

Prostaglandin Monotherapy, Now What?

Glaucoma Today invited five glaucoma specialists to share their thoughts on whether and how to advance therapy.

**BY TONY REALINI, MD; ALBERT S. KHOURI, MD; HOWARD BARNEBEY, MD;
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CASE PRESENTATION

A 65-year-old female with moderate primary open-angle glaucoma (moderate cupping and early visual field loss) enjoyed a significant IOP response to prostaglandin monotherapy, but her IOP has remained 3 to 5 mm Hg above target on three consecutive visits. What is your next therapeutic step?

TONY REALINI, MD

Prostaglandin monotherapy is my preference for those in whom it is adequate. From the information given, I will assume that I have gotten all I could hope for from the prostaglandin (ie, there is no compelling reason to switch to an alternate monotherapeutic agent). Thus, the choice is what to add to the prostaglandin to achieve the remaining IOP reduction to bring this patient's pressure under control.

There are a few good choices. I could add a medication—a beta-blocker, a carbonic anhydrase inhibitor (CAI), or an alpha adrenergic agonist. I could offer laser trabeculoplasty. If the patient has a visually significant cataract, removing it might also bring her IOP within my desired range. Assuming that she is not ready for cataract surgery, my discussion with the patient would involve offering her either an additional medication that will work well in combination with the prostaglandin or a laser trabeculoplasty to spare her the need for additional medications. If she prefers to add a medication, I would typically add a CAI twice daily. I tend not to add beta-blockers to prostaglandin analogues, because numerous data sets have demonstrated the suboptimal additivity of these two classes,¹⁻³ and the potential sys-

temic side effects of beta-blockers are less favorable than those of CAIs. Alpha adrenergic agonists are also less well tolerated systemically than CAIs, hence my choice to add a CAI. Specifically, I would prescribe brinzolamide, because it is equally effective as dorzolamide but better tolerated.

I would add the brinzolamide drop to both eyes simultaneously and then assess the patient's IOP at two or three consecutive visits beginning 3 to 4 weeks after initiating therapy. My basis for deciding whether adjunctive therapy were successful would be the difference between the mean of the three IOP measurements before adding brinzolamide and the mean of the two or three IOP measurements after adding brinzolamide, because spontaneous IOP variation precludes making this judgment accurately with fewer data points.

ALBERT S. KHOURI, MD

In the Ocular Hypertension Treatment Study, approximately 40% of subjects in the treatment arm needed multiple agents to achieve their target IOP.⁴ Because the possible combinations of glaucoma agents are innumerable, one should attempt to customize therapy for each patient. Challenges related to adherence and the cost of therapy are as relevant as its efficacy. Nonetheless, clinicians often focus mostly on a drug's efficacy when making therapeutic choices. The most robust data on pharmaceutical efficacy come from trials of medications as monotherapy (used for regulatory approval). Those studies, however, do not answer questions on the differences among agents or how they behave as adjunctive therapy. Moreover,

comparative studies often lack a uniform design and can be misleading.

In this case, I would probably add a topical beta-blocker. One should bear in mind that topical beta-blockers, CAIs, and alpha agonists are all effective adjunctive agents with good additivity to prostaglandins. The CAIs and alpha agonists are both safer in patients with contraindications to beta-blockers. There is insufficient evidence in this case to suggest that a particular regimen would be superior. I favor adding a beta-blocker, particularly in patients for whom cost is a consideration. Hypothetically, another prostaglandin could be substituted for the current agent, but I have rarely found doing so to be gratifying. Both CAIs and alpha agonists are used twice a day with a prostaglandin, whereas a beta-blocker may be used once daily (beta-blocker in the morning and prostaglandin in evening). I believe that administering a beta-blocker once daily is probably as effective as b.i.d. dosing.⁵ Interestingly, it is still unclear why adding a beta-blocker to a prostaglandin (but not vice versa) yields a modest reduction in IOP in some patients.⁶ This issue surely deserves further study.

HOWARD BARNEBEY, MD

The situation presented herein is not unique, because the IOP of approximately 40% of glaucoma patients is not controlled with a single medication.

Before considering adjunctive treatment to a prostaglandin, one must first ensure that this patient understands her disease and how the eye drop works. This step is important not only for the adherence aspect of the treatment program, but also to emphasize the significance of the proper technique for instilling the eye drop. For example, is the patient carefully minimizing blinking after instilling the medication (simple closure of the eyelids) and maintaining punctal occlusion for 1 to 2 minutes after the eye drop's administration? These points are germane if the prostaglandin is not lowering the IOP to the expected therapeutic level. For a prostaglandin analogue, that would be approximately 25% to 30% lower than baseline. One should also evaluate the patient's eyelids, tear film, and cornea. Ocular surface disease is not a rare comorbidity among glaucoma patients. We clinicians should consider whether the medical treatment we prescribe is contributing to a patient's underlying tendency toward ocular surface disease.

If, after reviewing—and, if necessary, addressing—all of the aforementioned subtle factors with this patient, the prostaglandin analogue were not lowering IOP to the anticipated level, I would present her with one of two options: adding a second medication or undergo-

ing laser trabeculoplasty. Each treatment carries advantages and disadvantages. If adding a second medication, I would select a different class and opt for a single agent (vs a combined one), because the treatment goal is within 3 mm Hg. Of the agents currently available, the choices are a topical CAI, an alpha agonist, a beta-blocker, or a miotic. Most of us would probably avoid miotics because of their significant ocular side effects. Beta-blockers are unlikely to reach the target consistently based on the results of clinical trials. The decision is then between a CAI and an alpha agonist. Both classes of medication can be effective in the situation presented herein. I would select a CAI based on my clinical experience and the literature, which supports the efficacy of a CAI administered in combination with a prostaglandin.^{7,8}

SANJAY G. ASRANI, MD

I would first like to know other information (eg, pachymetry readings, family history, etc.) that might influence the decision of whether the patient needs a lower IOP. Assuming that these factors have been taken into account before the clinician decided the target IOP range, I would first look to rule out a rise in IOP due to a persistent phacomorphic component from an incipient cataract or a component of narrow-angle pupillary block, as occurs in an eye with early cataract and hyperopia. I would be especially suspicious of such a mechanism in a diabetic patient. In these situations, of course, I either remove the cataract or, for pupillary block, perform a laser iridotomy.

If the angle is clearly wide open, my first choice would be to add a topical CAI to the prostaglandin. Topical CAIs provide a greater IOP-lowering effect when combined with prostaglandins compared with other medications.⁷ Typically, this family of drugs is relatively free of systemic side effects and contraindications. The only reason I would not prescribe a CAI would be if the patient had a documented angioedema such as a reaction to sulfa drugs.

I would also offer the patient the option of selective laser trabeculoplasty as a primary therapy. If she had rejected the procedure initially, I would offer it again at this stage, because the procedure would allow the patient to remain on monotherapy and its effect typically lasts for 2 years.

GEORGE L. SPAETH, MD

The case presentation is not adequate to allow a meaningful suggestion as to the appropriate next step. Based on the material provided, it is impossible to answer the critical question, what is happening to this patient?

First, a 65-year-old woman could have 2 days or 40 years to live. It is essential to have a meaningful estimate of the anticipated years to live.

Second, what was happening to the patient prior to the initiation of treatment is not known. Establishing a rate of change is essential in order to determine where a patient is going. For example, if she has had moderate cupping and early visual field loss for 15 years, it is unlikely that any change in treatment is necessary. On the other hand, the patient may have had no glaucomatous nerve damage and no visual field loss 1 year ago, and both the disc and the field are rapidly deteriorating. Assuming that she has more than a year to live, clearly, the treatment being employed is inadequate and needs to be increased.

There is also no comment on how well the prostaglandin monotherapy was tolerated. If the medication were well tolerated and had lowered the pressure markedly, perhaps 20% to 30%, and there had been no further change to the disc or field, then there would be no reason to alter the therapeutic approach. On the other hand, if the patient were already experiencing considerable irritation from the medication, it would make sense to try another agent, even though the prostaglandin lowered the pressure well.

Let me rephrase the case presentation with information that I have made up to fill the gaps. A 65-year-old woman in excellent health who probably has 20 or more years to live was examined 10 years ago, at which time the optic nerves and visual fields were normal. She began using a topical prostaglandin 2 years ago, because she had an IOP of 19 mm Hg OD and 16 mm Hg OS, and her right eye had developed significant optic nerve cupping and visual field loss. Following the initiation of treatment in her right eye, the IOP was consistently around 17 mm Hg. After 2 years, there appeared to be no change in either the disc or the field. There were no apparent side effects from the medication. What would be the next therapeutic step? The answer is no change in treatment.

Now, allow me to propose the same case scenario but with a few changes. After 2 years, there appeared to be a questionable change in the optic disc and, possibly, a slight deterioration of the visual field in the patient's right eye. Additionally, she complained of irritation in her right eye, which she related to her use of the prostaglandin. The next therapeutic step would be to stop the prostaglandin and start a different agent. One option would be timolol 0.5% gel once daily in the morning, if the patient had no contraindication to such an agent. Alternatively, she could instill a topical CAI twice daily if there were a concern about her using a

beta-blocker. A third alternative would be brimonidine twice daily if there were a concern about her using a beta-blocker and she had a definite allergy to sulfa drugs. □

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