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Subconjunctival Bevacizumab Injection in Treatment of Recurrent Pterygium

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Abstract

Objective: To determine the clinical effect of subconjunctival injection of bevacizumab in regression or halting growth in patients with recurrent pterygium.

Method and materials: The study was an off-label; 2-dosing, interventional case series involving 20 patients with recurrent pterygium. They received subconjunctival bevacizumab (0.2 ml/2.5 mg). Vascularity and thickness of Pterygium was graded. Size of the pterygium (measured by surface area in cm^2) was recorded from baseline to 6 months, after injection. Treatment-related complications and adverse events were reported. The main outcome of measurements was the change in grading, size, vascularity, thickness and color intensity.

Results: 9 males (45%), 11 females (55%) of 20 patients were conducted in study with a mean age of 50.46 years ± 18.30 (rang 38-70). There was a significant reduction in grading with significant difference in the mean surface area of pterygium at different intervals ($P<0.05$) and the size of pterygium was reduced. The reduction of color intensity was significant ($P=0.031$). No significant topical or systemic adverse reactions were recorded.

Conclusions: Subconjunctival bevacizumab injection is useful in management of patients with recurrent pterygium without significant local or systemic adverse effects.

Keywords: Subconjunctival injection; Bevacizumab; Recurrence; Pterygium

Introduction

Pterygium is a triangular sheet of fibro vascular tissue that invades the cornea [1,2]. It occurs in the interpalpebral fissure, more common on the nasal side of the eye and often bilateral [1-3]. Physicians have known pterygia for thousands of years [2,4-6] but the pathogenesis of pterygia is not fully understood [7-10].

Various studies have implicated environmental factors, such as ultraviolet light, chronic irritation, and inflammation. Recent studies have also provided evidence implicating genetic components, antiapoptotic mechanisms, cytokines, growth factors, extracellular matrix remodeling, immunological mechanisms, and viral infections in the pathogenesis of the disease [7-11].

Vascular growth factors such as vascular endothelial growth factor (VEGF) have been detected in pterygium [12-15].There is marked elevation of VEGF in pterygia in comparison to normal conjunctival samples [12-15]. Although the pathogenesis of pterygia is still poorly understood, their formation and progression are known to depend on neovascularization. It has been postulated that the development of pterygia depends on a changed angiogenic stimulator-to-inhibitor ratio. Jin et al. showed that pterygia contain drastically decreased levels of pigment epithelium-derived factor, angiogenic inhibitor, and elevated VEGF levels [15].

The treatment of pterygium is still controversial, with various treatments being advocated in the scientific literature [16]. As pterygia is composed of proliferating fibrovascular tissue and its formation and progression require neovascularization [17,18], many molecules that positively regulate angiogenesis have been identified, suggesting that growth factors may be involved directly or indirectly in the pathogenesis of pterygia.

Bevacizumab (Avastin) is a full-length, humanized, monoclonal antibody against all types of VEGF. It binds to and neutralizes the biologic activity of all types of human VEGF, so it prevents interaction with its receptors on the surface of endothelial cells [17]. Bevacizumab has been used to treat choroidal neovascularization due to age-related macular degeneration (ARMD), and more recently diabetic macular edema. Various clinical trials have shown that when administered intravitreally, it is well tolerated and associated with improvement in visual acuity, decreased central retinal thickness, and reduction in angiographic leakage [18-20]. This study determined the clinical effect and safety of subconjunctival injection of bevacizumab for recurrent pterygium.

Once validated, this technique may obviate the need for surgery as well as provide an alternative form of therapy for recurrent pterygia that is simpler, faster, and easier to perform compared to existing methods of pterygium removal.

Patients and Methods

This off-label, 2-dosing, interventional case series was conducted in patients with recurrent pterygium from March 2010 to July 2011. 20

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patients, 9 males (45%) and 11 females (55%) are involved with a mean age of (50.46 ± 18.30 years), range (38-70) (Table 1).

Each pterygium was measured and graded according to Tan and coworkers' grading scheme proposed in 1997 [21]. Grading was based on the visibility of the underlying episcleral blood vessels. This has been previously described and validated as a marker of severity. The pterygia were classified into grades 1, 2 and 3 based on slit lamp evaluation.

Grade 1 ("atrophic") had clearly visible episcleral vessels under the body of the pterygium.

Grade 2 ("intermediate") had partially visible episcleral vessels under the body of the pterygium.

Grade 3 ("fleshy") had totally obscured episcleral vessels underlying the body of the pterygium.

On baseline examination, at least Grade 2 patients with pterygium were included in the study.

Exclusion criteria

Exclusion criteria included previous ocular surgeries except pterygium removal, conditions in which Bevacizumab is contraindicated including (allergy to bevacizumab, hypertension, proteinuria, bleeding tendencies, previous myocardial infarction or stroke, pregnant and lactating women), evidence of other ocular diseases except refractive errors, history of ocular trauma, pterygium invading more than 3 mm of the cornea and inability to follow up patient for the duration of the study. Full detailed history and full informed written consent was obtained from all patients included in the study.

A complete eye evaluation was performed for each patient. This included visual-acuity measurement, applanation tonometry, slit lamp examination, and anterior segment photography. The dimensions of the pterygium were determined by measuring its length in centimeters from base (using the caruncle as landmark) to apex, and width in centimeters at the base and apical areas. All injections were performed in operating room. Topical anesthesia using 0.5% proparacaine hydrochloride eye drops (Alcaine, Alcon), subconjunctival injection of 0.2 ml (5 mg) of Bevacizumab (100 mg/4 ml Roche) following the injection of 0.2 ml lidocain 2% in subconjunctival area of pterygium body using a 1-ml syringe with 29-gauge needle, the patient was asked to direct the eye in extreme horizontal gaze to have adequate exposure of the pterygium and injection repeated on week 2, the patient contacted with predetermined follow-up schedule. Patients were followed up after a week, one month, three months and six months from the last injection. In each visit, complete ophthalmologic evaluation was performed; any complications and adverse events were noted. Anterior segment photography using Topcon fundus camera with lens adapter for anterior segment imaging was done.

Post injection complications such as subconjunctival hemorrhage, persistent epithelial defect, infection and uveitis were noted. Any adverse events were noted, these may include systemic effects such as hypertension or any thromboembolic incidents, or any allergic reactions to the medications and products used in the study.

The drug was considered having a biological effect when any regression in the size or decrease in vascularity and thickness of pterygium grading occurred.

Statistical analysis

Both descriptive and analytic approaches were used in the data analysis. Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS version 10). Chi-square was used to determine the association between grades and time intervals. A p value less than or equal to 0.05 was considered statistically significant.

Results

This study showed that is no statistically significant difference between males and females in the mean pterygium size (>0.05) during the follow up period. On comparing the pterygium gradings at different time intervals: statistically significant difference was noted (p<0.01).

This study showed that the average of pterygium size reduction and the reduction of color intensity after 6 months follow up period were statistically significant (P=0.01), (P=0.031) subsequently. At baseline, there were 11(55%) patients with grade 2 pterygium and 9 (45%) patients with grade 3. On 6 months follow up 9 patients (45%) fall in the grade 1, 9 (45%) patients in grade 2 and only 2 patients remained in grade 3 (10%) (Table 2 and Figure 1).

Regarding the visual acuity changes, comparison of the Snellen's visual acuity at different time intervals showed no statistically significant difference (p>0.05).

Systolic and diastolic blood pressure at different time intervals showed no significant difference (p>0.05) (Table 3).

Apart from subconjunctival hemorrhage which occurred in 4 patients (20%) and resolved within 2 weeks, no ocular surface toxicity, persistent epithelial defects, corneal abrasion, infections, or uveitis were reported during the study.

Age(years) Mean Range	 50.46 38-70
Gender Male Female	 9 11
Grade of pterygium Grade 2 Grade 3	 11 9
IOP (mm Hg) Mean range	 12.46 ± 2.42 12-19
Systolic Blood pressure(mm Hg) Mean Range	 122 ± 7.7 100-140
Diastolic blood pressure(mm Hg) Mean Range	 79.33 ± 5.94 60-100

Table 1: Demography of the patients.

Time interval	Grading			Total
	Grade I	Grade II	Grade III	
Baseline	0 .0%	11 55.0%	9 45.0%	20 100.0%
1 month	4 20.0%	11 55.0%	5 25.0%	20 100.0%
3 months	8 40.0%	9 45.0%	3 15.0%	20 100.0%
6 months	9 45.0%	9 45.0%	2 10.0%	20 100.0%

There is a significant relationship between grades and time interval, P<0.01

Table 2: Distribution of patients according to grading related to time interval.

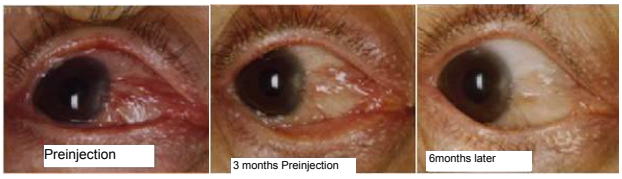

Figure 1: Regression of blood vessels and size of pterygium after 6 months of injection of avastin.

Time interval	Systolic blood Pressure (mmHg)		Diastolic blood Pressure (mmHg)	
	Mean	P	Mean	P
Baseline	122 ± 7.74		79.33 ± 5.94	
One month	120.67 ± 10.32	>0.05	76.66 ± 8.16	>0.05
3months	121.33 ± 10.6	0.64	81.33 ± 8.34	
6 months	119.3 ± 10.99		78.67 ± 8.34	

Table 3: Distribution of patients regarding the levels of blood pressure (means) at different time intervals.

Discussion

Surgery has been considered as a main treatment for primary pterygium [5,6]; however, complications such as recurrence and even worsening of pterygium following the surgery may occur [7]. The recurrence rate was estimated to be between 15% to 75% in simple excision and about 6% in the free flap operations. Some substances such as mitomycin C and 5-FU are recommended to decrease the chance of recurrence; however, their usage is associated with other undesirable complications such as infection and scleral necrosis [6-8]. On the other hand, many patients ask for conservative treatment at least to suppress further progression of corneal neovascularization and abolish the symptoms, especially the congestion. Medical therapies have failed to give acceptable benefits in this relation [4,5]. It is noteworthy to indicate that the pathophysiology of recurrent pterygium is different from that of primary pterygium, containing more fibrous tissues and abnormal neovascularization rather than elastic degeneration [4-6].

VEGF level has been shown to be increased in pterygium and is suggested to be either directly or indirectly involved in its pathogenesis [12-15,17]. Immunohistochemistry studies have shown that VEGF levels are more expressed in pterygium than in normal conjunctiva [12,15,22]. Decreased anti-angiogenic factors, together with increased stimulators, have been hypothesized in the formation and progression of pterygia [15]. The findings of abundant expression of VEGF in pterygium may lead to the anti-VEGF therapy development in order to induce the regression of blood vessels and size of pterygium. Pterygium is a chronic, degenerative disorder described histologically as elastotic degeneration of conjunctival tissue. It has a stromal overgrowth of fibroblasts and blood vessels accompanied by an inflammatory cell infiltrate and abnormal extracellular matrix accumulation composed of elastin and collagen [7].

In a study done by Asergadoo [23], he concluded that if pterygium is going to recur, it usually grows back or shows signs of recurrence during the first three months. Recurrence is sometimes seen as late as nine months. In a recent study to define the time interval necessary to follow patients after pterygium removal to identify a recurrence, a one - year follow up time was likely acceptable [24]. The minimum follow up in this study was 6 months.

In a study on a rat model of corneal alkali burns, Manzano et al. have shown a 40% reduction of corneal neovascularization by topical application of bevacizumab [25]. Over expression of VEGF in pterygium tissue [26,27] and ocular inflammation [28] together with the abundance of new vessels supported the role of angiogenesis in the formation of pterygia [26,27,29-31]. Vascular endothelial growth factor gene 460 polymorphism was associated with pterygium formation in Chinese female patients [32].

Bahar et al. [31] reported the use of subconjunctival bevacizumab on corneal vessel density in recurrent pterygia. Subconjunctival bevacizumab was well tolerated but did not cause regression of corneal vessels in recurrent pterygia. No side-effects of subconjunctival bevacizumab injections have been reported so far [33- 36].

No local irritation, allergic reaction, or surface epitheliopathy was observed. This is in contrast with a 60% rate of spontaneous loss of epithelial integrity as recently reported by Kim et al. [37], where the investigators used topical bevacizumab at a slightly higher concentration (1.25%) twice daily for a much longer period (3 months), and adverse effects generally appeared during the second month of treatment.

This suggests that the duration of treatment may well determine the safety of topical bevacizumab.

A study done by Dastjerdi shows a highly variable effect across the cohort treated with topical bevacizumab in the treatment of corneal neovascular vessels (NV). Generally, this study shows that topical bevacizumab 1% is effective in the treatment of clinically stable corneal NV as evidenced by a nearly 50% reduction in 2 corneal NV size [38].

Felipe et al. in their study showed that subconjunctival injection of 1.25 mg bevacizumab given every 2 weeks for 10 weeks did not result in significant change in the size of the pterygium. No serious ocular and systemic adverse events were noted [39] but in this study, subconjunctival injection of 0.2 ml (5 mg) Bevacizumab significantly reduced the size of pterygium.

Conclusion

This study showed that subconjunctival injection of bevacizumab is useful in treatment of patients with recurrent pterygium without local or systemic adverse effects. So simplicity of the procedure, cosmetic satisfaction and the lack of major complications after treatment lead us to recommend this regimen as the first choice for the treatment of recurrent pterygium.

References

1. Kaniski JJ (2010) Clinical Ophthalmology. (7th edn) Butterworth-Heinemann Ltd Publisher: 96.
2. Duke-Elders (2000) Systems of Ophthalmology. (7th edn) Henry Kipton Publisher, London: 568.
3. Pinkerton OD, Hokama Y, Shigemura LA (1984) Immunologic basis for the pathogenesis of pterygium. Am J Ophthalmol 98: 225-228.
4. Coster D (1995) Pterygium--an ophthalmic enigma. Br J Ophthalmol 79: 304-305.
5. Karukonda SR, Thompson HW, Beuerman RW, Lam DS, Wilson R, et al. (1995) Cell cycle kinetics in pterygium at three latitudes. Br J Ophthalmol 79: 313-317.
6. Hagen CA, Zimmerman LE (1962) Ophthalmic pathology. (2nd edn) W.B. Saunders Company: 252.
7. Di Girolamo N, Chui J, Coroneo MT, Wakefield D (2004) Pathogenesis of pterygia: role of cytokines, growth factors, and matrix metalloproteinases. Prog Retin Eye Res 23: 195-228.
8. Di Girolamo N, Coroneo MT, Wakefield D (2001) Active matrilysin (MMP-7) in human pterygia: potential role in angiogenesis. Invest Ophthalmol Vis Sci 42: 1963-1968.

9. van Setten G, Aspiotis M, Blalock TD, Grotendorst G, Schultz G (2003) Connective tissue growth factor in pterygium: simultaneous presence with vascular endothelial growth factor - possible contributing factor to conjunctival scarring. Graefes Arch Clin Exp Ophthalmol 241: 135-139.

10. Solomon A, Grueterich M, Li DQ, Meller D, Lee SB, et al. (2003) Overexpression of Insulin-like growth factor-binding protein-2 in pterygium body fibroblasts. Invest Ophthalmol Vis Sci 44: 573-580.

11. Maini R, Collison DJ, Maidment JM, Davies PD, Wormstone IM (2002) Pterygial derived fibroblasts express functionally active histamine and epidermal growth factor receptors. Exp Eye Res 74: 237-244.

12. Marcovich AL, Morad Y, Sandbank J, Huszar M, Rosner M, et al. (2002) Angiogenesis in pterygium: morphometric and immunohistochemical study. Curr Eye Res 25: 17-22.

13. Lee DH, Cho HJ, Kim JT, Choi JS, Joo CK (2001) Expression of vascular endothelial growth factor and inducible nitric oxide synthase in pterygia. Cornea 20: 738-742.

14. Gebhardt M, Mentlein R, Schaudig U, Pufe T, Recker K, et al. (2005) Differential expression of vascular endothelial growth factor implies the limbal origin of pterygia. Ophthalmology 112: 1023-1030.

15. Jin J, Guan M, Sima J, Gao G, Zhang M, et al. (2003) Decreased pigment epithelium-derived factor and increased vascular endothelial growth factor levels in pterygia. Cornea 22: 473-477.

16. Hirst LW (2003) The treatment of pterygium. Surv Ophthalmol 48: 145-180.

17. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, et al. (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350: 2335-2342.

18. Michels S, Rosenfeld PJ, Puliafito CA, Marcus EN, Venkatraman AS (2005) Systemic bevacizumab (Avastin) therapy for neovascular age-related macular degeneration twelve-week results of an uncontrolled open-label clinical study. Ophthalmology 112: 1035-1047.

19. Rosenfeld PJ, Moshfeghi AA, Puliafito CA (2005) Optical coherence tomography findingsafter an intravitreal injection of bevacizumab (Avastin) for neovascular agerelated macular degeneration. Ophthalmic Surg Laser Imaging 36: 331-335.

20. Avery RL, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, et al. (2006) Intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. Ophthalmology 113: 363-372.

21. Tan DT, Chee SP, Dear KB, Lim AS (1997) Effect of pterygium morphology on pterygium recurrence in a controlled trial comparing conjunctival autografting with bare sclera excision. Arch Ophthalmol 115: 1235-1240.

22. Chowers I, Pe'er J, Zamir E, Livni N, Ilsar M, et al. (2001) Proliferative activity and p53 expression in primary and recurrent pterygia. Ophthalmology 108: 985-988.

23. Asregadoo ER (1972) Surgery, thio-tepa, and corticosteroid in the treatment of pterygium. Am J Ophthalmol 74: 960-963.

24. Hirst LW, Sebban A, Chant D (1994) Pterygium recurrence time. Ophthalmology 101: 755-758.

25. Manzano RP, Peyman GA, Khan P, Carvounis PE, Kivilcim M, et al. (2007) Inhibition of experimental corneal neovascularisation by bevacizumab (Avastin). Br J Ophthalmol 91: 804-807.

26. Hosseini H, Nejabat M, Khalili MR (2007) Bevacizumab (Avastin) as a potential novel adjunct in the management of pterygia. Med Hypotheses 69: 925-927.

27. Aspiotis M, Tsanou E, Gorezis S, Ioachim E, Skyrlas A, et al. (2007) Angiogenesis in pterygium: study of microvessel density, vascular endothelial growth factor, and thrombospondin-1. Eye (Lond) 21: 1095-1101.

28. Nagy JA, Dvorak AM, Dvorak HF (2007) VEGF-A and the induction of pathological angiogenesis. Annu Rev Pathol 2: 251-275.

29. Hosseini H, Nejabat M, Mehryar M, Yazdchi T, Sedaghat A, et al. (2007) Bevacizumab inhibits corneal neovascularization in an alkali burn induced model of corneal angiogenesis. Clin Experiment Ophthalmol 35: 745-748.

30. Bock F, Onderka J, Dietrich T, Bachmann B, Kruse FE, et al. (2007) Bevacizumab as a potent inhibitor of inflammatory corneal angiogenesis and lymphangiogenesis. Invest Ophthalmol Vis Sci 48: 2545-2552.

31. Bahar I, Kaiserman I, McAllum P, Rootman D, Slomovic A (2008) Subconjunctival bevacizumab injection for corneal neovascularization in recurrent pterygium. Curr Eye Res 33: 23-28.

32. Tsai YY, Chiang CC, Bau DT, Cheng YW, Lee H, et al. (2008) Vascular endothelial growth factor gene 460 polymorphism is associated with pterygium formation in female patients. Cornea 27: 476-479.

33. Hurmeric V, Mumcuoglu T, Erdurman C, Kurt B, Dagli O, et al. (2008) Effect of subconjunctival bevacizumab (Avastin) on experimental corneal neovascularization in guinea pigs. Cornea 27: 357-362.

34. Kim TI, Kim SW, Kim S, Kim T, Kim EK (2008) Inhibition of experimental corneal neovascularization by using subconjunctival injection of bevacizumab (Avastin). Cornea 27: 349-352.

35. Papathanassiou M, Theodossiadis PG, Liarakos VS, Rouvas A, Giamarellos-Bourboulis EJ, et al. (2008) Inhibition of corneal neovascularization by subconjunctival bevacizumab in an animal model. Am J Ophthalmol 145: 424-431.

36. Manzano RP, Peyman GA, Khan P, Carvounis PE, Kivilcim M, et al. (2007) Inhibition of experimental corneal neovascularisation by bevacizumab (Avastin). Br J Ophthalmol 91: 804-807.

37. Kim SW, Ha BJ, Kim EK, Tchah H, Kim TI (2008) The effect of topical bevacizumab on corneal neovascularization. Ophthalmology 115: e33-e38.

38. Dastjerdi MH, Al-Arfaj KM, Nallasamy N, Hamrah P, Jurkunas UV, et al. (2009) Topical bevacizumab in the treatment of corneal neovascularization: results of a prospective, open-label, noncomparative study. Arch Ophthalmol 127: 381-389.

39. Anthony F, Ruben Lim Bon S, Harvey S (2009) Subconjunctival injection of bevacizumab for treatment of pterygium. Philipp J Ophthalmol 34: 44-50.