SMGroup

SM Ophthalmology Journal

Review Article

Application of Anti-Scarring Drugs and Drug Delivery Systems in Glaucoma Surgeries

Tetsuya Sugiyama

Nakano Eye Clinic of Kyoto Medical Co-operative, Japan

Article Information

Received date: Jun 11, 2015
Accepted date: Jul 25, 2015
Published date: Sep 14, 2015

***Corresponding author**

Tetsuya Sugiyama, Nakano Eye Clinic of Kyoto Medical Co-operative, Japan 604-8404, Tel: +81-75-801-4151; Fax: +81-75-822-7423; Email: tsugiyama@kyo-con.or.jp

Keywords Glaucoma filtration surgeries; Anti-scarring drugs; Drug delivery systems; Mitomycin C; Transforming growth factor-β; Vascular endothelial growth factor; Gelatin hydrogel

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 endopthalmitis [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 oligodeoxynucletides 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], sonepcizumab, a humanized monoclonal antibody for sphingosine-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 polylactioglycolic 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 impregnated with bFGF has been used to induce experimental models of subretinalor corneal neovascularization [28,29]. On the other hand, our research group has recently investigated application of GH containing anti-scarring drugs (a chymase inhibitor, MMC) after glaucoma surgery [17,30]. The results suggested that GH loading MMC and conventional application of MMC produced comparable effects on IOP reduction and bleb formation; further, compared to eyes treated with MMC via the conventional route, GH-treated eyes had reduced toxicity to conjunctiva, particularly the vessels, probably because the concentration of MMC in contact with these eyes was less [30]. The use of new DDSs such as GH may reduce toxicity to the eye, particularly the conjunctiva.

Conclusion

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

1. Higginbotham EJ, Stevens RK., Musch DC, Karp KO, Lichter PR, Bergstrom TJ, et al. Bleb-related endophthalmitis after trabeculectomy with mitomycin C. Ophthalmology. 1996; 103: 650-656.

2. Greenfield DS, Suner IJ, Miller MP, Kangas TA, Palmberg PF, Flynn HW. Endophthalmitis after filtering surgey with mitomycin. Arch Ophthalmol. 1996; 114: 943-949.

3. Mochizuki K, Jikihara S, Ando Y, Hori N, Yamamoto T, Kitazawa Y. Incidence of delayed onset infection after trabeculectomy with adjunctive mitomycin C or 5-fluorouracil treatment. Br J Ophthalmol. 1997; 81: 877-883.

4. Mead AL, Wong TT, Cordeiro MF, Anderson IK, Khaw PT. Evaluation of Anti-TGF-B2 Antibody as a New Postoperative Anti-Scarring Agent in Glaucoma Surgery. Invest Ophthalmol Vis Sci. 2003; 44: 3394–3401.

5. CAT-152 0102 Trabeculectomy Study Group, Khaw P, Grehn F, Holló G, Overton B, Wilson R, et al. A phase III study of subconjunctival human anti-transforming growth factor beta(2) monoclonal antibody (CAT-152) to prevent scarring after first-time trabeculectomy. Ophthalmology. 2007; 114: 1822-1830.

6. Sengupta S, Venkatesh R, Ravindran RD. Safety and efficacy of using off-label bevacizumab versus mitomycin C to prevent bleb failure in a single-site phacotrabeculectomy by a randomized controlled clinical trial. J Glaucoma. 2012; 21: 450-459.

7. Honjo M, Tanihara H, Kameda T, Kawaji T, Yoshimura N, Araie M. Potential role of Rho-associated protein kinase inhibitor Y-27632 in glaucoma filtration surgery. Invest Ophthalmol Vis Sci. 2007; 48: 5549-5557.

8. Zhong H, Sun G, Lin X, Wu K, Yu M. Evaluation of pirfenidone as a new postoperative antiscarring agent in experimental glaucoma surgery. Invest Ophthalmol Vis Sci. 2011; 52: 3136-3142.

9. Deva NC, Zhang J, Green CR, Danesh-Meyer HV. Connexin43 modulation inhibits scarring in a rabbit eye glaucoma trabeculectomy model. Inflammation. 2012; 35: 1276-1286.

10. Parkinson G, Gaisford S, Ru Q, Lockwood A, Khalili A, Sheridan R, et al. Characterisation of ilomastat for prolonged ocular drug release. AAPS PharmSciTech. 2012; 13:1063-1072.

11. Arslan S, Aydemir O, Güler M, Dağlı AF. Modulation of postoperative scarring with tacrolimus and octreotide in experimental glaucoma filtration surgery. Curr Eye Res. 2012; 37: 228-233.

12. Min J, Lukowski ZL, Levine MA, Meyers CA, Beattie AR, Schultz GS, et al. Prevention of ocular scarring post glaucoma filtration surgery using the inflammatory cell and platelet binding modulator saratin in a rabbit model. PLoS One. 2012; 7: e35627.

13. White AJ, Kelly E, Healey PR, Crowston JG, Mitchell P, Zoellner H. P-glycoprotein blockers augment the effect of mitomycin C on human Tenon's fibroblasts.Transl Vis Sci Technol. 2013; 2: 1.

14. Lukowski ZL, Min J, Beattie AR, Meyers CA, Levine MA, Stoller G, et al. Prevention of ocular scarring after glaucoma filtering surgery using the monoclonal antibody LT1009 (Sonepcizumab) in a rabbit model. J Glaucoma. 2013; 22: 145-151.

15. Van Bergen T, Marshall D, Van de Veire S, Vandewalle E, Moons L,Herman J, et al. The Role of LOX and LOXL2 in scar formation after glaucoma surgery. Invest Ophthalmol Vis Sci. 2013; 54: 5788-5796.

16. Maruichi M, Takai S, Sugiyama T, Ueki M, Oku H, Sakaguchi M, et al. Role of chymase on growth of cultured canine Tenon's capsule fibroblasts and scarring in a canine conjunctival flap model. Exp Eye Res. 2004; 79: 111-118.

17. Kojima S, Sugiyama T, Takai S, Jin D, Shibata M, Oku H, et al. Effects of gelatin hydrogel containing chymase inhibitor on scarring in a canine filtration surgery model. Invest Ophthalmol Vis Sci. 2011; 52: 7672-7680.

18. SooHoo JR, Seibold LK, Laing AE, Kahook MY. Bleb morphology and histology in a rabbit model of glaucoma filtration surgery using Ozurdex® or mitomycin-C. Mol Vis. 2012; 18: 714-719.

19. Min JK, Kee CW, Sohn SW, Lee HJ, Woo JM, Yim JH. Surgical outcome of mitomycin C-soaked collagen matrix implant in trabeculectomy. J Glaucoma. 2013; 22: 456-462.

20. Li W, Che WJ, Zhang MC. Study of self-made freeze-dried bilayered fibrin-binding amniotic membrane in ocular trabeculectomy in rabbits. Int J Ophthalmol. 2011; 4: 582-589.

21. Ang M, Yan P, Zhen M, Foo S, Venkatraman SS, Wong TT. Evaluation of sustained release of PLC-loaded prednisolone acetate microfilm on postoperative inflammation in an experimental model of glaucoma filtration surgery. Curr Eye Res. 2011; 36: 1123-1128.

22. Yan ZC, Bai YJ, Tian Z, Hu HY, You XH, Lin JX, et al. Anti-proliferation effects of Sirolimus sustained delivery film in rabbit glaucoma filtration surgery. Mol Vis. 2011; 17: 2495-2506.

23. Tabata Y. Biomaterial technology for tissue engineering applications. J R Soc Interface. 2009; 6: S311-S324.

24. Ozeki M, Ishii T, Hirano Y, Tabata Y. Controlled release of hepatocyte growth factor from gelatin hydrogels based on hydrogeldegradation. J Drug Target. 2001; 9: 461-471.

25. Ikada Y, Tabata Y. Protein release from gelatin matrices. Adv Drug Deliv Rev. 1998; 31: 287-301.

26. Tabata Y, Hijikata S, Ikada Y. Enhanced vascularization and tissue granulation by basic fibroblast growth factor impregnatedin gelatin hydrogels. J Control Release. 1994; 31: 189-199.

27. Yamamoto M, Tabata Y, Hong L, Miyamoto S, Hashimoto N, Ikada Y. Bone regeneration by transforming growth factor beta1 releasedfrom a biodegradable hydrogel. J Control Release. 2000; 64: 133-142.

28. Kimura H, Sakamoto T, Hinton DR, Spee C, Ogura Y, tabata Y, et al. A new model of subretinal neovascularization in the rabbit. Invest Ophthalmol Vis Sci.1995; 36: 2110-2119.

29. Yang CF, Yasukawa T, Kimura H, Miyamoto H, Honda Y, Tabata Y, et al. Experimental corneal neovascularization by basic fibroblast growth factorincorporated into gelatin hydrogel.Ophthalmic Res. 2000; 32: 19-24.

30. Kojima S, Sugiyama T, Takai S, Jin D, Ueki M, Oku H, et al. Effects of Gelatin Hydrogel Loading Mitomycin C on Conjunctival Scarring in a Canine Filtration Surgery Model. Invest Ophthalmol Vis Sci. 2015; 56: 2601-2605.