Original Article

Role of Subconjunctival Bevacizumab in Treatment of Pterygium

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Purpose: To assess the efficacy and role of sub-conjunctival Bevacizumab in treatment of primary and recurrent pterygium.

Material and Methods: This off-label, single-dose, interventional case series was conducted at Government Medical College Hospital in Srinagar from January 2011 to March 2011 in patients with primary pterygium. Twenty eyes of 20 patients with primary pterygium were selected and a single dose of sub-conjunctival injection of Bevacizumab (0.05 ml, 1.25mg) was given. Pterygium vascularity and thickness was graded. The size of the pterygium (measured by surface area in cm^2) was recorded from baseline to 6 weeks, after injection. Treatment-related complications and adverse events were reported. The main outcome measurements were the change in size, vascularity and thickness.

Results: There were 15 males (75%) and 5 females (25%) of 20 patients with a mean age of 45.5years (SD 11.68 years). There was a significant difference in the mean surface area of pterygium at different intervals ($P < 0.05$) and the size of pterygium were reduced. On comparison of the mean pterygium size, there was no significant difference between men and women ($P > 0.05$).

Conclusion: Sub-conjunctival bevacizumab injection is useful in management of patients with primary pterygium without local or systemic adverse effects.

Pterygium is a triangular sheet of fibro vascular tissue that encroaches the cornea[1,2]. It occurs in the inter-palpebral fissure, more commonly on the nasal side of the eye and is often bilateral[1,3]. Recent studies have provided evidence implicating genetic components, anti-apoptotic mechanisms, cytokines, growth factors, extra cellular matrix remodeling, immunological mechanisms, and viral infections in the pathogenesis of the disease[4-8]. Vascular growth factors such as vascular endothelial growth factor (VEGF) have been detected in pterygium[9-12]. Jin and colleagues showed that pterygia contain decreased levels of pigment epithelium-derived factor, angiogenic inhibitor, and elevated VEGF levels[12]. The treatment of pterygium is myriad, with various treatments being advocated in the scientific literature[13].

Bevacizumab is a full-length, humanized, mono-clonal antibody against all types of VEGF. It binds to and neutralizes the biologic activity of all subtypes of human VEGF[14]. Bevacizumab is now an established modality in treatment of choroidal neovascularization due to age-related macular degeneration (ARMD), and diabetic macular edema. Bevacizumab, when administered intra-vitreally, is well tolerated and associated with improvement in visual acuity, decreased central retinal thickness, and reduction in angiographic leakage[15-17]. We conducted this study to asses the effects of Bevacizumab on ptregium, which has been shown to have VEGF in its matrix.

MATERIAL AND METHODS

This off-label, single-dosing, interventional case series was conducted at Government Medical College Hospital in Srinagar from January 2011 to March 2011 in patients with primary and recurrent pterygium. Pterygium measurement and grading was done according to Tan and coworkers grading scheme proposed in 1997[18]. Grading is based on the visibility

of the underlying episcleral blood vessels. The pterygia were classified into grades I, II, or III based on slit lamp bio microscopy evaluation. Grade I (atrophic) had clearly visible episcleral vessels under the body of the pterygium. Grade II (intermediate) had partially visible episcleral vessels under the body of the pterygium. In grade III (fleshy) episcleral vessels were not visible under the body of the pterygium. On baseline examination, Grade II and grade III pterygium patients were included in the study.

Exclusion criteria included grade I pterygium, any condition for which bevacizumab is contraindicated (hypertension, proteinuria, previous myocardial infarction or stroke).

A complete eye evaluation was performed for each patient. This included visual acuity, applanation tonometry and slit lamp examination. 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. 0.05 cc of bevacizumab (1.25 mg) was injected in sub-conjunctival area of pterygium body using an insulin syringe with 30-gauge needle and lid retractor at place. Patients were followed up after1, 3, and 8 weeks. A complete ophthalmologic evaluation was done for each follow-up. Any complications and adverse events were noted. Post injection complications such as ocular surface toxicity, corneal abrasion, persistent epithelial defect, sub-conjunctival hemorrhage, infection, were noted.

RESULTS

From Jan 2011 to March 2011, 20 patients (15 males 75% and 5 females 25%) were involved in the study. Patient age ranged from 24 to 62 years with mean of 43.5 years [standard deviation (SD) 10.58 years]. According to the results of table 1, average pterygium size reduction in the right eye (P=0.004), left eye (P=0.041) and both the eyes (P=0.002) during four stages of the study was significant.

As seen from table 2 and 3, we had 12 cases of grade III and 8 cases of grade II pterygium selected for intervention. After a sub-conjunctival injection of Bevacizumab, 4 cases of grade III pterygium changed to grade II, and 3 changed to grade I. Also 4 cases of grade II pterygium changed to grade I after Bevacizumab injection.

No ocular surface toxicity, persistent epithelial defects, corneal abrasion, infections, or uveitis were reported during the study.

Table 1: Pterygium size (in cms, from caruncle)

Eye	Pre-injection		Post-injection						P value
			1st Week		2nd Week		8th Week		
Both	Mean	SD	Mean	SD	Mean	SD	Mean	SD	0.02
	3.02	1.09	2.75	1.01	2.39	0.88	2.20	0.92	

Table 2:

Grade of Pterygium	Pre-injection	Post-injection	P-value
Grade 1	0	7	0.0083
Grade 2	8	8	1.0000
Grade 3	12	5	0.0536

Table 3: Post-injection changes in grades of pterygium

No. of Cases	From Grade 3 to Grade 2	From Grade 3 to Grade 1	From Grade 2 to Grade 1
	4	3	4

DISCUSSION

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 extra cellular matrix accumulation composed of elastin and collagen[4].

Our study took into account the changes in the size and vascularity (grade) of pterygium after a sub–conjunctival injection of Bevacizumab. Comparing the size of pterygium, as seen in table 1 after an injection of Bevacizumab, we found a statistically significant reduction in length of pterygium as measured from caruncle (significant p-value using ANNOVA test). These results can be compared to a study done by Besharatiet al[19]. However, the dosage used by these workers was different. This encouraging result was supported by the changes seen in the vascularity or the grades of pterygium after our intervention. Eleven cases changed from a higher grade to a lower one, highlighting the decrease in the vascular component of the pterygia (significant p-value, using chi-square test). Over expression of VEGF in pterygium tissue[20] and ocular inflammation[21] together with the

abundance of new vessels supported the role of angiogenesis in the formation of pterygias[22-24]. In a study done by Asergadoo[25], it was found that if pterygium is going to recur, it usually grows back or shows signs of recurrence during the first three months. Our study observed effects maintenance of effects for at least 2 months.

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 where topical bevacizumab was used twice daily for a much longer period (3 months), and adverse effects generally appeared during the second month of treatment[26]. This suggests that the duration of treatment may well determine the safety of topical Bevacizumab.

CONCLUSION

This study showed that sub-conjunctival injection of bevacizumab is useful in treatment of patients with primary pterygium without local or systemic adverse effects.

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