**Abstract**

Anti-scarring Drugs And Drug Delivery systems (DDSs) that are more effective and safer than mitomycin C have been sought to improve the outcome of glaucoma filtration surgeries. Drugs that selectively inhibit wound healing, including anti-transforming growth factor-β and anti-vascular endothelial growth factor antibodies, have been investigated, although their advantages are yet to be verified in humans. In addition, novel sustained-release DDSs with fewer toxic effects have been studied for application after glaucoma surgeries. Several potential biomaterials for such DDSs, including gelatin hydrogel, have been introduced.

**Introduction**

Application of mitomycin C (MMC) as an antimetabolite in glaucoma filtration surgeries, particularly trabeculectomy, has greatly improved surgical outcomes through suppression of fibroblast proliferation. However, application of MMC increases the risk for complications including infectious endophthalmitis [1-3], since MMC also affects cells unrelated to wound healing and may produce a vascular thin blebs. In order to address this issue, safer drugs for glaucoma surgeries have been sought in recent times. In addition, application of novel biomaterials to control scarring and/or for sustained release of drugs has also been studied.

**Anti-Scarring Drugs for Glaucoma Surgeries**

Drugs that selectively inhibit wound healing after glaucoma filtration surgeries, including anti-transforming growth factor (TGF)-β and anti-vascular endothelial growth factor (VEGF) antibodies, have been investigated. Human monoclonal antibody that neutralizes TGF-β2 (CAT-152; lerdelimumab) was one of the postoperative anti-scarring candidates in glaucoma surgery [4]. However, there was no difference between subconjunctival application of CAT-152 and placebo in preventing the failure of primary trabeculectomy in a phase III study [5]. As for the anti-VEGF antibody, the 6-month outcomes of a pilot clinical study with a small number of subjects (13 patients in each group) suggested that 3 subconjunctival injections of 0.125 mg of bevacizumab (0.05 mL) were successful in reducing intraocular pressure (IOP), compared to the conventional use of 0.03% MMC [6]. In this study, the first, second, and third subconjunctival injections of bevacizumab were administered immediately before surgery 5mm from the limbus in the same quadrant as the proposed trabeculectomy, immediately after surgery at the edge of the formed bleb, and on the 7th postoperative day 5mm from the sclerostomy site in the superior quadrant, respectively. However, a long-term study with a large number of patients is still needed to verify the effectiveness and safety of anti-VEGF antibodies. A Rho-associated protein kinase inhibitor, Y-27632, was reported to have profound effect on activities of human Tenon fibroblasts and prevent fibroproliferation and scar formation in a rabbit model of glaucoma surgery [7].

Moreover, other candidates have been investigated as anti-scarring agents in glaucoma filtration surgery: Pirfenidone (anti-fibrotic potential was already established in other organs such as the lung, liver, and kidney) [8], antisense oligodeoxynucleotides for connexin 43 (a critical component of gap junctions) [9], ilomastat (a matrix metalloproteinase inhibitor) [10], tacrolimus (an immunosuppressive agent) [11], octreotide (a growth hormone inhibitor) [11], saratin (a platelet-binding modulator) [12], P-glycoprotein blockers (verapamil, cyclosporine) [13], sonliprozumab, a humanized monoclonal antibody for sphinogosine-1-phosphate (a regulator of tissue fibrosis) [14], simtuzumab, a humanized monoclonal antibody for lysyl oxidase-like 2 (a potential agent for pathologic angiogenesis, inflammation, and fibrosis) [15], Suc-Val-Pro-PheP (OPh)2, a chymase inhibitor [16,17]. Future clinical utilization of these agents is expected, although it is potentially challenging to verify their effects in human glaucoma surgeries.

**Drug Delivery Systems for Glaucoma Surgeries**

Novel drug delivery systems (DDSs) have also been investigated for sustained drug release, since
it is important to prevent scarring over an extended period following glaucoma surgeries. One such example is that of Ozurdex®, a polymer-based sustained-release intravitreal DDS containing dexamethasone, currently approved by the United States Food and Drug Administration for the treatment of macular edema. Experiments with rabbits suggested that subconjunctival implantation of Ozurdex® prolonged bleb survival after glaucoma surgery, although this effect was not significant compared to that observed following conventional application of MMC [18]. Ologen® is another DDS comprising MMC-soaked biodegradable collagen matrix and is clinically used in some Asian countries. Implantation of Ologen® resulted in comparatively stable IOP 12 months after glaucoma surgery. However, after the implantation, encapsulated blebs were generated at a more rapid pace than that observed after conventional trabeculectomy, mostly owing to the ability of Ologen® to induce a number of fibroblasts inside to move into a bleb [19]. Other types of biomaterials, including freeze-dried bilayered fibrin-binding amniotic membrane [20], microfilms composed of poly (DL-lactide-co-caprolactone) [21], and polymer polylactiglycolic acid films [22], have also been investigated for sustained release of anti-scarring drugs after glaucoma surgeries, although they are yet to be applied in humans.

Gelatin hydrogel (GH) is a biodegradable material developed in Japan and used as DDS for bioactive proteins in other fields of medicine [23]. Using GH, controlled release of bioactive growth factors, over the time range of 5 days to 3 months, was possible [24, 25]. Various growth factors, including basic fibroblast growth factor (bFGF) and TGF–β1, have been incorporated in GH, and their controlled release has been effective for regeneration therapy of various tissues [26,27]. For ophthalmological research, GH containing anti-scarring drugs (a chymase inhibitor, MMC) and conventional application of MMC produced comparable sustained release of anti-scarring drugs after glaucoma surgeries, although they are yet to be applied in humans. In summary, utilization of new anti-scarring drugs and/or novel DDSs, which are more effective and safer than conventional application of MMC, is anticipated in the near future for better postoperative outcome with better bleb survival and lower rates of complications after glaucoma filtration surgeries.

References


