

# Ranibizumab Injection for Corneal Neovascularization Refractory to Bevacizumab Treatment

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Vascular endothelial growth factor inhibitor is an emerging therapeutic modality for various ocular diseases with neovascularization (NV). However, for corneal NV, controversy remains regarding whether bevacizumab or ranibizumab is superior. A 32-year-old female diagnosed with herpetic keratoconjunctivitis with refractory corneal NV despite two previous subconjunctival and intrastromal bevacizumab injections, received two subconjunctival and intrastromal ranibizumab injections. Six months postoperatively, there was significant regression of the neovascular area and vessel caliber. Here, the authors report a case of improvement in corneal NV with subconjunctival and intrastromal ranibizumab injections, which was previously refractory to bevacizumab injection. The findings may suggest a new prospect in treating corneal NV.

**Key Words:** Corneal neovascularization, Herpetic keratitis, Ranibizumab, Subconjunctival and intrastromal injections

Corneal avascularity is essential for the preservation of optimal vision. However, the corneal angiogenic privilege is compromised under pathologic conditions such as hypoxia and inflammation [1-3], since the delicate balance between proangiogenic and antiangiogenic factors is lost under such conditions [4-6]. The proangiogenic factor, vascular endothelial growth factor (VEGF), regulates the development and maintenance of blood vessels, and is upregulated to maintain corneal avascularity when the cornea is injured, eventually resulting in corneal neovascularization (NV) [6,7]. Recent animal experiments and clinical trials revealed that bevacizumab and ranibizumab, two representative VEGF inhibitors, have anti-angiogenic effects on the cornea [8,9]. However, although there have been numerous studies at-

tempting to identify the superiority of topical bevacizumab and ranibizumab, the direct comparison between bevacizumab and ranibizumab in the subconjunctival and intrastromal forms remains unclear, requiring further investigation.

Here, we present a case of corneal NV improvement following subconjunctival and intrastromal ranibizumab injections, which was previously refractory to bevacizumab injections. The purpose of this report is to bring to the attention of ophthalmologists a new possible avenue for treatment of corneal NV, specifically subconjunctival and intrastromal ranibizumab injections, especially in those patients with unsatisfactory results after bevacizumab injection.

## Case Report

A 32-year-old female with known corneal opacity and decreased visual acuity of the right eye, which was noticed three weeks prior to visit, was referred to our clinic. Previously, in 2008, she visited an ophthalmologist due to decreased visual acuity measuring 20 / 50, and a pannus-like elevated nodular

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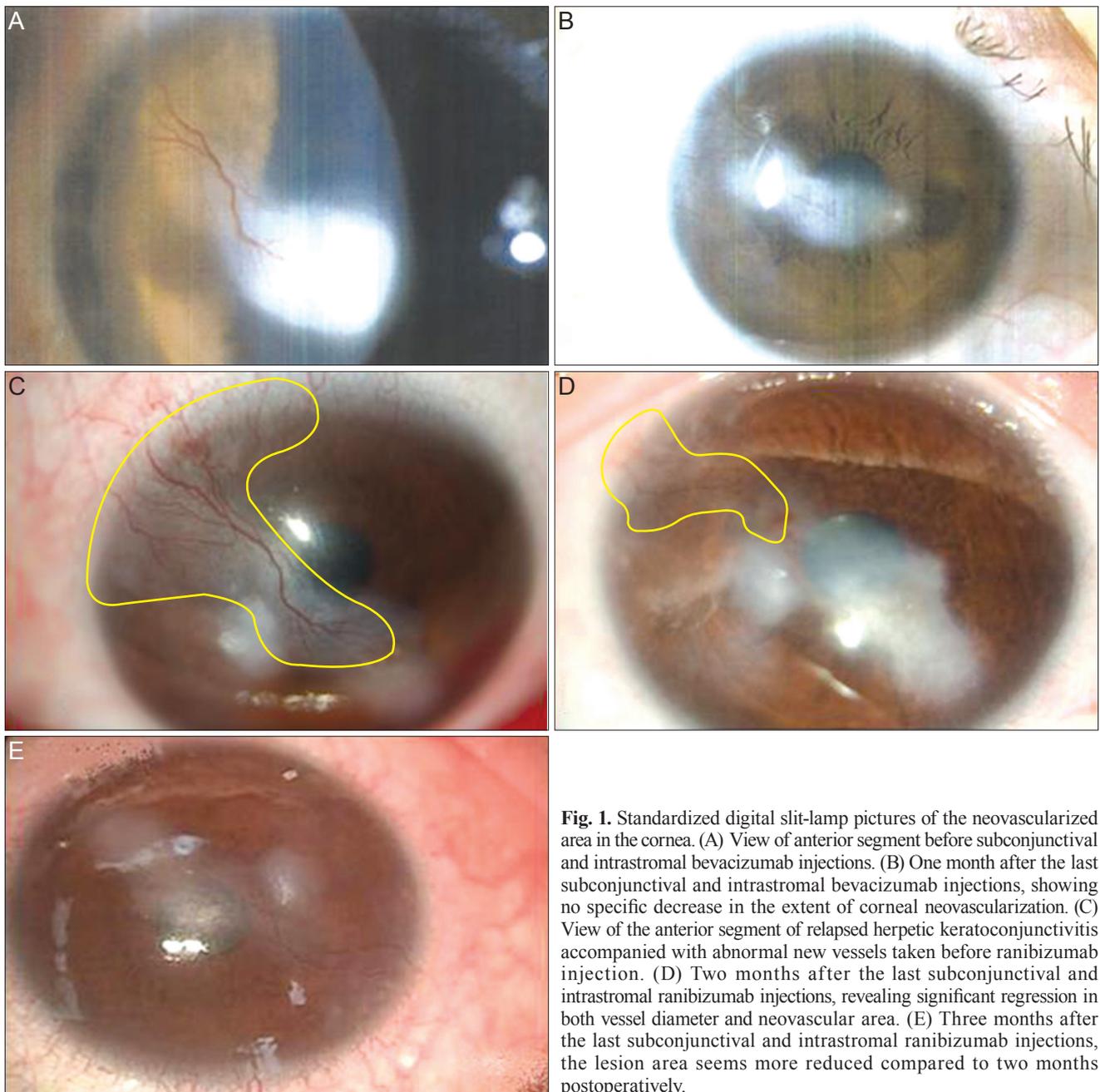
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opacity was found at the right superotemporal cornea (Fig. 1A). Following suspicion of herpetic keratoconjunctivitis, she received two subconjunctival and intrastromal bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA) injections with a one month interval. Within one month after the last injection, the diameter of abnormal new vessels decreased to some degree, but the extent of corneal NV and opacity remained stationary (Fig. 1B). Further bevacizumab treatment was abandoned because the lesion showed no

improvement during the next six months and no other treatment was given to the patient for the next four years.

At her first visit to our clinic, the patient's best-corrected visual acuity (BCVA) measured 20 / 250 in the right eye and a central corneal opacity was observed along with new, abnormal vessels growing in from the superotemporal side (Fig. 1C), suggestive of herpetic keratoconjunctivitis. After administration of Virgan (0.15% ganciclovir; Samil, Seoul, Korea) ointment and Gatiflo (0.3% gatifloxacin; Handok,



**Fig. 1.** Standardized digital slit-lamp pictures of the neovascularized area in the cornea. (A) View of anterior segment before subconjunctival and intrastromal bevacizumab injections. (B) One month after the last subconjunctival and intrastromal bevacizumab injections, showing no specific decrease in the extent of corneal neovascularization. (C) View of the anterior segment of relapsed herpetic keratoconjunctivitis accompanied with abnormal new vessels taken before ranibizumab injection. (D) Two months after the last subconjunctival and intrastromal ranibizumab injections, revealing significant regression in both vessel diameter and neovascular area. (E) Three months after the last subconjunctival and intrastromal ranibizumab injections, the lesion area seems more reduced compared to two months postoperatively.

Seoul, Korea) eye drops for six months, the patient underwent two subconjunctival and intrastromal ranibizumab (Lucentis, Genentech Inc.) injections in the right eye, with a one month interval. At two months postoperatively, there was significant decline in both the neovascular area (by 8.02%) and vessel caliber compared to the initial lesion (Fig. 1D). Anterior segment photograph taken by a built-in camera on a surgical microscope (Leica F40; Microsystems, Wetzlar, Germany) at three months after the initial injection also revealed reduction of the lesion extent (Fig. 1E). The BCVA was improved to 20 / 160 on her last visit at six months postoperatively and neither adverse reactions nor recurrence was apparent. Alteration in the corneal neovascular area was determined by sequential standardized digital slit-lamp pictures, which were analyzed morphometrically using image analysis software (Image J 1.40 g; Wayne Rasband at the Research Services Branch, National Institutes of Health, Bethesda, MD, USA). The procedure was approved by institutional review board of the Catholic University of Korea and the patient was provided with thorough explanation and filled out an informed consent form.

## Discussion

Corneal NV is a potential sequela of numerous conditions such as infection, injury, inflammation, limbal stem cell deficiency, and contact lens use, which eventually alters visual acuity by inducing stromal edema, cellular infiltration, lipid deposition, hemorrhage, and scarring [2,10]. Conventional therapeutic modalities for corneal NV include corticosteroids, nonsteroidal anti-inflammatory drugs, laser photocoagulation, and ocular surface reconstruction. However, these treatments demonstrated limited effects with considerable complications, leading to questions regarding whether the treatment should be continued [11-15]. The development of VEGF-inhibitors, a humanized monoclonal antibody which binds to isoforms of VEGF-A [16], introduced a new prospect in treating a variety of ophthalmic conditions, including ocular surface diseases with NV. Clinically, ranibizumab and bevacizumab are currently used for the treatment of corneal NV.

Stevenson et al. [8] compared the treatment efficacy of topical bevacizumab and ranibizumab by evaluating the neovascular area, vessel caliber, and invasion area of corneal NV. Considering the fact that bevacizumab is a large full-length immunoglobulin with a molecular weight of 149 kD and

ranibizumab has a molecular weight of 48 kD, this may allow ranibizumab to penetrate the ocular surface more effectively and establish a therapeutic concentration earlier in the course of treatment. The authors concluded that topical ranibizumab was efficacious earlier in the course of treatment than topical bevacizumab, as measured by neovascular area and vessel caliber.

There were several studies demonstrating that subconjunctival administration of a VEGF inhibitor was more effective than topical instillation. This is supported by subconjunctival injections generating higher intraocular concentrations compared to topical administration and contributing to the slower release of pharmacologic agents. Therefore, following subconjunctival injection, VEGF inhibitors have proven to spread into the corneal stroma and to remain there for several days [17-19]. This may explain why NV was more efficiently slowed after subconjunctival injections rather than after topical administration. Furthermore, there are major limitations for topical application such as low penetrance through intact epithelium, difficulty of formulation, and low stability in solution with consequent susceptibility to loss of bioactivity during long-term storage [20].

In our case, the patient had already received two subconjunctival and intrastromal bevacizumab injections due to corneal NV caused by herpetic keratoconjunctivitis, but the treatment turned out to be ineffective due to the extent of the lesion and lack of regression. The patient was initially treated with antiviral ointment and antimicrobial eye drops for six months, but the neovascular area remained stationary. Because the treatment could have restored the barrier function of the corneal epithelium, we performed two ranibizumab injections, which is smaller in molecular weight, both subconjunctivally and intrastromally. Six months postoperatively, there was significant decrease in neovascular area, leaving no noteworthy adverse effects.

However, to date, the direct comparison of currently applied VEGF inhibitors remains under debate. In order to justify the increased cost of ranibizumab, it will be necessary to demonstrate meaningful treatment superiority in a randomized comparison trial to draw authoritative conclusions. Additionally, long term follow-up is required to observe post-injection complications and the possibility of NV recurrence.

To the best of our knowledge, there have not been any identical reports domestically. Therefore, the authors present a case report demonstrating that subconjunctival and intra-

stromal ranibizumab injections may be effective therapeutic options in corneal NV associated with herpetic keratoconjunctivitis, especially for patients with refractory outcomes following bevacizumab injections.

## Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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