Post-trabeculectomy topical bevacizumab preventing bleb failure: a preliminary study

Shashi Kumar Bhasker · Sandeep Saxena ·
Kamlesh Singh

Received: 27 April 2013 / Accepted: 3 June 2013 / Published online: 27 June 2013
© Springer Science+Business Media New York 2013

Abstract This study aims to evaluate the efficacy and safety of post-trabeculectomy topical bevacizumab, in preventing bleb failure. A total of 11 females and 12 males were enrolled for the study. After a complete ophthalmic evaluation, the patients underwent trabeculectomy. Full ophthalmic examination was done the next day, which included visual acuity, intraocular pressure (IOP), and bleb morphology. Next, two drops of bevacizumab [0.25 mg (0.01 ml)] were instilled over the wound area with a tuberculin (1 ml) syringe. Pressure was applied at the medial canthus to prevent it from going into the lacrimal passage. Similar postoperative procedures were repeated at 1, 2, 3, and 4 weeks. So in all, five instillations of bevacizumab were completed. Later, the patients were followed at 1-month interval for 6 months. Target IOP was achieved in all eyes and was maintained during the study period of 6 months without any anti-glaucoma medication. Average IOP before trabeculectomy was 27.27 ± 8.92 mmHg, which decreased postoperatively to 8.77 ± 0.97 mmHg at 3 months and 9.27 ± 1.16 mmHg at 6 months. This drop in IOP was statistically significant on both occasions ($p=0.00$). A nice low filtering bleb was formed after the surgery, and it remained the same during the study period. The other parameters like cup-to-disc ratio and visual field did not change during the 6 months of study as expected because glaucoma is a slow progressive disease. Modulating the wound at multiple sites by bevacizumab (inflammation, proliferative, and remodeling stages) can lead to success of trabeculectomy.

Keywords Trabeculectomy · Topical bevacizumab · Wound healing

Introduction

Trabeculectomy is the most common surgery performed worldwide, for patients of glaucoma in whom the target pressure is not achieved or in patients where medical treatment is problematic (either due to noncompliance or side effects of the medications). Subconjunctival scarring is the main cause of failure for the standard trabeculectomy. Success rate of 71 to 98 % has been seen in various studies associated with different criteria of success [1–6].

To prevent its failure, trabeculectomy has been modified either by drugs or sutures. Steroids, perfluoropropane, antimetabolites (antifibrotics, mitomycin C, 5FU), and collagen cross-linking inhibitors (β -aminopropionitrile, D-penicillamine) are the commonly used drugs, while releasable/adjustable sutures or suturolysis is the procedures involving the sutures [7–18].

Besides these, β -radiation, amniotic membrane, and even photodynamic therapy have been used for the success of trabeculectomy [19–23].

Recently, the role of anti-vascular endothelial growth factor (VEGF) in preventing the failure of trabeculectomy has been documented. Various routes of anti-VEGF administration (intravitreal, intracameral, and subconjunctival) have been studied with successful outcome [24–26].

A pilot study was conducted at our university to evaluate the efficacy and safety of post-trabeculectomy topical bevacizumab. It was a prospective observational intervention study.

Material and method

This research study was conducted under the tenets of the Declaration of Helsinki and with applicable Institutional Review Board regulations. Patients for the study were enrolled from those attending the glaucoma clinic at a tertiary

S. K. Bhasker (✉) · S. Saxena · K. Singh
King George's Medical University, Lucknow, Uttar Pradesh, India
e-mail: skbhasker@yahoo.com

care center. Random table was used to select the patients for postoperative bevacizumab from those undergoing trabeculectomy from March 2011 to February 2012. Primary open-angle glaucoma patients without any previous ocular surgery or intervention were the main inclusion criteria. Patients receiving any prolonged treatment for any systemic condition (like diabetes mellitus, hypertension, tuberculosis, or arthritis) were not included. Glaucoma due to rubeosis iridis, iridocyclitis (uveitis), trauma, or any condition leading to secondary glaucoma were the conditions for exclusion. Children and pregnant females were also excluded. Full procedure was explained to the patient in presence of his or her attendant in the local language which they understood easily. Informed written consent was obtained for using bevacizumab after surgery. All patients were on anti-glaucoma medications initially. Surgery was opted because target intraocular pressure (IOP) was not achieved. The other reason was being the lack of compliance and the unaffordable cost of anti-glaucoma medicines. There was no control or comparative group.

After detailed ophthalmic work-up, the patients underwent uncomplicated trabeculectomy without any wound-modulating agent like mitomycin C by a single surgeon. Routine postoperative ophthalmic examination was done the next day. This included anterior chamber evaluation, IOP estimation using the Goldman Applanation Tonometer, and morphology of the filtering bleb. Bleb grading was done using the Indiana bleb appearance grading scale, advocated by Cantor et al. in 2003 [27]. In this, bleb is described and graded according to four variables, viz, bleb height, bleb extent, vascularity and Seidel test.

Finally, two drops of bevacizumab (Avastin by Genentech, Inc., South San Francisco, CA, USA) were instilled over the wound in the conjunctival sac with the help of a tuberculin 1-ml syringe fitted with a 26-G needle. Twenty drops were available in 0.1 ml of the syringe. By this method, 0.25 mg (0.01 ml) was over the trabeculectomy site. The patient closed his or her eyes, and the lacrimal puncta were blocked by the patient by putting pressure at the medial canthus. This prevented the drug (bevacizumab) going into the lacrimal passage and getting absorbed systemically and thus preventing any systemic side effect. The blockage was for 20 min. Patients were discharged with advice to use their regular postoperative medications (antibiotic, steroid, nonsteroid, and cycloplegic eye drops). All patients were asked to report to glaucoma clinic after 1 week.

The patients were inquired of any problem or adverse effect during the previous 1 week. Routine ophthalmic examination was done which included anterior chamber evaluation, IOP estimation, and morphology of the filtering bleb by the Indiana bleb appearance grading scale. Systemic examination including pulse rate, blood pressure, and respiration rate was also done.

This time again, two drops of bevacizumab were instilled by a tuberculin syringe fitted with 26-G needle, into the conjunctival sac, followed by eyelid closure and pressure at

medial canthus. Patients were instructed to continue their regular postoperative medications as before and to visit for next follow-up after 1 week.

Similar follow-up, evaluation of the bleb, and instillations were done after the second, third, and fourth weeks. So in all, five postoperative instillations of bevacizumab were completed during the first postoperative month.

Later, patients were told to visit the glaucoma clinic every month for 6 months. Success was defined as achieving and maintaining the target pressure without any IOP-lowering drug at the end of 6 months. Requirement of one anti-glaucoma drug was labeled as partial success. Failure was the condition where two or more drugs were required to maintain target IOP.

Pre- and postoperative (at 3 and 6 months) IOP and visual acuity (LogMAR) were compared statistically by using the STRATA 11.2 software. Wilcoxon signed rank test and paired *t* test were used to compare pre- and postoperative IOP and visual acuity (LogMAR), respectively, in all operated eyes. The difference between males and females were evaluated by using the two-sample Wilcoxon rank sum (Mann–Whitney) for IOP and two-sample *t* test for unequal variance for visual acuity (LogMAR).

Results

A total of 23 patients (11 females and 12 males) were enrolled for the study. One male and three females were lost to follow-up. So, finally 22 eyes of 19 patients [8 females (10 eyes) and 11 males (12 eyes)] were evaluated.

The average age for males was 50.73 ± 10.86 years ranging from 30 to 70 years. Females were from 30 to 65 years (average age being 46.5 ± 14.84 years).

Target IOP was achieved in all eyes and was maintained during the study period of 6 months without any anti-glaucoma medication (Table 1). Average IOP before trabeculectomy was 27.27 ± 8.92 mmHg, which decreased postoperatively to 8.77 ± 0.97 mmHg at 3 months and 9.27 ± 1.16 mmHg at 6 months. This drop in IOP was statistically significant on both occasions ($p=0.00$).

However, this decrease was not statistically significant among males and females both at 3 months (males, 8.75 ± 0.97 mmHg; females, 8.80 ± 1.03 mmHg; $p=0.87$) and 6 months (males, 9.00 ± 1.35 mmHg; females, 9.60 ± 0.84 mmHg; $p=0.57$).

There was no pre- and postoperative difference in visual acuity (LogMAR). The average preoperative LogMAR was 0.57 ± 0.40 . This changed to 0.49 ± 0.34 ($p=0.14$) at 3 months and 0.48 ± 0.33 ($p=0.09$) at 6 months. Similarly, there was no difference in visual acuity among males and females at 3 months (males, 0.52 ± 0.44 ; females, 0.47 ± 0.16 ; $p=0.70$) and at 6 months (males, 0.49 ± 0.43 ; females, 0.47 ± 0.16 ; $p=0.53$).

Table 1 The decrease in IOP at 1, 3, and 6 months postoperatively

Patient	Age	Sex	Eye	Pre-op	1 month Post-op	3 months Post-op	6 months Post-op
1	65	F	L	23	8	8	8
1	65	F	R	24	6	10	10
2	38	F	L	24	8	10	10
2	38	F	R	22	8	8	10
3	55	F	R	24	8	8	10
4	64	F	R	22	8	8	8
5	35	F	L	24	8	10	10
6	55	F	L	40	10	10	10
7	30	F	R	28	8	8	10
8	30	F	L	28	12	8	10
9	52	M	L	38	10	10	8
9	52	M	R	20	10	10	10
10	70	M	L	28	10	10	10
11	30	M	R	14	10	8	8
12	42	M	R	48	8	8	8
13	60	M	R	22	8	8	8
14	42	M	R	33	8	8	12
15	52	M	L	24	10	9	8
16	50	M	L	26	8	8	8
17	55	M	R	18	8	8	10
18	45	M	R	48	8	10	10
19	60	M	L	22	10	8	8

Though IOP sometimes reached a hypotensive level in the early postoperative period, no maculopathy developed. There was very little fluctuation of IOP (postoperative) during the 6 months (Fig. 1).

A nice low filtering bleb was formed after the surgery, and it remained the same during the study period (Table 2). The inflammation and the vascularity at the surgical site decreased during the first month (Figs. 2 and 3).

The other parameters like cup-to-disc ratio and visual field (mean deviation) did not change during the 6 months of study as expected because glaucoma is a slow progressive

disease. The systemic examination also remained within normal limits (pulse rate, blood pressure, and respiration rate did not showed any significant difference).

Discussion

Glaucoma is a major cause of irreversible blindness. According to the WHO, glaucoma is responsible for 12.3 % of global blindness and is the second most common cause of blindness in the world [28]. It may be associated with an increase in

Fig. 1 Graphical presentation of decrease in IOP at 1, 3, and 6 months postoperatively

Table 2 Trabeculectomy bleb characteristics at 1 and 6 months

Patient	Age	Sex	Eye	1 month				6 months			
				H	HE	Vas	ST	H	HE	Vas	ST
1	65	F	L	2	3	1	0	2	3	1	0
1	65	F	R	2	3	2	0	2	3	2	0
2	38	F	L	2	2	1	0	2	2	1	0
2	38	F	R	2	2	1	0	2	2	1	0
3	55	F	R	2	2	2	0	2	2	2	0
4	64	F	R	2	3	2	0	2	3	2	0
5	35	F	L	2	3	2	0	2	3	2	0
6	55	F	L	1	3	2	0	1	3	2	0
7	30	F	R	1	3	3	0	1	2	2	0
8	30	F	L	2	2	1	0	2	2	1	0
9	52	M	L	2	3	2	0	2	3	2	0
9	52	M	R	2	3	2	0	2	3	2	0
10	70	M	L	2	2	2	0	2	2	2	0
11	30	M	R	2	3	2	0	2	3	2	0
12	42	M	R	2	2	1	0	2	2	1	0
13	60	M	R	1	2	2	0	1	2	2	0
14	42	M	R	2	2	2	0	2	2	2	0
15	52	M	L	2	3	2	0	2	3	2	0
16	50	M	L	2	3	2	0	2	3	2	0
17	55	M	R	2	3	2	0	2	3	2	0
18	45	M	R	2	3	2	0	2	3	2	0
19	60	M	L	2	3	2	0	2	3	2	0

H height, *HE* horizontal extent, *Vas* vascularization, *ST* Seidel test

intraocular pressure, which is the only modifiable risk factor. Lowering of intraocular pressure can be achieved by medicines and lasers or by surgery.

Trabeculectomy is the most common and widely accepted form of surgical procedure where aqueous is directed to the subconjunctival space, from where it is absorbed. An opening

of 15 μ is sufficient to drain aqueous, but it is the inflammation which occurs after the procedure that closes the sclerostomy site [29].

Complete wound healing with a strong scar formation is essential after any surgical intervention, but trabeculectomy is the surgical procedure where complete excessive healing

Fig. 2 Photographs of patient 2 showing bleb characteristics at day 1; weeks 1, 2, and 4; and months 1, 3, and 6, postoperatively

Fig. 3 Photographs of patient 11 showing bleb characteristics at day 1; weeks 1, 2, and 4; and months 1, 3, and 6, postoperatively

at the incision site is not desired for its success. Failure in trabeculectomy occurs due to subconjunctival fibrous scar formation (which is a part of healing process) [20, 30–35].

Healing process starts from the time of injury (here, it is incision) and may be divided with overlapping stages of clot formation after bleeding (a few minutes), inflammation (0–8 days), proliferation (4–28 days), and remodeling (21 days onwards) stages. Platelets are exposed to collagen, and this triggers clot formation with release of platelet-derived growth factors and VEGF. Clot formation leads to hemostasis. Neutrophils and monocytes flood the wound initially, followed by lymphocytes and macrophages in the inflammation stage. Growth factors, cytokines, chemokines, and other molecules are released by the cells which mediate the inflammatory stage.

Proliferation stage is characterized by increased fibroblastic activity, angiogenesis, and formation of granulation tissue. Finally, the remodeling stage constitutes the wound contraction by fibroblasts, deposition of extracellular matrix, degradation and modification (lasting several months), and production of regulating growth factors [36].

VEGF is important in healing and scar formation after tissue damage. It is produced by platelets, mast cells, macrophages, astrocytes, Muller cells, and other cells which mediate inflammation and healing process. This growth factor upregulates the endothelial (vascular) and fibroblastic proliferation. It also helps in angiogenesis and in laying down of extracellular matrix, leading to granulation tissue formation. Finally, a scar is formed.

Tissue hypoxia results after injury due to a damage of the blood vessels (capillaries) and hemorrhage. This upregulates the production of VEGF, leading to formation of new blood vessels (angiogenesis). Angiogenesis is the key element of the proliferative phase, which supplies oxygen and other nutrients, for the rapid growth of cell-mediated repair of the damaged tissue [25].

Trabeculectomy is the surgical technique which causes injury (incision of the conjunctiva and scleral flap) and breakdown of the blood aqueous barrier. Injury and breakdown of the blood aqueous barrier leads to a cascade of events where many factors (including growth factors) are released which cause inflammation angiogenesis and fibrosis [37]. Significant increased levels of VEGF was present in aqueous of patients undergoing trabeculectomy. In addition to this, increased receptors for VEGF were found to be on Tenon's fibroblasts [26]. So healing process leads to episcleral fibrosis and thickening of conjunctival tissue over the scleral filtering bleb.

Bevacizumab is a humanized monoclonal antibody against the vascular endothelial growth factor. It has been approved for use in metastatic colorectal and renal malignancies, non-small cell lung cancer, and glioblastoma. Bevacizumab has been associated with slow or incomplete wound healing. According to recommendations, patients on bevacizumab therapy should undergo surgical intervention after 40 days of its cessation and further wait for at least 28 days or more before it is reinitiated to avoid wound healing complications [38].

Vascularity and scar formation was reduced on neutralizing the VEGF during wound healing. This study shows that VEGF has a strong influence in wound healing which upholds the previous studies by Li et al. and Wilgus et al. [26, 39]. Vascular endothelial growth factor also affects a fibroblastic activity in addition to angiogenesis [40]. In a study by Evelyn et al., found that bevacizumab disrupted fibroblast proliferation, and the constriction ability of collagen gel was disabled [41].

The authors have tried to exploit this property of incomplete wound healing (or wound modulation) for the success of trabeculectomy by using off-label bevacizumab topically after surgery.

By using topical bevacizumab, the required concentration may be achieved at the site of trabeculectomy without any

systemic side effect. It is easy and noninvasive. Intravitreal and subconjunctival injections achieved a high concentration in plasma and also in the fellow eye through systemic circulation after being absorbed systemically [42].

Regarding the safety, topical bevacizumab has been used earlier in the management of corneal neovascularization safely. The eye drops of bevacizumab showed no significant side effects on normal corneal wound healing, its integrity, or density in its nerve fiber [43–46]. Hosseini and Khalili have shown its usefulness in inhibiting the neovascularisation in herpetic stromal keratitis [47]. Successful off-label use of topical bevacizumab has been studied in patients with pterygium and in patients with Steven Johnson's syndrome [48–50].

The dose of topical bevacizumab used by the authors was very less to cause any adverse event systemically or locally. As the duration of its use was regular (weekly) for 1 month, it modulated all the stages of wound healing (inflammatory, proliferative, and remodeling). This leads to decreased scar formation postoperatively, resulting in adequate outflow of aqueous, thereby achieving the target intraocular pressure.

Comparing the patient group with a control group was the major limitation. Authors argue that the use of anti-glaucoma medication (with preservative) produces a subclinical inflammation [51, 52]. Therefore, after trabeculectomy (surgical trauma), increased inflammatory reaction is likely to occur leading to increased fibroblastic activity and scar formation, resulting in bleb failure [53]. But the use of anti-VEGF (topically also) prevents the bleb fibrosis and bleb failure as evidenced by this study.

Conclusion and limitation

Wound healing after trabeculectomy is affected by many factors of which neovascularisation and collagen laying down are important steps in scar formation (mediated by vascular endothelial growth factor). So modulating the wound at multiple sites (corticosteroids for inflammation, neutralizing the VEGF for proliferative and remodeling stages) can lead to a success of trabeculectomy or prevent bleb failure. This was shown in our study that by using off-label topical bevacizumab postoperatively, the successful outcome of trabeculectomy even at 6-months follow-up can be achieved.

This was a preliminary study, and there were no control or comparative groups. Even though topical bevacizumab as evidenced in our study may be acting in synergy with other anti-inflammatory medications in reducing the scar formation postoperatively and thereby preventing bleb failure, further well-planned case-control and comparative studies are required to establish its efficacy over other wound-modulating agents in the success of trabeculectomy.

References

1. Addicks EM, Quigley HA, Green WR, Robin AL. Histologic characteristics of filtering blebs in glaucomatous eyes. *Arch Ophthalmol*. 1983;101:795–8.
2. Mills KB. Trabeculectomy: a retrospective long-term follow-up of 444 cases. *Br J Ophthalmol*. 1981;65:790–5.
3. Ridgway AE, Rubinstein K, Smith VH. Trabeculectomy. A study of 86 cases. *Br J Ophthalmol*. 1972;56:511–6.
4. Ridgway AE. Trabeculectomy. A follow-up study. *Br J Ophthalmol*. 1974;58:680–6.
5. Schwartz AL, Anderson DR. Trabecular surgery. *Arch Ophthalmol*. 1974;92:134–8.
6. Schwartz PL, Ackerman J, Beards J, Wesseley Z, Goodstein S, Ballen PH. Further experience with trabeculectomy. *Ann Ophthalmol*. 1976;8:207–17.
7. Kahook MY, Camejo L, Noecker RJ. Trabeculectomy with intraoperative retrobulbar triamcinolone acetate. *Clin Ophthalmol*. 2009;3:29–31.
8. Lu D, Tai MC, Chiang C. Subconjunctival retention of perfluoropropane gas increases the success of rate of trabeculectomy. *Asian J Ophthalmol*. 1999;1:8–9.
9. Lu DW, Tai MC, Chiang CH. Subconjunctival retention of perfluoropropane (C3F8) gas increased the success rates of trabeculectomy. *J Ocul Pharmacol Ther*. 1997;13:235–42.
10. Skuta GL. Antifibrotic agents in glaucoma filtering surgery. *Int Ophthalmol Clin*. 1993;33:165–82.
11. Rockwood EJ, Parrish 2nd RK, Heuer DK, et al. Glaucoma filtering surgery with 5-fluorouracil. *Ophthalmology*. 1987;94:1071–8.
12. Akarsu C, Onol M, Hasanreisoglu B. Postoperative 5-fluorouracil versus intraoperative mitomycin C in high-risk glaucoma filtering surgery: extended follow up. *Clin Exp Ophthalmol*. 2003;31:199–205.
13. Membrey WL, Poinosawmy DP, Bunce C, Hitchings RA. Glaucoma surgery with or without adjunctive antiproliferatives in normal tension glaucoma: 1 intraocular pressure control and complications. *Br J Ophthalmol*. 2000;84:586–90.
14. Yoon PS, Singh K. Update on antifibrotic use in glaucoma surgery, including use in trabeculectomy and glaucoma drainage implants and combined cataract and glaucoma surgery. *Curr Opin Ophthalmol*. 2004;15:141–6.
15. McGuigan LJ, Cook DJ, Yablonski ME. Dexamethasone, D-penicillamine, and glaucoma filtering surgery in rabbits. *Invest Ophthalmol Vis Sci*. 1986;27:1755–7.
16. Mc Guigan LJB, Mason RP, Sanchez R, Quigley HA. D-Penicillamine and beta-aminopropionitrile effects on experimental filtering surgery. *Invest Ophthalmol Vis Sci*. 1987;28:1625–9.
17. Moorhead LC. Inhibition of collagen cross-linking: a new approach to ocular scarring. *Curr Eye Res*. 1981;1:77–83.
18. Moorhead LC, Smith J, Stewart R, Kimbrough R. Effects of beta-aminopropionitrile after glaucoma filtration surgery; pilot human study. *Ann Ophthalmol*. 1987;19:223–5.
19. Cameron ME. Beta irradiation as an adjunct to surgery in refractory glaucoma. *Trans Aust Coll Ophthalmol*. 1970;2:53–60.
20. Skuta GL, Parrish RK. Wound healing in glaucoma filtering surgery. *Surv Ophthalmol*. 1987;32:149–70.
21. Jordan JF, Diestelhorst M, Grisanti S, Kriegelstein GK. Photodynamic modulation of wound healing in glaucoma filtration surgery. *Br J Ophthalmol*. 2003;87:870–5.
22. Lu DW, Chang CJ, Chiang CH, Yeh MK, Chou PI. Wound modulation after trabeculectomy by different formulations of antimitotics in rabbits. *J Ocul Pharmacol Ther*. 2000;16:529–38.
23. Demir T, Turgut B, Celiker U, et al. Effects of octreotide acetate and amniotic membrane on wound healing in experimental glaucoma surgery. *Doc Ophthalmol*. 2003;107:87–92.

24. Vandewalle E, Spielberg L, Zeyen T, Stalmans I. Can preoperative bevacizumab improve trabeculectomy outcome? “Avastin Trab Study”. *Bull Soc Belge Ophthalmol*. 2010;314:51–2.
25. Choi JY, Choi J, Y-De K. Subconjunctival bevacizumab as an adjunct to trabeculectomy in eyes with refractory glaucoma: a case series. *Korean J Ophthalmol*. 2010;24:47–52.
26. Li Z, Van Bergen T, Van de Veire S, et al. Inhibition of vascular endothelial growth factor reduces scar formation after glaucoma filtration surgery. *Invest Ophthalmol Vis Sci*. 2009;50:5217–25.
27. Cantor LB, Mantravadi A, WuDunn D, Swamynathan K, Cortes A. Morphologic classification of filtering blebs after glaucoma filtration surgery: the Indiana bleb appearance grading scale. *Journal of Glaucoma*. 2003;12:266–71.
28. World Health Organization and International Agency for the Prevention of Blindness. The state of the world's sight. *VISION 2020: the Right to Sight: 1999–2005*. Geneva: WHO; 2005.
29. McEvan WK. Application of Poiseuille's law to aqueous outflow. *Arch Ophthalmol*. 1958;60:290–4.
30. Hitchings RA, Grierson I. Clinico pathological correlation in eyes with failed fistulizing surgery. *Trans Ophthalmol Soc UK*. 1983;103:84–8.
31. Lama PJ, Fechtner RD. Antifibrotics and wound healing in glaucoma surgery. *Surv Ophthalmol*. 2003;48:314–46.
32. Esson DW, Popp MP, Liu L, Schultz GS, Sherwood MB. Microarray analysis of the failure of filtering “blebs” in a rat model of glaucoma filtering surgery. *Invest Ophthalmol Vis Sci*. 2004;45:4450–62.
33. Chang MR, Cheng Q, Lee DA. Basic science and clinical aspects of wound healing in glaucoma filtering surgery. *J Ocul Pharmacol Ther*. 1998;14:75–95.
34. Grierson I, Joseph J, Miller M, Day JE. Wound repair: the fibroblast and the inhibition of scar formation. *Eye*. 1988;2(Pt 2):135–48.
35. Tahery MM, Lee DA. Review: pharmacologic control of wound healing in glaucoma filtration surgery. *J Ocul Pharmacol*. 1989;5:155–79.
36. Cordeiro MF, Schultz GS, Ali RR, Bhattacharya SS, Khaw PT. Molecular therapy in ocular wound healing. *Br J Ophthalmol*. 1999;83:1219–24.
37. Siriwardena D, Kotecha A, Minassian D, Dart JKG, Khaw PT. Anterior chamber flare after trabeculectomy and after phacoemulsification. *Br J Ophthalmol*. 2000;84:1056–7.
38. Gordon CR, Rojavin Y, Patel M, et al. A review on bevacizumab and surgical wound healing: an important warning to all surgeons. *Ann Plast Surg*. 2009;62(6):707–9.
39. Wilgus TA, Ferreira AM, Oberyzy TM, Bergdall VK, Dipietro LA. Regulation of scar formation by vascular endothelial growth factor. *Lab Invest*. 2008;88:579–90.
40. Methew R, Barton K. Anti vascular endothelial growth factor therapy in glaucoma filtration surgery. *Am J Ophthalmol*. 2011;152:10–5.
41. O'Neill EC, Qin Q, Van Bergen NJ, et al. Antifibrotic activity of bevacizumab on human Tenon's fibroblast in vitro. *Invest Ophthalmol Vis Sci*. 2010;51:6524–32.
42. Nomoto H, Shiraga F, Kuno N, et al. Pharmacokinetics of bevacizumab after topical, subconjunctival, and intravitreal administration in rabbits. *Invest Ophthalmol Vis Sci*. 2009;50:4807–13.
43. Dastjerdi MH, Al-Arfaz KM, Nallasamy N, et al. Topical bevacizumab in the treatment of corneal neovascularization: results of a prospective, open-label, non-comparative study. *Arch Ophthalmol*. 2009;127:381–9.
44. Bock F, Onderka J, Rummelt C, et al. Safety profile of topical VEGF neutralization at the cornea. *Invest Ophthalmol Vis Sci*. 2009;50:2095–102.
45. Kim SW, Ha BJ, Kim EK, Tchah H, Kim TI. The effect of topical bevacizumab on corneal neovascularization. *Ophthalmology*. 2008;115:33–8.
46. Koenig Y, Bock F, Horn F, Kruse F, Straub K, Cursiefen C. Short- and long-term safety profile and efficacy of topical bevacizumab (Avastin) eye drops against corneal neovascularization. *Graefes Arch Clin Exp Ophthalmol*. 2009;247:1375–82.
47. Hosseini H, Khalili MR. Therapeutic potential of bevacizumab (Avastin) in herpetic stromal keratitis (HSK). *Med Hypotheses*. 2007;69:568–70.
48. Heindl LM, Cursiefen C. Pterygium. Etiology, clinical aspects and novel adjuvant therapies. *Ophthalmologie*. 2010;107(517–20):522–4.
49. Wu PC, Kuo HK, Tai MH, Shin SJ. Topical bevacizumab eyedrops for limbal-conjunctival neovascularization in impending recurrent pterygium. *Cornea*. 2009;28:103–4.
50. Uy HS, Chan PS, Ang RE. Topical bevacizumab and ocular surface neovascularization in patients with Stevens-Johnson syndrome. *Cornea*. 2008;27:70–3.
51. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. *Arch Ophthalmol*. 1994;112:1437–45.
52. Liesegang TJ. Conjunctival changes associated with glaucoma therapy: implications for the external disease consultant and the treatment of glaucoma. *Cornea*. 1998;17:574–83.
53. Cevenkel B, Kopitar AN, Ihan A. Mediat Inflamm: Inflammatory molecule in aqueous humour and on ocular surface and glaucoma surgery outcome; 2010. doi:[10.1155/2010/939602](https://doi.org/10.1155/2010/939602).