Pragmatic adjunctive usage of netarsudil: A retrospective chart review from a tertiary care center

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Purpose: This retrospective chart review of netarsudil (Rhopressa) characterizes intra-ocular pressure (IOP) reduction, drug tolerance, drug cost, and compliance in a tertiary university Midwest clinic in a variety of glaucoma diagnoses on patients prescribed netarsudil 01/2017 to 5/2020. Methods: Patient demographics, primary diagnosis, indication for medication, prescription date, prescription fill status, duration of use, discontinuation reason, and number of IOP-lowering medications were noted. Confounding medication changes were excluded from IOP analysis. The IOP difference between the first visit after starting netarsudil and the baseline (mean before starting netarsudil on the stable medication regimen) was calculated. Results: A total of 133 patients were prescribed netarsudil (age 69 ± 20 years, 59% females, 79% white, 86% primary glaucoma) as adjunct glaucoma medication (mean medications 3.2 ± 0.9). Indications were lowering IOP (mean baseline IOP 20.0 ± 6 mmHg) and drug regimen simplification. Prescription was not filled by 22/133 subjects because of the cost (68%) and the need for surgery (23%). No demographic factors were associated with prescription fill status. A total of 101 eyes of 76 patients were used for IOP analysis. The mean change in IOP was −0.8 ± 6.4 mmHg. (IOP decrease in 67%, increase or no change in 33% eyes). Netarsudil was discontinued in 52% (80/96) patients; the reasons include surgery for IOP control (42%), allergies (30%), cost (14%), and paradoxical rise in IOP (12%). Conclusion: Netarsudil was used as adjunct third or fourth line medication at a glaucoma practice in Midwestern USA. 17% of prescriptions went unfilled; netarsudil was discontinued in 52% of patients. IOP response was variable in this population with severe complex glaucoma.

Key words: Glaucoma, intra-ocular pressure, netarsudil

Glucoma is the second leading cause of blindness worldwide. There were an estimated 76 million people in the world with glaucoma in 2020 with a predicted increase to 111 million people by 2040. Intra-ocular pressure (IOP) is the most commonly identified modifiable risk factor in glaucoma. In a large proportion of glaucoma patients, an estimated 40% require two or more medications to achieve their target IOP. When using multiple medications for IOP lowering, medications with different mechanisms of action are combined to achieve the maximum effect.

IOP-lowering medications act by four main mechanisms: 1) decreasing aqueous secretion, 2) increasing uveoscleral outflow, 3) increasing outflow through the trabecular meshwork (TM), and 4) lowering of episcleral venous pressure. Since the Food and Drug Administration (FDA) approval of latanoprost in 1996 for glaucoma treatment[7] and the subsequent introduction of latanoprostene bunod, no new glaucoma medications have been discovered, in terms of treatments employing novel IOP lowering methods of action,[8] until the FDA approval of netarsudil in December 2017.[9] Netarsudil (Rhopressa) is a potent rho kinase (ROCK) inhibitor which also inhibits the norepinephrine transporter. ROCK is a naturally occurring serine/threonine protein kinase that serves to promote assembly of actin stress fibers and focal adhesions within the TM. Netarsudil has been shown to decrease IOP by primarily increasing the outflow facility secondary to TM relaxation.[10,12] In pre-clinical studies, netarsudil has been shown to decrease IOP by lowering episcleral venous pressure and aqueous production.[12] Netarsudil is well suited for use as an adjunct topical medication in combination therapy regimens and has great potential as a regimen-simplifying strategy for some patients as it features once-daily dosing,[13] allowing for better patient compliance and adherence. In three phase three trials (ROCKET 1, ROCKET 2, and ROCKET 4), 0.02% netarsudil was shown to be non-inferior to 0.5% timolol for treating primary open-angle glaucoma (POAG) and ocular hypertension.[15,17] Netarsudil did not meet the non-inferiority criteria when compared to latanoprost in randomized trials,[18] however, netarsudil (0.02%) and latanoprost (0.005%) fixed dose combination showed greater IOP reduction than monotherapy with netarsudil or latanoprost alone in clinical trials.[19]

A critical gap in the literature currently exists in characterizing netarsudil’s use and effectiveness as an add-on treatment in combination drug therapies and for the treatment of secondary and pediatric glaucoma. The aim of our study was to capture...

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and characterize the prescription pattern of netarsudil in a tertiary care setting and study the overall benefits a physician might expect when writing a netarsudil prescription in terms of IOP reduction, drug tolerance, drug cost, and compliance.

**Methods**

This study was conducted in accordance with Institutional Review Board (IRB) protocol #271-20-EP. The electronic health record (EHR) was queried for patients with health records either listing netarsudil as an active medication or mentioning netarsudil in an ophthalmology office visit note between the dates of 01-01-2017 and 05-06-2020 at a tertiary glaucoma clinic in Midwestern USA.

For the purpose of IOP analysis, we excluded a) patients who were already on netarsudil and b) patients who had other medication adjustments, such as discontinuation or addition of another medication, during the visit in which netarsudil was prescribed.

Patient demographics including age, gender, and race were noted from the EHR. The patient’s primary diagnosis, reasons for prescribing netarsudil, the date of prescription, if the patient filled the medication or not, the patient’s reason for not filling the prescription, and new side effects or symptoms attributed to netarsudil were recorded from the office note. IOP-lowering medications, both topical and oral, and topical steroids, if any, used by the patient at each visit were also noted. If a particular medication was discontinued during the office visit, the reason for discontinuation was recorded as well. IOP data and statistics were documented per chart records. If multiple IOP measurements were present in the chart for a particular visit, preference was given to IOPs measured using the applanation method and IOPs recorded by a medical doctor.

Our main outcome measure was IOP change, which was calculated as IOP at the first visit on netarsudil minus baseline IOP. Baseline IOP was defined as the average of all IOP measurements during visits prior to starting netarsudil while the patient was on the same/stable glaucoma medication regimen.

**Statistics**

All data were stored and analyzed using the SQLite and Python open-source applications. Although data pertaining to patients in our discussion, such as demographics, fill rate, and so on, will be presented per patient, data related to IOP, IOP change, and topical medications will be discussed in terms of the number of eyes analyzed. To determine if a statistically significant difference exists between observed and expected statistical distributions (e.g., within a particular aspect of the patient demographic), the Chi-squared test was used. A P value of <0.05 was considered statistically significant. The NumPy open-source software package was used to calculate all statistics.

**Results**

Our query returned 177 patients with a total of 1800 office visits. Of the 177 patients returned, 44 patients were already using netarsudil prior to the initial visit returned by the query or had not made an ophthalmology office visit in the specified date range. These patients were excluded, whereas the remaining 133 patients were used in the analysis. A flowchart showing the number of subjects excluded and the number remaining at each step of the selection process is depicted in Fig. 1.

The mean age was 68.7 ± 19.6 years, and 54 patients (40.6%) were male, whereas 79 (59.4%) were female. The race was White or Caucasian in 98 patients (73.7%), Black or African American in 28 (21.1%), Asian in two (1.5%), Hispanic in one (0.8%), American Indian or Alaska Native in one (0.8%), and unknown in three (2.4%). The majority of the patients (80/133, 60%) had primary glaucomas with 67 primary open-angle glaucomas, seven congenital or juvenile open-angle glaucomas, one ocular hypertension, and five primary-angle closure glaucomas. The secondary glaucomas (53/133, 40%) included an extensive list of neovascular, uveitic, and post-operative glaucomas, among others.

As depicted in Fig. 1, of the 133 patients prescribed netarsudil, 22 patients (16.5%) did not fill the prescription and the fill status of 15 patients was unknown. Of the 22 who did not fill the prescription, 15 (68.2%) did not fill because of the cost or because insurance did not cover the medication.
Table 1: Characteristics of increase or decrease groups after starting netarsudil

|                             | All (Filled) (n=101 eyes) | IOP increase or no change (n=33 eyes) | IOP decrease (n=68 eyes) |
|-----------------------------|----------------------------|--------------------------------------|--------------------------|
| Baseline IOP               | 20.4±6.5                   | 19.3±5.5                             | 20.9±7.0                 |
| IOP at visit when netarsudil started | 22.6±6.5                   | 19.5±5.9                             | 24.0±6.3                 |
| IOP change (calculation from baseline IOP) | -0.8±6.4                   | 4.1±6.1                              | -3.2±5.1                 |
| IOP change (calculation from IOP at visit when netarsudil was started) | -3.0±6.3                   |                                     |                          |
| Age                         | 68.2±18.1                  | 68.4±16.0                            | 68.0±19.1                |
| Number of Medications at the time of starting netarsudil therapy | 3.4±0.8                    | 3.4±0.7                              | 3.4±0.8                  |
| Race (fill status: \(P=1.00\), increased/decreased: \(P=0.97\)) | White or Caucasian: 75 (74.3%) | White or Caucasian: 25 (75.8%)       | White or Caucasian: 50 (73.5%) |
|                            | Black or African American: 20 (19.8%) | Black or African American: 5 (15.2%) | Black or African American: 15 (22.1%) |
|                            | Asian: 3 (3.0%)            | Asian: 2 (6.1%)                      | Asian: 1 (1.5%)          |
|                            | Other: 2 (2.0%)            | Other: 1 (3.0%)                      | Other: 1 (1.5%)          |
|                            | American Indian or Alaska Native: 1 (1.0%) |                                  |                          |
| Gender (fill status: \(P=0.88\), increased/decreased: \(P=1.00\)) | Male: 52 (51.5%)          | Male: 17 (51.5%)                     | Male: 35 (51.5%)         |
|                            | Female: 49 (48.5%)         | Female: 16 (48.5%)                   | Female: 33 (48.5%)       |
| Primary glaucoma (%) (fill status: \(P=0.93\), increased/decreased: \(P=1.00\)) | 63.5                      | 54.5                                 | 72.0                     |
| Secondary glaucoma (%)      | 36.5                       | 45.5                                 | 28.0                     |

Table 2: IOP change by number of medications in use when netarsudil was first used

| No. of medications in use prior to starting netarsudil therapy (n=101 eyes) | IOP effectiveness (mm Hg) |
|---------------------------------------------------------------------------|---------------------------|
| 1 (n=3)                                                                  | -4.6±3.3                  |
| 2 (n=8)                                                                  | -3.1±2.5                  |
| 3 (n=40)                                                                 | -0.4±6.6                  |
| 4 (n=50)                                                                 | -0.5±6.8                  |

Table 3: Reasons netarsudil was discontinued

| Reason netarsudil was discontinued | % (n, of 50) |
|------------------------------------|--------------|
| Inability to achieve target IOP    | 42% (21)     |
| Allergies or other side effects    | 30% (15)     |
| Patient decision because of cost/inconvenience | 14% (7)     |
| Paradoxical rise in IOP            | 12% (6)      |
| Others                             | 2% (1)       |

five (22.7%) opted for surgery rather than adding more medications, and two (9.1%) patients were lost to follow-up. The patient's race, gender, and diagnosis (primary or secondary glaucoma) were not found to be associated with the decision to fill the netarsudil prescription. There was no difference in baseline IOP and the number of medications in patients who were prescribed netarsudil (n = 133), those who filled the prescription (n = 96/133), and those who did not fill (n = 22/133). Of the 96 patients who filled the prescription, 34 patients used the medication on both the eyes bilaterally and 62 patients used the medication in only one eye.

IOP was measured using either the applanation (645/1288) or pneumotonometer (304/1288) methods in 73.7% of patient visits. For visits in which an applanation or pneumotonometer measurement was not taken (317/1288, 24.6% of patient visits), an IOP measurement via the ICare method was used. For visits in which IOP was not measured using any of these methods (22/1288 or 1.7%), IOP using the Tono-Pen method was used. IOP change data are reported per eye for 76 patients (101 eyes).

The mean change in IOP after starting netarsudil was –0.8 ± 6.4 mmHg for 101 eyes, with an average baseline IOP of 20.0 ± 6.2 mmHg at the time the prescription was written. Of the 101 eyes analyzed, 67.3% (68/101) experienced a decrease in IOP, whereas 32.7% (33/101) experienced an increase or no change in IOP after starting netarsudil. IOP change was also calculated as the difference in IOP between the visit at which netarsudil was prescribed minus the IOP at the next office visit [Table 1].

To better characterize the effectiveness of netarsudil in terms of lowering IOP within the categories of increased and decreased IOP, patient demographics, diagnosis, and the number of IOP-lowering medications at the time of the netarsudil prescription were further analyzed within each category, and these results are depicted in Table 1. Both the increased and decreased IOP groups had similar characteristics, and none of these factors were statistically associated with IOP response after starting netarsudil.

Among the 68 eyes which exhibited a decrease in IOP with netarsudil, IOP lowering between 0% to 10% occurred in nine eyes (13%), between 10% to 20% in 19 eyes (28%), and between 20% to 30% in 13 eyes (19%), and IOP lowering more than 30% occurred in 27 eyes (40%).

Among the 33 eyes which exhibited no change or increased IOP, the IOP increase from 0% to 10% occurred in 13 eyes (40%), between 10% to 20% occurred in eight eyes (24%), and between 20% to 30% occurred in four eyes (12%), and an IOP increase greater than 30% occurred in eight eyes (24%).
There was no statistically significant difference in the number of medications in use and baseline IOP between the increased and decreased groups. IOP effectiveness was stratified based on the number of medications in use at the time the prescription was written [Table 2].

Of the 96 patients who filled the netarsudil prescription, 48% (46/96) of the patients continued the prescription through the last office visit on record in our study. The average number of days the prescription was used in this timeframe was 246.3 ± 170.1 days, with a median of 242.5 days and a range of 9 to 585 days. The average number of days the prescription was used before being discontinued was 78.3 ± 99.4 days, with a median of 26.0 days. The reasons discussed in the office visit note for discontinuing the medication are depicted in Table 3.

Discussion
A large proportion of glaucoma patients need more than one medication to control their IOP,[6] and netarsudil is a new drug in the glaucoma specialist’s armamentarium which may be used to achieve IOP control. The majority of studies published to date describing the efficacy of netarsudil were conducted in controlled clinical settings where the drug is used as primary monotherapy in the treatment of primary open-angle glaucoma or ocular hypertension.[15-17,20] We report the use of netarsudil in a heterogeneous population of glaucoma patients presenting to a tertiary care center. Netarsudil was used as an adjunctive therapy in all patients in our study, and in addition to primary glaucoma, netarsudil was also used to treat secondary and congenital glaucoma as an adjunctive therapy.

In this study, we looked at how well the effectiveness of netarsudil translates from the controlled setting of the ROCKET clinical trials to a glaucoma specialty practice. The “efficacy–effectiveness gap,”[20] described as the discrepancy in netarsudil’s IOP lowering ability between these two settings, is a well-known phenomenon. When factors such as prescription fill rate, drug cost to the patient, drug compliance, poly-pharmacy effects from other glaucoma or systemic drugs, and drug tolerance are considered, the effectiveness of a drug or procedure may differ from the results of controlled clinical trials. Pragmatic clinical data, such as those presented in this study, are important to aid clinicians in their medical management decision making.

In terms of IOP lowering effectiveness, the mean change in IOP from the baseline was −0.8 ± 6.4 mm Hg at the first office visit after prescribing netarsudil; however, IOP either increased or did not change for 32.7% of our study population. Our findings are understandably different from those of control trials such as the ROCKET trials[15-17] for a number of reasons. For example, the patient population in the ROCKET trial had POAG, and netarsudil was prescribed as monotherapy after an appropriate washout period for all other glaucoma medications. Our study, however, includes subjects with a myriad of diagnoses ranging from POAG to complex secondary glaucoma because of a combination of mechanisms.

Netarsudil was prescribed as an adjunct medication in all of our subjects, and additional medications have previously demonstrated lesser IOP lowering effectiveness as compared to the first medication used in a therapy plan. For example, in a study conducted by Jampel et al,[21] to determine medication effectiveness by washout, the largest effect on IOP was found with the first medication, whereas the second and third medications produced significant but smaller changes in IOP. We also found maximum IOP lowering (−4.6 ± 3.3 mm Hg) with netarsudil in subjects on only one other IOP-lowering medication, and the IOP lowering effect of netarsudil decreased in subjects on a greater number of IOP-lowering medications when netarsudil was added [Table 2]. Almost no IOP lowering effect was seen when netarsudil was prescribed as the fourth or fifth line therapy (−0.4 ± 6.6 mm Hg and −0.5 ± 6.8 mm Hg, respectively).

None of the patient characteristics (demographics, IOP, diagnosis) were statistically different between the subject groups who exhibited IOP lowering with netarsudil and those who did not [Table 1]. However, the number of subjects with secondary glaucoma was higher in the sub-group with increased IOP after netarsudil (46%), as opposed to the group with IOP lowering (28%). There may be a differential response to netarsudil in the eyes with secondary glaucomas, which are known to be more resistant to IOP lowering therapy, as opposed to most primary glaucomas. Addition of more medications is known to decrease compliance in glaucoma patients;[21] however, both groups were already using a mean of 3.4 meds at the time netarsudil was initiated. Studies with larger sample sizes and longer follow-up periods are needed to assess factors predictive of response to netarsudil and, further, to help guide physician decision making when prescribing the drug. Aqueous humor dynamics studies would be helpful to identify the exact mechanism of action of netarsudil in different patient populations.

Medication cost was a significant barrier to filling prescriptions in our study population. Generic alternatives to netarsudil are currently not available, and out-of-pocket medication cost is a chief concern for many glaucoma patients. Netarsudil was included in Medicare Part D formulary in 2019, which may lead to improved patient compliance with time.

Netarsudil was discontinued in 52% of our subjects with the most common reasons being poor IOP control and drug intolerance, including allergy or other side effects [Table 3]. In the ROCKET trial, 48% of the subjects developed a red eye; however, most of these cases were physician-reported and only 6% of these subjects stopped the drug because of intolerance.[17] The patients in our study were already on multiple glaucoma medications prior to the netarsudil prescription, which may help explain the higher rates of medication intolerance. A paradoxical rise in IOP (a rise in IOP above baseline IOP) was documented as the reason the medication was discontinued in 12% of netarsudil discontinuations in our cohort. This paradoxical rise in IOP has been reported previously in the literature when using brimonidine with re-challenge and in personal communications with netarsudil.[23] None of our patients were re-challenged with netarsudil, so we cannot definitively conclude that the IOP increase was a medication side effect. This paradoxical IOP increase could potentially be attributed to disease progression, medication interaction, or a combination of the above in our cohort of complex glaucomas.

Other reports of pragmatic netarsudil use in pediatric populations[21] and in patients with prior selective laser trabecuoplasty[26] have also shown variable results when compared to the ROCKET clinical trials. Our study provides a snapshot of netarsudil usage patterns and effectiveness in a tertiary care setting. The limitations include the retrospective study design and a small sample size. The IOP measurement technique and timing were also not standardized in our study,
and we did not take into account the patient history of prior selective laser trabeculoplasty, cataract surgery, or filtering glaucoma surgery. Baseline IOP was used for our IOP change analysis rather than IOP at the visit when netarsudil was prescribed – this was performed to avoid the “regression to mean” effect [Table 1] and portray the real-world effectiveness of the medication.

Conclusion

In conclusion, netarsudil was primarily used as a third or fourth line adjunct medication in a tertiary care setting in Midwestern USA. The IOP lowering effectiveness of netarsudil decreased as the number of adjunctive medications increased, which is a phenomenon common to many glaucoma therapeutics. The IOP response of netarsudil may be variable in complex glaucoma and in patients on multiple medications. Although the findings of our study are not comparable to other published reports assessing netarsudil as a standalone treatment, our study does highlight various factors that could affect physician decision making, such as medical diagnosis, medication cost, adverse effects attributable to medication, and compliance.

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Conflicts of interest

There are no conflicts of interest.

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