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"Rapid and reversible alteration in corneal contour and power associated with Netarsudil/Latanoprost"

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ABSTRACT

Purpose: To describe a previously unreported case of reversible myopic shift with corresponding changes in corneal contour in a patient treated with netarsudil/latanoprost.

Observations: A 72-year-old male with history of primary open angle glaucoma, prior cataract surgery, and remote radial keratotomy surgery was treated with fixed-dose combination of netarsudil/latanoprost. Despite no prior history of refractive shift in the twenty years since radial keratotomy surgery, on one month follow-up, he reported reduced visual acuity and presented with approximately 1.50 D shift in both eyes. There were associated corneal contour changes. No corneal epithelial bullae or edema were appreciated. Netarsudil/latanoprost was discontinued and timolol was initiated. One month later, both refractive error and corneal contour returned to prior levels.

Conclusions: Netarsudil is a rho-kinase and norepinephrine transporter inhibitor that may be effective in the treatment of primary open angle glaucoma resistant to other topical treatments. In addition to corneal epithelial bullous edema previously reported, this drug may induce reversible changes in corneal contour in patients with prior corneal or refractive surgery.

1. Introduction

Netarsudil is a rho-kinase (ROCK) and norepinephrine transporter (NET) inhibitor approved for the treatment of elevated IOP in patients with open-angle glaucoma (OAG) and ocular hypertension (OHT).[1] Although its exact mechanism of action is unclear, both *in vitro* and *in vivo* studies have shown that netarsudil lowers IOP by three distinct mechanisms: (1) increased outflow through the trabecular meshwork, (2) decreased episcleral venous pressure, (3) decreased production of aqueous humor.[2–5] While large phase 3 clinical trials have proven its efficacy and well tolerated safety profile, there have been reports of cases of reversible corneal epithelial edema with associated changes in visual acuity in patients treated with netarsudil.[6–13] We present a novel case of induction of significant, bilateral, symmetric, and reversible corneal steepening and myopic shift with netarsudil/latanoprost in a patient with prior radial keratotomy without history of refractive instability secondary to the procedure.

2. Case report

A 72-year-old male with a history of OAG in both eyes (OU), pseudophakic in the right eye (OD) for two years and in the left eye (OS) for six years, status post 16 incision radial keratotomy (RK) OU over 20 years ago and no prior history refractive changes or corneal instability presented to the office with new maximal intraocular pressures (IOP) of 28 mmHg OD and 30 mmHg OS despite compliance with latanoprost. Best corrected visual acuity (BCVA) was 20/20 OD with refractive error of +0.50 + 1.50 axis 165 and 20/30 OS with a refractive error of +1.00 + 2.25 axis 045. On examination, there was no evidence of corneal edema or verticillata. Latanoprost was discontinued and once daily netarsudil/latanoprost was started in both eyes.

One month later, the patient returned with complaints of decreased vision which began within one week of initiating netarsudil/latanoprost. BCVA was 20/30 OD with a refraction of −1.00 + 1.50 axis 155 and 20/25 OS with a refraction of −0.50 + 2.25 axis 045. IOP taken during this visit was 18 mmHg OD and 20 mmHg OS. Corneal topography with Zeiss Atlas topographer revealed changes in corneal contour in both eyes, compared to values obtained 25 months prior to starting netarsudil/

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latanoprost for intraocular lens calculation. In the right eye, 1 mm ring value changed from 33.63 D to 35.03 D and SimK changed from 36.72 D to 37.41 D (Fig. 1a and b). In the left eye, 1 mm ring value changed from 31.53 D to 32.54D and SimK changed from 36.23 D to 36.87 D (Fig. 2a and b). Both topographies showed characteristic changes consistent with prior RK. It should be noted that these sets of corneal topographies were both performed at the same time of day, at around 0900. On examination, there was no evidence of corneal edema or verticillata. Other pertinent examination findings included normal conjunctiva and sclera, no abnormalities of the anterior chamber, and pseudophakia. Given his acute change in refractive error with corresponding change in corneal topography, netarsudil/latanoprost was discontinued OU and replaced with timolol.

Four weeks following discontinuation of netarsudil/latanoprost, spherical refractive error and corneal contour returned to prior values. BCVA was 20/25 OD with refractive error of +0.50 + 1.00 axis 010 and 20/25 OS with refractive error of +0.75 + 2.00 axis 025. Interestingly, corneal topography values reverted to values close to those obtained 25 months prior to starting netarsudil/latanoprost. These measurements were taken in the morning at around 0800. In the right eye, 1 mm ring value was 33.13 and SimK was 36.65 (Fig. 1c). In the left eye, 1 mm ring value was 30.51 and SimK was 35.15 (Fib. 2c). IOP taken at the same visit remained relatively well-controlled on timolol at 16 mmHg OD and 23 mmHg OS. Eight months following discontinuation of netarsudil/latanoprost, refractive error did not undergo further myopic shifts and remained relatively stable at +0.50 + 1.00 axis 010 OD and +1.00 + 2.00 axis 030 OS. IOP at that time also remained well-controlled at 13 mmHg OU. Table 1 summarizes the patient's IOP and refractive error recorded at all visits to our practice.

3. Discussion

We report a case of a patient with a prior history of OAG, cataract surgery, and RK surgery over 20 years ago. The patient has never reported diurnal visual fluctuations in the decades since undergoing the procedure and in the five years since he came to our practice, his refractive error did not undergo significant changes prior to starting netarsudil/latanoprost. However, he presented with a 1.50 D myopic shift and corresponding steepening of corneal contour in both eyes shortly after initiating netarsudil/latanoprost. The change in refractive error in each eye correlated to changes in corneal power based both on the 1mm ring value and the SimK. At his one month visit after the drug's discontinuation, corneal topographical values and manifest sphere reverted to baseline. While visual acuity in his right eye did not revert completely at that visit, it did improve to within 1 Snellen line at 20/25. In the months following discontinuation of netarsudil/latanoprost, the patient did not experience further myopic shifts and spherical refractive error remained at his slightly hyperopic baseline.

During phase 3 clinical trials of the efficacy and safety of netarsudil in lowering IOP in patients with OAG or OHT, conjunctival hyperemia, cornea verticillata, and conjunctival hemorrhage were the most commonly reported adverse effects.[14–21] Most of these cases were rated as mild, had no impact on visual acuity, and resolved with discontinuation of the drug.[15,16,19] Cornea verticillata was only detectable via biomicroscopy and had no clinically meaningful impact on vision.[15] However, notable exclusion criteria for all of these studies included history of prior surgery for glaucoma or refractive error and prior history of significant ocular disease, including corneal edema and corneal endothelial dysfunction.[14–21] These exclusion criteria may explain the relative lack of clinically significant adverse corneal or visual effects in these trials.

Several case reports and case series have reported bullous reticular corneal epithelial edema with netarsudil use.[6,8–11,13] Many of these cases were associated with involvement of the visual axis and consequential worsening of VA. Both corneal epithelial edema and VA improved with discontinuation of netarsudil in these cases.[6,8,9,11] Prior history of corneal edema, risk factors for corneal edema, and pre-existing endothelial dysfunction appear to be risk factors for the development of epithelial edema associated with netarsudil use. While the mechanism is unclear, one hypothesis proposed that epithelial edema is the consequence of the effects of ROCK inhibition on cell migration, maturation, and adhesion.[6] In contrast, there was no evidence of corneal edema, bullae, or reticular changes or verticillata in our patient but rather a change in corneal contour as observed on topography. In addition, he had no history of underlying corneal endothelial dysfunction, nor did he have other risk factors for corneal edema such as anterior uveitis, angle-closure glaucoma, ocular trauma, or retinal surgery.

One case also reported reversible corneal endothelial anomalies on biomicroscopy in a patient started on the netarsudil/latanoprost.[7] In 3-month imaging studies of subsets of patients enrolled in the ROCKET-2 and MERCURY-2 phase 3 trials, there were no significant changes in corneal endothelial morphology or cell density between treatment groups.[17,21] However, it should again be noted that these trials excluded patients with prior ocular surgery or significant corneal disease.

Surgical histories in patients previously reported to develop corneal epithelial edema with netarsudil included uncomplicated cataract surgery, trabeculotomy, trabeculectomy, glaucoma drain implantation, vitrectomy, and various corneal procedures, including penetrating keratoplasty, Descemet's stripping endothelial keratoplasty (DSEK), and Descemet's membrane endothelial keratoplasty (DMEK).[6] However, we are not aware of any reports of complications related to netarsudil use in patients with prior RK or other refractive surgery, as in our patient.

Radial keratotomy is an incisional refractive surgery largely replaced by excimer laser ablation by the late 1990s. It treats myopia by flattening the cornea with the creation of radial incisions. A prospective 10-year postoperative follow-up of patients who underwent RK demonstrated the potential for long-term instability of the procedure.[22] 43% of patients developed a hyperopic shift of +1.00 D or greater between 6 months and 10 years of follow-up.[22] Diurnal fluctuations in corneal contour have also been well documented as a complication of RK. These changes are typically myopic shifts of about 0.5 D, although hyperopic

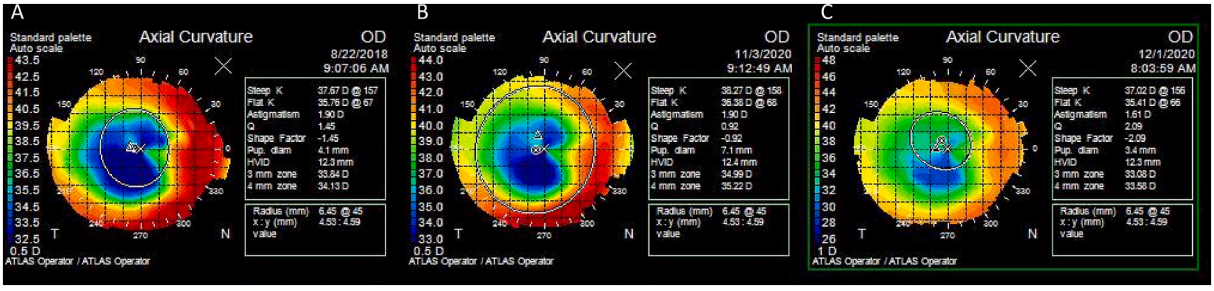

Fig. 1. Corneal topography in the right eye measured using a Zeiss Atlas topographer, 25 months prior to starting netarsudil/latanoprost (A), 1 month after starting netarsudil/latanoprost (B), and 1 month after discontinuing netarsudil/latanoprost (C).

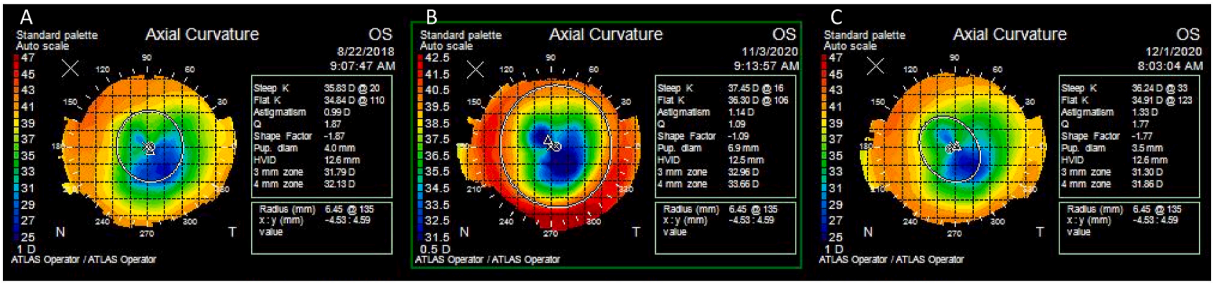

Fig. 2. Corneal topography in the left eye measured using a Zeiss Atlas topographer, 25 months prior to starting netarsudil/latanoprost (A), 1 month after starting netarsudil/latanoprost (B), and 1 month after discontinuing netarsudil/latanoprost (C).

Table 1
Timeline summarizing IOP and refractive error recorded at all visits.

Date	IOP OD	IOP OS	Rx OD	Rx OS
7/9/2014[a]				
7/15/2015	31	24		+ 0.50 + 2.75 axis 065
10/26/2018[b]	18	23	+ 0.75 + 1.75 axis 145	+ 0.75 + 2.50 axis 035
1/29/2019	12	21		
5/28/2019	12	18		
10/1/2019	21	20	+ 0.50 + 1.75 axis 160	+ 0.75 + 2.50 axis 050
2/4/2020	16	16		
6/2/2020	18	17		
10/6/2020[c]	28	30	+ 0.50 + 1.50 axis 165	+ 1.00 + 2.25 axis 045
11/3/2020[d]	18	20	−1.00 + 1.50 axis 155	−0.50 + 2.25 axis 045
12/1/2020	16	23	+ 0.50 + 1.00 axis 010	+ 0.75 + 2.00 axis 025
4/12/2021	13	13		
8/18/2021	13	13	+ 0.50 + 1.00 axis 010	+ 1.00 + 2.00 axis 030
12/14/2021	14	14		

[a] Cataract surgery OS.
[b] Post-operative visit following cataract surgery OD.
[c] Discontinuation of latanoprost and initiation of netarsudil/latanoprost.
[d] Discontinuation of netarsudil/latanoprost and initiation of timolol.

shift can be seen.[23] However, our patient had no history of long-term refractive shift or significant diurnal changes in the two decades since undergoing RK. Shortly after initiating netarsudil/latanoprost, our patient developed significant and symmetric changes in refractive error of 1.50 D in the myopic direction, which was not diurnal in nature, as evidenced from patient history and the fact that pre- and post-netarsudil/latanoprost corneal topographies were measured at the same time of day. Bilateral and symmetric involvement and the rapid reversible onset of topographical changes responsive to initiation and discontinuation of netarsudil suggests that the drug may have played a role in inducing onset of corneal contour changes related to RK.

Mechanism of diurnal fluctuations in corneal power after RK are thought to be related to changes in corneal hydration, corneal instability, and tension from extraocular and orbicularis muscles.[23] However, the role played by netarsudil in the induction of these corneal changes is unclear. It is known that the RhoA/ROCK pathway regulates the assembly and organization of actomyosin filaments required for corneal stromal keratocyte differentiation into fibroblasts and myofibroblasts following corneal injury.[24] It may be speculated that the change in corneal contour observed in our patient is related to the effect of ROCK inhibition on myofibroblast contractility in the context of previous corneal injury secondary to RK. However, processes involving structural changes in the stroma were considered less likely given the rapid and reversible contour changes. Another possible mechanism considered was alteration of corneal endothelial function. It was previously shown that ROCK inhibition may inhibit loss of adhesion between corneal endothelial cells *in vitro*.[25] There was also a recent pilot study demonstrating significant reduction of corneal thickness in patients with Fuchs' endothelial dystrophy treated with topical netarsudil versus placebo.[26] The proposed mechanism for this finding was improved barrier function of the corneal endothelium with ROCK inhibition, leading to reduction in corneal edema. However, a change in central corneal thickness, especially to the small absolute degree that was found in that study, should not significantly affect corneal topography or refraction.

One study reported a relationship between diurnal changes in IOP and diurnal changes in refractive error in eyes that underwent RK surgery.[23] Regression analysis showed a statistically significant, albeit weak, association between decrease in IOP and decrease in manifest spherical equivalent.[23] The authors suggested that decreased IOP may contribute to diurnal myopic changes after RK by causing peripheral corneal flattening and central steepening. Thus, it may be suspected in our case that the significant decrease in IOP following initiation of netarsudil/latanoprost may explain the initial steepening of the cornea in both eyes. However, reduction or change in IOP does not explain the topographical return to prior 1mm ring and SimK values after discontinuation of netarsudil/latanoprost and initiation of timolol, as IOP in both eyes while on netarsudil/latanoprost therapy were similar to values taken while on timolol therapy (18 vs 16 mmHg OD; 20 vs 23 mmHg OS, respectively). Furthermore, refractive error has continued to remain stable despite even lower IOP measurements taken eight months later (13 mmHg OU). It should be noted that Kemp and coauthors did not find a significant association between IOP changes and SimK values or IOP changes and average corneal power.[23] To our knowledge, no study has detected a significant relationship between IOP fluctuations and measurements of corneal curvature in RK eyes *in vivo*.[23,27,28]

Interestingly, unlike sphere, values for cylinder and axis in both eyes were stable after initiation of netarsudil/latanoprost but changed following its discontinuation and replacement with timolol. These changes were also not symmetric between eyes. In the right eye, cylinder changed from +1.50 D to +1.00 and axis changed from 155 to 010. In the left, cylinder changed from +2.25 D to +2.00 D and axis changed from 045 to 025. These changes in axis persisted eight months later at 010 OD and 030 OS. The reason for this observation is unclear. Currently there are no reports of changes in astigmatism induced by ROCK inhibitors, PGAs, or beta blockers in unoperated eyes or those that have undergone refractive surgery. While eyes that have undergone RK surgery may develop irregular astigmatism, a mechanism to explain the timing of cylinder and axis changes along with alterations in OAG therapy is unclear.

Lastly, to our knowledge, prostaglandin analogs (PGAs) have not been reported to affect corneal curvature. One study found no statistically significant difference in corneal curvature as measured by partial coherence interferometry between normal eyes, OAG eyes naïve to PGA treatment, and OAG eyes treated with a PGA for at least two years.[29] In addition, given that corneal topographical changes arose in our patient

after switching from latanoprost to netarsudil/latanoprost, it is unlikely that the PGA component played a causal role.

In conclusion, we report the case of a patient who previously underwent radial keratotomy presenting with myopic changes in corneal contour and power after initiation of netarsudil/latanoprost, which reversed rapidly after its discontinuation. To our knowledge, alteration of corneal topography or other adverse effects associated with use of netarsudil in those with prior refractive surgery have not yet been described. Those who have undergone RK are now older and at higher risk of developing open angle glaucoma. The treating ophthalmologist should be aware of the potential risk of inducing corneal steepening or other refractive change in patients with a history of RK with netarsudil.

Patient Consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors have no financial disclosures.

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