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Case Report

Topical Losartan Treatment of Herpes Simplex Virus- or Varicella-Zoster Virus-Induced Corneal Scarring: A Case Series

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Cornea · Topical losartan · Scarring · Fibrosis · Corneal haze · Herpes simplex virus · Varicella-zoster virus · Corneal wound healing

Abstract
Introduction: Topical losartan has emerged as a promising therapeutic option for preventing and treating corneal scarring fibrosis. Its mechanism of action involves the inhibition of ERK-mediated signaling in the noncanonical TGF-beta pathways, promoting apoptosis of myofibroblasts and facilitating a return of corneal transparency. While numerous studies in rabbits and several human case reports have demonstrated its efficacy and safety, published data on its use in clinical scenarios remain limited. This study presents 3 cases where topical losartan successfully treated corneal scarring induced by herpes simplex virus (HSV) or varicella-zoster virus (VZV) keratitis. ***Case Presentations:*** Three patients (ages 40, 38, 15 years) with corneal scarring and vision loss from HSV or VZV keratitis were treated with topical 0.8 mg/mL losartan 6 times a day for 4–9 months, depending on the clinical response, after failing traditional management with corticosteroids. Best spectacle-corrected vision and slit-lamp corneal opacity improved in each case. Anterior segment OCT documented improved stromal opacity in 1 case. ***Conclusions:*** Topical losartan, a known inhibitor of fibrotic TGF-beta signaling, is potentially an effective alternative in the treatment of stromal scarring fibrosis caused by

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corneal HSV and VZV infections. Patients with HSV- or VZV keratitis-induced corneal scarring may be ideal candidates for planned clinical trials of the efficacy and safety of topical losartan treatment.

Introduction

Several published studies in rabbits [1–7] and human case reports [8–10] have demonstrated the efficacy and safety of topical losartan in the prevention and treatment of corneal scarring fibrosis. Topical losartan functions by inhibiting the activation of extracellular signal-regulated kinase (ERK) mediated signal transduction in the noncanonical transforming growth factor (TGF)-beta pathways [11, 12]. This leads to apoptosis of myofibroblasts (and likely precursor cells that have begun development into myofibroblasts) which are dependent on ongoing TGF-beta-1 and TGF-beta-2 signaling from the tears and epithelium for survival. Once the myofibroblasts are eliminated, corneal fibroblasts can repopulate the fibrotic tissue to (1) coordinate with the epithelium to regenerate a normal epithelial basement membrane (EBM) to reestablish normal control of activated TGF-beta-1 and TGF-beta-2 entry into the stroma, and (2) reabsorb and reorganize disordered collagens and other extracellular matrix materials that were produced by the myofibroblasts in order to restore corneal transparency [1, 11, 12].

Dozens of successful cases in which topical losartan effectively treated corneal scarring after trauma, infection, or surgery have been reported at professional meetings in the USA and internationally or communicated to the authors over the past 2 years. However, only three publications of case reports of losartan efficacy have appeared to date in the literature, but none of these were related to corneal scarring caused by herpes viruses [8–10]. Some of the most striking cases noted by the authors that were successfully treated with topical losartan have been corneal opacities caused by herpes simplex virus (HSV) or varicella-zoster virus (VZV) keratitis. The authors report 3 cases that highlight the efficacy of losartan in the treatment of corneal scarring triggered by these herpes viruses.

Case Report

Case 1

A 40-year-old woman with a history of HSV in her right eye (OD) was referred for a complaint of persistent blurry vision and corneal scarring that had been present for 2 months and was unresponsive to topical corticosteroid treatment. Her uncorrected distance visual acuity (UDVA) was 20/60, and her best spectacle-corrected visual acuity (BCVA) was also 20/60, with minimal refractive error. Central corneal opacity was observed in the right eye, with no evidence of active infection (Fig. 1a). After informed consent, the patient was prescribed topical 0.8 mg/mL losartan, one drop to the right eye 6 times daily.

After 8 weeks of treatment, the patient reported subjective improvement in vision and therapy was continued for another 8 weeks. By the end of the 16-week course of treatment, her UDVA had improved to 20/30 and her BCVA to 20/25. A significant reduction in the corneal opacity was documented by comparing pre- and post-treatment slit-lamp examinations, clinical photographs (Fig. 1b), and cornea OCT imaging pretreatment (Fig. 1c) and post-treatment (Fig. 1d, 8 weeks and Fig. 1e, 16 weeks).

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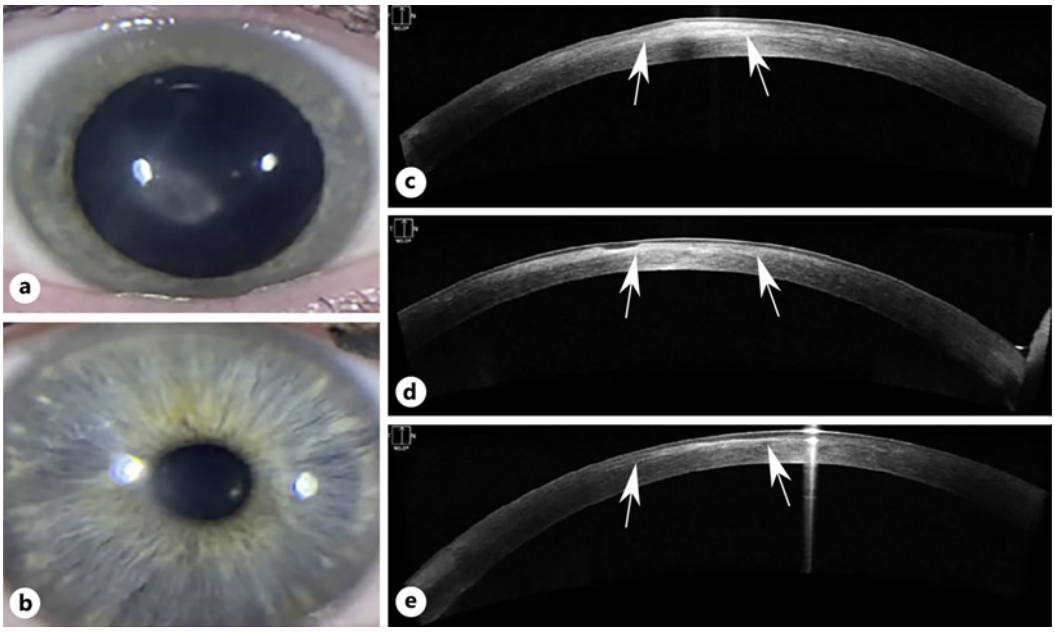

Fig. 1. HSV-related corneal scarring and OCT analysis of corneal opacity in case #1. **a** Slit-lamp photograph of the right cornea of case 1 with HSV-induced scarring before treatment with topical losartan (magnification, ×40). **b** Slit-lamp photograph of the patient's right eye after 16-week treatment with topical losartan. Significant regression of the corneal opacity can be noted. Magnification, ×40. **c** OCT analysis pretreatment. **d** OCT analysis after 8 weeks of treatment with topical losartan. **e** OCT analysis after 16 weeks of topical losartan treatment. Arrows in (**c–e**) indicate the area of subepithelial fibrosis. All OCTs were obtained at the same meridian.

Case 2

A 38-year-old man with history of recurrent herpes simplex keratitis in the right eye was referred with a complaint of reduced vision. He had experienced five prior episodes of HSV keratitis, with the most recent one occurring 7 months prior. During the most recent episode, he had been treated with acyclovir 2 g/day for 10 days and topical corticosteroids with no improvement in corneal opacity or vision.

At the initial consultation visit, his UDVA was 20/400 in the right eye (OD) and 20/15 in the left eye (OS), with no refractive improvement in the right eye and mild myopia (−0.25 D) in the left eye. The initial treatment included acyclovir 400 mg orally 5 times per day, prednisolone 1% 4 times daily, tacrolimus 0.03% eye drops 2 times daily, and artificial tears as needed. During subsequent follow-up visits, the visual acuity in the right eye improved to 20/100, and therapy was adjusted due to gastric irritation, replacing acyclovir with valacyclovir 500 mg per day, while continuing 0.03% tacrolimus 2 times daily and artificial tears as needed.

Four months later, the UCVA in OD had improved to 20/80−1, and the prednisolone acetate 1% was discontinued while maintaining the other medications (valacyclovir 500 mg/day, tacrolimus 0.03% drops twice daily, and artificial tears 5–6 times daily). After 1 month of this treatment, UDVA OD remained 20/80−1 and BCVA was 20/40 (−3.50 + 5.00 × 195) in this eye. Slit-lamp biomicroscopy showed persistent corneal scarring in the right eye (Fig. 2a).

One month later, UDVA was stable at 20/80−1 in the right eye and 20/20 in the left eye. The BCVA was 20/40 (−3.50 + 5.00 × 195) in the right eye. Slit-lamp biomicroscopy showed persistent corneal scarring in the right eye (Fig. 2b). The patient's treatment was continued with valacyclovir 500 mg/day, 0.03% tacrolimus twice daily, and artificial tears 5–6 times daily, but losartan 0.8 mg/mL 6 times daily was added in the right eye.

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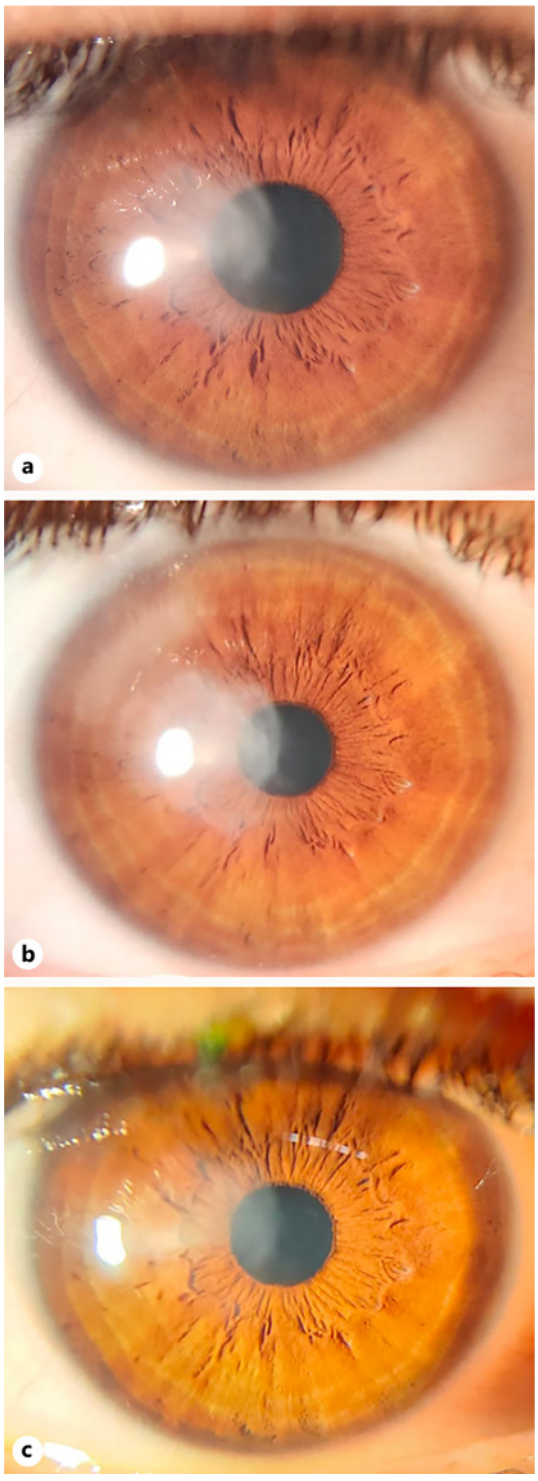

Fig. 2. HSV-related corneal scarring in case #2. **a** Slit-lamp photograph of the opacity in the right cornea of case 2 with HSV-induced scarring before treatment with topical losartan. **b** Slit-lamp photograph of the patient's right eye after 3-month treatment with topical losartan. There is persistent corneal opacity, with some improvement. **c** Slit-lamp photograph of the patient's right eye after 9 months of treatment with topical losartan. Progressive improvement of the corneal opacity can be noted. Magnification, ×40.

Three months after losartan treatment was started, the patient became noncompliant and soon felt new right eye irritation. Although the vision and the corneal scar were unchanged, the right cornea had a new opacity proximal to the previous scar, which was diagnosed as an HSV relapse resulting from discontinuation of the oral valacyclovir. The patient was instructed resume valacyclovir 500 mg/day, 0.03% tacrolimus twice daily and 0.8 mg/mL losartan 6 times a day.

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After 6 months of treatment with topical losartan and the other medications, the patient's BCVA had significantly improved from 20/40 to 20/25 in the right eye. No discomfort due to the medications was reported. Slit-lamp biomicroscopy of the right eye showed progressive improvement in corneal scarring.

At the latest follow-up examination after 9 months of topical losartan treatment, the patient's visual acuity had improved to 20/25 (−2.00 + 1.50 × 5) in the right eye. Slit-lamp biomicroscopy showed progressive improvement in corneal scarring (Fig. 2c). The patient was advised to continue the prescribed medications for six additional months before stopping topical losartan but to continue valacyclovir 500 mg/day indefinitely.

Case 3

A 15-year-old boy was referred for an assessment of corneal opacity and possible corneal transplantation. Three months prior, the patient was diagnosed with VZV keratitis with a periocular and temporal vesicular rash. As the skin infection resolved, he developed a central corneal scar in the right eye that reduced the BCVA to 20/200.

Slit-lamp examination of the right eye revealed central corneal scarring. There was no corneal fluorescein staining and no neovascularization. The left cornea was normal. Despite treatment with oral valacyclovir 1 g 3 times daily and topical dexamethasone 0.1% 4 times daily, there was no improvement in his vision or reduction in opacity during 3-month follow-up.

At this examination, BCVA was 20/200 (−4.00 D) in the right eye with scarring on slit-lamp examination (Fig. 3a). BCVA was only counting fingers in the left eye. Of note, fundoscopy was normal in the right eye, but revealed a toxoplasmosis macular scar in the left eye (originally diagnosed at age 7). The left cornea was normal. After informed consent of the patient and parents, treatment with topical losartan 0.8 mg/mL 6 times daily was initiated in the right eye.

After 2 months, his BCVA in the right eye improved to 20/40 (−3.50 + 0.50 × 105), and he continued topical losartan treatment. Five months after starting topical losartan treatment, his BCVA improved to 20/20 (−4.50 + 0.50 × 100) in the right eye, with a significant reduction in the corneal scar noted on slit-lamp examination (Fig. 3b). The patient continued topical losartan treatment 6 times a day for 3 months prior to discontinuing treatment.

The CARE Checklist has been completed by the authors for this case report, and is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000545215).

Discussion

The 3 cases reported here demonstrate the potential efficacy of topical losartan treatment in the management of corneal scarring due to HSV or VZV keratitis. Similar cases have been reported at international meetings during the past year. Importantly, the authors hypothesize that corneal scars due to HSV or VZV that have been present for years are likely to respond to topical losartan treatment. In these cases, the fibrotic corneal tissue is dynamic with viable myofibroblasts, which are dependent on TGF-beta-1 and TGF-beta-2 signaling from the tears and epithelium in the context of ongoing defective EBM function, actively sustaining the disorganization of the extracellular matrix that contributes to the opacity [13–15]. To date, the best example of this potential long-term efficacy of topical losartan treatment in herpetic corneal scars was a case reported by Renato Ambrosio, Jr. and colleagues in which a corneal scar due to VZV keratitis that had been present for 3 years was highly responsive to topical losartan treatment [Renato Ambrosio, Jr., unpubl. data, 2024]. Thus, herpetic scars and scars due to other injuries, may respond to topical losartan even many years after the initial insult to the cornea. Future studies will need to be performed to assess the efficacy of losartan in the

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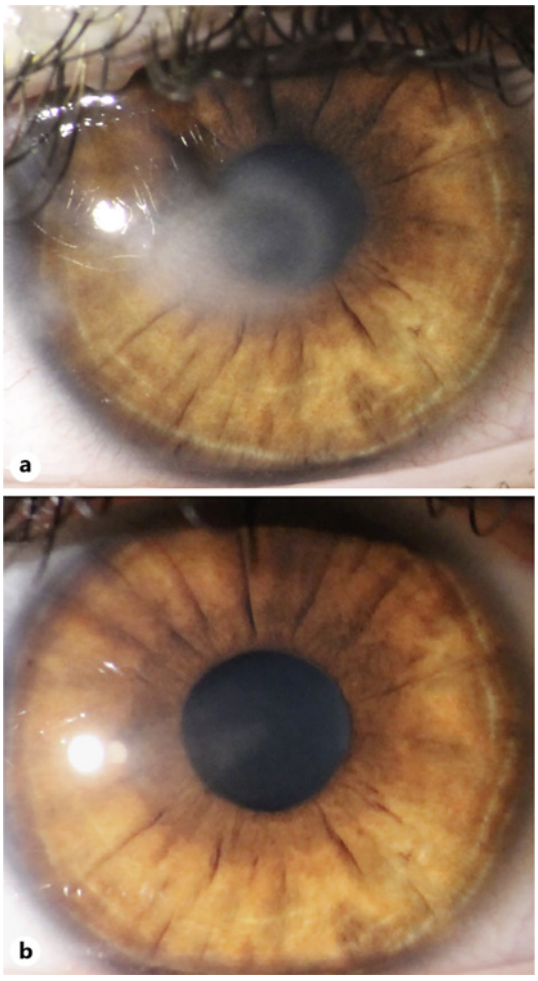

Fig. 3. VZV-related corneal scarring in case #3. **a** Slit-lamp photograph of the patient's right cornea of case 3 shows the central corneal opacity before treatment with topical losartan. **b** Slit-lamp photograph of the patient's right eye after 5 months of treatment with topical losartan. A marked decrease in corneal opacity can be noted. Magnification, ×40.

treatment of long-standing corneal opacities caused by HSV, VZV, and other infectious, traumatic, and post-surgical insults.

It is important to emphasize that some patients successfully treated with topical losartan for corneal scarring have not responded to the treatment until 6–9 months after treatment was initiated. The therapeutic response to topical losartan is a two-phase process in which most myofibroblasts undergo apoptosis within weeks of initiating treatment [6], but the regeneration of the defective EBM and removal of the disordered extracellular matrix that contributes to the opacity potentially takes much longer, as corneal fibroblasts repopulate the fibrotic tissue and perform these functions [11]. Therefore, when treating corneal scars with losartan, the authors believe that the therapy should be continued for at least 6 to 9 months before declaring a treatment failure. Further, we hypothesize that in the corneas that do not respond to the treatment, the EBM was never regenerated to the point where it could perform its normal critical role of modulating tear and epithelial TGF-beta entry into the stroma in order to augment the direct effects of losartan. In these corneas, other treatment modalities should be explored, such as phototherapeutic keratectomy, lamellar corneal transplantation, or penetrating keratoplasty. Conversely, we hypothesize that in corneas that respond relatively quickly to topical losartan (as in the cases reported here), the EBM was repaired relatively quickly, facilitating losartan's control of TGF-beta activity in the stroma by decreasing stromal entry of these pro-fibrotic growth factors. The authors now continue topical losartan treatment for 3 months after maximal resolution of the scarring fibrosis to help ensure that the EBM is fully regenerated and reinstate

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topical losartan treatment for a longer period of time if the opacity begins to recur after discontinuing therapy. Future clinical trials are needed to assess the efficacy of different treatment protocols with topical losartan. These could include starting at the recommended 6 times per day, dosing for several weeks or months, and then decreasing the frequency to 4 times per day for the duration of treatment. Four times a day treatment with topical losartan can be effective in some patients, but the failure rate of this lower frequency treatment is likely to be higher.

The authors recommend not to exceed the maximal dosage of topical losartan of 0.8 mg/mL 6 times a day. Studies have shown that higher concentrations are not more effective in eliminating myofibroblasts from the fibrosis [7], and they may be associated with increasing epithelial and stromal toxicity [7]. If a clinician wants to initiate prophylactic topical losartan treatment of scarring fibrosis while an epithelial defect is present, then the authors recommend that the dosage be limited to 0.2 mg/mL 6 times a day, a dosage that effectively treated scarring fibrosis in an alkali burn rabbit model [2], until the epithelial defect heals [7]. Conversely, a clinician could wait until an epithelial defect heals before initiating the standard 0.8 mg/mL 6 times a day treatment.

These cases highlight the potential efficacy of topical losartan treatment in the reduction of corneal scarring and fibrosis in corneas with history of HSV or VZV keratitis. At the present time, topical losartan is only available from compounding pharmacies throughout the world. Different compounding pharmacies have formulated 0.8 mg/mL losartan from pure USP grade losartan potassium powder available from PCCA (https://pccarx.com) in the USA and several other sources outside the USA It should not be formulated from crushed losartan tablets that contain "incipient" components for tablet formulation that could be toxic to the eye. It has been found effective when formulated in balanced salt solution (0.64% sodium chloride, 0.075% potassium chloride, 0.048% calcium chloride dihydrate, 0.03% magnesium chloride hexahydrate, 0.39% sodium acetate trihydrate, 0.17% sodium citrate dihydrate, pH 7.0–7.5), Dulbecco's phosphate buffered saline (137 mM sodium chloride, 2.7 mM potassium chloride, 8.1 mM disodium hydrogen phosphate, and 1.47 mM potassium dihydrogen phosphate, pH 7.0–7.4), and normal saline (0.9% NaCl, pH 7.0–7.4). The balanced salt solution and Dulbecco's phosphate buffered saline solutions have higher buffering capacity to maintain pH and, therefore, are probably better choices. It is critical that the 0.8 mg/mL topical losartan solution be sterilized by 0.2 μm filtration and not heat sterilization prior to use by patients. Future multicenter clinical trials are needed in order to gain regulatory approval so that this therapy can be more generally available from traditional pharmacies.

Statement of Ethics

This retrospective review of patient data from 3 cases did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images and from the parent/legal guardian of minor patients for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Steven E. Wilson and the Cleveland Clinic have submitted patents on the use of topical losartan and other angiotensin II receptor blockers to prevent and treat corneal scarring fibrosis and have licensed the technology to Rafarm Pharmaceuticals of Greece. None of the other authors have any commercial or proprietary interest in this study.

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Author Contributions

Drs Steven E. Wilson and Barbara A.L. Dutra had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design and drafting of the manuscript: Steven E. Wilson and Barbara A.L. Dutra. Acquisition, analysis, or interpretation of data and critical revision of the manuscript for important intellectual content: Barbara A.L. Dutra, Laura E. Drew-Bear, Samantha P. Herretes, Danielle Arroyo, Rodrigo Carlos de Oliveira, Lycia Pedral Sampaio, Marcony R. Santhiago, and Steven E. Wilson. Supervision: Steven E. Wilson.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries should be directed to the corresponding author.

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