PGA-TARGETED OUTFLOW PATHWAYS

A closer look at the mechanism of action for a familiar medication class.

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More than 20 years have passed since latanoprost was launched and forever changed the medical glaucoma landscape. Following the introduction of latanoprost, prostaglandin analogues (PGAs) quickly supplanted other available options to become the first-line therapy for glaucoma. Soon, other drugs in this class flooded the market, and travoprost, bimatoprost, and tafluprost were added to clinicians' armamentariums.

Recently, the PGA space has seen a flurry of activity with the introduction of several new treatment options. Currently available FDA-approved therapies now include Vyzulta (lanoprostene bunod, Bausch + Lomb), a nitric oxide–releasing PGA; Xelpros (latanoprost, Sun Pharmaceutical Industries), a benzalkonium chloride–free formulation of latanoprost; and Rocklatan (netarsudil and latanoprost ophthalmic solution, Aerie Pharmaceuticals), the first combination PGA to be approved in the United States. In addition to these topical therapies, several sustained-release PGA options are under investigation.

It is well known that PGAs decrease IOP by increasing outflow through the uveoscleral pathway. A deeper understanding of the specific mechanism of action for PGAs can help us broaden our knowledge and direct our therapeutic options as we strive to deliver the best outcomes to our patients.

MECHANISM OF ACTION

In the early 1970s, it was thought that PGAs led to irritation and initial IOP elevation. However, a 1977 article by Cameras et al[1] showed that prostaglandin F2-alpha and prostaglandin E2 lowered IOP. Although bimatoprost is technically a prostamide, this medication and all other PGAs reduce IOP by acting as prodrugs of prostaglandin F2-alpha. They target several of the nine prostaglandin receptors. Latanoprost binds to FP, EP1, and EP3, whereas travaprost binds with the greatest affinity to the FP receptor.[2,3] Brimatoprost binds to a receptor that has yet to be identified.[4] The EP and FP receptors have been found in the trabecular meshwork (TM), Schlemm canal (SC), and ciliary body. Stimulation of these receptors by PGAs leads to enlargement of the uveoscleral pathways.

In addition to ciliary body relaxation, these receptors disrupt extracellular matrix turnover. Remodeling of the extracellular matrix is upregulated by matrix metalloproteinases (MMPs) and downregulated by tissue inhibitors of metalloproteinases (TIMPs). MMPs are a group of proteolytic enzymes that function to remodel tissue architecture. Brimatoprost, tafluprost, and latanoprost have been shown to induce MMP-1, MMP-2, MMP-3, MMP-9, and MMP-17 and decrease TIMP-1 and TIMP-2 expression in the ciliary body.[5]

Upregulation of MMP and downregulation of TIMP ultimately change the balance toward an increased breakdown of collagens. Collagen remodeling is crucial to IOP regulation. Histologically, the upregulation of MMP and resulting degradation of collagen components lead to an increase in optically empty spaces between muscle bundles in the ciliary body. In the long term, these changes appear to be organized, thereby

AT A GLANCE

- Although all prostaglandin analogues target the same structures and ultimately lead to many of the same histologic outcomes, some of these agents target different receptors with different affinities.
- As glaucoma management moves toward a new era of multiple topical PGAs and eventually intracameral options, understanding the outflow pathway of this class of medications can help clinicians tailor therapy to their patients.

creating well-established outflow channels through the ciliary body and enhancing outflow facility.[6]

Although uveoscleral outflow is thought to be the primary mechanism of action for IOP reduction, PGAs have also been shown to act at the level of the TM. As previously mentioned, there are PGA receptors in both the TM and SC. In a human model containing only TM-based outflow, cultured human anterior segments showed increased outflow facility when treated with bimatoprost or latanoprost.[7,8] Histologically, PGAs have been shown to cause focal loss of SC endothelial cells; expansion of the juxtacanalicular region of the TM; and, in a similar fashion to the ciliary body, a widening of the intertrabecular spaces.[6,9] It is clear that PGAs act on both the conventional and nonconventional pathways.

CONCLUSION

PGAs have been entrenched in the medical treatment of glaucoma for more than 2 decades. Recent additions to this pool of options have increased therapeutic possibilities. Although all PGAs target the same structures and ultimately lead to many of the same histologic outcomes, some PGAs target different receptors with different affinities. This is likely why some patients respond to one agent but not to others.[10-12]

All additions to the PGA class could prove crucial to improving outcomes for our patients. As we move toward a new era of multiple topical PGAs and eventually intracameral options, understanding the outflow pathway of this class of medications can help us tailor therapy to our patients. ■

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