NOVEL ADDITION FOR IOP REDUCTION

Rho kinase inhibitors could shake up glaucoma medical therapy.

BY JANET B. SERLE, MD

The Rho kinase (ROCK) inhibitors are a new class of drugs under investigation for use in glaucoma. They are thought to increase aqueous outflow by reversing structural and functional damage at the trabecular meshwork. Additionally, the vasodilatory effect of some ROCK inhibitors reduces episcleral venous pressure.

NETARSUDIL

Netarsudil ophthalmic solution 0.02% (Rhopressa; Aerie Pharmaceuticals) lowers IOP by inhibiting both ROCK and the norepinephrine transporter (NET). The former enhances trabecular outflow and reduces episcleral venous pressure, while the latter decreases aqueous production. In contrast, ripasudil (Glanatec; Kowa), in clinical use only in Japan, is solely a ROCK inhibitor.

In phase 1, 2, and 3 clinical trials of netarsudil in more than 2,000 patients, the 0.02% concentration administered once daily in the evening was the most efficacious and well-tolerated dosing regimen. Clinical trials with netarsudil include a phase 2 comparison with latanoprost and four phase 3 trials comparing netarsudil to timolol (Table 1).

In the phase 2 trial comparing netarsudil and latanoprost, both drugs were administered once daily in the evening for 28 days. IOP reductions were similar in patients with a baseline IOP between 22 and 26 mm Hg (-5.8 mm Hg, netarsudil; 5.9 mm Hg, latanoprost). In all enrolled patients (with a baseline IOP up to 36 mm Hg), netarsudil was 1 mm Hg less effective than latanoprost (-5.7 vs 6.8 mm Hg) and did not meet the statistical analysis for noninferiority of netarsudil to latanoprost.

Rocket 1 (3 months), Rocket 2 (12 months), and Rocket 4 (6 months)—three completed phase 3 clinical trials—compared netarsudil administered in the evening to timolol 0.5% administered twice daily. Baseline IOP was higher than 20 mm Hg and lower than 27 mm Hg in Rocket 1 and 2. In Rocket 4, baseline IOP was higher than 20 mm Hg and lower than 30 mm Hg. In primary analysis, IOP reductions were similar with netarsudil and timolol in Rocket 2 and 4 among patients who had a baseline IOP below 25 mm Hg. In secondary analysis, IOP reductions were similar with the two drugs in Rocket 1 among patients who had a baseline IOP below 25 mm Hg and in Rocket 4 for patients with a baseline IOP below 30 mm Hg. In Rocket 2, IOP reductions with netarsudil were consistent through 12 months of dosing.

FIXED-COMBINATION THERAPY

By reducing the number of daily drop administrations, fixed-combination therapy can enhance patients’ compliance to prescribed medical treatment. A fixed-dose combination of netarsudil and latanoprost (Roclatan 0.02%/0.005%; Aerie Pharmaceuticals) was compared with the individual components in the clinical studies Mercury 1 (12 months) and Mercury 2 (3 months). Mercury 3 (6 months; Table 2), recently begun in Europe, compares netarsudil-latanoprost to a fixed combination of bimatoprost and timolol (Ganfort; Allergan; not available in the United States).

Mercury 1 and Mercury 2 demonstrated 1 to 3 mm Hg greater IOP lowering (P < .0001) with the fixed combination.
of netarsudil and latanoprost than with the individual components at all measurements. In Mercury 1, consistent efficacy of the fixed combination was maintained through 12 months. A responder analysis in Mercury 1 demonstrated that substantially more patients treated with the fixed combination achieved greater percentage reductions and lower target IOPs than those treated with the individual components. IOP reductions of at least 30% were achieved in 65% of patients treated with the fixed combination. The same reduction was achieved in only 40% of individual component-treated patients.

Of the patients treated with the fixed combination of netarsudil and latanoprost, a total of 61% achieved an IOP of 16 mm Hg or less, and 33% of patients achieved an IOP of 14 mm Hg or less. Among the patients treated with the individual components, the statistics were 40% or less and 15% or less, respectively. In short, the fixed combination was extremely efficacious and in many patients achieved the low target pressures that glaucoma patients typically require.

**Tolerability**

In clinical trials, both netarsudil and the fixed combination of netarsudil and latanoprost were well tolerated. The most frequent side effect was conjunctival hyperemia caused by the vasodilatory effect of the drug. It was observed in 50% to 60% of patients examined by ophthalmologists. Typically graded as mild, hyperemia was sporadic, occurring at every visit in only 10% of patients.

Other ocular adverse events, which have been reported in 5% to 25% of patients in these trials, included small conjunctival hemorrhages and cornea verticillata, both observed on slit-lamp examination. The cornea verticillata (microdeposits of intracellular phospholipids are observed in almost all patients taking systemic amiodarone) were asymptomatic and did not reduce visual function. The adverse events observed during the 12-month trials were consistent with those observed during the initial 90-day efficacy period. Few (Continued on page 66)
systemic side effects were reported, which can be explained by the systemic absorption of netarsudil, which is below the lower limit of quantification.\textsuperscript{11}

**SUMMARY**

Once-daily dosing of netarsudil and the fixed combination of netarsudil and latanoprost is efficacious, which should enhance patients’ compliance. The efficacy of netarsudil is similar to that of timolol, without the systemic side effects associated with topical \(\beta\)-blockers. The fixed combination of netarsudil and latanoprost is more efficacious than the individual components, and it was well tolerated over 12 months of dosing.

Netarsudil’s mechanisms of action are unique from those of drugs currently available for to treat glaucoma. The fixed combination of netarsudil and latanoprost dosed once daily confirms the additivity of these two classes of drugs, with enhanced outflow through both the trabecular pathway from netarsudil and the uveoscleral pathway from latanoprost. The additivity of netarsudil and the fixed combination of netarsudil and latanoprost to medications in use is anticipated.

The new drug application for netarsudil was filed during the first quarter of 2017, and the filing for the fixed combination of netarsudil and latanoprost is anticipated in 2018. When approved for clinical use, these drugs will expand the treatment options for glaucoma patients.

---

9. Serle JB, Lewis PA, Kopczynski C, Heah T. 3-month interim report of a prospective 12-month safety and efficacy study of topical PG324 (fixed combination of netarsudil 0.02% and latanoprost 0.005%) compared to the individual components in subjects with elevated intraocular pressure. Paper presented at The ARVO Meeting, May 9, 2017, Baltimore, MD.