

# Topical Bevacizumab and Ocular Surface Neovascularization in Patients With Stevens–Johnson Syndrome

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**Purpose:** To evaluate the efficacy and safety of topical bevacizumab on ocular surface neovascularization among patients with Stevens–Johnson syndrome.

**Methods:** This was a retrospective, interventional case report. Three eyes of 2 patients were examined. Bevacizumab (25 mg/mL) eyedrops were applied 4 times daily for a period of 3 months. Main outcome measures were improvement of symptoms, visual acuity, degree of ocular surface neovascularization, corneal opacification, conjunctival injection, and occurrence of adverse events.

**Results:** Both patients completed the 3-month observation period and reported that it significantly improved ocular comfort. At the end of the study period, visual acuity improved in all 3 eyes; all eyes were observed to have decreased ocular surface neovascularization, corneal opacification, and conjunctival injection. No serious adverse events were reported.

**Conclusions:** Topical bevacizumab is well tolerated and may be effective in improving comfort and inducing regression of ocular surface neovascularization, conjunctival injection, and corneal opacification in patients with ocular surface disease caused by Stevens–Johnson syndrome. Further controlled and long-term studies are needed to fully evaluate the long-term effects of this novel treatment.

**Key Words:** bevacizumab, ocular surface disease, neovascularization, Stevens–Johnson syndrome

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Stevens–Johnson syndrome (SJS) is a devastating cause of corneal blindness characterized by chronic ocular surface inflammation, dry eye, limbal stem cell deficiency (LSCD), stromal opacification, ocular surface keratinization, corneal/conjunctival or ocular surface neovascularization (OSN), and high corneal graft failure rates.<sup>1–5</sup> The lack of satisfactory

treatments for these sequelae has led to the development of extremely complex surgical procedures such as transplantation of conjunctival limbal stem cells, amniotic membranes and autologous oral mucosal epithelial cells, photodynamic therapy (PDT), and keratoprosthesis implantation.<sup>6–15</sup> These methods have not been widely used because of their high procedural costs, need for specialized skills and equipment, and lack of good long-term success rates.<sup>16–18</sup>

OSN is a prominent feature of SJS that results in visual loss because of accompanying scarring and lipid deposition.<sup>6</sup> There is extensive evidence supporting a causal role for vascular endothelial growth factor (VEGF) in promoting OSN.<sup>19–22</sup> Large clinical trials have shown that anti-VEGF antibodies can neutralize VEGF and induce regression of choroidal neovascularization (CNV).<sup>23–25</sup> A recent animal study showed regression of corneal neovascularization after topical administration of bevacizumab (Avastin; Genentech, San Francisco, CA).<sup>26</sup> We report here 3 eyes of 2 patients who exhibited regression of OSN, corneal opacification, and conjunctival injection, with resulting visual improvement after application of topical bevacizumab.

## CASE REPORTS

The compassionate off-label use of topical bevacizumab in this report was approved by the institutional review board of the Asian Eye Institute. Informed consent was obtained from patients in accordance with the principles of the Declaration of Helsinki for research involving human subjects. Three eyes of 2 otherwise healthy patients with SJS who developed blinding ocular surface disease were involved in this series. All 3 eyes had a history of corticosteroid-induced glaucoma and were maintained on topical intraocular pressure (IOP)–lowering medications.

Topical bevacizumab was prepared by transferring the contents of a 100 mg/4 mL vial (25 mg/mL) of bevacizumab into a sterile, brown-tinted storage bottle. The patients were instructed to store the bevacizumab bottle inside a commercial refrigerator (4°C) when not in use. The drug was applied to the ocular surface by using a commercial glass dropper. A fresh preparation of bevacizumab was provided at the start of each treatment month to minimize contamination and drug degradation.

### Case 1

A 43-year-old man was referred for management of bilateral eye pain and redness on June 26, 2006. He developed SJS in 2001 after a 2-week course of allopurinol. Since then, he experienced progressively deteriorating vision associated with recurrent eye pain and redness. He was maintained on carbomer gel twice a day,

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tobramycin and dexamethasone eyedrops twice a day, and, because of corticosteroid response, timolol and dorzolamide (Cosopt) twice a day for the past 12 months.

On consultation, his best-corrected visual acuity (BCVA) was 20/100 in the right eye and counting fingers in the left eye. His IOPs were 8 and 15 mm Hg, respectively. Slit-lamp biomicroscopy revealed bilateral conjunctival cicatrization, symblepharon formation, and fornix shallowing. The right cornea presented with severe dry eye with large areas of epithelial abrasion and surface irregularity, micropannus affecting 33% of total limbal circumference, and 3+ conjunctival injection (Fig. 1A). The left eye manifested dense, near-total corneal opacification preventing visualization of the pupil, pannus formation affecting 75% of the limbal circumference, and 3+ conjunctival injection suggestive of a “hot,” inflamed eye (Fig. 1B).

In an effort to reduce OSN without causing IOP elevation, the off-label use of topical bevacizumab was carefully discussed with the patient. After we obtained informed consent, topical bevacizumab (25 mg/mL) was applied 4 times daily to both eyes. The other topical medications were maintained.

Over the next 3 months, the patient reported gradual improvement in comfort, eye redness, and the ability to open both eyes. His BCVA eventually improved to 20/25 in the right eye and 20/80 in the left eye. Both eyes exhibited marked reduction in OSN and conjunctival injection. In the right eye, corneal surface abrasions and irregularity and micropannus disappeared (Fig. 1C). In the left eye, corneal opacification decreased, allowing visualization of the pupil and some iris details; pannus formation regressed to only 50%; and conjunctival injection disappeared, giving the appearance of a quiet eye (Fig. 1D). The IOP remained controlled in both eyes without the need for additional medication. No serious adverse events were reported.

## Case 2

A 50-year-old woman was referred to our clinic for management of SJS-associated corneal blindness on June 19, 2006. She

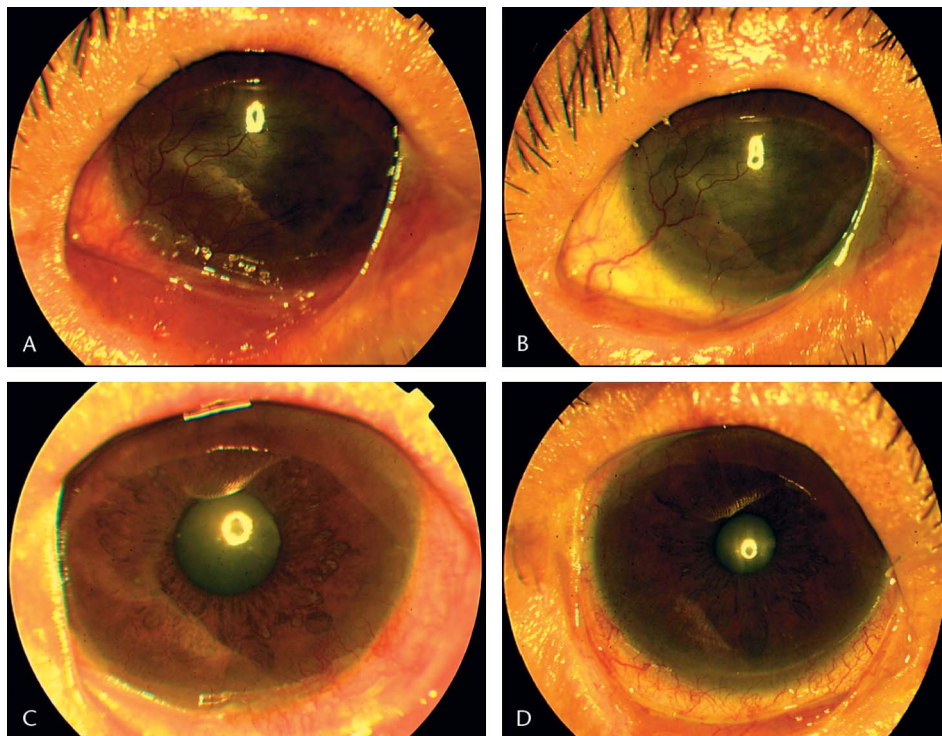
reported a history of progressively worsening vision, eye pain, and redness of the right eye after developing SJS from cotrimoxazole intake in 1998. She had undergone enucleation of the left eye in 2004 after rupture of a corneal ulcer. She had been maintained on cyclosporine (Restasis, Allergan, Irvine, CA) and fluorometholone (Flarex, Alcon Laboratories, Fort Worth, TX) eyedrops applied 3 times daily for the past 8 months. Because of a previous history of corticosteroid-induced glaucoma, she was using timolol maleate (Timoptol XE, Merck & Co., Whitehouse, NJ) once daily. During her initial consultation in December 2005, her BCVA was 20/400. Her IOP was 18 mm Hg. Slit-lamp biomicroscopy disclosed symblepharon formation and fornix shallowing. The corneal surface was abraded and irregular. Scarring and neovascularization caused total corneal opacification. There was prominent pannus affecting 75% of the limbal circumference (Fig. 2A).

After discussion of the potential risks and benefits and obtaining an informed consent, the patient was started on topical bevacizumab (25 mg/mL) applied 4 times daily. The other topical medications were maintained. Over the next 3 months, the patient reported subjective improvement in vision and ocular comfort. Her BCVA improved to 20/100. Surface epithelial defects healed, and the corneal surface became smooth. The central corneal opacity became thinner with significant clearing of midperipheral opacification. Pannus coverage was reduced to 60%. Conjunctival injection markedly decreased, with disappearance of all but the largest new blood vessels (Fig. 2B). No adverse events developed throughout the treatment course.

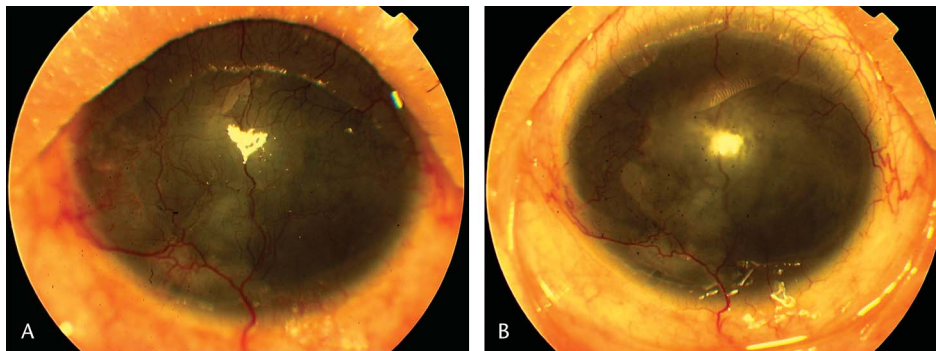
## DISCUSSION

Ocular surface disease (OSD) caused by SJS is characterized by chronic inflammation, LSCD, dry eye syndrome, cicatrization, and OSN. Although some of these components can be addressed (immunosuppressive therapy, limbal stem cell grafting, punctal plugging, tear substitutes, amniotic

**FIGURE 1.** A 43-year-old man with a 5-year history of ocular surface disease caused by SJS. A, Photograph of the right eye shows epithelial/stromal opacification, micropannus, and moderate conjunctival injection. B, After 3 months of topical bevacizumab, photograph shows marked reduction in corneal opacification, micropannus, and conjunctival injection. Visual acuity likewise improved. C, Photograph of the left eye shows severe epithelial/stromal opacification, large pannus, and marked conjunctival injection. After 3 months of topical bevacizumab, (D) photograph shows significant reduction in extent of opacification, pannus, and conjunctival injection, accompanied by improvement in visual acuity.



**FIGURE 2.** A 50-year-old woman presented with a 6-year history of ocular surface disease caused by SJS. The left eye was enucleated because of a ruptured corneal ulcer. A, Photograph of the right shows symblepharon, total epithelial/stromal opacification, prominent pannus formation, and marked conjunctival injection. B, After 3 months of topical bevacizumab, significant clearing of midperipheral opacification and reduction of pannus size were observed.



membrane, and oral mucosal epithelial transplantation), there is currently no specific treatment to address OSN.<sup>5–18</sup> PDT using various photosensitizing agents has previously been shown to induce regression of OSN in animal models and limited case series. However, PDT requires the use of special laser equipment and photosensitizing agents that may not be widely available.<sup>6,27–29</sup> In this report, we describe 3 eyes of 2 patients that underwent regression of SJS-associated OSN after a short course of topical bevacizumab.

Bevacizumab is a full-length humanized monoclonal immunoglobulin G antibody that binds to VEGF. It was the first anti-VEGF antibody to be approved by the U.S. Food and Drug Administration specifically for the treatment of metastatic colon cancer.<sup>30</sup> Intravitreal administration of bevacizumab for treatment of CNV has gained wide and rapid acceptance because of its safety, efficacy, and lower cost in comparison to other anti-VEGF drugs such as ranibizumab and pegaptanib.<sup>23–25</sup>

If intravitreal bevacizumab could penetrate the retinal surface and entire retinal thickness to induce regression of CNV, topical bevacizumab administration would probably permeate and penetrate the ocular surface to induce regression of OSN and modulate the neovascular process. Among patients with SJS, the severity of corneal vascularization and other ocular surface abnormalities has been correlated with visual outcome.<sup>31</sup> The results of this study showed that gradual regression of OSN could be achieved with regular application of topical bevacizumab with resulting improvement of visual acuity.

The dosage for intravenous administration of bevacizumab for the treatment of metastatic cancer is 5 mg/kg of body weight every 2 weeks, or for a 60-kg patient, 600 mg/mo. At this concentration, systemic treatment with bevacizumab has been associated with hypertension and thromboembolic events among cancer patients.<sup>27</sup> There are currently limited data available on ocular safety and systemic safety after intraocular administration. Two recent studies have shown the safety of intravitreal bevacizumab regarding inflammatory response and retinal toxicity.<sup>32,33</sup> In this report, neither patient developed significant adverse events with a potential cumulative dosage of 100 mg of bevacizumab per month if the whole bottle was used. We hypothesized that the relatively low dose would not produce any systemic complications; however, because of the short follow-up period, the long-term adverse effects of topical bevacizumab could not be determined in this report.

If the efficacy and safety of topical bevacizumab for the treatment of OSN are confirmed, this mode of treatment would be a welcome addition to the tools for preventing OSD-associated blindness. The advantages of topical bevacizumab include ease of preparation, titration, application, and accessibility, because many centers already stock bevacizumab for cancer and CNV treatment. Disadvantages include the potentially high cost of long-term treatment, need for storage, and lack of long-term safety data.

We were not able to establish the cause of neovascularization in this series because of lack of patient consent; however, chronic inflammation and LSCD are established processes in SJS-associated OSD.<sup>34</sup> Nonetheless, the good results observed here justify conducting long-term, multicenter clinical trials to determine the efficacy and safety profile of topical bevacizumab. Other avenues for study include optimal dosing for modulating the neovascular process and examination of the histopathologic effects of topical bevacizumab therapy.

In summary, despite decades of research work by some of the finest scientists and ophthalmologists, the SJS-associated OSD remains a therapeutic challenge. This report suggests a potential role for topical bevacizumab in treating one piece of the puzzle—that of inducing regression of corneal/conjunctival neovascularization.

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