

Deciding on First-Line Medical Therapy

Recently released preservative-free agents will create a new paradigm for the treatment of glaucoma.

BY LAWRENCE M. HURVITZ, MD

Many of us in glaucoma care now hesitate longer before prescribing initial treatment. Although not one new class of topical glaucoma medication has been introduced since latanoprost became available in the 1990s, there is greater diversity within each class of drugs, particularly the prostaglandin analogues. For example, Merck & Co., Inc., recently re-entered the US ophthalmic market with a new prostaglandin (tafluprost ophthalmic solution 0.0015%; Zioptan) but has packaged it as a preservative-free drug. The company has also rereleased Cosopt as a preservative-free drug (Cosopt PF). Concerns about ocular surface disease (OSD), the increasing number of preservative-free and alternatively preserved topical glaucoma medications, external influences, and other factors are causing a paradigm shift in our treatment of glaucoma.

For the purposes of this discussion, I will assume that most of us prescribe a β -blocker or a prostaglandin as our once-a-day, first-line agent of choice.

OCULAR SURFACE DISEASE

OSD is the focus of much of the controversy regarding preservatives in topical medication. Benzalkonium chloride (BAK) is a recognized cause of corneal and conjunctival toxicity, manifesting as changes to the corneal and conjunctival surfaces, ocular discomfort, tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial apoptosis, and the potential risk of failure in glaucoma surgery.¹ BAK can also damage the



Figure 1. Toxic conjunctival reaction to topical medications.

trabecular meshwork.²

Not all OSD is the same. There is a difference between corneal and conjunctival surface disease caused by medication (Figure 1) and limbal cell failure (Figure 2), which, in my experience, usually only occurs after multiple surgeries along with long-term medical treatment.

Several questions have yet to be answered. First, is BAK-induced OSD reversible after long-term medical therapy, or does it make the eye more susceptible to limbal cell failure with later surgery? Second, do less irritating preservatives such as SofZia (found in Travatan Z; Alcon Laboratories, Inc.) adequately protect the eye from

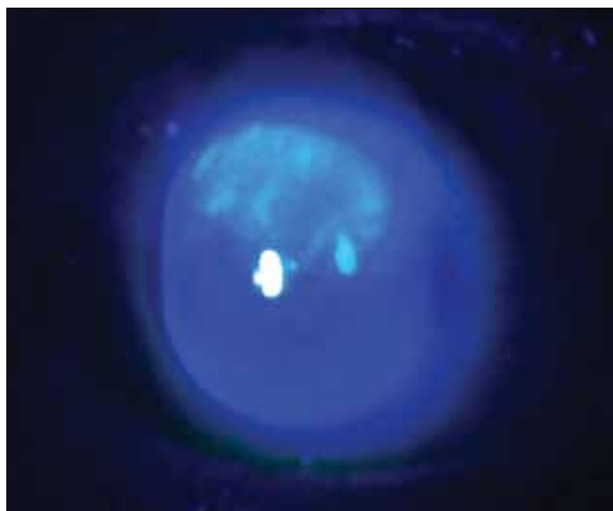


Figure 2. Corneal stem cell failure.

contamination (ie, an eye with a very thin bleb after filtering surgery)? Some research has shown SofZia to be less effective than BAK at preventing contamination of the bottled medication.³ Third, does Purite (found in Alphagan P; Allergan, Inc.) cause toxicity? This matter has not been specifically studied.

Most of us suggest nonpreserved artificial tears for our patients with severe dry eye disease, even though artificial tears are now free of BAK and use Purite, SofZia, or Polyquad (Alcon Laboratories, Inc.).⁴

PREScribing PATTERNS

Survey Results

In a 2012 survey of ophthalmologists, BioTrend Research Group found that many of us are switching patients to travoprost ophthalmic solution 0.004% (Travatan Z) or bimatoprost ophthalmic solution 0.01% (Lumigan; Allergan, Inc.) in order to avoid the substitution of generic latanoprost for Xalatan (Pfizer, Inc.).⁵ The survey also found that prostaglandin analogues continue to be the most commonly prescribed drug class, with 71% of patients using one of these agents and the market share of Lumigan growing significantly. The 0.01% formulation has a higher BAK level, presumably to provide better corneal penetration, but it is less effective than the 0.03% formulation, per the FDA-approved package insert.

In another noteworthy finding of BioTrend Research Group, however, more than half of the surveyed physicians reported that some patients had requested a generic medication, an increase from the group's 2011 survey. This change suggests increasing cost sensitivity among glaucoma patients. Major concerns about generic equivalents, of course, are whether these agents are formulated as carefully and work as well as their brand-

"Who is the doctor? The influence of outside forces on our prescribing patterns is growing."

name counterparts. Research presented at this year's ARVO Annual Meeting showed variability in the total amount of drug delivered, often less than administered with each drop of Xalatan.⁶

Back to β -blockers?

Amid the uncertainty posed by the prostaglandins' going off patent, an alternative is for us to switch back to β -blockers as first-line therapy. Will our use of these agents increase based on the lower cost of generic β -blockers (\$4 at Target and Wal-Mart) and our new recognition of prostaglandin-associated periorbitopathy? The latter is listed under "adverse reactions: post-marketing experience" in the prescribing information for all prostaglandins.⁷

Adding to the discussion is the aforementioned release of a new prostaglandin analogue. Tafluprost is an ester prostaglandin prodrug, as are latanoprost and travoprost. Even at the low concentration of 0.0015%, tafluprost has excellent corneal penetration without the need for BAK. The drug was released in Europe first as a preserved and later a preservative-free product. In the United States, it is only available as a preservative-free product. The drug's efficacy is similar to (or slightly less than) that of latanoprost, and their side effect profiles are similar.⁸ How this new prostaglandin will fit into our prescribing patterns will be determined by several factors.

Outside Forces

Who is the doctor? The influence of outside forces on our prescribing patterns is growing. Insurance plans use copays and cost sharing to manipulate our patients into using the drugs preferred by the plans, usually preserved generics. In addition, on a few occasions, a pharmacist has substituted a drug (within a class) for the agent I prescribed. At the annual meeting of the American Glaucoma Society, William Rich III, MD, reported that Medicare will begin collecting data in 2013 on our utilization of resources. He said that, as soon as 2014, this information could begin influencing our reimbursement, with our use of generic medications one determinant of the adjustment.⁹

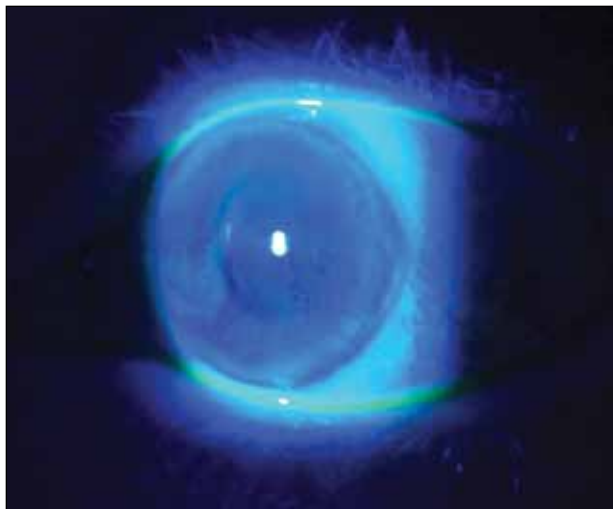


Figure 3. Irregular corneal surface. This finding will not be visible unless fluorescein is reapplied at the time the doctor sees the patient.

My staff tells me it takes an average of 15 to 20 minutes to fill out one insurance form for permission to use branded products.

Consensus

Can we practitioners reach a consensus about preservatives? Not all of us will agree on the advisability of nonpreserved glaucoma medications for young patients with a likelihood of long-term topical therapy but a normal history and corneal findings. I believe that most of us would agree, however, that our patients would fare better with preservative-free topical glaucoma drops, especially those individuals with

- preexisting OSD (Figure 3)
- chronic blepharitis/meibomitis
- symptomatic keratitis sicca, especially if they are already using only nonpreserved tears or cyclosporine ophthalmic emulsion 0.05% (Restasis; Allergan, Inc.)
- exposure keratitis
- poor tear breakup time
- evident toxicity from current treatment with medication

A careful examination and questioning consistent with the Ocular Surface Disease Index will find that almost half of our patients fit this profile. The clinical signs of iatrogenic disease usually are not specific but are identical to those resulting from other causes of OSD.¹⁰

Our Identities as Prescribers

Each of us falls into one of the following categories as a prescriber, and that identity will shape our use of

tafluprost and other drugs. I term category 1 “why fight City Hall?” These practitioners prescribe generics for all patients whenever possible in the belief that doing so saves patients money, cuts costs for the practice, requires fewer phone calls and less paperwork, and may result in rewards to the practice from Medicare. Category 2 comprises the “idealists,” those who believe that preservative-free or proprietary products are the best for patients. Category 3 I dub “middle of the road.” These practitioners choose which patients medically need preservative-free agents. Those individuals must be able to afford the extra cost, and the doctors must be able to afford the extra uncompensated chair time involved in the process of prescribing these agents.

CONCLUSION

Regardless of our identities as prescribers and external influence, I believe a paradigm shift is underway. For the same reason that most of us have switched to nonpreserved artificial tears, a majority of us will begin to favor preservative-free glaucoma medications in the near future. This change will be propelled by the increased availability of these agents and the growing awareness of OSD effected by manufacturers’ heavy marketing of these drugs. Moreover, we will begin to look and ask more about corneal surface disease. ■

Lawrence M. Hurvitz, MD, is a fellowship-trained glaucoma specialist in private practice at the Gulf Coast Glaucoma Clinic in Sarasota, Florida. Dr. Hurvitz is also an affiliate associate professor of ophthalmology at the University of South Florida in Tampa. He is a paid speaker for Merck & Co., Inc. Dr. Hurvitz may be reached at (941) 923-5491; info@glaucomaclicnic.com.



1. Baudouin C, Labbé A, Liang H, et al. Preservatives in eyedrops: the good, the bad and the ugly. *Prog Retin Eye Res.* 2010;29(4):312-334.
2. Hopes M, Broadway D. Preservative-free treatment in glaucoma is a sensible and realistic aim for the future. *European Ophthalmic Review.* 2010;4(1):23-28.
3. Ryan G Jr, Fain JM, Lovelace C, Gelotte KM. Effectiveness of ophthalmic solution preservatives: a comparison of latanoprost with 0.02% benzalkonium chloride and travoprost with the sofZia preservative system. *BMC Ophthalmol.* 2011;11:8.
4. *The Eye Digest. Medical Dictionary.* University of Illinois Eye & Ear Infirmary. <http://www.agingeye.net/dryeyes/dryeyesdrugtreatment.php>. Accessed May 11, 2012.
5. Comprehensive ophthalmologists and glaucoma specialists are either prescribing generic latanoprost in place of Pfizer’s Xalatan or switching patients to Alcon’s Travatan Z or Allergan’s Lumigan, according to a recent BioTrends Report [news release]. Exton, PA: BioTrends Research Group; March 26, 2012. <http://www.businesswire.com/news/home/20120326005881/en/Comprehensive-Ophthalmologists-Glaucoma-Specialists-Prescribing-Generic-Latanoprost>. Accessed June 26, 2012.
6. Brian S, Jayat C, Desmis A, Garrigue JS. Pharmaceutical quality evaluation of latanoprost delivered dose of US generics. Poster presented at: 2012 ARVO Annual Meeting; May 9, 2012; Fort Lauderdale, FL.
7. Pasquale LR. Prostaglandin-associated periorbitopathy. *Glaucoma Today.* Early summer 2011;9(3):51-52,58.
8. Uusitalo H, Pillunat L, Ropo A. Efficacy and safety of tafluprost 0.0015% versus latanoprost 0.005% eye drops in open-angle glaucoma and ocular hypertension: 24-month results of a randomized, double-masked phase III study. *Acta Ophthalmol.* 2010;88(1):12-19.
9. Rich WL III. DC update: the impact of PPACA on ophthalmology. Paper presented at: American Glaucoma Society 22nd Annual Meeting; March 2, 2012; New York, NY.
10. Fechtner R, Godfrey D, Budenz D, et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea.* 2010;29(6):618-621.