Topical losartan as a novel therapeutic approach for corneal scars: clinical outcomes from a case series

Losartana tópica como abordagem terapêutica inovadora para cicatrizes corneanas, resultados clínicos de uma série de casos

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ABSTRACT

The objective was to investigate the efficacy of topical losartan in treating corneal scars in patients with varying clinical backgrounds. A case series with six patients diagnosed with corneal scars resulting from herpetic keratitis or complicated photorefractive keratectomy were treated with topical losartan at a concentration of 0.8 mg/mL. Each patient underwent comprehensive ophthalmologic evaluations, including anterior segment optical coherence tomography and corneal tomography, to assess clinical outcomes after treatment. Improvement in visual acuity was noted in five out of six patients. Patient-reported outcomes and imaging demonstrated significant reductions in corneal scars and enhanced transparency following treatment. However, one patient continued to have stable visual acuity despite a decrease in opacity after 7 months of therapy. This series highlights the potential of topical losartan as a novel approach for managing corneal scars by targeting the TGF-β signalling pathway. With corroborating imaging assessments showing measurable improvements, losartan is a promising adjunctive therapy for corneal scarring. Vehicle-controlled clinical trials are warranted to establish its long-term efficacy and safety across diverse populations and clinical settings.

RESUMO

O objetivo deste estudo foi investigar a eficácia do losartana tópico no tratamento de cicatrizes corneanas em pacientes com diferentes contextos clínicos. Uma série de casos com seis pacientes diagnosticados com cicatrizes corneanas decorrentes de ceratite herpética ou de ceratectomia fotorrefrativa complicada foi tratada com losartana tópica na concentração de 0,8 mg/mL. Todos os pacientes foram submetidos a avaliação oftalmológica completa, incluindo tomografia de córnea e tomografia de coerência óptica do segmento anterior, para análise dos desfechos clínicos após o tratamento. Houve melhora da acuidade visual em cinco dos seis pacientes. Os desfechos relatados pelos pacientes e os exames de imagem demonstraram redução significativa das cicatrizes corneanas e aumento da transparência corneana após o tratamento. Entretanto, um paciente manteve acuidade visual estável, apesar da diminuição da opacidade após 7 meses de terapia. Esta série de casos destaca o potencial da losartana tópica como uma nova abordagem para o manejo de cicatrizes corneanas, por meio do direcionamento da via de sinalização do TGF-β. Com exames de imagem corroborando melhorias mensuráveis, a losartana se apresenta como uma terapia adjuvante promissora para cicatrização corneana. Ensaios clínicos controlados por veículo são necessários para estabelecer sua eficácia e segurança em longo prazo em diferentes populações e cenários clínicos.

Keywords:
Corneal injuries; Losartan; eIF-2 kinase; Herpes simplex

Descritores:
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Conflict of interest:
Steven E. Wilson and the Cleveland Clinic have filed patents that remain pending related to topical losartan treatment in the United States, EU, and several other countries. RAFARM Pharmaceuticals of Greece has licensed worldwide rights to topical losartan from the Cleveland Clinic. The other authors declare no conflicts of interest related to this study.

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All data generated or analysed during this study are included within this case series. No additional clinical data for these patients is available. For further inquiries, please contact the corresponding author.

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INTRODUCTION

Corneal fibrosis is a common complication resulting from chemical and mechanical injuries, infections, complex surgeries, and scarring diseases. This stromal scarring condition significantly reduces corneal transparency and is a leading cause of legal blindness worldwide, imposing substantial social and economic burdens.[1] Currently, no effective medical treatments exist for established corneal scarring, with surgical options such as excimer laser phototherapeutic keratectomy (PTK) and corneal transplantation being the primary interventions.

The scarring process is driven by myofibroblast activation and fibrosis and is regulated by a complex network of cytokines and growth factors. Notably, transforming growth factor-beta (TGF-β) plays a crucial role in promoting the differentiation of local keratocytes and bone marrow-derived fibroblasts into myofibroblasts, thereby contributing to corneal scarring.[2-5] Several studies have demonstrated that inhibiting TGF-β can diminish fibrotic responses following corneal surgeries.[6-8]

Losartan, an oral angiotensin II receptor blocker (ARB) primarily used for hypertension, has gained attention as a potential modulator of TGF-β signalling. Research over the past two decades suggests that losartan inhibits TGF-β activity and related fibrotic processes by interrupting the Smad and ERK signalling pathways. Reports indicate that topical losartan can reduce TGF-β signalling by as much as 50%.[3,9-15] Its application has also been potentially promising in decreasing corneal fibrosis, lowering stromal collagen IV production, and possibly minimizing neovascularization in animal models.[16] These findings support the investigation of topical losartan for treating corneal scarring.

Notably, a case report by Pereira-Souza et al. documented effective treatment of corneal scarring following complex laser in situ keratomileusis (LASIK), with topical losartan at a concentration of 0.8 mg/mL, administered six times daily for 6 months.[17] Additionally, Rodgers et al. reported significant improvement in corneal opacity when combining topical losartan with collagen cross-linking, even after unsuccessful steroid therapy.[18] These cases represent the only clinical evidence available for topical losartan's role in corneal scarring, signalling a need for further inquiry into its efficacy and safety across diverse clinical scenarios.

In this case series, we present the clinical outcomes of six patients with corneal scarring due to herpetic keratitis or complex photorefractive keratectomy (PRK), all treated with topical losartan at 0.8 mg/mL prepared from losartan potassium powder in a 0.9% sodium chloride solution. Comprehensive ophthalmological examinations and corneal imaging – using anterior segment optical coherence tomography (OCT) and Pentacam Cornea OCT – document the treatment effects.

The objective of this study was to investigate the efficacy of topical losartan in treating corneal scars in patients with varying clinical backgrounds.

This retrospective review of patient data was conducted in accordance with national guidelines and, therefore, did not necessitate Investigational Review Board approval in Brazil.

CLINICAL FINDINGS

Six patients diagnosed with corneal opacity were included in this case series: three were attributed to recurrent herpetic keratitis, two occurred in the context of PRK, and one was associated with either PRK or a systemic viral infection with SARS-CoV-2. Visual improvement was observed in five patients, while one patient with corneal opacity secondary to herpetic keratitis did not show any change in visual acuity following treatment, despite a reduction in opacity density on slit-lamp biomicroscopy. Patients' description, changes in visual acuity and treatment are detailed in table 1.

Patient A

A 57-year-old man was referred to ophthalmology for vision loss in his left eye over the past few months following a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. His medical history included photorefractive PRK in both eyes performed 12 years earlier, with pre-operative records indicating uncorrected distance visual acuity (UDVA) of 20/200 in both eyes and corrected distance visual acuity (CDVA) of 20/20 with -4.75 D in the right eye and -5.25 D in the left eye. At his initial visit, the patient had UDVA of 20/67 in the right eye and 20/50 in the left eye. Visual acuity improved to 20/20 in the right eye with -1.00 -2.00 x 75º and to 20/40 in the left eye with -0.50 -2.00 x 65º. A slit-lamp examination revealed central corneal opacity in the left eye, with dense subepithelial fibrosis (Figure 1). The diagnosis was late post-PRK *versus* SARS-CoV-2-related corneal fibrosis. Treatment included topical losartan 0.8 mg/mL four times daily for the left eye, a tapering schedule of topical prednisolone (10 mg/mL), preservative-free artificial tears, and nutritional supplementation with essential fatty acids. After 2 months, the patient reported no side effects nor visual improvement, although his CDVA improved to 20/30 in the left eye with -1.25 -1.50 x 55º.

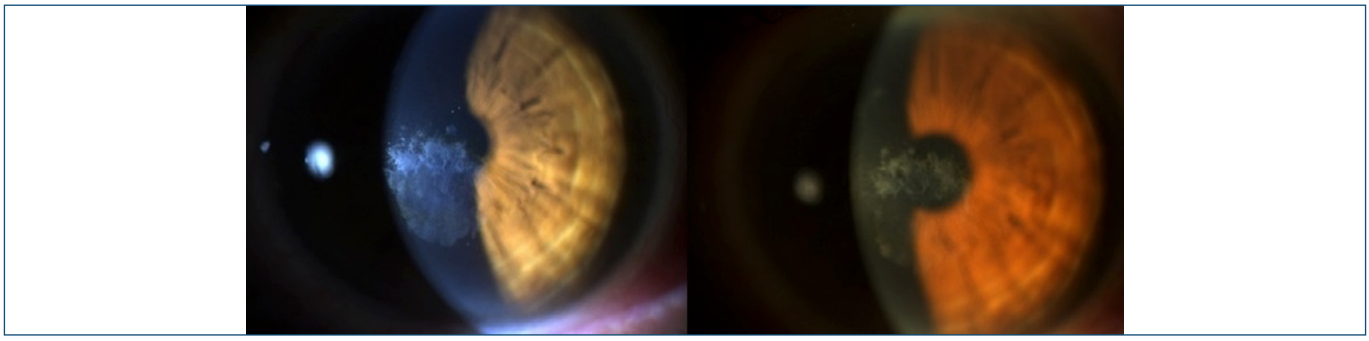

Figure 1. Slit-lamp biomicroscopy shows dense central subepithelial haze in the left eye of Patient A before topical treatment (left) compared to after 9 months of topical losartan treatment. A small reduction in corneal opacity after treatment can be noted.

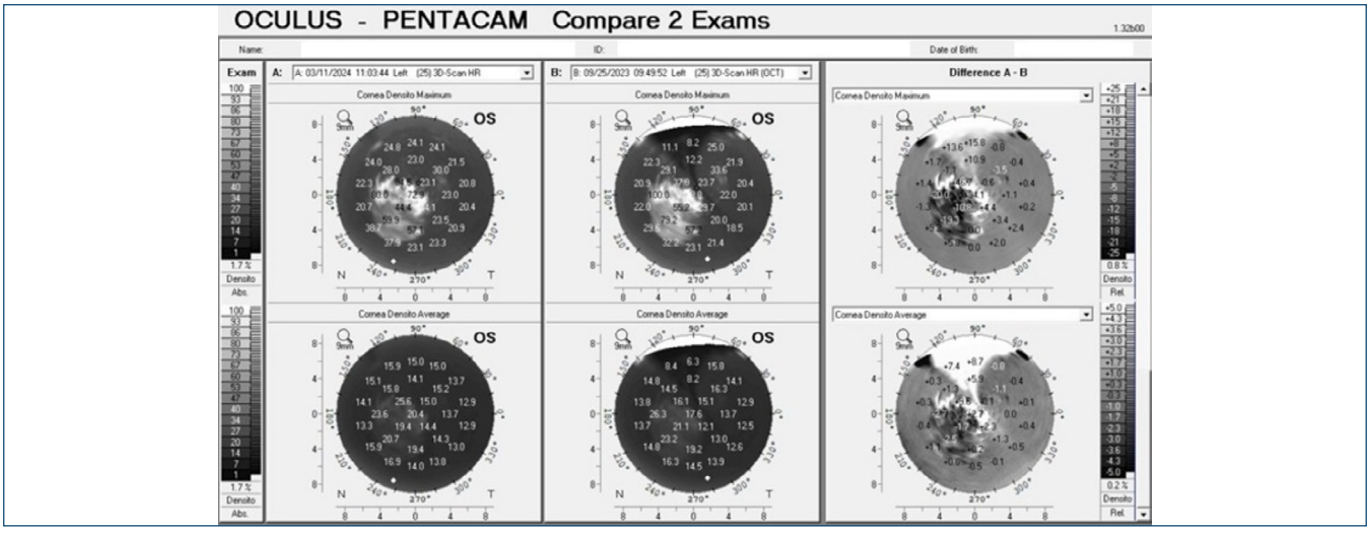

Figure 2. Corneal Densitometry. Pentacam (Oculus Optikgeräte GmbH) densitometric analysis of the right cornea of Patient A before topical treatment compared to densitometry after 8 months of losartan. The difference maps show the changes in corneal densitometry after treatment (right column).

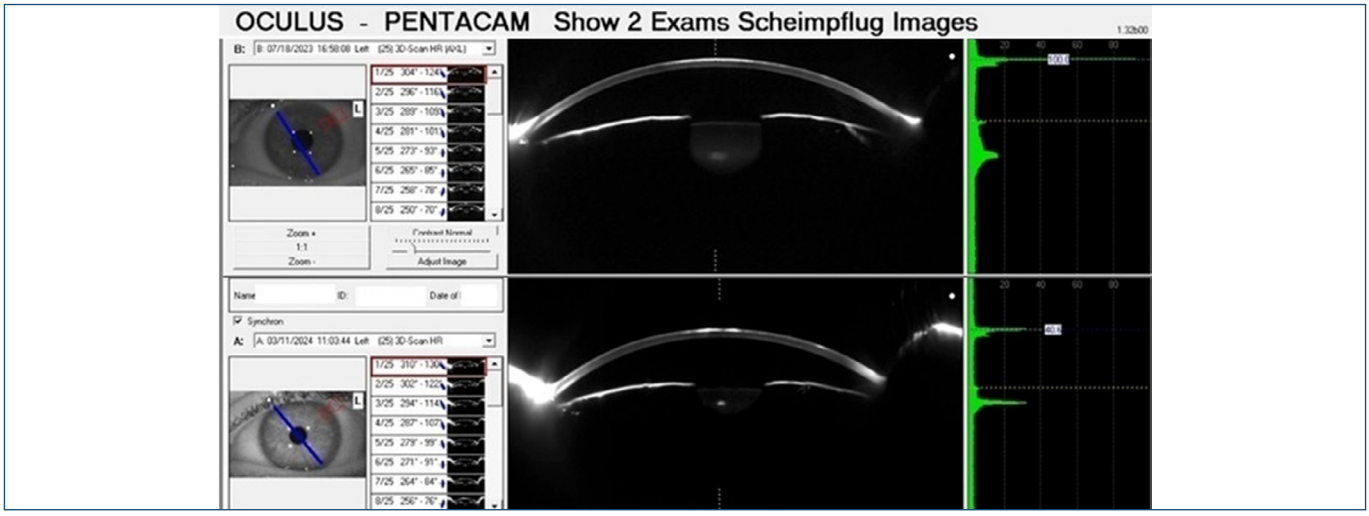

Figure 3. Scheimpflug Pentacam (Oculus Optikgeräte GmbH) image of the left cornea of Patient A in March 2024, after 8 months of treatment with topical losartan (bottom), compared to July 2023 (top), prior to treatment. Analysis of the same section of the cornea shows a marked reduction in hyperreflectivity after 8 months of topical losartan treatment.

The losartan dose was reduced to three times daily. Eight months later, both UDVA and CDVA were stable at 20/50 and 20/30, respectively, with a slight reduction in corneal opacity observed on slit-lamp biomicroscopy, confirmed by tomographic assessments (Figures 2 and 3). The patient was advised to undergo topography-guided PTK for

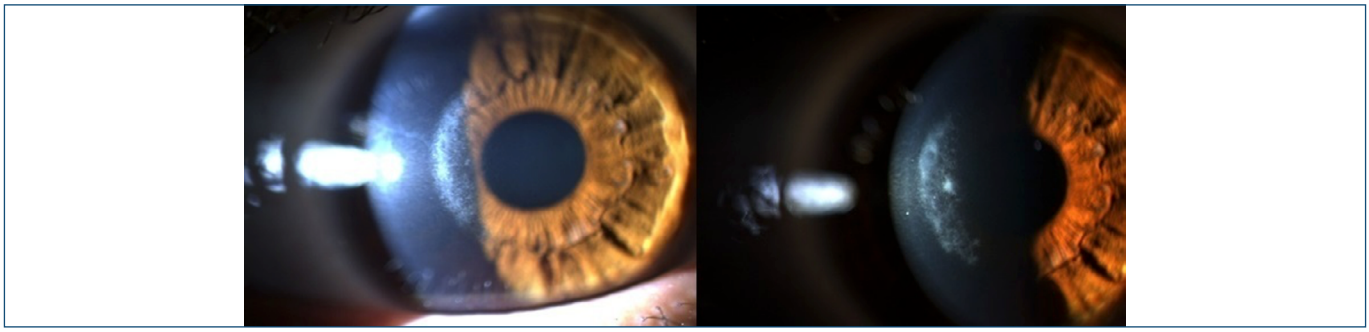

Figure 4. Slit-lamp examination of corneal opacity in the right cornea of Patient B before topical losartan (left) compared to 10 months following treatment (right). A small improvement in corneal opacity and transparency can be noted.

irregular astigmatism. At 1-month post-PTK, UDVA and CDVA improved to 20/30 and 20/25, respectively, with sustained improvements at 4 months, demonstrating UDVA of 20/25 and CDVA of 20/20 with -0.50 -0.50 x 125º.

Patient B

A 27-year-old man was referred to a corneal specialist for evaluation of corneal scarring in his right eye, which developed 2 months after undergoing bilateral PRK with mitomycin C (MMC). His past medical history was unremarkable, and he was managing with preservative-free artificial tears. At the time of consultation, his UDVA was 20/100 in the right eye and 20/20 in the left eye, which improved to 20/33 with -2.00 -0.50 x 65º in his right eye and 20/15 with -0.25 x 65º in his left eye. Slit-lamp examination revealed a significant ring-shaped corneal opacity in the right eye involving the visual axis, but no other findings were noted. The patient continued treatment with artificial tears and initiated a regimen of topical losartan 0.8 mg/mL four times per day in the right eye after informed consent, alongside loteprednol 5mg/mL once daily and nutritional supplementation with essential fatty acids and vitamin D. After 4 months of treatment, the patient reported a subjective improvement in vision in the right eye, with his UDVA measuring 20/67 and CDVA improving to 20/40 with the refraction unchanged.

At a follow-up visit after 10 months of treatment with topical losartan, his UDVA was 20/50 and his CDVA was 20/20 with refraction of -0.75 -0.50 x 80º in the right eye. Anterior segment evaluation revealed a mild reduction in corneal scarring and enhanced corneal transparency in the right eye (Figure 4). Anterior-segment OCT (Figure 5) and corneal tomography using Scheimpflug imaging (Pentacam) were performed before and after treatment with topical losartan in the right eye. These imaging studies demonstrated a reduction in subepithelial hyperreflectivity and improvements in corneal topography.

Patient C

A 73-year-old woman presented to the cornea clinic with a history of LASIK surgery in both eyes 23 years prior, and recurrent herpes simplex keratitis in her left eye for the past decade. She had cataract surgery 20 years before. Her medications included preservative-free artificial tears and valacyclovir 500 mg twice weekly. At her visit, she reported 2 weeks of vision loss in her left eye and decided to increase her valacyclovir to 500 mg daily on her own, without improvement. Uncorrected visual acuity was 20/100 in each eye; the right eye improved to 20/25 with +0.50 -2.25 x 90º, but the left eye did not change with correction. Slit-lamp examination (Figure 6) showed a dense subepithelial corneal opacity in the left eye, with no signs of active infection. After explaining the diagnosis, the treatment plan included topical losartan (0.8 mg/mL, one drop in the left eye five times daily) and a tapering regimen of prednisolone (10 mg/mL, four times daily) with informed consent. Four weeks later, the patient reported subjective improvement, and treatment with losartan continued. After 10 weeks, clinical improvement was noted: UDVA was 20/133 in the right eye and 20/100 in the left eye. The manifest refraction yielded a CDVA of 20/25 in the right eye (+1.00 -2.00 x 105º) and 20/40 in the left eye (-1.00 -2.00 x 95º). Slit-lamp examination confirmed decreased corneal opacity and improved transparency in the left eye. The patient maintained follow-up with topical losartan, administering one drop in her left eye daily. The change in corneal opacity during the treatment with losartan is shown in Figure 1. Anterior segment OCT and corneal tomography (Pentacam Cornea OCT) supported the clinical improvement (Figures 7 and 8).

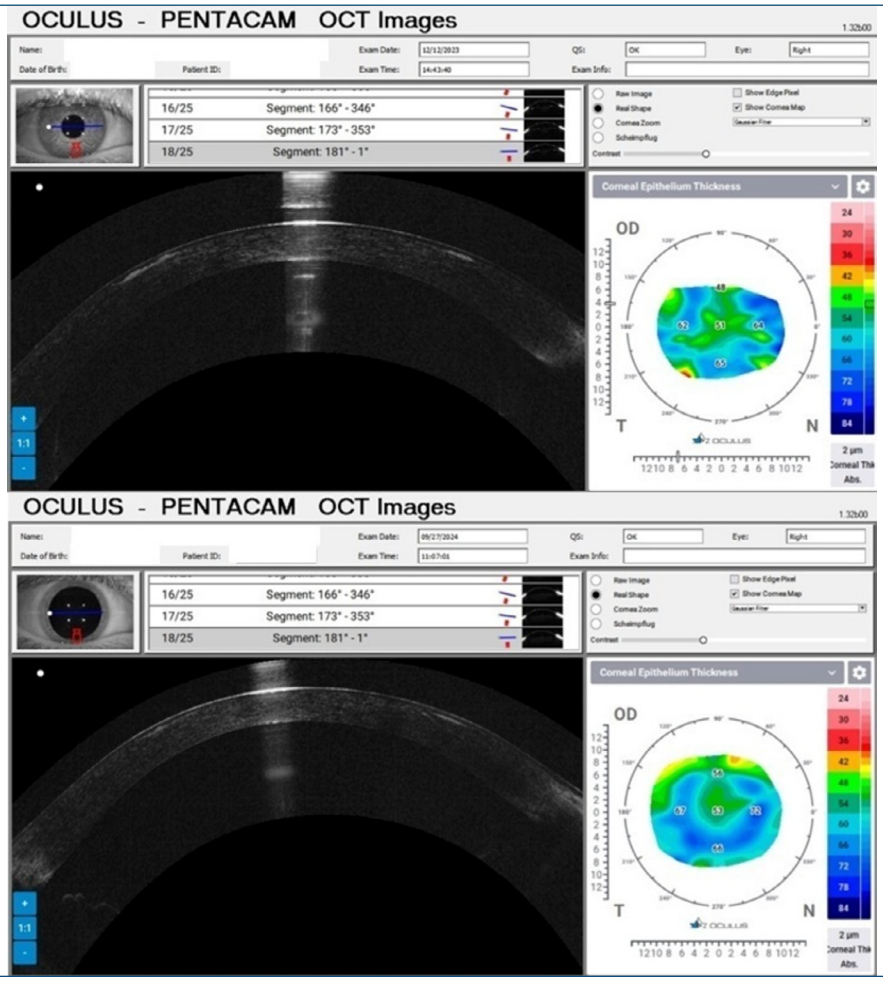

Figure 5. Anterior-segment optical coherence tomography (Pentacam Cornea OCT, Oculus Optikgeräte GmbH) through the same section of the right cornea in Patient B. A subepithelial hyperreflectivity corresponding to the ring-shaped corneal opacity may be noticed before treatment (top) compared to 10 months after topical losartan (bottom). After treatment, there is a decrease in the subepithelial hyperreflective layer.

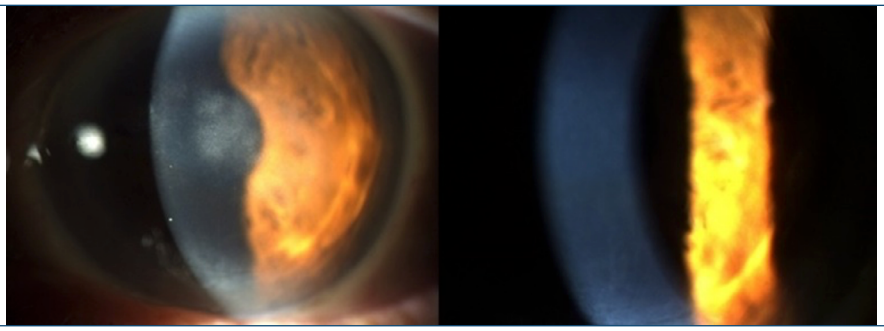

Figure 6. Slit-lamp biomicroscopy revealing a central corneal opacity in the left cornea before treatment with losartan (left) compared to 10 weeks after treatment initiation (right) in Patient C. A reduction in corneal opacity can be noted after topical losartan treatment.

Patient D

A 32-year-old man underwent PRK with MMC and was evaluated 2 months post-operatively due to vision loss in both eyes after an initial period of improvement. Pre-operative assessments showed UDVA of 20/250 in the right eye and 20/400 in the left eye, improving to 20/20 with -5.25 -0.25 x 25º in the right eye and -6.00 in the left eye. Initial corneal thickness was 495 µm and 503 µm respectively, with normal corneal asphericity. The surgical plan targeted partial monovision correction in the left eye, with a refractive goal of -0.65 dioptres. One-month post-PRK, UDVA was 20/20 in both eyes. However, at the 2-month follow-up, vision declined to 20/100 in the right eye and 20/67 in the left eye. Unfortunately, no CDVA was obtained at this visit. Slit-lamp examination

Figure 7. Corneal optical coherence tomography. Pentacam Cornea OCT (Oculus Optikgeräte GmbH) of the left cornea before treatment (upper image) shows a dense subepithelial layer of hyperreflectivity compared to 10 weeks after treatment with losartan (bottom image) in Patient C. A reduction in haze hyperreflectivity can be noted.

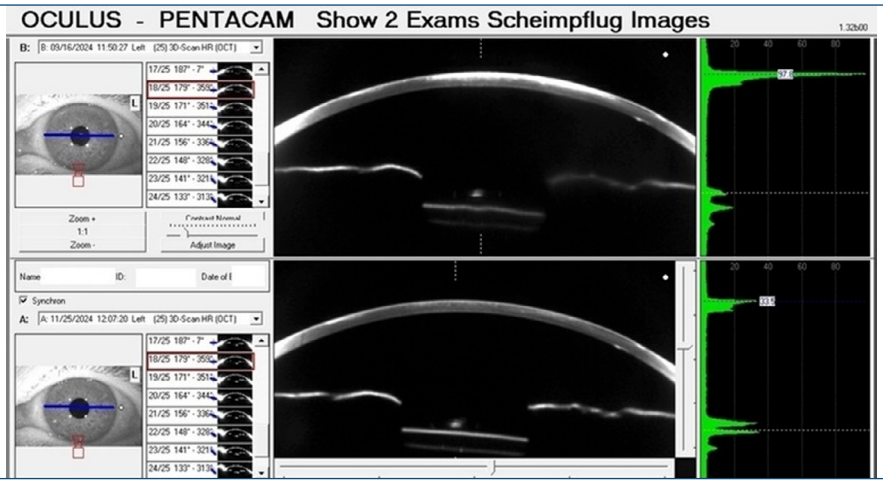

Figure 8. Scheimpflug Pentacam (Oculus Optikgeräte GmbH) image of the left cornea in November 2024, after 10 weeks of treatment with topical losartan (bottom), compared to September 2024 (top), before treatment in Patient C. Analysis of the same section of the cornea shows a marked reduction in hyperreflectivity after 10 weeks of topical losartan treatment.

revealed significant central corneal opacity, particularly in the right eye. The patient was initially treated with preservative-free artificial tears, topical prednisolone (10 mg/mL, four times daily), and nutritional supplementation with essential fatty acids. After 3 months without improvement, the treatment was enhanced to include topical losartan (0.8 mg/mL, four times daily), alongside prednisolone (10 mg/mL, once daily) and continued artificial tears. By the 6-month

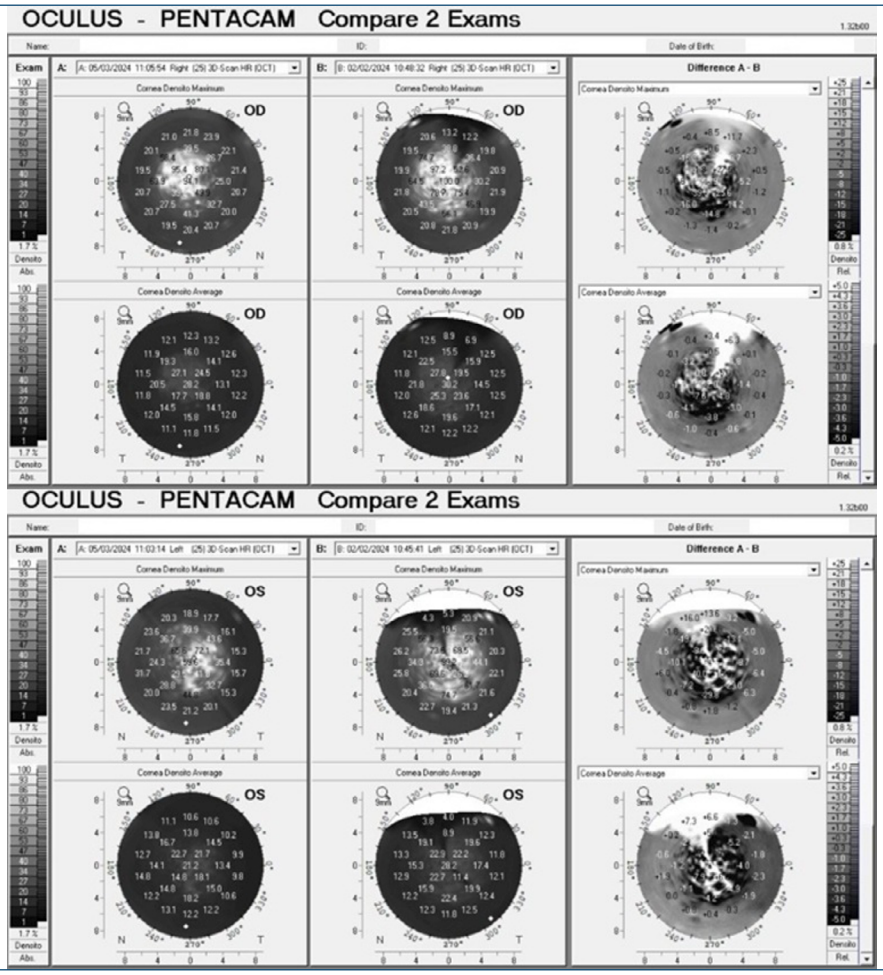

Figure 9. Corneal densitometry. Pentacam (Oculus Optikgeräte GmbH) analysis of the right (top) and left (bottom) corneas before (left column) and after (middle column) 3 months of treatment with topical losartan in Patient D. The difference map (right column) represents the changes of corneal densitometry after treatment, underscoring an improvement.

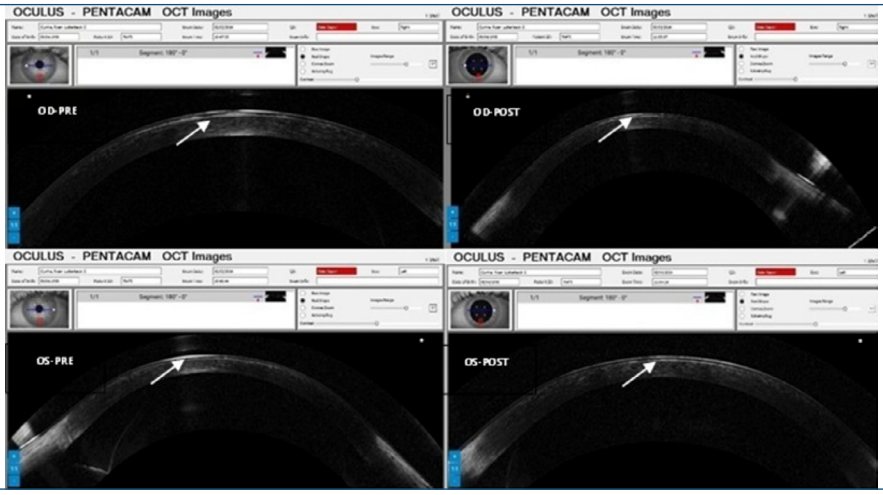

Figure 10. Corneal optical coherence tomography. Pentacam Cornea OCT (Oculus Optikgeräte GmbH) of the right (top) and left (bottom) corneas before treatment (left column) shows a dense subepithelial layer of hyperreflectivity (arrows) compared to 3 months after topical losartan (right column, arrows) in Patient D. A reduction in haze hyperreflectivity can be noted.

follow-up, after 3 months on losartan, UDVA improved to 20/50 in the right eye and 20/33 in the left. Manifest refraction at this visit was -0.75 -1.00 x 130º in the right eye and -0.50 -0.50 x 105º in the left eye, resulting in a CDVA of 20/25 for both eyes. Slit-lamp examination showed a marked reduction in subepithelial fibrosis and improved corneal clarity. Corneal imaging with Scheimpflug tomography and anterior-segment OCT (Pentacam) are shown in Figures 9 and 10.

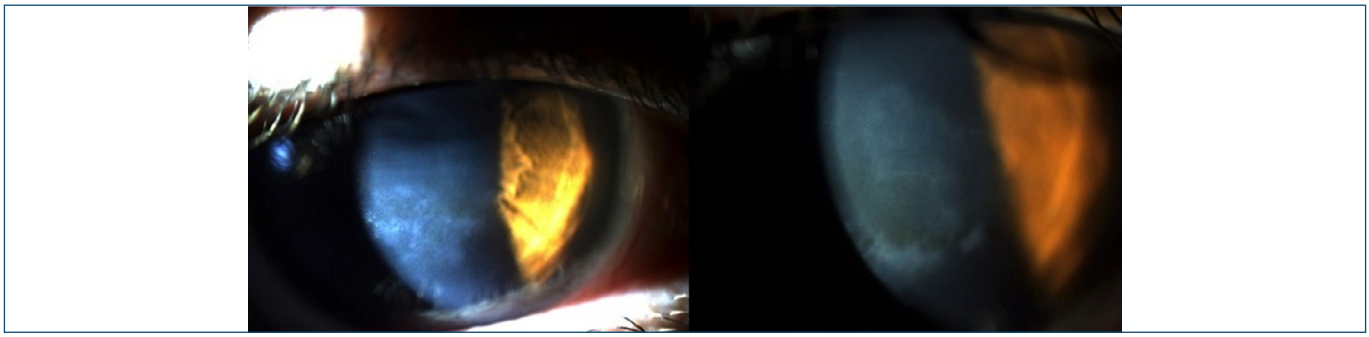

Figure 11. Anterior segment examination shows a dense central corneal subepithelial scar in the right eye (left) of Patient E, which improves after 7 months of treatment with topical losartan (right), with reduction in fibrosis density and increased corneal transparency, especially outside the visual axis.

Patient E

A 54-year-old woman was referred to a corneal specialist due to persistent blurred vision in her right eye, associated to recurrent herpes simplex virus keratitis. Examination revealed UDVA of 20/150 in both eyes. With correction, visual acuity improved to 20/80 in the right eye (+2.25 -1.00 x 30º) and 20/20 in the left eye (+3.25). Slit-lamp biomicroscopy showed a central corneal opacity with subepithelial fibrosis in the right eye, with no signs of active infection. The patient began a treatment regimen that included frequent applications of preservative-free artificial tears, topical prednisolone (10 mg/mL four times daily), and oral valaciclovir (500 mg twice daily). After 5 months, her UDVA remained at 20/100 in the right eye, unchanged with correction. Discussing the possibility of off-label treatment, she provided informed consent to initiate topical losartan therapy. Topical losartan (0.8 mg/mL) was added six times daily in the right eye. At a 7-month follow-up, the patient reported ongoing concerns about vision in her right eye. Her UDVA measured 20/133, improving to 20/100 with a correction of -3.00 x 105º. Although visual acuity showed limited improvement, anterior segment examination noted significant enhancement in corneal opacity, indicating improved transparency (Figure 11). Anterior-segment OCT and corneal tomography using Scheimpflug imaging (Pentacam) provided pre- and post-treatment assessments (Figures 12-14), albeit with no substantial changes observed compared to slit-lamp findings. The patient continues topical losartan six times daily, along with prednisolone once daily and regular lubrication, with a follow-up scheduled in 6 months.

Patient F

A 77-year-old woman was evaluated at the cornea clinic for vision loss and a central corneal scar in her right eye due to recurrent herpes zoster keratitis. She reported no active infections in the last 13 years and had used preservative-free artificial tears for lubrication. Visual acuity assessments revealed UDVA of 20/80 in the right eye and 20/67 in the left eye. With correction, her right eye improved to 20/67 with +1.00 -1.00 x 125º, while the left eye achieved 20/20 with +1.75. Slit-lamp biomicroscopy showed a central corneal scar involving the visual axis in the right eye and moderate cataracts in both eyes. The treatment plan, after informed consent, included the ongoing use of artificial tears and topical losartan (0.8 mg/mL), 1 drop in the right eye 6 times daily. After 3 months, the patient reported subjective vision improvements. Although corneal opacity decreased, UDVA and CDVA in the right eye remained unchanged at 20/80 and 20/67, respectively. At the 8-month follow-up, anterior segment observation confirmed further improvement, leading to a treatment adjustment of losartan to three times daily. At 14 months, the patient was satisfied with her vision, presenting UDVA of 20/100 in the right eye and 20/50 in the left eye, with CDVA of 20/40 (+1.75 -3.00 x 120º) in the right and 20/25 (+2.00 -2.50 x 145º) in the left. Slit-lamp examination demonstrated improved corneal transparency (Figure 15). Anterior-segment OCT and corneal tomography (Pentacam) findings are illustrated in figures 16 to 18. At the next follow-up, vision declined, prompting recommendations for cataract surgery. The treatment was modified to losartan four times daily. Before cataract surgery, her UDVA improved to 20/67 in the right eye and 20/40 in the left eye, with CDVA of 20/40 and 20/30, respectively.

DISCUSSION

Corneal fibrosis remains a significant clinical challenge, especially in refractive surgeries and following corneal injuries. This case series illustrates the potential of topical losartan, an ARB, to effectively modulate corneal scarring by inhibiting the TGF-β signalling pathway at the ERK level. This represents a valuable therapeutic option where traditional treatments have been limited. Our findings confirm and

Figure 12. Optical coherence tomography (Pentacam Cornea OCT, Oculus Optikgeräte GmbH). Anterior-segment optical coherence tomography showed a dense central hyperreflective subepithelial layer in the right eye of Patient E before treatment with topical losartan (top). After 7 months of treatment, the optical coherence tomography findings were similar to those observed before treatment (bottom).

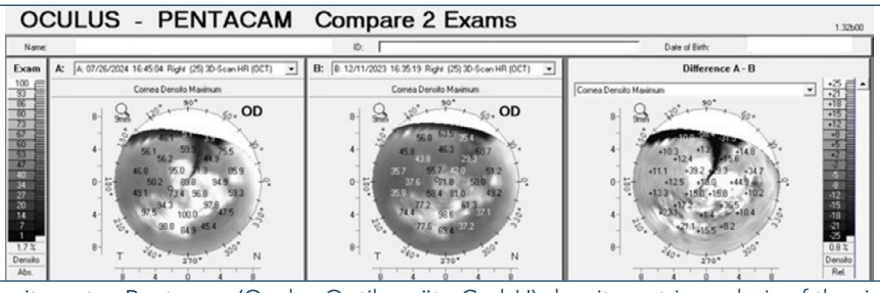

Figure 13. Corneal densitometry. Pentacam (Oculus Optikgeräte GmbH) densitometric analysis of the right cornea before topical losartan (left column) compared to densitometry measures after treatment (middle column) in Patient E. The difference map (right column) shows changes in densitometry after topical losartan treatment.

expand upon the preliminary successes reported by Pereira-Souza et al.[17] and Rodgers et al.,[18] highlighting the promise of losartan for patients dealing with corneal opacity caused by surgical or traumatic injuries. Notably, topical losartan at a concentration of 0.8 mg/mL, administered six times daily, has also proven beneficial in treating corneal fibrosis associated with radial keratotomy, with significant improvement in corneal transparency observed within 2 weeks.

Corneal haze is a fibrotic response characterized by the accumulation of extracellular matrix proteins and the differentiation of keratocytes and fibrocytes into myofibroblasts, primarily regulated by TGF-β. TGF-β exists in multiple isoforms (TGF-β1, β2, and β3), all of which play critical roles in the fibrotic response in the cornea and other tissues. Various injuries stimulate the release and activation of TGF-β from epithelial cells, corneal endothelial cells, and

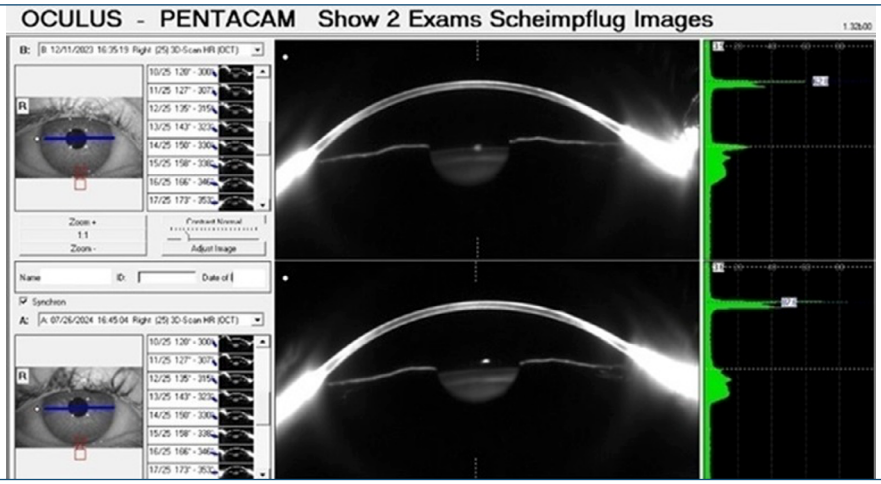

Figure 14. Scheimpflug Pentacam (Oculus Optikgeräte GmbH) image of the right cornea of Patient E after 7 months of topical losartan (bottom) compared to pre-treatment (top). Analysis of the same corneal section shows no improvement in stromal hyperreflectivity with treatment. No relevant changes were noted in other corneal sections as well.

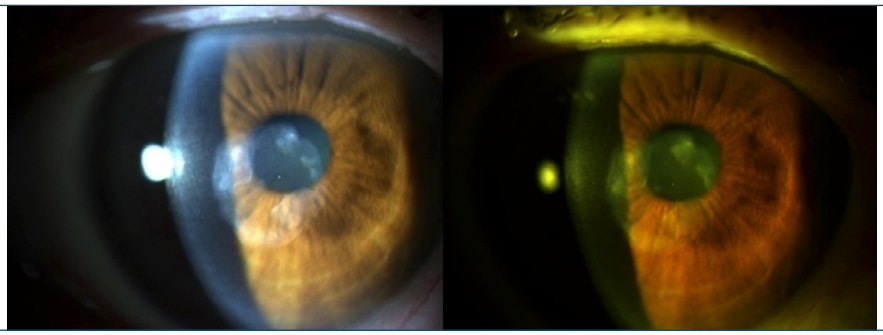

Figure 15. Slit-lamp biomicroscopy revealed a central corneal opacity in the right eye before losartan treatment (left) that marginally improved after treatment (right) in Patient F. Reduced haze density and the increased clear areas (lacunae) can be noted after treatment.

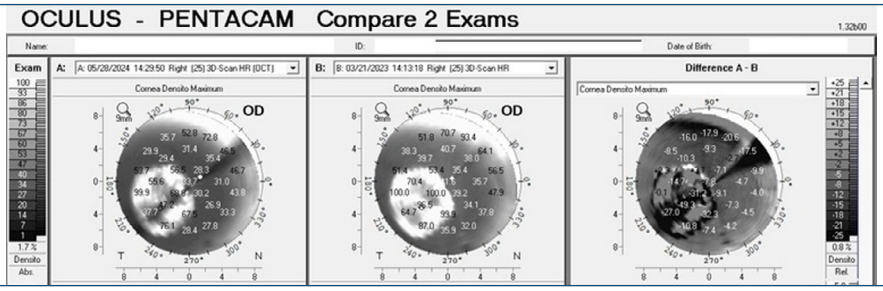

Figure 16. Corneal densitometry. Pentacam (Oculus Optikgeräte GmbH) analysis of the right eye of Patient F displayed densitometric assessment before (left column) and after (middle column) treatment. The difference maps (right column) represent the changes in corneal densitometry after treatment.

aqueous humour, promoting myofibroblast differentiation and excessive collagen production. Our findings align with the existing literature identifying TGF-β as a major driver of corneal fibrosis, including studies documenting a direct relationship between elevated TGF-β levels and corneal opacity following refractive surgery.[7,19] Additionally, disturbances to the epithelial basement membrane (EBM) due to surgical procedures can disrupt the normal balance of this signalling pathway, increasing the risk of fibrotic outcomes.

Corneal scars that are caused by fibrosis are maintained indefinitely by viable myofibroblasts that are dependent on TGFb for survival.[2,14,16] This TGFb is derived from the tears and epithelium and/or aqueous humour, depending on the injury, due to defective regeneration of the EBM and/or Descemet's membrane.[2] Even years or decades after the initial injury, topical losartan via its effects blocking ERK activation in response to TGFb binding to its receptors on these myofibroblasts can trigger their apoptosis and finally allow corneal fibroblasts to move into the fibrotic tissue, help the epithelium regenerate normal EBM to control further TGFb entry into the stroma, and remove the

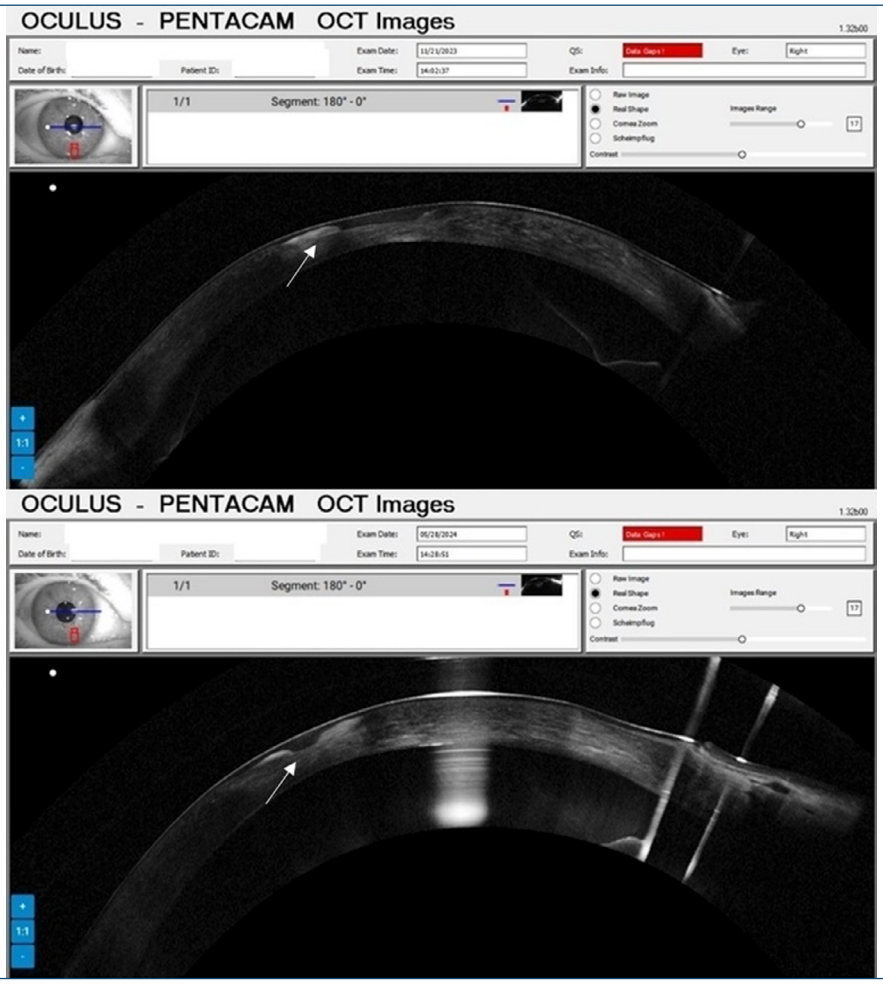

Figure 17. Corneal Optical coherence tomography. Pentacam Cornea OCT (Oculus Optikgeräte GmbH) of the right cornea of Patient F showed subepithelial hyperreflectivity and superficial irregularity (top) that improved after treatment with topical losartan (bottom).

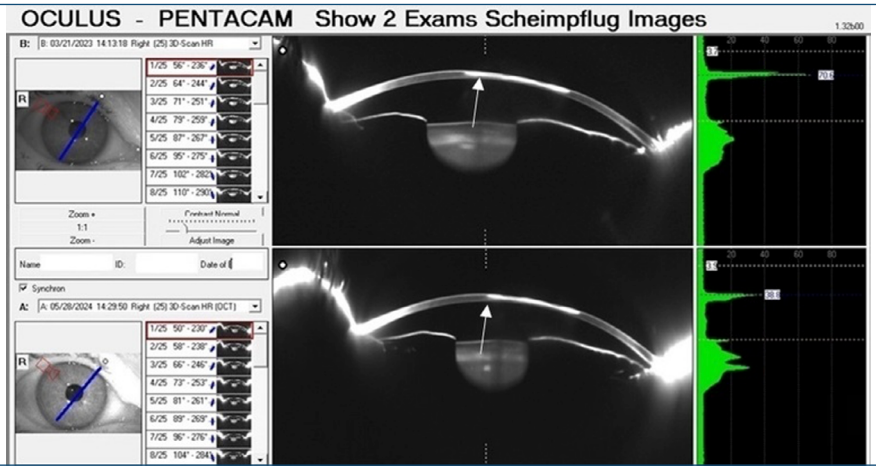

Figure 18. Scheimpflug Pentacam (Oculus Optikgeräte GmbH) image of the right cornea in May 2024 after treatment with losartan (bottom) compared to March 2023, before treatment (top) of Patient F. The analysis through the same section of the cornea showed a small reduction in hyperreflectivity (arrows) after 14 months of treatment with topical losartan.

disordered collagens and other matrix components deposited by the myofibroblasts. So, even longstanding corneal scars may respond to topical losartan. To date, to our knowledge, the longest post-injury case was successfully treated with topical losartan was three years after Varicella zoster virus keratitis.

Established treatments for corneal haze usually involve surgical interventions like PTK or corneal

Table 1. Patients' visual acuity before and after treatment with topical losartan. Patient A⁺ demonstrated an additional improvement after post-losartan phototherapeutic keratectomy, achieving a corrected distance visual acuity of 20/25. Treatment duration is also displayed. Corrected distance visual acuity was considered, except for Patient D*, for whom we compared uncorrected distance visual acuity, since both corrected distance visual acuity was not available. Patients underwent treatment with topical losartan at a concentration of 0.8 mg/mL

Patient		Diagnosis	Treatment	CDVA before treatment	CDVA after treatment	Losartan treatment duration
A⁺		Late post-PRK / SARS-CoV-2-related corneal fibrosis	Topical losartan 4 times/day Prednisolone 10mg/mL 4 times/day Preservative-free Lubricants Essential fatty acids	20/40	20/30	8 months
B		Post-PRK corneal fibrosis	Topical losartan 4 times/day Loteprednol 5mg/mL once daily Essential fatty acids Vitamin D	20/33	20/20	10 months
C		Herpes Simplex Keratitis	Topical losartan 5 times/day Prednisolone 10 mg/mL 4times/day	20/100	20/40	10 weeks
D*	Right	Post-PRK corneal fibrosis	Prednisolone 10mg/mL 4 times/day	20/100	20/50	3 months
	Left		Preservative-free lubricants Essential fatty acids Topical losartan 4 times/day	20/67	20/33	
E		Herpes simplex keratitis	Preservative-free lubricants Prednisolone 10mg/mL 4 times/day Valaciclovir 500 mg BID Topical losartan 6 times/day	20/100	20/100	7 months
F		Herpes zoster keratitis	Topical losartan 6 times/day Free-preservative lubricants	20/67	20/40	14 months

CDVA: corrected distance visual acuity; PRK: photorefractive keratectomy; BID: *bis in die* (2x/day); +: Additional improvement after post-Losartan PTK to a CDVA of 20/25; *: Both CDVAs were not available, comparisons were made using UDVA.

transplantation. While topical corticosteroids may help mitigate inflammation and TGF-β-driven fibrosis, they often come with significant side effects, including increased intraocular pressure, cataracts, and susceptibility to infections.[20] Other pharmacological options have demonstrated only modest efficacy in previous studies.[21,22] Although agents like MMC provide some benefits in controlled settings, corneal fibrosis continues to pose challenges, underscoring the need for innovative therapies that can be integrated into existing treatment frameworks.

In our series, six patients showed varying degrees of improvement in corneal transparency after topical losartan treatment. Significant reductions in corneal opacity were observed during slit-lamp examinations and with advanced imaging techniques, including anterior OCT and corneal tomography. Visual improvement was noted in five patients treated with losartan for periods ranging from 10 weeks to 14 months, while one patient experienced reduced opacity after 7 months without improvement in visual acuity. These results differ from those observed by Burgos-Blasco et al., in which there was no significant improvement in visual function or corneal densitometry.[23] The efficacy of topical losartan in preventing and treating corneal fibrosis likely hinges on achieving effective drug levels in the corneal stroma over time. While some of our patients benefited from a four-times-daily regimen, it is possible that more frequent (six-times-daily) administration could lead to higher success rates. Prolonging treatment duration might also enhance fibrotic reduction. It is probable that the stromal concentration must achieve a critical level for an extended period for the myofibroblasts to undergo apoptosis while the corneal fibroblasts are coming into the fibrotic tissue, repairing the EBM and leading to the removal/reorganization of the disordered fibrotic stroma, and six times a day is more likely to achieve that needed stromal level than four times a day regimen. We recommend continuing topical losartan for at least 3 months after optimal resolution of corneal scarring to support complete epithelial regeneration and prevent recurrence of fibrosis. It is important to note that oral losartan has shown no efficacy for corneal opacity.[13]

For topical losartan to effectively improve vision, the corneas overall morphology must be preserved despite injury. In cases of corneal damage from infection or trauma, although topical losartan can reduce fibrotic opacity, surgical interventions may still be necessary to restore corneal structure and enhance vision.

Losartan's efficacy is supported by its antagonistic effects on TGF-β signalling.[8,11,23] While primarily known as an ARB, its modulation of TGF-β activity by inhibiting ERK activation plays a vital role in its ability to treat corneal fibrosis. Losartan reduces TGF-β-driven myofibroblast activation and minimizes collagen type IV production, providing a strong rationale for its use in corneal scarring.[13,16]

The potential of losartan as a topical treatment represents a shift in the management of corneal scars. Given its excellent safety profile and existing use for other medical conditions, repurposing losartan could greatly benefit patients while minimizing risks associated with new therapies. The cases presented here enhance our understanding of how existing pharmacological agents can foster new avenues for promoting corneal healing

post-surgery or overcoming chronic conditions such as scarring from herpetic keratitis.

Importantly, our findings support the idea of losartan serving both as a therapeutic and preventative measure, particularly for patients at high risk of developing corneal fibrosis after refractive surgeries.[3,13] Its potential applications could also extend to other corneal fibrotic disorders. As noted in previous literature, the pharmacological modulation of losartan may inhibit myofibroblast survival after surgical procedures, potentially improving long-term visual outcomes and enhancing patient quality of life.[14]

While this case series offers promising evidence for the efficacy of topical losartan, each patient must be considered individually regarding their unique clinical setting. Further extensive and controlled studies are necessary to validate these results. Future clinical trials should focus on determining optimal treatment regimens, long-term effectiveness, and safety across diverse patient populations and corneal conditions.[2,16]

CONCLUSION

This case series presents strong evidence for the use of topical losartan as a novel treatment for corneal fibrosis arising from various challenges, including surgical complications and infections. By inhibiting the TGF-β signalling pathway, losartan addresses limitations of current therapies and provides a multifaceted strategy for managing corneal scarring. Ongoing research is essential to quantify losartan's effects and clarify its mechanisms of action on corneal fibroblasts and myofibroblasts. As our understanding of corneal wound healing advances, losartan and similar agents may play a crucial role in improving treatment for corneal scarring, ultimately enhancing standards of care in ophthalmology.

AUTHORS' CONTRIBUTION

Gonçalo Cavaco Tardão: Writing - Original Draft; Renato Ambrósio Júnior: Conceptualization, Methodology, Software, Formal analysis, Review & Editing. Júlio Brissos: Investigation. Alexandre Batista da Costa Neto: Conceptualization, Writing - Review & Editing. Inês Machado: Validation. Ana Cardoso: Validation. Nuno Campos: Validation. Steven Eugene Wilson: Conceptualization, Methodology, Software, Formal analysis, Review & Editing.

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