The Boston Ocular Surface Prosthesis as a Novel Drug Delivery System for Bevacizumab

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ABSTRACT

Corneal neovascularization causes deterioration of visual acuity and increases surface irregularities. Various techniques have been employed to help control the progression of corneal neovascularization; bevacizumab is a medication that targets the specific pathway of corneal neovascularization. The Boston Ocular Surface Prosthesis (BOSP) is a large diameter contact lens that aids in maintaining corneal surface integrity and may serve as a delivery system for topical bevacizumab. This paper reviews five patients who were treated with topical bevacizumab in their BOSP. All patients demonstrated improvement in their visual acuity and clinical exam. No adverse reactions were noted.

Keywords: corneal neovascularization, bevacizumab, scleral lens

INTRODUCTION

The cornea is an avascular organ. This avascularity contributes to its optical clarity and is maintained through a constant equilibrium among angiogenic and antiangiogenic factors.1 If the cornea undergoes inflammation or infection the balance may be tipped in favor of angiogenesis, leading to lipid deposition, scarring, decreased vision, and an increased risk of graft failure.2,3 Various approaches towards controlling corneal neovascularization have been reported including: topical corticosteroids, cryotherapy, nonsteroidal antiinflammatory agents, and photodynamic therapy.4,5,6 Success with these treatments varies depending on the location and degree of corneal neovascularization. Furthermore, these treatments may have deleterious side effects. Until recently, there have been no agents that specifically target the pathway of angiogenesis itself.

Many factors contribute to the process of corneal neovascularization; among the leading angiogenic factors are a group of vascular endothelial growth factors (VEGF), which have been shown to be upregulated in instances of corneal inflammation and neovascularization.7,8,9,10 Bevacizumab is a recombinant, humanized, monoclonal antibody that binds to and deactivates VEGF; it was FDA approved in 2004 as a treatment for patients with metastatic colorectal cancer. It has revolutionized treatment for wet age-related macular degeneration, when administered off-label by intra-vitreal injection, and it is now being explored for other areas of ocular angiogenesis.11,12,13,14,15 In particular, bevacizumab has been demonstrated to have inhibitory effects on corneal neovascularization in the laboratory setting when applied both topically and subconjunctivally.16,17,18,19 Miltiades and colleagues noted regression mostly of smaller branches of neovascularization in the rabbit cornea, suggesting bevacizumab is effective mostly on newly developing corneal neovascularization.20
Subconjunctival injections of bevacizumab have recently been studied clinically in small case settings with overall promising results. Topical administration of bevacizumab for corneal neovascularization was first reported in the clinical setting by DiStafeno and Kim in 2007; results showed clinical regression of corneal neovascularization with no demonstrable side effects. This regression was subsequently verified by additional reports from various groups. Uy et al. have demonstrated improvement in corneal neovascularization as well as patient comfort in their 2 patients with Stevens-Johnson syndrome. Kim et al. recently treated 10 eyes with topical bevacizumab, and although initial regression of vessels was observed, a 2-month follow-up demonstrated adverse effects such as epithelial breakdown and stromal thinning.

The Boston Ocular Surface Prosthesis (BOSP) lens is a large diameter, rigid, gas permeable lens that vaults over the corneal surface, bathing the entire cornea in oxygenated artificial tears. The BOSP is custom-designed for each patient using CAD-CAM technology. It made with a high Dk fluoro-silicone acrylate polymer, providing for oxygen transmission to the cornea. The device was originally designed for the treatment of ectasia and irregular astigmatism including cases after keratoplasty and keratorefractive procedures. This device has also been used with great success in treating patients with ocular surface disease, such as chronic ocular graft versus host disease (cGVHD), neurotrophic corneas, dry eye syndrome, and Stevens-Johnson syndrome. An additional benefit of the BOSP is its potential for drug delivery. Patients with non-healing corneal ulcers or persistent epithelial defects (PED), for example, are able to combine topical antibiotics with saline in the BOSP reservoir, providing a continuous, dilute dose of the drug for the duration the patient wears the lens. The Boston Foundation for Sight sees many patients with ocular surface disease and concomitant corneal neovascularization. Given the recently published reports of success with corneal neovascularization and topical bevacizumab, we decided to study the effects of topical bevacizumab delivered via the BOSP. In this paper we report 5 patients who were treated in this manner.

PATIENTS AND METHODS

Patients already fitted with the BOSP who had with corneal neovascularization that might be responsive to topical therapy were identified from our clinic population at episodic visits from 2006 to the present. After review of the potential risks and benefits of off-label use of topical bevacizumab, along with alternatives, treatment was undertaken. Written informed consent for the off-label use of bevacizumab was obtained. The patients were instructed to continue wearing the lens as usual, on a full-time daily wear basis, with nightly removal and disinfection. The prescribed dosage regimen was: one drop of 1% bevacizumab, compounded in sterile saline non-preserved, to be instilled each morning in the fluid reservoir of the BOSP. This reservoir was then filled with non-preserved, buffered, sterile saline and the scleral lens inserted as usual. The lens was removed, emptied, and cleaned, and the fluid reservoir was reconstituted after 6 hours with a second drop of bevacizumab, and the lens worn for an additional 6–10 hours unless otherwise specified. All topical and systemic medications were continued. Data collected included best-corrected visual acuity, slit lamp exam, and slit-lamp photography at each visit. Patients were monitored at 1 week, 1 month, 2 month, and 3 months. In order to decrease the potential for systemic absorption, punctal plugs or cautery were performed on all patients with patent punctae. After three months, dosage was tapered and discontinued except in case 2. Retrospective medical record review of the patients treated reveals that there were 2 females and 3 males aged 26–65 years old with a range of indications for BOSP wear (Table 1).

Patient 1

A 62-year-old man with herpes simplex virus neurotrophic keratitis in the left eye was initially fitted with a BOSP for a persistent epithelial defect (PED) 6 months after PK #2 in 1997. He healed with pannus and haze. A third penetrating keratoplasty was undertaken in 2005 for visual rehabilitation, and the BOSP wear was resumed at 2 weeks post-operative. One year after surgery the patient had a stable ocular surface and vision of 20/25. Eight months later, rapid progression of inferior neovascularization was noted. Four months later, at 2 years after surgery, vascular pannus impinged on the visual axis reducing acuity to Count Fingers vision. Topical bevacizumab treatment was prescribed as above. One month after initiating treatment, marked regression of pannus and improvement in vision was noted, with a plateau of vision to 20/40 at 3 and 10 months (Figure 1). Bevacizumab frequency was tapered to once daily and finally discontinued at 7 months. Vision remained at 20/40 while off bevacizumab for 17 months. There were no adverse ocular or systemic effects.

Patient 2

A 30-year-old woman with Stevens-Johnson syndrome at age 12 secondary to Tegretol began wearing the
Table 1. Patient demographics for topical bevacizumab/BOSP

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age(yrs)/Gender</th>
<th>Eye(s)</th>
<th>Diagnosis</th>
<th>Other topical medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65/Male</td>
<td>Left</td>
<td>PED/HSV neurotrophic keratitis</td>
<td>Predforte, Vigamox, Restasis</td>
</tr>
<tr>
<td>2</td>
<td>30/Female</td>
<td>Left</td>
<td>Vascularized nodule/Stevens-Johnson syndrome</td>
<td>Timoptic, Xalatan, Alphagan, Acular, serum drops</td>
</tr>
<tr>
<td>3</td>
<td>35/Male</td>
<td>Right</td>
<td>PED/Limbal stem cell deficiency</td>
<td>Timoptic, Lotemax</td>
</tr>
<tr>
<td>4</td>
<td>61/Female</td>
<td>Right</td>
<td>PED/Sterile Melt</td>
<td>Predforte, Artificial tears, Erythromycin ointment</td>
</tr>
<tr>
<td>5</td>
<td>26/Male</td>
<td>Both</td>
<td>Neovascular pannus and scar/Familial dysautonomia</td>
<td>Artificial tears</td>
</tr>
</tbody>
</table>

BOSP for comfort and maintenance of her ocular surface. She had previously suffered an episode of infectious keratitis in the right eye with perforation leading to a flat chamber, glaucoma, corneal neovascularization and scarring and LP vision. The left eye had a vascularized paraxial nodule after an episode of fungal keratitis. Once fitted with the BOSP she had no further episodes of microbial keratitis and her foreign body sensation and photophobia were much improved. She was noted that the vascular nodule was increasing in size requiring increased vault in the scleral lens. Vision at that time was 20/30. Topical bevacizumab treatment for the left eye was undertaken. At 3 months the patient’s vision had improved 1 line from 20/30 in the left eye to 20/25; moreover she subjectively noted improved comfort and a decrease in ocular surface debris while on the bevacizumab. The patient experienced such improvement in comfort she asked to use the bevacizumab in both eyes. She was tapered to daily dosing in both eyes but reported decreased comfort and has resumed twice daily dosing of the bevacizumab. She has continued treatment of her left eye with bevacizumab for 2 years at the time of this writing. Clinically at 7 months, the corneal neovascularization looked the same to slightly improved (Figure 2). There have been no adverse ocular or systemic effects.

Patient 3

A 35-year-old male was referred with a non-healing corneal epithelial defect in the right eye thought to be secondary to limbal stem cell deficiency. His history was significant for soft contact lens associated infiltrative keratitis. The ocular surface healed under the BOSP, but visual acuity remained 20/400 due to axial haze and vessels. Topical bevacizumab was prescribed and at 4 months the vision had improved to 20/200, with a significant decrease in the neovascularization by slit lamp photography (Figure 3). 6 months after bevacizumab was initiated the vision was 20/70. After being off bevacizumab for 7 months, the patient...
continued to improve to a vision of 20/60 in the right eye. There were no adverse ocular or systemic effects.

Patient 4
A 61-year-old female with a history of Sjogren’s disease and neurotrophic cornea after cataract and retinal surgery developed a corneal perforation that required an emergency patch graft in the right eye. The surface of the graft did not epithelialize after 4 weeks, so the patient was referred for and fitted with the BOSP. The surface healed in 5 days, but with substantial corneal neovascularization and vision of Count Fingers at 6 feet. Topical bevacizumab was initiated at 4 months postoperative from the emergency patch graft. 3 months later the vision had improved to Count Fingers at 2 feet. At 5 months the vision was 20/400, with a significant clinical improvement in the corneal neovascularization (Figure 4). 3 months after discontinuation of bevacizumab the vision remained at 20/400. There were no adverse ocular or systemic effects.

Patient 5
A 26-year-old male with familial dysautonomia was fitted with the BOSP 6 months earlier for protection of the ocular surface. He had pendular nystagmus, but good reading vision that had gradually declined in association with progressive neovascularization and opacification of the nasal and inferior corneas. He had been treated with lubrication, Restasis, and partial tarsorrhaphy. After stability of the ocular surface with BOSP was established over 6 months, treatment with topical bevacizumab was begun. In this case he was treated only QD, as his health aides were not able to offer lens removal and reservoir replenishment midday. He reported subjective improvement in vision for playing cards and reading the digital readout on his microwave at 1 month, and slit lamp exam at 5 months showed improvement in corneal haze (Figure 5). Subjective improvement continued and did not reach plateau at 3 months so QD treatment was continued. At 5 months the patient reported no further improvement and he stopped the bevacizumab. His blood pressure was monitored throughout with no
change in pattern of lability. He reports no decline in vision 4 months after discontinuation of bevacizumab.

DISCUSSION

Ophthalmologists currently possess several different therapeutic tactics in the struggle against corneal neovascularization; bevacizumab is the newest hope in this battle. Early reports on the treatment of corneal neovascularization have shown promising results with both subconjunctival and topical administration of bevacizumab with little side effects. However, long-term risks and benefits have not yet been determined. One interesting report from Kim et al. demonstrated a breakdown in epithelial integrity after treatment with topical bevacizumab.31 This observation occurred in the second month of treatment after an initial improvement in vision. Our 3 month treatment regimen did not result in epithelial compromise, even in patients who had poor baseline epithelium. We have continued following our patients for up to 24 months after beginning bevacizumab and have yet to note any adverse effects. Our dose and duration of treatment is similar to Kim et al. In order to avoid preservative toxicity with the BOSP, for our patients bevacizumab was compounded without the use of BAK. DeStafeno and Kim used BAK in their topical formulation to reduce likelihood of contamination and to enhance penetration. We observed drug effect without this additive and had no cases of superinfection.

We propose that the BOSP may play a protective role in supporting the corneal epithelium if indeed there is some deleterious effect of bevacizumab in patients with ocular surface disease. It is also possible that we did not see the adverse effects seen by Kim et al. because bevacizumab is diluted 1:10–20 in the reservoir so a less concentrated dose constantly bathes the epithelial surface. The bevacizumab may also be pH balanced by the Unisol saline solution, which fills the reservoir, allowing for less toxic effects.

All of our patients reported both a subjective and objective improvement in visual acuity (Table 2). Even

Figure 4. Patient 4: Prior to bevacizumab therapy (Count Fingers vision) and at 5 months (20/400).

Figure 5. Patient 5: Prior to bevacizumab therapy (20/200 OD, 20/200 OS) and at 5 months (20/100 OD, 20/200 OS).
though our Stevens-Johnson patient did not receive a significant improvement in vision, she opted to continue treatment due to a noted improvement in ocular surface comfort and decreased discharge. Uy and colleagues have also reported this phenomenon in their Stevens-Johnson population. This suggests that targeting VEGF can have anti-inflammatory as well as anti-angiogenic properties. Miltiades et al. reported regression of smaller, newer branches of corneal neovascularization and no change with the larger vessels. We found similar results in our study; old corneal neovascularization did not seem as responsive to the treatment as newer vessels. These results differ from other reports, which showed a decrease in both old and new angiogenesis. We specifically targeted patients who had a recent drop in vision due to corneal neovascularization, so this may be why we saw such results. In these 5 patients who continued to wear the BOSP for their ocular surface disease, the effect of bevacizumab treatment was durable with no recurrence of visually significant vessels 4–24 months after cessation of treatment.

Subconjunctival injection of bevacizumab has been shown to be a successful delivery method against corneal neovascularization; however, topical application is likely to be a more appealing option to patients. Subconjunctival delivery also carries potential complications such as subconjunctival hemorrhage, thinning/erosion of underlying sclera and even intraocular penetration. If topical administration is chosen, the BOSP may represent a novel method of delivering the drug in a safe manner over a prolonged period time. Furthermore, bevacizumab itself is a very large molecule; this may prevent its full absorption if only topical administration is used. The BOSP, by maintaining a fluid volume against the cornea, may improve the bio-availability of the large bevacizumab molecule. The BOSP also provides the additional benefit of epithelial protection in a likely already tenuous environment. Regression of corneal neovascularization can improve visual quality for patients who are not amenable to surgical therapy, for example those in whom grafts are likely to fail or maintenance of the graft is too burdensome. It may also improve the success of grafts if future surgery is undertaken.

Systemic bevacizumab has been shown to cause hypotension and an increased rate of thrombosis in patients with metastatic colorectal carcinoma. Fortunately, systemic side effects in our study and in other studies were not noted. Even our patient with familial dysautonomia, whose volatile blood pressure was measured regularly, did not demonstrate any systemic adverse effect. Regardless, punctal plugs or cautery should be used to decrease chance of systemic absorption when bevacizumab is administered topically.

Controlled studies and long-term follow-up are required to determine the optimal dose and duration of topical bevacizumab therapy for corneal neovascularization. The role of the BOSP in enhancing delivery and/or protecting the corneal surface warrants further investigation. The clinical impact in these first five patients shows great promise.

**Declaration of interest**

The authors have no proprietary or financial interest in the Boston Ocular Surface Prosthesis. Drs. Jacobs, Rosenthal, and Carraquillo are salaried, full-time employees of the Boston Foundation for Sight, a 501(c)3 non-profit. Their salaries are fixed, with no volume or productivity incentive, and are determined by the compensation committee of the Foundation’s independent board of directors.
REFERENCES


