Antifibrotics in glaucoma surgery: current practices and future directions

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Purpose of review
This review aims to cover the current landscape of antifibrotics used in glaucoma surgery and discuss developing antifibrotic agents. This review will inform the reader of new antifibrotic agents in development, clinical trials and clinical use that may alter the standard of care in glaucoma surgery in the near future.

Recent findings
Mitomycin-C (MMC) remains the most commonly used antifibrotic in glaucoma surgery to date with expanding use beyond trabeculectomy into the world of minimally invasive bleb forming surgeries. MMC continues to cause similar side effects due to toxicity which is a main driver of innovation. Newer antifibrotic agents are under investigation at all stages of drug development from bench research to clinical use. Familiar agents such as bevacizumab, sodium hyaluronate, and matrix metalloproteinases have shown noninferior success rates to MMC when used as adjunct agents with filtration surgery. Many other antifibrotics agents are being investigated with mixed results.

Summary
While MMC remains the gold standard antifibrotic agent for glaucoma surgery, there are numerous antifibrotic agents in development with safer side effect profiles and similar success rates that may change the surgical practice of glaucoma.

Keywords
antifibrotics, filtration surgery, mitomycin-C

Fibrosis is a leading cause of primary failure in glaucoma filtering surgery. Despite improvements in surgical techniques, scarring of the conjunctiva and sclera continues to pose a significant challenge. The introduction of mitomycin C (MMC) in 1983 and 5-fluorouracil (5-FU) in 1984 enhanced the effectiveness and durability of filtering blebs. These antifibrotic agents are standard of care for bleb forming filtration surgery. However, their off-label application comes with risks, including bleb leak, hypotony, blebitis, and endophthalmitis underscoring the need for alternative approaches to prevent filtration failure. The primary risk of failure remains wound scarring, particularly episcleral fibrosis, which can jeopardize long-term intraocular pressure (IOP) control. The wound healing process, characterized by inflammatory, proliferative, and remodeling phases, is influenced by fibroblasts, which play a crucial role in fibrosis development. This review examines current practices and emerging strategies in wound healing modulation for glaucoma surgery.

CURRENT STANDARD ANTIFIBROTICS

The two most commonly used antifibrotic agents in glaucoma surgery today are mitomycin-C (MMC) and 5-fluorouracil (5-FU). We will review their most recent updates.

5-Fluorouracil

5-FU is a chemotherapeutic agent that inhibits DNA synthesis, preventing fibroblast proliferation and collagen contraction [1–3]. 5-FU has been used to modulate the scarring process after filtering surgery as subconjunctival injections at the time of surgery or thereafter to revive a failing bleb [1–5]. 5-FU is primarily used on an ad-hoc basis or in cases of imminent bleb failure. It has fallen out of favor due to the need for increased visits, discomfort from repeated injections, and epithelial toxicity [1,3,6,7]. Current uses of 5-FU include postoperative failing

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KEY POINTS

- Mitomycin-C remains the most commonly used antifibrotic agent in bleb-forming glaucoma surgery to date.
- There are novel antifibrotic agents in trials and clinical use that may supplant MMC as antifibrotics of choice for bleb forming procedures given their promising results with fewer side effects as compared to MMC.
- Novel delivery methods may further augment these potentially novel antifibrotic agents.

bleb needling for trabeculectomy or XEN gel stent implants (AbbVie, North Chicago, Illinois, USA) [8].

Mitomycin-C

MMC is a DNA-crosslinking-alkylating agent that inhibits the cell cycle, DNA replication, cell mitosis, and protein synthesis [9–11]. MMC is currently the gold standard antifibrotic used at the time of glaucoma filtration surgery. It has a long history of reducing scar formation, increasing bleb survival, and maintaining IOP reduction in bleb forming, filtration procedures [12–18]. It is routinely used in subconjunctival/sub-Tenon's glaucoma filtration surgery, glaucoma drainage device implantation and with newer minimally invasive bleb surgery (MIBS) procedures [19].

Preoperative subconjunctival injection and intraoperative direct scleral application of MMC have shown comparable surgical outcomes [20]. Studies have shown mixed results regarding surgical failure rates providing no strong evidence that one application method is superior to another [20–26], however research has suggested sub-Tenon's injection of MMC may lead to more favorable bleb morphology [24]. MMC is more potent than 5-FU, and may be associated with higher complication rates [27–29]. Combining a lower dosage of MMC with valproic acid has shown promise to mitigate these complications and increase effectivity in rabbit models [30,31]. While it is well established that MMC improves outcomes after trabeculectomy, it has not clearly been shown to improve outcomes when used to augment tube shunt glaucoma drainage device surgery [32▪▪,33,34]. MMC C, as well as 5-FU, have been used to augment MIBS procedures with early evidence suggesting they improve success rates with these surgeries [35]. Over the course of their experience with gel stent implantation, surgeons have refined their techniques for using mitomycin-C (MMC), gradually moving toward lower doses than in trabeculectomy. Common approaches include the use of MMC-soaked sponges at concentrations of 0.2–0.4 mg/ml for 2–3 min, or the administration of sub-Tenon injections ranging from 10 to 40 μg. In the Gold Standard Prospective Study (GPS) comparing XEN gel stent with trabeculectomy, most surgeons incorporated a subconjunctival injection of 40 μg of MMC in both surgical procedures [36]. Similarly, in the primary needling study, a dose of 0.1 ml of MMC at a concentration of 0.02% was injected approximately 6 mm from the limbus [36].

EMERGING ANTIFIBROTIC AGENTS

These novel therapies aim to improve outcomes by providing more targeted and sustained modulation of wound healing, with the goal of reducing scarring while minimizing complications associated with traditional agents. We will review the latest updates on the most promising agents' development, clinical applications, and potential role in advancing glaucoma surgery. See Table 1 for a list of all agents that are currently in animal studies or more advanced stages of research and development.

Beta radiation

Beta radiation inhibits fibroblast proliferation, presumably through the upregulation of p53, a pivotal enzyme in the regulation of the cell cycle, thereby reducing the formation of fibrosis [37–41]. This form of radiation primarily affects extracellular matrix (ECM) production rather than influencing fibroblast migration or contraction. The advantages of beta radiation include its ease of application, cost-effectiveness, and wide accessibility. However, the disadvantages encompass the risk of cataract formation and keratopathy [38–41].

Transforming growth factor beta

Transforming growth factor beta (TGFβ) serves as a crucial cytokine in ocular fibrosis, facilitating the processes of fibroblast proliferation, migration, and collagen synthesis [42–45]. Among its isoforms, TGFβ2 is the most prevalent in ocular tissues and in vitro studies have shown its inhibition is comparable to MMC in antifibrosis [42,46]. The monoclonal antibody Lerdelimumab specifically targets TGFβ and was promising, however it did not demonstrate efficacy in human clinical trials [47]. SMAD proteins function as critical downstream effectors of the TGFβ signaling pathway. Strategies aimed at modulating SMAD proteins have demonstrated a reduction in ECM deposition, myofibroblast activation, and tissue scarring, underscoring the

Table 1. Overview of antifibrotic agents and drug delivery systems, with their molecular targets, and current developmental phase

Agent	Mechanism of action	Current development phase	References
5-Fluorouracil (5-FU)	Antimetabolite: inhibits pyrimidine metabolism	Clinical use	[1–8]
Mitomycin-C (MMC)	Alkylating agent: cross-links DNA	Clinical use	[8–28,36]
Bevacizumab and Ranibizumab	VEGF inhibitor	Clinical Use and Investigations	[61–66]
Cyclosporine and Sirolimus	IL-2 and IL-2 receptor down regulation	Clinical Investigations and Animal models	[91–94]
Human Amniotic Membrane	Multimodal: Anti-inflammatory, antifibrotic, antiangiogenic	Clinical trials and systematic reviews	[95–97]
Beta Radiation	Inhibit fibroblast proliferation via upregulation of p53	Clinical Trials	[37–41]
TGF Beta 2 inhibition (ITF2357, SB-431542, CAT-152)	Inhibit fibroblast proliferation, migration, and collagen synthesis	Clinical trials	[42–45,47]
Sodium Hyaluronate	Physical barrier and space occupier to inhibit fibrosis	Clinical trials	[102,103]
Ologen	Collagen matrix, physical barrier and space occupier	Clinical trials	[104,105▪▪]
Hydrogel	Physical barrier and space occupier	Clinical trials	[115,116▪▪,117–120]
Losartan	Angiotensin II Receptor Antagonist	Clinical Trials	[106–108]
Rho kinase inhibitors	Anti-inflammatory, antifibrotic, smooth muscle relaxation	Clinical trials	[55]
Decorin	TGF-Beta down regulator	Clinical trials	[132] Clinical Trial Number NCT03924544
Perfluoropropane Gas (C3F8)	Physical barrier and space occupier to inhibit fibrosis	Animal models and preclinical trials	[133]
Valproic Acid (in combination with MMC)	Reduces collagen expression	Animal models	[30,31]
SPARC inhibition	Inhibits ECM production and organization	Animal models	[57–58]
PDGF Subunit B inhibition	Inhibit fibrosis	Animal models	[134]
Saratin	Platelet aggregation inhibition and inhibition of collagen-platelets	Animal models	[67–69]
LOX inhibition	Inhibition of collagen and elastin	Animal models	[70–74]
Doxycycline and Ilomastat	Matrix-Metalloproteinase inhibitor	Animal models	[75–79,81–84]
MRTF/SRF inhibitors	Fibroblast and matrix-metalloproteinase inhibitors	Animal models	[135]
Epigenetic modifiers (vorinostat and trichostatin A)	DNA histone deacetylase inhibitors	Animal models	[85–88]
Nintedanib	Tyrosine-Kinase inhibitor	Animal models	[136]
Pirfenidone	Inhibits TGF-Beta	Animal models	[52,53]
CKDN1B	overexpression Cell-Cycle inhibition	Animal models	[90]

Table 1 (*Continued*)

Agent		Mechanism of action	Current development phase	References
	SB-43152	ALK5-inhibition (TGF-Beta pathway)	Animal models	[46]
	Metformin	AMPK/Nrf2 activation	Animal models	[137]
	Rapamycin	mTOR inhibition	Animal models	[138]
	Triamcinolone	Anti-inflammatory	Animal models	[111–113]
	GM6001	Matrix metalloproteinase inhibitor	Animal models	[80]
	3′, 4′-Dihydroxyflavonol	TGF-Beta inhibition	Animal models	[129,130]
	Rosiglitazone	PPAR-gamma inhibition	Animal models	[139]
Pathways				
	Retinoic acid signaling	Upstream fibrosis signaling	Animal models	[131]
Delivery systems				
	Expanded polytetrafluoroethylene	Tube shunt alternative material to silicone	Clinical trials	[128▪▪]
	Nanoparticle encapsulation	Enhance cell membrane penetration and resist enzymatic degradation	Preclinical models	[123–125]
	Liposomal delivery systems	Extend duration of pharmaceutical agents	Rabbit models	[121,122]
	Dendrimers	Anti-inflammatory	Rabbit models	[126,127]

therapeutic potential of SMAD-targeted interventions in controlling TGFβ-driven fibrosis [43,44,48–51]. TGFβ-induced factors (TGIFs) function to repress SMAD-dependent signaling. Gene editing of TGIF1 through CRISPR/Cas9 technology has resulted in a reduction of myofibroblast differentiation in vitro [43]. Vorinostat, a histone deacetylase inhibitor, has been found to enhance TGIF levels, subsequently leading to suppression of profibrotic gene expression [44]. Pirfenidone inhibits TGFβ while concurrently reducing TNFα levels and studies have suggested it enhances trabeculectomy success in rabbit models [52,53].

Yes-associated protein

The YAP and the transcriptional co-activator with a PDZ-binding motif (TAZ) play significant roles in the activation of SMAD2/3 and in mediating the transmission of mechanical stiffness to the myofibroblast phenotype [54–56]. Recent studies highlight the potential of targeting YAP/TAZ signaling pathways to enhance surgical outcomes in glaucoma by mitigating fibrosis and improving intraocular pressure control [54–56].

ROCK inhibitor

The selective ROCK inhibitor Y-27632 produced marked alterations in cultured human Tenon's fibroblasts (HTFs) without causing significant toxicity or impairing their proliferation. Topical administration of Y-27632 proved potentially effective in reducing scar formation in a rabbit model of glaucoma filtration surgery [55].

Attenuation of SPARC expression

The secreted protein acidic and rich in cysteine (SPARC), classified as a matricellular protein, is upregulated by TGFβ2 and is vital in ECM production and organization [57–59]. The attenuation of SPARC expression in Tenon's fibroblasts has been observed to diminish profibrotic gene expression without inciting apoptosis [57]. Mice lacking SPARC demonstrated enhanced outcomes following glaucoma filtration surgery, attributable to a reduction in collagenous ECM and collagen fibril diameter [58].

Antivascular endothelial growth factor agents

VEGF is integral to angiogenesis and the development of pathological blood vessels during the wound

healing cascade [59,60]. Bevacizumab has demonstrated the ability to inhibit fibroblast proliferation and enhance the quality of scarring through the attenuation of angiogenesis and the modulation of collagen deposition [60]. Some clinical studies indicate a comparable reduction in IOP in relation to MMC, alongside a potentially superior safety profile; however, certain studies reveal a lack of sufficient evidence to advocate for its extensive application [61–66]. A prospective, randomized control trial showed the IOP lowering effect of bevacizumab was as effective as MMC [62]. The combination of bevacizumab and 5-fluorouracil (5-FU) has been shown to result in diminished scarring when compared to either agent administered independently, both *in vitro* and *in vivo*[64].

Collagen-platelet interaction inhibitors

Saratin, a bioactive protein derived from the saliva of leeches, disrupts the binding interactions between platelet integrin α2β1 and collagen, as well as the association between von Willebrand factor and collagen, thereby inhibiting platelet aggregation [67,68]. One study demonstrated Saratin treated blebs survived as long as MMC treated blebs without the adverse tissue effects seen with MMC, such as avascularity or thinning, and no clinical toxicity was observed in rabbits [69].

Lysyl oxidases targeting antibodies

LOX represent a class of enzymes that facilitate the crosslinking of collagen and elastin, with LOXL2 being associated with a multitude of fibrotic pathologies [70–72]. *LOX* gene expression is significantly elevated in the bleb region subsequent to glaucoma filtration surgery [73]. Repeated administration of LOX or LOXL2-targeting antibodies in a rabbit trabeculectomy model significantly decreased collagen deposition and fibrotic changes in Tenon's capsule and conjunctiva [74].

Matrix metalloproteinases inhibitors

MMPs represent a class of proteolytic enzymes that are integral to wound remodeling and collagen synthesis [75–78]. MMP inhibition has been demonstrated to diminish collagen contraction, impede cell migration, and reduce collagen production while exhibiting minimal cytotoxic effects in vitro [75–77,79]. Rabbit models have shown significant reduction in IOP with subconjunctival injection of MMPs after trabeculectomy [80]. Ilomastat, a broad-spectrum MMP inhibitor, prolongs bleb survival in animal models with less surface thinning and more favorable morphology than MMC, suggesting a safer antifibrotic profile [81,82]. Ilomastat complexed with 2–hydroxypropyl–β–cyclodextrin (HP–β–CD) substantially increases solubility while retaining bioactivity, permeates conjunctival tissue ex vivo, and attains therapeutic concentrations in relevant ocular tissues after topical dosing in rabbits, supporting development of an ilomastat–CD eye drop as an antifibrotic therapy to prevent ocular scarring [83,84].

Epigenetic modifiers

Epigenetic modifiers play a pivotal role in the regulation of gene expression through mechanisms such as DNA methylation and histone acetylation [85,86]. Suberoylanilide hydroxamic acid (SAHA) and vorinostat, inhibitors of histone deacetylases (HDAC), have demonstrated reduction in postoperative scarring in rabbit models of glaucoma filtration surgery, showing decreased ECM deposition [86,87]. OBP-801 is an epigenetic regulator that suppresses many genes involved in inflammation and has been shown to effectively reduce fibrosis, collagen deposition, and scar formation after glaucoma filtration surgery in rabbits, leading to longer-lasting filtering blebs and lower IOP [88].

Cell cycle targets

The human p53 gene, recognized as a tumor suppressor, effectively halts the progression of the cell cycle and prompts the process of apoptosis [89]. The overexpression of p53 has been shown to markedly impede the proliferation of fibroblasts and the synthesis of DNA within human Tenon's fibroblasts [78]. The upregulation of CDKN1B, a cyclin-dependent kinase (CDK) inhibitor, in Tenon's fibroblasts after glaucoma filtration surgery in a rabbit model, mediated by the recombinant adenovector expressing exogenous CDKN1B, was shown to inhibit fibroblast proliferation and reduce scarring to improve surgical outcomes [90].

Broad-spectrum immunosuppressives

Cyclosporine inhibits activation of T-cells and their inflammatory response through the downregulation of IL-2 and IL-2 receptor expression [91,92]. The application of topical 2% cyclosporine in the intraoperative and postoperative setting in early animal and human studies failed to demonstrated improvement in bleb function following glaucoma filtration surgery [91–93]. Sirolimus, classified as a macrolide, attenuates the responsiveness of B and T lymphocytes and diminishes the cytokine response [94].

Sirolimus, administered via a sustained-release film, has proven effective in preventing the scarring of filtration blebs and enhancing surgical success rates in a rabbit experimental model [94].

Human amniotic membrane

Human amniotic membrane (HAM) exhibits anti-inflammatory, antifibrotic, and antiangiogenic characteristics [95,96]. Although HAM reduces the inflammatory response associated with healing, the enhancement of bleb longevity must be considered in relation to the potential for delayed recovery [96,97]. A Cochrane Review concluded that mean IOP after trabeculectomy with amniotic membrane transplantation (AMT) was significantly lower than without AMT [97]. A retrospective study indicated that trabeculectomy combined with MMC and AMT did not demonstrate superior outcomes compared to MMC administered alone [98].

Sodium hyaluronate

Healaflow [Healaflow, Geneva, CH], represents a cross-linked form of sodium hyaluronate that is absorbed at a gradual rate, and was found to suppress cytokine and inflammatory factor expression, thereby mitigating scarring and fibrosis [99–101]. Clinical trials conducted on human subjects indicate that Healaflow is likely a well tolerated adjunct in procedures such as trabeculectomy [99,100]. Most recently, a prospective study conducted in Southern India showed that the IOP reduction was statistically similar between the Healaflow and MMC patients undergoing trabeculectomy [101]. Another recent prospective, case-controlled study performed on Chinese patients concluded that complete success at 5 years was higher in the cross-linked sodium hyaluronate gel implantation group than in trabeculectomy alone [102].

Collagen matrix

Ologen (For-Sight Ophthalmics, Cumming, Georgia, USA) is a biodegradable collagen-glycosaminoglycan copolymer matrix implant that functions as a physical spacer [103]. There have been mixed results regarding Ologen's success in tube shunts and trabeculectomy, however clinical trials have demonstrated noninferiority in IOP reduction to MMC when Ologen was used as an adjuvant agent for trabeculectomy and has shown decreased need for postoperative interventions when Ologen and MMC were used in combination as compared to MMC alone [104,105▪▪].

Angiotensin II receptor blocker

Losartan is an FDA approved angiotensin II receptor blocker used for treatment of systemic hypertension. Losartan is known to have antifibrotic effects through downstream inhibition TGFβ signaling via its actions on angiotensin and ERK [106]. In rabbits, topical Losartan has been shown to suppress ocular fibrosis and conjunctival scarring as well as significantly attenuate scar formation in trabeculectomy when used in combination with MMC [106–108]. Similarly, Atorvastatin and Lovastatin were shown to potentially inhibit the proliferation and migration of human Tenon's capsule fibroblasts (HTFs) and improve bleb survival in the rabbit model of GFS [109,110].

Corticosteroids/triamcinolone

The use of corticosteroids as an antifibrotic and anti-inflammatory has a long history in glaucoma surgery. They are primarily used as an adjunct to MMC and have shown success in increasing the success of filtration surgery [111–113]. Different methods of application have been employed such as topical, intracameral, sub-tenon's, retrobulbar, and as a punctal plug with topical being the most popular. Sub-tenon's injection of triamcinolone as an adjunct to MMC has shown improved outcomes as far as 2 years postoperation with loss of statistical significance over longer follow-up [114].

INNOVATIVE ADMINISTRATION TECHNIQUES FOR ANTIFIBROTIC COMPOUNDS IN GLAUCOMA SURGERY

While outside the scope of this review there have also been innovative techniques for administration of these antifibrotics, including hydrogels [115,116▪▪, 117–121], liposomal delivery systems [122,123], nanoparticle encapsulation [124–126], and novel materials [127,128▪▪] with which to make implants that inherently induce less fibrosis.

CONCLUSION

Antifibrotics have transformed glaucoma surgery, not only improving success rates but also introducing risks of vision loss and ocular complications. The ongoing challenge is to develop therapies that act locally, provide consistent and adjustable responses, are safe, affordable, and minimally toxic. More likely than a single solution, a combination of pharmacologic agents and surgical techniques will be needed to achieve long-term, stable IOP reduction without harmful effects. As we search for better treatments,

it remains essential to adapt current approaches to maximize safety and minimize risk for each individual patient. An array of innovative delivery methodologies and biomaterials possesses the capacity to markedly enhance the success rates of glaucoma filtration surgeries through the improvement of drug delivery accuracy, the reduction of cellular toxicity, and the management of inflammatory processes, ultimately culminating in superior IOP regulation and a reduction in postoperative complications.

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Conflicts of interest

There are no conflicts of interest.

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