American Journal of Ophthalmology Case Reports 27 (2022) 101638

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Two pediatric cases of reticular corneal epithelial edema associated with netarsudil

Maria A. Guzman Aparicio [a,b], Daniel L. Liebman [a], James Chodosh [a,c], Suzanne K. Freitag [a,d], Melanie Kazlas [a,e], Derek D. Mai [a,b], Catherine M. Marando [a,b], Shizuo Mukai [a,f], Annie M. Wu [a,b], Teresa C. Chen [a,b,*]

[a] Harvard Medical School, Department of Ophthalmology, Boston, MA, USA
[b] Massachusetts Eye and Ear, Glaucoma Service, Boston, MA, USA
[c] Massachusetts Eye and Ear, Cornea Service, Boston, MA, USA
[d] Massachusetts Eye and Ear, Ophthalmic Plastic Surgery Service, Boston, MA, USA
[e] Massachusetts Eye and Ear, Pediatric Ophthalmology Service, Boston, MA, USA
[f] Massachusetts Eye and Ear, Retina Service, Boston, MA, USA

ARTICLE INFO

Keywords:
Netarsudil
Rhopressa
Reticular corneal epithelial edema
Pediatric patients

ABSTRACT

Purpose: To report two pediatric cases of reticular corneal epithelial edema associated with the use of netarsudil ophthalmic solution 0.02%.

Observations: In Case 1, a six-year-old male with glaucoma following cataract surgery was treated with netarsudil for thirteen months and developed diffuse reticular corneal epithelial edema on post-operative day one after undergoing transscleral diode cyclophotocoagulation for persistently elevated intraocular pressures. In Case 2, a three-month-old male with bilateral ocular hypertension developed unilateral inferior reticular corneal epithelial edema five weeks after initiation of netarsudil, which had been discontinued in the fellow eye two weeks prior. In both cases, the reticular epithelial edema resolved following cessation of netarsudil.

Conclusions and Importance: Netarsudil-associated reticular corneal epithelial edema can occur in infants and young children.

1. Introduction

The management of elevated intraocular pressure (IOP) in pediatric glaucoma can be challenging, often requiring a combination of medical and surgical treatments tailored to the physiologic needs of younger patients. Rho kinase (ROCK) inhibitors are a novel class of pharmacotherapeutics, which lower IOP by reducing resistance to aqueous humor drainage via the trabecular meshwork by disrupting actin fibers and decreasing smooth muscle contraction and stiffness.[1,2] Netarsudil ophthalmic solution 0.02% (brand name Rhopressa®; Aerie Pharmaceuticals, Inc., Irvine, California) is both a rho kinase inhibitor and a norepinephrine transporter inhibitor, which was approved by the US Food and Drug Administration (FDA) in 2017 for the treatment of ocular hypertension and primary open-angle glaucoma.

Initial clinical trials demonstrated netarsudil to be highly effective at lowering IOP through a combination of mechanisms, including increased aqueous humor drainage, decreased aqueous humor production by the ciliary processes, and lowering of episcleral venous pressure.[3,4] In the ROCKET-1 and ROCKET-2 trials, the most frequently reported adverse effects were generally mild, and included conjunctival injection, conjunctival hemorrhage, corneal verticillata, and discomfort.[4] Following FDA approval, however, cases of netarsudil-induced reticular corneal epithelial edema were reported as an additional side effect in adult patients, with or without pre-existing corneal disease. In contrast to stromal edema (which can be seen post-diode laser) and to microcystic epithelial edema (which occurs after acute rapid elevations of IOP), netarsudil-induced reticular epithelial edema can be more macrocystic or can have a characteristic honeycomb appearance.[5–8] To our knowledge, however, this side effect has yet to be reported in the pediatric population. In this case series, we report two cases of reticular corneal epithelial edema in pediatric patients who were on netarsudil.

* Corresponding author. Massachusetts Eye and Ear Infirmary, Glaucoma Service, 243 Charles Street, Boston, MA, 02114, USA.
E-mail address: teresa_chen@meei.harvard.edu (T.C. Chen).

https://doi.org/10.1016/j.ajoc.2022.101638
Received 2 March 2022; Received in revised form 19 June 2022; Accepted 23 June 2022
Available online 28 June 2022

2. Findings

2.1. Case 1

A monocular six-year-old male with a left eye (OS) history of microphthalmia, iris coloboma, chorioretinal coloboma, and persistent fetal vasculature with resulting secondary glaucoma presented to the Massachusetts Eye and Ear Glaucoma Service for management of persistent elevated IOP OS. He was born prematurely at 29 weeks with a history of congenital right-sided anophthalmia, for which he had sequential hydrogel expanders followed by a dermis fat graft. His surgical history was also notable for pars plana vitrectomy, lensectomy, and stalk resection at two years of age for a subluxated cataract OS. He was started on glaucoma medications within a month of this surgery. However, a few weeks before his fifth birthday, his best corrected visual acuity (VA) was 20/20 OS, with an IOP measured at 25 mmHg by Perkins applanation tonometry while on dorzolamide-timolol twice daily and latanoprost nightly. He was started on netarsudil 0.02% one drop nightly, which lowered his IOP OS to the 15–18 mmHg range. About a year after starting netarsudil 0.02%, his vision was 20/30 with an IOP of 30 mmHg OS. An inferior region of iris-corneal touch was associated with overlying macrocystic edema. Brimonidine 0.2% twice daily was added. Three weeks later, his IOP was 28 mmHg OS, so transscleral cyclophotocoagulation with G-probe diode laser was subsequently performed OS. An exam under anesthesia revealed corneal diameters of 8.5 mm horizontally and 8.25 mm vertically, with central pachymetry of 788 μm OS. Cup-disc ratio was 0.8 OS.

On post-operative day one, his best corrected vision was 20/300 and the IOP was 24 mmHg OS by Goldmann applanation without glaucoma medications. Diffuse reticular corneal epithelial edema was noted (Fig. 1A). As is routine after diode cyclophotocoagulation, he was started on prednisolone acetate 1% four times daily and atropine once daily. He was additionally re-started on all pre-operative eye drops because of a questionable IOP of 44 mmHg by rebound tonometry. On post-operative day seven, the IOP was 12 mmHg with persistent diffuse reticular corneal epithelial edema (Fig. 1B). Netarsudil was discontinued. Prednisolone and atropine were additionally discontinued after one week, as is typical after diode cyclophotocoagulation. At post-operative week six, there was complete resolution of the reticular epithelial edema (Fig. 1C) with normal IOP.

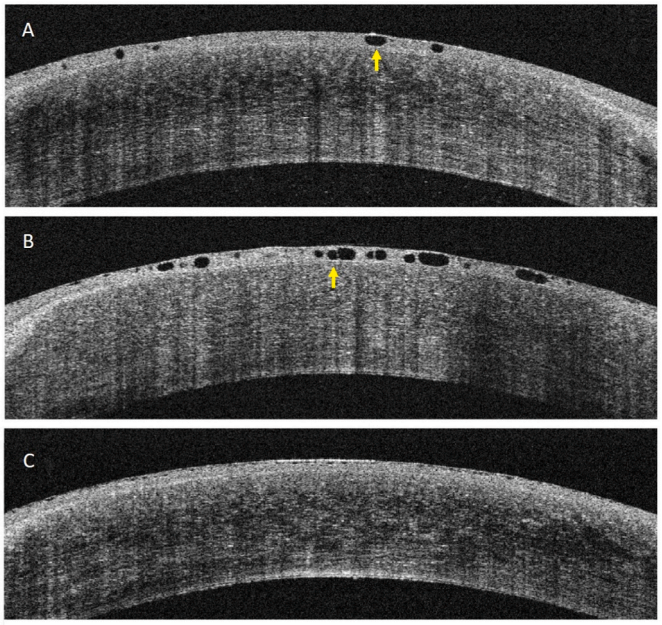

Fig. 1. Anterior segment optical coherence tomography scans in a six-year-old patient with netarsudil-associated reticular corneal epithelial edema of the left eye: (A) post-operative day one following cyclophotocoagulation, with diffuse reticular epithelial corneal edema (yellow arrow); (B) post-operative day seven, with persistence of reticular corneal edema (yellow arrow); and (C) six weeks after discontinuation of netarsudil, with complete resolution of reticular corneal edema. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.2. Case 2

A three-month-old full-term male presented to the Massachusetts Eye and Ear Glaucoma Service for evaluation of bilateral ocular hypertension. His past surgical history was notable for pars plana vitrectomy of both eyes (OU), at one month in the right eye (OD) and two months OS, for bilateral vitreous hemorrhage of uncertain etiology. When he presented to the Glaucoma Service, he was already on dorzolamide three times daily OD, latanoprost once daily OD, timolol twice daily OU, and liquid acetazolamide 250mg once daily. On initial examination, the visual acuity was fix and follow OU, and the IOPs were 32 mmHg OD and 34 mmHg OS. He was started on netarsudil 0.02% one drop daily in each eye.

Three weeks later, the IOPs were 32 mmHg OD and 24 mmHg OS. Three days later, Ahmed® glaucoma valve (New World Medical, Rancho Cucamonga, CA, USA) surgery was performed OD. While under anesthesia, both corneas appeared hazy (OD > OS) with Haab striae OD. Horizontal corneal diameters were noted to be 13 mm OD and 12 mm OS, and vertical corneal diameters were 13.75 mm OD and 13.0 mm OS. Pachymetry revealed central corneal thicknesses of 541 μm OD and 706 μm OS. Cup-disc ratios were 0.3 OU. On post-operative day one, the IOP was 19 mmHg OD. He was started on prednisolone acetate 1% drops four times daily, moxifloxacin drops four times daily, and erythromycin ointment nightly OD. Acetazolamide was discontinued. Of note, all glaucoma drops were stopped in the OD on the day of surgery and were not re-started in the postoperative period. All glaucoma drops were continued as before in OS. Because of worsening corneal clouding and in the setting of an IOP of 26 mmHg OS, Ahmed valve surgery OS was performed two weeks after the Ahmed valve OD. During the exam under anesthesia, horizontal corneal diameters were 13 mm OU, with new Haab striae inferior temporally OS and reticular epithelial edema inferior to the visual axis (Fig. 2). Glaucoma drops were discontinued in the OS after the surgery. By two months post-Ahmed valves OU, his IOPs were 21 OU on no medications. Anterior segment examination revealed a small amount of deep stromal haze, with complete resolution of the previously noted reticular epithelial edema.

3. Discussion

In this case series, we describe two pediatric cases of reticular corneal epithelial edema likely due to netarsudil use. Although netarsudil-induced reticular corneal epithelial edema has been reported in adult patients,[5–8] we report netarsudil-associated reticular epithelial edema in a six-year-old and an infant, the latter with pre-existing Haab striae. In our first case, this six-year-old patient did not develop reticular epithelial edema until approximately one year after initiating treatment with netarsudil. This stands in contrast to our second case, where our infant patient developed characteristic reticular corneal epithelial edema within several weeks of exposure to this medication. Our first patient initially developed macrocystic edema in an area of inferior irido-corneal touch, with subsequent evolution to diffuse reticular epithelial edema shortly after undergoing cyclophotocoagulation. This is similar to another case series, which reported an adult patient with netarsudil-associated reticular epithelial edema that occurred shortly after diode cyclophotocoagulation, which suggests that inflammation may increase the risk of reticular epithelial edema.[9] Our second patient manifested unilateral inferior reticular corneal epithelial edema five weeks after initiation of treatment with netarsudil. In some prior reports of adult patients, reticular epithelial edema was also initially noted in

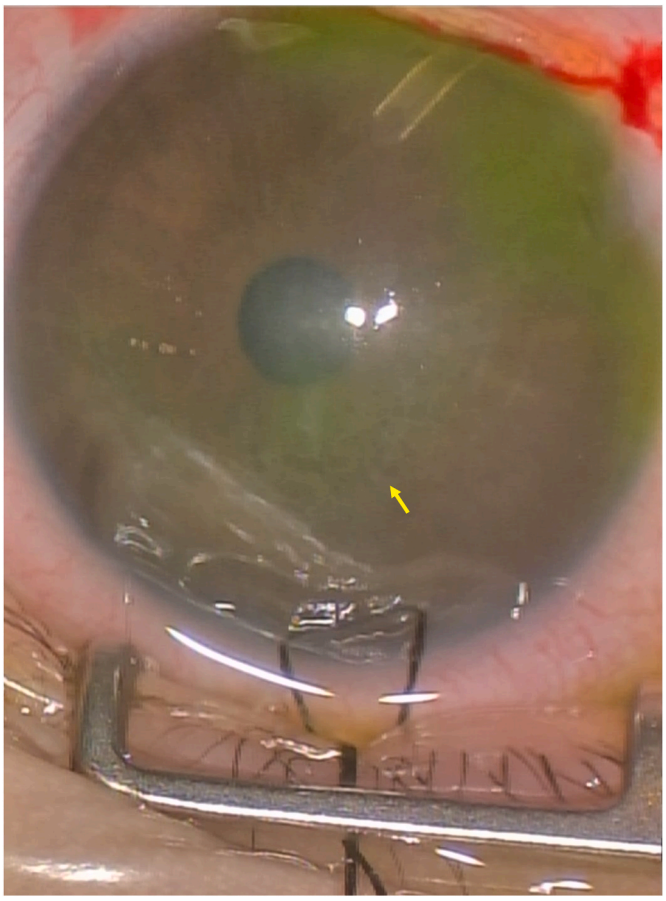

Fig. 2. Photograph taken during an examination under anesthesia of a then four-month-old infant with netarsudil-associated reticular corneal epithelial edema of the left eye. The classic honeycomb appearance of netarsudil-associated reticular epithelial edema was noted inferiorly (yellow arrow), while Haab striae were noted inferior temporally. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the inferior cornea.[6–8]

We note that in both cases, additional topical antihypertensive agents were used in conjunction with netarsudil, namely, dorzolamide, timolol, and latanoprost for both patients. It is possible that the initial corneal haze was due to dorzolamide or to the high eye pressures; however, brinzolamide- and dorzolamide-induced corneal edema usually presents as stromal edema and not reticular epithelial edema.[10] Plus, common preservatives, such as benzalkonium chloride (BAK), can induce corneal toxicity and proinflammatory effects[11–13]; however, these effects do not usually cause reticular epithelial edema, as noted in our two patients. In both patients, the reticular epithelial edema resolved after discontinuation of netarsudil.

4. Conclusion

Netarsudil 0.02% can be associated with reticular corneal epithelial edema in pediatric patients.

Patient consent

The patients' legal guardians consented to publication of the case in writing/orally.

Funding

SKF disclosures: Horizon Therapeutics (advisory board and consultant): Viridian Therapeutics (clinical advisory board); Poriferous (consultant and product development); WL Gore and Associates (consultant and product development); Thieme (textbook royalties); Springer (textbook royalties). SM's research is supported in part by gifts to the Mukai Fund, Massachusetts Eye and Ear, Boston. TCC's research is supported in part by Fidelity Charitable Fund. The following authors have no financial disclosure: MAGA, DLL, JC, MK, DDM, CMM, AMW.

Authorship

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

Declaration of competing interest

None.

Acknowledgements

SKF disclosures: Horizon Therapeutics (advisory board and consultant): Viridian Therapeutics (clinical advisory board); Poriferous (consultant and product development); WL Gore and Associates (consultant and product development); Thieme (textbook royalties); Springer (textbook royalties). SM's research is supported in part by gifts to the Mukai Fund, Massachusetts Eye and Ear, Boston. TCC's research is supported in part by Fidelity Charitable Fund. The following authors have no financial disclosure: MAGA, DLL, JC, MK, DDM, CMM, AMW.

References

1. Tanna AP, Johnson M. Rho kinase inhibitors as a novel treatment for glaucoma and ocular hypertension. *Ophthalmology*. 2018 Nov;125(11):1741–1756.
2. Chen SL, LoBue SA, Goyal H. Case report: the use of netarsudil to improve corneal edema after laser peripheral iridotomy and Descemet's membrane endothelial keratoplasty. *Am J Ophthalmol Case Rep*. 2021 Apr 14;22, 101087.
3. Dasso L, Al-Khaled T, Sonty S, Aref AA. Profile of netarsudil ophthalmic solution and its potential in the treatment of open-angle glaucoma: evidence to date. *Clin Ophthalmol*. 2018 Oct 4;12:1939–1944.
4. Serle JB, Katz LJ, McLaurin E, et al. Two phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure: rho kinase elevated IOP treatment trial 1 and 2 (ROCKET-1 and ROCKET-2). *Am J Ophthalmol*. 2018 Feb;186:116–127.
5. LoBue SA, Moustafa GA, Vu A, et al. Transient reticular cystic corneal epithelial edema with topical netarsudil: a case series and review. *Cornea*. 2021 Aug 1;40(8):1048–1054.
6. Ramakrishnan MS, Addis VM, Lehman AY, Sankar PS. Netarsudil-associated epithelial keratopathy. *Am J Ophthalmol Case Rep*. 2020 Jun;28(19), 100800.
7. Chen TC, Jurkunas U, Chodosh J. A patient with glaucoma with corneal edema. *JAMA Ophthalmol*. 2020 Aug 1;138(8):917–918.
8. Wisely CE, Liu KC, Gupta D, Carlson AN, Asrani SG, Kim T. Reticular bullous epithelial edema in corneas treated with netarsudil: a Case Series. *Am J Ophthalmol*. 2020 Sep;217:20–26.
9. Tran JA, Jukunas UV, Yin J, et al. Netarsudil-associated reticular honeycomb edema of the cornea: case series. *Am J Ophthalmol*. 2022 Jan;25, 101287.
10. Zhao J, Chen TC. Brinzolamide induced reversible corneal decompensation. *Br J Ophthalmol*. 2005;89:389–390.
11. Noecker RJ, Herrygers LA, Anwaruddin R. Corneal and conjunctival changes caused by commonly used glaucoma medications. *Cornea*. 2004 Jul;23(5):490–496.
12. Debbasch C, Brignole F, Pisella PJ, et al. Quaternary ammoniums and other preservatives' contribution in oxidative stress and apoptosis on Chang conjunctival cells. *Invest Ophthalmol Vis Sci*. 2001 Mar;42(3):642–652.
13. Malvitte L, Montange T, Vejux A, et al. Measurement of inflammatory cytokines by multicytokine assay in tears of patients with glaucoma topically treated with chronic drugs. *Br J Ophthalmol*. 2007 Jan;91(1):29–32.