Efforts evolve to control IOP in glaucoma

by Thomas Bournias, M.D.

Recent research supports lowering IOP as the best way to reduce glaucoma-related blindness

In a world where glaucoma remains a leading cause of blindness, it is more important than ever for ophthalmologists to use the best evidence-based approaches. The most effective treatments to prevent glaucoma-related blindness, according to the research, continue to center around lowering intraocular pressure (IOP).

As a worldwide problem, glaucoma affects millions of people. The U.S. impact includes 4 million people or 3% of the population who have glaucoma. The U.S. age of onset is the relatively young early 50s. Many people with glaucoma do not know that they have the disease, and about half of them remain undiagnosed.

Worldwide, researchers estimate that about six million people are blinded by glaucoma. This major health care challenge is exacerbated by obstacles to health care and poor patient adherence to therapy. Some fault in adherence problems may lie with physicians for poor explanations about the need for treatment and the impact of medical inconsistency on their prognosis.

Glaucoma patients steadily lose their visual function throughout the course of the disease. This results in continued on page 3
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large income losses for them, and those losses are expected to grow. Some estimates report that in the next 12 years there will be a 50% increase in visually impaired U.S. glaucoma patients as a greater number of older Americans develop the disease. These developments have sharpened our focus in aiming to diagnose this disease earlier and begin treatment sooner and more aggressively.

**Target pressure targeted**

For many years ophthalmologists have aimed to lower the absolute pressure or the mean pressure. Lately, IOP fluctuations have drawn greater attention from researchers, including daily fluctuation of the diurnal curve and long-term fluctuations from visit to visit.

Recent evidence has supported the view that IOP fluctuations can result in a loss of visual field. For example, a recent study in Minnesota looked at almost 300 glaucoma patients and divided them into those with blindness in one or both eyes and those with no blindness. These two groups were followed to track the extent of their IOP fluctuations, and the authors concluded that although both patient groups had similar mean pressures, those with blindness had a larger fluctuation. The study authors concluded that clinicians need to be more aggressive with some patients, and they need to monitor their patients’ visual fields more closely.

This development raised the question of how ophthalmologists should set a target pressure. Currently, many clinicians use a target pressure, but it is unclear on what that is based.

A recent study of managed care plans in southern California found that most glaucoma patients were not adequately treated. For example, half the patients with mild glaucoma had pressures that were 20 mm Hg or higher. Half of moderate to severe glaucoma patients had IOPs of 19 mm Hg or higher. Many patients who demonstrated pressure of 30 mm Hg or higher had no intervention on half of their visits. These findings demonstrated the importance of not only knowing what the best treatment is but aggressively pursuing it as well.

For clinicians who are going to aggressively seek the best target pressure for their glaucoma patients, the literature says little about how to find and set that target.

Important information has emanated from five major trials sponsored by the National Eye Institute. These can give ophthalmologists some idea about what to do.

The Early Manifest Glaucoma Trial (EMGT), which looked at newly diagnosed glaucoma patients, had two arms examining both untreated patients and treated patients. The study concluded that the patients who were treated had on average a 25% reduction in pressure. The study showed a 25% reduction in IOP resulted in less progression for newly diagnosed glaucoma patients.

The Collaborative Initial Glaucoma Treatment Study (CIGTS) also demonstrated that an aggressive 38% to 46% reduction allowed more patients to maintain even more stability and less visual field progression.

The Advanced Glaucoma Intervention Study (AGIS) examined advanced glaucoma patients and found that if IOP was kept consistently below 18 mm Hg, stability was possible, even among those advanced patients.

Patients not even diagnosed with glaucoma can apparently benefit, according to the Ocular Hypertension Treatment Study (OHTS), which found that patients without glaucoma but with an elevated IOP could maintain stability when they achieved a 20% reduction in pressure.

Finally, the Collaborative Normal-Tension Glaucoma Study (CNTGS) demonstrated that patients with normal pressure and glaucoma can have their visual field loss stabilized with a 30% reduction in pressure.

These recent data provide reference numbers for clinicians when looking at their own patient population, especially for ophthalmologists who utilize target pressure. The AGIS findings included the demonstration that patients who kept IOP under 18 mm Hg for the first six years of treatment did not have progressive visual field loss. The same group of patients had an average pressure of 12 mm Hg. This clearly demonstrated an advantage in keeping the pressure consistently under 18 mm Hg in advanced glaucoma patients.

Another significant finding in the EMGT and other studies was that among patients with pressures ranging between 15 mm Hg and the mid 20s, a 1 mm Hg reduction results in a 10% reduction in the risk of progression in visual field loss. A meta analysis of all five major studies showed that, in general, every 3 mm Hg of pressure reduction conferred a 50% reduction in progression.

Understood in their proper context, these studies show that a little bit of pressure reduction can have a large impact over the long term for many glaucoma patients.

**Where to set the pressure**

Clinicians trying to decide how much they should get their glaucoma patients’ IOPs down should examine the data in the literature because they depend on the practice approaches of others.

The preferred practice pattern of the American Academy of Ophthalmology, in general, suggests an initial 20% to 30% pressure reduction. But many glaucoma specialists aim for a 40% reduction in advanced cases and high IOP cases.

The best approach is to tailor treatments to individuals based on a combination of the IOP, the level of glaucoma, and family history.

Some clinicians have sought a target-setting formula, such as the authors of the CIGTS findings. That study’s formula set the target pressure based on the height of the baseline pressure and the height of the visual field score, and...
showed the plausibility of mathematical formulas for establishing IOP targets.

But that approach and others like it do not pretend to be an exact science, although it demonstrates and reinforces that as glaucoma worsens and as the pressure rises, ophthalmologists should set the target pressure lower.

Other approaches have devised treatment strategies based on the severity of the glaucoma. These approaches stratified glaucoma patients based on the severity of their condition and illustrated what target pressure would be most beneficial, either as a range, or a percent reduction in pressure.

These published guidelines are now widely used in the United States.

Fluctuation becomes a focus
Earlier pushes to lower the absolute pressure or mean pressure in glaucoma patients have evolved to a growing focus on understanding the impact of fluctuations in IOP. Although much remains unknown, some data shows that fluctuations—whether diurnal or between office visits—have resulted in progression of visual field loss.

Clinicians have long known that patients with glaucoma tend to have more fluctuation in their IOP. Even 50 years ago, researchers found three-fold IOP fluctuations in glaucoma patients throughout the day compared to people without glaucoma.

Additionally, a number of studies have demonstrated progression of visual field loss in patients who have more fluctuation than in those who do not.

One such 2000 study that is frequently referred to is one that looked at about 78 patients who were taught to check their own pressure at home five times a day for five days. This information was stored and these patients were followed for up to nine years. These patients had similar baseline IOPs in the office so it was thought they were similar, but the group that had the most progression was the group that had fluctuations of 12 mm Hg or more. Among these patients, 88% progressed while only 12% remained stable. Another group of patients with fluctuation of 8 mm Hg or less had progression in about half of the patients over the nine years. This study appeared to link increased progression with more IOP fluctuation.

Another 1999 study showed similar findings over two years in 76 patients. The research stratified patients by the amount of IOP fluctuation and found that the group that had the most fluctuation had the most worsening of the visual field over the 24 months.

A CIGTS analysis found that patients who had more fluctuation over the course of the six-year study tended to have worsening of the visual field. The 28% of patients who never had pressure over 17 mm Hg showed the most stability over the six years.

A post hoc analysis of the AGIS data found similar results. Among advanced glaucoma patients, the analysis showed that patients who demonstrated at least 3 mm Hg inter-visit variability had a greater rate of visual field loss progression.

An apparently contradictory piece of evidence was seen in the EMGT in which half of the 250 patients were treated and half untreated. This study did not demonstrate an association between field loss and fluctuation in IOP. However, it is important to keep in mind that the EMGT had a relatively low baseline of 20.5 mm Hg and half of these patients had normal pressure glaucoma.

Overall, researchers see that fluctuation control can be helpful in many types of glaucoma, while uncontrolled fluctuation can be a major risk factor for progression.

References
Primary therapy in glaucoma is selected based on several goals

The first goal is to lower the IOP as much as possible with the least amount of medication. Clinicians prefer agents that are highly predictable in terms of patient response because patients react better to immediate results and are more likely to take their treatment seriously and stick with it. The consistency is based on how well the medication lowers the pressure throughout the day. This consistency will increase the accuracy of the one-time measurement clinicians rely on to track progression in intraocular pressures.

Additionally, ophthalmologists have sought medications that will make it more likely—or at least not significantly less likely—that patients will remain compliant with their treatment regimen. This is a critical point because the best medical therapy is useless if patients are not able to comply with it for any reason on an ongoing, long-term basis.

These factors limit clinicians’ options for initial therapy to prostaglandin analogs, beta blockers, and alpha agonists, all of which have proven efficacy in controlling intraocular pressure for a patient who is using them for a first line or as a monotherapy option. These medications also are capable of hitting the initial 20% to 30% IOP target reduction goals set by the American Academy of Ophthalmology.

Proof is in the study

Study results for prostaglandin analogs show why they are often chosen as a first line therapy. When compared to beta blockers such as timolol, bimatoprost, latanoprost, and travoprost (various manufacturers) all lowered intraocular pressure significantly more. Latanoprost and travoprost lowered pressure about 1 mm Hg more than timolol. Bimatoprost lowered pressure on average about 2 mm Hg more than timolol. The first line use of prostaglandins is further cemented by a solid safety profile.

These medications also meet ophthalmologists’ initial goal to reduce IOP as much as possible, when medical treatment monotherapy is the preferred approach.
Always ask your patients what time of day they take their other medications, such as their blood pressure and cholesterol drugs. Physicians also should ask patients if there is someone who can help them with administering the eye drops. Everyone has trouble self-administering the drops, even physicians. So try targeting their dosing for any time of day when they are regularly visited by someone who can help them.

Assisted dosing can also help decrease side effects and increase the consistency that is so important when taking the medication.

Switching medications considered

Another important alternative to subresponsive initial therapy is to switch patients’ monotherapy. However, research has indicated that when switching the monotherapy, it is often worthwhile to attempt to keep patients within the prostaglandin class. An example of this was a study of latanoprost non-responders who switched over to bimatoprost.

Physicians should first remember that if there is an initial non-response rate with these drugs—particularly with latanoprost—it is important to determine your treatment goal. Patients started on latanoprost who fail to meet a target pressure, including those who get some but less-than-desired pressure reduction, may appear unquestionably worthy of the trouble of switching to another prostaglandin analog or even a beta blocker. This study found that the non-responders on average have a significant reduction in IOP when switched from latanoprost to bimatoprost.

During chronic disease drug therapy, clinicians should aim for simple dosing to enhance consistency with maximum efficacy and minimal side effects. The challenge in glaucoma is that it is asymptomatic, so part of a clinician’s job is to emphasize to patients at the beginning that while having glaucoma is not a death sentence and it is treatable, they also have to keep up with therapy and come back for the exam, visual field testing, and imaging.

Unfortunately some therapies provide more problems than solutions in the beginning. That is why it is important to keep patients looking ahead 5 or 10 years, and tell them they may have to go through several non-medical and medical therapies for the long term. This treatment reality means that switching medications has to include the goal of targeting IOP with the fewest number of medications.

Another study moved latanoprost patients to bimatoprost when the latanoprost was not providing effective results. Patients had IOPs in the mid-20s on latanoprost and dropped to an average of 18 mm Hg on bimatoprost. One interesting finding of this research was that when the patients were crossed back after their pressures had dropped on Xalatan (latanoprost, Pfizer, New York), the pressures went right back up on latanoprost.

The goal of these studies and of many physicians is to keep patients on one medication and the most effective drug they can find. This goal is important, although it doesn’t override the reality that sometimes monotherapy is not enough, especially when trying to meet milder 20% reduction goals set by OHTS and more aggressive target IOPs in the CIGTS.

For example, in CIGTS, nearly 75% of the patients needed two medications just to achieve a desired IOP reduction. Frequently effective drug therapy can be achieved with monotherapy and that is best when possible, but a significant minority of 30% or more will need that additional therapy.

Overall, clinicians should pursue glaucoma care with a building block approach that starts when they first look to initiate medical therapy and consider what might happen to the patient in the future. Whatever treatments are tried first are going to influence the success of later treatment modalities. That is why clinicians should take their time in the beginning of each patient’s treatment to figure out what medication works best for that individual.

References

1 Bimatoprost, Latanoprost, Travoprost: Phase III FDA Results, Drug approval package information available from the CDER.
2 Robin AL, Covert D. Does adjunctive glaucoma therapy affect adherence to the initial primary therapy? Ophthalmology. 2003;112:863-868.
5 Gandolfi SA, Cimino L. Effect of bimatoprost on patients with primary open-angle glaucoma or ocular hypertension who are nonresponders to latanoprost. Ophthalmology. 2003;110:609-614.
An increasingly common occurrence in most glaucoma practices is the appearance of a new patient who is referred for care and is already on multiple medications and trying to balance them and their different doses. Knowing how to address this patient’s needs is the art of glaucoma care.

In general, all glaucoma patients are trying to reach the primary goal of keeping the disease from progressing. That goal of intraocular pressure control is why there has been growing use of medications and other modalities.

Even from early in care there are many treatment options, including selective laser trabeculoplasty (SLT). A lot of clinicians consider SLT as a treatment option if the pressure is not low enough from a monotherapy drug. When the IOP is controlled, continuing on that track is something that works for a lot of patients.

When medication is the focus of treatment we need to concentrate on what drug options we have for the patient and how to decide between switching medications or adding other medications to unresponsive primary therapy.

Many ophthalmologists try both approaches. They may switch from the drug class, add a drug, or even do both of those things.

Choosing the medication is key
For most clinicians, searching for the medication is the favored way to find the ideal pressure. Those that take this approach have many options. Some research has indicated that adding a second drug when the patient is unresponsive on the first is counterproductive. That research indicates that additional medications can actually result in a loss of some of the pressure control clinicians were aiming to achieve.

So balancing the right medications together is the art of what we’re trying to do with the available medications.

Among the considerations clinicians should have when a patient is on monotherapy and the pressure remains too high is what action will be the most efficacious, cost effective, and tolerable for the patient.

Research on balancing the pressure indicates that an ideal approach would maximally decrease the aqueous inflow and maximally increase the outflow preferably from the eye through the trabecular meshwork and Schlemm’s canal.

We prefer to increase the conventional outflow to preserve this avenue of pressure control. If you can do this, it will result in a well balanced pressure.

Medications which increase the outflow through the meshwork include pilocarpine (various manufacturers) and dipivefrin (various manufacturers). These effectively shut off the aqueous production. Combinations of these drugs were released many years ago and seemed to make sense, based on the research.

In terms of the mechanisms of action, decreasing the aqueous production is achieved primarily through carbonic anhydrase inhibitors, alpha agonists, and beta blockers. Because prostaglandin analogs increase the uveoscleral outflow, it is important to determine which drugs work well with them. The drug clinicians most frequently reach for, based on the formulary review, is a beta blocker. The reasons for that choice are not completely clear.

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Patients on a prostaglandin analog at night are frequently put on a beta blocker because it works well and clinicians are very familiar with it. These drugs usually have a low co-pay because they are formulary drugs.

The research on combinations continues to evolve. The data on combining timolol (various manufacturers) with a prostaglandin analog drug has shown limited increased efficacy. The addition of a beta blocker with a prostaglandin analog, according to research, provides up to 1.5 mm Hg of increased pressure reduction. This impact should not be underestimated because each increase in a millimeter of mercury reduces the visual field by about 10%.

The impact of adding alpha-adrenergic agonists, such as brimonidine (various manufacturers), to prostaglandin analogs should not be overlooked. There is very good data to show that brimonidine is a great drug to be added into a prostaglandin analog, and the average pressure reduction is greater than that which you see with beta blockers.

Carbonic anhydrase inhibitors have received much attention over their role as an additive in prostaglandin analogs. That role is important for clinicians to consider, as there is some evidence it contributes to the similar outcomes seen in brimonidine use.

It is important to consider the impact of patients being burdened with multiple medication bottles. I have found that adding a third bottle can create problems for the treatment because at that point they frequently lose bottles or otherwise mix up their medications. These reasons are why fixed combinations have a place with our patients. Among the fixed combinations ophthalmologists have already had wide experience with are Combigan (brimonidine/timolol, Allergan, Irvine, Calif.) and Cosopt (dorzolamide hydrochloride–timolol maleate ophthalmic solution, Merck, Whitehouse Station, N.J.).

Clinicians considering fixed combination drugs take into account a number of factors. Among the issues that arise are whether patients will be faced with one bottle or two, the fact that combination drugs have a single co-pay, and that there is one less step for patients to remember when using a combination drug therapy.

Combination therapy makes particular sense when moving a patient who is already on one agent to multiple drugs. The search for a complete pressure solution has almost always led me to reach past monotherapy and go directly to a fixed combination. But the question remains whether this approach is better than trying each individual agent first.

Beyond the clinical evidence of efficacy, physicians should consider the patients’ realities and the clinical realities. Patients have to travel to their physician’s practice, find parking, pay for it, and make time for that, just to get their pressure checked on a regular basis. Sometimes it is worth it to choose a fixed combination from the beginning to cut down some of the hassle for them.

The research has shown that Combigan, through 12 months, is effective for this purpose. The study of 1,159 patients found that the peak effect pressure reduction for timolol or brimonidine used alone was 21% from baseline. Brimonidine was used three times a day, compared to the fixed combination of Combigan, which was dropping IOP down to about 31% of baseline.

That amount of reduction is very good for an individual agent and close to the level we have seen in the prostaglandin analog studies.

The combination provided the same peak pressure reduction throughout the 12 months of the study, and it was consistently better pressure reduction than each monotherapy used alone.

Another aspect of the research is that it looked at pressure throughout the day and found that the pressure curve was lower for the fixed combination of Combigan by several millimeters of mercury at almost all times during the day except in the late afternoon. Overall it was a lower curve than what we have seen with brimonidine alone.

Throughout one study, the mean IOP was consistently lower in the fixed brimonidine/timolol group than in either of the monotherapy groups.

References
A growing amount of information is available showing a good use and tolerability profile for the combination of brimonidine and timolol.

One recent study of approximately 1,200 patients followed for about a year compared the combination Combigan (brimonidine/timolol, Allergan, Irvine, Calif.) to Alphagan (brimonidine tartate ophthalmic solution, Allergan, Irvine, Calif.) and found the combination was generally well tolerated.¹

It is important to look specifically at a few of the unexpected results, which reinforce the importance of asking specific questions of your patients when giving them new medications. In the example of a beta blocker, it is important to ask patients if there are any changes in their breathing, or if they are using an inhaler, in which case the beta blockers should be stopped.

In this study there were two instances of treatment-related serious adverse events, including respiratory distress secondary to emphysema and another patient with nausea, sweating, and tachycardia.

When the study compared the Combigan combination to brimonidine, it found Combigan produced fewer side effects, including less oral dryness, less conjunctival follicles, less allergic conjunctivitis and puritus, and less conjunctival hyperemia. The only side effect that occurred more often in Combigan was ocular stinging, which is to be expected in beta blockers.

Theory on varying tolerability

We have been quite interested why patients put on Combigan have less allergic response over time. Some explanations for this include previous research that looked at the effect of certain molecules on conjunctival cells and found that brimonidine molecules cause cells to shrink and that permits inflammatory mediators to get to the deeper tissue, which may result in the allergic response.² The addition of timolol blocks the shrinking of cells and that may be the scientific explanation for why we see such a difference in the number of patients that are allergic.

It has also been shown in patients using fixed combination travoprost and timolol that there was less red eye and other problems, so that may be due to the beneficial effect of the timolol.

Another study randomized patients to Combigan and Cosopt (dorzolamide hydrochloride–timolol maleate ophthalmic solution, Merck, Whitehouse Station, N.J.) and examined the local side effects of stinging, burning, and unusual taste. In all three areas the Combigan performed better.³

Other research instilled drops of Combigan and Cosopt and waited 30 to 40 seconds before asking patients which one was more comfortable. A clear majority of Combigan patients reported better results.⁴

Another Merck study looked at a fixed combination of Cosopt compared to the combination of timolol and Alphagan and found very similar tolerability results as the other studies.⁵ In general, it found a less-than-statistically significant pressure lowering. However, it also found much less taste perversion or burning in brimonidine and timolol compared to Cosopt. Also, there was no statistically significant difference in the rate of conjunctival follicles or other side effects.

“This study found that the incidence of treatment-related adverse events associated with conjunctival allergy or inflammation was lower in the fixed combination group (26%) than in the brimonidine group.”

Paul J. Harasymowycz, M.D.
Cases
Several case studies may better illuminate some of the impacts and appearances of these allergy differences.

One patient of mine who had a sulphur allergy developed a serious reaction to Cosopt. This experience and others like it illustrated for clinicians how important it is to look for allergies in recipients of both fixed combination medications. These allergies need to be addressed because the overall benefit of a single bottle is critical to increase compliance and thereby improve outcomes.

Another case of a 64-year-old female patient with migraines—which are a known added risk factor—was tested with a formula to calculate target IOP. This formula uses the maximum pressure that the patient has ever had and adds to it the mean deviation from the visual field. So in this patient we wanted to reduce the pressure by 40%.

This was a difficult case where the maximum pressure was 25 mm Hg, she had already undergone SLT, and she was taking Xalatan (latanoprost ophthalmic solution, Pfizer, New York) and Cosopt. Her mother was blind from glaucoma.

We used mini-diurnal tension curves—which we encourage—through having the patient return at different times on subsequent visits or by keeping her for half of a day and measuring throughout. We found her IOPs were fluctuating between 17 mm Hg and 19 mm Hg in the right eye and 17 mm Hg and 20 mm Hg in the left eye.

The patient was followed with serial HRT measurements. Checking the RNFL thickness showed a decrease over time, which caused us to be worried about her optic nerve.

We found similarly concerning results from her GDx scan. The visual field in white-on-white perimetry was normal, but a larger inferior nasal step developed over time.

It all indicated that the patient was definitely getting worse. But the question was what treatment we should attempt next.

The availability of safer surgeries, including non-penetrating surgeries, allowed us to start talking to the patient about her options. At this point, she admitted that she wasn’t taking her drops as much as she should have been. In addition, she was adamant that the Cosopt was causing burning.

In the past, when we were confronted with strong complaints of discomfort from combination patients we would tell them whatever it took to get them to keep taking the needed medication. However, since we now had an option with the Combigan, we were able to switch her Cosopt to Combigan and since then she has been much more comfortable. In addition, we saw that her discomfort from the Cosopt was the likely reason her pressures were fluctuating because she wasn’t using her medications consistently. After the switch her IOPs remained in a more reasonable target pressure range.

So Combigan is tolerable. Some develop allergies but at a much lower rate than brimonidine.

In closing, always ask patients specific questions about side effects. When a patient is getting worse, make sure he or she is being compliant before moving on to the next step.

References
1 Sherwood MB, Craven ER, Chou C, et al; for COMBIGAN Study Groups I and II. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol. 2006;124(9):1230-1238.
2 Alvarado JA. Reduced ocular allergy with fixed-combination 0.2% brimonidine-0.5% timolol. Arch Ophthalmol. 2007;125:717.
4 Chan K, Testa M, McCluskey P. Ocular comfort of combination glaucoma therapies: brimonidine 0.2%/timolol 0.5% compared with dorzolamide 2%/timolol 0.5%. J Ocul Pharmacol Ther. 2007;23(4):372-376.
5 Sherwood MB, Craven ER, Chou C, et al; for COMBIGAN Study Groups I and II. Twice-daily 0.2% brimonidine-0.5% timolol fixed-combination therapy vs monotherapy with timolol or brimonidine in patients with glaucoma or ocular hypertension: a 12-month randomized trial. Arch Ophthalmol. 2006;124(9):1230-1238.
The combination of brimonidine and timolol, known as Combigan (Allergan, Irvine, Calif.), was approved in Canada four years ago. As a result, there is considerable clinical research and experience with this agent.

Recent research, called the Combigan Early Experience Data, CEED 1 and CEED 2, were phase four clinical trials with the purpose of looking at real world efficacy, tolerability, and safety of the fixed combination. The study examined how the fixed combination might fit within our treatment regimen and real world expectations.¹

The study was designed as a two-month surveillance study. The inclusion criteria were patients who needed pressure lowering either adjunctively or when switching from ineffective monotherapy in their drug regimen. The only exclusion criteria was a contraindication to either of the two components—the beta blocker or the alpha-adrenergic agonist. Patients also were excluded if they had a known allergy to either one.

The study began with enrolling patients and measuring baseline pressures, as well as pressures at one month and two months.

The final enrollment of 2,133 patients from 123 centers across Canada was a fairly large number, which provided some statistical force to this phase four open label study.

**Significant findings**

The overall average IOP lowering from baseline that the Combigan provided was an additional 4.1 mm Hg IOP (P<.0001), an almost 18% pressure lowering. The number of eyes tested at month two was 3,136.

The general “ideal” standard for further IOP lowering with an additive or adjunctive agent is accepted to be approximately 15%. That figure was developed by previous consensus of a number of glaucoma sub-specialists. It is rooted in the principle that at an IOP of 20 mm Hg, the error of the best calibrated Goldmann tonometer represents a 1 to 2 mm Hg error or under 10%. An IOP lowering of 15% by an additive agent would be well beyond this potential measurement error. The average of 18% IOP lowering achieved in all the patients exceeded this standard expectation for efficacy and was statistically significant P<.0001.

**Target pressure view**

The findings were significant for ophthalmologists who prioritize target pressures as well. Using the standard for efficacy suggested by the Advanced Glaucoma Intervention Study (AGIS) of 18 mm Hg or lower at all visits, the study also found that a significant number—77% of patients—were able to attain pressures of 18 mm Hg or lower. That compared to the 41% of patients at that level at the beginning of the study.

The overall pressure lowering goal of at least 15% was achieved by a significant 54% of patients.

The overall results also showed that 20% of patients demonstrated variations in responsiveness or compliance, and some had no improvement of a worsening of pressure. That included about 10% of patients who had an increase in pressure when they were switched to Combigan or when it was added to their drug regimen.

*Research found that when used as monotherapy, both Combigan and Cosopt significantly reduced IOP from baseline at month one and month three*
These results came in the context of 80% of patients showing at least some improvement from their previous drug regimen.

**Combination comparison subgroup**
Another part of the study was a subgroup comparison of 124 patients and almost 200 eyes of patients who were only on a fixed combination of dorzolamide and timolol, Cosopt (Merck, Whitehouse Station, N.J.). These patients were not achieving target pressures, so the fixed combination of dorzolamide and timolol was discontinued and they were switched over to the fixed combination brimonidine/timolol.

This subgroup efficacy comparison fits the U.S. market where there are two fixed combinations available to ophthalmologists. It highlights that these are two different medications with two sets of indications and contraindications for the safety of our patients.

When Cosopt was removed from the treatment regimen and patients were switched to Combigan, Combigan provided an additional IOP reduction of 11%, which represented a 2.5 mm Hg IOP reduction ($P<0.0001$). There were 538 eyes of 366 patients studied.

It also found target pressure reductions of 18 mm Hg or more among a larger number of Combigan than Cosopt patients at two months. Seventy-four percent achieved IOP of 18 mm Hg or lower from baseline with Combigan compared with 52% from baseline for Cosopt.

Additionally, 44% of patients achieved at least 15% additional pressure lowering after the switch.

**A second look**
Another recent study was a randomized, masked three-month clinical approach that pooled data from 10 sites. In the study, patients who were not controlled on medical therapy were randomized into two groups. One group of patients who were not at target pressure on prostaglandins had when either Combigan (n=37) or Cosopt (n=42) added to their regimen. Another group of patients with uncontrolled pressure who were not on prostaglandins were put on one of the two fixed combination medications as “monobottle” therapy (Combigan n=54, Cosopt n=47).

The first arm of the study looked at how efficacious the two fixed combinations available are when added to a prostaglandin, while the other arm looked at a head-to-head comparison of Combigan and Cosopt.

Both arms measured peak pressures and examined results at one month and three months.

The head-to-head comparison of the two combination drugs as “monobottle” therapy found both provided excellent results. The Combigan group had slightly better and statistically significant pressure lowering compared to baseline at three months. Combigan recipients’ mean IOP reduction from baseline at three months was 7.8 mm Hg, which represented a 34% IOP lowering from baseline, while Cosopt’s mean IOP reduction of 6.7 mm Hg was a 28% IOP reduction.

As adjunctive therapy to a prostaglandin, both medications showed excellent additivity. However, Combigan lowered the IOP 6.9 mm Hg (31% further IOP lowering) from baseline compared to Cosopt, which lowered the IOP 5.2 mm Hg (25% further IOP lowering) from baseline.

**References**