

Are Fixed Combinations Worthwhile?

One must consider a variety of issues, including patients' adherence to prescribed therapy, the complexity of their dosing regimens, and the safety and efficacy of the drugs themselves.

BY GILLIAN McDERMOTT, EDITOR-IN-CHIEF

Considering that patients often do not adhere to prescribed glaucoma therapy, physicians' interest in fixed-combination agents is little surprise. Many believe that patients are more likely to follow a simpler dosing regimen, which these combinations could achieve. Although some fixed-combination glaucoma drugs are approved for use in the US, no new agent of this type has entered the market in 7 years. A reasonable question, therefore, is what value do fixed-combination agents have in the treatment of glaucoma?

FEWER MEDICATIONS, HIGHER ADHERENCE TO THERAPY?

Alan L. Robin, MD, Clinical Professor of Ophthalmology at the University of Maryland and Associate Professor of International Health for the Bloomberg School of Public Health at Johns Hopkins University in Baltimore, refers to several major studies for an idea of glaucoma patients' drug burden: "The Ocular Hypertension Treatment Study found that, to achieve a long-term 20% reduction in IOP (a modest goal), more than 40% of individuals in the era of prostaglandin analogues need an additional medication.¹ The Advanced Glaucoma Intervention and Collaborative Initial Glaucoma Treatment Studies both found that the number of patients requiring more than one medication for IOP lowering might be closer to 80% when the disease is more advanced."^{2,3}

Because the long-term use of medication generally involves tying its administration to a routine activity such as going to bed or eating a meal, most people will find less frequent dosing easier, says George L. Spaeth, MD, FACS, Director of the William and Anna Goldberg Glaucoma Service and Research Laboratories at Wills Eye Hospital in Philadelphia. Numerous meta-analyses of the use of medication—not just in the area of glaucoma—

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have demonstrated that simplifying patients' drug regimens improves their adherence to prescribed therapy, according to Betsy Sleath, PhD, an associate professor at the UNC School of Pharmacy in Chapel Hill, North Carolina.^{4,5} A major factor is one of memory. Dr. Sleath and her colleagues surveyed 324 patients from four private ophthalmic practices across the country who were taking two or more medications for glaucoma.⁶ She states that "patients who were on more medications for glaucoma reported that they had more difficulty remembering to take them," which was the greatest predictor of adherence in the study. In other words, a higher number of medications was associated with greater difficulty remembering to take the drugs, which in turn led to poorer compliance.

Of importance is that many patients are dealing with more health problems than glaucoma. "We ophthalmologists tend to be very myopic and forget that these older glaucoma patients also have various systemic diseases," remarks Dr. Robin. "At least one-half of glaucoma patients are on multiple systemic medications ranging from antihypertensive, diabetic, arthritic, hormone replacement therapies, and other medicines."

Both Dr. Sleath and Dr. Robin have found that patients on multiple medications may not refill their prescriptions promptly.^{6,7} Dr. Sleath notes that the bottles of

glaucoma drops are small and therefore require frequent replacement. A higher number of medicines necessitates more trips to the pharmacy, because the medications will not all run out at the same time, she said.

A study by Dr. Robin and David Covert, MBA, of Alcon Research Ltd. (Fort Worth, TX) indicates that adding a second drug to patients' regimens alters how they take their first drop.⁷ "We found that individuals on latanoprost as their only glaucoma medication for 1 year normally refill their latanoprost approximately every 40 days," he says. "As soon as a second glaucoma medication is added, irrespective of the class of medication or the bottle size of the second medication, almost 50% of people delay the latanoprost refill by at least 6 additional days, and almost 20% delay the latanoprost refill by more than 2 weeks! ... This implies that patients probably don't consider this to be noncompliance (only taking one of two medications), since they are still taking some glaucoma medication."

Of course, a simpler drug regimen will not guarantee an adherence to prescribed therapy for every patient. Some will still not perceive a benefit to taking medications, especially if they have yet to sustain vision loss from the disease, and they may prefer to avoid side effects associated with their medications.

ASSESSING THE VALUE OF FIXED COMBINATIONS

Convenience

Certainly, taking fewer drops is more convenient for patients. Dr. Spaeth notes that someone taking a topical carbonic anhydrase inhibitor (CAI) and non-gel formulation of a beta-blocker, for example, would instill two drops in the morning and two drops in the evening. For a busy parent trying to get kids to school before racing to work, the prescribed pause between instilling drops one and two could be the downfall of their compliance, he observes.

"Realistically, even though they're both twice-daily drops, one of them might not get in," says Dr. Spaeth, who has a large number of patients on Cosopt (Merck & Co., Inc., West Point, PA). "I think a fixed combination offers a reasonable likelihood that a person is more likely to get in all the drops that have been ordered than not having a fixed combination."

Safety

Reducing the number of medications through a fixed combination also decreases the load of preservatives for the eye. Dr. Spaeth acknowledges a lack of scientific evidence proving that damage to the ocular surface in patients who have used glaucoma medications long

term is due to the agents' preservatives. Nonetheless, he says that the association makes sense.⁸ Moreover, he comments that there is no reason to think that a fixed combination will cause more adverse side effects than the two agents administered separately.

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One concern with fixed combinations, however, relates to a possible pairing of agents with different dosing schedules. As an example, Dr. Spaeth points to an early combination of pilocarpine (dosed four times daily) and epinephrine (dosed twice a day). If patients used the agent four times a day, they received more epinephrine than necessary; if they used it twice a day, they received less pilocarpine than ideal. Dr. Spaeth comments that a new fixed-combination agent of a prostaglandin analogue (once a day) and a CAI (two or three times daily) would be similarly problematic. Such combinations either cause unnecessary side effects or have less than maximum efficacy, he says.

Efficacy

The two agents in a fixed combination should work well together. One effective coupling, according to Dr. Spaeth, is that of a CAI and a topical beta-blocker, which he says has an additive effect. A newer combination of a beta-blocker and a prostaglandin analogue (Xalcom; Pfizer Inc., New York, NY) is approved for use in Europe but not the US (for more on the FDA and fixed-combination agents, see sidebar). According to Dr. Spaeth, this combination is not quite additive. For that reason, he says it may not be an optimal combination but adds that one could certainly argue the advantages of fewer preservatives in the eye and greater convenience to the patient.

Cost

If a fixed combination costs less than the agents purchased separately, it is an advantage for glaucoma patients, especially those on fixed incomes. In the study by Sleath et al,⁴ 44% of subjects reported difficulty paying for their medications. How US insurers would cover new fixed-combination agents is, of course, unknown.

FROM THE STANDPOINT OF THE FDA

In the following interview, Wiley Chambers, MD, Deputy Director of the Division of Anti-Infective and Ophthalmology Products at the FDA, discusses fixed-combination agents for the treatment of glaucoma with Gillian McDermott, Editor-in-Chief.

Ms. McDermott: What are the FDA's current requirements for a combination drug in glaucoma?

Dr. Chambers: A combination new drug product is potentially approvable if there are studies demonstrating that each of the components that make up the combination contributes in some manner to the safety and efficacy of the drug product. The contribution of each component is normally expected to be demonstrated in adequate and well-controlled studies.

Ms. McDermott: How did the agency develop these requirements?

Dr. Chambers: The requirement for demonstrating that each component contributes to the effect of the product, besides being common sense, is a regulation that was published in the Code of Federal Regulations. Regulations are first proposed and published in a Federal Register notice. There is an opportunity for public comments, ... [which] are taken into consideration when the rule is made final. The requirement applies to all fixed drug combinations.

Ms. McDermott: Is there a requirement for a fixed combination to lower IOP more than the individual components taken together?

Dr. Chambers: No.

Ms. McDermott: So, if you had two drugs melded in one product, it does not have to lower IOP more than if a patient took the components in two separate bottles?

Dr. Chambers: That is correct.

Ms. McDermott: How do the number and type of combination products for glaucoma compare, for instance, to the number of combination products available for other parallel indications (eg, systemic hypertension)?

Dr. Chambers: I do not know the specific numbers, because I do not specifically oversee the systemic hypertension products. There are relatively few ophthalmic fixed-dose combinations. If I had to guess, I would say that there are probably more systemic hypertensive combination medications, because there are many more patients with systemic hypertension.

Ms. McDermott: Is there any difference in the FDA's position on combination agents in glaucoma versus other areas (eg, asthma, diabetes, hormone therapy)?

Dr. Chambers: No, the regulation that I mentioned earlier applies to all new drug products and is not specific to ophthalmic drug products.

Ms. McDermott: How does the issue of patients' compliance with therapy factor into the FDA's position on fixed combinations currently under review, or does it?

Dr. Chambers: [A] demonstration of increased compliance leading to decreased IOP could be a way to show the contribution of each of the components. The bottom line remains that it is only worth taking a combination if you get something more out of the combination than taking just one of the single agents.

Ms. McDermott: Do you know when the last glaucoma combination product was approved for US patients?

Dr. Chambers: The last IOP-lowering combination approved was Cosopt [Merck & Co., Inc., West Point, PA] and was approved in 1998. The one before that was Betoptic-Pilo [Alcon Laboratories, Inc., Fort Worth, TX] and was approved in 1997.

Ms. McDermott: What is the status of the more recently developed combination agents for reducing IOP?

Dr. Chambers: None is currently approved, and I am generally not permitted to discuss [agents] unless they are approved.

Ms. McDermott: If a product is issued an approvable letter, what does that mean?

Dr. Chambers: An approvable letter means that the FDA has identified issues in the application that would need to be fixed before the application can be approved. The [FDA] identifies those specific items in the letter and communicates them to the holder of the application.

Ms. McDermott: Several glaucoma specialists and general ophthalmologists have expressed their desire for combination products. What hurdles must be overcome for the approval of fixed combinations containing prostaglandin analogues?

Dr. Chambers: I believe that glaucoma specialists, ophthalmologists, and patients are interested in products [that] more effectively lower IOP, have lower side effects, and/or have the same safety and efficacy but are easier to take. The FDA is interested in these types of products, too, but, first, it would have to be demonstrated that one of these three characteristics is true of the new product. Every component that is added to a product carries additional risks; it is important that you also actually get some benefit.

Ms. McDermott: From a regulator's perspective, is the same yardstick applied to today's combination applications as was used

in the case of the combination products already approved for glaucoma therapy?

Dr. Chambers: The standard that applied when I first came to the FDA 18 years ago was that the benefits outweighed the risks. That same standard still applies today.

Ms. McDermott: As both an ophthalmologist and an FDA officer, is there an advantage in having combination products available for glaucoma patients?

Dr. Chambers: There is an advantage to having products that are particularly effective, safer, or more convenient available. If that means having to combine more than one agent to get to a particularly effective agent, then there is an advantage to a combination. But, just putting two things together that do not provide any kind of advantage is not necessarily helpful.

Ms. McDermott: As an ophthalmologist who treats glaucoma patients, do you ever use approved fixed-combination agents?

Dr. Chambers: Yes.

Ms. McDermott: What goes into your decision to use those versus other modalities?

Dr. Chambers: If I think the combination will provide me with additional safety and efficacy that I am not getting over a single agent.

Ms. McDermott: The importation of drugs from Canada and elsewhere is a frequent topic in the news. Are there differences between these countries' regulations and those of the US? You may limit your response to Canada and Europe if you like.

Dr. Chambers: There are differences, but I am not an expert on the drug-regulation process for other countries in the world. I have certainly seen applications submitted to other countries, and I also have talked to the individuals performing the reviews. One difference is that the FDA has a complement of full-time clinical ophthalmologists who review ophthalmology products. Other regulatory agencies do not necessarily have similar dedicated resources.

Ms. McDermott: Are there any other points you think would be useful to currently practicing clinical ophthalmologists who are interested in new drugs for glaucoma?

Dr. Chambers: I think there is clearly a desire to have more effective drug products, and, while the hope is that combinations will achieve that, the reality has been very disappointing to a number of people, including myself.

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CONCLUSION

The development and availability of a new fixed-combination agent would certainly improve the compliance of many glaucoma patients. Until the FDA approves a new combination drug, however, research and clinical experience indicate that physicians should strive to simplify their patients' drug regimens as much as possible.

It is also wise to make specific inquiries about the possible side effects of each medication, says Dr. Spaeth. He has found that significantly more patients reveal drug-related problems when asked a question such as, do you feel more tired since using this drop? (for a beta-blocker), than a general inquiry such as, are you experiencing any side effects? One reason may be that patients do not always realize that a problem they are experiencing could be related to their glaucoma medications. Another, notes Dr. Spaeth, is that patients may be embarrassed by side effects such as erectile dysfunction and thus reluctant to discuss them. In short, he says, "you don't find side effects you don't ask for." □

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