

UCLA

UCLA Previously Published Works

Title

Netarsudil-Induced Corneal Flattening in a Child with Secondary Open-Angle Glaucoma

Permalink

<https://escholarship.org/uc/item/7dn4x7v9>

Journal

Case Reports in Ophthalmology, 13(2)

ISSN

1663-2699

Authors

Ganesh, Durga
Coleman, Anne L
Shibayama, Vivian P
[et al.](#)

Publication Date

2022

DOI

10.1159/000524362

Peer reviewed

Case Report

Netarsudil-Induced Corneal Flattening in a Child with Secondary Open-Angle Glaucoma

Durga Ganesh Anne L. Coleman Vivian P. Shibayama Victoria L. Tseng

Stein Eye Institute, University of California Los Angeles, Los Angeles, CA, USA

Keywords

Netarsudil · Secondary open-angle glaucoma · Corneal flattening

Abstract

We report a case of a child with secondary open-angle glaucoma who developed 6.5 diopters (D) of corneal flattening upon the addition of Rhopressa (0.02% netarsudil dimesylate solution) eye drops to a preexisting treatment regimen of timolol and latanoprost. This change in corneal power reversed after netarsudil, a rho-kinase inhibitor, was discontinued and replaced with Vyzulta (0.024% latanoprostene bunod ophthalmic solution). The 4-year-old female patient presented with bilateral secondary open-angle glaucoma from Paired Box 6 (PAX6)-related aniridia, aphakia, and persistent fetal vasculature. She was started on netarsudil to treat elevated intraocular pressure (IOP) in her right eye, which was not adequately controlled by latanoprost and timolol. Over 4 months, she developed 6.5D of corneal flattening in her right eye. Netarsudil was stopped and the corneal flattening reversed. There is evidence to support the ability of rho kinase inhibitors to increase the healing of the corneal endothelium in addition to their intended IOP-lowering effects. Rho kinase inhibitors may increase cell proliferation and adhesion within the corneal endothelium, hence decreasing apoptosis and promoting cell preservation. If there was an excess of cell proliferation; however, this might induce stromal cells to abnormally secrete enzymes or proteins, such as TGFβ-induced proteins. This could result in corneal fibrosis, thereby flattening the cornea. Further investigation is required to explore this phenomenon and elucidate its mechanism of action. Corneal flattening may be considered as a potential side effect of the use of netarsudil, particularly in young pediatric patients.

© 2022 The Author(s).

Published by S. Karger AG, Basel

Correspondence to:
Victoria L. Tseng, vtseng@mednet.ucla.edu

Introduction

In children, aniridic glaucoma is a type of secondary glaucoma that can result in worse best corrected visual acuity, compared to other pediatric glaucomas, such as primary congenital glaucoma, Peters/Rieger's anomaly-related glaucoma, and aphakic glaucoma after surgery for congenital cataracts [1, 2]. The trabecular meshwork plays an important role in aqueous outflow and regulation of intraocular pressure (IOP). Netarsudil (Rhopressa) is a rho-kinase inhibitor that acts as an ocular hypotensive agent [1, 3] by increasing aqueous humor outflow through the trabecular meshwork [3]. Adverse events reported from phase 3 clinical trials of netarsudil include conjunctival hyperemia, conjunctival hemorrhage, corneal deposits, blurry vision, increased lacrimation, eye pruritus, and erythema of the eyelid [4]. Existing literature has suggested potential corneal effects of netarsudil use in addition to its IOP-lowering effects. The ROCKET-1 and 2 trials found corneal verticillata to be an adverse effect of netarsudil usage in select patients [4]. In patients with Fuchs endothelial dystrophy, off-label usage of netarsudil has been shown to reduce corneal edema and improve visual acuity [5]. There have also been reported incidents of netarsudil-induced corneal edema that improved upon discontinuation of the drug [6]. The youngest pediatric participant in clinical trials of netarsudil was 14 years old, although pediatric and adult patients of all ages were eligible for enrollment [4]. The efficacy and side effects of netarsudil are not well studied or well understood in children at this time. In this case report, we describe a case of severe, reversible corneal power change after netarsudil usage in a child with secondary glaucoma.

Case Report case

A 4-year-old female presented with bilateral secondary open-angle glaucoma with elevated IOP in her right eye. Her ocular history was significant for bilateral aphakia from surgery for congenital cataracts as an infant, bilateral Paired Box 6 (PAX6)-related aniridia, and bilateral persistent fetal vasculature syndrome. She had very short axial lengths (16.45 mm in the right eye, 15.3 mm in the left eye) and multiple ocular conditions related to her aphakia and aniridia, including foveal hypoplasia, nystagmus, intermittent right exotropia, amblyopia of the right eye, band keratopathy, and Salzmann nodules temporally in the right eye.

The diagnosis of PAX6-related aniridia was confirmed by genetic testing. Genetic testing of the patient and her mother and father revealed that the PAX6 variant in the patient was a de novo mutation, therefore not placing her at an increased risk for Wilms tumor. She was also a heterozygous carrier of a pathogenic frameshift variant in the RPE65 gene. She had a past medical history of jaundice. There was no pertinent ophthalmic family history, besides early onset of cataract in one paternal aunt (in her late 20s) and paternal grandmother (in her early 40s).

At examination under anesthesia prior to netarsudil initiation, IOP by a Tonopen at the time of induction was elevated at 28 mm Hg in the right eye and at target between 19 and 22 mm Hg in the left eye. The patient was on timolol twice a day and latanoprost once a day in the right eye, and on no medication in the left eye. The patient's visual acuity was 20/300 in the right eye and 20/200 in the left eye. Anterior segment examination was significant for aphakia, aniridia, and microphthalmos. Posterior segment examination was significant for foveal hypoplasia. Given that IOP in the right eye was elevated despite treatment with latanoprost and timolol, as well as her history of allergy to carbonic anhydrase inhibitors, netarsudil was initiated in the right eye. An alpha-agonist was not used out of concern for respiratory depression in this patient, given her young age. At this time, the patient had cycloplegic

refraction of +23.0D sphere in the right eye and +24.0D sphere in the left eye with +3.00D added in both eyes. Her refractive error was treated with Advanced Vision Technologies PedaSITE contact lenses with a base curve of 7.76 mm, a diameter of 9.5 mm, a sphere of +38.5D in the right eye, and a base curve of 7.63 mm, a diameter of 9.5 mm, and a sphere of +44.5D in the left eye. This corresponded to an average corneal power of +43.5D in the right eye and +44.25D in the left eye. Corneal topography could not be obtained during contact lens fitting due to the patient's nystagmus.

Three months after netarsudil initiation, the patient presented for redness and discharge in her right eye. Examination in the clinic at this time indicated visual acuity of 20/250 in the right eye and 20/100 in the left eye, as well as IOPs of 16 mm Hg in the right eye and 14 mm Hg in the left eye by i-Care tonometer. Her right conjunctiva had 1+ injection. Bilaterally, she had delayed clearance of fluorescein administered more than 1 h prior and trace corneal epithelial haze. The remainder of her anterior and posterior segment exam was stable from the prior exam under anesthesia. She was noted to have a large bubble under her contact lens. A repeat contact lens fitting was performed, and the patient was noted to have improved contact lens fit in the right eye with a lens of a base curve of 9.12 mm, corresponding to 37.0D of average corneal power. No other treatments were initiated at this time.

After the new lens was fit, the patient continued to have persistent redness and discharge in her right eye. As such, the decision was made to replace netarsudil with 0.024% latanoprostene bunod ophthalmic solution (Vyzulta) 4 months after netarsudil was prescribed. An alpha-agonist was not considered due to safety concerns with the patient's age, and a carbonic anhydrase inhibitor was not used as the patient was allergic. One month after changing netarsudil to latanoprostene bunod, the patient presented for repeat contact lens fitting, as the lens was suddenly popping out and not staying on the cornea. At this visit, the redness and discharge of the right eye were resolved. The +37.0D contact lens was noted to be too flat. The patient had improved contact lens fit at this time with a 7.85 mm (+43.0D) lens, which was similar to the corneal power prior to netarsudil. Her IOP remained well controlled at 13 mm Hg by a tonometer after this switch in medications.

Discussion and Conclusions

We have described a case of severe corneal flattening, which occurred after the initiation of netarsudil therapy in a pediatric patient with secondary glaucoma. Flattening reversed after discontinuation of the medication. A limitation of this case report is not being able to acquire topography measurements, slit-lamp photographs, or anterior segment OCT of the cornea of the treated eye due to the patient's young age and inability to participate in several of these exams in the clinic, and limited availability of equipment during exam under anesthesia. Instead, contact lens refitting was used as evidence of corneal curvature change. If corneal topography was measured, one might expect to observe central corneal flattening with relative steepening in the periphery and an abnormal prolate shape factor [7]. Anterior segment OCT might have revealed hyperreflective regions under the corneal epithelium and deep corneal stroma in the affected eye [8].

Multiple ocular side effects of netarsudil have been reported in the literature, with many affecting the cornea. For example, among 4 patients with preexisting corneal stromal edema, the initiation of netarsudil induced a variety of ocular side effects, including epithelial edema in a reticular, honeycomb-like pattern in the interpalpebral and inferior cornea, increased central corneal thickness, and decreased lens-correctable visual acuity [7]. These adverse effects of netarsudil were reversed within 2 weeks of discontinuing treatment [7]. Conjunctival hyperemia is the most commonly cited side effect of netarsudil [4] and rho-kinase

inhibitors as a whole [9]. There is evidence to support the ability of rho-kinase inhibitors to increase the healing of the corneal endothelium [7] in addition to decreasing IOP, with multiple clinical trials demonstrating the beneficial effects of rho-kinase inhibitors on the corneal endothelium [10–12].

The main hypothesis for this mechanism of action conjectures that rho-kinase inhibitors may increase cell proliferation and adhesion within the corneal endothelium, hence decreasing apoptosis and promoting cell preservation [13]. If there was an excess of cell proliferation, however, this might induce stromal cells to abnormally secrete enzymes or proteins, such as TGF β -induced proteins [8]. This could result in corneal fibrosis, thereby flattening the cornea [8]. It is worth considering how corneal flattening may fit within the proposed mechanism of action of rho-kinase inhibitors.

A similar mechanism of action has been described for the formation of Salzmann nodules [14]. Increased epithelial MMP-2 expression could disrupt basement membrane integrity, allowing for stromal penetration of TGF β -1 and PDGF [14]. At high enough levels, this could promote keratocyte differentiation into activated myofibroblasts and fibroblasts, which could deposit a disorganized extracellular matrix, thereby forming the Salzmann nodule [14]. Thus, the nodules could themselves create a flattened central cornea and steepened mid-peripheral cornea. Given that the patient had Salzmann nodules temporally in the right eye prior to the initiation of netarsudil, it is possible that the preexisting disruption of the basement membrane from the Salzmann nodule could have predisposed the patient's cornea to penetration by an increased level of TGF β -1 promoted by netarsudil, further favoring the occurrence of corneal flattening. If this was a contributing factor, it is unclear whether these changes of corneal flattening would occur in a normal cornea, without a history of Salzmann nodules.

Additional considerations in this patient include the concomitant use of timolol and latanoprost. Timolol is a nonselective β -blocker that is topically used to treat open-angle glaucoma and ocular hypertension [15] and is hypothesized to reduce IOP by reducing aqueous humor production [12]. Latanoprost is a prostaglandin F2 alpha analog that reduces IOP via increased uveoscleral outflow of aqueous humor [16]. Timolol does not have known corneal effects, while latanoprost may be associated with the development of pseudodendrites [17] or reactivation of herpetic eye disease [18]. It would be worthwhile to investigate whether the corneal effects of netarsudil can be altered or potentiated by the simultaneous use of different classes of IOP-lowering therapy. Finally, the patient's complex ocular history including aniridia, aphakia, and amblyopia may have also contributed to the observed corneal changes after initiation of netarsudil.

Corneal flattening may be considered as a potential side effect of the use of netarsudil, particularly in young pediatric patients. Further investigation is required to explore this phenomenon and elucidate its mechanism of action.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with the University of California Los Angeles Institutional Review Board guidelines. Written informed consent was obtained from the parent/legal guardian of the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was supported by an unrestricted grant to the UCLA Department of Ophthalmology from Research to Prevent Blindness and the UCLA Stein Eye Center for Community Outreach and Policy. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Durga Ganesh, Anne L. Coleman, and Victoria L. Tseng: conception and design, data acquisition/analysis/interpretation, manuscript drafting, manuscript revision critically for important intellectual content, final approval of the manuscript version to be published, agreement to be accountable for all aspects of the work to be published. Vivian P. Shibayama: conception and design, data acquisition/analysis/interpretation, manuscript revision critically for important intellectual content, final approval of the manuscript version to be published, agreement to be accountable for all aspects of the work to be published.

Data Availability Statement

The patient's electronic medical record is not being provided publicly to maintain patient privacy. Further inquiries can be directed to the corresponding author.

References

- 1 Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. 2014 May;311(18):1901–11.
- 2 Moschos MM, Nitoda E, Fenzel I, Song X, Langenbucher A, Kaesmann B, et al. Prognostic factors of pediatric glaucoma: a retrospective study. *Int Ophthalmol*. 2019 Feb;39(2):359–73.
- 3 Lin CW, Sherman B, Moore LA, Laethem CL, Lu DW, Pattabiraman PP, et al. Discovery and preclinical development of netarsudil, a novel ocular hypotensive agent for the treatment of glaucoma. *J Ocul Pharmacol Ther*. 2018 Mar;34(1–2):40–51.
- 4 Serle JB, Katz LJ, McLaurin E, Heah T, Ramirez-Davis N, Usner DW, 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;186:116–27.
- 5 U.S. Food and Drug Administration. Full prescribing information: Rhopressa (netarsudilophthalmic solution) 0.02%, for topical ophthalmic use. 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208254lbl.pdf (accessed March 17, 2022).
- 6 Chu MJ, Song M, Palmares T, Song A, Song J. Rhopressa-induced corneal edema: a case report. *J Med Case Rep*. 2021 Dec;15(1):182.
- 7 LoBue SA, Moustafa GA, Vu A, Amin M, Nguyen T, Goyal H. Transient reticular cystic corneal epithelial edema with topical netarsudil: a case series and review. *Cornea*. 2021 Aug;40(8):1048–54.
- 8 Hirai H, Maruoka S, Yoshikawa T, Ogata N. Case of progressive hyperopia due to flattening of cornea. *Am J Ophthalmol Case Rep*. 2018 Jun 1;10:169–71.
- 9 Moshirfar M, Parker L, Birdsong OC, Ronquillo YC, Hofstedt D, Shah TJ, et al. Use of Rho kinase inhibitors in ophthalmology: a review of the literature. *Med Hypothesis Discov Innov Ophthalmol*. 2018;7(3):101–111.
- 10 Okumura N, Fujii K, Kagami T, Makiko N, Kitahara M, Kinoshita S, et al. Activation of the Rho/Rho kinase signaling pathway is involved in cell death of corneal endothelium. *Invest Ophthalmol Vis Sci*. 2016 Dec;57(15):6843–51.
- 11 Okumura N, Kinoshita S, Koizumi N. Application of Rho kinase inhibitors for the treatment of corneal endothelial diseases. *J Ophthalmol*. 2017;2017:2646904.
- 12 Nakagawa H, Koizumi N, Okumura N, Suganami H, Kinoshita S. Morphological changes of human corneal endothelial cells after rho-associated kinase inhibitor eye drop (ripasudil) administration: a prospective open-label clinical study. *PLoS One*. 2015 Sep;10(9):e0136802.

- 13 Price MO, Price FW Jr. Randomized, double-masked, pilot study of netarsudil 0.02% ophthalmic solution for treatment of corneal edema in fuchs dystrophy. *Am J Ophthalmol*. 2021 Jul;227:100–5.
- 14 Paranjpe V, Galor A, Monsalve P, Dubovy SR, Karp CL. Salzmann nodular degeneration: prevalence, impact, and management strategies. *Clin Ophthalmol*. 2019 Jul;13:1305.
- 15 Barnes J, Moshirfar M. Timolol. In: *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; 2021 Jul 25. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK545176/> (accessed March 17, 2022).
- 16 Tripathy K, Geetha R. Latanoprost. In: *StatPearls [Internet]*. Treasure Island, FL: StatPearls Publishing; 2021 Aug 21. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK540978/> (accessed March 17, 2022).
- 17 Sudesh S, Cohen EJ, Rapuano CJ, Wilson RP. Corneal toxicity associated with latanoprost. *Arch Ophthalmol*. 1999 Apr;117(4):539–40.
- 18 Wand M, Gilbert CM, Liesegang TJ. Latanoprost and herpes simplex keratitis. *Am J Ophthalmol*. 1999 May;127(5):602–4.