An Overview of Statins

How this class of drugs became of interest in glaucoma, and why research continues.

BY DAVID L. EPSTEIN, MD

Statins inhibit the enzyme (hydroxy-methylglutaryl-coenzyme A reductase) in the liver that is responsible for producing cholesterol and thus reduce the level of cholesterol present in the blood. Physicians use these drugs to prevent and treat atherosclerosis, which causes plaques containing cholesterol to form within the arteries. These plaques reduce blood flow, and their rupture produces a blood clot that further blocks the artery. When the flow of blood decreases sufficiently, angina or a heart attack will ensue. Blood clots in the brain will lead to a stroke, whereas clots in the legs cause intermittent claudication. Statins slow the formation of new plaques by decreasing the production of cholesterol. These drugs also seem to stabilize the plaques and reduce their risk of rupture.[1]

Recently, researchers have found that inflammation of the arterial wall may be an important component in atherosclerosis. Investigators have also discovered that statins reduce inflammation—a potentially beneficial effect not related to cholesterol.[2] Intriguingly, this class of drugs may also play a role in the management of glaucoma.

AFFECTING THE CYTOSKELETON

I believe that glaucoma is a disease of two tissues, the trabecular meshwork and the optic nerve. No specific treatments currently exist that directly target either of these tissues. Instead, available medications lower IOP and treat glaucoma through nonspecific means by decreasing the flow of aqueous into the eye or by increasing uveoscleral outflow.

At Duke University School of Medicine in Durham, North Carolina, my colleagues and I have been developing several drugs that have the potential to revolutionize the treatment of glaucoma if they could be delivered directly to the trabecular meshwork. Our obstacle is creating an eye drop that will pass through the cornea. We found that these drugs alter the cytoskeleton (proteins that provide cellular structure) of the trabecular meshwork's cells.[3] This alteration creates new pathways between cells for fluid flow,[4,5] and we suspect that the cytoskeleton may regulate this flow in healthy eyes.[6] Other investigators currently focusing on the cytoskeleton include Paul Kaufman, MD, in Madison, Wisconsin, and Benny Geiger, PhD, in Rehovot, Israel. Our experiments at Duke University revealed that rho kinase is one of the master cytoskeletal enzymes and that its inhibition increases outflow and relaxes the cells in the trabecular meshwork.[7]

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THE STATIN CONNECTION

Vasanth Rao, PhD, Associate Professor of Ophthalmology at Duke University School of Medicine, mentioned to me that he was using a statin in a study he was conducting of cultured cells from the trabecular meshwork. When I asked why, he responded that the statin was an inhibitor of rho kinase. I realized that we should study whether the drug had any effect on glaucoma in humans already taking it and asked my clinical

faculty for suggestions on how we might proceed. Six months later, my colleague Paul Lee, MD, remembered the database kept by the UAB School of Medicine in Birmingham, Alabama. Through his contacts there, he helped to initiate the cross-sectional study of a primarily Veterans Administration population.[8] We found that, 1.5 years into treatment with statins, the drugs became protective against the development or progression of glaucoma and that the effect grew stronger with time.

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Although investigators were able to monitor the occurrence of glaucoma and the number of medications that subjects were taking, the database unfortunately did not include patients' IOPs. The results of this study obviously need to be reproduced. More importantly, there needs to be a prospective study in which subjects with glaucoma are randomized to receive treatment with statins or to serve as controls. My colleagues and I are now looking into how to conduct such a study, which we hope will determine whether patients with glaucoma should begin treatment with a statin.

IMPLICATIONS

Because oral drugs do not reach the eye well, I began to wonder whether the protective effect observed with statins was not due to a lowering of IOP but to some sort of neuroprotection of the optic nerve or ganglion cells. Researchers have since shown that rho kinase inhibitors prevent apoptosis,[9,10] which has been proposed as the mechanism of glaucomatous damage.[11] Perhaps our research on statins unintentionally revealed something fundamental about why ganglion cells die in glaucoma and the optic nerve cups.

If a statin eye drop were found to lower IOP, it would be important for two reasons. First, this class of drug is already approved by the FDA, and this therapy would therefore involve the use of an approved drug in an unapproved location. It would only be necessary to prove ocular safety, because the agents' systemic safety has already been established. Second, although ophthalmologists do not know what normally regulates outflow through the trabecular meshwork and what may be abnormal in glaucoma, rho kinase may well be involved,[7] and statins inhibit this enzyme. The effects and actions of both topically and orally administered statins on glaucoma may provide different specific treatments to each of the two tissues involved in glaucoma's pathogenesis.

CONCLUSION

The story of how statins became the subject of research in glaucoma illustrates that the translation of fundamental science into clinical application is a complex process. I believe that the MD clinician scientist plays a vital role in these situations.

Right now, I would not use statins as a routine glaucoma treatment based on the results of a single study. I might, however, consider such therapy in individuals with glaucoma who also have a borderline blood-lipid abnormality. ❑

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