Efficacy of Intralesional Bevacizumab Injection in Decreasing Pterygium Size

Mohammad Reza Fallah Tafti, MD, Keivan Khosravifard, MD, Mehrdad Mohammadpour, MD, Mohammad Naser Hashemian, MD, and Mohammad Yaser Kiarudi, MD

Purpose: To evaluate the efficacy of intralesional bevacizumab injection in decreasing size of pterygium.

Methods: Seventeen patients with pterygium (14 with primary and 3 with recurrent pterygium) received intralesional injections of bevacizumab (2.5 mg/0.1 mL). Digital photographs were analyzed by image analysis software to determine the change of corneal involvement as a percentage of the total corneal surface.

Results: The mean age of the patients was 45.5 ± 15.8 years. The mean percentage size of lesions before injection was 17.2% ± 4.3% of corneal surface. The mean percentage size of lesions 1 week, 1 month, and 3 months after injection was 15.1% ± 4.3%, 13.4% ± 4.0%, and 14.1% ± 4.4% of corneal surface, respectively. The mean percentage decrease of lesion size was 3.97% ± 3.84%. There were statistically significant differences between percentage of lesion size before and 1 week ($P < 0.001$), 1 month ($P < 0.001$), and 3 months ($P < 0.001$) after injection of bevacizumab. There were neither postinjection ocular complications such as rise of intraocular pressure nor systemic adverse events. Visual acuity did not change after injection of bevacizumab. Despite statistically significant decrease in pterygium size, this decrease does not seem to be clinically significant.

Conclusions: Intralesional bevacizumab injection is fairly effective in reducing the size of pterygium and is well tolerated; however, this effect is not clinically significant.

Key Words: bevacizumab, pterygium, VEGF

(*Cornea* 2011;30:127–129)

Pterygium is a common ocular disorder with different reported prevalence rates ranging from 0.3% to 29% in different parts of the world.[1,2] The treatment of choice for pterygium is surgical excision, which includes simple excision (the bare sclera technique) and excision with grafting (conjunctival or amniotic membrane grafts).[3] To prevent recurrence of the pterygium, several studies have evaluated the efficacy of adjunctive therapies, like β-radiation, mitomycin C (MMC), 5-fluorouracil (5-FU), and corticosteroids, together with simple excision.[4,5] However, these methods could have unwilling side effects like punctate epitheliopathy, bacterial superinfection, delayed onset scleral melting, and rise in intraocular pressure.

Several active angiogenic and epithelial growth factors such as basic fibroblast growth factor, heparin-binding epidermal growth factor, connective tissue growth factor, and vascular endothelial growth factor (VEGF) have been shown to be significantly increased in pterygium, suggesting that growth factors may be involved directly or indirectly in its pathogenesis.[6,7] However, the most prominent of these factors is VEGF, which is the main target of many current antiangiogenic therapies.[8] Bevacizumab (Avastin; Genentech, South San Francisco, CA) is a monoclonal antibody to VEGF A that binds to both VEGF receptors VEGFR2 and VEGFR1 and inhibits both receptors.[9,10]

There are several studies to evaluate the efficacy of bevacizumab (Avastin) in regression of the corneal neovascularization,[11–13] but the use of Avastin as an adjunct in the treatment of pterygium is scarce. Herein, we report our experience in evaluation of the efficacy of intralesional injection of bevacizumab in decreasing the size of pterygium.

PATIENTS AND METHODS

Seventeen consecutive patients with pterygium (14 with primary and 3 patients with recurrent pterygium) were enrolled. Informed consents were obtained from all patients before enrollment. The study was approved by Farabi Eye Hospital Ethics Committee. Patients were examined before injection and, in each visit, at 1 week, 1 month, and 3 months after injection, including visual acuity, slit-lamp examination, indirect ophthalmoscope funduscopy, and applanation tonometry. The platelet count and blood pressure were also measured.

Patients underwent injection of 2.5 mg/0.1 mL of bevacizumab into the base of the pterygium with a 25-gauge needle in the operating room and under the microscope. Two patients of primary cases and 1 patient of recurrent pterygium received a second subconjunctival injection. Patients with a history of myocardial infarction and vascular thrombosis in the last 6 months were excluded.

At each visit and before treatment, photographs were taken from corneal surface with ×16 magnifications using

Received for publication June 16, 2009; revision received March 26, 2010; accepted April 3, 2010.

From the Eye Research Center, Farabi Eye Hospital, Cornea Department, Tehran University of Medical Sciences, Tehran, Iran.

No grants or funds were received in support of this study.

The result of this study was presented in the 18th Iranian Congress of Ophthalmology, November 25–27, 2008, Tehran, Iran.

The authors had no proprietary interest.

Reprints: Mehrdad Mohammadpour, Eye Research Center, Farabi Eye Hospital Tehran University of Medical sciences, Tehran, Iran (e-mail: mahammadpour@yahoo.com).

a Nikon digital camera attached to the slit-lamp microscope. Corneal involvements were measured on the digital photographs as the percentage of the total area of the cornea. Image analysis was performed using an image processing and analysis software program (Image J 1.37 v; Wayne Rasband at the Research Services Branch, National Institute of Mental Health, Bethesda, MD). All measurements and analyses were performed by a person who was unaware to the study and medications.

Statistical analysis was performed by using SPSS (version 13; SPSS, Chicago, IL). Student *t* test was used for continuous variables, and *P* values less than 0.05 were considered significant. Data were expressed as mean ± SD.

RESULTS

The study group included 17 eyes of 17 patients, 14 patients with primary pterygium and 3 patients with recurrent pterygium. The demographic data of the patients is shown in Table 1. The mean percentage size of lesions before injection was 17.2% ± 4.3%. The mean percentage size of lesions 1 week, 1 month, and 3 months after injection was 15.1% ± 4.3%, 13.4% ± 4.0%, and 14.1% ± 4.4%, respectively. The mean percentage decrease size of lesion in primary cases was 3.970% ± 3.843% (range: 0.04%–14.47%) (Table 2).

However, in recurrent cases, progression was observed. The mean percentage of progression of the size of corneal involvement in recurrent cases was 1.11% ± 0.450% (range: 0.6%–1.44%). There were significant differences between percentage size of lesion before injection and 1 week ($P < 0.001$), 1 month ($P < 0.001$), and 3 months ($P < 0.001$) after injection.

Visual acuity, blood pressure, intraocular pressure, and platelet count did not change significantly in any patient before injection and in the end of study. The only complication was subconjunctival hemorrhage in 3 patients, which was resolved after 1 week.

TABLE 1. Baseline Demographic Characteristic and Side Effects of Subconjunctival Bevacizumab Injections for Pterygium

Patient Number	Age (yr)/Eye	Visual Acuity Preoperatively	Side Effects	Visual Acuity Postoperatively
1*	78/L	20/400	-	20/400
2	43/L	20/40	-	20/40
3	32/R	20/200	-	20/200
4	63/L	20/30	-	20/25
5	56/R	20/40	-	20/40
6	45/R	20/100	Subconjunctival hemorrhage	20/100
7	32/L	20/40	-	20/40
8	28/L	20/25	-	20/25
9	49/R	20/40	-	20/40
10*†	54/L	20/400	Subconjunctival hemorrhage	20/400
11*	41/L	20/25	-	20/30
12	17/L	20/20	-	20/20
13†	45/R	20/30	-	20/30
14	65/R	20/200	Subconjunctival hemorrhage	20/200
15	57/R	20/40	-	20/40
16†	32/L	20/20	-	20/20
17	38/R	20/100	-	20/100

*Patients with recurrent pterygium.
†Patients with two injections.
L, left eye; R, right eye.

TABLE 2. The Proportion of Involved Corneal Surface Before Subconjunctival Injection and in the End of Follow-up Period

Patient Number	Involved Corneal Surface Before Injection	Involved Corneal Surface in the End of Follow-up
1*	27.91	29.21
2	3.19	1.60
3	21.99	12.41
4	4.96	2.00
5	9.88	7.87
6	13.55	13.51
7	6.45	5.08
8	12.84	9.42
9	14.42	9.23
10*†	78.75	79.35
11*	3.82	5.26
12	4.64	4.08
13†	27.02	12.55
14	24.91	19.90
15	12.59	10.25
16†	6.36	2.82
17	19.90	16.40

All data are presented as percentage of involved corneal surface (%).
*Patients with recurrent pterygium.
†Patients with two injections.

DISCUSSION

Pterygia, defined as a degenerative disorder, may be associated with chronic exposure to sunlight; however, their formation and progression are known to depend on neovascularization.[7,14] The process of angiogenesis is normally mediated by a balance between angiogenic stimulators and angiogenic inhibitors.[15] It has also been suggested that the development of pterygia depends on a changed angiogenic stimulator–inhibitor ratio. Pterygium tissues contain decreased levels of angiogenic inhibitors such as pigment epithelium–derived factor, whereas they contain increased VEGF levels.[7] Gebhardt et al[6] reported that VEGF is increased in pterygia in comparison with that in healthy human conjunctiva.

Recent studies report successful outcomes after administration of bevacizumab for the treatment of corneal neovascularization. Erdurmus et al[16] evaluated the efficacy of subconjunctival bevacizumab injection (2.5 mg/0.1 mL) in 2 patients with corneal neovascularization and different etiologies: one patient with dry eye, whose vessels significantly regressed a week after the injection, but the other patient with a failed graft, who had only a minor vessels regression. Awadein[17] described 3 patients with corneal neovascularization after keratoplasty treated with a single subconjunctival

injection of 2.5-mg bevacizumab. In all patients, the number and caliber of blood vessels decreased after the subconjunctival injection. The regression of the corneal new vessels was more marked in patients with smaller and/or fewer blood vessels. However, in patients with old rejected vascularized graft, there was little change in the number and caliber of blood vessels. The authors (M.N.H. and M.M.) recently reported a novel technique of intrastromal injection of bevacizumab for management of deep corneal intrastromal vascularization after deep anterior lamellar keratoplasty.[13]

Review of the literature shows that there are few reports of administering of bevacizumab in the treatment of recurrent pterygia with different route of administering (intralesional injection or topical) with some controversies. Bahar et al[18] reported the effect of subconjunctival bevacizumab on corneal vessel density in recurrent pterygia in 5 patients. None of them demonstrated any significant clinical regression of vessels. There are 2 studies in favor of use of bevacizumab for decreasing the size of pterygium. Mansour[19] presented 2 cases with inflamed residual pterygial bed unresponsive to topical antiinflammatory therapy and 1 case with inflamed pterygium underwent intralesional injections (followed for 1 month–1.5 year). The inflammation was promptly controlled by subconjunctival anti-VEGF. In another report, Teng et al investigated the effect of subconjunctival bevacizumab on primary pterygium. They described a patient with an inflamed nasal primary pterygium, refractory to topical medications. Bevacizumab (1.25 mg/0.05 mL) was injected subconjunctivally near the limbus. They found that 1 week after procedure, irritation and hyperemia regressed. At week 2, the pterygium maintained this appearance. After 7 weeks of follow-up, the degree of vascularization and symptoms of irritation regressed to its preinjection state.[20]

There are 2 reports suggesting use of topical bevacizumab. Wu et al[21] reported a patient with impending recurrent pterygium treated with topical bevacizumab eyedrops (25 mg/mL) administered 4 times daily for 3 weeks. Treatment prominently decreased limbal–conjunctival neovascularization. At 6-month follow-up, no recurrent pterygium was noted, and slit-lamp examination revealed no adverse ocular effects. Also, Leippi et al[22] reported use of bevacizumab eyedrops to prevent recurrence of pterygia in 5 eyes (4 patients) treated with topical bevacizumab eyedrops (25 mg/mL) 2–8 times per day for 5–24 weeks as an adjunct after excision of recurrent pterygia and conjunctival autograft. Patients were examined preoperatively and over a follow-up period ranging from 3 to 14 months. Two eyes showed conjunctival hyperemia (stage 1 recurrence), 1 eye showed fibrosis of the limbus (stage 2 recurrence), 1 eye an early recurrence (stage 3 recurrence), and in 1 eye no pterygium recurrence was noted. They proposed the use of topical VEGF inhibitors in recurrent pterygia. In our study, the percentage size of vascularized cornea significantly decreased at the end of 3-month follow-up; however, corneal haziness was still present to some extent.

All of these studies are preliminary and with low sample size of patients. The promising point of view is that in these studies, there was no reported adverse effect for bevacizumab. The important question is to quantify the therapeutic concentrations of such antibodies in the cornea. It is postulated that for control of corneal neovascularization, higher doses of bevacizumab than the classic 2.5-mg dosage given in intravitreal injections may be needed for subconjunctival injections.

In conclusion, intralesional bevacizumab is well tolerated and the percentage size of vascularized cornea showed a statistically significant decrease at the end of 3-month follow-up and fibrovascular lesion in patients with primary pterygium did not progress. Despite statistically significant decrease in pterygium size, a decrease of 4% in the pterygium size does not seem to be clinically significant. However, repeated injection of bevacizumab (to decrease the pterygium size more efficiently) or its adjuvant role before or during surgical removal of pterygium may help to address its clinical significance in future studies.

REFERENCES

1. Moran DJ, Hollows FC. Pterygium and ultraviolet radiation: a positive correlation. *Br J Ophthalmol*. 1984;68:343–346.
2. Taylor HR, West S, Muñoz B, et al. The long-term effects of visible light on the eye. *Arch ophthalmol*. 1992;110:99–104.
3. Prabhasawat P, Tesavibul N, Leelapatranura K, et al. Efficacy of subconjunctival 5-fluorouracil and triamcinolone injection in impending recurrent pterygium. *Ophthalmology*. 2006;113:1102–1109.
4. Frucht-Pery J, Siganos CS, Ilsar M. Intraoperative application of topical mitomycin C for pterygium surgery. *Ophthalmology*. 1996;103:674–677.
5. Maldonado MJ, Cano-Parra J, Navea-Tejerina A, et al. Inefficacy of low-dose intraoperative fluorouracil in the treatment of primary pterygium [letter]. *Arch Ophthalmol*. 1995;113:1356–1357.
6. Gebhardt M, Mentlein R, Schaudig U, et al. Differential expression of vascular endothelial growth factor implies the limbal origin of pterygia. *Ophthalmology*. 2005;112:1023–1030.
7. Jin J, Guan M, Sima J, et al. Decreased pigment epithelium-derived factor and increased vascular endothelial growth factor levels in pterygia. *Cornea*. 2003;22:473–477.
8. Hosseini H, Nejabat M, Khalili MR. Bevacizumab (Avastin) as a potential novel adjunct in the management of pterygia. *Med Hypotheses*. 2007;69: 925–927.
9. Ferrara N. Vascular endothelial growth factor: basic science and clinical progress. *Endocr Rev*. 2004;25:581–611.
10. Ferrara N, Hillan KJ, Novotny W. Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. *Biochem Biophys Res Commun*. 2005;333:328–335.
11. Bahar I, Kaiserman I, McAllum P, et al. Subconjunctival bevacizumab injection for corneal neovascularization. *Cornea*. 2008;27:142–147.
12. DeStafeno JJ, Kim T. Topical bevacizumab therapy for corneal neovascularization. *Arch Ophthalmol*. 2007;125:834–836.
13. Hashemian MN, Zare MA, Rahimi F, et al. Deep intrastromal bevacizumab injection for management of corneal stromal vascularization following deep anterior lamellar keratoplasty. *Cornea*. 2010.
14. Maini R, Collison DJ, Maidment JM, et al. Pterygial derived fibroblasts express functionally active histamine and epidermal growth factor receptors. *Exp Eye Res*. 2002;74:237–244.
15. Jiménez B, Volpert OV. Mechanistic insights on the inhibition of tumor ngiogenesis. *J Mol Med*. 2001;78:663–672.
16. Erdurmus M, Totan.Y. Subconjunctival bevacizumab for corneal neovascularization. *Graefes Arch Clin Exp Ophthalmol*. 2007;245:1577–1579.
17. Awadein, A. Subconjunctival bevacizumab for vascularized rejected corneal grafts. *J Cataract Refract Surg*. 2007;33:1991–1993.
18. Bahar I, Kaiserman I, McAllum P, et al. Subconjunctival bevacizumab injection for corneal neovascularization in recurrent pterygium. *Curr Eye Res*. 2008;33:23–28.
19. Mansour AM. Treatment of inflamed pterygia or residual pterygial bed. *Br J Ophthalmol*. 2009;93:864–865.
20. Teng CC, Patel NN, Jacobson L. Effect of subconjunctival bevacizumab on primary pterygium. *Cornea*. 2009;28:468–470.
21. Wu PC, Kuo HK, Tai MH, et al. Topical bevacizumab eyedrops for limbal–conjunctival neovascularization in impending recurrent pterygium. *Cornea*. 2009;28:103–104.
22. Leippi S, Grehn F, Geerling G. Antiangiogenic therapy for pterygium recurrence. *Ophthalmologe*. 2009;106:413–419.