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Original Research

Effectiveness of Netarsudil versus Brimonidine in Eyes already Being Treated with Glaucoma Medications at a Single Academic Tertiary Care Practice: A Comparative Study ☆

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ABSTRACT

Background: Rho kinase inhibitors, such as netarsudil, are a relatively new class of medications recently introduced into the market for the treatment of glaucoma, the leading cause of irreversible blindness in the world. Previous clinical trials have studied netarsudil's efficacy when used as a first- or second-line agent but limited studies have investigated its effectiveness in the real world where it is more commonly used as a third, fourth, or fifth agent in combination with other topical medications. Equally important, prior studies have not compared its effectiveness to its peer medications in these settings.

Objective: To compare intraocular pressure (IOP) lowering after initiation of netarsudil or brimonidine therapy in patients with glaucoma using >2 medications for IOP management.

Methods: A chart review of 369 eyes from 279 patients followed at a single academic tertiary practice was performed with an institutional review board waiver of consent to compare IOP lowering after prescription of netarsudil (n = 176) versus brimonidine (n = 193) as a third, fourth, or fifth IOP-lowering agent. Patients were identified by querying the electronic medical record for those with a glaucoma-related diagnosis who were prescribed either medication. Five sequential IOP measurements were obtained to determine the mean change in IOP before and after treatment (ΔIOP = mean $IOP_{4,5}$ – mean $IOP_{1,2,3}$). A multilevel linear mixed-effects model assessed the influence of medication (independent variable) on ΔIOP (dependent variable). Additional independent variables of interest included the number of glaucoma medications at baseline, age, sex, glaucoma type and severity, race, and pretreatment IOP. Bootstrap analysis was performed to remove sampling bias and confirm mixed-effects model findings. Kaplan-Meier survival analysis evaluated the probability of requiring additional intervention within 3 years following the date of medication prescription.

Results: The unadjusted mean (SD) ΔIOP for netarsudil and brimonidine was −2.20 (4.11) mm Hg and −2.21 (3.25) mm Hg, respectively ($P = 0.484$). The adjusted linear mixed-effects models and bootstrap analysis demonstrated that there was no statistical difference in IOP-lowering effectiveness between the medications. Netarsudil and brimonidine failed to adequately control IOP at similar rates with 42% and 47% probabilities of survival respectively by the 3-year follow-up ($P = 0.520$).

Conclusions: When escalating pharmacologic therapy, the IOP-lowering effect of netarsudil appeared to be similar to that produced by brimonidine. (*Curr Ther Res Clin Exp.* 2023; 84:XXX–XXX)

Introduction

Glaucoma is the leading cause of irreversible blindness in the world, affecting approximately 80 million people globally.[1] Intraocular pressure (IOP) is the only known modifiable risk factor that has been shown to preserve visual function in patients with glaucoma.[2–4] Currently available treatments for glaucoma are solely

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aimed at lowering IOP through the use of topical pharmacologic agents, laser therapy, or surgical procedures. Topical pharmacologic therapy has been and continues to be the mainstay of glaucoma management.

For the past two decades, glaucoma medications could fall into five general classes: prostaglandin analogs, β-blockers, α-agonists, carbonic anhydrase inhibitors, and muscarinic agonists. Generally, prostaglandins are considered first-line agents in pharmacotherapy due to their superior efficacy and tolerance among glaucoma patients.[5,6] Following prostaglandins, β-blockers are typically used as second-line agents. Meanwhile, α-agonists, carbonic anhydrase inhibitors, and muscarinic agonists are kept in reserve after prostaglandins and β-blockers do not produce adequate IOP lowering.

A new class of topical medications, rho kinase inhibitors (netarsudil), was approved by the Food and Drug Administration in 2017 for the treatment of glaucoma and ocular hypertension and reduces IOP through three mechanisms: improving trabecular aqueous outflow, reducing aqueous humor secretion, and decreasing episcleral venous pressure.[7–10] Prior clinical trials have demonstrated that netarsudil effectively reduces IOP when used as a first-line or second-line agent.[11–13] However, in real-world clinical practice such as at the Wilmer Eye Institute Glaucoma Center of Excellence, netarsudil is more commonly used as a third-, fourth-, or fifth-line agent after other therapeutic options have been exhausted. The reluctance of providers to introduce netarsudil can be attributed to its cost and adverse ocular surface effects making patient adherence challenging. Because target IOPs are usually not achieved with a single ocular hypotensive medication and the effectiveness of drops decreases with an increasing number of medications, it is imperative to determine the effectiveness of netarsudil when coadministered with other glaucoma medications.[14–16]

A literature search conducted in PubMed revealed four studies investigating the effectiveness of netarsudil in patients already taking multiple IOP-lowering agents in real-world settings.[17–20] However, previous studies lack a control cohort that would be beneficial in comparing changes across time, avoiding potential biases, and clarifying the role of netarsudil in comparison to its peer medications. Among the different classes of medications that may be considered after prostaglandins, α-agonists are also poorly tolerated agents that are commonly prescribed.[21] In clinical practice, α-agonists such as brimonidine are likely to be used most similar to netarsudil because they are often prescribed as a third- or fourth-line agent. Thus, the purpose of this investigation is to determine the effect on IOP of netarsudil, compared with brimonidine, in eyes with glaucoma requiring more than two classes of medications to control IOP and whether the IOP lowering effect changes with the number of different classes of medications the eye is using at baseline.

Material and Methods

The study protocol adhered to the tenets of the Declaration of Helsinki. Approval was obtained from the Johns Hopkins University School of Medicine Institutional Review Board (IRB00222739) with a waiver of consent on June 24, 2021.

Study population and data collection

The electronic medical record was queried for all patients with a glaucoma-related diagnosis seen at the Wilmer Eye Institute who were prescribed netarsudil and had at least five sequential IOP measurements (two encounters before the prescribing visit, one at the prescribing encounter, two encounters after the prescribing visit) within two years. Patients and their insurance carriers were billed for treatment as part of their standard glaucoma care. From the patient list generated by the electronic medical record, each patient was manually screened to confirm eligibility. The IOP measurement after the prescribing encounter (fourth IOP measurement) had to be at least one week after starting the medication. Measurements had to be performed in the clinic mostly with Goldmann applanation tonometry but iCare tonometry, or Tono-Pen tonometry could be used as well. Patients who had any eye-related surgical or laser procedure within a month of the first IOP measurement or within the time frame of the five total IOP measurements were excluded from the study. In addition, patients were also excluded if netarsudil was stopped at any point before two post-treatment IOP measurements were obtained, if netarsudil was prescribed as a first- or second-line agent, or if the patient's glaucoma medication regimen changed (ie, removal or addition of another class of glaucoma medication) within the time frame of the study.

A chart review of each included patient was performed by one of two authors responsible for data collection to collect the following variables: age, gender, race, past ocular surgical history, glaucoma type, glaucoma severity, and classes of glaucoma medication. Glaucoma type was determined based on the most recent clinical documentation available for the patient and was categorized as either primary open-angle glaucoma or suspect, primary angle-closure glaucoma or suspect, or secondary glaucoma. Patients with ocular hypertension but no evidence of glaucoma visual field defects were included as suspects. Glaucoma severity was determined based on the mean deviation (MD), a statistical index of the average difference in the visual function of an individual compared to an age-correct norm. Because glaucoma worsening is often tracked with MD followed longitudinally through visual field testing, the baseline disease severity was established by the MD obtained from the visual field test completed closest to the date of prescription. Mild, moderate, and severe disease were defined as an MD greater than –6 dB, –6 to –12 dB, and less than –12 dB, respectively. The classes of glaucoma medication in this study include prostaglandins (including latanoprostene bunod ophthalmic solution), α-agonists, β-blockers, carbonic anhydrase inhibitors (excluding oral acetazolamide/methazolamide), muscarinic agonists, and rho kinase inhibitors.

Glaucomatous eyes that were prescribed brimonidine were also eligible for this study as a comparison group based on similar criteria described above for netarsudil. Brimonidine eyes were selected for this study by filtering for baseline glaucoma characteristics (type, severity, and IOP at the time of prescription) and the number of baseline medications to the included netarsudil eyes. For example, an eye prescribed brimonidine as a third-line agent was included if there was an analogous eye with the same baseline glaucoma characteristics and was prescribed netarsudil as a third-line agent. As brimonidine was never used as a fifth-line agent, data collection for eyes prescribed brimonidine was only performed until each netarsudil eye used as a third- or fourth-line agent had at least one corresponding brimonidine eye. After data collection, multiple potential brimonidine eyes could be paired with a similar netarsudil eye, and these additional eyes were included in the statistical analysis as well. To make use of the entire dataset, analysis of the netarsudil sample still included the fifth-line and sixth-line netarsudil eyes that did not have a corresponding brimonidine eye, and the number of baseline medications was included as a potential confounding variable in the adjusted analysis described in the section below. A flow diagram of the data collection process can be seen in **Figure 1**.

Primary aim: The effect of netarsudil on IOP compared with brimonidine

The main outcome of this study was the mean change in IOP after the addition of pharmacologic therapy. The baseline IOP for

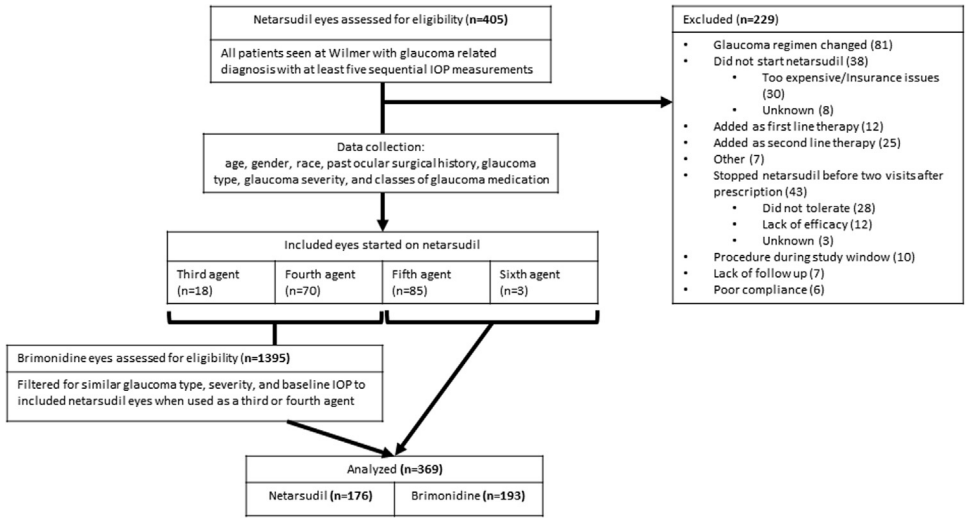

Figure 1. Flow diagram of data collection for eyes prescribed netarsudil and brimonidine. IOP = intraocular pressure.

each eye was defined as the average of the first three IOP measurements before treatment. The posttreatment IOP was defined as the average of the two IOP measurements following the prescribing visit. The primary outcome was the change in IOP, ΔIOP, defined as the difference in baseline IOP and post-treatment IOP ($\Delta IOP = IOP_{4,5} - IOP_{1,2,3}$, where $IOP_{4,5}$ is the mean of the fourth and fifth IOP measurements, and $IOP_{1,2,3}$ is the mean of the first three measurements).

For statistical analysis, a χ^2 test was used to compare eye characteristics between the two groups such as glaucoma type, severity, number of baseline medications, classes of medications before prescription, baseline IOP, and surgical history. A two-sample *t* test was used to compare the unadjusted means of the ΔIOP resulting from netarsudil and brimonidine. A multilevel linear mixed-effects model was employed to assess the overall influence of netarsudil and brimonidine (independent variables) on ΔIOP (dependent variable). Other independent variables of interest (confounders) included in the model were the number of glaucoma medications the patient was using before the addition of netarsudil or brimonidine, age, sex, glaucoma type, glaucoma severity, race, and baseline IOP. Additionally, the model included a random effect term to account for both eyes from the same patient. As the mixed-effects model estimated the overall effect of netarsudil relative to brimonidine, a multiple linear regression was also performed to estimate the effect of netarsudil compared with brimonidine for a specific given number of baseline medications (independent variables) on the ΔIOP (dependent variable). Additionally, to remove the effects of sampling bias that are not accounted for in the mixed-effects model and the presence of multiple brimonidine eyes for a corresponding netarsudil eye, a bootstrap analysis was performed that randomly resamples each dataset multiple times to create many simulated samples. To account for the differences in the potential confounding variables mentioned above between the brimonidine and netarsudil groups, the distributions of these variables were equated during the bootstrap analysis. The mean ΔIOP for the netarsudil sample was compared with the 95% CI of a bootstrapped distribution of mean ΔIOP for brimonidine. Lastly, a sensitivity analysis was conducted using only two pretreatment IOP measurements ($IOP_{2,3}$) because the use of three IOP measurements may underestimate the results.

For statistical analyses involving multiple comparisons such as the χ^2 test on baseline eye characteristics, a Bonferroni comparison was used with $\alpha = 0.05/N$ where *N* is the number of comparisons. Meanwhile, a correction was not applied to the two-sample *t* test, mixed-effects model, multiple linear regression, and bootstrap analysis of ΔIOP between netarsudil and brimonidine.

Secondary aim: Failure of pharmacologic therapy to control IOP

The secondary aim of this study was to determine rates at which pharmacologic therapy with either netarsudil or brimonidine failed to control IOP and whether any differences in these failure rates are dependent on the number of glaucoma medications a patient is on at baseline. Failure was defined as the escalation of therapy due to inadequately controlled IOP. Escalation could be the addition of another glaucoma medication, glaucoma-specific ocular surgery (eg, trabeculectomy, tube shunt, iStent/Hydrus, cyclophotocoagulation, or bleb needling), or a laser procedure (eg, trabeculoplasty or peripheral iridotomy) to further reduce IOP.

For statistical analysis, a Kaplan-Meier survival analysis was used to evaluate the time from initiation of netarsudil or brimonidine to the time of additional intervention (event of interest). Eyes were censored from the analysis if they discontinued the medication for any reason (eg, tolerance or cost) or did not have follow-up through three years. To determine statistical significance, survival rates were compared using the log-rank (Mantel-Cox) test. Additionally, to compare differences in the types of interventions performed between the two groups, a χ^2 test was used, and a Bonferonni correction was applied because there were multiple comparisons involved.

Results

The overall demographic characteristics of the patients included in this investigation are shown in **Table 1**. The investigation included a total of 369 eyes obtained from 279 patients. Of these patients, 138 (176 eyes) were treated with netarsudil and 141 (193 eyes) were treated with brimonidine. The average age, biological sex, and race were similar between the different treatment groups. Among the netarsudil eyes considered for this study, 229 eyes (56.54%) were excluded from the study based on a variety of reasons as shown in **Figure 1**. The most common reason eyes were excluded was due to a change in the patient's medication regimen throughout the five sequential clinic visits (81 eyes [20.00%]). The second most common reason for exclusion was an inability to start netarsudil due to cost. Among eyes that received netarsudil, 28 (15.91%) stopped due to poor tolerance. Among the brimoni-

Table 1
Demographic characteristics of patients studied.

Characteristic	Netarsudil	Brimonidine	Total
Patients*	138 (176)	141 (193)	279 (369)
Age†	69 (14.57)	71 (15.14)	70 (14.87)
Biological sex†			
Female	59 (42.75)	72 (51.06)	131 (47.00)
Male	79 (57.25)	69 (48.94)	148 (53.00)
Race†			
Asian	6 (4.35)	8 (5.67)	14 (5.02)
Black or African American	53 (38.41)	46 (32.62)	99 (35.48)
White or Caucasian	72 (52.17)	80 (56.74)	152 (54.48)
Other	6 (4.35)	6 (4.26)	12 (4.30)
Unknown	1 (0.72)	1 (0.71)	2 (0.72)

* Values are presented as number of patients (number of eyes).
† Values are presented as number of eyes (%).‡Values are presented as mean (SD).

dine eyes, 1202 eyes (86.16%) were excluded with the most common reason being regimen changes (438 eyes [31.40%]).

The ocular characteristics of the included eyes are shown in Table 2. There were 20 comparisons made between the netarsudil and brimonidine groups and the threshold for statistical significance was $\alpha = 0.003$ with Bonferonni correction. Glaucoma type and disease severity were similar between the cohorts. In the netarsudil group, 18 (10.23%), 70 (39.77%), 85 (48.30%), and 3 (1.70%) eyes had netarsudil added as a third-, fourth-, fifth-, and sixth-line agent respectively. In contrast, brimonidine was added only as a third- or fourth-line agent in 62 (32.12%) and 131 (67.88%) eyes, respectively. Thus, for eyes with only two or three baseline medications, 193 brimonidine eyes could be paired with one of 88 netarsudil eyes. The distribution of baseline IOP was similar between netarsudil and brimonidine. Most eyes in both cohorts had baseline IOPs between 15 and 20 mm Hg. The average baseline IOP from all eyes for netarsudil and brimonidine were 20.91 and 20.46 mm Hg, respectively. Moreover, the average pretreatment IOP in the first, second, and third clinical visits for netarsudil and brimonidine was 17.16, 18.76, 20.91 mm Hg, and 17.05, 17.90, and 20.46 mm Hg, respectively. Approximately 85% of IOP measurements were performed with Goldmann applanation for both netarsudil and brimonidine. Eyes receiving netarsudil had significantly higher proportions of past laser or surgery history than eyes receiving brimonidine ($P < 0.001$).

With regard to the primary aim of the study, a Bonferonni correction was not applied in the subsequent results and the threshold for statistical significance was $\alpha = 0.05$. The unadjusted ΔIOPs for netarsudil and brimonidine were similar ($P = 0.484$) with mean (SD) ΔIOPs of −2.20 (4.11) mm Hg and −2.21 (3.25) mm Hg, respectively. The results of the linear mixed-effects model are shown in Table 3. The intercept represents white female patients with mild, primary open-angle glaucoma given brimonidine with no other antihypertension medications at baseline. Baseline IOP and

Table 3
Results of linear mixed-effects model assessing the influence of various factors on the change in intraocular pressure (IOP) before and after the addition of therapy.

Fixed effect	ΔIOP (95% CI)
Intercept	−1.50 (−4.98 to 1.99)
Netarsudil vs brimonidine	−0.27 (−1.17 to 0.63)
Each additional class of glaucoma medication	0.53 (−0.14 to 1.21)
1-mm Hg increase in baseline IOP*	−0.25 (−0.33 to −0.17)
1-year Increase in age	0.02 (−0.01 to 0.05)
Sex	
Male vs female	0.52 (−0.28 to 1.33)
Race	
Black vs white*	0.99 (0.11 to 1.87)
Asian vs white	0.44 (−1.34 to 2.22)
Glaucoma severity	
Moderate vs mild	−0.40 (−1.35 to 0.53)
Severe vs mild	−0.31 (−1.19 to 0.55)
Glaucoma type	
Primary angle-closure vs primary open-angle	−0.25 (−1.54 to 1.04)
Secondary vs primary open-angle	−0.20 (−1.22 to 0.83)

* Indicates statistically significant difference ($P < 0.05$).

Table 2
Ocular characteristics of eyes studied.

Characteristic	Netarsudil (n = 176)	Brimonidine (n = 193)	Total (N = 369)
Glaucoma type*			
Primary open-angle glaucoma/suspect	122 (69.32)	131 (67.88)	253 (68.56)
Primary angle-closure glaucoma/suspect	16 (9.09)	26 (13.47)	42 (11.38)
Secondary glaucoma	38 (21.59)	36 (18.65)	74 (20.06)
Glaucoma severity*			
Mild	44 (25.00%)	68 (35.23%)	112 (30.35%)
Moderate	39 (22.16)	50 (25.91)	89 (24.12)
Severe	93 (52.84)	75 (38.86)	168 (45.53)
No. of glaucoma meds before addition*			
2	18 (10.23)	62 (32.12)	80 (21.6)
3	70 (39.77)	131 (67.88)	201 (54.47)
4	85 (48.30)	0	85 (23.04)
5	3 (1.70)	0	3 (0.81)
Classes of glaucoma meds before addition*			
Prostaglandin analogues	167 (94.88)	182 (94.30)	349 (94.58)
β-adrenergic blocker	150 (85.23)	181 (93.78)	331 (89.70)
α-adrenergic agonist†	124 (70.45)	193 (100.00)	317 (85.9)
Carbonic anhydrase inhibitor	155 (88.07)	152 (78.7)	304 (82.38)
Cholingergic agonist	5 (2.84)	2 (1.0)	4 (1.08)
Baseline IOP (Mean $IOP_{1,2,3}$)*			
<15	33 (18.75)	46 (23.83)	79 (21.41)
15-20	81 (46.02)	78 (40.41)	159 (43.09)
20-25	37 (21.02)	49 (25.39)	86 (23.31)
≥25	25 (14.21)	20 (10.36)	45 (12.19)
Prior surgical or laser history treatment*,†	114 (68.26)	84 (43.75)	198 (53.66)

IOP = intraocular pressure.
* Values are presented as number of eyes (%).
† Indicates χ^2 test resulted in a statistically significant difference ($P < 0.003$ with Bonferroni correction) between netarsudil and brimonidine.

Table 4
Description of additional medical, laser, and surgical intervention in netarsudil and brimonidine treatment of eyes.

Netarsudil	Third agent (n = 5)	Fourth agent (n = 34)	Fifth agent (n = 35)	Total (N = 75)
Days to intervention*	328 (244)	425 (287)	383 (244)	396 (262)
Additional medication as next step‡	0 (0.00)	0 (0.00)†	0 (0.00)	0 (0.00)†
Laser as next step‡	0 (0.00)	3 (8.82)	0 (0.0)	3 (4.00)
ALT/SLT	0 (0.00)	3 (8.82)	0 (0.00)	3 (4.00)
LPI	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Surgery as next step‡	5 (100.00)	31 (91.18)	35 (100.00)	71 (94.67)†
Trabeculectomy	3 (60.00)	9 (26.47)	11 (31.43)	23 (30.67)
Tube shunt	0 (0.00)	8 (23.53)	13 (37.14)	21 (28.00)
iStent/Hydrus	1 20.00)	6 (14.71)†	5 14.29)	11 (14.67)†
Cyclophotocoagulation	0 (0.00)	6 (17.65)	4 (11.43)	10 (13.33)
GATT	0 (0.00)	3 (8.82)	0 (0.00)	3 (4.00)
Bleb needling	1 (20.00)	0 (0.00)	2 (5.71)	3 (4.00)

Brimonidine	(n = 30)	(n = 60)	(n = 90)
Days to intervention*	455 (303)	403 (247)	420 (267)
Additional medication as next step‡	18 (60.00)	16 (26.67)†	34 (37.78)†
Laser as next step‡	2 (6.67)	2 (3.33)	4 (4.44)
ALT/SLT	2 (6.67)	2 (3.33)	4 (4.44)
LPI	0 (0.00)	0.00 (0)	0 (0.00
Surgery as next step‡	10 (33.33)	42 (70.00)	52 (57.78)†
Trabeculectomy	9 (30)	29 (48.33)	38 (42.22)
Tube shunt	0 (0.00)	9 (15.00)	9 (10.00)
iStent/Hydrus	1 (3.33)	0 (0.00)†	1 (1.11)†
Cyclophotocoagulation	0 (0.00)	4 (6.67)	4 (4.44)
GATT	0 (0.00)	0 (0.00)	0 (0.00)
Bleb needling	0 (0.00)	0 (0.00)	0 (0.00)

ALT = argon laser trabeculoplasty; SLT = selective laser trabeculoplasty; LPI = laser peripheral iridotomy; GATT = gonioscopy-assisted transluminal trabeculotomy.
* Values are presented as mean (SD).
† Indicates χ^2 test resulted in a statistically significant difference ($P < 0.001$ with Bonferroni correction) between netarsudil and brimonidine.
‡ Values are presented as number of eyes (%).

race (Black) were the only factors with statistically significant effects on ΔIOP. Specifically, every 1.00 mm Hg increase in baseline IOP was associated with a −0.25 (−0.33 to −0.17) mm Hg decrease in IOP (better IOP) after starting medical therapy. Compared with White patients, Black patients showed a 0.99 (0.11 to 1.87) increase in IOP (worse IOP). Other fixed variables such as the medication (netarsudil vs brimonidine), the number of baseline medications, glaucoma type, age, sex, glaucoma severity, and race (Asian) did not have a significant effect on ΔIOP.

The multiple linear regression model revealed the estimated ΔIOP (95% prediction interval) of netarsudil when added as a third-, fourth-, and fifth-line agent is −3.29 (−10.57 to 4.00), −2.52 (−9.75 to 4.72), and −1.75 (−8.99 to 5.49) mm Hg, respectively. The estimated ΔIOP for brimonidine when added as a third- and fourth-line agent was −2.73 (−9.97 to 4.51) and −1.96 (−9.19 to 5.27) mm Hg, respectively. The regression model also demonstrates statistically a significant difference in the number of base medications ($P = 0.023$).

Bootstrap analysis reveals the mean (95% CI) ΔIOP for all eyes on netarsudil is −2.64 (−2.91 to −2.28) mm Hg, whereas the reference mean ΔIOP for brimonidine is −2.48 mm Hg. The bootstrapped brimonidine distribution consists of 10,000 samples with distributions of confounding variables equated across all brimonidine samples to those of the netarsudil samples. No statistical difference between the medications is present when equating the samples. The sensitivity analysis utilizing only two pretreatment IOP measurements also confirms this finding.

With regard to the secondary aim of the study, eyes that ultimately required additional intervention within the first 3 years of starting pharmacologic treatment with netarsudil or brimonidine are shown in **Figure 2**. Netarsudil had similar probabilities of survival as brimonidine ($P = 0.520$). The types of interventions stratified by the number of baseline medications for each group are shown in **Table 4**. There were 36 comparisons made between the netarsudil and brimonidine groups and the threshold for statistical significance was $\alpha = 0.001$ with Bonferonni correction. Netarsudil and brimonidine had a similar mean time from the initiation of therapy to the time of additional intervention ($P = 0.560$). Brimonidine had lower rates of surgical intervention than netarsudil ($P < 0.001$). Most eyes received either trabeculectomy or tube shunt when either medical therapy failed to control the disease. Among eyes that required surgical intervention, greater rates of trabecular

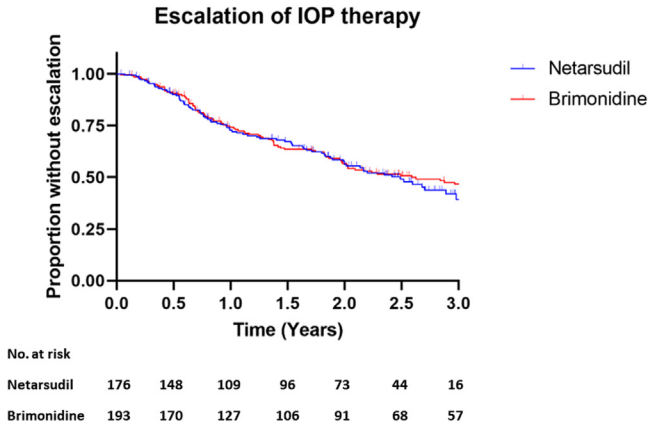

Figure 2. Kaplan-Meier survival curve of additional intervention for netarsudil versus brimonidine. IOP = intraocular pressure.

bypass stents ($P < 0.001$), tube shunt ($P = 0.003$), and cyclophotocoagulation ($P = 0.041$) were seen in the netarsudil group.

Discussion

Overall, netarsudil still provided modest IOP improvements when added to a combination therapy of two or more medications. Although multivariate regression demonstrated a trend suggesting diminishing effects with a greater number of medications at baseline, this was not statistically significant when adjusting for other confounding variables in the linear mixed-effects model. Secondly, unadjusted ΔIOP, the linear mixed-effects model, and bootstrap analysis showed that the IOP-lowering effects of netarsudil are similar to brimonidine. Finally, the probability of additional intervention after the prescription was similar between brimonidine and netarsudil.

Effectiveness of netarsudil in combination therapy with two or more medications

To date, there have been four studies examining the effect of netarsudil as an adjuvant agent.[17–20] Both the unadjusted measurements and linear regression models demonstrated that netarsudil still improved IOP when added as adjunctive therapy but to a lesser extent than reports from monotherapy clinical trials. Specifically, netarsudil reduces IOP by −2.20 mm Hg. On the other hand, prior monotherapy studies report IOP reduction between 3.4 and 5.7 mm Hg.[11,22,23] When compared with previous netarsudil combination studies, these findings are consistent with Prager et al[18] who observed a mean IOP reduction of 2.2 mm Hg when netarsudil was used as an adjunctive agent among those with two to four baseline medications. In contrast, Villegas et al,[19] Shiuey et al,[20] and Zaman et al[17] found the effectiveness of adjunctive netarsudil therapy was similar to monotherapy with IOP reductions between 3.5 and 4.5 mm Hg under similar circumstances. There are multiple possible explanations for the discrepancies with previous studies. First, measurements may have been confounded by regression to the mean as baseline IOP was determined from only a single pretreatment IOP measurement in these studies. Because this investigation averages three pretreatment IOP measurements, with two of three being slightly lower, this leads to a smaller effect observed for netarsudil. Second, unlike prior studies that found that the effectiveness of netarsudil did not depend on the number of baseline medications,[18–20] this study observed that netarsudil had smaller effects on eyes on more medications according to predictions from linear regression. Previously, multiple studies have demonstrated that the effectiveness of other IOP-lowering medications diminishes with a sequential increase in medications and so it is reasonable to expect this with netarsudil as well.[15,24,25] Third, several confounding variables were accounted for statistical analysis, which was not the case in previous netarsudil combination studies.

Netarsudil compared with brimonidine

The 4 prior investigations on the IOP-lowering effectiveness of netarsudil in real-world settings mentioned above have not yet compared netarsudil with a peer medication in combination therapy consisting of more than two agents.[17–20] This study may provide clarification for clinicians to make evidence-based decisions on the use of netarsudil as an adjuvant agent in these settings. Contrary to expectations based on the mechanism of action, the unadjusted results, mixed-effects model, and bootstrap analysis demonstrated similar effectiveness of netarsudil to brimonidine at lowering IOP when used as an adjuvant agent. One would expect netarsudil to be more effective as its unique ability to lower episcleral venous pressure as well as its ability to target trabecular outflow would be additive to other mainstream medications targeting aqueous humor production and uveoscleral outflow. Meanwhile, brimonidine targets the same pathways as first-line prostaglandins. A possible reason for this study's finding may have been due to differences in prior ocular history between the netarsudil and brimonidine groups. Eyes that began netarsudil more frequently had prior treatment such as trabeculoplasty, trabeculectomy, or tube shunts. In these eyes, netarsudil's advantages from targeting trabecular outflow may have been diminished.

Equally important, when clinicians are deciding between netarsudil and brimonidine, another factor that must be considered is individual side-effect tolerance to each medication. In this study, an adverse reaction rate of 16% was observed which is consistent with previous reports of 10% to 27% in patients that have received netarsudil.[17,18,20] This is comparable with the adverse reaction rate of 10% to 30% in patients that have received brimonidine.[18] The final consideration for clinicians will be individual financial barriers to the patient. Among the eyes considered for netarsudil, 30 (7.40%) could not start it due to lack of insurance coverage or inability to afford long-term use of netarsudil.

Pharmacologic failure and additional interventions

Between glaucomatous eyes managed with netarsudil and brimonidine in multidrop therapy, there were similar rates of failure defined as needing additional medical, laser, or surgical intervention. The netarsudil group had a higher rate of surgery than the brimonidine group. This may be because, during the period of netarsudil availability, microinvasive glaucoma surgery had become more widespread, likely leading to the earlier surgical intervention in netarsudil eyes. This is supported by the statistically higher rates of subsequent iStent/Hydrus in the netarsudil group compared with the brimonidine group. Although surgical history may be a confounding variable in the findings, the literature concerning the influence of surgical history on the IOP-lowering effectiveness of glaucoma medications in real-world circumstances, especially with netarsudil, remains unclear and warrants further investigation.

To date, this is the first postmarket independent study investigating netarsudil as an adjunctive agent in combination therapy with a comparative control cohort, such as brimonidine, in a real-world clinical setting. Because netarsudil is usually added after other therapies have been exhausted, this study may offer guidance to clinicians on the role of netarsudil, specifically on whether to continue the current practice of considering it last in therapy escalation. Also, the present investigation included a broad range of glaucoma types as opposed to prior clinical trials.[11,23,26]

Nonetheless, it is also important to acknowledge the limitations of the study. As a retrospective study, the method and timing of IOP measurement could not be controlled, which could have led to systematic bias and diurnal fluctuations affecting the measurements. Although the influence of systematic bias due to tonometry methodology is suspected to be minimal because Goldmann applanation was consistently used across all five clinic visits for the majority of eyes. The effects of regression to the mean were also mitigated by averaging multiple IOP measurements. Furthermore, the effect of adding netarsudil as a third-, fourth-, and fifth-line agent was examined, but specific combinations and whether there is an optimal regimen for a particular number of medications could not be investigated. Adherence was assessed through self-report at each clinical visit. Patients were under the care of multiple providers who may have had different views on when to escalate drop therapy or when to stop netarsudil (due to lack of effectiveness or patient tolerance), which could have influenced

the number of eyes included in this study. Many eyes followed throughout the five sequential clinic visits were excluded in this study based on medication regimen changes. Proportionally more brimonidine eyes were excluded for this reason compared with netarsudil throughout the filtering process and this may have biased the results more favorably toward brimonidine. While other methods of matching such as propensity score matching were considered, a simpler matching method was employed due to recent challenges concerning the statistical validity of propensity score matching.[27] Bonferroni correction was also not applied to the mixed-effects model, which may affect findings regarding whether race and baseline IOP have a significant influence on each medication's effectiveness; however, this would not affect the estimates of the model. Lastly, for investigating rates of pharmacologic failure, the microinvasive glaucoma surgery procedures captured in this study may have been performed as a concurrent procedure where the primary motivation was cataract extraction rather than uncontrolled IOP.

Conclusions

Using netarsudil as a supplemental agent in patients with glaucoma already on multiple medications resulted in modest improvements in IOP. Clinicians can expect smaller improvements when patients are taking a greater number of medications before initiation. Netarsudil and brimonidine were not statistically significantly different with respect to lowering IOP and had similar rates of adverse reactions.

Conflicts of Interest

J. Yohannan is a consultant for Abbvie and Ivastis and receives research support from Genentech. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2022.100689.

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