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 cm²) 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 [7-11].

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
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 lidocain 2% in subconjunctival area of pterygium 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.

### Table 1: Demography of the patients.

<table>
<thead>
<tr>
<th>Age(years)</th>
<th>Gender</th>
<th>Grade of pterygium</th>
<th>IOP (mm Hg)</th>
<th>Systolic Blood pressure(mm Hg)</th>
<th>Diastolic blood pressure(mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
<td>range</td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>50.46</td>
<td>38-70</td>
<td>12.46 ± 2.42</td>
<td>12-19</td>
<td>122 ± 7.7</td>
<td>100-140</td>
</tr>
<tr>
<td>79.33</td>
<td>5.94</td>
<td>60-100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Time interval</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>11</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>1 month</td>
<td>4</td>
<td>11</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>3 months</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>6 months</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>20</td>
</tr>
</tbody>
</table>

There is a significant relationship between grades and time interval, P<0.01
Diastolic blood Pressure (mmHg) | Systolic blood Pressure (mmHg)
---|---
Mean | 120.67 ± 10.32 | 81.33 ± 8.34
P | 79.33 ± 5.94 | 122 ± 7.74

The minimum follow up in this study was 6 months. The 1-year follow time was likely acceptable [24]. The minimum follow patients after pterygium removal to identify a recurrence, a one nine months. In a recent study to define the time interval necessary to detect 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 avoid surgical complications such as recurrence and even complications such as infection and scleral necrosis [6-8]. On the other hand, many patients ask for conservative treatment at least to avoid surgical complications such as recurrence and even complications such as infection and scleral necrosis [6-8].

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 regress the size of pterygium [16]. Subconjunctival injection of 0.2 ml (5 mg) Bevacizumab significantly reduced the size of pterygium.

This 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. 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**


