REVIEW ARTICLE

Modulation Agents of Wound Healing in Ocular Surgeries

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ABSTRACT

Wound healing is a complex process that includes haemostasis and inflammation, followed by a proliferation period and repair and finally remodelling. Ocular surgeries, particularly in glaucoma cases, aim at minimal fibrosis to preserve the function of trabeculectomy as an alternative pathway for aqueous drainage. Hence, it is important to find an agent to modulate the wound healing process. This review presents compilation of wound modulation agents that have been tested in vitro, in vivo, or clinically on patients undergoing ocular surgeries, particularly for glaucoma. We identified agents into four groups, mostly for glaucoma filtration operations: anti-metabolites, anti-growth factors, mechanical barriers and rho kinases. The effect of these agents is highlighted in this review. In conclusion, despite recognized drawbacks of antimetabolites, they are still regarded as the gold standard and the most efficient treatment as anti-scarring agents use in ocular surgeries. More studies are needed to inquire agents that efficient yet has minimal adverse effects both in short and long term.
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INTRODUCTION

Wound healing is a complex dynamic process. It is divided into four overlapping phases. The initial process begins with haemostasis phase and inflammation phase, followed by destruction of the inflammation debris to clean the wound. Once the wound is cleaned, a proliferative phase of angiogenesis and re-epithelialization ensues. At the end of the process, remodelling phase set in where the collagen fibres which mainly produced by fibroblast are reorganized, rearranged and mature to create a permanent scar at their ends (1). The process often involves excessive fibroblastic proliferation that results in a hypertrophic scar confined to the wound site. In some cases, keloid formation occurs where the scar extends beyond the region of the original insult. Post-operative scarring may lead to aesthetic deterioration, loss of function, restriction of movement of the tissue, adverse psychological effects, and failure of certain procedures such as trabeculectomy (2,3).

In any surgical intervention, wound healing is important to ensure the success of the procedure. However, excessive scarring resulted in unfavourable long-term outcome especially involving ocular surgeries which may result in failure of these procedure. Minimizing scarring is essential especially in glaucoma filtration surgeries which include trabeculectomy and glaucoma drainage device implantation. To overcome this challenge, researchers and surgeons have sought modulation agents in various type of surgical procedures. In clinical practice, the use of antineoplastic agents mitomycin C (MMC) and 5-fluorouracil (5-FU) in trabeculectomy is considered the gold standard. However, the existing modulating agents failed to prevent long term excessive scarring and cause potential side effects such as scleral thinning and conjunctival toxicity have prompted researchers to explore new strategies for optimum outcomes (4).

Prior to development of potential new modulating agents, understanding the available agents are crucial. This article provides an overview of the agents that have been used or studied to modulate wound healing in ocular surgeries. Ocular surgeries discussed in this study include glaucoma filtration, oculoplastic, orbital, and strabismus surgery.

MODULATING AGENTS IN OPHTHALMOLOGY

Summary of wound healing and scarring pathway, and how the modulating agents play their role are shown in Fig. 1.

The modulating agents in ocular surgery can be divided into four categories namely anti-metabolites, anti-growth factors, mechanical barriers and Rho-kinase inhibitors.

Antimetabolites

Anti-metabolites which are currently used in modulating ocular wound healing include Mitomycin C and 5-Flurouracil.

Mitomycin C

Mitomycin C (MMC) is a drug used in chemotherapy for decades. It is a methylazirino-pyrroloindoledione antineoplastic antibiotic isolated from the bacterium Streptomyces caespitosus and congeneric species (5). MMC acts by selectively inhibits deoxyribonucleic acid (DNA) synthesis. MMC is toxic to hypoxic cells and prevents protein synthesis (5). It also inhibits B cell, T cell, and macrophage proliferation, antigen presentation, and interferon gamma, tumour necrosis factor alpha (TNF-α), and interleukin-2 secretion in vitro. The main mechanism of action for MMC is alkylation of DNA. MMC requires enzymatic bio reduction to exert its biological effects. The bio reduced MMC in the form of highly reactive bis-electrophilic intermediate alkylates cellular nucleophiles. Other modes of action of MMC are redox cycling and inhibition of r-ribonucleic acid (rRNA).

Primary indication for MMC is as chemotherapy regime for solid tumours (6). It is also used in combination with other chemotherapy agents in the treatment of non-small cell lung, cervical, colorectal, breast, kidney, pancreatic, and oesophageal carcinomas (7–11).

MMC has wider usage other than as chemotherapy regime due to the ability to inhibit all phases of cell synthesis. MMC has regained popularity in ophthalmology due to the nature of ophthalmic surgery, where partial healing is required to determine the surgical success especially in glaucoma surgeries, strabismus surgery and dacryocystorhinostomy. MMC is well accepted worldwide as standard augmentation agent in glaucoma filtering surgery for almost 30 years. In glaucoma surgery, MMC is used as local application on scleral bed using sponge cell soaked with 0.2 to 0.4 mg/ml of MMC for two to three minutes. Based on multiple randomized clinical trials between 1996 and 1997, MMC showed significant effectiveness in lowering the intraocular pressure (IOP) and reducing the scarring (12–22). Andreanos et al. (1997) reported the use of MMC in re-operation for primary open-angle glaucoma achieved significantly lower IOP. However, it was associated with a higher rate and more severe postoperative complications (12). Carlson et al. (1997) reported the usage of MMC during combined phacoemulsification and trabeculectomy surgery, showed improvement in early filtration and IOP reduction (13). There was strong evidence to suggest the superiority of MMC in glaucoma filtration surgeries. A meta-analysis by De Fendi et al. involving five randomised controlled clinical trials, showed MMC usage was associated with a significant lower post-

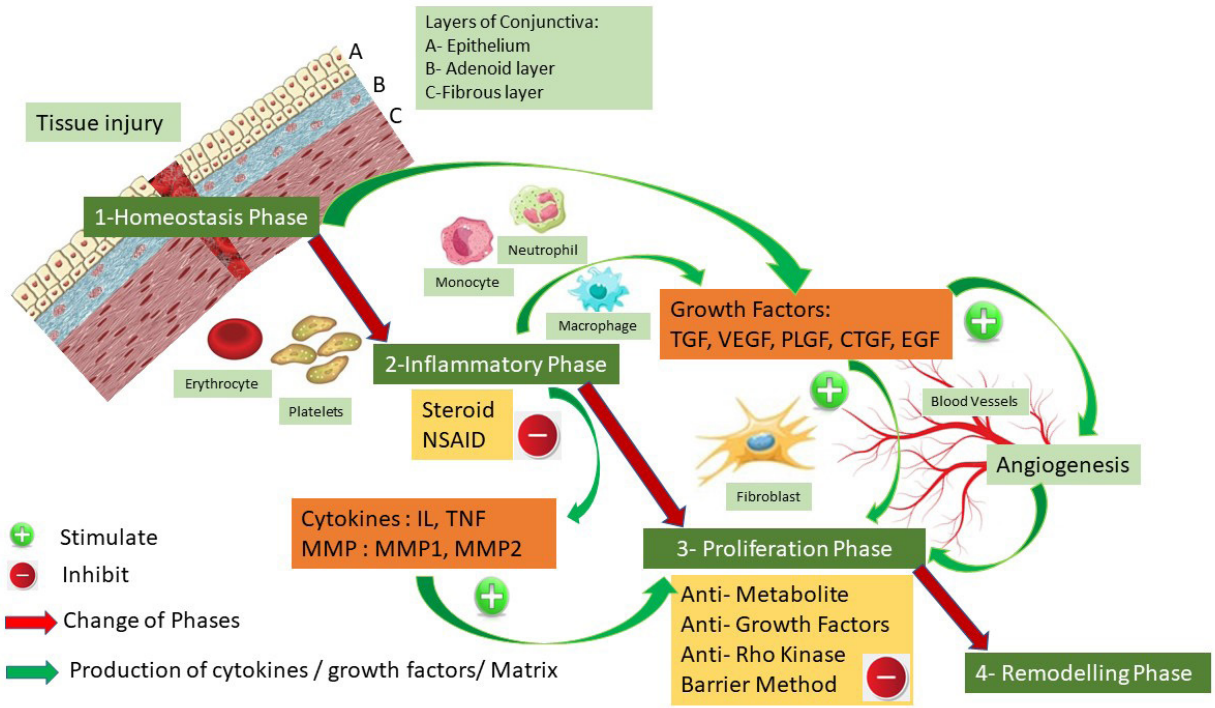

Figure 1: Pathway of wound healing and the modulation agents

operative mean IOP and higher rates of complete and qualified surgical success (23).

In strabismus surgery, the use of MMC is not well established. Oscar et al. reported the adhesion over the area of musculoscleral junction at 6 weeks post-operative was significantly low with MMC usage. However, the muscle strength was reduced (24). Another experimental squint surgery on rabbit showed no significant difference in the areas of the granulomas of the extraocular muscle reattachment sites in MMC group compared to control (25). The use of MMC in strabismus study on humans were limited but showed positive short-term result in reducing adhesion despite a higher degree of inflammation observed earlier (26). MMC is also used to ensure long term patency of dacryocystorhinostomy (DCR). Penttila et al. reported MMC in doses of 0.4 mg/ml, 5 minutes application significantly improved the success rate of endoscopic DCR after 6 months follow up in a small sample population (15 eyes/group) (27). Another study that was conducted in a larger population (65 eyes/group), using lower concentration of 0.2 mg/ml MMC in longer duration of application (30 minutes) showed no significant difference in the success rate (28). Despite the good reputation of effectiveness in lowering the IOP and reducing the scarring, the use of MMC is known to cause local complications. The common early complications are shallow anterior chamber with or without hypotonus maculopathy and bleb leak. Vision threatening complications include retinal detachment, blebitis and endophthalmitis (29-31).

5-Fluorouracil

Fluoropyrimidine 5-fluorouracil (5-FU), an antimetabolite drug, also an anti-cancer drug acts both by inhibiting basic processes of biosynthesis and the normal functioning of macromolecules, including DNA and RNA. The mechanism of action is misincorporation of fluoronucleotides into RNA and DNA, which induces downregulation of the synthetic nucleotide enzyme thymidylate synthase (32). 5-FU enters the cell using the facilitated transport mechanism and transforms intracellular metabolites into active metabolites (33). These active metabolites disrupt RNA synthesis and the action of thymidylate synthase (32,34).

Clinically, 5-FU is used as a chemotherapy agent for solid tumours such as colorectal, stomach, pancreatic, and breast cancer (35–38). It is also used in the treatment of dermatological conditions, including actinic keratosis, basal cell carcinoma, and squamous cell carcinoma (39,40).

5-FU has been used as a wound modulating agent for glaucoma filtration surgery since the early 1990s. 5-FU is often used to rescue encapsulated filtering blebs, refractory glaucoma, failed filtering surgery, and even primary glaucoma surgery (41-49). 5-FU can be administered as intraoperative application on the scleral flap area and post-operatively as subconjunctival injection (41-49). Unlike MMC, 5-FU can be administered via subconjunctival injection in repeated doses (29). For 5-FU most clinicians prefer 5 mg per injection in 0.1- or 0.5-mL saline solution in repeated injections or using sponge soaked with 50-mg/ml on sclera bed with the total doses ranging from 15 to 50 mg (49).

Meta-analysis studies comparing the effectiveness of 5-FU and MMC in glaucoma surgeries concluded that MMC are more effective than 5-FU if used intraoperatively in term of lowering the IOP and rate of complete and qualified success outcomes (23,50,51). Both MMC and 5-FU reported similar post operative complications, but epithelial corneal defects was unique complication frequently seen in 5-FU than MMC treatment (23). Other complications include wound leakage, corneal toxicity, uveitis, and cataract (52).

5-FU has also been tested for anti-scarring agent in other eye surgeries, such as strabismus and pterygium (53-55). In animal experimental strabismus study, the operated muscles received a 5-min topical application of 50 mg/mL solution of 5-fluorouracil (5-FU). Result showed significant reduction in scarring eyes treated with 5-FU however, there was also a reduction in the tensile strength (53).

In the use of 5-FU in pterygium surgery, Said et al. reported 93.3% of patients showed regression of the fibrovascular tissue and arrest of progression following a dose of 0.1-0.2 ml (2.5-5 mg) intralesional 5-FU injections in patients with recurrent pterygium (55).
In a systematic review by Brendon et al. (2022) concluded the usage of intralesional 5-FU in impending recurrent and established recurrent pterygium were promising, however, the use primary pterygium showed suboptimal result. The usage of 5-FU in pterygium surgery has potential risks of scleral thinning, cornea toxicity and graft related complications which was increased in rate and severity with higher doses (56).

Anti-Growth Factors

A growth factor is a molecule that promote or hinder mitosis and promote cellular differentiation which act on specific cell surface receptors and transmitting growth signals (57). Many growth factors involve in wound healing process as shown in Figure 1 which include vascular endothelial growth factors (VEGF), transforming growth factors (TGF, epidermal growth factor (EGF) and placenta growth factors (PlGF).

Anti–vascular endothelial growth factors (Anti-VEGF)

There are many types of anti-VEGF in the market namely bevacizumab, ranibizumab, pegaptanib, aflibercept and brolucizumab which have different molecular weight (58). Anti-VEGF was initially produced for the treatment of neovascular Age Macular Degeneration (NV-AMD),

which is the advanced stage of AMD characterised by choroidal neovascularisation. Later, anti VEGF was found to be effective in treatment of other retina oedema and neovascularization diseases which include retinopathy of prematurity, myopic choroidal neovascularisation, diabetic macula oedema, and macular oedema secondary to retinal vein occlusion (59).

Angiogenesis plays a major role in wound healing as it facilitates the nutrients and oxygen to the wound site to be used by rapidly proliferating cells. Growth factor responsible for the angiogenesis is known as vasoendothelial growth factors (VEGF). VEGF is produced by many cells include endothelial cells, keratinocytes, fibroblasts, smooth muscle cells, macrophages, neutrophil, platelets and monocytes in response to injury (60). VEGF binds to VEGF receptors (VEGFR-1, VEGFR-2) and undergoes transphosphorylation process on the cell surface of endothelial cells leading to dimerization and activation of VEGF (61). Almost all known cellular reactions to VEGF appear to be mediated by VEGFR-2. Through these receptors, signalling occurs regulating proliferation, migration, spread on endothelial cells and sprouting of new vessels (60-63). Formation of new vessels will further facilitate the cells proliferation and contribute to scar formation.

There was evidence that support the presence of VEGF in the aqueous humour in patients with glaucoma compared to age-matched non-glaucoma patients (64,65). Aqueous humor VEGF is elevated in primary open angle glaucoma, neovascular glaucoma, acute angle closure and pseudoexfoliative glaucoma. The cause of elevated aqueous VEGF concentration in eyes with glaucoma is postulated to be related to the ischemia, hypoxia, or elevated reactive oxygen intermediates caused by glaucomatous damage and possible mechanical stress of RPE (64). Glaucoma filtration surgery is aimed to provide alternative passage for aqueous drainage that is easily affected by excessive fibrosis. In glaucoma filtration surgeries, this aqueous which contains higher level VEGF will be drained through the channel to subconjunctival space. This may contribute to the development of scar, forming a blockage surrounding the area of bleb leading to failure of procedures.

Anti-VEGF has been found to be effective in reduction of neovascular retinopathies such as neovascular age-related macular degeneration and proliferative diabetic retinopathy (66,67). Bevacizumab, an anti-VEGF, is a recombinant humanized monoclonal immuno-globulin G1 (IgG1) antibody that binds and inhibits the biological activity of all VEGF-A isoforms (68,69). The common dose used in experimental ocular surgery in animals ranges from 1.25 to 3.5 mg, often administered in the subconjunctival region, has shown promising results in inhibiting fibroblast proliferation to prevent scarring. The effect is further enhanced with the combination with antimetabolite drugs (70–72). However, in human study, the effectiveness of bevacizumab is not well established. Nilforushan et al. found that 2.5 mg/ml subconjunctival bevacizumab as a single agent, shown to effectively inhibit fibroblast proliferation but less prominent compared to MMC (73).

Ranibizumab is another anti-VEGF, which approved by FDA in 2006 for the treatment of NV-AMD has invited researcher's interest to study on glaucoma filtering surgery. It is a recombinant humanized IgG1 kappa isotype monoclonal antibody directed against human VEGF-A. Ranibizumab binds to VEGF-A and its physiologically active variants, such as VEGF165, VEGF121, and VEGF110 preventing it from binding to two trans-membrane tyrosine kinase VEGFR receptors. This led to reduction in endothelial cell proliferation, vascular leakage, and the growth of new blood vessels (74).

Ranibizumab is often used as OFF LABEL drug in neovascular glaucoma (NVG) cases. The recommended dosage is 0.5mg in 0.05ml intravitreally before the glaucoma surgeries. (75-80). Most of these studies reported regression of rubeosis iridis and less complications such as hyphaema intraoperatively. Luke et al. reported that after 14 days of ranibizumab injection in addition to standard treatment in NVG group showed a considerable intraocular pressure (IOP) reduction in addition to the iris rubeosis' fast remission (77). Similar observation was reported by Sun et al. (2017) in NVG cases underwent trabeculectomy and glaucoma implant (78). In another larger and longer duration study, there were no significant differences noted in the two groups with respect to intraocular pressure, best corrected visual acuity, anti-glaucoma medications or postoperative complications at 12 months after intraoperative ranibizumab combined with Ahmed glaucoma valve implants (81).

Another anti VEGF that been studied in glaucoma surgery is pegaptanib. Pegaptanib is a pegylated oligonucleotide that selectively binds to one of the VEGF isoforms known as VEGF165 which also play a role in angiogenesis. However, the study of pegabtanib in vitro and vivo trabeculectomy showed no effect on fibrosis (82). A meta-analysis of nine studies in human trabeculectomy, using the anti-VEGF drugs bevacizumab (9 studies) and ranibizumab (1 research) indicated no statistically significant difference between the anti-VEGF and anti-metabolite medicines (MMC/5-FU) (83-90). Another meta-analysis by Qi Xiong et al. also supported the findings. They concluded that antimetabolites were more efficient than anti-VEGF drugs for lowering IOP in trabeculectomy, although intraoperative use of these two classes of medications did not reveal statistically significant differences in complete success, qualified success, or adverse event incidence (91).

Anti–transforming growth factors

Transforming growth factors (TGFs) is an important cytokine that play a major role in wound healing process. It comprised of two groups of polypeptide growth factors: TGF-α and TGF-β. TGF-α is found in macrophages, brain cells, and keratinocytes. Most types of cells, including cells in the eyes, secrete TGF-β. TGF-β present in three isoforms: TGF-β1, TGF-β2, and TGF-β3. All these isoforms are found in human eye (92-96).

TGF controls cell proliferation and migration, differentiation, the creation of extracellular matrix (ECM), and immunological regulation in wound healing. In an animal experimental trabeculectomy, the rhAnti-TGF-β2 mAb (lerdelimumab) greatly improved the success of glaucoma filtration surgery compared to control following subconjunctival administration (97). However, during Phase III clinical study, it was found there was no difference compared to placebo group in preventing trabeculectomy failure leading to study discontinuation (98).

Other anti-growth factors

Epidermal growth factor (EGF) is another growth factor being studied for wound modulating agents. EGF binds to an EGF receptor (EGFR) on the cell surface, activates the receptor's intrinsic protein–tyrosine kinase activity (99) which initiates a signal transduction cascade, resulting in several biochemical changes including increase in intracellular calcium levels, glycolysis and protein synthesis. EGFR activation is linked to angiogenesis and wound healing and upregulation of angiogenic factors such as interleukin-8 and VEGF (100). Trastuzumab (Herceptin) is a humanized monoclonal IgG1 kappa antibody that selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2). Trastuzumab was developed in a mammalian cell culture using recombinant DNA technology and is used in the treatment of breast cancer. An animal experimental glaucoma filtration study reported that in doses of 1.2 mg/0.1 ml, trastuzumab significantly suppressed fibroblast proliferation compared to a placebo, however the sample of this study was small and not compared with standard antimetabolites (101).

Placental growth factor (PGF) is an angiogenic protein which solely binds to VEGF-R1 receptor (102). PGF is not involved in physiological angiogenic processes but only acts on pathological angiogenesis (103) and inflammation (104). PGF expression in human atherosclerotic lesions is associated with inflammation of the plaque and neo-vascularization (105,106). PGF deficiency impaired the response to VEGF and cause impaired angiogenesis (103). PGF antibody, clone 5D11D4 (ThromboGenics NV) tested in-vivo glaucoma filtration surgery showed a single injection was able to improve the surgical outcome, where the bleb area was significantly larger with lower inflammatory area (107). However, the duration of the study was up to 14 days after surgery only.

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) has been shown to have anti-inflammatory and anti- fibrosis in numerous animal models, including fibrosis of the lung, liver, heart, and kidney (108). Pirfenidone inhibits fibroblast proliferation (109,110), TGF-β-induced collagen production (111,112) and downregulate inflammatory mediators such as TGF-β (113), connective tissue growth factor (CTGF) (109), platelet-derived growth factor (114), and TNF-α (115). An in-vitro study by Na et al. (2015) reported that PFD and MMC inhibited cell migration and reduced α-smooth muscle actin (α-SMA) protein expression levels, while 5-FU showed neither inhibition of cell migration nor reduction in α-SMA expression level (116). Another study conducted in rabbits by Jung and Park (2016) reported that postoperative intrableb pirfenidone injection followed by topical administration reduced fibrosis following glaucoma drainage device implantation (117).

Mechanical Barriers

Mechanical barriers such as biodegradable collagen matrix implant and amniotic membrane are another potential solution to reduce scarring post-ocular surgery. In trabeculectomy, a biodegradable collagen matrix, an implant that acts as a spacer separating the conjunctiva from the episcleral surface is used to prevent adhesion between the two layers. It also prevents fibroblast aggregation at the fistula, enabling the continuous outflow of aqueous humour and preventing the failure of the surgery.

A study on 31 eyes of POAG patients by Yuan Fei et al. reported biodegradable collagen matrix implant provides significantly higher rates of surgical success compared with MMC only undergoing trabeculectomy at 5 years follow up (118). Meta-analysis of seven randomized controlled trials including 227 eyes was done by He et al. It was reported that, in terms of IOP-lowering effectiveness, a reduction in the need for glaucoma drugs, success rates, and tolerability, the biodegradable collagen matrix implant is comparable to MMC for trabeculectomy (119). A retrospective study investigating the effects of combining biodegradable collagen matrix implant with MMC conducted by Castejyn et al. in patients undergoing filtering surgery combined with phacoemulsification. They reported that the combination improve postoperative IOP results over two years (120).

Amniotic membrane use was explored in trabeculectomy and strabismus surgery to reduce fibrosis. Amniotic membrane has ideal biological tissue characteristics since it is nonimmunogenic, semipermeable to aqueous solutions, and capable of reducing inflammation, fibrosis, and angiogenesis. In trabeculectomy, amniotic membrane is inserted in the filtration side showed a lower tendency to scar than conjunctiva (121). In contrary, a randomized controlled trial comparing the use of amniotic membrane graft with control in

trabeculectomy showed no statistically significant difference in IOP reduction across the 16 patients at the 1-year follow-up (122). However, a study that combined MMC and amniotic membrane showed promising result in glaucoma surgery in refractory glaucoma cases. The combined study group showed higher success rate in terms of IOP reduction at one year and less hypotony complications compared to MMC group (123).

Rho kinase inhibitors

The Rho kinase (ROCK) family consists of three small guanosine triphosphate–binding proteins (RhoA, RhoB, and RhoC) that regulate cell structure, motility, proliferation, and apoptosis throughout the body (124). Researchers established the use of ROCK inhibitor eyedrop as lowering IOP agent for glaucoma patients. Researchers had investigated the potential of ROCK inhibitors as a modulating agent in reducing the scarring post glaucoma surgical and showed promising outcome (125, 126).

Experimental data from in-vitro investigations showed that human tenon fibroblasts proliferation, adhesion, and contraction were dramatically inhibited after exposure to the ROCK inhibitors (127). Honjo et al. also demonstrated; ROCK inhibitors significantly decreased subconjunctival scarring at day 7 following experimental glaucoma surgery in rabbits (127). Experiments showed that ROCKs were significant regulators of gene expression during inflammation. The fact that ROCK inhibitors reduced the generation of interleukins and tumour necrosis factor suggested that they may have anti-inflammatory effects (128,129). Other than reducing the inflammation, ROCK also aids in cells migration and differentiation (130).

CONCLUSION

To date, researchers have investigated several prospective drugs with various modes of action to reduce scarring after ocular procedures. Despite their recognized drawbacks, antimetabolites are still regarded as the gold standard and the most efficient treatment. To find the optimum anti-scarring agent that is efficient with few adverse effects, more study is required.

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