FIXED COMBINATIONS

A mainstay of glaucoma management today and tomorrow.

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The role of fixed-combination therapies for the treatment for ocular hypertension has grown. IOP lowering can be achieved medically, by laser surgery, or through incisional surgery. Whereas laser surgery may be the appropriate first-line treatment for some patients, medical therapy is commonly initiated or maintained at any stage of the glaucoma spectrum.

Monotherapy with a once-daily prostaglandin analogue remains the foundation of medical therapy for most patients with glaucoma, and it is the most common initial choice of agent. If IOP control is not sufficient or if the disease progresses, treatment should be advanced.

Patients' adherence to prescribed medical therapy remains one of the great unmeasurable challenges of glaucoma care. Although even a single medication may present a dosing regimen that challenges patients, we clinicians accept that increasing the complexity and burden of treatment cannot possibly help adherence rates.[1,2] Fixed combinations are highly effective and reduce complexity.

USING FIXED COMBINATIONS

We must expect that there will be nonresponders to every class of medication, including prostaglandins. For a patient who has not responded to prostaglandin monotherapy, it is appropriate to try a different class of medication. For patients who exhibit at least a 20% to 30% reduction in IOP with a prostaglandin, we can add either a single agent from another class (ie, a topical β-adrenergic antagonist, selective α-2 agonist, topical carbonic anhydrase inhibitor) or a fixed-combination medication. Our choices are guided by the patient's degree of disease and comorbidities, the target IOP, and our experiences (and biases). There are few studies of sufficient size and quality to give us clear guidance, but the available published information can help set our expectations. In the end, every patient responds differently to treatment, and we need to assess whether our choices are successful on an individual basis.

FIXED COMBINATIONS AS MONOTHERAPY

The modern fixed combinations of IOP-lowering medications available in the United States are dorzolamide 2%-timolol 0.5% (Cosopt [Akorn] or generic), brimonidine 0.2%-timolol 0.5% (Combigan; Allergan), and brinzolamide 1%-brimonidine 0.2% (Simbrinza; Alcon). Other fixed combinations available internationally either have not received approval by the FDA or have not been submitted to the agency. A key consideration in the approval of modern fixed-combination agents is that they lower IOP to a greater extent than either component alone. In a disease such as

TABLE 1. EFFICACY OF FIXED COMBINATIONS AS INITIAL MONOTHERAPY

Study	Boyle et al[a]	Craven et al[b]	Katz et al[c]
Fixed combination	Timolol-dorzolamide N = 114	Timolol-brimonidine N = 385	Brinzolamide-brimonidine N = 209
Untreated baseline IOP, mm Hg	27.8 (hour 0) 27.0 (hour 2)	24.7 (8:00 AM) 23.3 (10:00 AM) 22.1 (3:00 PM) 21.8 (5:00 PM)	26.9 (8:00 AM) 25.3 (10:00 AM) 23.7 (3:00 PM) 23.2 (5:00 PM)
IOP on Fixed Combination			
Treated IOP, mm Hg	-7.7 (hour 0 trough) -9.0 (hour 2 peak)	-6.9 (8:00 AM) -7.6 (10:00 AM) -5.3 (3:00 PM) -4.9 (5:00 PM)	-7.1 (8:00 AM trough) -8.8 (10:00 AM peak) -5.7 (3:00 PM trough) -6.9 (5:00 PM peak)

[a] *Data from Boyle et al.*[3]
[b] *Data from Craven et al.*[4]
[c] *Data from Katz et al.*[5]

TABLE 2. WHAT TO EXPECT WHEN ADDING A FIXED COMBINATION TO A PROSTAGLANDIN

Study	Fechtner et al[a]	Konstas et al[b]	Fechtner et al[c]	Feldman et al[d]
Design	Prospective parallel	Prospective crossover	Prospective parallel	Prospective parallel
PGA	Latanoprost	Latanoprost	Any	Travoprost
FC added	Timolol-brimonidine N = 102	Timolol-dorzolamide N = 31	Brinzolamide-brimonidine N = 88	Brinzolamide-brimonidine N = 103
IOP on PGA alone, mm Hg	23.7 (8:00 AM) 23.4 (10:00 AM)	22.1 (24 hour, every 4 hours)	24.5 (8:00 AM) 22.9 (10:00 AM) 21.6 (3:00 PM) 22.7 (5:00 PM)	24.2 (8:00 AM) 22.8 (10:00 AM) 21.5 (3:00 PM) 21.3 (5:00 PM)
IOP on PGA alone mean, mm Hg			22.7	22.5
IOP with FC added				
Peak and trough, mm Hg	-6.7 (8:00 AM trough) -8.3 (10:00 AM peak)		-5.1 (8:00 AM trough) -7.1 (10:00 AM peak) -4.5 (3:00 PM trough) -6.0 (5:00 PM peak)	-4.6 (8:00 AM trough) -6.3 (10:00 AM peak) -3.9 (3:00 PM trough) -5.1 (5:00 PM peak)
Mean, mm Hg		-5.6 (24 hour)	-5.7	-5.1
Comparator	Timolol N = 102	No other comparator added to PGA	Vehicle N = 94	Vehicle N = 112
IOP on PGA alone, mm Hg	23.5 (8:00 AM) 23.0 (10:00 AM)		24.3 (8:00 AM) 22.6 (10:00 AM) 21.3 (3:00 PM) 21.2 (5:00 PM)	24.2 (8:00 AM) 22.8 (10:00 AM) 21.9 (3:00 PM) 21.6 (5:00 PM)
IOP on PGA alone mean, mm Hg			22.4	22.7
IOP with comparator added				
Peak and trough, mm Hg	-5.8 (8:00 AM trough) -6.1 (10:00 AM peak)		-2.9 (8:00 AM) -2.4 (10:00 AM) -1.4 (3:00 PM) -1.2 (5:00 PM)	-2.5 (8:00 AM) -2.2 (10:00 AM) -2.4 (3:00 PM) -1.7 (5:00 PM)
Mean, mm Hg			-2.0	-2.2

Abbreviations: PGA, prostaglandin analogue; FC, fixed combination.
[a] *Data from Fechtner et al.*[6]
[b] *Data from Konstas et al.*[7]
[c] *Data from Fechtner et al.*[8]
[d] *Data from Feldman et al.*[9]

glaucoma where every millimeter of pressure lowering matters, this requirement is meaningful. The design of registration trials (fixed combination vs each component from an untreated baseline) gives us clear information about what to expect when initiating therapy.

For the fixed combinations containing timolol, the dosing is twice daily (that of timolol), although the indication for the other component (dorzolamide or brimonidine) is three times daily. This schedule can show an advantage for the pressure lowering of the single agent, with a peak in the late afternoon after the additional dose. Table 1 shows the efficacy of fixed combinations as initial monotherapy.[3-5] (Some values for the Craven study were not reported in the text and were derived from the graphs.[4])

If viewed as a single treatment rather than two medications, fixed combinations are highly efficacious both at

WATCH IT NOW

Robert Fechtner, MD, shares tips on the selection of adjunctive medical therapy and the timing of laser trabeculoplasty in this episode of Glaucoma Today Journal Club.

trough and peak, and they offer a reasonable alternative when prostaglandins either are not sufficiently effective or are poorly tolerated.

For the most common scenario today, where a patient is on a prostaglandin, we have some useful information about the additivity of fixed-combination medications. These studies are not directly comparable because of differences in design, inclusion criteria, baseline IOPs, and times of pressure measurements. They can, however, give us a clear idea of what to expect when adding a fixed combination to a prostaglandin (Table 2).[6-9]

In particular, we can extract some peak and trough efficacy data from these studies. There are a few points worth noting when looking at the summarized data:

- For the additivity of brimonidine-timolol to a prostaglandin, the time points measured are 8:00 AM (trough) and 10:00 AM (peak).[6] For the other studies, additional time points were measured. [7-9] In the brimonidine-timolol study, timolol demonstrated substantial additivity to the prostaglandin (5.8-6.1 mm Hg additional IOP lowering), greater than is usually expected with this medication.[6] The reasons for this finding are not clear.
- The studies on brinzolamide-brimonidine additivity used a vehicle as the comparator.[8,9] We can draw no conclusions on how much better the fixed combination was than either of its components as an adjunct to a prostaglandin. (It is worth noting that most studies that use a vehicle as a control demonstrate 1 to 2 mm Hg of IOP lowering in the vehicle arm. This might not be regression to the mean but might actually be an effect of the vehicle. No one has investigated whether a vehicle contributes to IOP lowering.)

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- The dorzolamide-timolol study was relatively small (N = 31) and had a complex crossover design looking at switching from latanoprost to one of two fixed combinations (dorzolamide-timolol or latanoprost-timolol) or adding dorzolamide-timolol to latanoprost.[7]

Although the study designs varied greatly, the fixed combinations reduced IOP by more than 5 mm Hg on average and substantially more than that at peak efficacy. It is reasonable to conclude from the available data that today's fixed combinations represent the most powerful single-bottle therapies to add to a prostaglandin (see *Watch It Now*).

POTENTIAL ADVANTAGES OF FIXED COMBINATIONS

Efficacy

Fixed combinations are highly effective as monotherapy or when added to a prostaglandin. At least one small study suggested that, in the real world, a fixed combination lowered IOP better than an unfixed combination.[10] This might have been owing to better adherence, less washout effect thanks to lack of spacing of medication administration, or other properties of the formulations.

Tolerability

Patients using IOP-lowering medications often have symptoms of ocular surface disease. In one large study, the prevalence was 50%, with 25% of patients having moderate to severe symptoms.[11] The likelihood of signs and symptoms rises as the number of medications a patient uses and the duration of that therapy increase.[12,13] Fixed-combination medications allow us to administer rational maximal medical therapy for most patients with two bottles and three to four drops daily.[14]

DISADVANTAGES OF FIXED COMBINATIONS

We make the recommendations we feel are best for our patients, but there are other forces at play in the health care system. The formulary selections by pharmacy benefit managers can create substantial financial burdens that

AT A GLANCE

- Fixed combinations are highly effective and reduce the complexity of glaucoma medical therapy.
- Unfortunately, formulary selections by pharmacy benefit managers can make the use of these products more expensive than the purchase of their individual components.
- The first fixed combination including a prostaglandin to become available in the United States may be netarsudil 0.02%-latanoprost 0.005% ophthalmic solution.

essentially eliminate a patient's access to the medication we might select as best for him or her. In some instances, the preferred medications are the generic unfixed components rather than the fixed combination. This selection may save money for the payer (and the patient), but it adds complexity, affects adherence, and may unfavorably influence disease progression. It is important to note, however, that generic prices vary widely and have increased over time, possibly diminishing cost savings to patients and payers.[15] Using the two components in an unfixed combination will require five to six drops daily rather than two to three with a fixed combination.

In addition to the potential financial burden exerted by formulary choices, fixed combinations can have other disadvantages. The dosing frequency of fixed combinations containing timolol is less frequent than that of the nontimolol component. This could allow for an increase in IOP late in the afternoon, as was seen in the timolol-dorzolamide study of a fixed combination versus an unfixed combination.[16] For patients experiencing this phenomenon, we can prescribe an afternoon dose of a single agent.

THE FUTURE

An obvious unmet need in the United States is an effective fixed combination containing a prostaglandin. Timolol-prostaglandin combinations are widely available internationally, but it is unclear if companies will again attempt to get one approved here. Recently, however, a phase 3 trial of a prostaglandin-Rho kinase inhibitor (netarsudil 0.02%-latanoprost 0.005% ophthalmic solution [Roclatan; Aerie Pharmaceuticals]) met its main goal: an IOP lower with the fixed combination than with either component for each of nine different time points over a 3-month period. This product may become the first fixed combination containing a prostaglandin to obtain approval in the United States (see Dr. Bacharach's article on p. 40).

As new medications are developed for the reduction of IOP, we should expect to see companies develop additional fixed combinations to increase our options for convenient, effective medical therapy. The possibility of sustained delivery as an alternative to eye drops presents another clear opportunity for future combination therapies. Ideally, we will be able to prescribe combined, optimal therapy for individual patients based on what will work best for them. ■

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