American Journal of Ophthalmology Case Reports 25 (2022) 101287

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Netarsudil-associated reticular corneal epithelial edema

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ARTICLE INFO

Keywords:
Netarsudil
Rhopressa
Reticular edema
Honeycomb edema
Corneal edema

ABSTRACT

Purpose: To describe 8 cases of reversible reticular corneal epithelial edema of the cornea that developed after use of the topical Rho-kinase inhibitor netarsudil.
Methods: This is a retrospective chart review case series of 8 patients treated with netarsudil at an academic medical center.
Observations: Patients had predisposing corneal conditions including penetrating keratoplasty, corneal decompensation after trabeculectomy-associated endophthalmitis, congenital glaucoma with Haab striae, aphakic bullous keratopathy, history of Ahmed valve and silicone oil, and Fuchs endothelial corneal dystrophy undergoing Descemet stripping only. One patient did not have clear predisposing corneal disease other than low endothelial cell density and a history of trabeculectomy. All patients developed reticular corneal epithelial edema, which appeared as collections of moderate sized superficial epithelial bullae arranged in a reticular pattern resembling a honeycomb. Most developed these changes within weeks of initiating netarsudil, but unique to this series are 2 cases in which netarsudil was tolerated by the cornea for months before developing reticular corneal epithelial edema after diode laser cyclophotocoagulation. In cases which underwent anterior segment optical coherence tomography, the imaging demonstrated that the corneal stroma was not edematous, and the reticular corneal epithelial edema involved both host and donor corneal epithelium in cases of penetrating keratoplasty. This fully resolved in all cases upon cessation of netarsudil, and this series is the first to document resolution via a pattern in which the individual bullae become smaller and more widely spaced apart.
Conclusion: Netarsudil can cause a reversible reticular corneal epithelial edema.

1. Introduction

Netarsudil (Rhopressa; Aerie Pharmaceuticals, Durham, NC) is a Rho-kinase inhibitor that was approved by the U.S. Food and Drug Administration in 2017 for reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Although the most common documented side effect is conjunctival hyperemia that develops in over half of patients, visually insignificant corneal verticillata has also been reported in up to 26% of patients.[1,2] Rho-kinase inhibitors have found use in treating corneal edema, possibly by enhancing function of corneal endothelial cells or encouraging their migration and/or proliferation.[3,4] Conversely, ophthalmologists have reported several cases of worsening reticular corneal epithelial edema associated with netarsudil use in eyes with predisposing risk factors or prior surgeries that include corneal endothelial keratoplasty, penetrating keratoplasty, Fuchs endothelial corneal dystrophy (FECD) undergoing Descemetorhexis without endothelial keratoplasty (DWEK)/Descemet stripping only (DSO), Descemet stripping endothelial keratoplasty, uveitis, pseudophakic bullous keratopathy, glaucoma tube shunt, and trabeculectomy.[5–14] Most of these cases were described as corneal epithelial reticular honeycomb edema changes that completely resolved with cessation of netarsudil. Guttata-like endothelial changes with polymegathism and indistinct borders on specular microscopy have also been described,[15] but other studies have not found significant changes in endothelial cell metrics.[16]

In this case series, we present 8 patients who developed reticular corneal epithelial edema. To the best of our knowledge, this is the largest series of patients with netarsudil-related reticular corneal epithelial edema, a phenomenon that has been described in under 25 cases in the literature. Our series is unique in that it includes two cases with

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https://doi.org/10.1016/j.ajoc.2022.101287
Received 11 March 2021; Received in revised form 17 September 2021; Accepted 16 January 2022
Available online 20 January 2022

photographic documentation of the changes in corneal appearance as the edema is resolving, two cases in which netarsudil was well tolerated for months but then was associated with reticular corneal epithelial edema on the first post-operative day after diode laser cyclophotocoagulation (CPC), and a case in which anterior segment optical coherence tomography (AS-OCT) imaging demonstrated that reticular corneal epithelial edema can affect both host and donor cornea simultaneously in eyes with a history of penetrating keratoplasty.

2. Subjects and methods

This case series includes 8 patients managed at an academic medical center who developed reticular corneal epithelial edema following initiation of netarsudil. Slit lamp photography, AS-OCT, and clinical notes were reviewed.

3. Findings

3.1. Case 1

A 32-year-old Caucasian male with a history of left eye open globe repair at age 19 years, penetrating keratoplasty and aphakia at age 21, and trauma-related glaucoma presented with left eye visual acuity (VA) of 20/200 with pinhole improvement to 20/40, IOP of 14 mm Hg on timolol, latanoprost, and loteprednol etabonate 0.2% (Alrex, Bausch and Lomb, Bridgewater, NJ) twice per day. There was corneal graft endothelial cell attrition and ectasia, with uncountable endothelial cells on specular microscopy, central corneal thickness (CCT) 567 μm, and maximum corneal power of curvature 67 diopters. The patient elected to replace latanoprost with netarsudil because of concerns regarding periocular hyperpigmentation.

The patient returned three months later with VA of 20/150 with pinhole improvement to 20/30, IOP of 20 mm Hg, CCT of 598 μm, and mild fine microcystic edema inferiorly and temporally. The patient did not return for another 15 months, at which time he had decreased VA now measured at 20/500, with no pinhole improvement. IOP was 25 mm Hg, CCT was 643 μm, and examination showed diffuse reticular corneal epithelial edema, greatest inferiorly and temporally (Fig. 1, row 1). Netarsudil was discontinued, and timolol was switched to timolol/dorzolamide. One week later, VA was 20/300, IOP was 24 mm Hg, CCT was 607 μm, and the bullae appeared smaller and more widely spaced. All bullae decreased in size throughout the cornea at approximately the

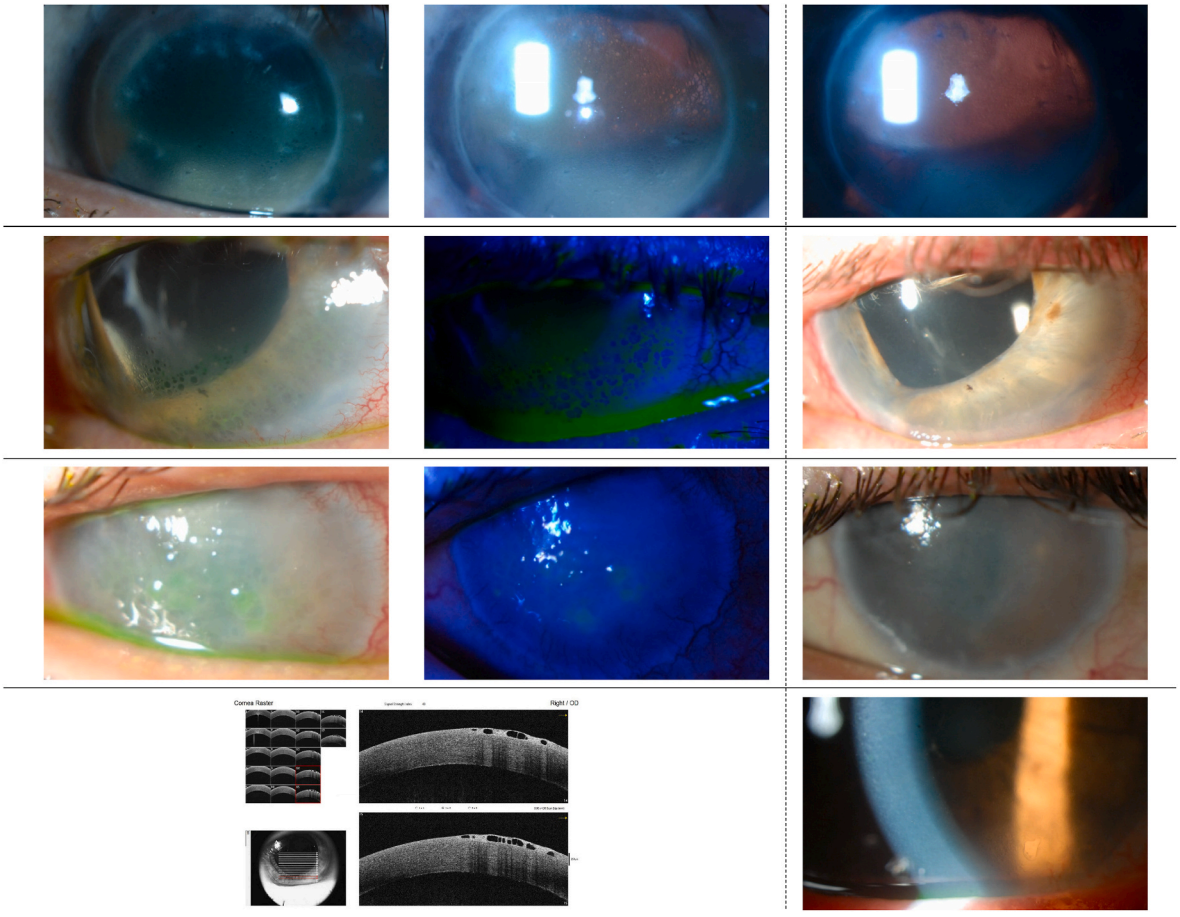

Fig. 1. Row 1: Slit lamp photographs under diffuse illumination (left) and retroillumination (middle) of reticular corneal epithelial edema in the right eye of the patient in case 1, 16 months after starting netarsudil. One week after stopping netarsudil, the bullae had begun to appear smaller and more widely spaced apart (right).
Fig. 1, row 2: Slit lamp photographs under diffuse illumination (left) and cobalt blue light (middle) of reticular corneal epithelial edema in the right eye of the patient in case 2, 6 months after starting netarsudil and 1 day after diode laser cyclophotocoagulation. One week after stopping netarsudil, the bullae had nearly completely resolved (right).
Fig. 1, row 3: Slit lamp photographs under diffuse illumination (left) and cobalt blue light (middle) of reticular corneal epithelial edema in the left eye of the patient in case 3, 2 months after starting netarsudil. Two months after stopping netarsudil, the bullae had nearly completely resolved (right).
Fig. 1, row 4: Anterior segment optical coherence tomography (left) demonstrates superficial epithelial edema in the right eye of the patient in case 4, following 6 months of netarsudil treatment. Slit lamp photograph (right) shows near resolution of the corneal edema, 1 week after stopping netarsudil. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

same rate, without preferential faster clearance centrally, peripherally, or inferiorly. The reticular corneal epithelial edema completely resolved after 2 more months.

3.2. Case 2

A 64-year-old Caucasian male with a history of mixed-mechanism (congenital and uveitic) glaucoma of both eyes was seen for routine follow-up. The right eye had a history of combined cataract surgery and trabeculectomy, inferior Ahmed tube shunt that was subsequently explanted due to erosion, and a second trabeculectomy. VA was 20/40 and IOP was 21 mm Hg in the right eye, which was buphthalmic, had Haab striae, and had iris-cornea touch inferiorly and superiorly. Ophthalmic medications included netarsudil, latanoprost, brimonidine/timolol, and dorzolamide in both eyes and acetazolamide 500mg twice daily. Two months later, right eye VA was 20/30, but IOP had risen to 42 mm Hg. The patient underwent diode laser CPC in the right eye the next day. The laser was initially set at 1750 mW (mW) and was ultimately increased to 2350 mW over the course of 17 applications lasting 2000 milliseconds each, sparing the nasal quadrant. On post-operative day 1, right eye VA was 20/30, and IOP was 33 mm Hg. The exam was notable for 1+ anterior chamber cell and no flare. New inferior nasal reticular corneal epithelial edema was noted (Fig. 1, row 2), and netarsudil was stopped in the right eye, 6 months after it had been initiated. At post-operative day 8, right eye VA was 20/30, IOP was 13 mm Hg, and the reticular corneal epithelial edema was nearly completely resolved, with only trace residual edema inferiorly. At most recent follow-up, VA was 20/40, IOP was 9 mm Hg, and the cornea remained without edema off netarsudil.

3.3. Case 3

A 57-year-old legally-blind Caucasian male with a history of Marfan disease status post bilateral lens extraction, left eye aphakic glaucoma status post trabeculectomy and bleb revision for leak, and left eye aphakic bullous keratopathy presented with VA of hand motion and IOP of 19 mm Hg. Medications in the left eye included latanoprost, dorzolamide/timolol, and brimonidine. Netarsudil was started in the left eye. Two months later, the patient presented with VA of light perception, IOP of 15 mm Hg, and diffuse reticular corneal epithelial edema (Fig. 1, row 3). Netarsudil was stopped, and the patient returned two months later, at which point the edema had resolved. VA was hand motion, and IOP was 35 mm Hg. The patient decided to pursue comfort care.

3.4. Case 4

This case from our institution has previously been published.[6] We present additional photographic documentation and AS-OCT (Fig. 1, row 4). A 68-year-old Caucasian male with severe stage primary open-angle glaucoma in both eyes, bilateral cataract surgery, right eye Trabectome (MicroSurgical Technology, Redmond, WA), and bilateral trabeculectomies was started on a unilateral trial of netarsudil in the right eye. VA was 20/40, and IOP was 21 mm Hg. At follow-up 3 weeks later, the right eye IOP had improved to 15 mmHg, the cornea remained clear, and the left eye was also started on netarsudil due to IOP of 20 mm Hg, which was above target. Six months after starting netarsudil in the right eye, it was found to have inferior nasal reticular corneal edema. VA worsened to 20/500, and IOP was 28 mm Hg. One week after stopping netarsudil, the reticular corneal epithelial edema had nearly completely resolved, VA improved to 20/200 with pinhole to 20/70, and IOP was 18 mm Hg. There was no predisposing history of prior corneal edema or damage prior to the development of the reticular corneal epithelial edema, but corneal endothelial cell density was measured to be 1,015 cells/mm^2 in the right eye and 1,258 cells/mm^2 in the left.

3.5. Case 5

A 59-year-old Caucasian female with bilateral congenital glaucoma presented with right eye VA of hand motion and an IOP of 30 mm Hg while taking prednisolone acetate 1% for prevention of graft rejection after having undergone penetrating keratoplasty 4 months prior due to previous pseudomonal corneal ulcer. The eye was pseudophakic and had a history of trabeculectomy over 30 years prior to presentation, as well as retinal detachment repaired with pars plana vitrectomy and gas 2 years prior to presentation. The eye was started on timolol and brimonidine with improvement in the IOPs to 12–16 mm Hg.

Netarsudil at night was started for better IOP control and potential benefits for corneal endothelial recovery. The patient returned two months later with IOPs of 15–20 mm Hg. Examination revealed reticular corneal epithelial edema involving both host and donor cornea (Fig. 2). The cornea stroma appeared relatively compact throughout, as confirmed by AS-OCT. Netarsudil was discontinued, and the patient continued on timolol and brimonidine. At follow-up two months later, the cornea was clear of the netarsudil-related keratopathy. The patient subsequently underwent micropulse *trans*-scleral CPC and continues to have VA of hand motion, an IOP of 10 mm Hg on timolol and brimonidine, and no recurrence of reticular corneal epithelial edema.

3.6. Case 6

A 66-year-old Hispanic male with a history of severe mixed-mechanism glaucoma of both eyes presented with VA of 20/20 and IOP of 17 mm Hg in the right eye, VA of hand motion and IOP of 28 mm Hg in the left. Prior history included bilateral laser peripheral iridotomy and selective laser trabeculoplasty, pseudophakia of the left eye, mild cataract in the right eye, and left eye trabeculectomy 1 year prior to presentation which was complicated by early post-operative endophthalmitis. Ophthalmic medications included latanoprost in the right eye, dorzolamide and brimonidine in the right eye, netarsudil in the right eye, and prednisolone three times daily in the left eye. The left cornea was diffusely hazy, with fine microcystic edema throughout. Due to elevated IOP, the left eye was started on latanoprost, brimonidine, and netarsudil.

One month later, the left eye was noted to have stable VA of hand motion, IOP of 22 mmHg, and new reticular corneal epithelial edema, with much larger bullae than the previous fine microcystic edema that was present prior to starting netarsudil (Fig. 2, bottom left). Netarsudil was discontinued in the left eye, and the edema had resolved at the next examination one week later. The cornea returned to its prior baseline appearance with diffuse stromal haze and fine microcystic edema. The right eye continues on netarsudil with no appreciable corneal changes on examination, despite having started netarsudil in the right eye 3 months before it was started in the left eye.

3.7. Case 7

A 22-year-old Caucasian female with a history of mixed-mechanism glaucoma of the left eye presented with VA of counting fingers at 3 feet and IOP 25 mmHg. She had a history of lensectomy and aphakia as an infant and coloboma-related proliferative vitreoretinopathy in the setting of rhegmatogenous retinal detachment of the left eye status post scleral buckle, pars plana vitrectomy, silicone oil, and endolaser. IOP was elevated to 44 mmHg in the post-operative period and improved with latanoprost, brinzolamide/brimonidine, and timolol. The patient was started on netarsudil in the left eye and initially tolerated it well.

In the following nine months, she underwent trabeculectomy in that eye, followed by anterior chamber placement of an inferior temporal Ahmed valve with a corneal patch graft. The patient gradually needed to resume glaucoma medications, eventually adding netarsudil again shortly after post-operative month 2 when VA was hand motion and IOP 44 mmHg, with a clear cornea. She subsequently underwent two

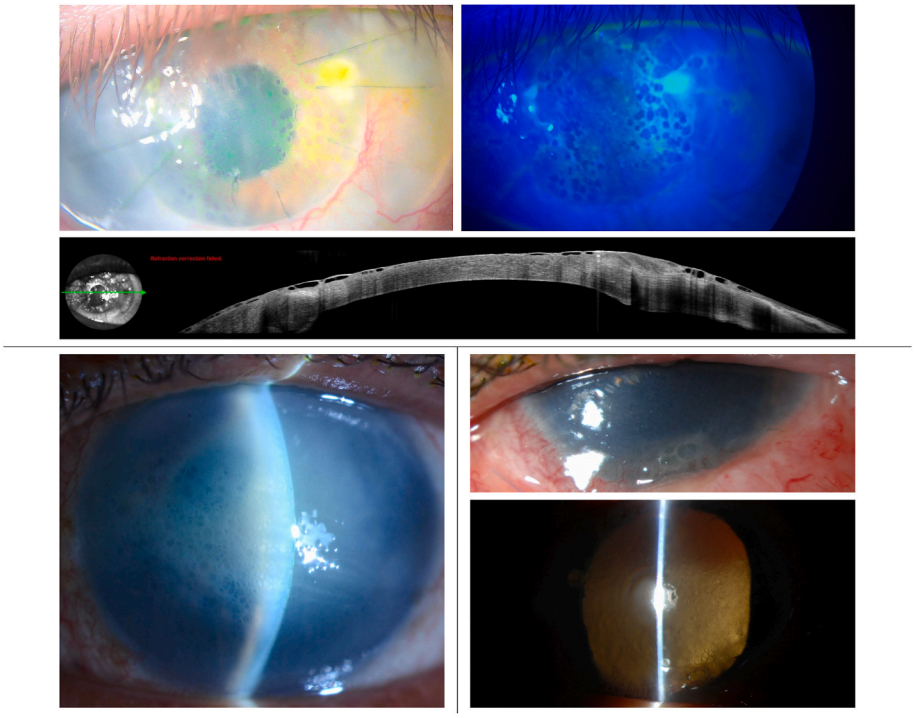

Fig. 2. Top: Slit lamp photographs under diffuse illumination (top left) and cobalt blue light (top right) of reticular corneal epithelial edema in the right eye of the patient in case 5, 3 months after starting netarsudil. Anterior segment optical coherence tomography (row 2) demonstrates superficial epithelial edema in both host and donor cornea.
Fig. 2, bottom left: Slit lamp photograph of reticular corneal epithelial edema in the left eye of the patient in case 6, 1 month after starting netarsudil.
Fig. 2, bottom right: Slit lamp photographs under diffuse illumination (top) and retroillumination (bottom) of reticularcorneal epithelial edema in the left eye of the patient in case 7, one day after combined diode laser cyclophotocoagulation, explant of Ahmed valve, and silicone oil granuloma excision. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

treatments with diode laser CPC nine months apart, initially at 1750–2250 mW for 20 spots of 2000 milliseconds, sparing the inferior temporal quadrant, and then at 1600–1750 mW for 18 spots of 2000 milliseconds, again sparing the inferior temporal quadrant. Concurrently with the second CPC, the Ahmed tube and a large overlying silicone oil granuloma were removed for comfort and cosmesis. She developed new inferior temporal reticular corneal epithelial edema in the left cornea on post-operative day 1 after this combined procedure (Fig. 2, bottom right). No anterior chamber cell was noted. VA was light perception, and IOP was 18 mmHg. Netarsudil was continued per patient preference, and the reticular corneal epithelial edema was stable the next week but resolved one month later.

3.8. Case 8

A 77-year-old Caucasian male with a history of Fuchs endothelial corneal dystrophy of both eyes presented with VA of 20/60 and IOP 18 mmHg in the left eye. He underwent DSO in the left eye. On post-operative day one, he had central cornea stromal edema and Descemet folds but no reticular corneal epithelial edema (Fig. 3, top). He was prescribed netarsudil daily for the left eye but was unable to obtain it until post-operative day 5. He returned on post-operative day 7, having taken netarsudil for 3 days, and was found to have reticular corneal epithelial edema (Fig. 3, middle). VA was 20/125 and IOP was 23 mmHg. Over 3 more visits, the epithelial bullae decreased in size and became more widely spaced apart, with the central bullae resolving slightly more quickly than the paracentral areas (Fig. 3, bottom). At post-operative week 7, the reticular corneal epithelial edema had completely resolved, VA improved to 20/25, and netarsudil was discontinued.

4. Discussion

This case series is the largest to detail the reticular corneal epithelial edema phenomenon to date and the first to provide photographic evidence that it resolves over time via a pattern in which the individual bullae become smaller and more widely spaced apart, as seen in cases 1 and 8. Cases 2 and 7 also demonstrate a previously unreported phenomenon in which a cornea tolerated netarsudil for months, but then developed reticular corneal epithelial edema immediately after diode laser CPC. We also document the appearance of reticular corneal epithelial edema as superficial epithelial bullae with AS-OCT in both the host and donor cornea in an eye with penetrating keratoplasty, as seen in case 5.

As in previous reports of reticular corneal epithelial edema, there are patients in this case series who had predisposing risk factors, namely history of corneal transplant, corneal edema and decompensation after endophthalmitis, congenital glaucoma with Haab striae, tube shunt, aphakic bullous keratopathy, and corneal edema after DSO. Case 4 lacked any clear predisposing risk factors, but corneal endothelial cell count was later found to be low.

As described in other case reports, this reticular corneal epithelial edema was reversible and completely resolved following discontinuation of netarsudil. Reticular corneal epithelial edema also resolved despite continuing netarsudil in cases 7 and 8. Interestingly, case 6 had a history of long-term well-tolerated netarsudil usage in the right eye but soon exhibited corneal changes after starting it in his left eye. This asymmetric response has been previously described.[9] The patient's existing corneal edema of the left eye likely predisposed him to netarsudil-related corneal insult, while the relatively healthy right cornea remained tolerant of netarsudil.

Cases 2 and 7 demonstrated new intolerance to netarsudil shortly after undergoing diode laser CPC, a change that was perhaps secondary to post-surgical inflammatory reactions. This would support the idea that inflammation increases the risk of developing reticular corneal epithelial edema, as was suggested in a previous case series describing patients with a history of anterior uveitis.[11] Curiously, case 7 immediately developed reticular corneal epithelial edema only after her second procedure at decreased laser power, and it ultimately resolved after one month despite continuation of netarsudil, which had been previous tolerated for almost 2 years. We hypothesize that her risks for developing these corneal changes were compounded by two laser procedures, as well as the added stress of Ahmed valve explantation and silicone oil granuloma excision. Additionally, the resolution of these findings could be attributed to more robust healing capabilities at a young age. Nevertheless, further research is required to elucidate these

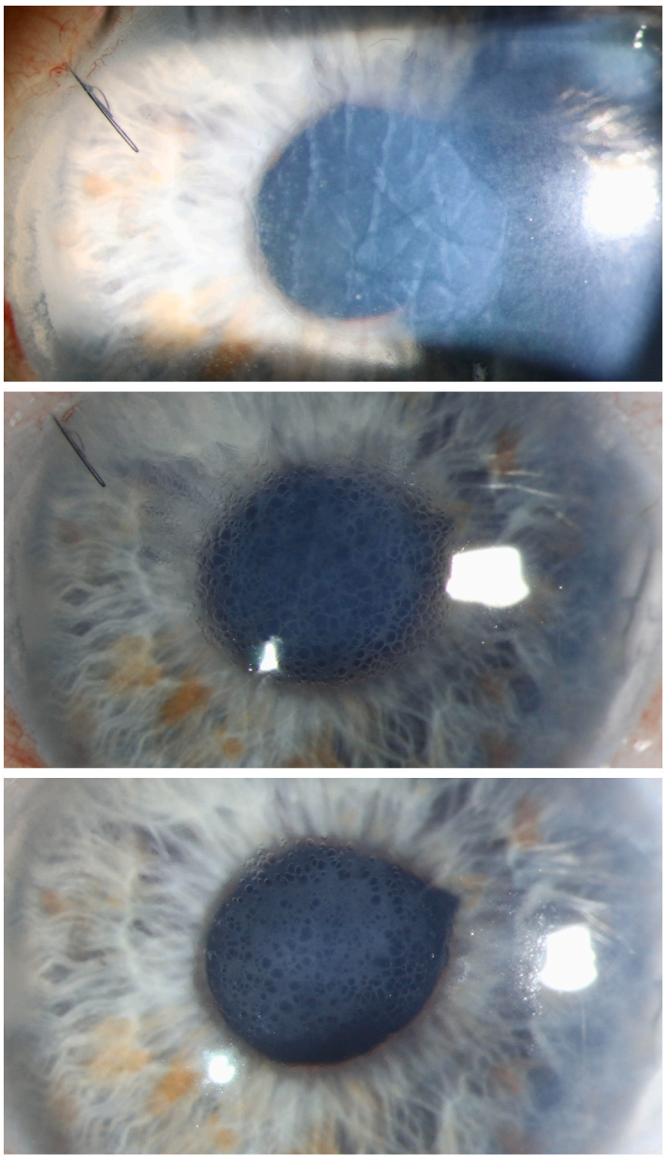

Fig. 3. Slit lamp photographs under diffuse illumination of the cornea in the left eye of the patient in case 8. One day after Descemet stripping only (DSO) and before starting netarsudil, Descemet folds were present without reticular corneal epithelial edema (top). One week after DSO and three days after starting netarsudil, reticular corneal epithelial edema developed (middle). One month after DSO, the bullae became smaller and more widely spaced apart (bottom).

observations in patients who undergo diode laser CPC.

It is important to appreciate that cornea edema can be the result of many etiologies, such as Fuchs dystrophy, elevated IOP, trauma, and scleral lenses, among others. Nevertheless, it is reasonable to consider the role that netarsudil played in the development of the observed reticular honeycomb changes of the cornea given the timeline of these developments following the initiation of this agent. In several cases, reticular corneal epithelial edema preferentially impacted the inferior cornea rather than being evenly distributed. A possible explanation is that this is secondary to pooling of the medication after the administration of drops. Furthermore, it is interesting to note the varying timeframes of reticular corneal epithelial edema development and resolution; some eyes such as case 2 and case 7 in this series seem to tolerate netarsudil for 6 or more months before onset of reticular corneal epithelial edema after an inciting factor such as CPC, while the majority develop reticular corneal epithelial edema within weeks of starting netarsudil.[5–14] Improvement has been described to occur within one week to three months.[11] Cases 1 and 8 in this series suggest that reticular corneal epithelial edema resolves via all bullae becoming smaller and more widely spaced apart. Case 1 showed uniform clearance of bullae throughout the cornea, while case 8 had faster clearance centrally and midperipherally than paracentrally, though this may be a pattern specific to DSO. It is important to note that these conclusions are limited by the timing of patients' scheduled follow-up appointments.

The etiology for reticular corneal epithelial edema could partially be explained by the fact that Rho-kinase inhibitors may modify corneal endothelial cell (CEC) structure, though there is less information about Rho-kinase inhibitor impact on CEC function. Animal studies involving the Rho-kinase inhibitor ripasudil have demonstrated temporary morphologic changes to CECs, hypothesized to be due to decreased CEC actomyosin contractility via the inhibition of focal adhesions and actin stress fiber formation, both key to the structural integrity of cells.[17,18] A prospective study in humans similarly showed transient ripasudil-related morphological changes that were characterized by indistinct cell borders and pseudo guttae, without evidence of CEC loss.[19] Wisely et al. also described mild morphological CEC changes in humans following three months of therapy with either netarsudil alone or fixed combination netarsudil/latanoprost when compared to latanoprost alone.[16] These changes in CEC density, coefficient of variation, and percentage of hexagonal cells were deemed clinically insignificant and resolved upon discontinuation in most subjects. However, patients who had significant corneal disease were excluded from the study, and therefore the impact of netarsudil on this at-risk patient population has yet to be elucidated.

The previously reported cornea endothelial structural changes do not clearly explain the more superficial cornea epithelial changes seen in netarsudil-associated reticular corneal epithelial edema. Rho-kinase inhibitors are known to disrupt tight junction barriers and actin cytoskeleton organization of the corneal epithelium, and perhaps this allows the development of bullae, but the mechanism by which netarsudil results in reticular corneal epithelial edema remains largely unclear.[20]

It is worth noting that even though reticular corneal epithelial edema can have deleterious effects on the cornea and vision, netarsudil has been reported to aid in corneal clearance after DWEK/DSO in FECD, iridocorneal endothelial syndrome, and penetrating keratoplasty graft failure.[4,11,21] Furthermore, related Rho-kinase inhibitors have longer track records of research supporting their role as therapy for CEC dysfunction in FECD by promoting CEC adhesion and proliferation.[22–25]

Another interesting finding in this study and some other reports of reticular corneal epithelial edema is a paradoxical lowering of IOP after cessation of netarsudil. Similar paradoxical IOP response has been reported with increase in IOP in response to brimonidine, with subsequent IOP lowering after stopping brimonidine.[25] The mechanisms for higher IOP in the setting of these medications are unclear but could include elevation of episcleral venous pressure in the setting of conjunctival congestion, subclinical trabeculitis, or paradoxically increased production of aqueous humor. In addition, the presence of reticular corneal epithelial edema may make it challenging to measure IOP accurately, leading to falsely elevated IOP readings in its presence and more accurate lower IOP readings once the edema has resolved.

The exact mechanisms by which netarsudil exerts its differential effects on the anterior segment remain elusive, highlighting the need for further research and patient monitoring. Physicians should be aware of netarsudil-induced keratopathies, especially when treating patients with pre-existing corneal pathologies, because these changes seem to be largely reversible with medication cessation.

Author contributions

JAT was responsible for reviewing medical records and writing the manuscript. UVJ, JY, ECD, DAS, and TCC contributed cases and provided feedback on the manuscript. MML contributed cases and was

responsible for reviewing medical records and writing the manuscript.

Patient consent

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

Funding

No funding or grant support.

Declaration of competing interest

No conflicting relationship exists for any author.

Acknowledgements

None.

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