RHO KINASE/NOREPINEPHRINE TRANSPORTER INHIBITION FOR THE TREATMENT OF GLAUCOMA AND OCULAR HYPERTENSION

An update on the clinical development of a new class of drugs.

BY JASON BACHARACH, MD

A long-standing gap in the therapeutic armamentarium for open-angle glaucoma and ocular hypertension is a class of drugs that reduces IOP by increasing aqueous outflow through the trabecular meshwork. The ongoing interest in Rho kinase (ROCK) inhibitors, which increase outflow by relaxing the trabecular meshwork, is based on these agents' potential to fill this role. One such agent, Rhopressa (AR-13324; Aerie Pharmaceuticals), is the first to approach regulatory submission in the United States. Rhopressa is a small-molecule inhibitor of both ROCK and norepinephrine transporter (NET), and the drug is thought to have three principal mechanisms of action. ROCK inhibition increases outflow through the trabecular meshwork and lowers episcleral venous pressure, while NET inhibition decreases inflow by reducing the production of fluid.

Laboratory experiments with Rhopressa confirmed that it increases the perfusion of aqueous humor through the trabecular meshwork and suggested that the agent might have antifibrotic effects on the tissue, a potentially disease-modifying activity.[1] Clinical research to date suggests that the drug could be a useful option for both initial and adjunctive therapy, particularly in the large number of patients who first present with low- or normal-tension glaucoma. This body of clinical evidence includes data from a phase 2b trial and the results of two phase 3 studies. It will be expanded when two additional phase 3 studies and the registration trials for a fixed-dose combination of Rhopressa with latanoprost (Roclatan; Aerie Pharmaceuticals) are completed.

PHASE 2 COMPARISON TO LATANOPROST

Two concentrations of AR-13324 (0.01% and 0.02%) were compared to latanoprost (0.005%) in a phase 2b double-masked, randomized, multicenter, 28-day study.[2] Both drugs were dosed once daily. The primary endpoint was mean diurnal IOP across the study subjects within each arm at day 28. AR-13324 0.02%, the concentration chosen for Rhopressa, reduced IOP by 5.2 to 6.6 mm Hg across all time points. This decrease was approximately 1 mm Hg less than with latanoprost, but the two agents were statistically equivalent in patients with starting pressures below 26 mm Hg.

AT A GLANCE

- ROCK inhibition increases outflow through the trabecular meshwork and lowers episcleral venous pressure. NET inhibition decreases inflow by reducing the production of fluid.
- Data from Rocket 2, along with supportive data from Rocket 1, will form the basis of a new drug application for Rhopressa once daily, which Aerie expects to file in the third quarter of 2016.
- Roclatan could be the first fixed-dose combination with latanoprost in the United States and would provide all four of the known mechanisms for lowering IOP in one medication.

AR-13324 produced a consistent reduction in IOP regardless of starting pressure, but as expected, latanoprost was slightly less effective at lower baseline pressures. The most frequently reported adverse event associated with AR-13324 in the study was conjunctival hyperemia. This effect was generally mild and transient, usually milder in the morning than immediately following evening installation, and it declined over time.

These results paved the way for a comprehensive international registration program for Rhopressa, eventually comprising Aerie's four phase 3 Rocket studies.

> **"The complete analysis of Rocket 2, along with supportive data from Rocket 1, will form the basis of a new drug application (NDA) for Rhopressa dosed once daily."**

ROCKET 1

Rocket 1 was a 3-month trial comparing the efficacy of Rhopressa 0.02% once daily to timolol twice daily, with IOP measurements taken at the end of weeks 2 and 6 and on day 90. This trial enrolled 182 patients in the Rhopressa arm and 188 patients in the timolol arm. The range of baseline IOPs included in the primary analysis ranged from above 20 to below 27 mm Hg.

Rocket 1 missed the primary endpoint, which was noninferiority to timolol at the three time points. It did demonstrate noninferiority compared to timolol in patients with IOPs below 26 mm Hg at all nine measured time points and numerical superiority over timolol at the majority of measured time points. In a prespecified analysis, Rhopressa demonstrated noninferiority to timolol and numerical superiority over timolol at all time points for patients with baseline pressures below 24 mm Hg. An additional review of the trial data suggested that the explanation for the missed primary endpoint might be the synergy between Rhopressa and prostaglandin analogues (PGAs). Prospective (prespecified) analysis by pre-study medication status showed that prior PGA use enhanced Rhopressa's IOP-lowering effect at week 2 ($P = .003$). This effect declined over time, creating an apparent drop in efficacy in the Rhopressa arm for patients who had received prior PGA therapy. This observation was supported by a retrospective analysis of phase 2 data that showed prior PGA use enhanced IOP lowering by Rhopressa by 1 mm Hg ($P = .007$) and 1.2 mm Hg ($P = .002$) at weeks 2 and 4, respectively, compared to patients not previously on a PGA (data on file with Aerie Pharmaceuticals).

The most frequent adverse event associated with Rhopressa treatment in Rocket 1 was conjunctival hyperemia, which was reported by approximately 35% of patients, with the majority of cases (80%) rated as mild.

ROCKET 2

Rocket 2 was also a noninferiority trial comparing Rhopressa 0.02% (dosed both once and twice daily at the FDA's request) to timolol dosed twice a day (data on file with Aerie Pharmaceuticals). To achieve noninferiority, Rhopressa had to be within 1.5 mm Hg of timolol at all time points and within 1 mm Hg at a majority of time points (95% CI). Originally, the IOP range for the primary endpoint was greater than 20 mm Hg and less than 27 mm Hg, but after discussions with the FDA in the wake of findings from Rocket 1, this range was modified to baseline pressures above 20 and below 25 mm Hg. A sufficient number of patients had already been enrolled to meet the statistical power requirements of this modified endpoint without adding patients and extending the trial.

In the topline results recently reported, Rhopressa dosed both once and twice daily met the criteria for noninferiority to timolol dosed twice daily in the primary efficacy analysis. Importantly, Rhopressa dosed once daily showed stable efficacy from week 2 to month 3, with consistent results across all three statistical analysis populations (per protocol, intent to treat and last observation carried forward). Although less pronounced than in Rocket 1, prior PGA use by patients in Rocket 2 enhanced IOP lowering by Rhopressa, with larger overall IOP reductions in the prior-PGA group that were statistically significant. The difference between the trials may be attributable to a more effective washout of PGAs in the Rocket 2 study.

The safety profile of Rhopressa in this study was similar to that in Rocket 1, with no drug-related serious adverse events. There was a systemic safety finding in the timolol arm, however, with a statistically significant reduction in heart rate from baseline observed at all visits. The most common increased incidence in adverse events associated with Rhopressa treatment was conjunctival hyperemia, reported by about 35% of patients receiving the drug once daily. Most hyperemia was graded mild (83%), with 16% of cases considered moderate. Although the mean hyperemia range for the Rocket 1 and Rocket 2 studies is approximately 52%, this incidence falls within the range of hyperemia reported for the three leading PGAs.[3]

PROGRESS TOWARD A NEW DRUG APPLICATION

The complete analysis of Rocket 2, along with supportive data from Rocket 1, will form the basis of a new drug

application (NDA) for Rhopressa dosed once daily, which Aerie expects to file in the third quarter of 2016.

Two additional Rocket trials are currently underway: a 12-month safety trial being conducted in Canada (Rocket 3) and a two-arm, 90-day, noninferiority efficacy study with a 6-month safety evaluation comparing once-daily Rhopressa to twice-daily timolol (Rocket 4). The baseline IOP inclusion range in the primary analysis of the 700 patients who will be enrolled in Rocket 4 matches the modified range in Rocket 2 (above 20 mm Hg to below 25 mm Hg). Although data from these studies will be provided to the FDA, neither of these trials is required for the Rhopressa NDA submission but will be used instead to support a European application (which requires a larger number of patients with 6 months of safety data).

FIXED-DOSE COMBINATION WITH LATANOPROST

While the clinical development of Rhopressa is being completed, Aerie has embarked on registration trials for Roclatan. This move follows a successful phase 2b trial that compared two concentrations of Roclatan to both Rhopressa and latanoprost in a trial design that followed the FDA's requirements for fixed-dose combinations. In this study, Roclatan 0.02% achieved statistical superiority over the individual components at all time points ($P < .001$). The IOP-lowering effect of the fixed-dose combination was unprecedented. For example, on day 29, 50% of the Roclatan 0.02% patients had IOP reductions of greater than 35%, compared to 17% for Rhopressa alone and 28% for latanoprost alone. At this time point, 46% of Roclatan patients had their pressures lowered to 16 mm Hg or less, compared to 21% for Rhopressa and 18% for latanoprost.[4]

WATCH IT NOW

Jason Bacharach, MD, speaks with Robert Weinstock, MD, about ROCK inhibitors as the first new class of glaucoma agents in over 2 decades for management of the disease.

> "It has been nearly 20 years since a truly novel IOP-lowering agent has been introduced for glaucoma management."

The international Roclatan phase 3 clinical program includes three studies, two of which are US registration trials comparing Roclatan to both Rhopressa and latanoprost. These include Mercury 1, a 1-year safety study with a 3-month interim efficacy readout, and Mercury 2, a 3-month efficacy study. The third is a European registration trial, Mercury 3, a 6-month safety and efficacy study comparing Roclatan to a fixed-dose comparator chosen by agreement with regulators for the European Union. Mercury 1 is already enrolling patients, and Mercury 2 will commence in the second quarter of 2016.

A NEW CLASS OF GLAUCOMA MEDICATIONS

It has been nearly 20 years since a truly novel IOP-lowering agent has been introduced for glaucoma management. Offering three principal mechanisms of action, including outflow through the trabecular meshwork, in a single once-daily drop, the ROCK/NET inhibitor Rhopressa could be a welcome addition to therapeutic options, particularly for patients with lower baseline pressures. Rhopressa's evident synergy with PGAs suggests it could fill an important adjunctive role and bodes well for Roclatan, which could be the first fixed-dose combination with latanoprost in the United States. That agent would provide all four of the known mechanisms for lowering IOP in one medication. ■

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