Corneal endothelial wound healing after Descemet tear with a rho kinase inhibitor

Jamal Azhari, MS4, Umangi Patel, MD, Mitul Vakharia, MD

Introduction:
To the authors’ knowledge, this is the first report of Descemet tear postcataract surgery that was successfully treated with ripasudil hydrochloride hydrate.

Patient and Clinical Findings:
An 85-year-old pseudophakic man presented with blurry vision and mild photophobia in the left eye. Slitlamp biomicroscopy showed moderate corneal edema and a central Descemet tear from cataract surgery 7 years earlier.

Diagnosis, Intervention, and Outcomes:
The patient was treated for 1 month with prednisolone acetate 1% and sodium chloride 5% hyperosmotic ophthalmic solution with no clinical improvement. He declined surgical intervention and opted for medical management with ripasudil 0.4% ophthalmic solution, a rho kinase inhibitor. He applied it topically 4 times daily for 3 months, with improvement of corneal edema and corrected distance visual acuity. After discontinuation of ripasudil, his edema and vision worsened and then improved again after retreatment, showing a strong clinical response. 2 years after starting ripasudil therapy, the patient had continued to use ripasudil 3 times daily and reported worsened vision at lower doses.

Conclusions:
The use of topical ripasudil may be a viable medical intervention for corneal edema due to Descemet tear instead of surgery, although chronic use may be required.

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CASE REPORT

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Pseudophakic/aphakic corneal edema results from endothelial injury at the time of cataract surgery. Conservative treatment for mild disease consists of lubrication and hyperosmotic drops. The standard of care for moderate-to-severe endothelial cell decompensation is surgical replacement of the endothelium with endothelial keratoplasty.1 To date, there are no U.S. Food and Drug Administration (FDA)-approved pharmaceutical interventions to reverse corneal edema from endothelial injury and the only therapeutic choice is surgery. However, there is mounting evidence of pharmaceutical agents that may promote corneal endothelial healing. Rho kinase (ROCK) inhibitor Y-27632 has been shown to promote endothelial wound healing after endothelial injury in monkeys in vitro and rabbits in vivo and later in 3 human cases of Descemet tears from previous cataract surgery.1,2 We report a similar clinical case of corneal endothelial healing after Descemet tear with a different ROCK inhibitor, ripasudil hydrochloride hydrate (Glanatec ophthalmic solution 0.4%). Ripasudil has been shown to promote corneal wound healing after Descemet-stripping only surgery for Fuchs endothelial corneal dystrophy.3,4

Patient Consent Statement
Informed consent was obtained from the patient after explanation of the nature and possible consequences of this treatment. The tenets of the Declaration of Helsinki were followed, and clearance was obtained from the Institutional Review Board of the University of Illinois College of Medicine at Rockford.

CASE REPORT
An 85-year-old pseudophakic man presented with symptoms of blurry vision and photophobia in his left eye worsening over the past 2 months. He had been prescribed lid scrubs and prednisolone acetate (PA) 1% 6 times daily per his previous ophthalmologist with no improvement. He had cataract surgery in both eyes 7 years earlier. and reported his left eye vision was worse compared with that of the right eye since the postoperative period. On initial visit, the patient’s corrected distance visual acuity (CDVA) was 20/30 in the right eye and 20/70 in the left eye, and intraocular pressure measured 9 mm Hg and 11 mm Hg respectively. A slitlamp examination of the left eye revealed moderate focal corneal stromal edema and a central Descemet tear with mild punctate epithelial keratitis, with posterior chamber intraocular lens in a good position. The cause of the patient’s corneal edema was attributed to Descemet tear, which was suspected to be because of inadvertent contact between the phacoemulsification handpiece tip and the central Descemet membrane at the time of cataract surgery (Figure 1). The torn end of
Descemet membrane was re-adherent to the cornea, forming a small bubble (Figure 2). The suspected cause of his recent worsening of vision was the combination of the Descemet tear and endothelial attrition with age. The patient continued with PA 6 times daily and was started on sodium chloride 5% hyperosmotic ophthalmic solution twice daily. At his 2-week follow-up visit, the patient reported vision had improved slightly and CDVA measured 20/60 in the left eye; however, the slitlamp examination did not show clinical improvement. The patient was tapered off PA while continuing sodium chloride 5% twice daily.

At the 1-month follow-up, the slitlamp examination was unchanged, CDVA remained at 20/60 in the left eye, and central pachymetry measured 549 μm in the healthy right eye and 672 μm in the affected left eye. Surgical and medical interventions were discussed, and the patient continued sodium chloride 5% twice daily and chose to add ripasudil 0.4% ophthalmic solution 4 times daily in the left eye. The patient was informed that ripasudil is not FDA-approved, and he ordered it online from a pharmacy in Japan. At the 6-week follow-up, the patient reported improvement in vision, left eye CDVA measured 20/40, central pachymetry measured 632 μm, and the slitlamp examination showed improvement of focal corneal stromal edema surrounding the central Descemet tear (Figure 1). Sodium chloride 5% was discontinued, and the patient continued ripasudil 4 times daily, and at the next 6-week follow-up visit, left eye CDVA improved to 20/25, central pachymetry remained at 632 μm, and the slitlamp examination was unchanged. Ripasudil was then discontinued after 3 months of treatment. However, at the next follow-up visit at 6 weeks, left eye CDVA had dropped to 20/40, central pachymetry measured 705 μm, and the patient reported his vision had worsened within 4 days of discontinuing ripasudil. Ripasudil was then restarted 4 times a day and at the 6-week follow-up, his left eye CDVA had again improved to 20/25. The patient did not report any side effects from his use of ripasudil. The patient attempted to taper the ripasudil drops many times over the next several months, and this was always accompanied by a subjective worsening of vision. At the final follow-up 2 years after starting ripasudil therapy, the patient continued to use it 3 times a day and maintained a CDVA of 20/25. He reported that he preferred chronic ripasudil therapy to surgery given his age.

**DISCUSSION**

Peripheral Descemet tears are a relatively common minor complication of cataract surgery typically associated with the corneal incision. Most occur far from the visual axis and resolve without consequences. When the visual axis is involved, as in our patient, the resultant pseudophakic/aphakic corneal edema can be visually significant. In case reports of similar cataract surgery complications, there was resolution of corneal edema over an extended period with no intervention, unlike our patient who noted worsened vision and photophobia 7 years postoperatively.1

Once Descemet membrane is surgically stripped or torn, endothelial cells were known to spread; however, they were not known to proliferate.5 In 2009, Okumura et al. identified a ROCK inhibitor, Y-27632, that promoted corneal endothelial adhesion, survival, and proliferation in primate-derived cells in vitro.6 In 2011, they demonstrated Y-27632 could promote endothelial wound healing after scraping endothelial injury in monkeys in vitro and in rabbits in vivo after transcorneal freezing and in 2013 in monkeys in vivo after transcorneal freezing.7,8 A case report in 2013 of a patient with Fuchs corneal endothelial dystrophy demonstrated improvement in CDVA and reduced corneal edema after treatment with transcorneal freezing and subsequent topical Y-27632.9 A pilot clinical study of 3 patients with a history of corneal edema with large Descemet tears from previous cataract surgeries were treated with Y-27632 topical eyedrops for 3 to 6 months and achieved corneal clarity.9 Our case demonstrated the
efficacy of ripasudil in a patient with a Descemet tear and corneal edema.

Clinically available ophthalmic ROCK inhibitors include netarsudil dimesylate 0.02% ophthalmic solution (Rhopressa), which is FDA-approved for glaucoma and ocular hypertension, and ripasudil, which is not FDA-approved but was approved in Japan in 2014 for a similar indication. Ripasudil has been shown to promote corneal wound healing after Descemet-stripping only surgery for Fuchs dystrophy, whereas netarsudil in a small case series showed worsened vision due to bullous edema in 5 of 6 cases.3,4,10

Our patient pursued medical management with ripasudil for corneal edema. He achieved similar results with ripasudil as Okumura et al. reported with Y-27632.6 To the authors’ knowledge, this is the first reported case achieving corneal clarity with ripasudil after previous Descemet tear. In our patient, the worsening of edema and vision after ripasudil was discontinued, followed by the improvement of edema and vision after it was restarted, suggests a significant clinical effect, especially after failure of previous treatment with steroid and hyperosmotic drops.

This relapse edema effect was seen in more than a third of patients after discontinuation of ripasudil in a recent study of edema with retreatment with ripasudil.9 The authors suspect ripasudil provides functional support to immature endothelial cells.4 Different mechanisms have been proposed to describe the mechanism of benefit of ripasudil with migration, proliferation, or both, being the driving forces of endothelial regeneration.11 It was also shown that ripasudil induced upregulation of proteins important for endothelial pump and barrier function, indicating that the restored endothelial cells were functionally competent.11

Given the Descemet bubble limits normal endothelial migration in our patient, it is likely that the improved endothelial pump function induced by ripasudil is the cause of clinical improvement (Figure 2). This would explain why he requires chronic therapy as endothelial cell activation unlike proliferation is not a permanent condition after a few months of treatment. The cost of approximately $55 per bottle, which lasts around 6 weeks, should be taken into consideration when comparing chronic ripasudil therapy with the cost and morbidity of endothelial keratoplasty. While the use of ripasudil for corneal endothelial healing is currently not FDA-approved, our patient’s results are encouraging for patients with Descemet tears and corneal edema who choose not to pursue surgery or are poor surgical candidates.

Enrollment has begun in a multinational multicenter randomized controlled trial of ripasudil after Descemet-stripping only surgery, which should enhance our understanding of this pharmaceutical agent.12 A recent small study of 3 patients suggests ripasudil may have an endothelial protective effect when used perioperatively for cataract surgery.13 Treatment of the corneal endothelium with ripasudil is promising as it seems to promote corneal clarity while avoiding the morbidity associated with corneal surgery.

WHAT WAS KNOWN
- The standard of care for moderate to severe pseudophakic/aphakic corneal edema due to Descemet tear is endothelial keratoplasty.
- Another rho kinase inhibitor (Y-27632) has been shown to promote endothelial wound healing in 3 human cases of Descemet tears from previous cataract surgery.

WHAT THIS PAPER ADDS
- To the authors’ knowledge, this is the first report of Descemet tear with corneal edema that was successfully treated with ripasudil hydrochloride hydrate.
- Chronic ripasudil therapy may be required to maintain a clinical response.

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