

Why Are There Not More Pharmacotherapies for Glaucoma?

There is plenty of interest but relatively few drugs in advanced-stage development.

BY GARY D. NOVACK, PhD

At present, all the medications that we use to treat glaucoma are approved on the surrogate endpoint of a reduction of elevated IOP. I have been involved in three major changes in glaucoma pharmacotherapy. I entered ophthalmic research at a time when glaucoma pharmacotherapy was undergoing the paradigm shift from pilocarpine dosed four times daily to timolol (Timoptic [Merck], approved in the United States in 1978) twice daily. I was actively involved in the development of novel pharmacotherapies during the next evolution in glaucoma drugs in 1996 with the approval of latanoprost ophthalmic solution (Xalatan; Pfizer) dosed daily. I was still actively involved in developing novel pharmacotherapies during the subsequent paradigm shift in 2011, which was not marked by a new class of agents but rather the availability of generic latanoprost in the United States. Why are there not more pharmacotherapies for glaucoma, and what can we do about it?

WHAT IS APPROVED?

In fiscal year 2014 (October 1, 2013, through September 30, 2014), of the 115 approved original New Drug Applications for all of medicine, there were four ophthalmic products, one of which was for glaucoma. The products for eye care were phenylephrine and ketorolac injection (Omidria; Omeros), travoprost ophthalmic solution 0.003% (Izba; Alcon) preserved with polyquaternium (Polyquad; Alcon), a fluocinolone acetonide intra-vitreous implant (Iluvien; Alimera Sciences), and atropine (Akorn).

Since the turn of the century, eight molecules have been approved in the United States to treat elevated IOP: one α -adrenergic agonist (brimonidine [Alphagan-P; Allergan]), one β -adrenergic antagonist



(timolol [Istalol; Bausch + Lomb]), four prostaglandin analogues (bimatoprost ophthalmic solution 0.01% or 0.03% [Lumigan; Allergan], tafluprost ophthalmic solution 0.0015% [Zioptan; Merck], travoprost [Travatan; Alcon], and unoprostone isopropyl [Rescula; Novartis Ophthalmics]), one muscarinic agonist (pilocarpine), and one chemotherapeutic (mitomycin C as a surgical adjunct). Some of these were reformulations of the originally approved product, and three were fixed-dose combinations (dorzolamide-timolol [Cosopt; Merck], brimonidine-timolol [Combigan; Allergan], and brinzolamide-brimonidine [Simbrinza; Alcon]). All of these agents were therapeutic advances, including the potential advantages of fixed-combination therapies of greater convenience and compliance. Only a few were novel molecules, however, and none was a new class.

IN THE PIPELINE

What about products in late-stage development? Aerie Pharmaceuticals is developing AR-13324, a Rho kinase and norepinephrine reuptake inhibitor,¹ currently in phase 3 trials for monotherapy and phase 2 studies for a fixed-dose combination with latanoprost. Kowa is developing K-115, a Rho kinase inhibitor, and recently published articles on phase 1 and phase 2 studies of the agent.^{2,3} Rho kinase inhibitors are also being evaluated by other companies, although the exact development status is not well known. Additionally, a few companies are in the early stages of developing modulators of adenosine receptors.

OBSTACLES

I have focused on the US experience mainly because the regulatory data are readily available from the FDA. Is the relative paucity of glaucoma pharmacotherapies under development limited to the United States? There are two examples of novel therapeutics in other major markets: bunazosin (Detantol; Santen)⁴ in Japan and the fixed-dose combinations of a prostaglandin analogue and timolol in Europe and Japan.⁵⁻⁷ These examples hardly support a postulate that the FDA is a major regulatory hurdle for new compounds.

I recently asked the same question about novel pharmacotherapies for dry eye disease.⁸ In that field, the obstacles to bringing a drug to market are the complex, multifactorial nature of ocular surface disorders; ineffective drugs; the way in which the disease is measured; and the high regulatory bar. Many of these challenges do not apply to glaucoma. From a therapeutic perspective, at least for the present, we know how to measure the disease—IOP with a tonometer. We know what a clinically significant difference is in IOP. We have many effective drugs. Finally, we know the requirements for regulatory approval. In the United States, a novel agent has to be at least as effective as timolol and have a favorable risk-to-benefit ratio.⁹

Could the lack of new glaucoma drugs be that all the good ideas are taken, that there are no more scientific ideas about novel ways to influence aqueous humor dynamics? Given the wealth of basic science articles in our journals, I do not think that this is the case. For example, there is continuing research on the trabecular meshwork in health and disease as well as novel ideas on modulation of these functions.¹⁰ There is interest in the sclera and its role in glaucoma, which may also be an alternate therapeutic approach to the classic Goldmann equation.¹¹⁻¹³

Could the problem be related to aqueous humor dynamics, as described by Goldmann?¹⁴ That is, after one

of the existing effective ocular hypotensive agents lowers the IOP, it becomes harder and harder to further reduce IOP. It is certainly true that the absolute reduction in IOP is more for a given molecule as the initial agent than as an additive agent. For most drugs, the lower the baseline, the lower the absolute lowering of IOP.^{15,16} Possible exceptions to this generalization are AR-13324 and an earlier molecule, AR-12286, which seem to produce the same absolute reduction in IOP regardless of baseline (both agents from Aerie Pharmaceuticals).^{1,17,18} Nonetheless, given the regulatory requirement in which the novel agent is compared to timolol or latanoprost, a lower baseline (whether due to reduction with a primary agent or less severe disease) is statistically more challenging to demonstrate than comparable efficacy for second-line therapies.

FINANCIAL OPPORTUNITY

The only remaining explanation for the lack of new therapies is financial. For the most part, the private sector rather than the government develops drugs. For the private sector to make an investment, there needs to be the potential for profit, either in the stock price or in product revenue. With the expiration of patents on prostaglandins, many patients' diseases may initially be managed with a more affordable agent.

As readers of *Glaucoma Today* know, patients often need more than a prostaglandin eye drop to manage their glaucoma. Today's topical treatment of the disease requires patients who are able to correctly instill eye drops (performance) and to do so at the right time (adherence).¹⁹ Many firms are working on products to improve the delivery of ocular hypotensive medications.^{20,21} It is estimated that approximately 50% of patients receiving ocular hypotensive therapy require two or more drugs.²² This leads to the development of fixed-dose combination therapies and provides an opportunity for novel pharmacotherapy in a field with lower-revenue first-line drugs. In the United States, the current regulatory pathway is to gain approval as a monotherapy. This also includes labelling for use as additivity with other agents (ie, second-line therapy). Of course, elevated IOP is also treated with surgery and lasers. There is growing interest in improving glaucoma surgery through devices that are less invasive and safer than trabeculectomy.²³ Such devices would also tend to make pharmaceuticals appear less attractive as investments.

In my opinion, there is a financial opportunity in developing novel pharmacotherapies for glaucoma. It may not be as the drug of choice for first-line therapy. However, there is still financial opportunity with second-line therapeutic

agents. Additionally, there is financial opportunity with drug delivery systems. I encourage those who manage patients with glaucoma to convince health care system payors that there is value in improving therapeutics through better delivery of today's drugs or in novel agents that may be additive therapy. ■

Gary D. Novack, PhD, is the president of PharmaLogic Development in San Rafael, California. He consults for numerous pharmaceutical and medical device firms but owns no stock or holds no proprietary interest. Dr. Novack may be reached at (415) 472-2181; gary_novack@pharmalogic.com.



1. Bacharach J, Dubiner HB, Levy B, et al. Double-masked, randomized, dose-response study of AR-13324 vs. latanoprost in patients with elevated intraocular pressure. *Ophthalmology*. 2015;122(2):302-307.
2. Tanihara H, Inoue T, Yamamoto T, et al. Phase 1 clinical trials of a selective Rho kinase inhibitor, K-115. *JAMA Ophthalmol*. 2013;131:1288-1295.
3. Tanihara H, Inoue T, Yamamoto T, et al. Phase 2 randomized clinical study of a Rho kinase inhibitor, K-115, in primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol*. 2013;156:731-736.
4. Kobayashi H, Kobayashi K, Okinami S. Efficacy of bunazosin hydrochloride 0.01% as adjunctive therapy of latanoprost or timolol. *J Glaucoma*. 2004;13:73-80.
5. Higginbotham EJ, Olander KW, Kim EE, et al. Fixed combination of latanoprost and timolol vs individual components for primary open-angle glaucoma or ocular hypertension: a randomized, double-masked study. *Arch Ophthalmol*. 2010;128:165-172.
6. Schuman JS, Katz GJ, Lewis RA, et al. Efficacy and safety of a fixed combination of travoprost 0.004%/timolol 0.5% ophthalmic solution once daily for open-angle glaucoma or ocular hypertension. *Am J Ophthalmol*. 2005;140:242.
7. Brandt JD, Vandenburgh AM, Chen K, Whitcup SM. Comparison of once- or twice-daily bimatoprost with twice-daily timolol in patients with elevated IOP: a 3-month clinical trial. *Ophthalmology*. 2001;108:1023-1031.
8. Novack GD. Pipeline: why aren't there more pharmacotherapies for dry eye? *Ocul Surf*. 2014;12:227-230.
9. Weinreb RN, Kaufman PL. The glaucoma research community and FDA look to the future: a report from the NEI/FDA CDER Glaucoma Clinical Trial Design and Endpoints Symposium. *Invest Ophthalmol Vis Sci*. 2009;50:1497-505.
10. Overby DR, Zhou EH, Vargas-Pinto R, et al. Altered mechanobiology of Schlemm's canal endothelial cells in glaucoma. *Proc Natl Acad Sci USA*. 2014;38:13876-13881.
11. Pijanka JK, Coudrillier B, Ziegler K, et al. Quantitative mapping of collagen fiber orientation in non-glaucoma and glaucoma posterior human sclerae. *Invest Ophthalmol Vis Sci*. 2012;53:5258-5270.
12. Coudrillier B, Pijanka JK, Jefferys J, et al. Collagen structure and mechanical properties of the human sclera: analysis for the effects of age. *J Biomech Eng*. 2015;137(4).
13. Kimball EC, Nguyen C, Steinhart MR, et al. Experimental scleral cross-linking increases glaucoma damage in a mouse model. *Exp Eye Res*. 2014;128:129-140.
14. Goldmann H. Out-flow pressure, minute volume and resistance of the anterior chamber flow in man. *Doc Ophthalmol*. 1951;5:6:278-356.
15. Novack GD. Pipeline: how should we display our data? What is the best number? *Ocul Surf*. 2012;10:193-198.
16. Novack GD, Lue JC, Duzman E. Power estimates in designing glaucoma trials. *Glaucoma*. 1989;11:166-168.
17. Kopczynski C, Novack GD, Swearingen D, van Haarlem T. Ocular hypotensive efficacy, safety and systemic absorption of AR-12286 ophthalmic solution in normal volunteers. *Br J Ophthalmol*. 2013;97:567-572.
18. Levy B, Ramirez N, Kopczynski CC, Novack GD. Ocular hypotensive safety and systemic absorption of AR-13324 ophthalmic solution in normal volunteers [Epub ahead of press January 28, 2015]. *Am J Ophthalmol*. doi:10.1016/j.ajo.2015.01.026.
19. Novack GD, Muir KW, Newman-Casey PA, Robin AL. Ocular hypotensive medications: adherence and performance. In: Shaarawy TM, Sherwood MB, Hitchings RA, Crowston JG, eds. *Glaucoma*. Elsevier, Saunders: London; 2014:521-524.
20. Novack GD. New horizons in glaucoma drug delivery. *Glaucoma Today*. July/August 2014;12:42-44. <http://bmctoday.net/glaucomatoday/2014/08/article.asp?i=new-horizons-in-glaucoma-drug-delivery>.
21. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. *Ophthalmology*. 2001;108:1943-1953.
22. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol*. 2002;120:701-713.
23. Samuelson TW, Katz LJ, Wells JM, et al. Randomized evaluation of the trabecular micro-bypass stent with phacoemulsification in patients with glaucoma and cataract. *Ophthalmology*. 2011;118:459-467.