Randomized, Double-Masked Trial of Netarsudil 0.02% Ophthalmic Solution for Prevention of Corticosteroid-Induced Ocular Hypertension

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• PURPOSE: To assess whether prophylactic use of netarsudil 0.02% ophthalmic solution reduces the risk of intraocular pressure (IOP) elevation associated with prolonged use of topical corticosteroids to prevent cornea transplantation rejection.

• DESIGN: Prospective, randomized clinical trial.

• METHODS: In this study, 120 subjects were randomized to use netarsudil (off-label) or placebo once daily for 9 months after Descemet membrane endothelial keratoplasty, and 71 fellow eyes were enrolled and assigned to the opposite treatment arm. Participants concurrently used topical prednisolone acetate 1% 4× daily for 3 months, 3× daily for a month, twice daily for a month, and once daily for 4 months. The main outcome was IOP elevation (defined as IOP ≥24 mm Hg or an increase of ≥10 mm Hg over baseline) assessed by Kaplan-Meier and proportional hazards analyses, taking loss to follow-up into consideration.

• RESULTS: Overall, 95 eyes were assigned to netarsudil and 96 to placebo; 15 eyes (16%) were withdrawn early from the netarsudil arm because of ocular irritation. The rate of IOP elevation was 14% with netarsudil and 21% with placebo (relative risk: 0.6; 95% confidence interval: 0.3-1.3; $P = .23$). IOP was > 30 mm Hg in 7.8% assigned to netarsudil versus 7.4% assigned to placebo ($P = .84$). Median 6-month central endothelial cell loss was 31% versus 29% with netarsudil versus placebo, respectively ($P = .49$).

• CONCLUSIONS: Netarsudil did not produce a statistically significant reduction in the risk of steroid-induced IOP elevation after corneal transplantation relative to placebo. (Am J Ophthalmol 2021;222:382–387. © 2021 Elsevier Inc. All rights reserved.)

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TOPICAL CORTICOSTEROIDS ARE COMMONLY USED TO control postoperative ocular inflammation. They are also the mainstay for preventing and treating corneal transplantation rejection and for treating ocular conditions involving immune hyper-reactivity.[1] The principal drawbacks include steroid-induced ocular hypertension and steroid-induced glaucoma. The incidence varies with the type of glucocorticoid and its formulation, the dosing frequency, and the treatment duration.[1]

Prednisolone acetate (PA) 1% ophthalmic solution is the most commonly used topical corticosteroid in the United States.[2] Treatment duration ranges from a few weeks for controlling postoperative inflammation, to years for preventing cornea transplantation rejection.[2,3] Up to 35% of patients without a previous glaucoma diagnosis and up to 80% with pre-existing glaucoma experience clinically significant post-keratoplasty intraocular pressure (IOP) elevation with long-term topical corticosteroid use.[4] IOP elevation is primarily caused by increased outflow resistance and is associated with reduced visual acuity and increased risk of transplantation failure.

Corneal transplantation offers a unique opportunity to evaluate potential methods for preventing IOP elevation associated with long-term use of topical corticosteroids, without the confounding factors present with immune hyper-reactivity disorders. The purpose of this study was to determine whether use of netarsudil reduces the risk of steroid-associated ocular hypertension when used (off-label) by cornea transplantation recipients as an adjunct to PA 1% ophthalmic solution. Netarsudil is a Rho kinase inhibitor that inhibits the downstream pathway of the Rho family of small G-proteins to increase outflow from the conventional (trabecular) outflow pathway in the eye.[5,6] The U.S. Food and Drug Administration approved netarsudil (Rhopressa, Aerie Pharmaceuticals, Irvine, California, USA) in 2018 for reduction of IOP in patients with open-angle glaucoma or ocular hypertension. First, because of its mechanism of action, we hypothesized that it might be effective for prevention of steroid-associated ocular hypertension. Second, we were interested in determining whether use of netarsudil might affect Descemet membrane endothelial keratoplasty (DMEK) attachment or endothelial cell loss, because related Rho kinase inhibitors were

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shown to facilitate corneal endothelial cell migration, and potentially, proliferation when used with Descemet stripping only or endothelial cell injection.[7,8]

METHODS

THIS WAS A DOUBLE-MASKED, PROSPECTIVE, RANDOMIZED, controlled trial conducted at a single site (Price Vision Group, Indianapolis, Indiana, USA). An independent review board (IRBCo, Buena Park, California, USA) approved the study, and each participant completed an informed consent process for participation in the clinical trial. The study complied with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act and was registered on the clinical trials website (www.clinicaltrials.gov; Trial of Netarsudil for Prevention of Corticosteroid-induced Intraocular Pressure Elevation; NCT03248037). Participants were recruited between August 2017 and September 2018 and follow-up was completed in July 2019.

• **INCLUSION AND EXCLUSION CRITERIA:** The study inclusion criteria were male or female DMEK recipients who were at least 18 years of age, able and willing to administer the study medication, and likely to complete the 9-month course of the study. The exclusion criteria were: preoperative intraocular inflammation; abnormal eyelid function; active corneal ulceration, keratitis, or conjunctivitis; history of herpetic keratitis; known sensitivity to any of the ingredients in the study medications; history of uncontrolled glaucoma, previous aqueous shunt, trabeculectomy, or preoperative IOP >22 mm Hg; presence of ocular disease or systemic condition that might put the patient at risk or confound the study results; history of noncompliance with using prescribed medications; or pregnancy.

• **RANDOMIZATION AND STUDY TREATMENT REGIMEN:** Netarsudil ophthalmic solution 0.02% and placebo (netarsudil vehicle) eye drops were provided by Aerie Pharmaceuticals in 2.5 mL bottles, identical in appearance. A designated, unmasked, dosing coordinator applied a coded sticker to each bottle. Using a computer-generated randomization table, study subjects were enrolled between 2 and 5 days after DMEK and randomized to receive netarsudil or placebo. If the study participant elected to have DMEK and enroll the fellow eye in the study, the dosing coordinator automatically assigned the fellow eye to the opposite treatment arm from the assignment in the first eye.

Subjects were instructed to instill the assigned eye drop into the study eye once every evening for the 9-month study duration. For immunologic rejection prophylaxis (off-label use), subjects were provided with PA 1% eye drops to be used 4× daily for the first 3 months, 3× daily during month 4, twice daily during month 5, and once daily during months 6 to 9. During the study, IOP elevation was managed by early steroid reduction and/or addition of glaucoma medication as deemed appropriate by the treating physician. A change in glaucoma medications or early steroid reduction only occurred if a participant reached or exceeded the predefined IOP elevation threshold.

• **STUDY PROCEDURES:** Study visits were scheduled at 1 month (window: 3-6 weeks), 3 months (window: ± 1 month), 6 months (window: ± 1 month), and 9 months (window: 8-11 months) after DMEK with interim examinations scheduled as needed to appropriately monitor any adverse events. The study procedures included slit-lamp examination, assessment of IOP by Goldmann applanation, uncorrected and best-corrected vision, ultrasonic pachymetry, adverse event assessment, and measurement of endothelial cell density by specular microscopy (manual centers method, Noncon Robo, Konan Medical, Inc., Irvine, CA, USA). The study did not include visual field testing.

• **OUTCOME MEASURES:** The main outcome measure was clinically significant IOP elevation defined as either IOP ≥24 mm Hg or a relative increase over the baseline preoperative IOP of ≥10 mm Hg. Ancillary analyses assessed an IOP increase of ≥10 mm Hg, maximum postoperative IOP ≥31 mm Hg, 6-month endothelial cell loss, and adverse events. The percent cell loss was calculated by subtracting the 6-month endothelial cell density from the baseline donor endothelial cell density assessed by the provider eye bank (VisionFirst, Indianapolis, Indiana, USA) using specular microscopy (KeratoAnalyzer EKA-10, Konan Medical, Inc.). The difference was divided by the donor cell density and multiplied by 100.

• **SAMPLE SIZE DETERMINATION AND STATISTICAL ANALYSIS:** Results in previous prospective studies suggested that the rate of clinically significant IOP elevation, as defined previously, would be ≥20% in the placebo control arm.[9,10] Based on the mechanism of action and clinical trial results, we estimated that the relative odds ratio would be 0.25 in the netarsudil study arm. A sample size of 84 eyes per study arm (total: 168) would provide 80% power to detect a statistically significant difference between groups at a 5% significance level (2-sided test). Assuming 10% drop out, the required recruitment would be 185 study eyes.

The rate of clinically significant IOP elevation was compared between treatment arms using Kaplan-Meier survival analysis (with the log-rank test) and Cox proportional hazards modeling. These methods took loss to follow-up into consideration. The proportional hazards model also took potential confounding between fellow eyes into consideration. Between-group comparisons of the maximum postoperative IOP, 6-month endothelial cell density, and 6-month endothelial cell loss were performed using generalized estimating equations.

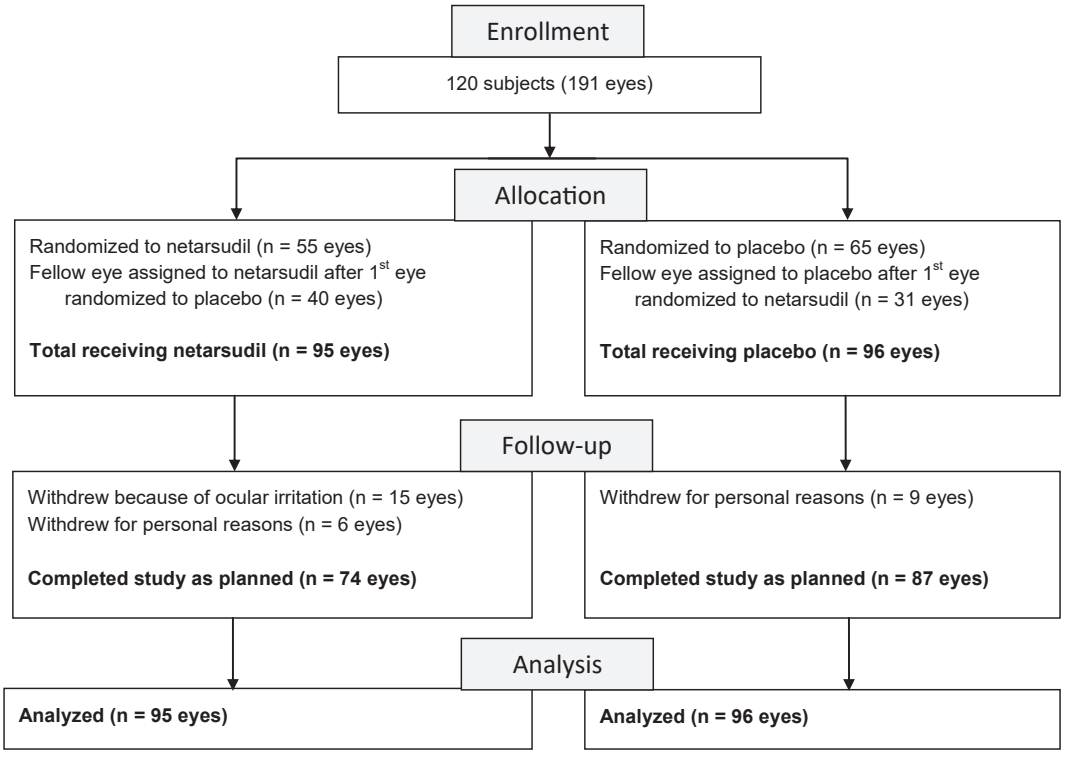

FIGURE 1. Study Flowchart.

The statistical analyses were performed with SAS software (version 9.3; SAS Institute, Cary, North Carolina). Tests were 2-sided, and *P* values <.05 were considered statistically significant.

RESULTS

THE ENROLLMENT, RANDOMIZATION, FOLLOW-UP, AND analysis flowchart is shown in Figure 1. Overall, 191 eyes were enrolled and assigned to treatment (95 to netarsudil and 96 to placebo). Seventy-four eyes (78%) in the netarsudil arm completed the study as planned; 15 (16%) eyes were withdrawn because of ocular irritation and 6 (6%) eyes were withdrawn for personal reasons. Eighty-seven eyes (91%) in the placebo arm completed the study as planned; 9 (9%) eyes were withdrawn for personal reasons, such as the subject not wanting to use extra eye drops or complete the study visits.

The baseline patient characteristics are described in Table 1. The main indication for DMEK was Fuchs endothelial dystrophy. The median recipient age was 67 years (range: 40-90 years). All participants were noted to have open angles at the screening visit.

• **IOP:** The proportion of eyes that exceeded the defined IOP elevation threshold (IOP ≥24 mm Hg or an increase of ≥10 mm Hg over the baseline preoperative IOP) was 14% in the netarsudil arm versus 21% in the placebo arm ($P = .23$) (Table 2 and Figure 2). Compared with the placebo arm, the relative risk (RR) of IOP elevation in the netarsudil arm was 0.6 (95% confidence interval [CI]: 0.3-1.3). There was no significant confounding between fellow eyes assigned to opposite treatment arms ($P = .72$). In a secondary analysis, the proportion of eyes with an IOP increase ≥10 mm Hg was 11% in the netarsudil arm versus 17% in the placebo arm (RR: 0.6; 95% CI: 0.3-1.4) (Table 2).

The degree of steroid response could be categorized as moderate (<31 mm Hg) or high (≥31 mm Hg).[11] The number and cumulative proportion of moderate responder eyes was 5 (7%) in the netarsudil arm versus 12 (15%) in the placebo arm (RR: 0.43; 95% CI: 0.15-1.23) (Figure 3A). The number and cumulative proportion of high steroid responder eyes was 6 (7.8%) in the netarsudil arm and 6 (7.4%) in the placebo arm (RR: 1.0; 95% CI: 0.33-3.2) (Figure 3B).

The median IOP was 15 mm Hg (interquartile range [IQR]:13-17 mm Hg) in the netarsudil arm and 14 mm Hg (IQR: 12-17 mm Hg) in the placebo arm at the baseline preoperative examination. At the final 9-month postoperative study visit, the median IOP was 13 mm Hg (IQR: 11-17 mm Hg) in the netarsudil arm and 15 mm Hg (IQR:12-17 mm Hg) in the placebo arm.

• **CORNEAL ENDOTHELIAL CELL DENSITY:** The baseline donor endothelial cell density and the 6-month endothelial

TABLE 1. Baseline Characteristics

	Netarsudil Arm (n = 95 Eyes)	Placebo Arm (n = 96 Eyes)
Sex		
Female	54 (57)	61 (64)
Male	41 (43)	35 (36)
Indication for graft		
Fuchs dystrophy	91 (95)	92 (96)
Pseudophakic corneal edema	0 (0)	1 (1)
Failed endothelial keratoplasty	4 (4)	3 (3)
Previous open angle glaucoma, medically controlled	2 (2)	2 (2)
Keratoplasty combined with cataract surgery		
Yes	49 (52)	47 (49)
No	46 (48)	49 (51)
	Median (Range)	Median (Range)
Age, y	68 (40-88)	67 (40-90)

Values are n (%) and median (range).

TABLE 2. Outcomes in Eyes Treated With Netarsudil Ophthalmic Solution or Placebo After Descemet Membrane Endothelial Keratoplasty

	Netarsudil Arm (95 Eyes)	Placebo Arm (96 Eyes)	Relative Risk (95% CI)
Main outcome			
IOP ≥24 mm Hg or ≥10 mm Hg IOP increase	11 (14)	18 (21)	0.6 (0.3-1.3)
Exploratory IOP elevation analyses			
Moderate response (IOP <31 mm Hg)	5 (7)	12 (15)	0.4 (0.2-1.2)
High response (IOP ≥31 mm Hg)	6 (8)	6 (7)	1.0 (0.3-3.2)
Secondary Outcome: Central Endothelial Cell Density, cells/mm^2			*P* Value
Baseline donor	2,933 (2,801-3,115)	2,899 (2,755-3,096)	.26
6-month postoperative	2,012 (1,776-2297)	2,083 (1,818-2,353)	.77
6-month cell loss (%)	31 (23-40)	29 (22-36)	.49

CI = confidence interval.

The rate of intraocular pressure (IOP) elevation was determined by Kaplan-Meier survival analysis and the relative risk and 95% CI by proportional hazards analysis; both took loss to follow-up into consideration.

Values are n (%), and the endothelial cell density outcomes are reported as median and interquartile range.

cell density did not differ significantly between the netarsudil and placebo arms (Table 2). The median cell loss was 31% in the netarsudil arm (n = 70) and 29% in the placebo arm (n = 75; $P = .49$) at 6 months and remained about the same at the 9-month study exit examination (31% in the netarsudil arm and 28% in the placebo arm; $P = .43$).

• **ADVERSE EVENTS:** One graft failed to clear and was replaced (0.5%); the eye continued in the study. One graft (0.5%) experienced an immunologic rejection episode that was successfully treated with increased topical steroid dosing, and the eye continued in the study. Air was reinjected to promote graft attachment in 20 eyes in the netarsudil arm (21%) and in 18 eyes in the placebo arm (19%) ($P = .72$).

Consistent with Rhopressa package labeling, corneal verticillata were observed in 34 eyes assigned to netarsudil (36%), including 5 of the 11 netarsudil-assigned eyes

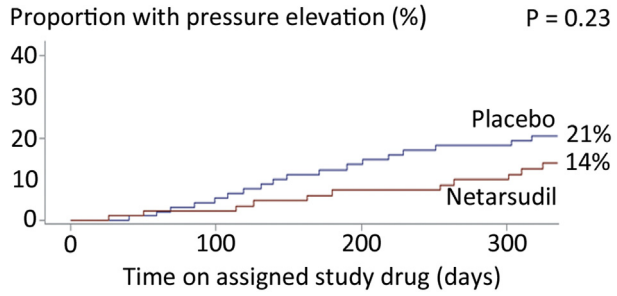

FIGURE 2. Kaplan-Meier curves showing the estimated probability of intraocular pressure elevation (≥24 mm Hg or a relative increase of at least 10 mm Hg over the baseline preoperative reading) after Descemet membrane endothelial keratoplasty, by study arm.

(45%) that experienced IOP elevation. Ocular irritation believed to be related to use of the study drug was reported in 22 eyes (23%) and led to early withdrawal of 15 eyes (16%) from the netarsudil arm.

DISCUSSION

THE CLINICAL USEFULNESS OF PROPHYLAXIS DEPENDS UPON the proportion that derives benefit, the magnitude of benefit, the cost, the risks, and the alternatives. In this study, netarsudil prophylaxis reduced the overall risk of steroid-associated ocular hypertension from 21% to 14% and the risk of a moderate steroid response (IOP <31 mm Hg) from 15% to 7%; however, these differences did not reach statistical significance. In addition, netarsudil prophylaxis did not reduce the 7%-8% risk of experiencing a high steroid response (IOP ≥31 mm Hg). The main side effect was ocular irritation (23% incidence). For keratoplasty procedures with a relatively low risk of immunologic rejection, such as DMEK, the risk of IOP elevation can be reduced more effectively by decreasing steroid potency a month or two after the procedure.[9,10,12] Early steroid reduction is particularly effective for reducing the risk of high steroid response.[9,10,12] Thus, we concluded that the results of this study did not support clinical use of netarsudil for prophylaxis of steroid-associated ocular hypertension following DMEK.

We did not detect any beneficial or deleterious effect on the air reinjection rate or central endothelial cell loss at 6 or 9 months after DMEK with use of netarsudil. Rho kinase inhibitors such as netarsudil can stimulate endothelial cell migration to facilitate coverage of areas where the endothelium was removed or damaged. Such areas are primarily located on the host cornea outside the area covered by the DMEK donor tissue, but it is difficult to accurately assess endothelial cell density changes in the corneal periphery with specular microscopy.

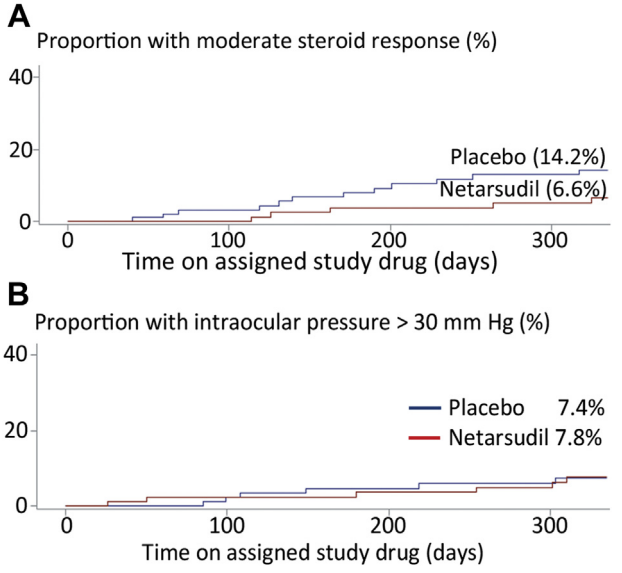

FIGURE 3. Kaplan-Meier curves showing the estimated probability of moderate or high intraocular pressure elevation after Descemet membrane endothelial keratoplasty, by study arm. (A) Moderate IOP elevation (< 31 mm Hg). (B) High intraocular pressure elevation (> 30 mm Hg).

A number of study eyes exhibited an initial IOP spike at the 9-month examination (Figure 2). This reinforced the importance of regular pressure checks to minimize the risk of glaucomatous nerve damage in patients who used long-term topical corticosteroids, particularly higher potency steroids.

Comparisons of corticosteroid-induced IOP elevation across different studies could be hindered by the lack of a standard format for assessment and reporting.[13] In this study, the main outcome measure was IOP ≥24 mm Hg or an increase of ≥10 mm Hg over the baseline preoperative reading, to maintain consistency with our previous studies of post-keratoplasty IOP elevation.[4,9,10] An emerging consensus suggested that an increase of ≥10 mm Hg was the most clinically relevant parameter,[13] so we also reported that outcome.

• **STUDY LIMITATIONS:** The study strengths included the randomized, prospective design, the enrollment of fellow eyes as intra-subject controls, and the use of statistical methods that took loss to follow-up into consideration by assessing whether an IOP elevation event occurred during the specific length of time each participant was followed. Study limitations included the sample size (approximately 20 patients per arm were expected to be steroid responders) and the relatively frequent appearance of corneal verticillata and ocular irritation, which might have unmasked a minority of patients and introduced potential bias. Also, a complete glaucoma evaluation, including visual fields and optic nerve analysis, was not performed; the randomization was assumed to balance eyes with or without glaucoma.

CONCLUSIONS

IN CONCLUSION, THE REDUCTION OF STEROID-ASSOCIATED IOP elevation was not statistically significant and not considered sufficiently clinically compelling to justify the medication burden of prophylaxis. Use of netarsudil did not significantly affect the air re-injection rate or central endothelial cell loss after DMEK. With keratoplasty procedures that have a relatively low risk of immunologic rejection, such as DMEK, early reduction of steroid potency is a more effective way to reduce the risk of steroid-associated ocular hypertension.[9,10]

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

MARIANNE O. PRICE: CONCEPTUALIZATION, METHODOLogy, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Matthew T. Feng:** Formal analysis, Data curation, Writing - review & editing. **Francis W. Price:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - review & editing.

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