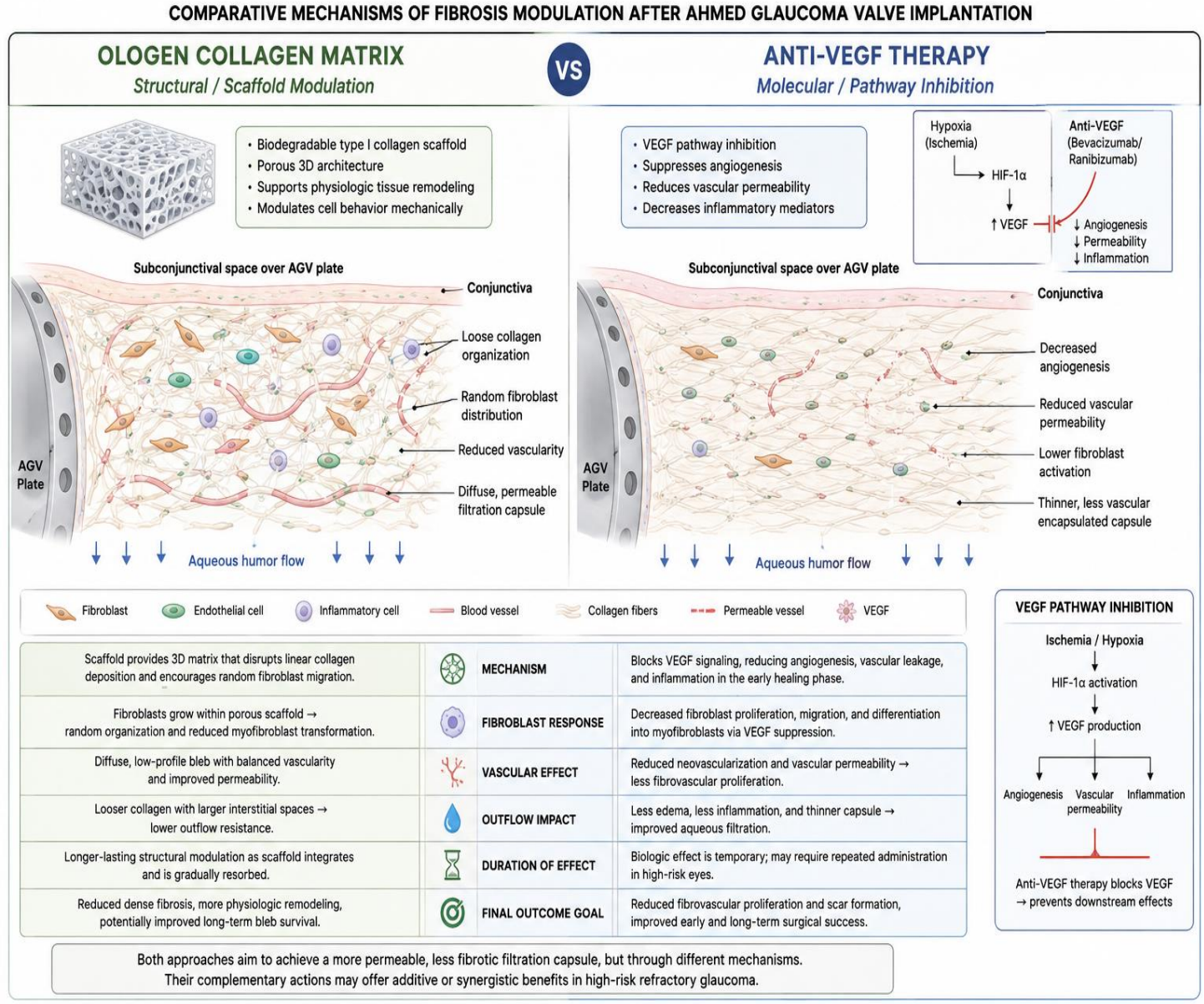
Another important outcome measure is the postoperative need for topical antiglaucoma medications. Both Ologen augmentation and anti-VEGF therapy have generally been associated with reduced dependence on medications following AGV implantation. Improved aqueous outflow through less fibrotic bleb architecture may explain this finding. However, long-term maintenance of medication-free IOP control remains inconsistent among published studies, suggesting that wound healing modulation alone may not completely prevent progressive capsular remodeling over time. [11,41]

With regard to complications, Ologen offers the theoretical advantage of physiologic tissue remodeling without inducing the excessive wound suppression associated with traditional antimetabolites. The implant is biodegradable and generally demonstrates favorable biocompatibility with reduced risk of avascular bleb formation or tissue necrosis. Nevertheless, concerns remain regarding implant positioning, biodegradation variability, and the possibility of insufficient antifibrotic activity in highly inflamed eyes. In contrast, anti-VEGF therapy provides selective molecular inhibition of angiogenesis but may exhibit only temporary biologic effects because VEGF represents one component of the complex wound healing cascade. Furthermore, repeated anti-VEGF injections may occasionally be required in severe neovascular glaucoma to maintain suppression of ischemia-driven VEGF production. [31,35]

Direct comparative studies between Ologen and anti-VEGF therapy in AGV surgery remain extremely limited. Existing literature largely consists of isolated studies evaluating each modality independently rather than true head-to-head comparisons. Consequently, definitive conclusions regarding superiority of one strategy over the other cannot currently be established. Mechanistically, Ologen primarily functions as a structural scaffold that modifies tissue architecture and fibroblast organization, whereas anti-VEGF therapy targets molecular pathways involved in angiogenesis and inflammatory fibrosis. These differing

mechanisms suggest that both therapies may potentially provide complementary rather than mutually exclusive effects. [16,31,35]

Current evidence suggests that both Ologen collagen matrix and anti-VEGF therapy may improve surgical outcomes after Ahmed glaucoma valve implantation through reduction of postoperative fibrosis and modulation of wound healing responses. However, variability among published studies and absence of large randomized comparative trials continue to limit evidence-based recommendations. Future investigations should focus on standardized surgical protocols, long-term follow-up, and exploration of combined biologic approaches capable of targeting multiple pathways involved in postoperative fibrosis and bleb encapsulation. [11,35,41]



Histopathologic and Molecular Perspectives of Fibrosis Modulation

Histopathologic evaluation of filtering capsules surrounding Ahmed glaucoma valve (AGV) implants has provided important insights into the mechanisms responsible for long-term surgical failure. The fibrous capsule formed around the episcleral plate is the principal determinant of aqueous humor permeability and postoperative intraocular pressure (IOP) control. Successful filtration depends not only on formation of a

capsule itself, but also on its thickness, vascularity, cellular composition, and extracellular matrix organization. Excessive fibrosis results in development of dense poorly permeable tissue that increases resistance to aqueous drainage and compromises long-term surgical efficacy. [45,46]

Microscopic studies of encapsulated blebs after glaucoma drainage device implantation have demonstrated marked fibroblast proliferation, dense collagen deposition, inflammatory cell infiltration, and increased vascularity. Activated fibroblasts and myofibroblasts are considered the major cellular mediators responsible for extracellular matrix production and tissue contraction within the capsule. Histologically, failed blebs often exhibit thick irregular collagen bundles arranged in compact parallel orientation with reduced interstitial spaces available for aqueous diffusion. This dense connective tissue architecture significantly impairs transcapsular filtration and contributes directly to development of the hypertensive phase. [28,45]

Angiogenesis plays an equally important role in postoperative fibrosis. Newly formed vessels increase vascular permeability and facilitate migration of inflammatory mediators and fibroblasts into subconjunctival tissues surrounding the implant. VEGF-driven vascular proliferation therefore acts synergistically with fibroblast activation to accelerate scar formation. Experimental studies demonstrated that increased VEGF expression correlates with greater fibrovascular activity and more aggressive postoperative fibrosis following glaucoma surgery. Consequently, suppression of VEGF signaling has become a major molecular target in efforts to improve long-term glaucoma drainage surgery outcomes. [18,35]

The antifibrotic effect of anti-VEGF therapy is believed to extend beyond simple inhibition of angiogenesis. VEGF blockade reduces endothelial cell proliferation, decreases vascular leakage, and suppresses inflammatory cytokine recruitment into healing tissues. In addition, VEGF inhibition appears to reduce fibroblast migration and myofibroblast differentiation, thereby limiting collagen synthesis and extracellular matrix remodeling. Histopathologic studies following anti-VEGF administration demonstrated thinner filtering capsules with reduced vascularity and lower fibrocellular density compared with untreated eyes. These findings support the concept that anti-VEGF therapy may improve aqueous humor filtration by producing a less fibrotic and more permeable subconjunctival environment. [18,35]

In contrast to molecular inhibition of fibrosis, Ologen collagen matrix acts primarily through biomechanical and structural modulation of tissue healing. The porous three-dimensional architecture of Ologen distributes fibroblasts randomly throughout the scaffold and prevents the linear organization of collagen fibers typically observed in dense scar tissue. Histologic studies have shown that Ologen-assisted healing is associated with loosely arranged connective tissue, diffuse extracellular matrix deposition, and reduced myofibroblast transformation. Instead of forming thick encapsulated tissue, the subconjunctival space develops a more physiologic architecture with enhanced filtration capacity and improved aqueous diffusion. [31,42]

Bleb morphology analysis has further supported the beneficial effect of Ologen on subconjunctival remodeling. Imaging studies demonstrated that Ologen-assisted blebs tend to be more diffuse, less vascularly congested, and less encapsulated than conventional blebs after AGV implantation. Reduced capsular thickness and improved filtration characteristics have also been observed in short-term follow-up studies. These findings suggest that mechanical modulation of fibroblast behavior through scaffold engineering may represent an effective strategy for regulating postoperative wound healing without inducing the tissue toxicity associated with antimetabolites. [42,43]

Despite the favorable biologic effects observed with both Ologen and anti-VEGF therapy, fibrosis after AGV implantation remains multifactorial and highly complex. Multiple cytokines, growth factors, inflammatory mediators, and cellular pathways contribute simultaneously to postoperative wound healing. Transforming growth factor-beta (TGF-β), fibroblast growth factors, macrophage activation, and extracellular matrix metalloproteinases all interact with VEGF-mediated pathways during subconjunctival remodeling. Consequently, inhibition of a single pathway may not completely prevent progressive fibrosis in high-risk eyes. This complexity likely explains the variability observed among clinical studies evaluating individual antifibrotic modalities. [16,27]

The evolving understanding of fibrosis biology has shifted modern glaucoma surgery toward more targeted and physiologic wound healing modulation. Rather than indiscriminate suppression of tissue repair, current strategies increasingly focus on selective regulation of fibroblast activity, angiogenesis, extracellular matrix remodeling, and inflammatory signaling. Future therapies may combine structural biomaterials such as Ologen with molecular inhibitors including anti-VEGF agents to achieve synergistic control of postoperative fibrosis. Such combined approaches may ultimately improve long-term AGV survival and reduce the incidence of encapsulated bleb failure in refractory glaucoma surgery. [27,35]

Current Limitations of Available Evidence

Despite the growing interest in fibrosis modulation after Ahmed glaucoma valve (AGV) implantation, the currently available literature regarding Ologen collagen matrix and anti-vascular endothelial growth factor (anti-VEGF) therapy remains limited by several important methodological and clinical factors. These limitations significantly affect interpretation of published outcomes and complicate direct comparison between different adjunctive strategies. Consequently, although preliminary findings are encouraging, definitive conclusions regarding long-term superiority and optimal therapeutic protocols cannot yet be established. [47,48]

One of the major limitations is the relatively small sample size of most published studies. Many investigations evaluating Ologen or anti-VEGF therapy in AGV surgery were conducted on limited patient populations, reducing statistical power and increasing susceptibility to selection bias. In addition, refractory glaucoma itself represents a highly heterogeneous disease spectrum that includes neovascular, uveitic, post-vitrectomy, traumatic, pediatric, and secondary glaucomas, each with distinct inflammatory and fibrotic profiles. Pooling such heterogeneous cases may significantly influence surgical outcomes and limit the generalizability of study conclusions. [11,41]

Another important issue is the variability in surgical techniques and adjunctive protocols among different studies. Considerable differences exist regarding implant model selection, tube positioning, use of patch grafts, intraoperative antimetabolite application, timing and dosage of anti-VEGF administration, and positioning of Ologen implants. Some studies utilized subconjunctival anti-VEGF injection, whereas others employed intravitreal administration or combined approaches. Similarly, Ologen placement techniques varied between implantation over the plate, beneath Tenon’s capsule, or around the filtration area. Such procedural heterogeneity complicates interpretation of comparative efficacy and makes direct inter-study comparison difficult. [21,43]

Duration of follow-up also represents a significant limitation in the current literature. Fibrosis after AGV implantation is a dynamic long-term process that may continue for years after surgery. However, many studies evaluating Ologen or anti-VEGF therapy report outcomes limited to short-term or intermediate follow-up periods. Early postoperative improvement does not necessarily predict long-term implant survival because progressive subconjunctival remodeling and delayed encapsulation may still occur over time. Therefore, the absence of prolonged follow-up data limits understanding of the durability of these antifibrotic interventions. [24,26]

The hypertensive phase itself lacks complete standardization across studies. Although generally defined as postoperative elevation of intraocular pressure following initial surgical success, variations exist regarding diagnostic criteria, timing, and severity thresholds. Some studies consider any transient pressure elevation as hypertensive phase, whereas others apply stricter criteria requiring sustained IOP elevation above specific thresholds. Such inconsistency contributes to variability in reported incidence rates and limits accurate assessment of the true effect of fibrosis modulation strategies on hypertensive phase prevention. [25,26]

Another important limitation is the relative scarcity of true head-to-head comparative studies between Ologen and anti-VEGF therapy. Most currently available evidence evaluates each modality independently against conventional AGV implantation rather than directly comparing the two approaches. Furthermore, several anti-VEGF studies primarily involve bevacizumab rather than ranibizumab specifically, despite pharmacologic differences between these agents regarding molecular size, tissue penetration, and biologic activity. Consequently, extrapolation of results between different anti-VEGF agents should be interpreted

cautiously. [35,38]

Potential publication bias may also influence the current literature. Studies reporting favorable surgical outcomes are generally more likely to be published than investigations demonstrating limited benefit or negative results. In addition, many studies originate from single centers with limited patient populations and variable surgeon experience, further reducing external validity. Because glaucoma drainage surgery outcomes are highly dependent on surgical expertise and postoperative management, variability between centers may substantially affect reported efficacy rates. [21,47]

Finally, postoperative fibrosis is mediated through multiple overlapping biologic pathways involving fibroblast activation, inflammatory cytokines, angiogenesis, extracellular matrix remodeling, and immune responses. Therefore, targeting a single pathway alone may be insufficient to completely prevent progressive bleb encapsulation. Future investigations should focus on integrated multimodal approaches capable of simultaneously modulating structural, inflammatory, and molecular components of wound healing. Larger prospective randomized controlled trials with standardized surgical protocols and long-term follow-up are essential to establish evidence-based recommendations regarding the optimal use of Ologen and anti-VEGF therapy in AGV surgery. [16,27]

Future Directions and Emerging Perspectives

The growing understanding of postoperative fibrosis following Ahmed glaucoma valve (AGV) implantation has led to a major shift in glaucoma surgery research toward development of targeted biologic and biomaterial-based wound modulation strategies. Conventional antimetabolites such as mitomycin-C remain effective in suppressing fibroblast proliferation; however, their nonspecific cytotoxicity and associated complications continue to limit their ideal long-term use. Consequently, future therapeutic approaches are increasingly focused on achieving selective regulation of wound healing pathways while preserving physiologic tissue repair and maintaining long-term filtration function. [49,50]

One of the most promising future directions involves combined multimodal antifibrotic therapy. Because postoperative fibrosis is mediated through multiple overlapping pathways involving angiogenesis, fibroblast activation, inflammatory cytokines, and extracellular matrix remodeling, targeting a single pathway alone may be insufficient in high-risk refractory glaucoma. Combining structural biomaterials such as Ologen collagen matrix with molecular inhibitors including anti-VEGF agents may potentially provide synergistic effects by simultaneously modulating tissue architecture and suppressing inflammatory angiogenesis. Such combined approaches may improve long-term bleb permeability and reduce progressive encapsulation around the AGV plate. [16,35]

Advances in tissue engineering and biomaterial science have also stimulated development of newer biodegradable scaffolds capable of more sophisticated wound healing control. Future collagen-based implants may incorporate controlled-release pharmacologic agents, anti-inflammatory molecules, or growth factor modulators within the scaffold itself. These bioengineered matrices may allow prolonged localized delivery of antifibrotic therapy directly to subconjunctival tissues while minimizing systemic exposure and reducing the need for repeated postoperative interventions. Improvement in scaffold porosity, biodegradation kinetics, and biomechanical properties may further optimize subconjunctival remodeling after glaucoma drainage surgery. [31,32]

Sustained-release anti-VEGF systems represent another evolving area of interest in glaucoma surgery. Current anti-VEGF administration methods provide relatively temporary biologic activity because of rapid intraocular drug clearance. Consequently, recurrent VEGF expression and fibrovascular proliferation may occur several weeks or months after surgery. Long-acting drug delivery platforms including biodegradable microspheres, hydrogels, and implantable reservoirs may provide prolonged VEGF suppression during the critical postoperative healing period. Such technologies could potentially improve long-term fibrosis control while reducing the burden of repeated injections. [35,36]

Increasing attention has also been directed toward identification of novel molecular targets involved in subconjunctival fibrosis. In addition to VEGF, several cytokines and signaling pathways including transforming growth factor-beta (TGF-β), connective tissue growth factor, matrix metalloproteinases, and inflammatory macrophage pathways contribute significantly to postoperative scar formation. Future

therapies may involve selective inhibition of multiple profibrotic mediators simultaneously, thereby achieving more comprehensive modulation of wound healing responses. Advances in molecular biology and genomic profiling may further facilitate development of individualized antifibrotic therapies tailored to specific patient risk profiles. [16,27]

Artificial intelligence and advanced ocular imaging technologies may also contribute significantly to future glaucoma surgery optimization. High-resolution anterior segment optical coherence tomography and ultrasound biomicroscopy can already provide detailed assessment of bleb morphology, capsular thickness, and subconjunctival remodeling after AGV implantation. Integration of imaging biomarkers with predictive artificial intelligence algorithms may eventually allow early identification of eyes at high risk of fibrosis and hypertensive phase development. Such predictive systems could facilitate personalized postoperative management and earlier intervention before irreversible filtration failure occurs. [21,42]

Future randomized controlled trials remain critically needed to establish standardized protocols regarding the use of Ologen and anti-VEGF therapy in AGV surgery. Larger multicenter studies with longer follow-up durations and uniform outcome definitions are essential to accurately determine long-term efficacy, safety, cost-effectiveness, and optimal patient selection criteria. Particular attention should be directed toward direct comparative studies between different antifibrotic modalities as well as evaluation of combination therapies in severe refractory glaucoma subtypes such as neovascular and uveitic glaucoma. [43,44]

The future of glaucoma drainage surgery is likely to evolve toward more biologically targeted and personalized modulation of wound healing rather than indiscriminate suppression of fibrosis. Improved understanding of subconjunctival tissue biology, combined with advances in biomaterials, pharmacology, molecular therapeutics, and imaging technologies, may ultimately enhance long-term AGV survival and significantly improve visual outcomes in patients with refractory glaucoma. [16,35]

Conclusion

Postoperative fibrosis remains the principal factor limiting long-term success after Ahmed glaucoma valve implantation in refractory glaucoma. Excessive fibroblast proliferation, angiogenesis, and extracellular matrix remodeling contribute significantly to encapsulated bleb formation and hypertensive phase development, ultimately compromising aqueous humor drainage and intraocular pressure control. Both Ologen collagen matrix and anti-vascular endothelial growth factor therapy have emerged as promising adjunctive approaches for modulation of postoperative wound healing through different yet potentially complementary mechanisms. Ologen promotes physiologic subconjunctival remodeling by providing a biodegradable scaffold that reduces dense scar formation, whereas anti-VEGF therapy suppresses angiogenesis and VEGF-mediated inflammatory fibrosis at the molecular level. Current evidence suggests that both modalities may improve surgical outcomes, reduce postoperative fibrosis, and enhance bleb function after Ahmed glaucoma valve surgery. However, available studies remain limited by heterogeneity in design, surgical protocols, and follow-up duration, with insufficient direct comparative evidence to establish clear superiority of one strategy over the other. Future large-scale prospective studies are required to better define optimal indications, administration techniques, and long-term efficacy of these antifibrotic approaches. Continued advances in tissue engineering, molecular therapeutics, and personalized wound healing modulation are expected to further improve the long-term success of glaucoma drainage surgery in patients with refractory glaucoma.

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