ORIGINAL ARTICLE

A Trial of Subconjunctival Injection of Bevacizumab as a Treatment of Pterygium

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ABSTRACT

Purpose: To evaluate the efficacy and safety of subconjunctival Bevacizumab on primary and recurrent Pterygium.

Materials and Method: 35 patients with either Primary or recurrent Pterygium (extending on corneal surface) were given a single subconjunctival injection of 1.25mg/0.05ml of Bevacizumab (Avastin) and were evaluated for periodic clinical results at Day 1, 2weeks, 4 weeks and monthly for 3 month. Ophthalmic evaluation including Snellen's visual acuity, intra-ocular pressure and complete examination was done at baseline and on every follow up. Digital photograph of eyes with Pterygium were taken at baseline and at each follow-up and analyzed. Size and height of tissue on digital photograph was measured by using Universal desktop ruler version 3.5.

Results: Visual acuity and intraocular pressure remained stable.1-2mm regression in size of Pterygium from corneal surface occurred at 2 weeks post injection but reversed again to pre injection state at 1 month follow up. Mean size (9.70+1.55mm) and height (5.24+0.9mm) remained the same at baseline and at last follow up (3 month). No progression of Pterygium occurred. No ocular or systemic adverse effects of Bevacizumab were observed.

Conclusion: Short term results suggest that subconjunctival bevacizumab injection is well tolerated and cause a partial temporary regression in size of Pterygium. However, it does not cause complete regression of corneal vessels in Pterygium.

INTRODUCTION

Pterygium, a degenerated condition is an elevated, superficial, external ocular mass that usually forms over the perilimbal conjunctiva and extends onto the corneal surface.[1]It may be a small to rapidly growing fibrovascular lesion that can extend to optical centre of cornea and beyond, distorting corneal topography and effecting vision. Whatever the appearance, it remains a benign lesion commonly found on nasal bulbar conjunctiva, although can be seen on temporal side too.

In a 30 year survey, (1971-2001) by Cornea and External Disease Clinic of Department of Ophthalmology and Visual Sciences, University of Phillipine, Pterygium is ranked among 10 commonly leading conditions seen in the clinic and third among the most common non-infectious conditions.[2]

The pathogenesis of Pterygium is not fully understood. Various studies have implicated environmental factors such as UV 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.[3, 4, 5]

Though histologically benign lesion, (consist of atrophic conjunctival epithelium and body of atrophic and elastotic connective tissue) [6, 7] it is aggressive in nature and cause cosmetic disfigurement and visual impairment.

Vascular growth factors such as VEGF have been detected within Pterygial tissue in a level higher than normal conjunctival samples.[8, 9, 10, 11] It has been postulated that development of Pterygium depends upon changed angiogenic stimulator to inhibitor ratio.

Hill and Maske[12] speculated that limbal blood vessels are prevented from growing onto cornea because of growth inhibiting substance in the cornea.

VEGF stimulate the growth of new blood vessels, a process called angiogenesis. Bevacizumab is a humanized, monoclonal antibody that recognizes and block vascular endothelial growth factor A (VEGF-A). It is available marketed under brand name Avastin.

The antibodies in Bevacizumab are designed to bind tightly to VEGF. This inactivates the VEGF so that it is no longer stimulant. As a result, new vessels are not formed. Thus, Bevacizumab prevents growth by reducing its blood supply. Bevacizumab has been used to treat ophthalmic condition like choroidal neovascularization in age related macular degeneration, in proliferative diabetic retinopathy and recently for reducing macular edema and improving visual acuity.[13] Clinical trials show that Avastin is well tolerated when injected intravitreally.[14]

Though Pterygium at present is managed with surgical excision, its recurrence rate is very high. As such, search for other safer, simpler and effective forms of treatment continues.

In our study, we will use subconjunctival injection of Bevacizumab as an alternative treatment for Pterygium. As Bevacizumab (Avastin) blocks vascular endothelial growth factor in Pterygial tissue, we hypothesize that it should reduce vascularity and cause regression of fibrovascular tissue and block any further new vessel formation. If successful, Pterygium can, then, be treated with simple injection in its belly thereby reducing the need for surgical excision of tissue.

MATERIALS AND METHOD

This off-label, single dose interventional case series was conducted at the Ophthalmology department of Sir Ganga Ram Hospital, Lahore. The study lasted one year from January 2009-February 2010. Thirty five patients (35) volunteered for the study. Twenty two (22) (62.9%) were males and (13) (37.1%) were females. Age range was between 35 -60 years. Patients with both Primary (19) and Recurrent (16) were included in the study. Follow-up period was 3 month after baseline injection. Procedure was explained to each patient and consent for treatment was obtained. Ethical committee was informed. Examination protocol was same for each patient.

Inclusion criteria:

1. Pterygium whose apex had reached the corneal limbus and beyond.
2. Pterygial tissue showing visibly raised vascularization.

Exclusion criteria: Pterygium that had not extended onto cornea. Ocular associations e.g Glaucoma, Uveitis, ocular surgery beside Pterygium in the involved eye and those unable to maintain follow-ups.

This off-label drug and its potential risks were discussed with each patient. Complete history and detailed ocular examination was taken and noted in the questionnaire. A set examination protocol was used both at baseline and each subsequent visit. The examination protocol included Snellen's visual acuity, Applanation tonometry, Slit-lamp examination, anterior segment photograph of Pterygium (covering its extent, vascularization, any signs of regression).

Anterior segment photograph of Pterygium was taken using Topcon camera attached to Topcon slit-lamp (SL-D2, serial no 201508). Patients were asked to direct the eye in direction opposite to Pterygium so that adequate exposure of Pterygium is obtained. Pterygium extent, vascularity, any visible signs of regression or decrease in vascularіy from base (using Caruncle as base) to apex was analyzed. Size of tissue on the Anterior Segment Photograph was measured in millimeters using Universal desktop ruler version 3.5.

Single dose of Bevacizumab 1.25mg**/**0.05ml was injected by single investigator under microscope. After sterilizing the skin of injecting site with Povidone-Iodine, use of opsite,the lids were separated using lid speculum. Patient was requested to keep looking in the opposite direction for adequate exposure. After instilling topical 0.5% proparacaine hydrochloride (Alcaine), using 1ml insulin syringe, 1.25mg/0.05ml of Bevacizumab was injected in the belly of Pterygium close to apex. Topical antibiotic Ofloxacin was instilled, speculum removed and after padding the eye for two hours, patient were sent home with instructions of using topical antibiotic 3 times a day for 4-5days.

Patients were followed up for 3 months. First visit on Day 1 after subconjunctival injection, then 2weeks, 1month, 2 month and finally 3 month post-injection. A total of five visits were scheduled. At each visit, anterior segment photograph (using Topcon camera) of Pterygium were taken and analyzed. Slit-lamp examination and Applanation Tonometry were done at each follow-up. Any post injection adverse effects or complications were noted.

Our objective had been to study the effect of Bevacizumab on Pterygium in terms of regression in size from corneal surface and visibly reduced vascularity.

RESULTS

In one year study period (January 2009-February 2010), thirty five (35) patients were included. 22 (62.9%) were males and 13 (37.1%) were females. The age ranged between 35-60 years. Visual acuity was noted as 6/18 (corrected to 6/6) in 12 patients, 6/12 (corrected to 6/6) in 14 patients, 6/9 in 5 patients and 6/6 in remaining 4 patients. 19 (54.3%) presented with primary Pterygium and 16 (45.7%) had recurrent Pterygium. 10 patients had Pterygium in right eye, 8 patients in left eye and 17 had bilateral condition.

Table 1: Age and sex distribution of patients with Pterygium

AGE (Years)	
Mean	48.6
Range	35-60
GENDER	35
Males	22 (62.9%)
Females	13 (37.1%)

Table 2: Visual acuity

No of Pts (35)	6/60	6/36	6/24	6/18	6/12	6/9	6/6
				12			
					14		
						5	
							4

Table 3: Presentation and location of Pterygium

PTERYGIUM	
Primary	19
Recurrent	16
EYE INVOLVED	
R.E	10
L.E	8
B.E	17

Pre-injection, in all 35 patients, Pterygium had crossed the limbus and extended onto corneal surface to varying distance. None reached the visual axis. The Pterygium was vascular, raised and cosmetically disfiguring in all cases. By observing the anterior segment photographs of Pterygium and measuring the size and height with the help of a Universal Desktop Ruler Version 3.5, the mean size of Pterygium from base to apex came out to be 9.7mm with a standard deviation of 1.55mm. Range was 7.80 to 13.0mm. The mean height of tissue at limbus was 5.24mm with SD of 0.90mm. Range was 3.70 to 7.0mm.

Table 4: Surface area of Pterygium at Baseline

Size (Base to Apex) In mm		Height (at Limbus) In mm
Range	7.8 -13.0	3.70 -7.0
Mean	9.70 + 1.55	5.24 + 0.90

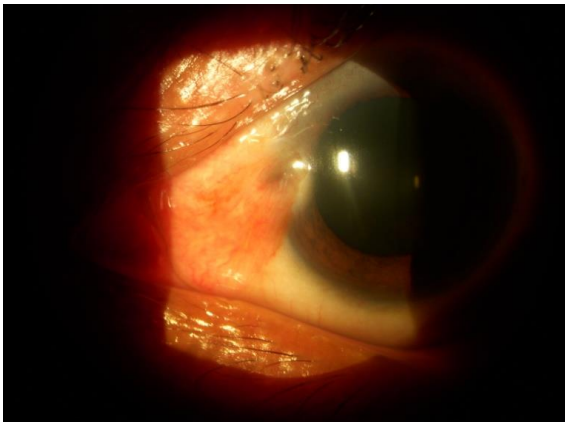

Figure 1: Pterygium

Day 1, post injection. 5 eyes (14.3%) had localized sub-conjunctival hemorrhage at site of injection. This occurred due to accidental touch of insulin syringe needle with conjunctival vessels. However, the hemorrhage settled within a few days. Remaining 30 (85.7%) eyes showed no change from the pre-injection state. No other complication was seen.

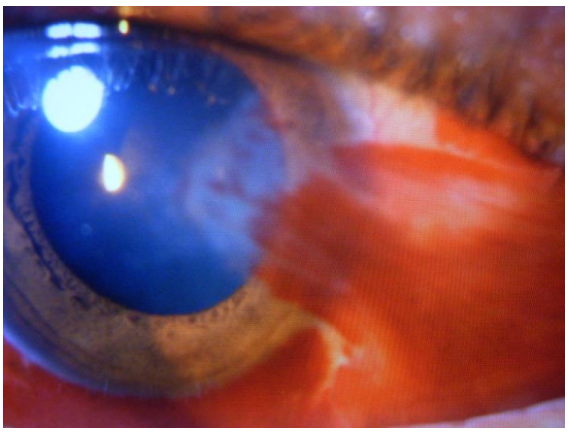

Figure 2: Subconjunctival Hemorrhage (Day 1) Post injection

Visual acuity remained stable with no change from pre-injection state. Intraocular pressure remained within normal limits. Anterior chamber showed no reaction.

Day 14, post injection. Sub-conjunctival hemorrhage seen in 5 eyes had completely disappeared. All 35 eyes showed some clinical improvement in appearance of Pterygium. Slight regression in size of Pterygium tissue on corneal surface was seen. When measured with Universal Desktop Ruler Version 3. 5 the photograph showed regression on an average of 1-2mm (mean 1.6mm). This difference was noted with reviewing the pre-injection and post-injection (day 14) photographs of Pterygium. The rest of the clinical examination remained the same as baseline.

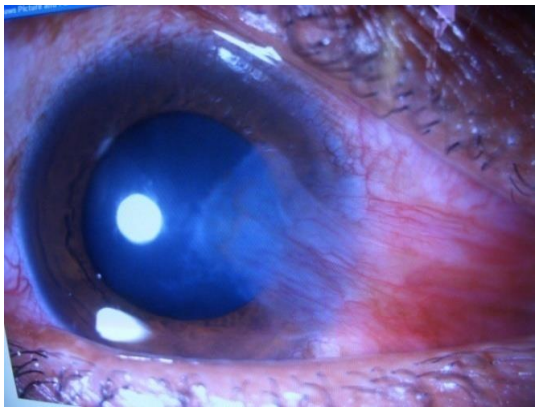

Figure 3: Pterygium (Same patient) (Pre injection) Post injection (2 weeks)

1 Month follow up

The clinical improvement seen at 2nd week had reversed to pre-injection state. This was confirmed by viewing the anterior segment photograph of Pterygium taken on this follow up. Size of tissue, its vascularity looked the same as pre injection state. Rest of the examination parameters (VA, IOP, SLE exam) remained unchanged. Moreover, no ocular surface toxicity appeared.

2 Month, 3 Month follow up

Pterygium did not increase in its surface area (mean size 9.7mm and mean height 5.24mm), and its clinical appearance remained unchanged. This was confirmed by observing the anterior segment picture of Pterygium taken at this last follow-up and compared with the serial photographs. No ocular complications were observed and rest of ocular parameters (VA, IOP, AC reaction) remained unchanged.

DISCUSSION

Elastoid degeneration of the conjunctiva resulting in Pterygia (fibrovascular growth on the surface of cornea), can lead to visual loss secondary to induced astigmatism and /or encroachment upon visual axis.[15]Over expression of vascular endothelial growth factors (VEGF) in Pterygial tissue led us to use anti VEGF therapy. Bevacizumab, in a dose of 1.25mg/0.05ml (same dose used for intravitreal injection of Avastin) was used in our patients with Pterygium (that advanced onto cornea) to see if subconjuntival injection of the drug (Avastin) in the belly of Pterygium (close to limbus) will help in regression of fibrovascular tissue from corneal surface and thus help eliminate visual astigmatism.

Our study results showed improvement in clinical appearance of pterygium two weeks after a single subconjunctival injection of bevacizumab in the tissue belly. The level of hyperemia reduced giving this eye a better cosmetic appearance. There was some regression (1-2mm) in size of fibrovascular tissue from corneal surface. The injection was well tolerated and no ocular complications were seen. Visual acuity, IOP remained stable throughout.

Lee J W et al[16], in their study reported similar clinical findings after two weeks post injection. However, the total number of subjects in their study group were less (20) than in our study (35) group. Moreover, they included test subjects presenting with recurrent Pterygium only while our study group included both primary and recurrent cases and had no restriction in this criteria. Also, the dose of Bevacizumab injected was higher (0.3ml) than our study (0.05ml). Still, the results at that time period (2weeks) matched.

Clinical response noted at 2nd week post injection was totally lost on next follow ups i.e 1 month, 2 month and finally 3rd month post injection. Pterygium clinical appearance had returned to its pre injection state. Level of extention of tissue on cornea, its vascularity and size all looked the same as baseline. However, size of the fibrovascular tissue remained stationary till last follow up (3 month).

Anthony F Felipe et al [2] reported similar findings in their study. Their patients showed transient improvement in clinical appearance in first two weeks followed by return to pre injection

state. Similar findings are also highlighted in study published by Irit Bahar et al [17]. They however injected a greater dose of Bevacizumab (2.5mg/0.1ml) in their patients and included recurrent Pterygium only. Also, their total patient population (5) was quite less than our study population (35). However, the results were the same. Short term clinical improvement in Pterygium appearance and size occurred but long term results were unsatisfactory in their as well as our study.

Failure to get any clinical improvement (regression in size of pterygium, reduction in level of vascularity) could be dose related. In our study we injected the same concentration of drug subconjunctivally (1.25mg/0.05ml) as used for intravitreal injection. Irit Bahar et al [17] used higher concentration of subconjunctival Bevacizumab (2.5mg/1.0ml) than our study yet the results were unsatisfactory. Maybe, a concentration higher than this is required with multiple treatments for achieving a better result.

We restricted our study to single subconjunctival injection so as to see the maximum beneficial effect of the drug and minimize any side effects. Repeated injections (total of 6) used by Anthony F Felipe[2] on their trial patients did not gain any desired results. Thus, frequently injecting the drug subconjunctivally failed to achieve better results.

The single application of Bevacizumab was well tolerated by our patients. Except for early subconjuntival hemorrahage, (which occurred due to accidental touch of injection needle with conjunctival blood vessels and which resolved completely within 2 weeks) no other ocular complications developed. Visual Acuity, IOP remained unchanged. Both Anthony F Felipe[2] and Irit Bahar et al[17] studies also had no ocular complications.

In our study, we failed to get permanent regression of fibrovascular tissue from corneal surface by injecting the drug Subconjunctivally. Wei Pei Chang et al[18] used topical Bevacizumab eye drops 25mg/ml 4 times a day on one case of recurrent Pterygium. They got complete regression in Pterygium within 6 month. However, their study had a single patient. At present, this is the only documented successful result of use of Bevacizumab on Pterygium and that too in topical form.

Conclusion, it can be said that single injection of Bevacizumab subconjunctivally for Pterygium failed to produce desired results. Increasing the strength of dose, frequency of injection, a longer follow up or topical use of this drug on larger group of patients may show promising results. Further studies need be done.

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