

Reticular epithelial corneal edema as a novel side-effect of Rho Kinase Inhibitors: An Indian scenario

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Purpose: To describe clinical course, characteristics, and outcome of reticular epithelial corneal edema (RECE) occurring as a not-so-infrequent adverse effect of a novel drug, Rho-kinase inhibitors (ROCK-I)- netarsudil (0.02%) and ripasudil (0.4%). **Methods:** This was a retrospective observational non-randomized study. In this study, 12 eyes of 11 patients presenting at a tertiary eye care center between April 2021 and September 2021 were included. All 12 eyes developed a distinctive honeycomb pattern of RECE after starting topical ROCK-I. All patients were subjected to detailed ophthalmic examinations. **Results:** Eight patients were started on netarsudil (0.02%) and three on ripasudil (0.4%). Five eyes had a prior history of corneal edema. The remaining seven had the presence of ocular comorbidities predisposing to corneal edema. The average time for RECE occurrence was 25 days for netarsudil and 82 days for ripasudil. Visual acuity decreased in two eyes, remained unaffected in four eyes, and could not be quantified in four eyes due to preexisting profound visual impairment. Five eyes had symptoms of ocular surface discomfort associated with bullae. Symptoms and bullae resolved in all eyes in whom ROCK-I was stopped. The average time to resolution of RECE was 10 days for netarsudil and 25 days for ripasudil. **Conclusion:** RECE after ROCK-I occurs with the use of both netarsudil and ripasudil, although the characteristics differ. The presence of corneal edema and endothelial decompensation seem to be a risk factor, and cautious use is warranted in these patients. Four clinical stages of RECE are described. ROCK-I act as a double-edged sword in patients with endothelial decompensation. Large-scale studies are required to know the exact incidence, pathophysiology, and long-term consequences of the aforementioned side-effect.

Key words: Anterior segment optical coherence tomography, honeycomb edema, reticular epithelial corneal edema, rho-kinase inhibitors

Rho-associated kinase (ROCK) inhibitors, netarsudil (AR-13503) and ripasudil (K-115), are two novel drugs being used in the medical management of glaucoma and ocular hypertension.^[1] They have been approved by the Pharmaceuticals and Medical Devices Agency of Japan in September 2014^[2] and by the US Food and Drug Administration in December 2017.^[3]

ROCK inhibitors (ROCK-I) lower the intraocular pressure (IOP) by increasing the aqueous humor outflow through trabecular meshwork by disrupting actin stress filaments and decreasing cell stiffness.^[3,4] Netarsudil is also a norepinephrine transporter (NET) inhibitor that contributes to decreased aqueous humor production and reduced episcleral venous pressure.^[5] Other areas of potential use include (1) as a neuroprotective agent by reducing axon cell apoptosis,^[6] (2) to enhance endothelial healing and function, resulting in decreased corneal edema,^[7] (3) as an anti-fibrotic agent to slow down or prevent tissue scarring following glaucoma filtration surgery,^[8] and (4) to attenuate retinal neovascularization and reduce the areas of avascular retina and thus may have

potential in retinal neovascular diseases such as diabetic retinopathy.^[9]

ROCK-I are generally well tolerated and have an optimistic safety profile.^[10] The Rho kinase-elevated IOP treatment (ROCKET) trials, which investigated the efficacy and safety of netarsudil (0.02%), reported conjunctival hyperemia (50%), cornea verticillata (20.9%), and subconjunctival hemorrhages (17.2%) to be the most common adverse effects.^[11] Similarly, for ripasudil (0.4%), the results from a randomized, open-label, placebo-controlled, crossover, multicenter study (JapicCT) showed conjunctival hyperemia (dose-dependent), subconjunctival hemorrhage, and ocular irritation to be most common.^[12,13] Pseudo guttae formation in eyes with preexisting endothelial pathologies post topical ripasudil (0.4%) has also been described in the literature.^[7] Honeycomb-type reticular epithelial corneal edema (RECE) leading to a sudden-onset decrease in visual acuity (VA) was not mentioned in the above safety trials. It

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has recently been described after netarsudil use only by a few authors.^[14-18] For ripasudil, we could only find a mention of it in an article on Descemet's stripping without endothelial keratoplasty (DWEK) by Garcerant *et al.*,^[19] and that too as an additional clinical sign.

Here we report the occurrence, clinical course, probable risk factors, associated symptoms, clinical and anterior segment optical coherence tomography (ASOCT) characteristics, and resolution of RECE following use of topical netarsudil (0.02%) ophthalmic solution (henceforth mentioned as netarsudil) in eight eyes and topical ripasudil (0.4%) ophthalmic solution (henceforth mentioned as ripasudil) in four eyes, the largest compilation of cases by a single author at a single center and largest for ripasudil to date. Also, we hypothesize the clinical stages of RECE and compare it with pseudophakic bullous keratopathy (PBK) and micro-cystic edema (MCE) of high IOP.

Methods

We report a retrospective observational descriptive study in 12 eyes of 11 patients presenting within a span of 6 months (April–September 2021) at a tertiary ophthalmic care center with honeycomb-like RECE after being started on ROCK-I, netarsudil, and ripasudil. Dosing frequency for netarsudil was once daily and twice daily for ripasudil. The patients either had symptoms of sudden onset, painless diminution of vision (DOV), or constant foreign body sensation, ocular discomfort, or no significant symptoms at all. Routine parameters such as age, gender, laterality of eye, presenting complaints, time of onset of symptom, past ocular medical, and surgical history were taken. All patients were then subjected to routine check-up for visual acuity (VA), refraction, IOP with Goldman's applanation tonometer or tonopen, slit-lamp biomicroscopic examination (SLE), and routine fundus examination with an indirect ophthalmoscope at presentation, on development of RECE and on its resolution. Slit-lamp photograph, ASOCT (Spectralis, Heidelberg Engineering), and central corneal thickness (CCT) by ultrasound pachymetry (OcuscanRxP, Alcon) were taken whenever possible.

The data collection and analysis were performed in compliance with the Helsinki Declaration of ethical principles for medical research involving human subjects. Either participating patient or their legal relatives signed an informed written consent, which was provided in the original data collection in the database. The study was undertaken following approval from the ethics board of the institution.

Case description

Among the 12 eyes of 11 patients reported, eight eyes were started on netarsudil and four on ripasudil. Tables 1 and 2 vividly describe all the characteristics; hereby, we enumerate the salient points. Out of 11 patients, eight were males and three were females. The mean age was 51 years (14–77 years). The right eye (OD) was affected in five cases and the left eye (OS) in seven. Ten patients had unilateral eye involvement, while one patient with Fuch's endothelial corneal dystrophy (FECD) on ripasudil presented with bilateral RECE. Indication for starting ROCK-I's was IOP control in nine eyes and off-label use for endothelial decompensation in three eyes. Three patients (patients 2, 3, and 9) were started on ROCK-I's from elsewhere; eight were from

the same center. ROCK-I's were stopped in all but four patients, either due to absence of symptoms or non-involvement of the visual axis (patients 2, 8, and 10) or as a stop-gap measure prior to diode cyclo-photocoagulation (patient 11).

Discussion

"Reticular" epithelial edema associated with netarsudil use in the setting of endothelial cell dysfunction and existing corneal edema was initially reported and coined by Fernandez.^[20] Previous authors have described preexisting corneal edema as a risk factor for the occurrence of RECE.^[14-18] All but two patients (one by Mounneh *et al.*^[14] and one by Wisely *et al.*^[15]) reported to date had a history of previous corneal edema. Only five eyes in our series had prior documented corneal edema. Out of the remaining seven, three had a history of angle-closure glaucoma-related IOP spikes, two had clear penetrating keratoplasty (PK) graft, one had an epithelial defect, and one had clear cornea with decreased endothelial cell counts, all of which are probable risk factors for corneal edema. Further studies are required to see if the association of RECE with the presence of corneal edema or risk factors for corneal edema is statistically significant or is a mere coincidence as drugs are mostly started in eyes known to have risk factors as opposed to normal eyes.

The exact cause of RECE is not known. Wisely *et al.*^[15] postulated a shift in some of the preexisting stromal edema to the corneal epithelial layers causing RECE. Rho kinase, a serine/threonine-protein kinase, is instrumental in regulating and modulating cell shape and size by changes on the cytoskeleton.^[21] Ripasudil is known to cause rounding of the cell bodies of the trabecular meshwork;^[22] the same mechanism could also lead to the rounding of epithelial cells. On confocal microscopy, stratified squamous epithelial cells were seen to adopt spindle shape with loss of cell polarity and organized stratification.^[19] Transient alteration in morphology of endothelial cells has also been reported with ripasudil.^[23-26] Authors think that the role of rho kinase in mediating actomyosin contractility, cell adhesion, cell stiffening, cell morphology, and cytoskeletal dynamics is responsible for RECE and is critical to analyze.

ROCK-I has been used off-label for endothelial wound healing, and positive results in terms of clearing of corneal edema are noticed.^[27] In three eyes of our series, indication for ROCK-I initiation was endothelial decompensation. In patient 1 [Fig. 1a], although the indication to start ROCK-I was IOP control, significant endothelial decompensation was already present. On the contrary to as one would expect, there was occurrence of new-onset epithelial edema in two eyes with FECD [Fig. 1c] and worsening of pre-existing micro-cystic edema in other two eyes with PBK [Fig. 1b]. In all cases, it was considered as progressive endothelial decompensation by elsewhere treating physician and hypertonic sodium chloride eye drops were started without any resolution of bullae. In two eyes with PBK, it rather led to the conversion of micro-cystic edema to macro-cystic reticular bullae. It was only on stopping the drug that the bullae resolved completely. Here we would like to highlight that in the initial stages, RECE can mimic as worsening of endothelial function, and it is very important to be aware of this adverse effect to differentiate between two entities and be able to manage them appropriately.

Time to occurrence of RECE with netarsudil in our series varied from as early as 1 day to as long as 80 days, with the

Table 1: Clinical characteristics of patients

Patient	Age	Sex	Eye	Type of ROCK-I	Corneal clinical diagnosis	History of corneal edema	Corneal edema at time of starting ROCK-I	Indication for starting ROCK-I	Before initiation of rock inhibitors			Ocular co-morbidities	Ocular surgical history	Other ocular medication (eye drops)
									BCVA (snellen equivalent)	Baseline IOP (mm hg)	Baseline CCT (microns)			
1	60	M	OS	N	PBK	YES	YES (MCE +stromal)	IOP control	6/120	26	525	Complicated pseudophakia with optic capture and supero-temporal iridodialysis in 3 clock hours with secondary glaucoma	PE + IOL AGV post RECE resolution	Dorzolamide (2%), brimonidine (0.2%) + timolol (0.5%), Bimatoprost (0.03%)
2	57	M	OD	N	Corneal epithelial Defect	NO	NO	IOP control	NO PL	23	Not recordable (epithelial defect)	Secondary glaucoma	PE + IOL + PPV + ILM peeling	Brimonidine (0.2%) + timolol (0.5%), Ciprofoxacin (0.3%), Carboxy-methylcellulose sodium (0.5%)
3	62	M	OD	N	PBK	YES	Not known (presented with RECE)	Endothelial decompensation	Not known with RECE	Not known	NA	Nil	PE + IOL Awaiting EK/PK	Sodium chloride (5%)
4	42	F	OS	N	Clear cornea	No	NO	IOP control	HM+, PL+, PR2+	28	541	PACG, YAG PI, Advanced glaucomatous cupping	Nil Awaiting glaucoma shunt surgery	Dorzolamide (2%), brimonidine (0.2%) + timolol (0.5%), Bimatoprost (0.03%)
5	64	M	OD	N	Clear cornea	No	NO	IOP control	6/60	24	NR	Anterior irido-cyclitis with cataract, PAS, YAG PI, secondary ACG	Nil	Brimonidine (0.2%) + Brinzolamide (1%)
6	77	M	OS	N	Micro-cystic edema due to raised IOP	YES	YES	IOP control	HM+, PL+, PR4+	38	Not recordable OD- 455	CRVO, NVG with 0.8CDR, ischemic macular atrophy	Awaiting DIODE CPC	Dorzolamide (2%), brimonidine (0.2%) + timolol (0.5%), Bimatoprost (0.03%)
7	40	M	OD	N	Clear cornea	No	NO	IOP control	HM+, PL+, PR4+	22	NR	Uveitic cataract with secondary ACG, YAG PI	Nil Awaiting PE + IOL	Brimonidine (0.2%) + timolol (0.5%), brinzolamide (1%)
8	25	M	OS	N	Clear PK graft	No	NO	IOP control	6/45	20	NR	Traumatic corneal opacity and aniridia, Secondary glaucoma	Corneal tear repair, Optical PK	Brimonidine (0.2%) + timolol (0.5%),

Contd...

Table 1: Contd...

Patient	Age	Sex	Eye	Type of ROCK-I	Corneal clinical diagnosis	History of corneal edema	Corneal edema at starting ROCK-I	Indication for starting ROCK-I	Before initiation of rock inhibitors			Ocular co-morbidities	Ocular surgical history	Other ocular medication (eye drops)
									BCVA (snellen equivalent)	Baseline IOP (mm hg)	Baseline CCT (microns)			
9	77	F	OD	R	FECD	YES (stromal edema due to decompensating endothelium)	YES	Endothelial decompensation	6/9	12	540	Cataract	Nil	Sodium chloride (5%), Carboxy-methylcellulose sodium (0.5%), Flourometholone (0.1%),
			OS	R	FECD	No	NO	Endothelial decompensation	6/7.5	12	478	Cataract	Nil	
10	14	M	OS	R	Clear PK graft	NO	NO	IOP control	6/24	24	NR	Mycotic corneal abscess, Failed graft, Secondary glaucoma	TPK, Optical PK	Brimonidine (0.2%) + timolol (0.5%),
11	49	F	OS	R	Failed graft	YES (diffuse graft edema due to persistent raised IOP and endothelial decompensation)	YES	IOP control	HM+, PL+, PR4+	32	NR	Mycotic corneal abscess, secondary glaucoma	TPK	Dorzolamide (2%), brimonidine (0.2%) + timolol (0.5%), Bimatoprost (0.03%)

mean being 25 days, which is less as compared to 4 weeks in other series.^[15,17] Also, with netarsudil, bullae tend to occur early, are more widespread, and are bigger [Fig. 1a and b] as compared to ripasudil. Out of seven patients with netarsudil in whom baseline VA was recorded, a decline in VA as a presenting symptom was noted only in two. One patient had absent perception of light (PL), in one visual axis was spared [Fig. 2a], three had profound visual impairment secondary to other causes; all of which did not allow for a quantifiable decline in VA. In three eyes, the presenting complaint was ocular surface discomfort with a foreign-body sensation. In four eyes, bullae remained asymptomatic and was identified on SLE.

RECE following ripasudil has never been described in detail before. We describe the clinical characteristics of four such eyes with ripasudil-induced distinct corneal bullae. First, RECE occurs less frequently with ripasudil. Also, the time to edema occurrence was slightly longer, the mean being 82 days. Bullae remained micro-cystic and localized to small areas [Figs. 1c and 2b] but can also involve larger areas gradually [Fig. 2c and d]. Progression from micro to macro-bullae seemed slower. Three of four eyes did not experience any DOV due to RECE as it was localized inferiorly [Figs. 1c and 2b]. Patient 11 [Fig. 2c and d] already had decreased BCVA due to graft failure; thus, RECE did not have any significant effect on BCVA. The cause of the abovementioned findings is not known, but the different pharmacokinetics of the two drugs could be a possible explanation. Ripasudil has a good intraocular penetrability,^[26] while netarsudil is maximally absorbed by cornea and conjunctiva, aqueous having < 3% concentration of that in the cornea.^[3,27] The presenting complaint in two eyes (patient 9) was ocular discomfort, and in the other two eyes, bullae were diagnosed on SLE.

The decline in VA was the only significant symptom reported in all previous reports describing RECE.^[14-18] No other symptoms associated with bullae have been reported. In our study, we found additional symptoms of foreign body sensation, eye pain, and ocular surface discomfort attributable to bullae in five eyes. All patients were initially treated with hypertonic saline, lubricating, and anti-allergic eye drops in various combinations but without resolution of symptoms. Symptoms drastically improved and all patients were comfortable after stopping ROCK-I. Resolution of bullae after stopping the drug was the only thing helpful in alleviating symptoms and making the patient comfortable.

RECE usually occurred in the inter-palpebral or inferior cornea [Fig. 2b].^[17] We report similar preponderance with both ROCK-I, the cause of which is unknown, although GHJ was also a site of predilection in our patients [Fig. 2a and b]. RECE can occur at any site though and in various shapes such as ring, disc, triangular, circinate [Fig. 2a], or sectoral as described in the table. One characteristic of this edema is that it only involves epithelium not affecting the stroma. Also, epithelial bullae are contiguous, of varying sizes in the same patient with a steep transition from involved to the normal cornea. Both above findings are beautifully seen on ASOCT [Fig. 3], which also helps differentiate between RECE and PBK. In endothelial compromise, ROCK-I acts as a double-edged sword as they decrease the stromal edema but cause epithelial edema.^[28] In patient 3, stromal edema increased from 558 to 628 microns after stopping ROCK-I.

Table 2: Comparison of clinical characteristics pre and post RECE

Patient	Eye	After initiation of ROCK-I, at time of RECE				After stopping of ROCK-I, after resolution of RECE						
		Time for Occurrence (Days)	Area of Involvement Of RECE	Associated with symptoms	Best-corrected Visual Acuity (mmHg)	IOP (mmHg)	CCT (microns)	Time For Resolution	Resolution Of Symptoms	Best-corrected Visual Acuity (mmHg)	IOP (mmHg)	CCT (microns)
1	OS	16	Total cornea	YES	HM+, PL+, PR4+	20	530	10	YES	CF close to face	28	525
2	OD	Epithelial roughening-30 RECE -45	Entire cornea sparing limbus, Bullae started inferiorly More pronounced inferiorly	NO	NO PL	16	NR	Not stopped	NA	NA	NA	NA
3	OD	14	Inferior 2/3 rd of cornea More pronounced inferiorly	YES	6/120	12	558	7	YES	6/120	16	628
4	OS	16	Fine RECE involving inferior and central cornea, sectoral area in TRIANGULAR fashion	NO	HM+, PL+, PR4+	24	542	10	NA	HM+, PL+, PR4+	24	512
5	OD	80	Inferior 2/3 rd of central cornea	YES	HM+, PL+, PR4+	16	NR	20	YES	5/60	20	NR
6	OS	7	Central cornea	NO	HM+, PL+, PR4+	32	NR	14	NA	HM+, PL+, PR4+	36	NR
7	OD	1	Paracentral cornea in a RING fashion	NO	HM+, PL+, PR4+	16	556	7	NA	HM+, PL+, PR4+	16	NR
8	OS	Microcystic changes-7 RECE - 25	Circumferential ring shaped near GHJ	NO	6/45	19	NR	Not stopped as not involving VA	NA	NA	NA	NA
9	OD	Not known Presented with RECE (on ripasudil since 5 months)	Two large bullae with surrounding fine RECE in sectoral area of inferio-temporal cornea	YES (more in OD than OS)	6/9	10	534	25	YES	6/9	14	545
	OS		Fine reticular network of micro-cystic bullae in inferio-temporal perilibal cornea	YES	6/7.5	10	478	25	YES	6/7.5	14	480
10	OS	Epithelial roughening- 30 RECE- 45	Inferior sectoral Bullae near GHJ	NO	6/24	18	NR	Not stopped as not involving VA	NA	NA	NA	NA
11	OS	Epi rough-5 days Inf MCE- 22 days Reticular edema-	RECE involving total graft	NO	HM+, PL+, PR4+	24	NR	Not stopped as awaiting diode CPC	NA	NA	NA	NA

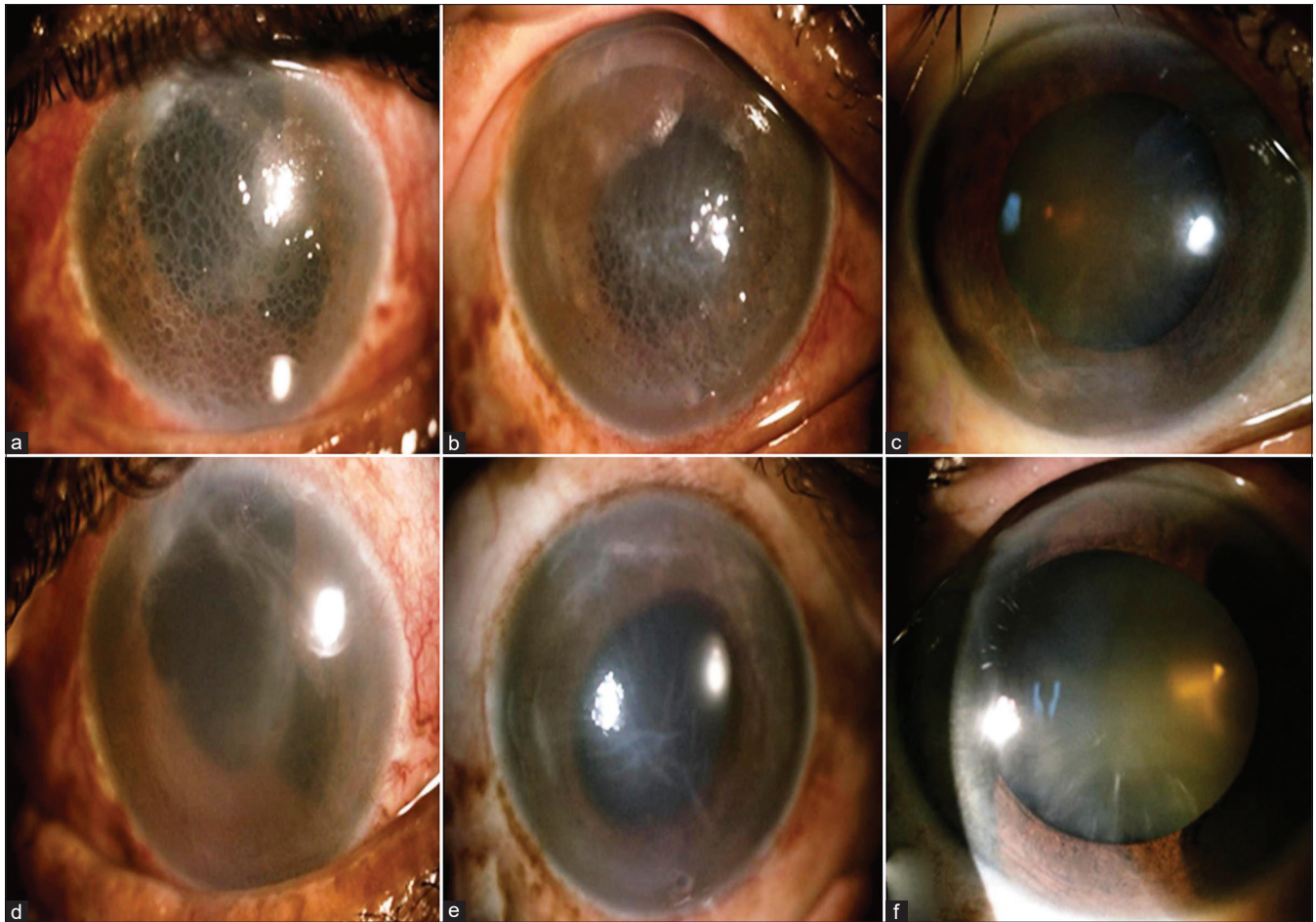


Figure 1: Manifestation and resolution of RECE (a), (b) honeycomb RECE after netarsudil use; (c) inferiorly localized bullae in FECD after ripasudil use; (d), (e), (f)-resolution of bullae after stopping ROCK-I

Both DOV and RECE are reversible on stopping the medication as the effects of ROCK-I on cytoskeleton and tight junctions are reversible.^[29] In all cases where the drug was stopped, bullae resolved clinically as well as on ASOCT [Fig.1 d-f; Fig. 3b and c]. The average time to resolution after stopping the drug was 10 days for netarsudil (earliest being 3 days) and 25 days for ripasudil. BCVA either improved or remained the same, which can be attributed to other ocular co-morbidities

In our series, looking retrospectively, we found epithelial roughening in three cases and inferior scattered small bullae preceded the development of frank reticular pattern in two cases. We hypothesize the following clinical course or stages: (1) epithelial roughening, (2) small scattered micro-cystic bullae mimicking MCE/early endothelial decompensation, (3) confluent micro-cystic and macro-cystic bullae in a reticular pattern involving the para-central and inferior cornea or GHJ, and (4) macro-cystic bullae confluent and contiguous in a honey-comb pattern throughout the cornea [Fig. 4a-d].

RECE in its early stages can also be confused with micro-cystic edema (MCE) associated with raised IOP. In MCE, epithelial cysts are small, uniformly sized, with diffuse corneal involvement, associated with underlying stromal haze and raised IOP. They respond to IOP lowering medications. On the contrary, in RECE, cysts have a typical honeycomb appearance.

They are variable in size, small, and localized to begin with, eventually becoming macro-bullae with widespread corneal involvement on continued use of the drug. They have no relation to IOP (occur with normal IOP also), will not respond to other IOP lowering medication, and most importantly, have a temporal association with the use of ROCK-I.

Our study has its limitation in form of it being retrospective with a small sample size. Also, CCT measurements before initiation and after stopping of ROCK-I's were not done for all patients, making a statistical analysis for corneal edema as a risk factor impossible. Due to the short duration of follow-up, we could not report any long-term results in cases where the drug was continued.

Long-term, schematic, prospective studies are required to understand the pathophysiology and to establish incidence, predisposing factors, safety, and other side-effects. Also, any difference in the incidence of RECE in normal versus proposed predisposed corneas needs to be evaluated. We also think that specular microscopy and confocal microscopy can give more insight into the understanding of the pathophysiology.

Nonetheless, we intend to create awareness about this characteristic edema as a side-effect of ROCK-I which is not-so-infrequently seen, probably because of the increased use of these novel drugs. A strong eye of suspicion and knowledge

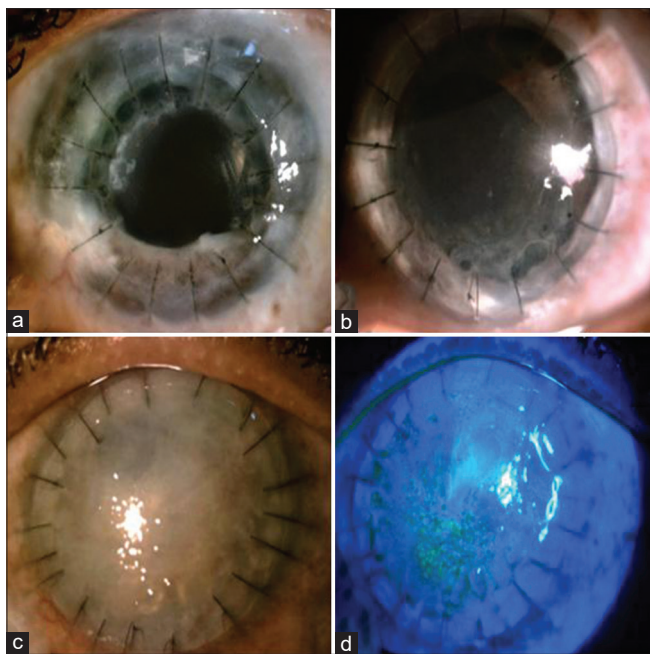


Figure 2: RECE in corneal grafts (a) 360° of RECE in a circinate pattern near GHJ sparing visual axis after netarsudil use; (b) inferiorly localized bullae near GHJ after ripasudil instillation; (c) diffuse micro and macro-bullae in failed graft after ripasudil use; (d) better visualization of RECE in the same patient as (c) after fluorescein stain with cobalt blue filter

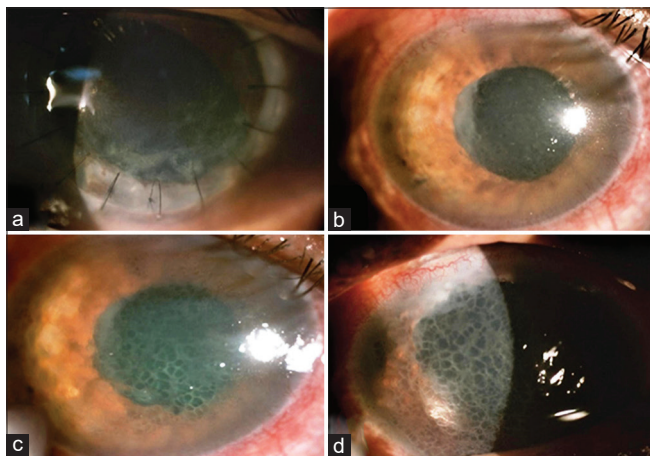


Figure 4: Stages of RECE (a) epithelial roughening; (b) microcystic bullae; (c) micro and macro-bullae; (d) full-blown RECE

about this rare possible side-effect is imperative for diagnosing and differentiating from other causes of epithelial bullae, especially with the conversion of micro to macro-bullae in cases of endothelial decompensation, thus gauging the need for continuity or withdrawal of the drug.

Conclusion

RECE can be considered a well-established side effect of ROCK-I which was seen with both netarsudil and ripasudil. It occurred more frequently, with more severity and widespread distribution, less time to occurrence, and faster resolution with netarsudil as compared to ripasudil. Preexisting corneal edema, presence of ocular comorbidities which can predispose to corneal edema, previous intraocular surgeries leading to

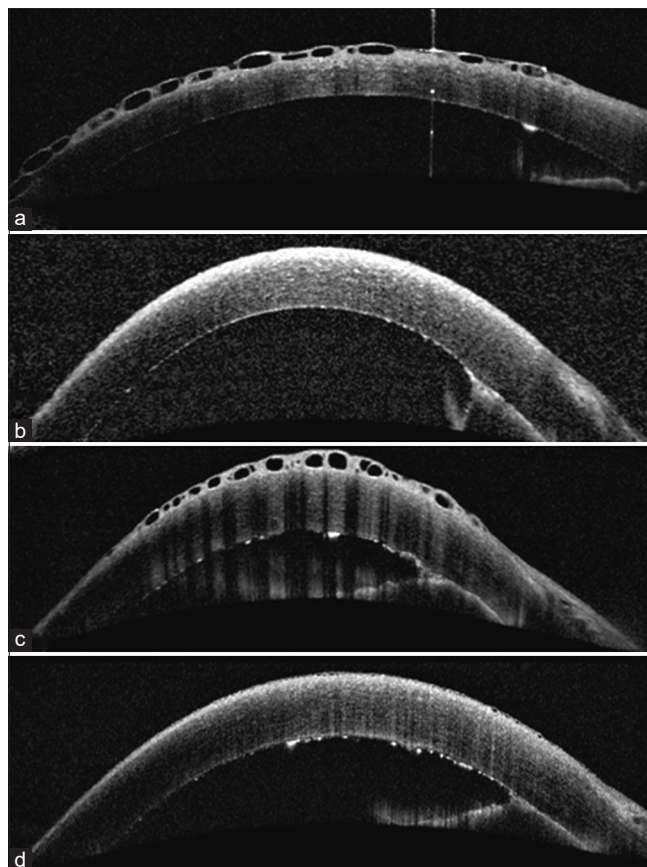


Figure 3: ASOCT features of RECE (a), (c) epithelial macro-bullae due to ROCK-I use. Note the contiguous nature of epithelial bullae and non-involvement of stroma; (b), (d) resolution of bullae post cessation of ROCK-I

endothelial cell loss, and corneal transplant surgeries appear to be potential risk factors for RECE, and ROCK-I should be used cautiously in these circumstances. RECE causes not only DOV but also bullae-associated foreign-body sensation and ocular discomfort, which can be troublesome to patients warranting discontinuation of the drug. For endothelial decompensation (PBK or FECD), they act as a double-edged sword by decreasing stromal edema and causing epithelial edema.

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Conflicts of interest

There are no conflicts of interest.

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