

Netarsudil and Corneal Edema: An Update and Review of the Literature

Duncan C Troup¹, Muhammad Z Chauhan¹, Zhuojun Guo¹, Carina T Sanvicente¹, David B Warner¹, Ahmed B Sallam^{1,2}

¹Department of Ophthalmology, Harvey and Bernice Jones Eye Institute, the University of Arkansas for Medical Sciences, Little Rock, AR, USA;

²Department of Ophthalmology, Ain Shams University, Cairo, Egypt

Correspondence: Ahmed B Sallam, Department of Ophthalmology, Jones Eye Institute, the University of Arkansas for Medical Sciences, 4301 W Markham Street # 523, Little Rock, AR, 72205, USA, Email ahmedsallam1@yahoo.com

Abstract: Netarsudil, a Rho-associated protein kinase (ROCK) inhibitor, was initially approved for the treatment of glaucoma and ocular hypertension due to its intraocular pressure-lowering effects. More recently, its pharmacologic activity in corneal tissues has generated interest in its therapeutic use for endothelial dysfunction. However, with widespread adoption, an unanticipated and visually significant adverse effect has emerged, reticular epithelial edema (REE). This condition is characterized by superficial microcystic epithelial changes arranged in a distinctive honeycomb pattern. REE most commonly arises in eyes with reduced endothelial reserve, such as those with Fuchs endothelial dystrophy, prior keratoplasty, or glaucoma drainage devices, and typically resolves following drug discontinuation. Experimental and clinical data suggest that while netarsudil enhances endothelial pump function and cellular adhesion, it may concurrently disrupt epithelial tight junctions, leading to paracellular fluid accumulation and REE. This review provides the first comprehensive synthesis of case reports, case series, clinical studies, and experimental data to characterize the dual effects of netarsudil on the cornea, with particular emphasis on the pathogenesis and risk factors for REE. By integrating mechanistic and clinical evidence, the review aims to support risk stratification and inform patient selection. Further research is needed to clarify the incidence, risk modifiers, and pathophysiology of REE, and to better identify patient populations most likely to benefit from netarsudil versus those at increased risk for epithelial adverse effects.

Keywords: netarsudil, rho kinase inhibitor, corneal edema, reticular epithelial edema, corneal endothelium, adverse drug reactions

Introduction

Netarsudil is a Rho-associated protein kinase (ROCK) inhibitor approved for the treatment of primary open-angle glaucoma (POAG) and ocular hypertension.¹ Its primary mechanism involves relaxation of the trabecular meshwork through actomyosin modulation, enhancing aqueous humor outflow and lowering intraocular pressure (IOP).¹ Beyond lowering IOP, netarsudil also acts on other ocular tissues, including the cornea, where ROCK signaling influences cellular adhesion, migration, and wound healing.^{2,3} These additional corneal effects have drawn attention to netarsudil's potential therapeutic use in corneal endothelial dysfunction, particularly in conditions such as Fuchs endothelial corneal dystrophy (FECD) and in the perioperative period following endothelial keratoplasty.^{2,4,5} Preliminary studies suggest that netarsudil may enhance endothelial recovery and promote corneal clearance in select patients.⁶ In early clinical trials, netarsudil demonstrated a favorable safety profile, with reported adverse effects limited to mild, non-vision-threatening findings such as conjunctival hyperemia and corneal verticillata.⁶⁻⁸ However, as clinical use of netarsudil has expanded, case reports have revealed an unanticipated corneal adverse effect: reticular epithelial edema (REE), also referred to as corneal honeycombing.^{6,9,10} Because patients treated for glaucoma often have coexisting corneal disease, awareness of these tissue-specific responses is essential for safe and effective use of ROCK inhibitors. This review focuses primarily on clinical outcomes and risk factors associated with netarsudil-induced REE, with mechanistic findings incorporated to support interpretation and patient risk stratification. Additionally, the review briefly addresses netarsudil's therapeutic potential in endothelial disease to provide a balanced perspective on its evolving corneal safety and utility profile.

Methods

We performed a PubMed search using the terms “netarsudil” AND “corneal edema”. Additional searches were done for “reticular epithelial edema” and “corneal honeycombing”. We further checked for other relevant publications through manual review of reference lists in key articles and related reviews on ROCK inhibition. There was no statistical analysis or formal study quality assessment performed.

Background and Pathophysiology of Corneal Edema

The cornea’s transparency depends on the precise organization and controlled hydration of its layers. This balance is maintained primarily by the corneal endothelium, which regulates fluid content through a “pump-leak” mechanism.¹¹ The stromal extracellular matrix, rich in hydrophilic glycosaminoglycans, creates a constant osmotic pressure that draws fluid in from the aqueous humor. To counter this, endothelial cells actively transport ions, and thus fluid, out of the stroma, maintaining a state of relative dehydration.¹¹ Corneal clarity is compromised when hydration deviates from the normal physiological level of approximately 78%.¹² Any disruption to endothelial function or cell density can upset this equilibrium, resulting in corneal edema and impaired vision.

A crucial limitation of the human corneal endothelium is that it is nonregenerative *in vivo*. Instead, neighboring cells enlarge and increase their pump activity to compensate for cell loss, but only to a limited extent.¹¹ When cell density declines below 500–1000 cells/mm², from a normal of ~2500, the remaining cells can no longer maintain proper stromal dehydration, resulting in chronic corneal edema.¹³ This decline in cell density narrows the margin of safety against further stress, and damage from disease, intraocular surgery, inflammation, or toxic exposures may lead to irreversible endothelial decompensation, as lost cells cannot be replaced through mitosis.¹⁴

Although not the focus of this review, it is important to recognize that corneal edema may be more likely to occur in patients with underlying endothelial compromise, whether primary or secondary. FECD, the most common primary endothelial disorder, is characterized by progressive endothelial cell loss, guttae formation, and stromal thickening. It typically presents in women in their 50s or 60s, driven by oxidative stress and genetic factors.^{13,14} Secondary endothelial dysfunction may also arise from prior cataract surgery in the form of pseudophakic bullous keratopathy (PBK), especially when complicated or performed in eyes with low endothelial reserve.^{14,15} Glaucoma-related stressors, including chronically elevated intraocular pressure and surgical interventions such as drainage devices, also contribute to endothelial dysfunction.¹⁶ Additionally, patients with prior corneal transplants are at risk of endothelial failure from chronic loss or immunologic rejection.^{14,17} Pediatric patients with congenital ocular abnormalities such as Axenfeld-Rieger syndrome, congenital glaucoma, and persistent fetal vasculature may also have low endothelial reserve due to multiple early-life procedures and structural anomalies, rendering them susceptible to decompensation under pharmacologic stress.^{18–20}

Across these etiologies, the mechanism of chronic corneal edema remains the same, dysfunction of the endothelial pump leading to disruption of stromal dehydration, resulting in loss of corneal transparency. This broader physiologic context is essential to understanding why some patients develop adverse corneal responses to agents like netarsudil, while others may benefit from its endothelial support.

Netarsudil’s Mechanism of Action

Being a Rho-associated protein kinase (ROCK) inhibitor, netarsudil lowers intraocular pressure by promoting relaxation of the trabecular meshwork and Schlemm’s canal.¹ ROCKs, specifically the isoforms ROCK1 and ROCK2, are downstream effectors of RhoA, a small GTPase regulated by guanine nucleotide exchange factors (GEFs), GTPase-activating proteins (GAPs), and guanine nucleotide dissociation inhibitors (GDIs).²¹ Upon activation, ROCK enzymes phosphorylate target proteins involved in actin cytoskeletal dynamics, including myosin light chain (MLC), leading to changes in actomyosin contraction, cellular stiffness, and adhesion.²¹ Netarsudil directly inhibits ROCK1 and ROCK2, disrupting phosphorylation of cytoskeletal targets downstream of RhoA.²² In the trabecular meshwork, this results in cytoskeletal relaxation and increased aqueous outflow through the conventional pathway.^{1,22} Additionally, netarsudil inhibits the norepinephrine transporter (NET), which reduces aqueous humor production and may also lower episcleral venous pressure.¹ These combined effects result in clinically meaningful IOP reductions, particularly in patients with elevated baseline pressures or those inadequately controlled with standard therapies.^{1,6}

A recent *in vitro* study by Schlötzer-Schrehardt et al provided mechanistic insight into the dual effects of ROCK inhibition, evaluating netarsudil in human corneal endothelial and epithelial cell layers separately.³ In endothelial cells, netarsudil induced actin cytoskeletal reorganization and reinforced tight junctions. These structural changes were accompanied by enhanced proliferation and migration, along with upregulation of ion transport proteins including Na⁺/K⁺-ATPase, bicarbonate transporters, and aquaporins at clinically relevant concentrations (Figure 1).³ Functionally, these effects reduced paracellular permeability and supported barrier integrity, demonstrating improved endothelial pump and barrier performance *in vitro*.³ Clinically, these mechanisms are consistent with reports of central corneal thickness reduction, accelerated clearance after Descemetorhexis Without Endothelial Keratoplasty (DWEK), and improved visual acuity in FECD and post-transplant patients.²

In contrast, in corneal epithelial cell cultures, ROCK inhibition has been shown to impair epithelial barrier function. The pan-ROCK inhibitor Y-27632 disrupted tight junction architecture, reduced transepithelial electrical resistance (TEER), and caused occludin mislocalization, consistent with increased paracellular permeability.²³ Netarsudil similarly downregulated expression of tight junction proteins ZO-1 (TJP1), occludin (OCLN), and claudin-1 (CLDN1), as well as hemidesmosomal components including integrin $\alpha 6$ (ITGA6) and $\beta 4$ (ITGB4), with corresponding reductions in ZO-1, E-cadherin, and integrin $\alpha 6$ immunostaining (Figure 2).³ These changes destabilize both cell–cell and cell–matrix adhesion in the epithelium, increasing FITC–dextran permeability and reducing TEER. Importantly, these epithelial effects are reversible upon drug discontinuation, paralleling the resolution of REE observed in clinical settings.³

Collectively, these findings underscore the nuanced biology of ROCK inhibition. While netarsudil confers beneficial effects on the endothelium, enhancing pump and barrier function, it may simultaneously compromise epithelial barrier integrity, predisposing the patient to REE. This balance between therapeutic benefit and epithelial risk is critical to understanding netarsudil's role in corneal disease and will be further explored in subsequent sections.

Clinical Evidence

Several clinical studies have evaluated the ocular effects of netarsudil, beginning with Phase 3 trials conducted in patients with open-angle glaucoma and ocular hypertension. The two trials, ROCKET-1 and ROCKET-2, enrolled 411 and 756 patients, respectively. ROCKET-1 had a follow-up duration of 3 months, while ROCKET-2 extended to 12 months.^{7,8} Neither trial reported corneal epithelial complications; however, both excluded patients with preexisting corneal disease

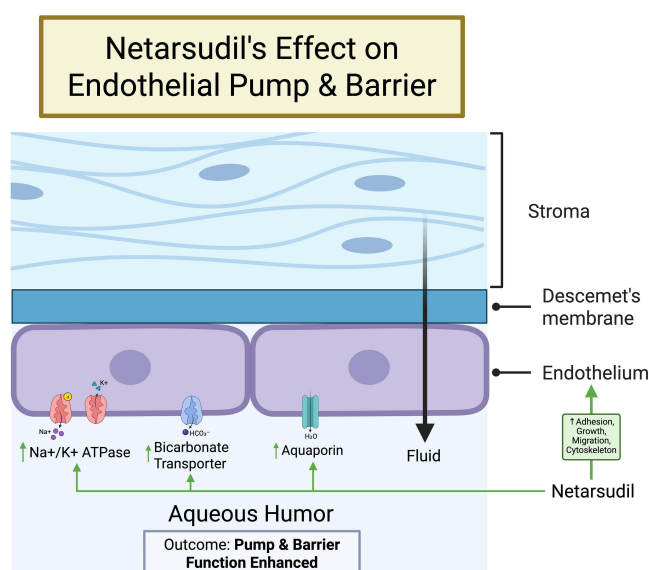


Figure 1 Netarsudil promotes corneal endothelial pump and barrier function through ion transporter upregulation and improved cytoskeletal organization. (Created in BioRender. Troup, (D) (2025) <https://BioRender.com/x0n3vkf>). Netarsudil upregulates Na⁺/K⁺-ATPase, bicarbonate transporters, and aquaporins in corneal endothelial cells, promoting fluid movement to the aqueous humor. Together with improved cytoskeletal organization, adhesion, migration, and proliferation, these changes strengthen pump and barrier function, facilitating stromal fluid clearance.

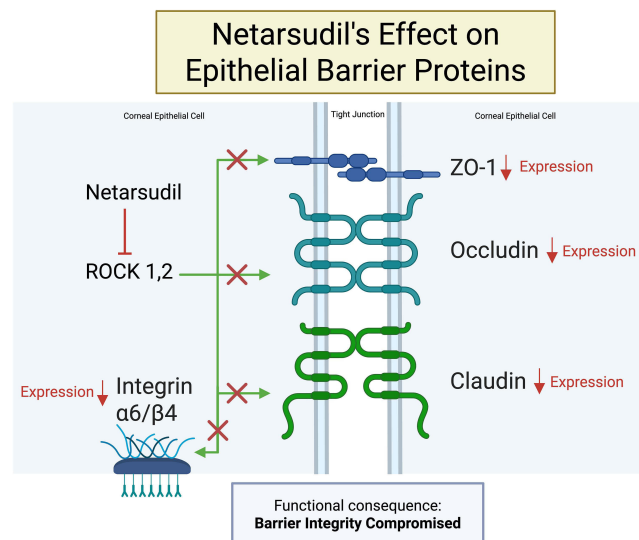


Figure 2 Netarsudil inhibits ROCK1/2, reducing tight junction protein expression and compromising epithelial barrier integrity (Created in BioRender. Troup, (D) (2025) <https://BioRender.com/x0n3vkf>). Netarsudil inhibits Rho-associated protein kinases ROCK1 and ROCK2, leading to reduced expression of tight junction proteins ZO-1, occludin, and claudin-1. These changes disrupt cell–cell junctional stability and compromise epithelial barrier integrity, contributing to increased paracellular permeability and reduced transepithelial electrical resistance (TEER).

or recent intraocular or refractive surgery, including those with prior surgical intervention for glaucoma, secondary glaucoma such as pseudoexfoliation or pigment dispersion, central corneal thickness greater than 600 μm , or clinically significant ocular pathology.^{7,8} These exclusion criteria selected patients with structurally normal corneas, thereby limiting generalizability to populations with compromised endothelial function or reduced reserve. While neither trial reported corneal epithelial complications, subsequent case reports and early-phase studies have revealed a more complex profile.^{7,8} A growing body of literature now documents both therapeutic and adverse corneal responses to netarsudil across a range of clinical contexts. This section summarizes available clinical evidence, including pilot trials, case series, and individual reports, with attention to two major patterns: (1) therapeutic benefit in the setting of endothelial decompensation and (2) the development of reticular epithelial edema (REE). Emerging data suggest that certain ocular comorbidities and clinical contexts may significantly influence the corneal response. The following subsections examine these patterns and their clinical implications.

Therapeutic Use of Netarsudil in Endothelial Dysfunction

Multiple studies support the therapeutic potential of netarsudil for managing corneal edema related to endothelial dysfunction, particularly in cases of FECD or following Descemet stripping procedures.⁶ In a randomized Phase 2 trial of 40 patients with FECD, once-daily netarsudil reduced central corneal thickness by a mean of $\sim 28.4 \mu\text{m}$ at week 4; across both dosing groups, 25% gained ≥ 10 ETDRS letters and 12.5% achieved complete edema resolution, supporting a potential role for enhancing endothelial pump and barrier function.⁴ Notably, however, one patient in the study developed netarsudil-associated REE.⁴ Additionally, Davies et al conducted a prospective pilot study evaluating corneal clearance after DWEK.⁵ In this study of 20 eyes from 10 patients, netarsudil administered immediately postoperatively led to significantly faster corneal clearance (mean 4.6 weeks) compared to delayed administration (mean 8 weeks), with a corresponding improvement in central endothelial cell density at 6 months.⁵ These findings support the hypothesis that early initiation of netarsudil may facilitate corneal recovery by promoting endothelial cell migration and function during the critical perioperative period. Similarly, Price et al conducted a randomized, double-masked pilot study in 29 subjects with FECD, which demonstrated that once-daily netarsudil 0.02% for 3 months significantly reduced central corneal thickness by a mean of $24 \mu\text{m}$ compared with a $2 \mu\text{m}$ increase in the placebo arm and improved scotopic CDVA by a mean of 1.9 lines versus 0.3 lines with placebo.²⁴ While most patients tolerated treatment well, a few ocular side effects were reported, including glare and irritation.²⁴ Beyond FECD, case reports have described improvement in other causes

of endothelial decompensation. In one report, a 31-year-old man with corneal endothelitis–associated endothelial decompensation (baseline BCVA 0.05, CED 436 cells/mm²) failed four months of steroids/antivirals but improved rapidly with netarsudil 0.02% twice daily, achieving BCVA 0.7 and CED 1527 cells/mm² by seven months with normalization of corneal structure.²⁵ Davies (2021) described a case series in which netarsudil led to substantial corneal clearance in patients with endothelial dysfunction from diverse causes, including ICE syndrome and penetrating keratoplasty failure.²⁶ In three of four cases, corneal edema resolved within 2–4 weeks of treatment, with no recurrence after cessation.²⁶ The single nonresponder experienced pain upon instillation and required surgical intervention.²⁶ These findings suggest that netarsudil may offer a reversible, non-invasive treatment for select patients with endothelial disease, though its efficacy may depend on baseline endothelial health and tolerability.

Reticular Epithelial Edema

Multiple case reports and series, encompassing at least 70 reported patients, have documented a distinctive reticular honeycomb pattern of corneal epithelial edema associated with netarsudil therapy.⁶ A summary of published cases of netarsudil-associated REE is provided in Table 1.

Clinically, netarsudil-associated REE presents as collections of superficial microcystic epithelial bullae arranged in an interconnected reticular network across the cornea, typically confined to the epithelium; slit-lamp examination reveals diffuse epithelial microbullae, often most prominent inferiorly (Figure 3).³⁹

In eyes with prior transplants, both the donor and host epithelium can be involved.⁴⁰ The mean time to clinical diagnosis of REE, calculated from cases with clearly reported dates, was ~31 days after starting netarsudil; the shortest diagnosis occurred 1 day after initiation, whereas the longest was after 6 months of treatment.^{38,40} However, delayed presentations have been reported; in four cases, patients tolerated netarsudil for 2 to 13 months before REE emerged rapidly, often within days of additional stressors such as diode cyclophotocoagulation, phacoemulsification, and DSAEK.^{30,33,36,40} Most affected eyes (~87%) had pre-existing endothelial compromise or risk factors, including prior corneal transplant, Fuchs endothelial dystrophy, glaucoma drainage devices, chronic glaucoma with elevated IOP, or inflammatory damage.^{10,31,37,40} Uveitis has been reported in seven cases of REE.^{9,10,28,37,40,46} In only two, both with recent or minimally active anterior uveitis, was the inflammation present at onset.^{28,46} In the remainder, the uveitis was quiescent or remote. Importantly, all seven cases had additional ocular comorbidities likely to compromise corneal endothelial health, including Fuchs endothelial dystrophy, prior corneal transplantation (PK or DSEK), aphakia, anterior basement membrane dystrophy, chronic glaucoma, and recent intraocular surgery. Several cases also had extensive history of previous glaucoma surgery, such as Ahmed valve placement, multiple trabeculectomies, or both. This consistent overlap suggests that while uveitis may contribute to susceptibility, it is rarely the sole driver of REE in the absence of other corneal risk factors.^{9,10,28,37,40,46} Notably, REE has also been reported in eyes without any corneal risk factors, uveitis or prior glaucoma surgery including those with primary open-angle, neovascular, and traumatic glaucoma.^{27,31,32} In two of these reports, clinical details such as intraocular pressure, disease duration, evidence of prior ocular injury, or corneal compromise were not provided, making it unclear whether subclinical endothelial dysfunction may have been present. REE has also been reported in pediatric populations, and in one prospective study, nine of sixteen children treated with netarsudil developed corneal honeycombing.³⁵ The majority of these patients had congenital or developmental ocular conditions such as Axenfeld-Rieger syndrome, congenital glaucoma, persistent fetal vasculature, coloboma, or microphthalmia, along with a history of prior intraocular surgeries.^{31,35,38} This high rate of REE in children with underlying structural anomalies suggests that complex pediatric ocular pathology may increase susceptibility to netarsudil-associated REE.

Importantly, REE is reversible; nearly all reports note improvement in the reticular edema and corresponding visual acuity after netarsudil is discontinued.⁶ Additionally, several cases have demonstrated that REE can resolve despite continued netarsudil use, suggesting that the edema may be transient in certain contexts where endothelial function is temporarily compromised. Examples include clearance within 15 days in a patient with a partially detached DMEK graft, improvement over weeks in a post-rejection PK patient with graft–host junction REE, near-complete resolution within 1 week in a monocular patient with mild inferior REE after anterior uveitis, complete resolution over 6 weeks in a patient with neovascular glaucoma and baseline stromal edema, and resolution of REE with improved endothelial graft rejection with topical steroids, all while

Table I Summary of Published Cases of Netarsudil-Associated Reticular Epithelial Edema

Author (Year)	Study Type	Patient Demographics, Ocular History, and Comorbidities	Indication for Netarsudil	Edema Features	Onset	Management	Time to Resolution and Outcome	Additional Notes
Schlötzer-Schrehardt et al (2025)³	Case report + in vitro lab study	32F with CHED, secondary open-angle glaucoma, and multiple prior surgeries (4 PKs, trabeculectomy, CPC)	IOP control with Roclanda (netarsudil/latanoprost)	Inferior cornea developed REE ~6 months after initiation	~6 months	Roclanda Discontinued	REE resolved within 4 weeks	First REE case with Roclanda; in vitro data suggest netarsudil improves endothelial function but disrupts epithelial junctions, supporting reversible, cell-specific toxicity
Kamdar et al (2024)²⁷	Case report	65M with NVG secondary to CRAO, diabetes, pseudophakia, no recent surgery	IOP control (initial IOP 36 mmHg)	Honeycomb-like subepithelial lesions OS	1 week	Continued netarsudil	REE resolved by 6 weeks without discontinuation	No known risk factors; diagnosis confirmed via slit lamp and AS-OCT
Dellostritto et al (2024)²⁸	Case report	46F with monocular advanced POAG OD, high myopia OU, prior RD (laser retinopexy) OD, recent CE and rebound uveitis OD	IOP spike (38 mmHg); Netarsudil added to multi-agent regimen	Inferior subepithelial bullae and stromal edema OD	1 week	Continued netarsudil	Resolved in ~1 weeks with continued use; VA improved; no recurrence	First case of REE resolving without stopping netarsudil; may be self-limiting in mild cases
Park et al (2024)²⁹	Case report	74M with Fuchs dystrophy, POAG, and prior CME	IOP control, likely steroid-induced	Diffuse REE with 3+ microcystic edema OS	3 weeks	Netarsudil stopped; superficial keratectomy	Moderate improvement at 7 weeks; VA improved from 20/200 to 20/80 after superficial keratectomy	Initially misdiagnosed as bullous keratopathy; underscores diagnostic challenge in compromised corneas
Rashad et al (2023)³⁰	Case report	76M, OS; PBK; chronic angle closure glaucoma; dislocated PCIOL → PPV + sutured IOL (suture revised); macular scar; baseline VA 20/200, CCT 664 µm	IOP control + endothelial support for edema	360° peripheral REE at graft edge 1 wk post-DSAEK; later focal REE over inferior graft rejection; persistent peripheral REE outside graft	1 week post DSEK after ~8 mo tolerance	Continued netarsudil; NaCl 5% QID; prednisolone 1% (restarted hourly → taper) for rejection	Focal REE improved in 2 wks and resolved by ~1 mo with steroids; peripheral REE improved but persisted at 14 mo; VA back to baseline (20/200), IOP 21	REE tracked endothelial function; improved despite continued netarsudil; delayed onset; supports endothelial-dependence hypothesis
Mandlik et al (2023)³¹	Case series (2 patients)	Case 1: 12M, post-PK, steroid-induced OHT; Case 2: 75F, NVG	IOP control	Honeycomb-like REE in inferior cornea, including graft-host junction	Case 1: 2 weeks; Case 2: 4 months	Discontinued netarsudil	REE resolved in 7–10 days	Occurred in eyes with grafts or NVG; supports reversibility with drug cessation
Kumar et al (2023)³²	Case series (2 patients)	40M and 20M, both with traumatic glaucoma on multiple topical agents	IOP control in traumatic glaucoma	Diffuse, limbus-to-limbus bullous REE OD in both cases	Case 1: 3 weeks; Case 2: 1 week	Netarsudil discontinued; both underwent valved GDI placement	Case 1: REE resolved in 1 week (BCVA 20/240 → 20/80); Case 2: resolved in 2 days (BCVA 20/120 → 20/40)	REE occurred despite absence of typical risk factors; highlights need for vigilance even in low-risk eyes

Rodgers et al (2023) ³³	Case report	68F with CACG OU (severe OD), amblyopia OD, prior trab + CE/IOL OD, no baseline edema	IOP control OS (13 mo of netarsudil pre-op)	Central honeycomb REE OS, onset 1 wk post-CE	1 week postoperatively (after 13 months of prior tolerance)	Netarsudil stopped; NaCl 5% ointment used	Resolved by wk 3; BCVA improved from CF to 20/40; residual edema; ECD <500	REE after phaco despite prior tolerance; highlights periop risk with ROCK inhibitors
Parmar et al (2023) ³⁴	Case series (4 patients)	Case 1: 60M, phacomorphic glaucoma, recent CE; Case 2: 45F, large eccentric PK; Case 3: 60F, DM, post-DSEK; Case 4: 24M, post-repeat PK with prior rejection	IOP control and off-label use to support endothelial function in eyes with preexisting or surgical risk of corneal edema.	Case 1: Diffuse REE; Case 2: Diffuse REE; Case 3: Central REE; Case 4: Peripheral REE near graft-host junction	Case 1: 1 week Case 2: 10 days Case 3: 17 days Case 4: 2 weeks	Netarsudil stopped in 3 cases; continued in Case 4 (spared visual axis, no symptoms)	REE resolved in Cases 1 and 2 within 1 week, Case 3 resolved in 10 days; REE persisted in Case 4; stromal edema partially cleared in all	REE developed in all cases with endothelial compromise (PK, DSEK, CE); mimicked transplant edema; one case tolerated ongoing netarsudil with preserved vision
Lindstrom et al (2022) ⁴	Phase 2 randomized, open-label parallel-group study	40 pts with Fuchs dystrophy; mean age ~68 y; CCT ≥600 µm; BCVA 20/40–20/400; no recent surgery or advanced disease	Off-label use for corneal edema in Fuchs	1 pt (2.5%) in BID group developed REE	Not reported; presumed within 8-wk treatment	Stopped netarsudil	REE resolved 5 weeks after discontinuation	REE was rare, self-limited, and only seen with BID; caution advised in compromised endothelia
Gupta et al (2022) ³⁵	Prospective cohort study	16 children (mean age 6.1 y); 9 developed REE (median age 3.1 y); diagnoses: PCG (5), ARS with glaucoma (2), JOAG (2); 7/9 had preexisting edema; mean IOP 35.6 mmHg	IOP control in refractory pediatric glaucoma	REE after ≥2 wks netarsudil 0.02% QD; confirmed via slit lamp and AS-OCT; involved interpalpebral/inferior/superior zones	≥2 wks after starting netarsudil; individual onset not specified	Netarsudil stopped after REE identified	REE resolved in all affected eyes within 1–3 wks of discontinuation	REE linked to young age, high IOP, and preexisting edema; may involve epithelial barrier dysfunction and fluid shift; supports caution in pediatric eyes with angle or corneal pathology
Guzman Aparicio et al (2022) ³⁶	Case series (2 patients)	Case 1: 6M with anophthalmia OD and complex OS (PFV, coloboma, microphthalmia) s/p lensectomy + vitrectomy; long-term netarsudil use; Case 2: 3-mo-old boy with bilateral ocular HTN s/p PPV for vitreous hemorrhage	IOP control in refractory pediatric glaucoma	Case 1: Diffuse REE following transscleral cyclophotocoagulation after 13 months on netarsudil. Case 2: Inferior REE noted OS.	Case 1: 1 day post-op after 13 months on netarsudil Case 2: 5 weeks	Netarsudil discontinued in both cases	REE resolved by 6 wks in Case 1, 2 months in Case 2	Case 1 onset post-op suggests inflammatory trigger; Case 2 had delayed, unilateral REE despite bilateral use; both underscore caution in pediatric eyes post-surgery or with complex history
Jeang et al (2022) ³⁷	Case report	76F with JIA, aphakia, mixed-mechanism glaucoma, PK OU (chronically edematous OD)	IOP control post-PK	Inferior REE on left PK graft 10 days after starting netarsudil; confirmed by slit lamp and AS-OCT	10 days	Netarsudil stopped; NaCl 5%; pre-existing steroid/timolol continued	REE resolved by 4 mo; VA improved to 20/60	REE occurred in the relatively healthy PK eye; ROCK inhibition may disrupt junctions; underscores need to stop with pain or vision decline

(Continued)

Table 1 (Continued).

Author (Year)	Study Type	Patient Demographics, Ocular History, and Comorbidities	Indication for Netarsudil	Edema Features	Onset	Management	Time to Resolution and Outcome	Additional Notes
Bhargava et al (2022) ³⁸	Retrospective observational study	12 eyes from 11 patients (8 on netarsudil, 4 on ripasudil) (mean age 51, 8 male, 3 female); varied comorbidities (FECD, PBK, prior PK, PACG, NVG, corneal ulcers); some with preexisting edema or endothelial decompensation.	IOP control (9 eyes), off-label endothelial decompensation (3 eyes)	REE with honeycomb pattern; micro- to macrocystic bullae typically paracentral/inferior; confined to epithelium on AS-OCT	Mean 25 days (range 1–80 days)	Netarsudil discontinued in most cases; conservative treatment with hypertonic saline, lubricants, and anti-allergic drops before cessation. In select asymptomatic cases or where the visual axis was spared, netarsudil was continued.	Resolution of REE in all eyes where drug was stopped; mean resolution 10 days for netarsudil; symptoms improved; BCVA improved or unchanged	REE may mimic progression of endothelial decompensation; risk factors include prior corneal edema, endothelial disease, or prior intraocular surgery; netarsudil acts as double-edged sword in compromised endothelium
Khalili et al (2022) ³⁹	Case report	39-year-old man with POAG OD; history of CE at age 14, scleral-sutured IOL, PPV, and Ahmed valve placement OD	IOP control in context of advanced glaucoma with multiple prior surgeries	Diffuse, limbus-to-limbus bullous REE OD; confirmed with AS-OCT	Not precisely specified, but presented while on netarsudil	Netarsudil discontinued; patient underwent cyclophotocoagulation for IOP control	REE resolved after 4 months; VA improved from CF to 20/70; CCT decreased from 768 µm to 598 µm	REE confirmed on AS-OCT. Surgical history suggests impaired endothelial reserve, despite no overt decompensation.
Tran et al (2022) ⁴⁰	Case series (8 patients)	8 patients (22F–77M) with aphakia, complex glaucoma, and extensive ocular surgery; most had endothelial risk factors (eg, low ECD, FECD, bullous keratopathy, prior intraocular procedures).	Primarily for IOP control in glaucoma; some cases with endothelial support intent	Reticular epithelial edema with moderate-sized bullae in a honeycomb pattern; inferior cornea most affected	Case 1: ≥3 mo (poor FU) Case 2: 6 months (REE 1 day post-CPC) Case 3: 2 months Case 4: 6 months Case 5: 2 months Case 6: 1 month Case 7: 2 months (REE 1 day post-2nd CPC) Case 8: 3 days	Netarsudil discontinued in 6/8 cases; continued in 2 (per patient preference or observed improvement).	REE resolved in all cases within 1 week to 2 months; resolution occurred even with continued netarsudil use in 2 patients	REE may emerge acutely post-CPC despite prior netarsudil tolerance, implicating inflammatory triggers; bullae spread and shrink with resolution.

Lyons et al (2022)⁹	Case series (3 patients)	Case 1: 79M with POAG, pseudophakia + ACIOL, prior trab/PPV Case 2: 63F with mixed-mechanism glaucoma, chronic uveitis, pseudophakia, extensive surgical history (Trabectome, CPC, Baerveldt and Ahmed valves with multiple revisions) Case 3: 22F with Axenfeld-Rieger, juvenile glaucoma OD, pseudophakia, chronic corneal edema	IOP control in all patients	Unilateral REE despite bilateral use; honeycomb/cystic epithelial changes, often peripheral; occurred in eyes with preexisting edema or endothelial compromise.	Case 1: 3 weeks Case 2: 4 weeks Case 3: 4 weeks	Netarsudil discontinued in all; case 1 also received Baerveldt implant, case 2 underwent diode laser CPC	Case 1: 1 week; Case 2: 4 weeks; Case 3: 4 weeks	All had complex ocular histories suggesting endothelial compromise; supports hypothesis that REE risk is higher in eyes with endothelial dysfunction
LoBue et al (2021)⁴¹	Case series (4 patients)	Case 1: 69M, traumatic cataract, PCIOL, bullous keratopathy; Case 2: 70M, mixed-mech. glaucoma, endophthalmitis, corneal melt/patch graft; Case 3: 66M, FECD, post-CE, bullous keratopathy Case 4: 84M, POAG, iStent, post-CE, bullous keratopathy	Off-label use for corneal edema (cases 1, 3, and 4), IOP control (case 2)	REE (honeycomb pattern), typically interpalpebral and inferior cornea.	Case 1: 4 weeks Case 2: 2 weeks Case 3: 1 month Case 4: 3 months	Netarsudil discontinued in Cases 1, 2, 4; Continued in Case 3 due to marked improvement in central edema and vision	Case 1: 2 weeks after discontinuation; Case 2: <2 months after discontinuation; Case 3: Persistent REE at 3 months but central edema resolved, VA improved to 20/25, continued netarsudil; Case 4: 2 weeks after discontinuation	REE was transient and reversible. Preexisting corneal edema likely a major risk factor. Authors suggest tight junction disruption as a mechanism.
Chu et al (2021)⁴²	Case report	79F; angle-closure glaucoma OU, pseudophakia, Baerveldt tubes OU, SLT OS	Netarsudil started due to worsening visual field defects OS despite IOP of 17mmHg on Vyzulta	2+ edema with Descemet folds OS; CCT increased from 549 μ m to 808 μ m; VA dropped from 20/40 to 20/200	5 days	Discontinued netarsudil; prescribed sodium chloride drops and ointment OS; added loteprednol later	Timeline not specified; Improved VA and decreased CCT after discontinuation; CCT normalized to 560 μ m and VA improved to 20/30 by 4 months	Unique in that patient had no prior corneal edema or uveitis; suspected interaction between netarsudil and prior ocular surgeries or Vyzulta
Chen et al (2020)⁴³	Case report	66F with advanced POAG OD; trabeculectomy, 3 tube shunts, pseudophakia, and DSEK for bullous keratopathy	IOP control	REE OD (2–9 o'clock, both sides of graft-host junction)	4 weeks	Discontinued netarsudil	REE resolved within 4 weeks; BCVA improved from 20/80 to 20/50; stromal edema persisted	Patient had pre-existing inferior stromal edema; authors suggest endothelial dysfunction may predispose to REE

(Continued)

Table 1 (Continued).

Author (Year)	Study Type	Patient Demographics, Ocular History, and Comorbidities	Indication for Netarsudil	Edema Features	Onset	Management	Time to Resolution and Outcome	Additional Notes
Ramakrishnan et al (2020) ⁴⁴	Case series (2 patients)	Case 1: 72M, POAG OU, CSR OS, CDR 0.8–0.9; Case 2: 29M with aphakia and bilateral glaucoma from congenital rubella, Ahmed valve OD, PPV OS, chronic steroid use OS	IOP control	Inferior REE; Case 1 had bilateral conjunctival hyperemia and keratic precipitates; Case 2 had mild injection without uveitis	Case 1: 3 days Case 2: 3 days	Discontinuation of netarsudil; Case 1 also received oral methazolamide and prednisolone acetate QID; Case 2 had no additional treatment	Case 1: 1 week; Case 2: 2 weeks	REE onset rapid and reversible; may mimic microcystic edema/ bullous keratopathy; no prior endothelial data available; authors emphasize clinician awareness
Wisely et al (2020) ¹⁰	Case Series (5 patients) ^a	Case 1: 82F OS – Fuchs dystrophy, ABMD, prior DSEK (OD), anterior uveitis, CME, OAG; Case 2: 55F OS – Uveitic glaucoma, anterior uveitis OU, Ahmed valve OS, sickle cell trait; prior CE + bleb revision; Case 3: 73F OD – Severe POAG, prior DSEK, Ahmed valves ×2, stromal haze; Case 4: 68M OD – PBK, prior DSEK ×2, ACIOL, Ahmed valve, VMT, retinoschisis; Case 5: 62F OS – Endothelial failure post CE/Ex-Press trab, severe POAG	IOP control (Case 1–4); corneal edema (Cases 3 and 5)	Reticular bullous epithelial edema (inferior-predominant, often paracentral or extending to visual axis); associated with microcystic changes and epithelial irregularities; often preceded by stromal edema	Case 1: 8 weeks Case 2: 2 weeks Case 3: 3 weeks (1st episode), 8 weeks (second episode) Case 4: 2 weeks Case 5: 4 weeks	Netarsudil stopped; some underwent additional surgical procedures (eg, PPV, Ahmed revision, Baerveldt implant)	Case 1: 10 weeks; Case 2: 5 weeks; Case 3: 4 weeks (1st episode), REE improved at 12 weeks though not fully resolved (second episode); Case 4: 2 weeks; Case 5: 4 weeks	All had either preexisting corneal edema or risk factors; proposed mechanism includes epithelial barrier disruption and fluid shift from stroma to epithelium
Chen et al (2020) ⁴⁵	Case report	60M; open-angle glaucoma OU; history of cataract surgery OU, SLT OU, trabectome OD, and trabeculectomies OU with mitomycin	IOP control	1.5 mm inferonasal microcystoid epithelial edema and neovascularization OD; progressed to diffuse epithelial and stromal edema OU; appeared within ~1 month	6 months	Discontinued netarsudil and brimonidine	Complete resolution of edema in both eyes 1 month after discontinuation of netarsudil; CCT returned to near baseline	First known case of REE in glaucoma patient without prior lamellar surgery or cell therapy use, possible ROCK-mediated endothelial change; OCT key to diagnosis

Moumneh et al (2020)⁴⁶	Case series (3 patients)	Case 1: 75F, controlled POAG, prior GATT OU, cataract surgery, ERM peel OU, developed macular edema after netarsudil stopped; Case 2: 75M, POAG, prior PK OD, CME, bilateral trabs, GDI, on multiple drops; Case 3: 76F, secondary glaucoma from idiopathic uveitis, prior PPV, Ahmed valve, cataract surgery	IOP control	Inferior microcystoid epithelial edema with honeycombing pattern; progressed to diffuse reticular edema in graft or native cornea; resolved after netarsudil cessation	Case 1: 1 month Case 2: early edema at 6 months, REE recognized at 11 months Case 3: 3 weeks	Discontinued netarsudil; surgical intervention in Case 1 (Ahmed GDI); medical substitution (pilocarpine, acetazolamide) in Case 3	Case 1: 1 week; Case 2: 1 month; Case 3: 3 weeks; partial VA improvement; Case 1 had persistent 2+ corneal haze; Case 2 had low-grade corneal edema	Case 1 had no prior corneal pathology; authors highlight netarsudil-induced REE may occur even in absence of existing endothelial dysfunction
Fernandez (2018)⁴⁷	Case series (2 patients)	Case 1: Patient with failed DSAEK and stromal edema. Case 2: Patient with partially detached DMEK unresponsive to re-bubbling (demographics not reported)	Off-label use to reduce corneal edema and improve visual acuity	Case 1: Reticular epithelial edema with large epithelial bullae after 5 days of netarsudil; Case 2: REE onset at 11 days after initiation	Case 1: 5 days Case 2: 11 days	Case 1: Superficial keratectomy and repeat DSAEK; Case 2: Continued netarsudil for 15 days	Timeline for resolution not specified; Case 1: VA improved to 20/200 post-op, edema resolved; Case 2: Cornea cleared and BSCVA improved to 20/25 while on netarsudil	First published visual documentation of netarsudil-associated REE; Case 2 suggests REE may spontaneously resolve without drug discontinuation

Abbreviations: ABMD, Anterior Basement Membrane Dystrophy; ACIOL Anterior Chamber Intraocular Lens; ARS, Axenfeld-Rieger Syndrome; AS-OCT, Anterior Segment Optical Coherence Tomography; BCVA, Best Corrected Visual Acuity; BID, Twice Daily; BSCVA, Best Spectacle-Corrected Visual Acuity; CACG, Chronic Angle-Closure Glaucoma; CCT, Central Corneal Thickness; CDR, Cup-to-Disc Ratio; CE, Cataract Extraction; CF, Counting Fingers; CHED, Congenital Hereditary Endothelial Dystrophy; CME, Cystoid Macular Edema; CPC, Cyclophotocoagulation; CRAO, Central Retinal Artery Occlusion; CSR, Central Serous Retinopathy; DMEK, Descemet Membrane Endothelial Keratoplasty; DSAEK, Descemet Stripping Automated Endothelial Keratoplasty; DSEK, Descemet Stripping Endothelial Keratoplasty; ECD, Endothelial Cell Density; ERM, Epiretinal Membrane; F, Female; FECD, Fuchs Endothelial Corneal Dystrophy; FU, Follow up; GATT, Gonioscopy-Assisted Transluminal Trabeculotomy; GDI, Glaucoma Drainage Implant; IOL, Intraocular Lens; IOP, Intraocular Pressure; JIA, Juvenile Idiopathic Arthritis; JOAG, Juvenile Open-Angle Glaucoma; M, Male; NVG, Neovascular Glaucoma; OAG, Open-Angle Glaucoma; OCT, Optical Coherence Tomography; OHT, Ocular Hypertension; OD, Right Eye; OS, Left Eye; OU, Both Eyes; PACG, Primary Angle-Closure Glaucoma; PBK, Pseudophakic Bullous Keratopathy; PCG, Primary Congenital Glaucoma; PCIOL, Posterior Chamber Intraocular Lens; PFV, Persistent Fetal Vasculature; PK, Penetrating Keratoplasty; POAG, Primary Open-Angle Glaucoma; PPV, Pars Plana Vitrectomy; RD, Retinal Detachment; REE, Reticular Epithelial Edema; ROCK, Rho-associated Protein Kinase; s/p, status post; SLT, Selective Laser Trabeculoplasty; VA, Visual Acuity; VMT, Vitreomacular Tracton.

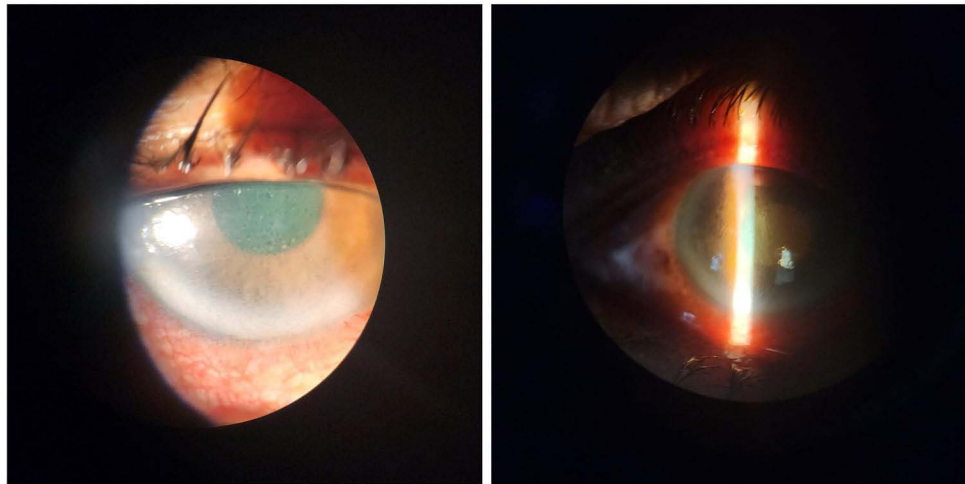


Figure 3 Reticular-pattern epithelial corneal edema in a patient on netarsudil, with a history of anterior uveitis and cataract surgery. Two slit-lamp photographs of the same eye are shown under different illumination angles.

maintaining IOP control.^{27,28,30,34,47} In one rare instance, REE persisted despite discontinuation of netarsudil; the patient required a superficial keratectomy for persistent corneal edema seven weeks after stopping the medication.²⁹ Resolution has been documented as early as 2 days and as late as 4 months after discontinuing netarsudil; however, most cases in the literature resolved within approximately 4 weeks, with serial observations showing the honeycomb epithelial bullae shrinking and gradually vanishing as the cornea clears.^{28,39–41} Though the overall incidence is unknown, REE appears to be an uncommon but increasingly recognized phenomenon in patients with risk factors for corneal compromise. Together, these reports indicate that REE is typically self-limited and resolves with appropriate management. Table 2 summarizes the dual corneal responses to netarsudil, contrasting its therapeutic endothelial and adverse epithelial effects.

Table 2 Comparison of Therapeutic and Adverse Corneal Effects of Netarsudil

	Therapeutic Corneal Effects	Adverse Corneal Effects (REE)
Primary tissue target	Corneal endothelium	Corneal epithelium
Cellular mechanism	ROCK inhibition promotes actin cytoskeletal reorganization, enhances cell adhesion and migration, and upregulates fluid transporters, strengthening pump and barrier function ³	ROCK inhibition downregulates tight-junction and hemidesmosomal proteins, weakening epithelial cohesion and increasing paracellular permeability ^{3,23}
Functional consequence	Accelerated clearance of endothelial-related edema, leading to improved corneal transparency	Loss of epithelial barrier integrity and fluid accumulation within the epithelial layer, forming a reticular “honeycomb” edema pattern
Typical clinical context	Eyes with preserved or partially impaired endothelial reserve, including mild-to-moderate FECD, ⁴ early postoperative recovery after DWEK, ⁵ and select cases of secondary endothelial decompensation (eg. ICE syndrome, post-keratoplasty, or endophthalmitis-associated) ^{25,26}	Eyes with markedly reduced endothelial reserve or cumulative risk factors, including advanced FECD, prior keratoplasty, glaucoma drainage devices, uncontrolled glaucoma, significant ocular surgical history, or congenital structural anomalies ^{10,31,35,37,40}
Clinical implication	May serve as an adjunctive therapy to enhance corneal clarity in eyes with adequate endothelial reserve	Requires caution in eyes with reduced endothelial reserve, where epithelial barrier disruption may precipitate REE

Abbreviations: DWEK, Descemetorhexis Without Endothelial Keratoplasty; FECD, Fuchs Endothelial Corneal Dystrophy; ICE syndrome, Iridocorneal Endothelial Syndrome; REE, Reticular Epithelial Edema; ROCK, Rho-associated Protein Kinase.

Discussion

As clinical use of netarsudil has expanded, an important paradox has emerged: while it offers therapeutic benefit in endothelial dysfunction, it has also been associated with REE, a visually significant adverse effect. This reflects the tissue-specific responses to ROCK inhibition within the cornea, enhancing endothelial pump function and cell adhesion on one hand, while disrupting epithelial tight junctions and increasing paracellular permeability on the other.³ Recognizing this balance is key to identifying patients most likely to benefit, or be harmed, by ROCK inhibition.

Two complementary hypotheses have been proposed to explain the development of REE in patients treated with netarsudil. The first suggests that enhanced endothelial pump activity, stimulated by ROCK inhibition, facilitates stromal fluid clearance while leaving epithelial fluid unaddressed, thereby unmasking subclinical epithelial edema.¹⁰ The second centers on a direct effect on the epithelial barrier, in which tight junction disruption increases paracellular permeability and permits fluid to accumulate within the epithelium.⁴¹ These mechanisms are not mutually exclusive and may act together to account for the reticular pattern of edema observed in clinical practice. Experimental studies support the second hypothesis and have shown that ROCK inhibition compromises epithelial tight junction integrity, allowing fluid to move between cells rather than through them. Importantly, these effects were reversible following drug discontinuation, mirroring the typical clinical course of REE, which often resolves once netarsudil is stopped.³ While direct evidence is limited, it has also been proposed that the epithelial and endothelial layers may influence one another through crosstalk. This could help explain how barrier dysfunction in one layer might affect fluid regulation across the cornea, potentially contributing to the development of REE in susceptible eyes.⁴⁸

Understanding REE as the product of an impaired endothelium and a disrupted epithelial barrier allows clinicians to identify high-risk patients more accurately. A review of reported REE cases reveals a consistent association with underlying or acquired endothelial dysfunction. The most frequent comorbidities include FECD, prior endothelial keratoplasty (eg, DSEK, DMEK), penetrating keratoplasty, and chronic corneal edema, all conditions marked by diminished endothelial cell density or function. Many cases also involved eyes with Ahmed glaucoma valves, typically placed for long-standing or refractory glaucoma. Ahmed valve implantation has been associated with progressive endothelial cell loss, particularly when the tube lies close to the cornea. Thus, the presence of a drainage device not only reflects advanced disease and prior surgical manipulation but also constitutes a direct risk to endothelial integrity.⁴⁹ Uveitis was occasionally reported but rarely occurred in isolation; instead, it coexisted with other high-risk features, suggesting it may augment rather than independently cause REE. REE has also been observed in eyes without predisposing ocular surface disease or prior glaucoma surgery.^{28,32,37} In one such report, a patient with neovascular glaucoma presented with an IOP of 36 mmHg and diffuse corneal stromal edema, suggesting significant endothelial stress.³² Pediatric populations with congenital and structural anomalies also seem to be at an elevated risk for REE. Taken together, these reports strongly suggest that compromised endothelial health renders the cornea more vulnerable to netarsudil-induced REE. Rather than serving as a primary driver, endothelial dysfunction may act as a permissive factor that allows subclinical stromal edema to accumulate, and ROCK inhibitor-induced epithelial barrier dysfunction may serve as the trigger, allowing fluid to shift into the epithelium and produce the characteristic reticular pattern. This framework aligns with emerging mechanistic evidence implicating epithelial compromise as a central event in the pathogenesis of REE.

These findings carry important implications for clinical practice. Patients with significant endothelial dysfunction, such as those with advanced FECD, history of keratoplasty, chronic uncontrolled glaucoma (particularly with glaucoma drainage devices), or congenital anomalies in pediatric patients, may be especially susceptible to REE, particularly when the dysfunction has already resulted in epithelial edema. In such cases, a thorough evaluation of corneal status should precede the initiation of netarsudil therapy, including corneal pachymetry. Once treatment has begun, patients with known risk factors should be informed about the signs of REE and may benefit from follow-up within the first month of therapy, as most reported cases have occurred during this period. However, REE can also emerge later, particularly following added ocular stress in patients who had previously tolerated netarsudil, underscoring the importance of ongoing vigilance in eyes with limited endothelial reserve.^{33,36,40} Slit-lamp examination or anterior segment OCT may

facilitate early detection of reticular changes before they lead to significant visual disturbance. If REE is detected, netarsudil should be discontinued promptly, as the condition appears to be reversible following drug cessation.

Further research is needed to clarify which patients are most likely to benefit from netarsudil and which may be at increased risk for adverse effects such as REE. There are important limitations to our research. While mechanistic insights and case reports have elucidated potential risk factors, important gaps in the literature remain. This review is based primarily on case reports and case series, which represent a lower level of evidence and may be subject to publication bias, and the lack of denominator data in the published literature prevents reliable estimation of the true incidence of REE. Further, pediatric outcomes have been reported only in small series,^{31,35,38} highlighting uncertainty about prevalence and age-specific risk. Broader epidemiologic data are needed to define the incidence of netarsudil-associated REE and to guide patient selection and risk stratification. Randomized controlled trials, though essential for establishing efficacy and safety, often lack the statistical power or duration necessary to detect infrequent or delayed adverse events. The emergence of REE as a rare but clinically meaningful complication highlights the importance of ongoing pharmacovigilance and underscores the need for real-world, post-marketing database studies when assessing medication safety.

Conclusion

Netarsudil has expanded the therapeutic landscape for patients with glaucoma and, more recently, for those with corneal endothelial dysfunction. However, the emergence of REE as an uncommon but distinct adverse effect underscores the complexity of ROCK inhibition in corneal tissue. As this review highlights, netarsudil's corneal effects are tissue-specific, offering potential benefit to the endothelium while simultaneously posing risk to epithelial barrier integrity. While most cases of REE resolve with drug discontinuation, its potential to impair vision warrants careful patient selection and monitoring. Future research should aim to clarify the incidence, risk modifiers, and long-term consequences of REE, ideally through large-scale observational studies and ongoing post-marketing surveillance. Until then, clinicians should remain vigilant and weigh both the therapeutic potential and epithelial risks of netarsudil when managing complex corneal disease.

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