Prostaglandin Nonresponders

How common are they, and how should one proceed?

BY GEOFFREY T. EMERICK, MD

The widespread discussion of responders, nonresponders, and response rates is a relatively recent phenomenon in the field of glaucoma. In other areas of medicine, the terms most often describe patients being treated for hepatitis C, a chronic disease with potentially devastating consequences that is often difficult to treat and can require long-term therapy. The characteristics of hepatitis C should sound familiar to anyone caring for glaucoma patients.

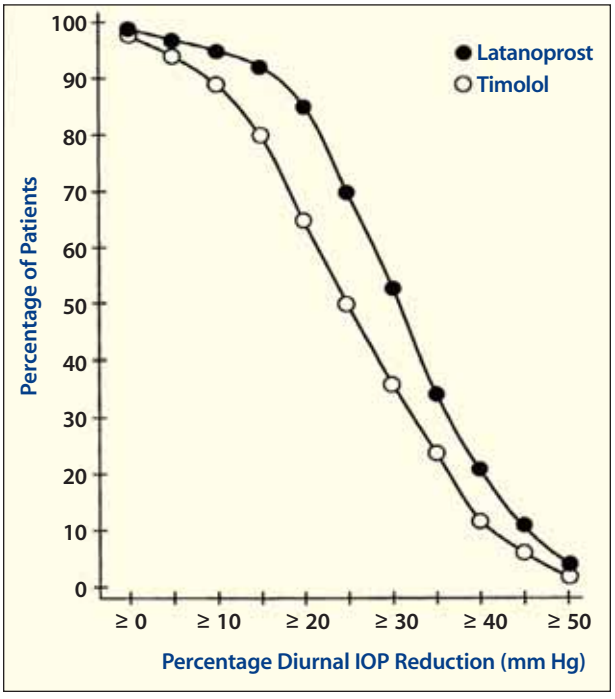

Figure 1. This graph shows the percentage of patients (n = 829) who reached specific reductions in diurnal IOP after 6 months' treatment with latanoprost or timolol. (Reprinted with permission from Hedman K, Alm A. A pooled-data analysis of three randomized, double-masked, six-month clinical studies comparing the intraocular pressure reducing effect of latanoprost and timolol. *Eur J Ophthalmol*. 2000;10:95-104.)

Although the prostaglandin analogues represent a breakthrough in achieving low IOPs with a remarkable level of safety, not all patients have a similar experience with these agents. Some achieve little or no reduction in IOP or experience intolerable side effects. Although physicians expect an average IOP reduction of 30% in eyes with open-angle glaucoma or ocular hypertension (OHT), such a reduction often does not occur. Patients already on glaucoma medications or with lower baseline pressures often "respond" less dramatically. Certain types of glaucoma (eg, neovascular, uveitic, or those associated with episcleral venous pressure) also do not typically respond as well. This article shares my approach to eyes that are nonresponders or underresponders to prostaglandin analogues, and it draws from the literature for guidance in these cases.

ESTABLISHING PATIENT RESPONSE

Controversy surrounding the utility of the uniocular trial continues, as evidenced by articles by Tony Realini, MD,[1] including one for the September/October edition of *Glaucoma Today* that included a discussion by Theodore Krupin, MD, and John W. Yang, MD.[2] Nevertheless, I still advocate the one-eye trial as the best way of assessing the IOP-lowering effect of a medication.

When initiating a one-eye trial, I first discuss its purpose with the patient. Perhaps he has been instilling eye drops for a long time, and I want to be as certain as I can of how much benefit they are. I also discuss with patients their daily routine and suggest timing the instillation of drops to best fit their schedule. Bedtime is the worst time for patients to take drops if they tend to fall asleep while reading or watching television. Earlier in the evening or other times of the day, even if off-label, may be better. I have patients return in approximately 4 weeks for an evaluation of IOP and any side effects. I choose this time period because nearly all eyes will have achieved maximal IOP-lowering at that point and one sample bottle will last at least that long, even with significant wastage. At the 4-week return visit, I assess IOP re-

duction by using the patient's opposite eye as a control or comparing the measurement with baseline values.

WHO ARE THE NONRESPONDERS?

The definition of *nonresponder* is arbitrary. A true nonresponder would be an eye that experiences no change in diurnal IOP, including no alterations within the range of day-to-day variability or measurement error. A reasonable working definition of a nonresponder is an eye in which the measured degree of IOP reduction does not justify the costs and risks of the treatment. In such a case, the physician should stop the medication and prescribe something else to lower IOP.

The few studies examining prostaglandin nonresponders have chosen a wide variety of definitions, including a percentage IOP reduction of ≤ 10%, 15%, or 20% or an absolute reduction of < 3 or 5 mm Hg. Choplin et al[3] stated, "attaining a minimum pressure-lowering of at least 15% is necessary to assure that the observed change in IOP is not just from diurnal variation, and to justify the continued use of the medication." I would argue that lowering IOP by 15% may, in some circumstances, be quite significant, for example, in a patient experiencing nerve damage at an IOP of 13 mm Hg whose pressure drops to 11 mm Hg. Results of the Early Manifest Glaucoma Treatment Study[4] and other trials indicated a 10% reduction in risk with each 1-mm Hg decrease in IOP.

Regardless of the definition, prostaglandin nonresponders seem to be rare, much more so than beta-blocker nonresponders. In original phase III studies involving 829 patients treated for 6 months, 5% of latanoprost-treated patients and 11% of those treated with timolol had IOP reductions of less than 10%.[5] These values were based on mean diurnal IOP at 6 months. Significant differences in response rates were seen no matter what degree of IOP reduction was targeted (Figure 1).

Most subsequent studies have found similar response rates to prostaglandins. An analysis of data from a 6-month study comparing bimatoprost and latanoprost showed a response rate of 89% to 98% and 77% to 95%, respectively.[3] This analysis was based on an IOP reduction of at least 10% at each diurnal time point at week 1 and months 1, 3, and 6. A crossover study of unoprostone and latanoprost found a nonresponder rate of 7.1% and 5.4%, respectively.[6] Interestingly, in that study, no patients were nonresponders to both medications.

HOW TO PROCEED

Gandolfi et al[7] reviewed their clinical records to identify patients with primary open-angle glaucoma or OHT who had ≤ 10% IOP-lowering with latanoprost. They did not mention if a one-eye trial were performed or how many baseline or treatment IOP measurements they took to determine nonresponder status. Patients received bilateral treatment and had to have IOPs of greater than 22 mm Hg in both eyes on three separate readings, more than 24 hours apart, to be eligible.

Fifteen patients agreed to enter the study. After a 30-day washout, one eye of each patient was randomized to latanoprost or bimatoprost q.d. for 30 days. After another 30-day washout, the eye received the other medication. Gandolfi et al performed diurnal IOP measurements. The mean diurnal IOP at baseline was 24.7 ±0.9 mm Hg and, after washout, 24.8 ±1.1 mm Hg. IOP after 30 days of treatment with latanoprost was 24.1 ±0.9 mm Hg versus 18.1 ±1.7 mm Hg with bimatoprost. This change represented a 27% reduction in IOP with bimatoprost. Two of the 15 patients experienced an IOP reduction of less than 20% with bimatoprost, and one had a reduction of less than 10% (Figure 2).

In a prospective "switch" study, Williams[8] conducted an open-label, monocular, two-phase trial to determine whether bimatoprost is effective in patients with open-angle glaucoma or OHT who are not responsive to latano-

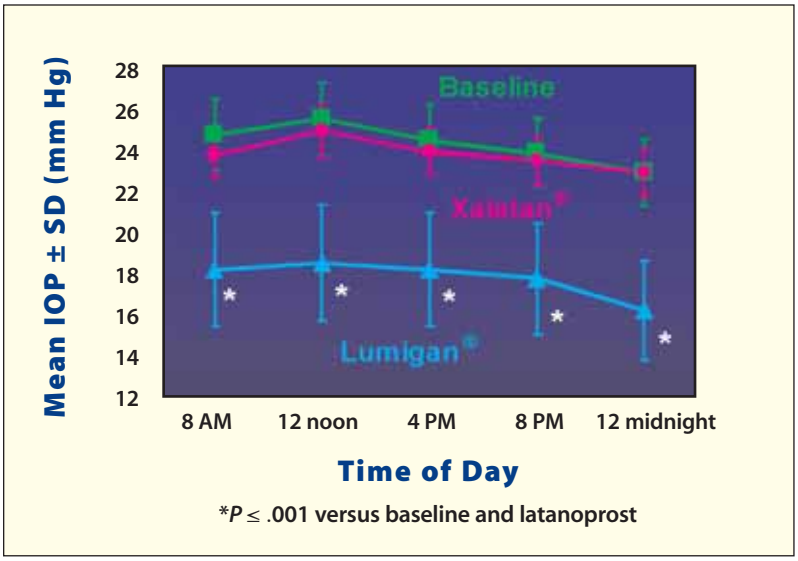

Figure 2. This graph shows the mean diurnal IOP at baseline and at the end of each treatment phase in the study eye(s). (Data adapted from Gandolfi SA, Cimino L. Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost. *Ophthalmology*. 2003;110:609-614.)

prost. After a 4-week washout of any ocular hypertensive agents, patients with IOPs of between 22 and 34 mm Hg (n = 51) instilled latanoprost in one eye and were evaluated at weeks 4 and 8 (phase I). Patients with an IOP reduction of no more than 3 mm Hg at both visits were classified as nonresponders to latanoprost, and they switched to bimatoprost for 8 weeks (n = 21, phase II). In the treated eyes, the mean reduction in IOP from baseline after 4 weeks of each medication was 2.3 mm Hg with latanoprost (P=.012) and 6.1 mm Hg with bimatoprost (P<.001). After 8 weeks, respective IOP reductions were 1.9 mm Hg (P=.027) and 5.4 mm Hg (P<.001). After the switch from latanoprost, 8 weeks of bimatoprost provided an additional mean IOP reduction of 3.5 mm Hg (P<.001).

Finally, Katz et al[9] presented a prospective study of 13 patients who had not achieved an IOP reduction of 15% with latanoprost. After 4 weeks of bimatoprost treatment, 77% had achieved an IOP reduction of ≥ 15% (20% on average).

> "I recommend great caution in interpreting two-phase or 'switch' studies, because regression to the mean and other factors can have a major influence on the results."

All of these studies show that some patients who have a less-than-expected (ie, 10% or 15%) lowering of IOP with latanoprost may achieve a reduction of 20% or greater with bimatoprost. The same may be true for travoprost, although there are insufficient data to support that claim. I recommend great caution in interpreting two-phase or "switch" studies, because regression to the mean and other factors can have a major influence on the results. More blind, prospective, crossover studies are needed in this area.

CONCLUSIONS

The evidence suggests that patients who are poor responders to one prostaglandin when used as a single agent may respond to another prostaglandin. In such individuals, I usually consider a switch or reconsider beta-blockers. Nonresponse is best documented by a one-eye trial of at least 2 weeks' duration. If this documentation is missing, a reverse one-eye trial may be helpful.

The relatively uncommon patient who truly does not respond to one of the prostaglandins may respond to another agent in the class, sometimes with surprising results. I would refrain from too many trials using different combinations of eye drops, however, because they may only delay needed surgery. ❑

Geoffrey T. Emerick, MD, is Director of the Glaucoma Service at Loyola University Medical Center in Maywood, Illinois. He is on the Speakers' Bureaus for Alcon Laboratories, Inc., Allergan, Inc., and Pfizer Inc. Dr. Emerick may be reached at (708) 216-3408; gemeric@lumc.edu.

1. Realini T, Fechtner RD, Atreides SP, Gollance S. The uniocular drug trial and second-eye response to glaucoma medications. *Ophthalmology.* 2004;111:421-426.
2. Realini T. The uniocular trial myth. *Glaucoma Today.* 2004;2:5:18-22.
3. Choplin N, Bernstein P, Batoosingh AL, et al. A randomized, investigator-masked comparison of diurnal responder rates with bimatoprost and latanoprost in the lowering of intraocular pressure. *Surv Ophthalmol.* 2004;49(suppl):19-25.
4. Leske MC, Heijl A, Hussein M, et al. Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: the Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 2003;121:48-56.
5. Hedman K, Alm A. A pooled-data analysis of three randomized, double-masked, six-month clinical studies comparing the intraocular pressure reducing effect of latanoprost and timolol. *Eur J Ophthalmol.* 2000;10:95-104.
6. Aung T, Chew PTK, Yip CC, et al. A randomized double-masked crossover study comparing latanoprost 0.005% with unoprostone 0.12% in patients with primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol.* 2001;131:636-642.
7. Gandolfi SA, Cimino L. Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost. *Ophthalmology.* 2003;110:609-614.
8. Williams RD. Efficacy of bimatoprost in glaucoma and ocular hypertension unresponsive to latanoprost. *Adv Ther.* 2002;19:6:275-281.
9. Katz LJ, Magacho L, Steinmann WC, Myers JS. The pressure lowering effects of bimatoprost once daily at bedtime in patients who failed previous latanoprost treatment. Paper presented at: The Wills Eye Hospital 55th Annual Conference; March 13, 2003; Philadelphia, PA.