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Real-World Clinical Impact of Netarsudil 0.02% at an Urban Safety-Net Hospital

Gabrielle Fridman,* Natalie Sadlak, Babak Eliassi-Rad, and Manishi A. Desai

Abstract

Purpose: To analyze the efficacy, safety, and accessibility of netarsudil 0.02% in patients with glaucoma (suspect, open or closed) at a safety-net academic medical center, Boston Medical Center (BMC).
Methods: Retrospective chart review of patients prescribed netarsudil 0.02% for uncontrolled glaucoma at BMC between December 2017 and September 2019. Outcome measures included change in intraocular pressure (IOP) from baseline and evaluation of adverse events (AEs).
Results: One hundred thirty patients (60% severe stage) were analyzed. The IOP reduction from baseline was about 3 mmHg. Fifty-four patients (42%) experienced an AE (eg, conjunctival hyperemia). Thirty-eight patients (29%) started netarsudil 0.02% in lieu of laser or surgery. Ninety-nine patients (71%) required prior authorization for insurance coverage of netarsudil 0.02%. Ten patients (7%) were unable to obtain netarsudil 0.02% due to issues with insurance coverage.
Conclusion: Netarsudil 0.02% yielded significant IOP reduction in our cohort, however, to a smaller degree compared with prior studies that bore equivocal IOP reduction regardless of baseline IOP. Conjunctival hyperemia was the most common AE. In a limited number of patients, netarsudil 0.02% was not covered by insurance.

Keywords: netarsudil, glaucoma, ocular hypertension, intraocular pressure, rho kinase inhibitor

Introduction

Glaucoma is a leading cause of irreversible blindness.[1,2] Despite the many pathways and known associations with this disease entity, the predominant and solely modifiable factor influencing its progression is intraocular pressure (IOP).[1] A number of ocular hypertensive agents are available, but there has not been a new medication in nearly a decade until the approval of netarsudil in 2017. Netarsudil is an amino isoquinoline amide that is a potent Rho-associated protein kinase (ROCK) and norepinephrine transport (NET) inhibitor.[3]

ROCK serves as an important downstream effector of Rho GTPases that regulate cytoskeletal and cell adhesion dynamics. Within the trabecular meshwork and Schlemm's canal, ROCK drives actomyosin contraction, promotes extracellular matrix (ECM) production, and increases cell stiffness.[4] As such, inhibitors of ROCK reduce cell contraction, decrease expression of fibrosis-related proteins, and reduce cell stiffness.[4] Netarsudil, as a potent ROCK inhibitor, is believed to disrupt actin stress fibers and focal adhesions in the trabecular meshwork cell and block the profibrotic effects of transforming growth factor-beta 2, a cytokine involved with promoting increased ECM stiffness and cell contraction in the trabecular meshwork.[4] Thus, netarsudil is believed to lower IOP via 3 primary mechanisms: increasing aqueous outflow by relaxing the trabecular meshwork, decreasing aqueous humor production, and decreasing episcleral venous pressure.[3,5]

The greater efficacy and longer duration of action for netarsudil may be related to its NET inhibitory activity. The inhibition of NET blocks the reuptake of norepinephrine at noradrenergic synapses, thus increasing the strength of endogenous norepinephrine signaling, which may act to reduce aqueous humor formation and blood flow to the ciliary processes.[4]

Department of Ophthalmology, Boston Medical Center/Boston University School of Medicine, Boston, Massachusetts, USA.
*ORCID ID (https://orcid.org/0000-0002-2065-4568).

Comparatively, latanoprost is a prostaglandin F2-alpha analog that increases uveoscleral outflow and timolol is a beta receptor inhibitor that reduces aqueous humor production.[6,7] Latanoprost is believed to induce remodeling of the ECM and to regulate matrix metalloproteinases, resulting in higher tissue permeability, which impacts outflow resistance and rate.[6] The exact mechanism of timolol, however, is not yet fully understood.[7]

The IOP-lowering effect of netarsudil has been compared with both timolol and latanoprost in clinical trials.[4] Its efficacy proved to be similar to that of timolol without known systemic side effects, and its combination with latanoprost proved to be more efficacious than the individual components alone.[1,2,5] However, as with any topical medication, netarsudil has ocular side effects. Some of the most frequently observed side effects include conjunctival hyperemia, conjunctival hemorrhage, and corneal verticillata; other less common side effects include blepharitis and blurred vision.[2] Cost is also a major factor that may limit its utility, as the medication is new to the market. Aside from the lack of coverage by Medicaid or Medicare without prior authorization (PA), even for patients with commercial insurance a single bottle is estimated to cost a minimum of $25 per month ($50 if a commercial provider does not cover the medication).[8]

The purpose of this study is to report a retrospective analysis of all patients who were prescribed netarsudil at the Boston Medical Center (BMC) ophthalmology clinic since its Food and Drug Administration (FDA) approval to evaluate its efficacy, particularly in an academic glaucoma practice where most patients are already on 2 or more medications. We hypothesize that the effect will be less robust than reported given concurrent therapy with other medications, but the actual amount of lowering is unknown. The primary outcome measure included change in IOP from the date of initial prescription to at least 4 weeks. Secondary measures included side effects and their impact on compliance as well as insurance coverage and necessity of PAs. The BMC is the largest safety-net hospital in New England such that a significant portion of our patients rely on government-issued insurance plans (eg, Medicaid and Medicare), so our tertiary analysis will explore the accessibility of netarsudil in our clinical setting.

Methods

This study received Institutional Review Board approval and complied with the Health Insurance, Portability and Accountability Act and the doctrine of the Declaration of Helsinki. Medical records of all patients with ocular hypertension, open angle, narrow angle, and secondary glaucoma who were prescribed netarsudil for uncontrolled glaucoma at the BMC ophthalmology clinic between December 18, 2017 and September 21, 2019 were reviewed. Inclusion criteria were as follows: (1) netarsudil prescription placed between the aforementioned dates at the BMC ophthalmology clinic; (2) a follow-up appointment with measurement of IOP. Exclusion criteria included: (1) patients who were lost to follow-up after being prescribed netarsudil; (2) patients who had confounding variables to unbiased IOP measurement, including, but not limited to, those who reported poor or no compliance to netarsudil or underwent concurrent intervention with multiple medications (eg, started on multiple IOP-lowering agents at once) or confounding procedures (when initiating netarsudil); (3) IOP measurement by any instrument other than a Goldman tonometer; and (4) multiple ocular comorbidities, for example, history of corneal disease or uveitis that would confound results.

The following patient data were collected from the electronic medical records: sex, age, ethnicity, date of netarsudil prescription, diagnosis at time of prescription, glaucoma medication use and surgical history at time of prescription, need for a PA for netarsudil and time frame to have it completed, IOP in each eye pre-initiation of netarsudil and post-initiation of netarsudil at the first follow-up, and adverse events (AEs) secondary to netarsudil at any point during therapy. The AEs were noted if identified by the patient or by the physician on exam. Glaucoma severity was staged as per the 10th International Code of Diseases (ICD-10).[9] Mild-stage glaucoma was defined as optic nerve abnormalities consistent with glaucoma but no visual field abnormalities on any white-on-white visual field test, or abnormalities present only on short-wavelength automated perimetry or frequency-doubling perimetry. Moderate-stage glaucoma was defined as optic nerve abnormalities consistent with glaucoma and glaucomatous visual field abnormalities in 1 hemifield, and not within 5° of fixation. Severe-stage glaucoma was defined as optic nerve abnormalities consistent with glaucoma and glaucomatous visual field abnormalities in both hemifields, and/or loss within 5° of fixation in at least 1 hemifield.

Data from each eye individually were used to assess the difference in mean change in IOP after the introduction of netarsudil via a paired *t*-test. The change in IOP was then compared with previously published values, ranging from 3.9 to 4.1 mmHg, by using a 1-sample *t*-test. One-way analysis of variances (ANOVAs) were performed to assess for the effect of glaucoma severity and the number of concurrent topical medications, respectively, on overall change in IOP. P values <0.05 were considered statistically significant.

The rate of incidence of AEs was also examined in this analysis. Binomial tests were performed to determine whether the rate of drug-related AEs observed in this population was as expected given the numbers published in the safety report released by the U.S. FDA.[10] Three separate 2-tailed binomial tests were performed to assess the rate of incidence of all AEs, the rate of conjunctival hyperemia, and the rate of all other AEs observed in this population.

Results

Of the 285 patients who were prescribed netarsudil between December 18, 2017 and September 21, 2019, 140 met the inclusion criteria for this study. Ten patients were not able to obtain the medication and, thus, were excluded from the IOP and AEs arms of the study. Baseline demographics are detailed in Table 1. The mean IOP before starting netarsudil was 18.27 and 18.16 mmHg in the right and left eye, respectively, as compared with 15.27 and 15.14 mmHg after starting netarsudil. Given the variable follow-up among our patients, a secondary analysis was performed to assess a subset of patients (105 of 115) who presented for 2 follow-up encounters within a 6-month period after initiating netarsudil (Table 2). Within this subset, the mean IOP before starting netarsudil was 18.47 and 18.23 mmHg in the right

Table 1. Baseline Demographics of All Patients

Glaucoma severity, *n* (%)	
Mild	4 (3.08)
Moderate	32 (24.6)
Severe	78 (60)
unspecified	16 (12.3)
Glaucoma type, *n* (%)	
POAG	98 (75.4)
ACG	4 (3.1)
MMG	15 (11.5)
PDG	2 (1.5)
PXG	2 (1.5)
NTG	8 (6.2)
Suspect	1 (0.8)
Sex	
Female	69 (53.1)
Male	61 (46.9)
Age	
<65 years	38 (29.2)
≥65 years	92 (70.8)
Mean age, years	69.1
Race/Ethnicity	
Black/African American	78 (60)
Hispanic	15 (10.7)
White	12 (9.3)
Asian	4 (2.9)
Unspecified	21 (17.1)
Prior hypotensive therapy	
None[a]	1 (0.01)
Topical monotherapy	4 (3.1)
Topical combination therapy	125 (96.2)
Mean number of prior topical medication classes[b]	3.42
Patients concurrently on previously prescribed oral hypotensive	24 (20.9)
Patients who previously had in-office laser therapy (LPI or SLT)	72 (62.6)
Patients who previously had CPC	11 (9.5)
Patients who previously had MIGS	12 (10.4)
Patients who previously had filtering surgery	37 (32.2)

[a]One patient who had negligible response to prior topical medications.

[b]Including prostaglandin analogs, beta blockers, alpha agonists, and carbonic anhydrase inhibitors.

ACG, angle closure glaucoma; CPC, trans-scleral cyclophotocoagulation; LPI, laser peripheral iridotomy; MIGS, minimally invasive glaucoma surgery; MMG, mixed mechanism glaucoma; NTG, normal tension glaucoma; PDG, pigment dispersion glaucoma; POAG, primary open angle glaucoma; PXG, pseudoexfoliation glaucoma; SLT, selective laser trabeculoplasty.

and left eye, respectively, as compared with 15.28 and 15.01 mmHg after starting netarsudil. For the full group, the percent reduction per eye averaged 16.5%, which equates to a significant mean reduction of 3.01 mmHg ($P < 0.001$). For the subset group, the percent reduction per eye averaged 17.5%, which equates to a significant mean reduction of 3.21 mmHg ($P < 0.001$). For both the full set of study participants and the subset group, these values were found to be significantly less than the previously reported reductions of 3.9–4.1 mmHg (full set: $P = 0.0005$; subset: $P = 0.020$); however, this group was on monotherapy. There was no statistically significant difference in group means based on either severity of glaucoma ($P = 0.30$) or the number of current topical medications ($P = 0.46$).

Approximately 11.5% ($n = 15$) of patients stopped taking netarsudil secondary to AEs. Table 3 describes the drug-related AEs noted, with the most common being conjunctival hyperemia, which was also the most common reason why the medication was stopped. Other AEs included blurry vision (3.1%), itchiness (2.3%), pain (2.3%), tearing (2.3%), corneal verticillata (1.5%), dry eye (1.5%), eyelid swelling (0.8%), discharge (0.8%), and burning (0.8%). The rate of incidence of all AEs was found to be lower in this study population than that described in the initial FDA approval form.[10] *P* values are included in Table 3.

The majority of our patient population is covered by government-issued insurance versus the private sector, and, subsequently, 70.7% ($n = 99$) of these patients required a PA to obtain netarsudil. On average, the wait time from the start of a PA to the time of approval was 16.33 days with a range of 0–68 days (standard deviation = 17.18). Ten patients (7.14%) were never able to obtain netarsudil secondary to either lack of insurance coverage or inability to afford the co-payment for the medication.

Within our cohort, 38 patients with severe-stage glaucoma were given the option of trying netarsudil versus immediately preceding with laser or surgical treatment. Of this subgroup, only 5.2% of patients ($n = 2$) demonstrated a sufficient response to actually delay further intervention. Thirty-six patients, 94.7% of this subgroup, still required further laser or surgical intervention, which amounted to 27.7% of the total cohort.

Discussion

The primary objectives of this study were to evaluate the efficacy and safety of netarsudil via a retrospective chart review at our tertiary care center in a cohort at various levels of treatment and stages of glaucoma that represent typical daily clinical encounters (Table 1). We also sought to assess AEs and how many patients required a PA to obtain the medication. The major clinical trials assessing rho kinase inhibitors, such as netarsudil, predominantly looked at patients on monotherapy and had less diverse subjects.[1,2]

The major clinical trials for netarsudil quote a mean change in diurnal IOP ranging from 3.9 to 4.1 mmHg.[1] They also demonstrate that the IOP-lowering efficacy is consistent per patient regardless of baseline IOP; this is likely related to netarsudil's distinct mechanisms of action affecting trabecular outflow as compared with other drug classes.[2,5,10] However, these trials had patients undergo a medication washout period and excluded those with secondary glaucoma, or a history of prior laser or surgical intervention as they were establishing efficacy and non-inferiority.

Given that the majority of our patients have severe glaucoma, we assessed netarsudil as an adjunct medication to patients whose target pressure was not reached, which more accurately portrays its current clinical use. We found an $\sim$16.5%–17.5% IOP reduction rate in our patients equating to about 3.01–3.21 mmHg. This effect is constant across various stages of glaucoma and the number of concurrent medications when these factors are assessed independently. However, the effect of prior lasers or surgeries could not be separately evaluated given the retrospective nature of this study.

There are multiple factors that might explain why our results differ from those in other studies, including the concurrent use

Table 2. Intraocular Pressure Changes Pre- and Post-Initiating Netarsudil

Paired t-*test*	*Mean ± SD (mmHg)*		*Mean (mmHg) difference (post-baseline)*		t *stat*		df		P	
	OD	*OS*	*OD*	*OS*	*OD*	*OS*	*OD*	*OS*	*OD*	*OS*
Full set										
IOP 1	18.27 ± 5.28	18.16 ± 3.85	−3.0	−3.02	6.58	8.23	101	102	<0.001	<0.001
IOP 2	15.27 ± 4.48	15.14 ± 3.75								
Subset										
IOP 1	18.47 ± 5.4	18.23 ± 3.94	−3.19	−3.22	6.93	8.57	92	93	<0.001	<0.001
IOP 2	15.28 ± 4.4	15.01 ± 3.67								

IOP 1: IOP before initiating netarsudil.
IOP 2: IOP after initiating netarsudil.
Full set: These values reflect all study patients.
Subset: These values reflect 105 of 115 patients who attended 2 follow-up visits within a 6-month time frame after initiating netarsudil. The 10 patients who were omitted from this data set had only 1 encounter within 6 months after the initiation of netarsudil.
IOP, intraocular pressure (mmHg); OD, right eye; OS, left eye; SD, standard deviation.

of roughly 4 other drug classes in nearly all patients, which may result in a lower aqueous suppression effect, and a significant cohort already having undergone either a laser or surgical intervention (Table 1). In addition, there is the possibility that drugs may act differently in people of different ethnic backgrounds, though prior studies attempting to provide evidence that race affected the IOP-lowering effect of medications had insufficient power to detect such a difference.[5,11] At the same time, though not statistically significant, our results show that although there is an IOP-lowering effect in a refractory population, an additional intervention is likely required to reach low target pressures.

In our experience, most insurance companies did not cover netarsudil, with the majority requiring PA to receive the medication. This finding is not entirely unexpected given the novelty of the medication. However, these authorizations can take time and pose risks of delay in treatment for those wanting to trial the medication. Approval for medication ranged from same day to as long as 68 days. Although this places additional administrative burdens and costs in this high-risk population, in addition to treatment delays, our findings showed that only 7% were unable to obtain the medicine. In those cases where netarsudil was successfully obtained, about a third of patients had an insufficient IOP-lowering effect and required further intervention. In terms of AEs, our study mirrored others in finding that conjunctival hyperemia is the most commonly reported. As per the FDA report, the expected rate of incidence of all AEs, conjunctival hyperemia, and of all other AEs was determined to be 76.1%, 53.2%, and 20%, respectively.[10] Our findings also had an 11.5% rate of treatment withdrawal secondary to side effects.[5,12]

Table 3. Adverse Events Occurring in Patients Started on Netarsudil

	This report	*FDA report*[12]
Patients who experienced any AE[a]	41.5 ($P = 1.3e-12$)	71.6
Patients who experienced conjunctival hyperemia[b]	29.6 ($P = 4.6e-7$)	53.2
Patients who experienced other AE[b]	9.6 ($P = 0.003$)	20.0

Data expressed as (%).
[a]Data among all patients ($n = 130$), including those who stopped netarsudil quickly after initiation secondary to an AE.
[b]Data compared among patients ($n = 115$) who continued using netarsudil despite AEs.
AE, adverse event; FDA, Food and Drug Administration.

Given its retrospective nature, this study has limitations, including varying documentation practices among physicians, limiting the ability to analyze the frequency of incidence of each of the AEs individually aside from conjunctival hyperemia, bias in patient reports related to costs without independent verification, issues with patient compliance, and short follow-up. In addition, our IOP measurements were completed at varying times between 8 AM and 4:30 PM, possibly confounding our results due to diurnal IOP fluctuation. It also brings to light the need for important future investigation of potential in differences in IOP response after laser trabeculoplasty given its mechanism, and the projected added health care cost burden for novel therapies in patients with glaucoma. We did find that netarsudil can provide benefit in lowering eye pressure in patients with glaucoma already on multiple agents, though the effect can be insufficient and requiring further medical or surgical intervention in a notable percentage.

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Address correspondence to:
Dr. Manishi A. Desai
Department of Ophthalmology
Boston Medical Center/
Boston University School of Medicine
85 East Concord Street, 8th Floor
Boston, MA 02118
USA

E-mail: manishi.desai@bmc.org