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Double-masked, Randomized, Dose–Response Study of AR-13324 versus Latanoprost in Patients with Elevated Intraocular Pressure

*Jason Bacharach, MD,[1] Harvey B. Dubiner, MD,[2] Brian Levy, OD, MS,[3] Casey C. Kopczynski, PhD,[3] Gary D. Novack, PhD,[4] for the AR-13324-CS202 Study Group**

Objective: AR-13324 is a small-molecule inhibitor of Rho kinase and a norepinephrine transporter. The objective of this 28-day study was to evaluate the ocular hypotensive efficacy and safety of AR-13324 ophthalmic solution compared with a positive control, latanoprost ophthalmic solution, in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Design: Double-masked, randomized study in 22 private practice ophthalmology clinics.

Participants: Participants were required to be adults with a diagnosis of OAG or OHT with unmedicated intraocular pressure (IOP) in the range of 22 to 36 mmHg.

Methods: Patients were randomized to receive AR-13324 ophthalmic solution 0.01%, daily (PM), AR-13324 ophthalmic solution 0.02% daily (PM), or latanoprost 0.005% daily (PM) for 28 days.

Main Outcome Measures: The primary efficacy endpoint was the mean diurnal IOP across subjects within the treatment group at day 28.

Results: Randomized and treated were 224 patients, 213 (95.1%) of whom completed the study. On day 28, mean diurnal IOP was 20.1, 20.0, and 18.7 mmHg in the AR-13324 0.01%, 0.02%, and latanoprost groups, respectively, representing a decrease from unmedicated baseline of 5.5, 5.7, and 6.8 mmHg ($P<0.001$). The 5.7-mmHg reduction in IOP by AR-13324 0.02% did not meet the criterion for noninferiority to latanoprost. The most frequently reported adverse event was conjunctival/ocular hyperemia, with a combined incidence of 52%, 57%, and 16%, respectively. On day 28 at 08:00 hours, the incidence of mild to moderate hyperemia by biomicroscopy was 18%, 24%, and 11%, respectively.

Conclusions: AR-13324 0.02% was less effective than latanoprost by approximately 1 mmHg in patients with unmedicated IOPs of 22 to 35 mmHg. The major safety finding was ocular hyperemia, which was more common for both concentrations of AR-13324 than for latanoprost. *Ophthalmology 2015;122:302-307 © 2015 by the American Academy of Ophthalmology.*

*Supplementary material is available at www.aaojournal.org.

Large, multicenter, prospective studies have shown that elevated intraocular pressure (IOP) is a major risk factor for glaucomatous progression and that pharmacologically lowering IOP reduces the risk of glaucomatous progression in patients with ocular hypertension (OHT) and open-angle glaucoma (OAG).[1–4] The most commonly prescribed topical ocular medications for lowering IOP belong to 1 of 4 drug classes: prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, and α-agonists. These drugs work primarily by increasing uveoscleral outflow and/or decreasing aqueous humor production. Although these medications have been shown to effectively lower elevated IOP, many patients with elevated IOP require co-administration of ≥2 glaucoma medications to achieve the desired IOP-lowering effect.[5–7] Although second and third medications provide additional ocular hypotensive efficacy, they also can induce additional adverse events and introduce complexity to the treatment regimen. Given that increased resistance to aqueous outflow through the trabecular meshwork is the cause of elevated IOP in glaucoma, there may be some advantages to novel agents that increase trabecular outflow.[8]

Rho kinase inhibitors are currently being clinically evaluated as potential ocular hypotensive agents for the treatment of patients with OAG or OHT. A number of these agents have been shown to effectively reduce IOP in these patients (Kopczynski C, Lin C-W, Delong M, et al. IOP-lowering efficacy and tolerability of AR-13324, a dual mechanism kinase inhibitor for the treatment of glaucoma. Invest Ophthalmol Vis Sci 2012; 53:ARVO E-abstract 5080).[9,10] Mechanism of action studies in animal models

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Table 1. Biomicroscopic Hyperemia Scale Used by Investigators

Scale	Definition
None (0)	Normal; appears white with a small number of conjunctival blood vessels easily observed
Minimal (+0.5)	Slightly noticeable pinkish-red color predominantly confined to the bulbar conjunctiva. The response may involve the entire bulbar conjunctiva or be confined to select sector(s)
Mild (+1)	Prominent pinkish-red color of both the bulbar and palpebral conjunctiva; individual vessels more numerous and more engorged than "minimal"
Moderate (+2)	Bright scarlet red color of the bulbar and palpebral conjunctiva
Severe (+3)	"Beefy red" with petechiae—dark red bulbar and palpebral conjunctiva with evidence of subconjunctival hemorrhage

indicate that Rho kinase inhibitors reduce IOP by increasing aqueous humor drainage through the trabecular meshwork (Kopczynski et al, 2012).[9–11]

AR-13324 is the first of a new class of ocular hypotensive compounds that inhibits both Rho kinase and the norepinephrine transporter. In both rabbit and monkey studies, AR-13324 produced large reductions in IOP (20%–25%) with a longer duration of action than reported for previously characterized Rho kinase inhibitors. Consistent with its inhibition of Rho kinase, AR-13324 seems to reduce IOP in part by increasing outflow facility (Kopczynski et al, 2012). In addition, AR-13324 seems to lower IOP by decreasing the production of aqueous humor.[11] This latter activity may be related to the inhibition of norepinephrine transporter, although this relationship has not been directly demonstrated.

In the first study of human patients with OAG or OHT, administration of AR-13324 ophthalmic solution, 0.01% to 0.04% daily (AM) for 7 days produced large reductions in IOP that were statistically and clinically significant. The IOP decreased steadily for 8 hours after dosing and lasted ≥24 hours. The 0.02% concentration of AR-13324 seemed to reach the top of the dose–response curve. The only safety finding of note was dose-related ocular hyperemia that declined in incidence and severity with repeated dosing (NCT01528787 clinicaltrial.gov; Weiss MJ, Levy B, Kopczynski C, et al. Evaluation of AR-13324, a novel dual mechanism agent, in lowering of IOP in glaucoma and OHT. Invest Ophthal Vis Sci 2013; 54:ARVO E-abstract 754).

The objective of this study was to evaluate the ocular hypotensive efficacy and safety of 2 concentrations of AR-13324 ophthalmic solution compared with a positive control, latanoprost ophthalmic solution, in a 28-day study.

Methods

In this double-masked, parallel comparison study, patients were randomized to receive AR-13324 ophthalmic solution 0.01%, daily (PM), AR-13324 ophthalmic solution 0.02% daily (PM), or latanoprost 0.005% daily (PM) for 28 days. To be included in the study, the subjects were required to be adults with a diagnosis of OAG or OHT (based on IOP, visual fields, and optic nerve cupping) with corrected visual acuity of +1.0 logarithm of the minimum angle of resolution or better by Early Treatment Diabetic Retinopathy Study criteria in each eye (20/200 Snellen). Because AR-13324 seems to act on the trabecular outflow pathway, we excluded patients with pseudoexfoliation or pigment dispersion glaucoma to avoid adding potentially confounding variables to this early stage study. Also excluded were patients with a history of angle closure or narrow angles; laser peripheral iridotomy; previous glaucoma intraocular surgery, glaucoma laser procedures in study eye(s), refractive surgery in study eye(s), ocular trauma within the past 6 months, or ocular surgery or laser treatment within the 3 months before screening; evidence of ocular infection, inflammation, clinically significant blepharitis, or conjunctivitis at screening; a history of herpes simplex keratitis; or central corneal thickness >600 μm (related to tonometer accuracy). Individuals were also required to demonstrate correct eyedrop instillation (i.e., instilling 1 drop only without touching the tip of the dropper to the eye).[12] We measured IOP with a calibrated Goldmann tonometer. Two consecutive measurements of IOP in each eye were obtained at each time point. If the 2 measurements differed by >2 mmHg, a third measurement was obtained. We analyzed IOP as the mean of 2 measurements or as the median of 3 measurements.[13] Heart rate and blood pressure were measured at screening and throughout the study. After a complete dilated eye examination (including hyperemia, scored as described in Table 1), individuals using ocular hypotensive medications underwent a washout (Table 2).[14] For randomization into the study, individuals were required to have an unmedicated IOP ≥24 mmHg at 2 eligibility visits (08:00 hours), 2 to 7 days apart, and ≥22 mmHg at 10:00 and 16:00 hours at the second qualification visit, with IOP <36 mmHg at each qualification visit. Patients were dispensed masked study medication and instructed to instill it daily in both eyes between 20:00 and 22:00 hours. Patients returned to the investigator's office on days 7, 14, and 28, with diurnal examinations (08:00, 10:00, and 16:00 hours) carried out on days 14 and 28. No ocular medication (other than nonmedicated lubricating drops) was allowed during the study. This study was approved by governing institutional review boards (Schulman Associates, Cincinnati, OH, and Wills Eye Hospital, Philadelphia, PA) and all patients provided written informed consent consistent with standards of the Declaration of Helsinki.

A priori, the primary efficacy endpoint was the mean diurnal IOP across subjects within treatment group at day 28 with no endpoint substitution. The planned sample size of 65 to 70 study eyes per group gave ≥80% power to conclude noninferiority for each concentration of AR-13324 compared with latanoprost,

Table 2. Ocular Hypotensive Medication Washout Period

Medication Class	Minimum Washout Period
Prostaglandins	4 weeks
β-Adrenoceptor antagonists	4 weeks
Adrenergic agonists (including α-agonists such as brimonidine and apraclonidine)	2 weeks
Muscarinic agonists (e.g., pilocarpine), carbonic anhydrase inhibitors (topical or oral)	5 days

From Hughes et al.[14]