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Research article

Early Results of Netarsudil for Glaucoma

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Abstract

Purpose: Netarsudil, a Rho-associated protein kinase inhibitor combined with a norepinephrine transporter inhibitor, is a novel anti-glaucoma medication. Approval trials have demonstrated a reduction in the intraocular pressure (IOP), but phase IV data has been sparse. This study was designed to provide real-world efficacy and safety data for netarsudil in clinical use.

Methods: A single center retrospective review at a University Hospital outpatient clinic was performed to assess the pressure-lowering effect of netarsudil 0.02% on patients with glaucoma. We included all patients who were treated with netarsudil at our institution. Exclusion criteria included less than one month of follow-up. The indication for adding netarsudil 0.02% at bedtime was determined on a case-by-case basis by the treating glaucoma specialist. The main outcome measure was the change in intraocular pressure (IOP) following the addition of netarsudil. The secondary outcome measure was the rate of adverse events throughout the 6-month treatment period.

Results: A total of 147 patients were started on netarsudil. The average age was 72 +/- 12 years old. The mean baseline IOP was 20.1 +/- 6.5 mmHg. After 6 months, the mean IOP had decreased 5 mmHg to 15.1 +/- 5.1 mmHg, a 25% reduction, while 44% achieved an IOP < 14 mmHg. The mean number of medications was similar at 3.8 +/- 1 medications at baseline and 3.6 +/- 1 at 6 months. Adverse events occurred in 60 patients (41%). The most common adverse event was conjunctival hyperemia which occurred in 19%, followed by dryness in 19%.

Conclusion: Adding netarsudil to a group of patients on previously core topical therapy still reduced the IOP at 6 months by a mean of 25%. Netarsudil was effective as an additive treatment to patients on multiple medications.

Keywords: *Netarsudil; Rho Kinase Inhibitor; Norepinephrine Transporter Inhibitor; Glaucoma*

Abbreviation

IOP: Intraocular Pressure

Introduction

Netarsudil, a Rho-associated protein kinase inhibitor combined with a norepinephrine transporter inhibitor, is a novel anti-glaucoma medication that was approved in the USA in 2017. The proposed mechanism of action is increased trabecular outflow by disrupting actin fibers and adhesions in trabecular meshwork cells [1]. Phase III trials demonstrated a reduction in the intraocular pressure (IOP), but phase IV data has been less common. This study was designed to provide efficacy and safety data for netarsudil in clinical use. Our study aims to determine the change in IOP following the administration of netarsudil.

Methods

A retrospective chart review was performed on consecutive cases of glaucoma who received netarsudil 0.02% at our institution. Inclusion criteria consisted of all patients who received netarsudil as part of their routine care. The exclusion criteria was less than one month of follow-up. The main outcome measure was reduction in IOP after 6 months. The study complied with the Health Insurance Portability and Accountability Act of 1996 and the Declaration of Helsinki and was approved by the Institutional Review Board at Stony Brook University.

All patients underwent a complete ophthalmologic examination prior to starting the medication. This included best-corrected visual acuity, slit-lamp biomicroscopy, Goldmann applanation tonometry and funduscopic evaluation. The indication for starting netarsudil was determined by the physician when the IOP was elevated over the individual target. The decision was made on a case-by-case basis by the treating physician. In cases where both eyes were treated with netarsudil, we only included the eye with the higher baseline IOP. Continuous data was analyzed using the student's t-test. Categorical data was compared using a chi-squared test. A finding of $p < 0.05$ was considered statistically significant.

Results

A total of 147 patients were started on netarsudil. The average age was 72 +/- 12 years old. There were slightly more males in the study, composing 52% of the group. Primary open-angle glaucoma was the most common diagnosis (74%), with the next two most common diagnoses (Table 1) being primary angle-closure (5%) and pseudoexfoliation glaucoma (4%).

Variable	Number (%)
N	147
Mean age (years)	71.9 ± 12.1
Gender, n (%)	
Male	77 (52%)
Female	70 (48%)
Ethnicity	
Caucasian	104 (71%)
Black or African American	17 (12%)
Hispanic or Latino	11 (8%)
Asian	7 (5%)
Other Race	1 (0.7%)
Declined to state	7 (5%)
Number of previous glaucoma surgeries	0.5 +/- 0.8
Diagnosis	
Primary open angle glaucoma	96 (74%)
Primary angle closure glaucoma	7 (5%)
Pseudoexfoliative glaucoma	5 (4%)
Pigmentary glaucoma	3 (2%)
Ocular Hypertension	3 (2%)
Other	17 (13%)

Table 1: *Baseline demographics.*

Mean baseline IOP was 20.1 +/- 6.5 mmHg. After one month, the mean IOP had decreased by 18% to 16.4 +/- 5.8 mmHg ($p < 0.05$, Table 2). Six months after adding netarsudil, the mean IOP decreased by 5 mmHg to 15.1 +/- 5.1 mmHg ($p < 0.05$, Figure 1). This represents a 25% reduction in IOP at 6 months. The proportion of patients who achieved a 20% reduction in IOP was 48%, while 44% achieved an IOP < 14 mmHg. The mean number of medications at baseline was 3.8 +/- 1. At baseline, only 1% of patients were on 1 medication, 7% were on 2 medications, 27% were on 3, 46% were on 4, and 18% were on more than 4 medications. After 6 months the number of medications did not change significantly at 3.6 +/- 1, $p = 0.29$.

Timepoint	Number of cases	Mean IOP (mmHg)	Mean # medications	P-value for comparison to baseline for IOP	P-value for comparison to baseline for # medications
Baseline	147	20.1 +/- 6.5	3.8 +/- 1	-	-
1 month	113	16.4 +/- 5.8	3.6 +/- 1	< 0.05	0.28
3 months	62	17.7 +/- 6.8	3.5 +/- 1	< 0.05	0.14
6 months	48	15.1 +/- 5.1	3.6 +/- 1	< 0.05	0.29

Table 2: *Intraocular pressure values over time.*

IOP=Intraocular Pressure.

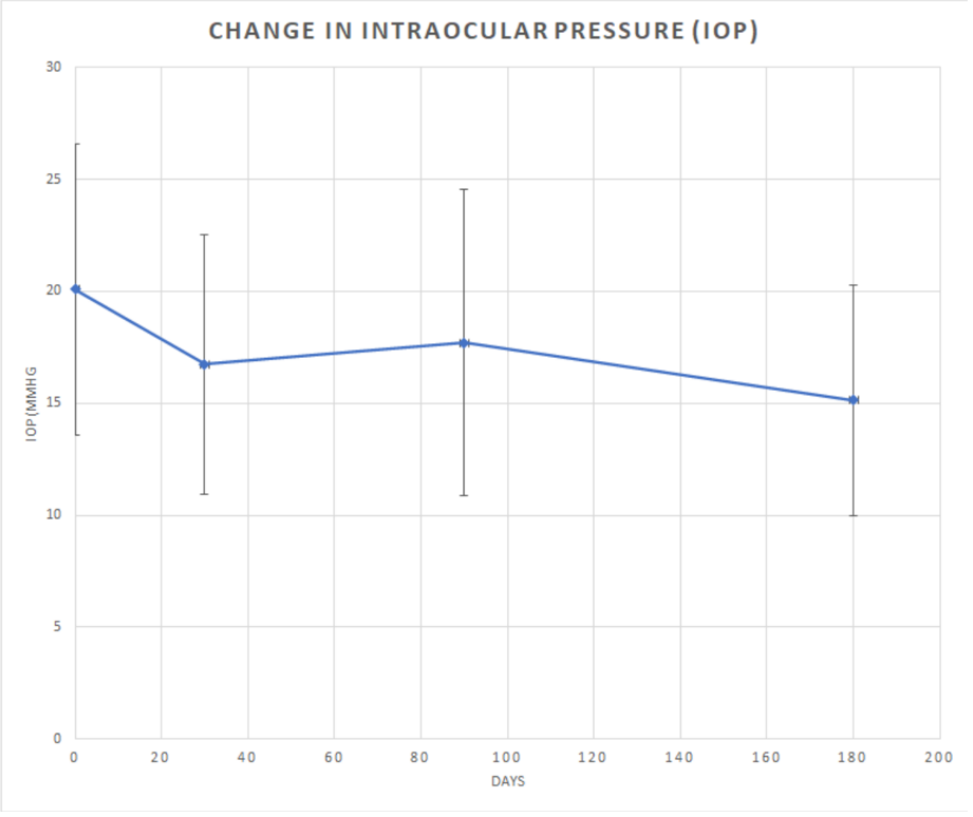

Figure 1: *Time course of intraocular pressure lowering after adding netarsudil.*

Adverse events occurred in 60 patients (41%). The two most common adverse events (Table 3) were hyperemia and dryness which each occurred in 19%. The most serious complication was a single case (0.7%) of non-granulomatous iritis. There were 21 patients (14%) who were included in the study since they used netarsudil for at least one month but stopped it prior to the end of the study period. Of these 21 patients, 90% discontinued because of irritation and 10% were unable to continue the medication due to cost.

Symptom	Number of cases (%)
Hyperemia	28 (19%)
Dryness	28 (19%)
Itching/allergy	27 (18%)
Foreign body sensation	13 (9%)
Blurry vision	12 (8%)
Iritis	1 (1%)

Table 3: *Adverse events following netarsudil administration.*

Discussion

It has been almost 25 years since the last major anti-glaucoma drug class was released. The novel rho-kinase inhibitors appear to lower the IOP by increasing aqueous outflow. The main mechanism appears to be decreasing the contractile tone of trabecular outflow by reducing actin stress fibers and focal adhesions in TM cells which could double the available area of TM and Schlemm's canal, while also making Schlemm's canal less compressible [2]. There are other mechanisms reported including decreasing aqueous production [3], lowering the episcleral venous pressure [4] and even possible neuroprotection [5].

Previous reports of the IOP lowering with netarsudil comes mostly from the approval studies. Although not directly comparable as those studies had very different methodologies including washout IOP measurements, our mean IOP decrease at 6 months of 5 mmHg (25%) is comparable to the average 18% reduction from a higher mean baseline of 23 mmHg seen in previous studies (Table 4). Besides different methodologies and populations, other studies frequently excluded patients who were already on > 2 medications [6]. Our study population started on a mean of 3.8 +/- 1 medications, and 91% were already on at least 3 medications. While 48% of cases in this study achieved an IOP decrease of at least 20%, the successive addition of a third and particularly a fourth anti-glaucoma medication has commonly been reported to have decreasing success rates. In one previous study, adding a fourth drop only lowered the IOP by 20% in 26% of patients [7]. For patients who are hesitant to move forward with a procedure, the addition of another medication class offers another option. Also, this newer medication has shown early promise in achieving lower IOP's, as in our study where 44% achieved an IOP < 14 mmHg.

First Author	N	Baseline IOP (mmHg)	Final IOP (mmHg)	% IOP Reduction	Study Length (months)	Incidence of Hyperemia (%)	Incidence of Subconjunctival Hemorrhage (%)	Incidence of Verticillata (%)
Our Study	147	20.1	15.1	25	6	19	8	Not recorded
Bacharach [10]	72	25.6	20	22	1	57	6	Not recorded
Khouri [11]	186	21.4	17.2	20	3	48	16	25
Serle, part 2 [6]	129	21.4	17.5	18	3	50	15	9
Kahook [9]	129	22.5	18.8	17	12	61	20	26
Serle, part 1 [6]	182	22.5	19.1	15	3	53	13	5

Table 4: *Summary of previous reports on netarsudil, IOP = Intraocular Pressure.*

The most common complication reported in the approval trials was hyperemia, occurring in 50 - 60% of patients [6]. The high incidence is thought to be due to the drug's vasodilatory effects [8]. Of those who develop hyperemia, it appears in over half of cases within 24 hours of starting the medication [9] and appears to decrease over time [6]. Only 19% of our cases were noted to have hyperemia. Our lower rate is likely due at least in part to the timing of visits. Subconjunctival hemorrhage occurred in 6 - 20% of previous studies (Table 4) and similarly occurred in 8% of our cases.

The main weakness comes from being a retrospective case series. To minimize selection bias, we evaluated all cases treated with netarsudil by a single physician at a single institution. Our patient attrition rate of 67% at 6 months is also high. As we offered netarsudil as an additional treatment to current treatment, the relatively high average number of baseline medications of 3.8 (only 35% were on < 4 medications) limits the generalizability of the study.

Conclusion

In our case series of patients who added netarsudil to their current medication regimen, there was still an appreciable reduction in IOP. After 6 months, the IOP had decreased by a mean of 25%, while 44% of cases achieved an IOP < 14 mmHg. Netarsudil was effective as additive treatment to patients on multiple medications.

Conflict of Interest

There are no conflicts of interest for this research article.

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