

The Literature

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DOUBLE-MASKED, RANDOMIZED, DOSE-RESPONSE STUDY OF AR-13324 VERSUS LATANOPROST IN PATIENTS WITH ELEVATED INTRAOCULAR PRESSURE

Bacharach J, Dubiner HB, Levy B, et al¹

ABSTRACT SUMMARY

Bacharach et al reported the findings of a phase 2b clinical trial of a new drug. AR-13324 (Aerie Pharmaceuticals) is a combination of a Rho kinase (ROCK) inhibitor to increase trabecular outflow and a norepinephrine transporter inhibitor to decrease aqueous production. In this parallel study, 224 patients with open-angle glaucoma or ocular hypertension were randomized into three groups. The first received AR-13324 0.01%, the second received AR-13324 0.02%, and the final group received latanoprost 0.005%. All patients administered one drop of medication nightly for 28 days.

All three groups started with a baseline mean IOP of 26 mm Hg after a medication washout period. After 28 days, the IOP decreased by 22% with both concentrations of AR-13324 and by 27% with latanoprost. AR-13324 did not reach noninferiority to latanoprost, except when investigators only analyzed the group of patients with a baseline IOP $\leq$ 26 mm Hg. The most common side effect by far was hyperemia, which occurred overall in 52% of patients using AR-13324 0.01%, in 57% of patients using AR-13324 0.02%, and in 16% of patients using latanoprost. The hyperemia improved over time; the incidence decreased by approximately 10% from day 7 to day 28. The other two significant side effects were subconjunctival hemorrhage (5% of all AR-13324 patients) and foreign body sensation (3% of all AR-13324 patients). No major adverse events were attributed to AR-13324, and no patient lost vision.

DISCUSSION

Is AR-13324 an effective medication?

ROCK inhibitors offer a potentially new avenue for the medical treatment of glaucoma. In studying the molecular pathways modulating trabecular outflow, one responsible protein that researchers found was the Ras Homolog (Rho) family of proteins.² Rho GTPase regulates, among other proteins, a Rho-associated protein

kinase. ROCK inhibitors have numerous downstream effects, the main one inhibiting the contraction of trabecular cells, which increases aqueous outflow, in part by altering the orientation of extracellular matrix proteins. The increase in outflow was confirmed in human culture cells, with knockout cells showing an 80% increase in outflow facility.³ By showing that AR-13324 can reduce IOP by 22% from a baseline of 26 mm Hg, this phase 2b clinical trial provides promising preliminary evidence that eye care specialists may soon have another class of glaucoma medication available for patients.

Is AR-13324 safe?

The main side effect noted in the study was conjunctival hyperemia (possibly from smooth muscle dilation in the vessel walls) in over half the patients. The hyperemia became less common later in the study. There were no major side effects attributed to the medication. This was only a phase 2b clinical trial, however, so more studies must be conducted to confirm the agent's high safety profile.

Are there other potential uses of ROCK inhibitors?

ROCK inhibitors have also been studied for the inhibition of bleb fibrosis after trabeculectomy, because fibroblasts depend on a type of contractility that can be targeted with the ROCK inhibitor Y-27632.⁴ In a rabbit study, the medication successfully reduced collagen deposition and subsequent scar formation surrounding the bleb. Finally, ROCK inhibitors have been shown in vitro to cause dose-dependent arterial dilation, so it is feasible that they could be used to improve blood flow to the optic nerve head.⁵

ASSOCIATION BETWEEN PROGRESSIVE RETINAL NERVE FIBER LAYER LOSS AND LONGITUDINAL CHANGE IN QUALITY OF LIFE IN GLAUCOMA

Gracitelli CP, Abe RY, Tatham AJ, et al⁶

ABSTRACT SUMMARY

Gracitelli et al reported on a prospective, longitudinal study of the association between retinal nerve fiber layer (RNFL) thinning, as imaged with optical coherence

tomography (OCT), and changes reported on a quality-of-life (QOL) survey. The investigators observed 130 patients for an average of 3.5 years. The baseline average RNFL thickness was 84 μm in the thicker eye and 74 μm in the thinner eye. In order to investigate a more global change in OCT, the researchers used the average RNFL measurement of whichever eye was thicker at each visit. The average mean deviation on visual field testing in the worse eye was -5.1 ± 5.3 dB. The QOL data were derived from the National Eye Institute Visual Function Questionnaire (NEI VFQ-25).

After multivariable analysis, the researchers found that, for each micron of thinning on OCT per year, the QOL score decreased by 1.3 units. There was a high level of correlation with an r^2 coefficient of 0.59. Even after adjustment for the effect of worsening visual fields, 26% of the decrease in QOL scores was associated only with the decrease in RNFL thickness.

DISCUSSION

What information does this study provide, and how can it help patients?

The finding that OCT measurements of decreasing RNFL seem to be uniquely associated with worsening QOL survey scores, even after accounting for changes in visual fields (and visual acuity as well), offers another way for eye care specialists to monitor their patients. Decreases in vision are not always reflected in visual acuity testing, and some visual deficits arise from the optic neuropathy (ie, decreased contrast sensitivity⁷), which may be detected earlier on structural measurements such as OCT.

What other information does OCT add?

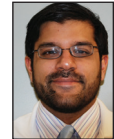
Other reasons that OCT measurements may capture information not available with visual field testing include artificial testing conditions. Visual acuity and visual field testing is usually performed in a dark room with a bright white background—a very different environment than for most activities. The investigators also noted that OCT provides more information on macular fibers compared with standard automated perimetry, which only has four data points in the entire central 8°. Finally, OCT may be a more reliable test. This study supports the idea that the best way to assess glaucomatous changes involves a combination of structural and functional testing. ■

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