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A Patient With Glaucoma With Corneal Edema

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A Slitlamp photograph

B Spectral-domain optical coherence tomography

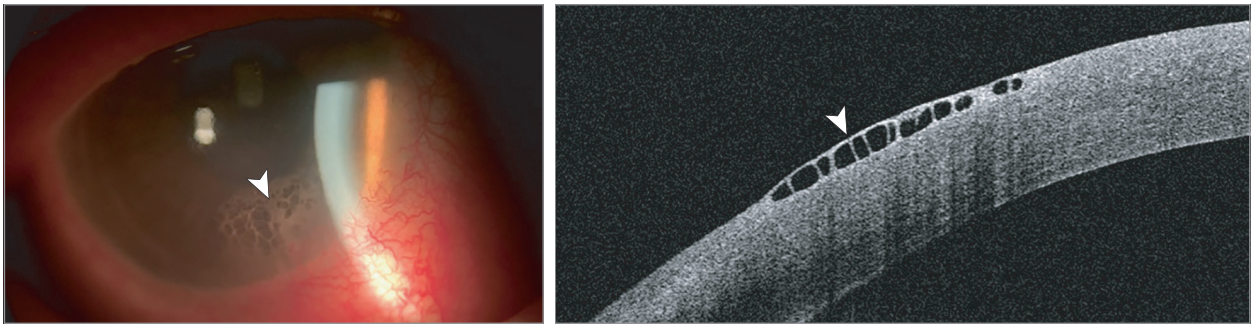

Figure 1. A, Netarsudil-associated reticular epithelial edema was most marked inferior nasally in the right eye (white arrowhead), although diffuse microcystoid epithelial and stromal edema were present in both eyes. B, Anterior segment spectral-domain optical coherence tomography (RTVue; Optovue) of the corresponding inferior nasal cornea in the right eye (white arrowhead).

A white man in his 60s with open-angle glaucoma presented with a 1-month history of pain and irritation in the right eye. Prior surgeries included cataract surgery in both eyes, selective laser trabeculoplasty in both eyes, trabectome in the right eye (NeoMedix), and mitomycin trabeculectomies in both eyes. On presentation, his visual acuity was 20/50 OD and 20/200 OS with correction (1 line worse from baseline in the right eye). Pressures were 18 mm Hg OU. Medications included latanoprost in both eyes once daily, dorzolamide-timolol in the right eye twice daily, and brimonidine in the right eye once daily without complications until a few months prior to presentation when netarsudil in both eyes once a day was added for high intraocular pressures of 21 mm Hg OD and 17 mm Hg OS. Netarsudil was used in both eyes after a monocular trial of netarsudil in the right eye, which was judged successful owing to a 9–mm Hg pressure reduction in the right eye relative to the left eye. Slitlamp examination revealed conjunctival hyperemia and papillae in both eyes. The right cornea had 1.5 mm of inferonasal microcystoid epithelial edema with neovascularization. Cup-disc ratios were 0.8 OD and 0.9 OS. Dorzolamide in the right eye was discontinued. A few weeks later, the patient returned with worsening pain in the right eye, and visual acuity was 20/500 OD and 20/250 OS. There was diffuse microcystoid epithelial and stromal edema in both eyes, worsening reticular changes in the right eye (**Figure 1**), a new inferocentral wavelike superficial opacification in the left eye, and high pressures (28 mm Hg OD and 13 mm Hg OS).

WHAT WOULD YOU DO NEXT?

A. Stop timolol in the right eye

B. Stop latanoprost in both eyes

C. Stop netarsudil in both eyes

D. Resume dorzolamide in the right eye

Diagnosis

Reticular epithelial edema owing to netarsudil (Rhopressa 0.02%; Aerie Pharmaceuticals Inc)

What to Do Next

C. Stop netarsudil in both eyes

Discussion

The leading diagnosis was netarsudil-associated reticular epithelial edema greater in the right eye than left eye. The patient was instructed to stop netarsudil in both eyes (choice C) and brimonidine in the right eye because brimonidine may exacerbate irritation in the right eye. Dorzolamide-induced corneal decompensation in the right eye was in the differential[1]; however, stopping dorzolamide in the right eye was associated with progression of cornea edema from the right to both eyes. Timolol and latanoprost were not stopped (choices A and B) because both do not commonly cause follicular conjunctivitis or corneal edema. Resuming dorzolamide in the right eye (choice D) could exacerbate corneal decompensation.

Netarsudil is a once-daily Rho-associated kinase (ROCK) inhibitor and norepinephrine transport inhibitor that targets the trabecular meshwork and was approved by the US Food and Drug Administration in December 2017 for intraocular pressure reduction. Ocular adverse effects include conjunctival hyperemia (60.6%), verticillata (25.5%), and perilimbal conjunctival hemorrhage (19.5%).[2]

Netarsudil-associated reticular epithelial edema was reported in 2 patients who had Descemet stripping automated endothelial keratoplasty and Descemet membrane endothelial keratoplasty.[3] In those cases, epithelial edema was seen 5 and 11 days, respectively, after starting netarsudil, which was used to treat stromal edema. Rho

kinase may halt corneal endothelial cell progression through the cell cycle, resulting in endothelial cell proliferation, substrate attachment, and apoptosis suppression.[4-7] Some ROCK inhibitors, such as ripasudil and netarsudil, have been used in Descemet stripping only for endothelial wound healing.[6-8]

To our knowledge, reticular epithelial edema has not been associated with a patient with glaucoma who did not have prior lamellar surgery and who is not using netarsudil for cell therapy. Epithelial edema was not reported in ROCKET-2[2] or MERCURY-1[9] as a potential adverse effect. In this patient, epithelial edema in the right eye occurred 6 months after starting a 1-month monocular trial of netarsudil in the right eye. In another epithelial-related adverse effect, ROCKET-2 investigators noted that mean onset of verticillata was 6 months for the once-daily dosing and that verticillata were self-resolving within several months after drug cessation.[2] The ROCKET-2 investigators further suggested that many cationic and amphiphilic drugs, including netarsudil, can induce verticillata via a process called phospholipidosis that results in lysosomal phospholipid accumulation within epithelial cells.[2] Reticular changes may be associated with corneal drug deposits or a resulting by-product.

Reversible corneal edema after netarsudil discontinuation suggests reversible endothelial cell alterations. Rho-kinase signaling activates cellular amoeboid movement and suppresses mesenchymal movement. Therefore, netarsudil may promote cellular transition toward the mesenchymal phenotype, thus stalling endothelial function.[10] Because cellular phenotype is often interconvertible depending on environmental conditions, cells likely switched back to the less mesenchymal mode after drug discontinuation.

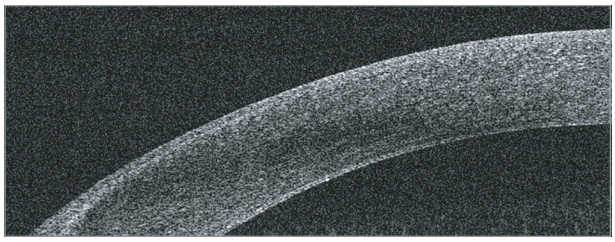

Figure 2. Anterior segment spectral-domain optical coherence tomography of the inferior nasal cornea of the right eye demonstrates complete resolution of netarsudil-associated reticular edema 3 weeks after discontinuation of netarsudil in both eyes.

At the visit netarsudil was discontinued, central corneal thicknesses were 675 µm OD and 594 µm OS (baseline, 599 µm OD and 596 µm OS). Endothelial cell counts were 1015 OD and 1258 OS.

In summary, netarsudil can be associated with reticular epithelial edema, which can be associated with resolution following drug discontinuation. Optical coherence tomography may aid in the diagnosis.

Patient Outcome

Corneas were clear and without edema in both eyes 1 month after netarsudil discontinuation (**Figure 2**). At this point, which was also 3 weeks following trabeculectomy in the right eye, pressures in the right eye were normal (central corneal thicknesses, 631 µm) without glaucoma medications.

ARTICLE INFORMATION

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