Topical Losartan for Treating Corneal Fibrosis (Haze): First Clinical Experience

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ABSTRACT

PURPOSE: To report the first clinical experience with topical losartan for treating a case of severe corneal haze after complicated laser in situ keratomileusis (LASIK).

METHODS: A 36-year-old woman presented with corneal haze in the left eye after femtosecond laser–assisted LASIK. The left eye had flap dislocation and significant striae, which had been re-lifted. Uncorrected distance visual acuity (UDVA) was 20/200 and corrected distance visual acuity was 20/30 in the left eye at the first presentation, 52 days after the first procedure. A dense layer of subepithelial opacity (haze) was noted in the left cornea. The patient elected to start the off-label treatment with topical losartan 0.8 mg/mL six times per day.

RESULTS: Four and one-half months after initiating topical losartan, UDVA improved to 20/30 and CDVA improved to 20/25 in the left eye. A significant reduction of corneal haze was observed at the slit lamp and using Scheimpflug corneal tomography (Pentacam AXL; Oculus Optikgeräte GmbH) and anterior segment optical coherence tomography (Revo NX 130; Optopol).

CONCLUSIONS: Losartan is an inhibitor of transforming growth factor-β signaling. Topical treatment is promising to treat corneal haze formation after corneal injuries, chemical burns, and surgeries. Further clinical studies are needed to optimize losartan dosages and treatment durations.

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Refractive corneal laser vision correction surgery has become popular.[1] It is expected that the numbers of patients treated with laser vision correction will increase even further with the increasing prevalence of myopia.[2] As of 2009, laser in situ keratomileusis (LASIK) had been performed in more than 28 million patients.[3] Other laser vision correction procedures, including photorefractive keratectomy (PRK), small incision lenticule extraction, and femtosecond lenticule extraction, further augment the numbers of patients who have refractive error corrected with surgery. PRK has a higher incidence of clinically significant haze than LASIK, especially when used for the correction of high myopia.[4-6] Clinically significant haze is reported to occur in up to 3% of patients who have laser vision correction for low to moderate levels of myopia and has been noted in up to 15% of patients undergoing high-level corrections for myopia.[7]

The treatment of corneal haze after laser vision correction is often challenging. Although some drugs, such as topical mitomycin C (MMC), are effective when used prophylactically to minimize the development of opacity-producing myofibroblasts after laser vision correction, this treatment is typically ineffective once haze is established in a cornea. The most common treatment used after PRK to prevent corneal inflammation is the application of topical corticosteroids. However, corticosteroid use is not recommended for prolonged periods due to potential side effects. Moreover, when "late haze" occurs 2 to 3 months af-

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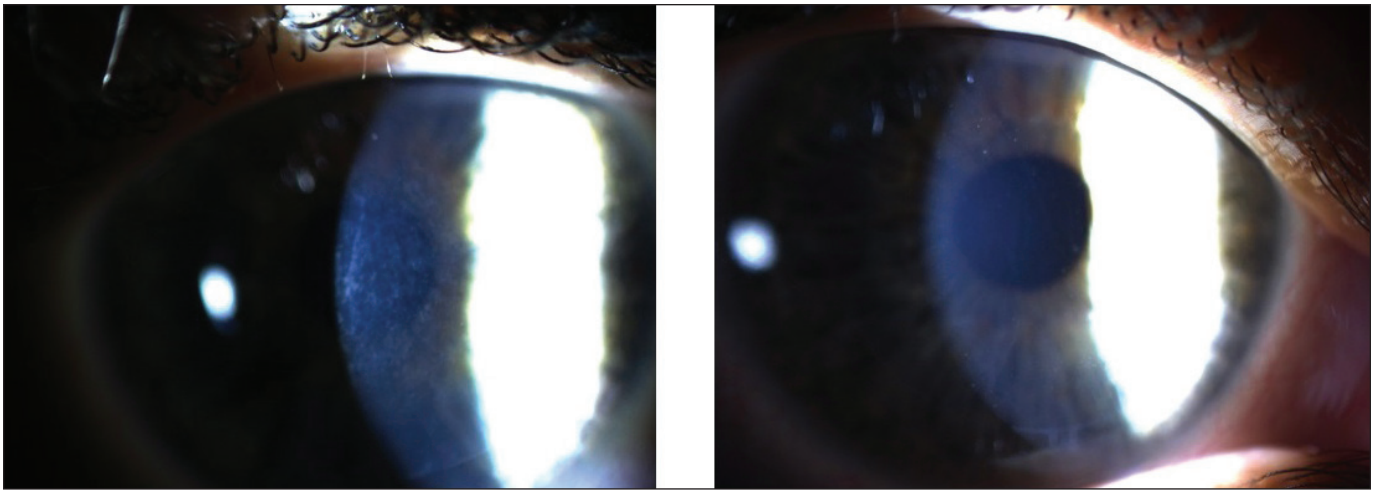

Figure 1. Slit-lamp biomicroscopy of the patient's left eye in December 2021 (left), pre-medication, compared to May 2022 (right), after 4 months of losartan application. A marked reduction in opacity was noted within the slit lamp after topical losartan treatment (original magnification ×20).

ter PRK surgery, clinical studies showed that only 5% to 15% of eyes are responsive to corticosteroids, and have a decrease in opacity in response to treatment.[4]

Haze formation involves a loss of cellular transparency and deposition of disorganized extracellular matrix that accompanies corneal fibroblast proliferation, migration, and differentiation into transforming growth factor (TGF)-β–dependent myofibroblasts. TGF-β1 and TGF-β2 have been shown to play a central role in the generation and persistence of myofibroblasts and their disappearance from the stroma in corneal haze pathophysiology.[8-10]

Recently, topical losartan has been found to have efficacy in reducing corneal scarring fibrosis haze produced by surgical injury[11] or alkali burns[12] in rabbits. This case report presents a patient who had complicated LASIK and developed severe haze, and to the best of our knowledge was the first human treated with topical losartan in the eye.

CASE REPORT

A 36-year-old woman was referred for a second opinion for corneal haze in the left eye after bilateral femtosecond laser–assisted LASIK 52 days prior to consultation. The preoperative records of LASIK indicated uncorrected distance visual acuity (UDVA) of counting fingers in each eye and corrected distance visual acuity (CDVA) of 20/20 with -5.25 -0.50 @175 in the right eye, and 20/20 with -4.75 -0.50 @155 in the left eye. The preoperative corneal thickness was 512 and 517 µm in the right and left eyes, respectively. Corneal asphericity was within normal limits. The LASIK flap was planned using the femtosecond laser with 90 µm and 9 mm in diameter with a planar cut with 70º angulation with the Ziemer LDV Z8 (Ziemer Group). The patient had a planned correction partial monovision in the left eye with a target of -0.75, with maximum ablation profiles of 80 µm in the right eye and 63 µm in the left eye.

The left cornea had clinically significant striae 4 days after the original procedure, and was re-treated with flap lift and epithelial debridement. The macrostriae resolved and the epithelium closed, and the procedure was otherwise uneventful. After that procedure, the eye was treated with prednisolone 1% every hour and cyclosporine A 0.05% four times per day.

Forty-eight days after the re-treatment, UDVA was 20/20 in the right eye and 20/200 in the left eye on presentation. Manifest refraction was -0.50 -0.50 × 18, giving a CDVA of 20/15- in the right eye and -2.00 -1.75 × 179, giving a CDVA of 20/30 in the left eye. A dense layer of subepithelial haze was noted in the cornea of the left eye. The patient was advised about the possibility of off-label treatment with topical losartan as an inhibitor of the TGF-β signaling that maintains myofibroblast survival. The patient agreed to a trial of topical losartan. Pure 0.8 mg/mL of losartan potassium powder (Bristol-Myers Squibb) was prepared in sodium chloride 0.9%, pH 6.7 to 7.0, and treatment was initiated at one drop in the eye six times per day. Topical cyclosporine A (Restasis) treatment was continued twice per day, along with frequent preservative-free artificial tears and nutritional supplementation with essential fatty acids.

RESULTS

After 1 month of topical losartan treatment, the patient reported no adverse effects and noticed an improvement of the UDVA in the left eye to 20/80, and CDVA in that eye to 20/25 with -1.25 -1.00 × 175. At that point treatment with topical 0.8 mg/mL of losar-

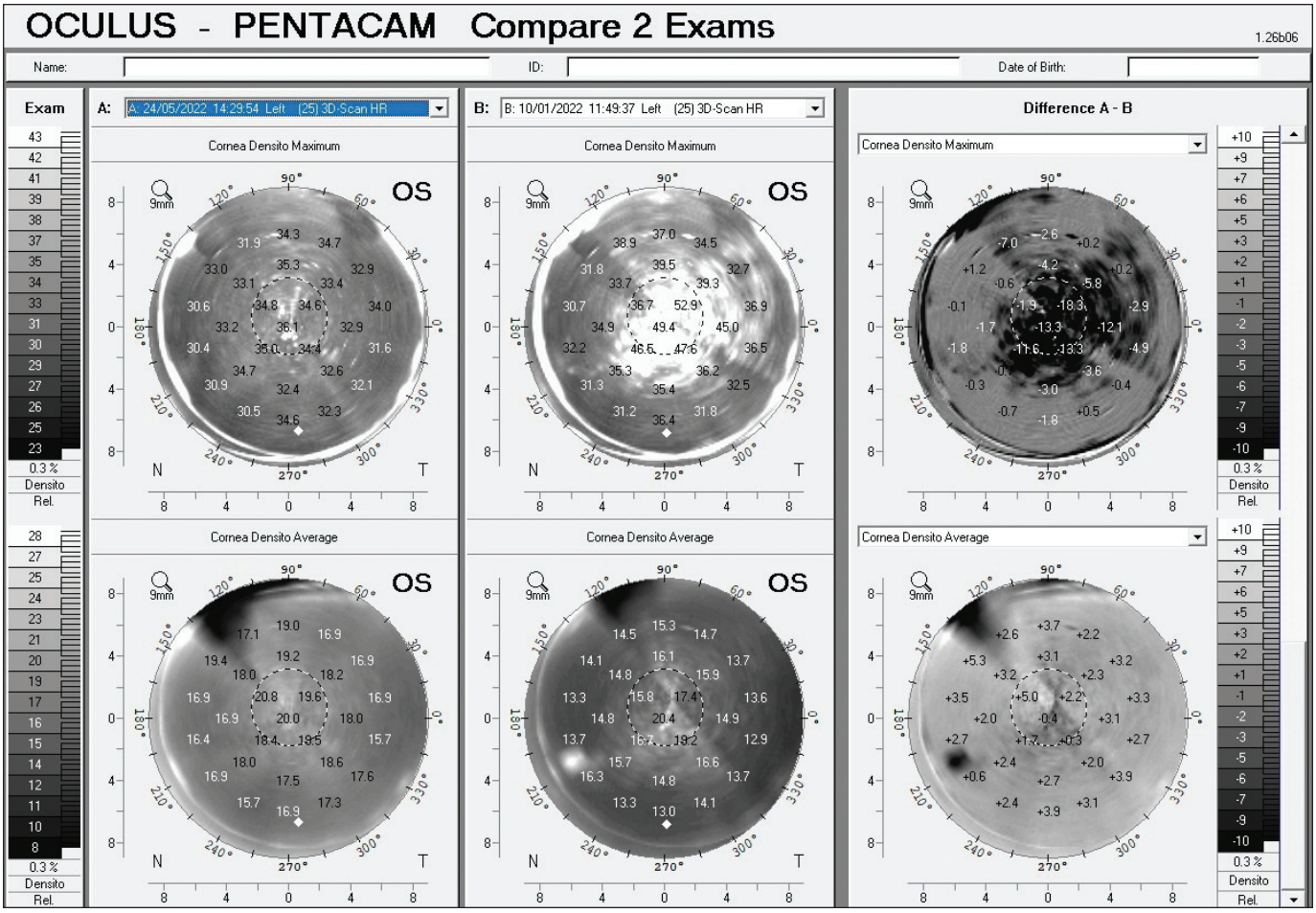

Figure 2. Corneal densitometry. Pentacam (Oculus Optikgeräte GmbH) analysis of the left cornea in May 2022 (left column) compared to January 2022 (middle column) shows densitometry measurements after and before treatment, respectively. The difference maps (right column) demonstrated the change after treatment with topical losartan.

tan was reduced to four times per day and continued over 4 more months.

Four and one-half months after initiating topical losartan treatment, UDVA improved to 20/30, and CDVA was 20/25 with -0.50 -1.25 × 3 in the left eye. A significant reduction of corneal haze was observed with the slit lamp and using Scheimpflug corneal tomography (Pentacam AXL; Oculus Optikgeräte GmbH) and anterior segment OCT (REVO NX 130; Optopol) (**Figures 1-3** and **Figures A-B**, available in the online version of this article).

DISCUSSION

The treatment of clinically significant haze after refractive laser vision correction surgery remains a major challenge for specialists. The prophylactic application of a topical solution of MMC immediately following laser ablation is commonly effective in preventing myofibroblast-related stromal haze after PRK, but cases of "breakthrough haze" continue to occur.[13] LASIK, small incision lenticule extraction, and other laser vision correction procedures do not typically include MMC treatment and fibrotic haze only develops at the site of epithelial basement membrane (EBM) perforation (eg, at the flap edge in LASIK). In addition, other substances have been proposed to prevent haze, such as vitamin E, probucol, and heparin, but these medications have not been approved for topical use due to low efficacy or adverse effects.[4] Once clinically significant haze has developed after surgery, several drugs have been tested to treat corneal haze, including corticosteroids, plasmin inhibitors, growth factors, or anti-metabolites.[4] However, these alternative treatments have usually been found to have limited efficacy in reducing haze.[4-6]

Corneal wound healing has been shown to be regulated by several growth factors, including epidermal growth factor, fibroblast growth factor, TGF-β, keratinocyte growth factor, hepatocyte growth factor, platelet-derived growth factor, insulin-like growth factor, interleukins (IL-1, IL-6, IL-8), tumor necrosis factor-

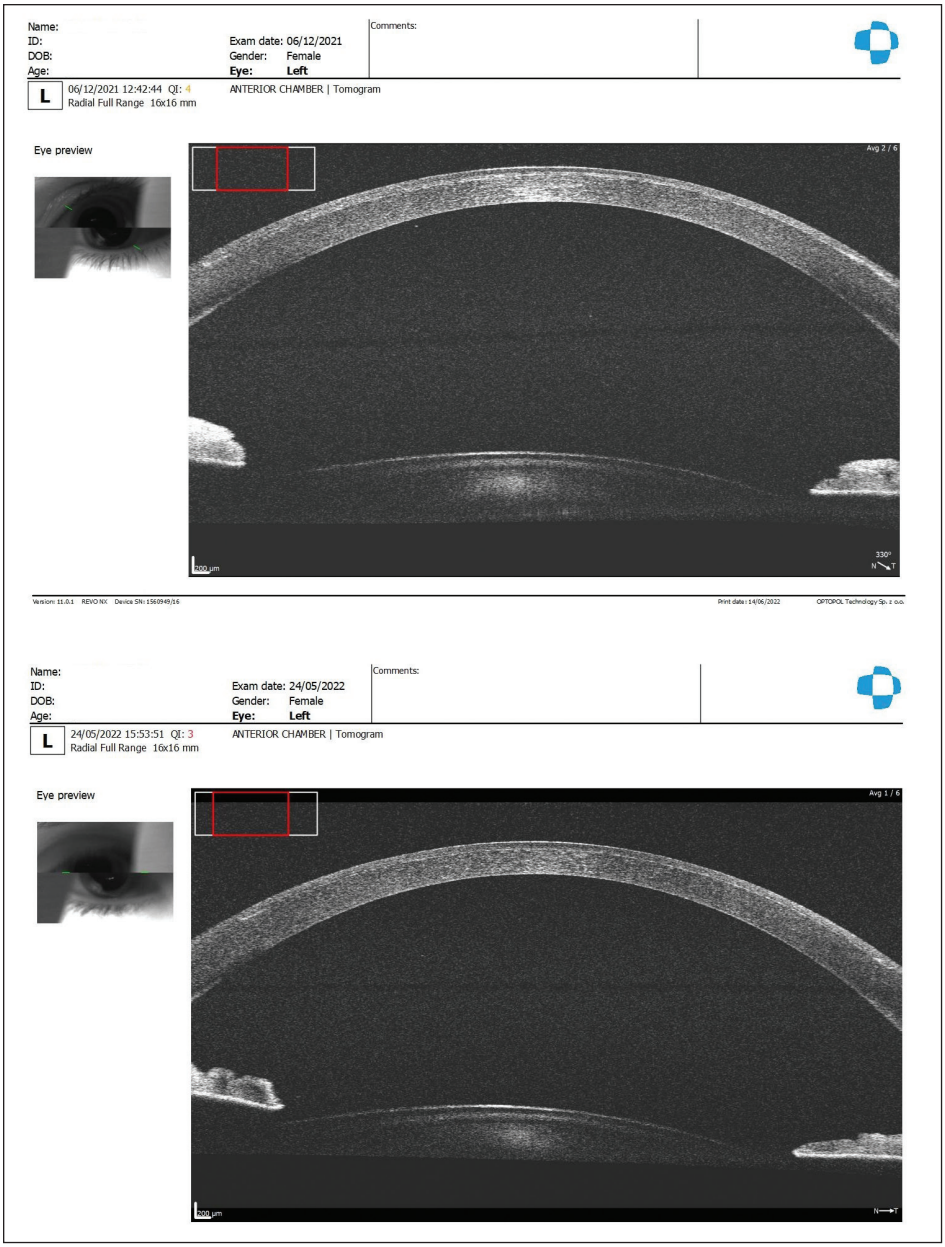

Figure 3. Optical coherence tomography (REVO NX 130; Optopol) of the left cornea in December 2021 (top) prior to topical losartan treatment compared to May 2022 after 5 months of topical losartan treatment (bottom). The top image has subepithelial hyperreflectivity, which is reduced in the bottom image after topical losartan treatment.

alpha, and secreted acidic cysteine-rich protein. Evidence has accumulated, supporting the hypothesis that TGF-βs (TGF-β1 and TGF-β2, and possibly TGF-β3) are the most significant regulators of fibrosis in the cornea and other tissues through their effects on myofibroblast development and apoptosis.[9,10,14]

Studies have also demonstrated a relationship between the level of corneal haze formation after PRK and the level of stromal surface irregularity[15] that likely impacts the normal regeneration of the epithelial basement membrane, which in turn regulates entry of TGF-β1 and TGF-β2 into the corneal stroma from the tears and epithelium.[9,10] The smoothing of phototherapeutic keratectomy with methylcellulose masking effectively reduces stromal surface irregularity and decreases haze and associated myofibroblast density[15] by facilitating regeneration of the EBM through the coordinated efforts of the epithelium and keratocytes/corneal fibroblasts.[9,10] Late apoptosis appears to play a role in the disappearance of myofibroblasts and haze over time,[15,16] and is likely mediated via a drop in stromal TGF-β1 and TGF-β2 levels following full regeneration of the EBM. The possibility of a pharmacological treatment for haze, without consumption of corneal tissue using procedures such as phototherapeutic keratectomy, could help preserve the biomechanical properties of the cornea. Pharmacological agents that inhibit TGF-β signaling would be good candidates to

modulate myofibroblasts and the stromal fibrosis they produce and maintain.

Collagen type IV is an important component of basement membranes in all body organs. It has the function of organizing the basement membrane and modulating the migration of growth factors between tissues within an organ. Collagen type IV binds TGF-β1 and TGF-β2 and prevents their binding to cognate receptors, and is, therefore, an essential modulator of the profibrotic functions of TGF-β.[17] After injury to the cornea, collagen type IV is produced in the stroma by corneal fibroblasts to modulate stromal TGF-βs. There are several potential sources of TGF-β1 and TGF-β2, with the major sources being the tears, epithelium, corneal endothelium, and aqueous humor.[9-11] TGF-β drives the development of myofibroblasts from corneal fibroblasts and bone marrow–derived fibrocytes, and TGF-β levels in the stroma are sufficient in the absence of normal EBM[9,10] and/or Descemet's basement membrane[11] function. Thus, after a fibrotic corneal injury, TGF-β enters the stroma in sufficient amounts from the tears, epithelium, endothelium, and/or aqueous humor to drive myofibroblast development and maintain their survival. TGF-βs also significantly increase collagen type IV production by stromal corneal fibroblasts apart from the basement membranes to directly modulate binding to TGF-β receptors expressed by stromal cells.[17] Thus, non-basement membrane stromal collagen type IV binds to TGF-β1 and TGF-β2 in competition with the binding of growth factors to cognate TGF-β receptors and serves as a negative feedback regulatory pathway to reduce the effects of TGF-β on stromal cells.[17] Topical losartan inhibits TGF-β–mediated corneal fibroblast production of collagen type IV after corneal injury throughout the full thickness of the stroma,[11,12] providing strong evidence that losartan penetrates the intact corneal epithelium—an essential property for a pharmacological agent that would be used to modulate TGF-β–driven myofibroblast development or long-term myofibroblast survival.[11,12]

Losartan is used as a systemic medication by millions of people to treat conditions such as hypertension, kidney disease, heart failure, and left ventricular enlargement. It is an angiotensin II receptor antagonist that has been shown to also inhibit TGF-β–modulated processes.[11] To date there have been no reports regarding oral losartan modulating corneal scarring fibrosis. This has been demonstrated in rabbit studies that showed that only topically administered losartan could reach sufficient levels in the stroma to regulate myofibroblast development and survival after corneal injury.[11,12] This case demonstrates the potential for topical losartan to modulate corneal fibrotic haze after corneal surgical injury. Thus, topical losartan is likely to be effective in both preventing and treating myofibroblast-mediated scarring fibrosis of the cornea after traumatic or surgical injuries, microbial infection, chemical injuries, and possibly some corneal diseases.[11,12] It is our hope that this case report will spur clinical trials where topical losartan is used for both preventative and therapeutic modulation of corneal stromal fibrotic haze.

Topical losartan treatment holds promise for both prophylactic and therapeutic treatments to modulate stromal fibrotic haze after numerous types of corneal injuries and surgeries. Losartan may be an alternative therapy to current standard treatments for corneal haze fibrosis. Although the exact mechanism of losartan action in blocking TGF-β signaling is not entirely understood, studies of this topical drug in animals and humans have shown its potential to prevent the development of fibrosis in response to injury or to treat fibrosis once it is already present. Prospective clinical studies are needed to further evaluate the efficacy, safety, and duration of topical losartan treatment needed in different corneal scarring disorders.

AUTHOR CONTRIBUTIONS

Study concept and design (RA, MQS, ASL, SEW); data collection (ALP-S, FB); analysis and interpretation of data (RA, FB, MQS, SEW); writing the manuscript (ALP-S, RA, FB, MQS, SEW); critical revision of the manuscript (ALP-S, RA, FB, MQS, ASL, SEW); supervision (SEW)

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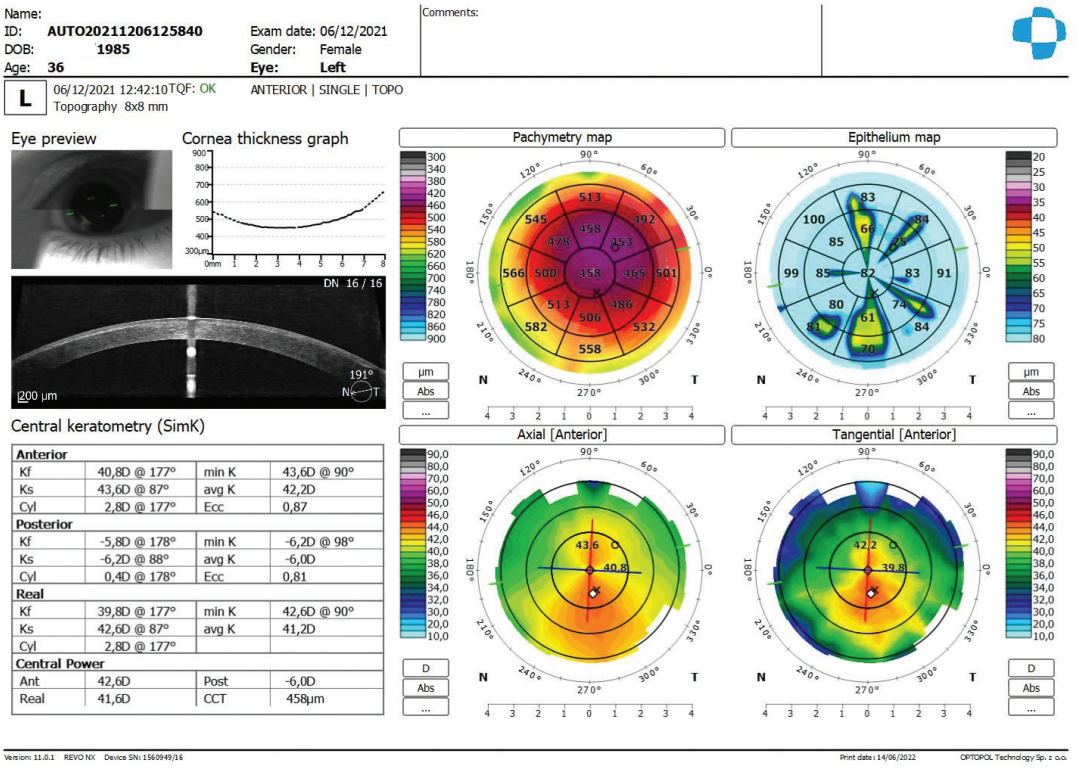

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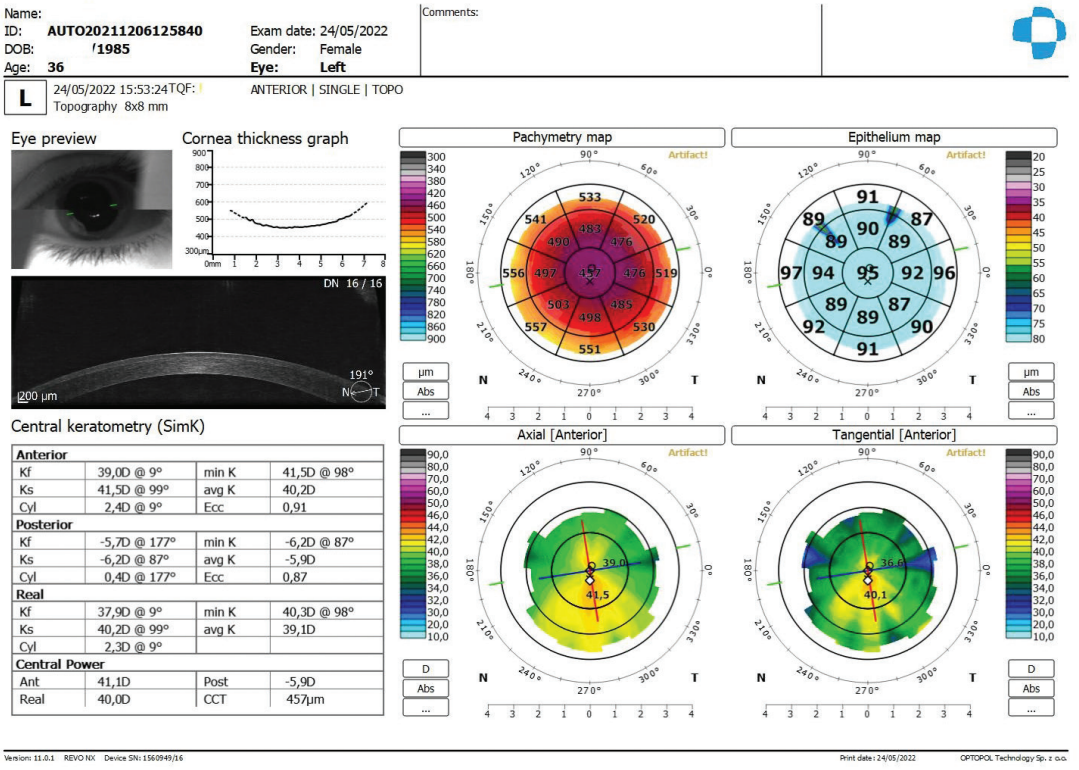

Figure A. Optical coherence tomography (REVO NX 130; Optopol) of the left cornea in (A) December 2021 compared to (B) May 2022. The top analysis shows an irregular and thinner corneal epithelium prior to treatment with topical losartan compared to after 5 months of treatment.

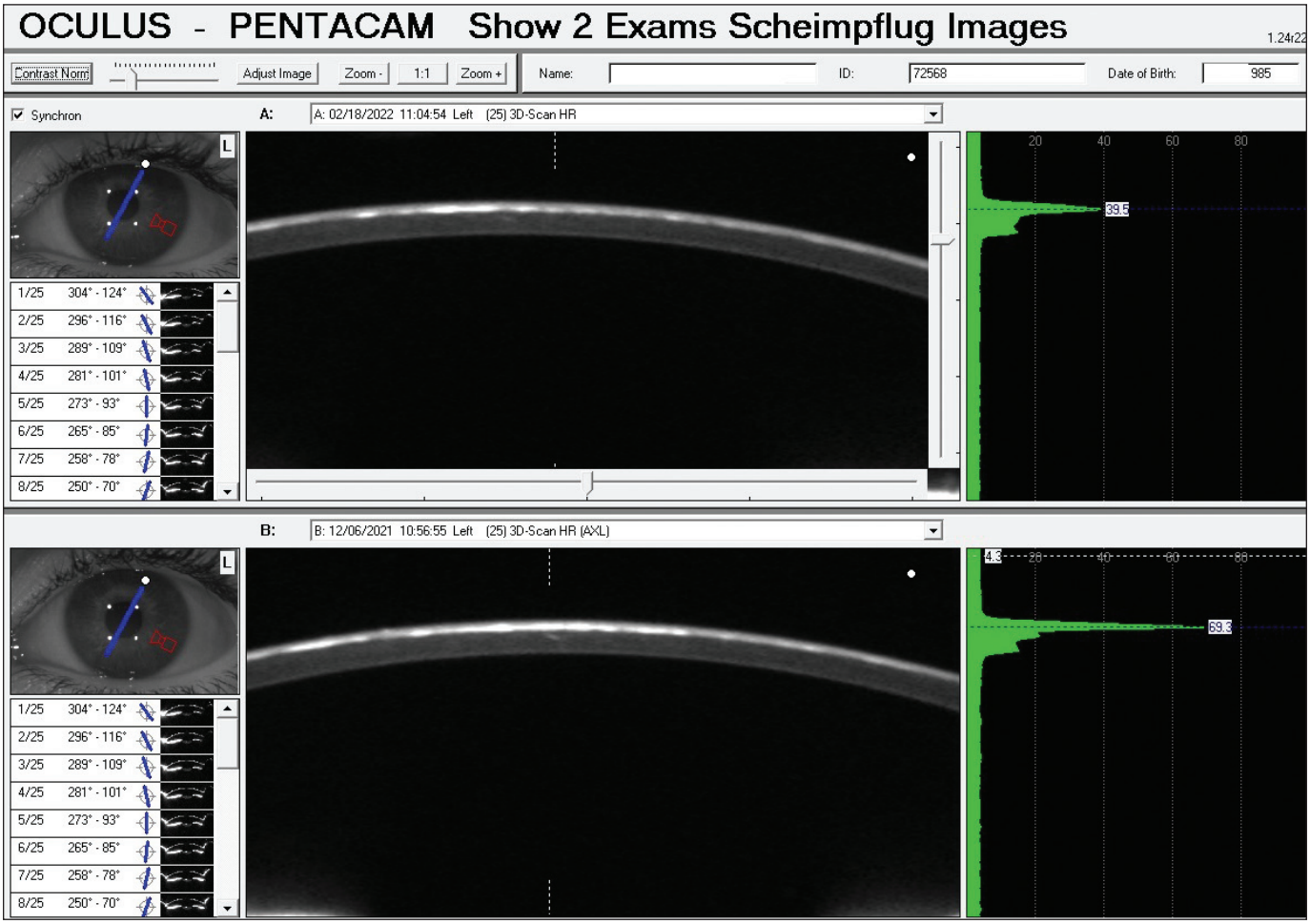

Figure B. Scheimpflug Pentacam (Oculus Optikgeräte GmbH) image of the left cornea in February 2022 (top) after 2 months of topical losartan treatment compared to December 2021 (bottom) prior to treatment. The analysis through the same section of the cornea at the two analyses shows decreased hyperreflectivity after only approximately 2 months of the topical losartan treatment.