Subconjunctival Bevacizumab Injection in Treatment of Pterygium

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Abstract- This study determined the clinical effect of subconjunctival administration of bevacizumab in patients with primary and recurrent pterygium. The study was an off-label, single-dosing, interventional case series involving 22 patients with primary and recurrent pterygium. They received subconjunctival bevacizumab (0.2cc). Pterygium vascularity and thickness was graded. The size of the pterygium (measured by surface area in cm^2) was recorded from baseline to 12 weeks, after injection. Treatment-related complications and adverse events were reported. The main outcome of measurements was the change in size, vascularity, thickness, color intensity. There were 15 males (68.2%) and 7 females (31.8%) of 22 patients with a mean age of 45.5 years (SD 11.68 years). One cases didn't cooperate, and excluded. There was a significant difference in the mean surface area of pterygium at different intervals ($P < 0.05$) and the size of pterygium was reduced. On comparison of the mean pterygium size, there was no significant difference between men and women ($P >0.05$). There was a significant reduction in the mean pterygium size of patients younger than 45 years in comparison to those older than 45 years after three month ($P =0.037$), but after 6 months, this difference was not significant ($P = 0.338$). Average changes in pterygium size for both eyes were not different. The reduction of color intensity in both eyes was significant ($P =0.031$). Subconjuctival bevacizumab injection is useful in management of patients with primary and recurrent pterygium without significant local or systemic adverse effects.

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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 and colleagues 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.

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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 primary or recurrent pterygium.

Patients and Methods

This off-label, single-dosing, interventional case series was conducted at Shahid Sadoughi Hospital in Yazd from January 2009 to July 2010 in patients with primary and recurrent pterygium.

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, or 3 based on slit lamp bio microscopy 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 pterygium patients were included in the study. Exclusion criteria included any form of ocular surgery except pterygium removal, any condition for which bevacizumab is contraindicated (allergy to bevacizumab, hypertension, proteinuria, bleeding tendencies, previous myocardial infarction or stroke, pregnant and lactating women), evidence of other ocular diseases except refraction errors, administration of topical medications for pterygium, other complaints not attributable to the pterygium, prior ocular trauma, hypertrophy ,acute pterygia ,more than one recurrent ,pterygium invading more than 1.3 mm into the cornea and inability to follow up for the duration of the study. The patients were interviewed prior to injection using a questionnaire in order to obtain information such as general data, contact number, demographic factors, medical, surgical, and ocular history. A complete eye evaluation was performed for each patient. This included visual-acuity determination, applanation tonometry, slit lamp examination, and anterior segment photography. The dimensions of the pterygium were determined in the anterior-segment photo 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 by a single investigator in operating room. 0.2cc of bevacizumab was injected in subconjunctival area of pterygium body using a 1-ml syringe with 30-gauge needle and lid retractor at place. The lid retractor was removed and the patient went back home with a predetermined follow-up schedule. Patients were followed up after a week, one month and three months. A complete ophthalmologic evaluation was performed for each follow-up. Any complications and adverse events were noted. Anterior-segment photography, using the same camera and the same photographer, was done for every follow-up.

Post injection complications such as ocular surface toxicity, corneal abrasion, persistent epithelial defect, subconjunctival hemorrhage, infection, and uveitis were noted. Every adverse event that did not necessarily have a causal relationship with the treatment also was noted.

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

Both descriptive and analytic approaches were used in the data analyses. A p value less than or equal to 0.05 was considered statistically significant.

Results

From Jan 2009 to Jul 2010, 22 patients (15males (68.2%) and 7females (31.8%)) were involved in the study. The range of patients' age was 28 to 64 years with mean of 45.5 years {standard deviation (SD) 11.68 years}.

One case was excluded because of non-cooperation. From 22 patients, 13cases (61.9%) had pterygium in both eyes, 5 cases (23.8%) in right eye and 3 cases (14.3%) in left eye. Overall, 34 eyes had pterygium. There was no significant difference between males and females in the mean pterygium size, during the follow up (P >0.05). There was a significant reduction in the mean pterygium size of patients younger than 45 years old in comparison to those older than 45 years after three month of treatment (P =0.037), but after 6 months, this difference was not significant (P = 0.338).

Table 1. Mean pterygium size in both of eyes

Pterygium size	First month		3 months		6 months		*P*-value	*P*-
eye	mean	SD	mean	SD	mean	SD	(time effect)	value
right	2.60	0.98	2.14	0.85	2.03	0.84	0.004	0.97
left	2.81	1.09	2.53	0.93	2.34	1.01	0.045	
Both eyes	2.69	1.02	2.32	0.90	2.18	0.92	0.001	

According to the results of table 1 (variance analyze repeated measure), average pterygium size reduction in the right eye (P =0.004), left eye (P =0.045) and both the eyes (P =0.001) during three stages of the study was significant, but changes in both of eyes were not different.

According to the results of table 2 (Friedman test), there were no significant changes in color intensity of the right eye (P =0.155) and left eye (P =0.174), but reduction of color intensity in both eyes was significant (P =0.031). During the follow up color intensity in both age and sex groups was not significant. No ocular-surface toxicity, persistent epithelial defects, corneal abrasion, infections, or uveitis were reported during the study.

Discussion

VEGF 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 conjunctival (12-15,22). Decreased antiangiogenic 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).

Overexpression 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 pterygias. (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 (37).

Table 2. Color intensity in both the eyes

Color intensity	First month			3 months			6 months			*P*-value
eye	median	mean	SD	median	mean	SD	median	mean	SD	(time effect)
Right	1.5	1.55	0.54	2.0	1.42	0.60	1.0	1.22	0.43	0.031
Left	1.5	1.81	0.77	1.5	1.59	0.71	1.25	1.43	0.59	
Both eye	1.5	1.68	0.66	0.66	1.5	0.65	1.0	1.32	0.49	

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

The study by Dastjerdi shows a highly variable effect across the cohort treated with topical bevacizumab in the treatment of corneal neovascular vessele (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 a 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 our study, subconjunctival injection of 0.2cc bevacizumab reduced the size of pterygium.

In conclusion, this study showed that subconjunctival injection of bevacizumab is useful in treatment of patients with primary and recurrent pterygium without local or systemic adverse effects.

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