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Managing pseudophakic bullous keratopathy with a topical rho kinase inhibitor: a case series

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Abstract

Background Cataract surgery is common procedure globally. Among its adverse effects is pseudophakic bullous keratopathy (PBK), a corneal disorder characterized by stromal edema and the formation of epithelial and subepithelial bullae due to endothelial cell loss and decompensation. This case series examines the outcomes of using the topical Rho kinase inhibitor Ripasudil for managing pseudophakic bullous keratopathy (PBK) in three patients treated at Hadassah Medical Center. Clinical data, including visual acuity, intraocular pressure, central corneal thickness (CCT), and endothelial cell count, were extracted from electronic medical records before and after treatment. Patients were treated with topical Ripasudil for periods ranging from three to eleven months, three times daily, with adjustments based on disease severity.

Case presentation The first case involved a 66-year-old Jewish female, who presented with persistent corneal edema in the left eye. Following three months of Ripasudil therapy, the patient exhibited notable improvement in best-corrected visual acuity (BCVA), a reduction in central corneal thickness (CCT), and decreased central stromal edema. Similarly, the second case featured a 58-year-old Jewish male with a history of cataract surgery in the right eye performed 3 years prior at an external institution. After 3 months of Ripasudil treatment, the patient demonstrated measurable improvements in both BCVA and CCT, mirroring the therapeutic trend observed in the first case. In parallel, the third case described a 69-year-old Jewish male who presented with a 6-month history of blurred vision. In total, 11 months of Ripasudil administration led to resolution of stromal haze and corneal edema, along with a significant reduction in CCT and an enhancement in BCVA.

Conclusion These findings suggest that Ripasudil has potential as an effective treatment option for PBK, possibly delaying or avoiding the need for corneal transplantation. Further studies are required to confirm the long-term efficacy and safety of Ripasudil for PBK.

Keywords Pseudophakic bullous keratopathy, Ripasudil, Rho kinase inhibitor, Corneal edema, Cataract surgery, Endothelial cell function

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Introduction

Cataract surgery is common procedure globally with high patients' satisfaction rates. The cornea, responsible for ocular refraction and transparency, relies on the endothelium to regulate hydration and fluid balance. Among its adverse effects is pseudophakic bullous keratopathy (PBK), a corneal disorder characterized by stromal edema and the formation of epithelial and subepithelial bullae owing to endothelial cell loss and decompensation [1]. PBK incidence is 1–2% of all cataract surgeries, and can be caused by endothelial trauma during lens extraction and lead to loss of transparency, alongside other symptoms such as tearing, and pain from ruptured epithelial bullae [2].

PBK, characterized by irreversible corneal edema following cataract surgery and intraocular lens implantation, typically manifests between 8 months to 7 years post-operatively. Risk factors include surgical factors such as intraoperative mechanical trauma, anterior chamber or iris-fixated intraocular lens implantation, chemical injury, and postoperative inflammation. Other risk factors include advanced age, pre-existing Fuchs' corneal dystrophy, anterior chamber IOL insertion, previous intraocular surgery, shallow anterior chamber, glaucoma, and previous ocular trauma [3–6]. Understanding these factors is crucial for identifying high-risk patients and implementing preventive measures. The definitive treatment for severe cases of PBK is corneal transplantation, with options including penetrating keratoplasty (PKP), Descemet membrane endothelial keratoplasty (DMEK), and Descemet stripping automated endothelial keratoplasty (DSAEK). Temporary measures, such as corneal collagen cross-linking, amniotic membrane transplant, anterior stromal puncture, and phototherapeutic keratectomy (PTK), can provide symptomatic relief [1, 2].

Recently, the topical Rho kinase (ROCK) inhibitor Ripasudil, which is approved for the treatment of glaucoma and ocular hypertension, has shown promise in managing corneal edema. It demonstrated the ability to enhance endothelial cell function and reduce stromal edema, potentially delaying, or even avoiding the need for corneal transplantation in cases of corneal edema [7, 8].

Here, we present a case series of three patients of Jewish ethnicity, demonstrating the use of a Ripasudil in managing patients with PBK.

Cases series and ethical considerations

Ethical approval is not required for this study in accordance with local or national guidelines.

Data collection and sources

The clinical data for the 3 patients were systematically extracted from the electronic medical record system, "Mahar," at Hadassah Medical Center. This retrospective review of the Electronic Medical Records (EMR) was conducted between November 2019 and November 2022. The patients' medical histories, clinical examination findings, and treatment outcomes were obtained from the electronic medical records. Additionally, supplementary imaging data, such as digital slit lamp and Picture Archiving and Communication System (FACS) scans, were retrieved from Hadassah's ophthalmic care infrastructure databases to support the clinical information.

Study variables pre and post treatment

The current case series involved evaluations before and after treatment. The pretreatment assessments included measurements of visual acuity, IOP, central corneal thickness (CCT), and endothelial cell count (ECC), as well as the duration of treatment. The post-treatment assessments included the same parameters.

Treatment protocol

The treatment regimen involved the topical application of Ripasudil hydrochloride hydrate (Glanatec® ophthalmic solution 0.4%; Kowa Company, Ltd., Nagoya, Japan). The eye drops were administered three times per day, with the frequency adjusted in accordance with the severity of the patient's condition, as per the manufacturer's dosing guidelines. All three patients in this case series were treated with Ripasudil at the same dosage and frequency as specified in the current protocol treatment.

Assessment parameters

In all three patients, tests, examinations, and assessments were conducted both before and after the Ripasudil treatment. Pretreatment assessments included best corrected visual acuity (BCVA) using the logMAR scale. Intraocular pressure (IOP) was measured using the iCARE model TA01i (Icare Ltd, Vantaa, Finland) with an average of three measurements. Central corneal thickness (CCT) was measured using the Pentacam HR (Oculus, Wetzlar, Germany) and endothelial cell count (ECC) was obtained using specular microscopy (Konan NonCon-ROBO specular microscope; Konan Medical, Irvine, CA). Slit lamp examinations and photos were conducted using the Haag-Streit Photo-Slit Lamp BX 900 (Haag-Streit AG, Koeniz, Switzerland). Additionally, anterior segment spectral-domain Optical Coherence Tomography (OCT) was performed using the Optovue RTVue-100 (Optovue Inc., Fremont, CA, USA).

Post-treatment assessments were conducted to evaluate the impact of the intervention. These assessments replicated the pretreatment evaluations, including remeasurements of BCVA, CCT, and ECC. The duration of Ripasudil treatment, measured in months, was documented. Slit lamp and OCT analyses were repeated and compared to the pretreatment findings.

Case presentation

Case 1

A 66-year-old female patient of Jewish ethnicity presented with a history of corneal edema in the left eye, with no prior ocular trauma and no history of alcohol consumption or smoking. The patient had undergone cataract surgery with phacoemulsification and IOL implantation 5 years prior at an external institution and was subsequently diagnosed with PBK in the left eye after primary complaints of blurred vision, with corneal edema persisting for 4 months.

Slit-lamp examination revealed superior stromal edema of grade 1 in the patient's left eye. Prior to treatment, assessments showed a CCT of 594 μm, BCVA of 0.08 logMAR, an IOP of 17 mmHg, and ECC of 1189 cells/mm^2.

The patient was treated with sodium chloride 5% drops administered four times daily and sodium chloride 5% ointment (Muro 128, Bausch & Lomb Pharmaceuticals, Rochester, NY, USA) applied nightly. However, after 6 weeks of this regimen, there was no significant improvement in the patient's signs and symptoms. Following this, the patient was treated with Ripasudil to address the corneal decompensation. After 3 months of Ripasudil treatment, there was still grade 1 stromal edema centrally, the CCT value was 584 μm, BCVA improved to 0 logMAR, the IOP was 18 mmHg, and the ECC was 1208 cells/mm^2.

Case 2

A 58-year-old male patient of Jewish ethnicity had a history of cataract surgery in the right eye at an external institution 3 years prior to his first presentation. He presented with a main complaint of blurred and hazy vision for 2 months. The patient had no prior ocular surgeries except for the cataract surgery, no history of ocular trauma or injury, no known familial ocular diseases including glaucoma, and reported neither current nor past tobacco use or alcohol consumption. Slit-lamp examination of the right eye revealed central stromal edema of grade 1 as well as temporal stromal edema with stromal folds. Specular microscopy was attempted, but no image could be obtained, and the patient's ECC was not measurable. Prior to treatment, the patient's assessments showed a CCT of 686 μm in the right eye, BCVA was 1 logMAR, IOP was 16 mmHg.

Initially, the patient was treated with sodium chloride 5% drops administered four times daily and sodium chloride 5% ointment (Muro 128, Bausch & Lomb Pharmaceuticals, Rochester, NY, USA) applied nightly. However, after 4 weeks of this regimen, there was no significant improvement observed in the patient's signs and symptoms, and the patient subsequently discontinued the treatment.

Following 3 months of Ripasudil treatment, repeat topography imaging demonstrated a CCT value of 654 μm, an improved BCVA of 0.39 logMAR, an IOP of 16 mmHg, the patient's endothelial cell count was 987 cells/mm^2.

Case 3

A 69-year-old male patient of Jewish ethnicity reported a six-month history of blurred vision. The patient underwent cataract extraction surgery 15 years before his initial presentation. His ocular history included left eye iridotomy 12 years ago. He had no history of ocular trauma, nor family history of ophthalmological conditions, and abstains from both tobacco and alcohol. Slit-lamp examination revealed stromal haze and inferior edema with stromal folds. The patient's CCT was 582 μm in the affected eye, BCVA was 0.3 logMAR, IOP was 18 mmHg, with an ECC of 554 cells/mm^2.

The patient then underwent treatment utilizing the Hyper-CL therapeutic contact lens (EyeYon Medical, Ness Tziona, Israel). The Therapeutic Hyper-CL™ contact lens was designed with a reservoir between the corneal surface and the lens, which aims to retain and prolong the exposure of ophthalmic medications over the corneal surface. The patient was fitted with a Hyper-CL lens measuring 15.5 mm in diameter and 8.2 mm in base curve, with a plano refractive power. The patient continuously wore the Hyper-CL lens for a period of 7 days and was instructed to administer a 5% sodium chloride solution six times daily. However, after 4 weeks, He discontinued the Hyper-CL treatment, as no significant improvement was observed in the clinical signs and symptoms. Subsequently, The patient was monitored for 3 weeks while using prednisolone 1% four times daily, but this regimen also failed to improve the corneal edema.

After discontinuing the prednisolone regimen, Ripasudil was applied three times daily to the patient's lest eye. After 11 months of Ripasudil treatment, repeat slit-lamp examination revealed no stromal haze and no stromal edema in the left eye. The patient's repeat topography imaging demonstrated a CCT of 540 μm, an improved BCVA of 0.04 logMAR, an IOP of 19 mmHg, and endothelial cell count of 562 cells/mm^2.

Slit lamp pictures and anterior segment OCT of the patients before and after the treatment are shown in

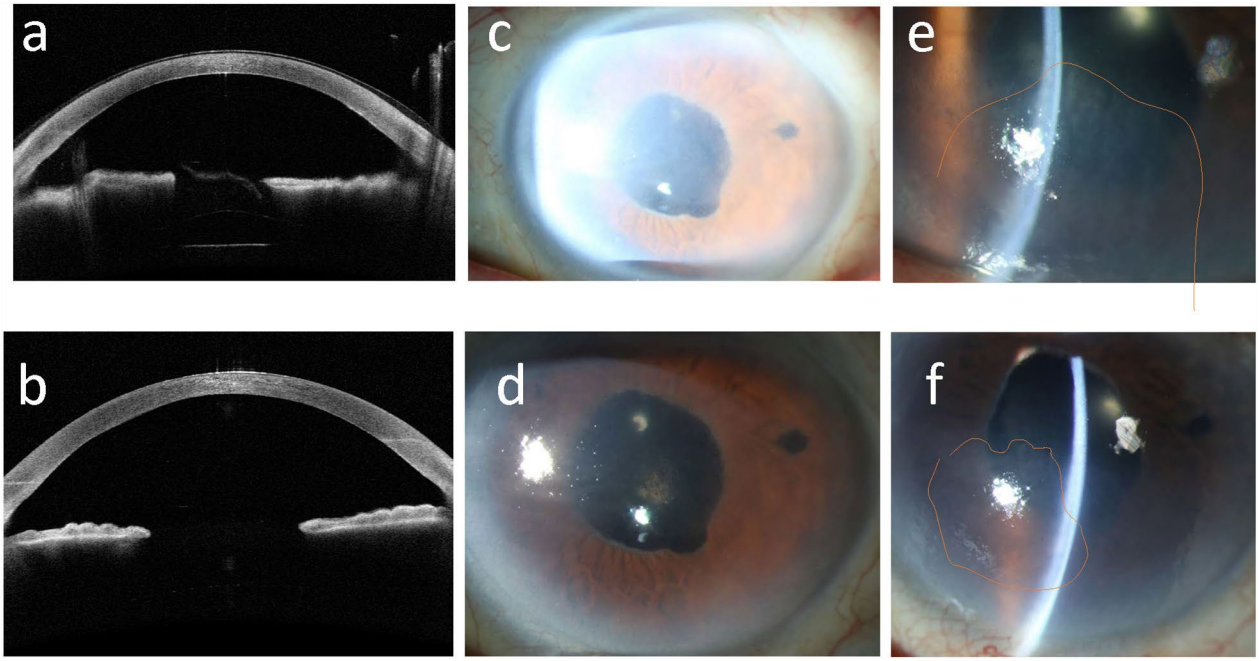

Fig. 1 Pre- and post-treatment images of the left eye undergoing 11 months of Repusdil treatment (case 3)

Table 1 Timeline of treatment interventions and clinical outcomes cross three PBK cases

Time point	Case 1	Case 2	Case 3
T = 0 (initial presentation)	Corneal edema in the LE diagnosed as PBK	Blurred and hazy vision in the RE	PBK diagnosed in the LE (symptoms for 6 months)
Baseline measurements	CCT: 594 µm BCVA: 0.08 logMAR ECC: 1189 cells/mm^2 IOP: 17 mmHg	CCT: 686 µm BCVA: 1 logMAR ECC: not measurable IOP: 16 mmHg	CCT: 582 µm BCVA: 0.3 logMAR ECC: 554 cells/mm^2 IOP: 18 mmHg
T = 1 month	NI with sodium chloride 5% (6 weeks)	NI with sodium chloride 5%	NI with Hyper-CL lens
T = 3 months	After Ripasudil treatment: CCT:584 µm BCVA:0 logMAR ECC:1208 cells/mm^2 IOP: 18 mmHg	After Ripasudil treatment: CCT:654 µm, BCVA:0.39 logMAR ECC: 987 cells/mm^2 IOP:16 mmHg	Prednisolone 1% trial (3 weeks): NI
T = 11 Months			After Ripasudil treatment: CCT:540 µm, BCVA = 0.04 logMAR ECC:562 cells/mm^2 IOP:19 mmHg

NI no improvement, *LE* left eye, *RE* right eye, *Sx* symptoms

Fig. 1. The chronological treatment response and clinical data across the three PBK cases are presented in Table 1.

OCT scans (Fig. 1a, b) and slit-lamp images (Fig. 1c–f), with Fig. 1a, c, and e representing pretreatment, and Fig. 1b, d, and f representing post-treatment. The OCT scan shows a slight reduction in CCT (Fig. 1b compared to Fig. 1a). Diffuse lighting in the slit-lamp images reveals a decrease in signs of corneal edema (Fig. 1d compared to Fig. 1c), and iris retro illumination in the slit-lamp images shows a decrease in volume and area, along with compression of the stromal folds (bounded by an orange line, Fig. 1f compared with Fig. 1e).

Discussion

In this case series, we have demonstrated the use of Ripasudil, a ROCK inhibitor, in improving visual acuity and CCT in all three cases while the ECC was at least maintained.

The first case showed a gradual improvement in the patient's visual acuity and corneal thickness after

3 months of Ripasudil treatment, with a decrease in central stromal edema. The second case demonstrated a similar pattern, with improvement in BCVA and CCT after 3 months of therapy. The third case revealed a more dramatic effect, with the complete resolution of stromal haze and edema after 11 months of Ripasudil treatment, along with a decrease in CCT and an improvement in visual acuity.

The failure of hypertonic saline and Hyper-CL prior to Ripasudil underscores the limitations of osmotic therapies in chronic edema, as literature shows they only provide transient efficacy in mild cases [9, 10]. In contrast, Ripasudil's success in resolving stromal haze aligns with its observed antifibrotic and anti-inflammatory properties in Fuchs' dystrophy [7, 11–13]. These findings suggest that earlier initiation of Ripasudil should be considered in the management of Pseudophakic Bullous Keratopathy.

The observed reductions in central corneal thickness and improvements in best-corrected visual acuity across all three cases align with studies demonstrating the efficacy of Ripasudil in enhancing endothelial pump function and reducing stromal edema in pseudophakic bullous keratopathy. Notably, case 1 showed a 10 µm decrease in central corneal thickness and normalization of best-corrected visual acuity, consistent with reports of Ripasudil's anti-edematous effects [14, 15]. However, minimal changes in endothelial cell density suggest that Ripasudil primarily addresses functional decompensation rather than promoting cellular regeneration, a finding echoed in prior trials [7, 11–15].

The case of patient 2 illustrates the limitations in managing severe endothelial dysfunction. Despite a 32 µm reduction in central corneal thickness and improvement in best-corrected visual acuity, the patient's post-treatment endothelial cell count remained critically low at 987 cells/mm^2, underscoring Ripasudil's inability to reverse advanced endothelial cell loss. This finding aligns with studies cautioning against relying solely on Rho kinase inhibitors in late-stage Pseudophakic Bullous Keratopathy, where endothelial transplantation remains the definitive treatment approach [7, 11–14].

Similarly, the modest increase in endothelial cell count observed in case 3 after 11 months of treatment supports the hypothesis that Ripasudil stabilizes, rather than regenerates.

Treatment for PBK can be categorized as medical or surgical, with the choice largely dependent on the severity of the condition and the patient's individual needs. Medical management is typically the first line of treatment for mild cases and aims to reduce corneal edema and relieve symptoms [1, 2]. This often involves the use of hypertonic saline solutions to draw water out of the cornea, therapeutic contact lenses for comfort and improved vision, and medications like topical steroids to reduce inflammation. Autologous serum tears, rich in growth factors, can also be used to promote corneal healing [1, 2].

However, in cases where medical management fails to control the condition or the patient presents with more advanced disease, surgical intervention becomes necessary. Corneal transplantation, which involves replacing the damaged cornea with a healthy donor cornea, is a mainstay of surgical treatment for PBK like penetrating keratoplasty and endothelial keratoplasty [1, 2, 16].

Beyond these established treatments, emerging therapies are being investigated for their potential in PBK management. One such avenue involves ROCK inhibitors, a class of medications that have shown promise in glaucoma treatment by improving fluid outflow from the eye. Research suggests that ROCK inhibitors may also promote corneal endothelial cell survival and function, potentially offering a novel therapeutic target for PBK [17, 18].

These findings align with previous studies that have shown the efficacy of Ripasudil, in improving corneal edema and visual acuity in various corneal disorders [7], playing a crucial role in regulating corneal endothelial cell function and maintaining corneal transparency [17, 18].

Ripasudil, a selective ROCK inhibitor, mechanism of action involves inhibiting the Rho-associated coiled-coil forming protein kinase, which plays a critical role in cellular processes, such as actin cytoskeleton organization, cell contraction, and apoptosis [8]. This inhibitory action is particularly relevant in ocular diseases where elevated ROCK activity is implicated. In conditions, such as glaucoma and corneal endothelial dysfunction, increased ROCK activity contributes to disease progression [8, 19, 20]. By inhibiting ROCK, Ripasudil effectively intercepts this pathway, leading to beneficial outcomes. Specifically, Ripasudil promotes aqueous humor outflow, thereby reducing intraocular pressure, which is a primary therapeutic goal in glaucoma management. Furthermore, Ripasudil's action extends, protecting corneal endothelial cells by suppressing ROCK-mediated apoptosis, enhancing cell survival, contributing to its efficacy in treating corneal edema [17, 18].

The role of ROCK in apoptosis, particularly in the corneal endothelium, is complex and can vary depending on the phase of apoptosis and the initiating stimulus. While some studies suggest that ROCK is primarily involved in the execution phase of apoptosis, such as membrane blebbing, evidence also indicates that ROCK activation contributes to the initiation phase[8, 19, 20]. For instance, ROCK activation, potentially triggered by UV stimulation, can lead to myosin light

chain phosphorylation, actin cytoskeleton contraction, and ultimately, loss of cell adhesion, which may trigger apoptosis in corneal endothelial cells. This nuanced understanding of ROCK's role in apoptosis, particularly in the context of corneal endothelial cells, underscores the importance of further research into the specific mechanisms and potential therapeutic targets for ocular diseases[8, 19, 20].

Another notable finding from the study is the duration of treatment with Ripasudil. In case 3, the patient underwent treatment for a period of eleven months, which led to significant clinical improvement.

With respect to adverse side effects, no severe reactions were observed across all three patients, including the patient in Case 3 who underwent treatment for 11 months, aside from mild conjunctival hyperemia and ocular surface discomfort. Notably, conjunctivitis, eyelid inflammation, eye irritation, and blepharitis were not detected in any of the subjects. All patients were strictly adherent to the relatively short treatment regimen, including patient number 3, with no temporary interruptions or missed applications. The patients received their medication through pharmacy preparation. The findings in this case series suggest that the use of Ripasudil, appears to be a promising approach for managing corneal edema associated with PBK, indicate its potential to mitigate the corneal dysfunction characteristic of PBK. Ripasudil provides a hopeful alternative to traditional treatments, such as hypertonic saline solutions and corticosteroids, which can have limited efficacy or significant side effects, respectively. The small sample size limits conclusions. Larger, controlled studies are needed to fully assess Ripasudil's efficacy, optimal dosage, duration, and long-term safety in treating this condition.

Conclusion

Ripasudil, shows promise in managing corneal edema in PBK. The present findings corroborate existing evidence that Ripasudil effectively mitigates corneal edema and improves visual acuity in mild-to-moderate PBK. This case series demonstrated improvements in visual acuity and reduced central corneal thickness. However, varied outcomes in corneal thickness and endothelial cell count indicate different impacts across patients, implies that Ripasudil primarily enhances cell function rather than proliferation. Further studies, involving a larger number of patients, should be conducted in the future to improve the understanding of treatments for patients with PBK.

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Author contributions
NE wrote the manuscript and examined the patient. NS collected the data from the patient's examination, performed the examination, and revised the manuscript. SM, IN, DS, DL, and IL contributed to revising the manuscript and interpreting the findings. YW examined the patient, collected data, and revised the final version of the manuscript. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

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Availability of data and materials
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Hadassah Medical Center.

Declarations

Ethics approval and consent to participate
Ethical approval is not required for this study in accordance with local or national guidelines.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
None.

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