Adherence and Fixed-Combination Agents

Evidence shows that patients benefit from a simple dosing regimen.

BY ROBERT D. FECHTNER, MD

Topical medication is the initial treatment for most patients with ocular hypertension or glaucoma. Clinical experience and data from clinical trials, however, show that a large proportion of patients do not achieve or sustain their target IOP with a single agent. In the Collaborative Initial Glaucoma Treatment Study (CIGTS), subjects' target IOPs were calculated individually, and greater than 75% required two or more pressure-lowering medications after 2 years.[1] Investigators for the Ocular Hypertension Treatment Study (OHTS) set a relatively modest target for IOP reduction, yet approximately 50% of subjects required more than one glaucoma medication by 5 years.[2] These studies were initiated before the introduction of topical prostaglandin analogues, which are now the most commonly prescribed IOP-lowering medications.[3] In March 2010, a follow-up study to the OHTS was published in which the former observation group was treated initially with a prostaglandin. Even with this therapy, about 50% required additional medication to achieve a targeted 20% reduction in IOP.[4]

Despite the wide use of prostaglandins, many patients' IOP will not be controlled with monotherapy. Because glaucoma and ocular hypertension are lifelong conditions, it is reasonable to expect that the percentage of patients requiring adjunctive therapy will increase as the world's population continues to age. Complex and expensive medical regimens present a barrier to our patients.[5] Fixed-combination agents may play an important role in facilitating their adherence and persistence with prescribed medical therapy as they come to require multiple drugs to control their IOP.

THE LIMITATIONS OF ADJUNCTIVE THERAPY

When monotherapy does not adequately lower patients' IOP, prescribing another agent can help, but adjunctive therapy has limitations. Perhaps of greatest importance, patients' adherence to prescribed therapy decreases as the dosing regimen becomes more complex.[5-7] In a study by Robin and colleagues, adherence with the prostaglandin was relatively good, but adherence to adjunctive therapy was not.[7] Moreover, these investigators reported that the interval between refills of the first agent stretched on average 1 additional week for patients with multiple prescriptions compared with those who were only using a prostaglandin. For 22%, the interval was 2 weeks or longer.[8] Patients on adjunctive therapy do not appear to be refilling their prescriptions as often as needed. If there is any encouraging news from research on dosing complexity and adherence, it is a strong likelihood that patients will at least continue to use their initial medication.[7]

Other problems with adjunctive therapy include that instilling the second medication too soon after the first risks a washout effect.[9] In addition, the use of adjunctive therapy increases patients' exposure to preservatives. Finally, prescribing additional bottles follows the law of diminishing returns. In one retrospective study in which success was defined as at least a 20% decrease from baseline IOP, the cumulative probability of success from adding a third or fourth drug was only 14% at 1 year.[10]

THE BENEFITS AND LIMITATIONS OF FIXED COMBINATIONS

Fixed-combination agents offer some obvious benefits to patients who would need the component medications. A fixed combination permits a simple regimen with three medications: two bottles and three drops daily in the treated eye. This may represent maximal rational therapy for most patients.[11] In addition to a lower exposure to preservatives, fewer drops mean a less-

er chance of washing out the previously administered drop due to an inadequate interval between the medications' instillation. Depending on the patient's insurance, fixed combinations may also represent a cost benefit with fewer copayments.

Fixed-combination agents are not without their limitations. The component drugs of a fixed combination may not be the ideal concentration for a given patient. For example, both of the fixed-combination products available in the United States contain the highest available concentration of each component (timolol 0.5% with brimonidine 0.2% or dorzolamide 2%). There is some logic to the use of the maximum approved concentrations of the individual drugs in a fixed combination. By the time clinicians advance medical therapy to include a fixed-combination agent, they are usually treating patients whose IOP is not sufficiently controlled by a single medication or, often, two drugs. Physicians therefore want to advance to maximal rational therapy.[11,12]

Another limitation of fixed combinations is that they may not have the optimal dosing schedule. In a research setting, the decrease in IOP was greater in the late afternoon with the unfixed combination (timolol dosed b.i.d., dorzolamide or brimonidine dosed t.i.d.) versus the fixed combinations of timolol-dorzolamide and timolol-brimonidine (dosed b.i.d.).[13] I would suggest, however, that this comparison is one of apples and oranges. Research subjects are very different from the everyday glaucoma patient, and five drops daily are far more burdensome than two. A real-world analysis compared patients who were switched from an unfixed combination to a fixed combination in one eye only and maintained on the unfixed combination in their fellow eye. The investigators found that the reduction in IOP was greater in the fixed-combination eyes than in the unfixed-combination eyes.[14] A possible reason for this apparent contradiction is that clinical trials represent the best possible conditions: motivated research subjects who instill all of their drops as directed. Unfixed combinations entail five doses from two bottles, however, whereas fixed combinations entail two doses from one bottle. In the real world, simplifying patients' dosing regimens produced a greater IOP lowering.[14]

By offering patients simpler, more convenient, and sometimes more affordable medical therapy, fixed combinations offer an effective approach that may improve patients' adherence to prescribed medical therapy.[15]

CONCLUSION

In my opinion, maximal rational medical therapy for most patients is one or two bottles. Typically, there is no strong evidence that patients will benefit from advancing beyond a prostaglandin analogue dosed once a day and a fixed combination administered twice daily. By keeping therapy as simple as possible, practitioners help patients to adhere to prescribed drug therapy.

To ensure the best care for patients, clinicians must bear in mind that fixed combinations are not a single drug and that they thus must be attentive to the potential side effects of each component. Moreover, no large prospective trials have been published studying the additivity of fixed-combination agents to prostaglandin analogues. It remains the clinician's responsibility to confirm that, when added to a prostaglandin, a fixed combination is the appropriate choice for adjunctive therapy. ❑

Robert D. Fechtner, MD, is the director of the Glaucoma Division at UMDNJ, and he is a professor of ophthalmology at the Institute of Ophthalmology, both at New Jersey Medical School in Newark. He is a consultant to and has received research support from Alcon Laboratories, Inc., and Allergan, Inc. Dr. Fechtner may be reached at (908) 972-2030; fechtner@umdnj.edu.

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