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Doctor

José Luis Salazar

Director de División de Nuevas Creaciones (C)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

E. S. D.

Referencia: Expediente No. 12.122.166
Solicitud de Patente de Invención titulada: "Combinación triple para reducir la presión intraocular"

Solicitante: Allergan, Inc.

MEMORIAL DE ALCANCE

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, como complemento al recurso de reposición presentado para este asunto, allego una declaración de la Dra. Margot Goodkin, MD, PhD y experta en el campo de la oftalmología y glaucoma y en investigación y desarrollo clínico.

Con la mencionada declaración y anexos se muestra con mayor claridad el nivel inventivo de la presente solicitud por cuanto queda claro el efecto inesperado que demuestra el presente invento.

La siguiente es una de las afirmaciones de la Doctora Goodkin en esta declaración.

"La mayor efectividad mostrada por la triple combinación, que administra bimatoprost dos veces al día, para tratar pacientes con glaucoma y/u OHT (por su sigla en inglés) mas severo comparada con aquella del Combigan®, un fármaco ya efectivo y exitoso para disminuir la IOP (por su sigla en inglés), fue sorpresiva e inesperada."

BAKER & McKENZIE

Agradezco que se tenga en cuenta la anterior declaración al momento de decidir sobre la patentabilidad de la presente solicitud.

Atentamente,

ÁLVARO CORREA ORDÓÑEZ
C.C. No. 79.143.366 de Usaquén
T.P. 20.281

Anexos:
- Declaración de la Dra. Goodkin
- Anexos A, B, C, y D

3068186-v1\BOGDMS

DOCKET NO. 18637CIP (AP) PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Allergan, Inc.	)	Group Art Unit: 1621
Serial No.:	14/147,302	)	Examiner: Fay A. Zohreh
Filed:	January 3, 2014	)	Conf. No.: 1018
For:	COMPOSITIONS AND METHODS FOR LOWERING INTRAOCULAR PRESSURE	)	

DECLARATION REGARDING FACTS RELEVANT TO PATENTABILITY UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PURPOSE OF DECLARATION

1. This declaration is to establish evidence of patentability of one or more claims of the above referenced application, and to show the surprising and unexpected results thereof.

2. The person making this declaration is Dr. Margot Goodkin, MD, PhD, an expert in the field of ophthalmology and glaucoma, and clinical research and development. She is currently employed at Allergan, Inc. as a Medical Director in Ophthalmology.

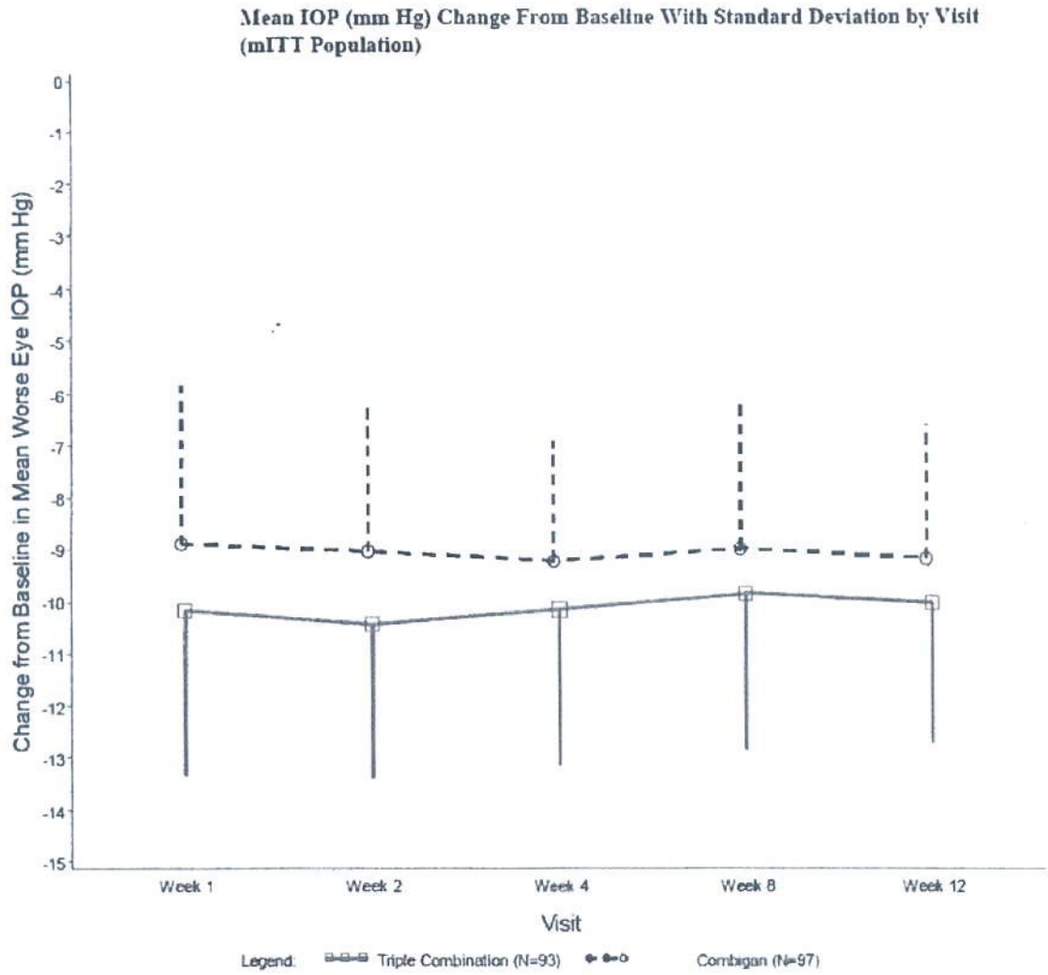
TESTIMONY OF UNEXPECTED RESULTS

3. The fixed combination referred to in the foregoing as "Triple Combination" is an ophthalmic drug in development at Allergan, Inc. for the treatment of patients with glaucoma and/or ocular hypertension ("OHT") to lower intraocular pressure ("IOP"). The Triple Combination composition comprises a fixed combination of about 0.01% bimatoprost, about 0.15% brimonidine tartrate, and about 0.68% timolol maleate, and uses about 50 ppm benzalkonium chloride ("BAK") as a preservative.

4. Elevated IOP is a major risk factor for the development and progression of glaucomatous optic neuropathy. There is a high correlation between higher levels of IOP and increased visual field loss (Zimmerman and Fechtner, 1997; submitted as Exhibit A), and reduction of IOP is important to the prevention of progression to advanced glaucomatous disease (Heijl et al, 2002; submitted as Exhibit B). Pharmacological means of lowering IOP are typically attempted before escalating treatment to laser or surgical options. In patients who require more than one medication to lower the IOP, physicians will often seek to use medications with complementary mechanisms of action. The three active ingredients in Triple Combination decrease IOP via complementary mechanisms of action to both decrease aqueous humor production and increase aqueous fluid outflow from the eye.

5. A Phase III clinical trial was conducted to compare the efficacy and safety of Triple Combination to that of an existing fixed combination drug—Combigan® (0.2% brimonidine tartrate, 0.68% timolol maleate)—in the treatment of patients with glaucoma and/or OHT. The trial was a 12-week, multicenter, double-masked, randomized, active controlled, parallel-groups study comparing twice-daily bilateral administration of Triple Combination with Combigan® in patients with primary open-angle glaucoma or ocular hypertension. There were up to 8 scheduled visits (screening, washout safety visit [if needed], baseline [day 0], and weeks 1, 2, 4, 8, and 12/study exit), with 192 enrolled patients (of which 175 patients completed the study).

6. At the study outset, there were no statistically significant differences in the baseline IOP between the Triple Combination and Combigan® treatment groups. After 12 weeks of treatment, however, Triple Combination showed a statistically-significantly greater IOP lowering effect than Combigan® (0.85 mmHg, p=0.028).



mITT= All randomized patients with at least 1 post-baseline efficacy evaluation
Week 1 p=0.006; Week 2 p=0.001; Week 4 p=0.019; Week 8 p=0.047; Week 12 p=0.028

Figure 1

7. As shown in Figure 1 above, patients administered Triple Combination had a greater IOP lowering at all measured time points compared to those administered Combigan®.

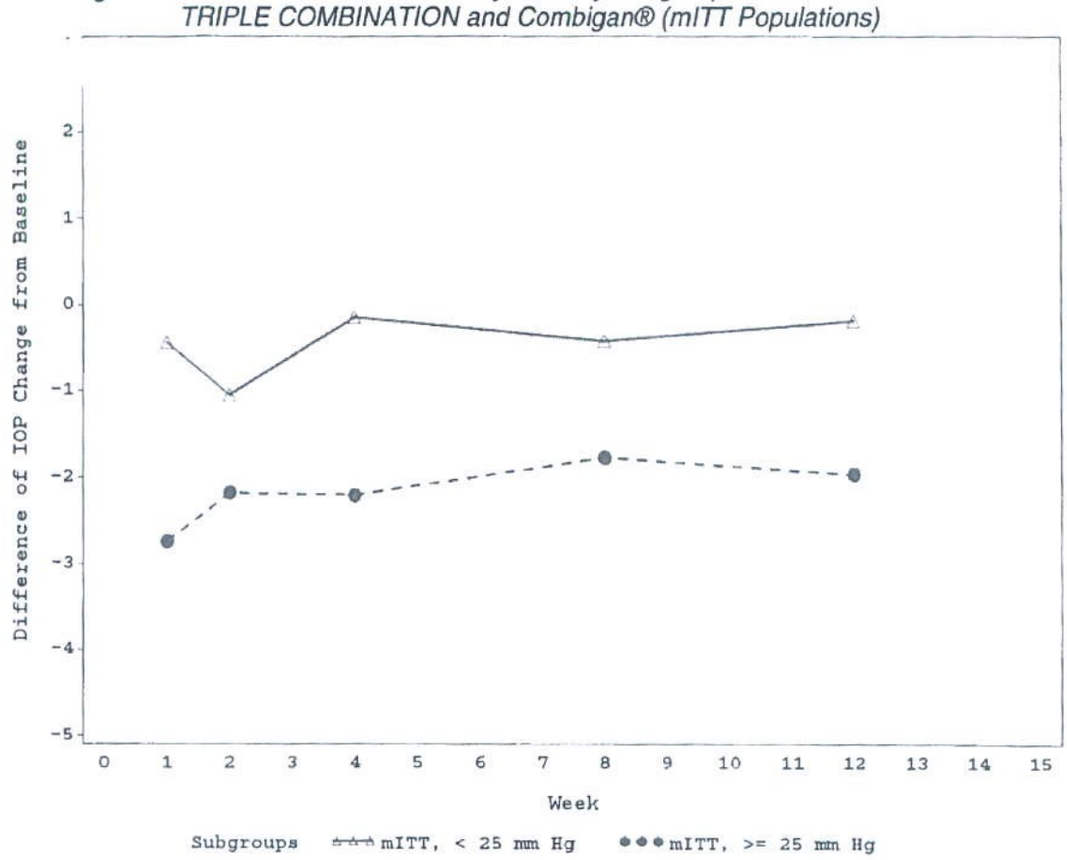
8. The additional efficacy shown by Triple Combination in reducing IOP was unexpected, as it was not certain that the addition of bimatoprost to a twice-daily dosed fixed combination such as Combigan® (brimonidine/timolol) would necessarily lead to any additional reduction in IOP.

9. To the point above, studies have shown that bimatoprost administered twice daily is less effective than bimatoprost administered once daily. In an article by

Sherwood and Brandt (attached hereto as Exhibit C), the authors state that "reasons for loss of efficacy with twice-daily versus once-daily dosing of bimatoprost are unknown" and that "regardless of the mechanism for the dosing effect, it is clear that bimatoprost should be used once daily". See Exhibit C Figures 1, 2 and 3. In an article by Higginbotham et al. (attached hereto as Exhibit D), patients administered 0.03% bimatoprost only once daily ("QD") showed a statistically significantly lower mean IOP than bimatoprost administered twice daily ("BID"). See Exhibit D, Figure 2. Because of the counterintuitive result in bimatoprost's dose response—BID administration having less IOP-lowering effect than QD—it was surprising and unexpected that BID administration of Triple Combination (containing bimatoprost in combination with brimonidine and timolol) nevertheless resulted in an additional reduction in IOP as compared to Combigan®.

10. Returning to the trial, additional analyses were performed on patient subpopulations with more severe disease (where the mean baseline IOP was greater than or equal to 25 mmHg) in comparison to patients with less severe disease (mean baseline IOP less than 25 mmHg). These results are shown in Figure 2 below, which plots the difference in IOP change from baseline (Triple Combination minus Combigan®; a negative number favors Triple Combination) in each of the patient subpopulations (more severe disease and less severe disease).

Change from Baseline in Mean Worse Eye IOP by Subgroup Mean Difference between TRIPLE COMBINATION and Combigan® (mITT Populations)



[a] Difference = TRIPLE COMBINATION - COMBIGAN.

Figure 2

11. With reference to Figure 2 above, the patient group with more severe disease (IOP≥ 25mmHg, denoted with the hatched line), showed an approximately 2-3 mm Hg greater IOP-lowering effect from baseline with Triple Combination than with Combigan® ($p <= 0.011$ at all visits). IOP at Week 12 (the primary endpoint), favored Triple Combination over Combigan® by 1.96 mmHg ($p=0.002$). The patient group with less severe disease (IOP<25 mmHg, denoted with the solid line) showed no clinically meaningful difference (≤ 1.05 mm Hg) between Triple Combination and Combigan® in IOP change from baseline.

12. Even though there was a slightly higher overall incidence of adverse events compared with Combigan®, the majority of patients on Triple Combination reported that it was comfortable, and patients were willing to continue therapy. Especially in patients with more severe disease, the greater IOP-lowering effects of Triple Combination may outweigh a slight increase in mild ocular side effects.

13. The greater effectiveness demonstrated by Triple Combination, which administers bimatoprost twice daily, in treating patients with more severe glaucoma and/or OHT compared with that of Combigan®--an already effective and successful IOP-lowering drug—was surprising and unexpected. These results are clinically significant, as landmark clinical trials have shown that patients with elevated IOP (e.g., IOP ≥ 25 mmHg) are likely to be at a greater risk of disease progression. Lowering this IOP can therefore lower the risk of progressing to loss of visual function. Additionally, patients with elevated IOP often require multiple medications in order to achieve a target IOP. Providing Triple Combination to patients with more severe glaucoma and/or OHT could therefore not only simplify their treatment regimen (only one fixed dose combination to administer versus three different bottles) but also offer an unexpected opportunity to achieve a required IOP reduction so as to avoid further disease progression.

14. The results discussed above show that while Combigan® is usually an acceptable and effective drug in the treatment of glaucoma and/or OHT, certain patient populations suffer from more severe disease. These patients may therefore require multiple medications to manage IOP, and without such multiple medications may be unable to prevent their disease from progressing to visual field loss and potentially eventual blindness. However, using multiple topical ophthalmic medications on a daily basis can be challenging and time consuming to administer, and a complicated medication regimen can cause compliance problems, especially in elderly patients. Use of the three active ingredients in Triple Combination as individual monotherapies would require instillation of multiple drops per day, multiple times per day. The multiple instillations of drops also expose the eye to multiple instillations of preservatives, which can cause ocular discomfort, and a corresponding reluctance of the patient to use their ophthalmic medications. As such, there is a need for a single fixed-dose combination IOP-lowering treatment that is able to deliver a greater therapeutic benefit while providing a dosing regimen that improves adherence to treatment. As discussed here, patients with severe glaucoma and/or OHT who were administered Triple Combination twice daily surprisingly and unexpectedly showed a significant therapeutic benefit in the reduction of IOP over Combigan® administered twice daily. This represents a substantial benefit to such patients.

DECLARATION

15. As a person signing below:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on Information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE

Full name: Margot Goodkin
Medical Director, Ophthalmology
Allergan, Inc.

Signature: Margot Goodkin Date: 8/27/2015

Country of Citizenship:
Residence: United States of America
Post Office Address: 2525 Dupont Dr.
Irvine, California 92612

ATTACHMENTS

Exhibit A: Zimmerman TJ, Fechtner RD, Maximal medical therapy for glaucoma. *Arch Ophthalmol.* 1997;115:1579-1580

Exhibit B: Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, Early Manifest Glaucoma Trial Group. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. *Arch Ophthalmol.* 2002;120:1268-1279

Exhibit C: Sherwood et al., "Six-Month Comparison of Bimatoprost Once-Daily and Twice-Daily with Timolol Twice-Daily in Patients with Elevated Intraocular Pressure" *Surv. Ophthalmol.*, vol. 45, suppl. 4, May 2001, S362-S368.

Exhibit D: Higginbotham et al., "One-Year, Randomized Study Comparing Bimatoprost and Timolol in Glaucoma and Ocular Hypertension" *Arch Ophthalmol,* vol. 120, Oct. 2002, 1286-1293.

ARCHIVES OF OPHTHALMOLOGY

Editor
Daniel M. Albert, MD

Editorial - December 1997

Maximal Medical Therapy for Glaucoma

NOT TOO LONG AGO, maximal tolerated medical therapy (MTMT) for glaucoma usually meant a beta-blocker, a cholinergic agent (usually pilocarpine or carbachol), and an oral carbonic anhydrase inhibitor (CAI) (usually diamox or neptazane). Sometimes epinephrine or dipivefrin was added to the regimen. Prescribing MTMT for an individual patient depended on whether or not that patient could tolerate any or all of this regimen. With MTMT compliance was always suspect, not just because of the side effects of these drugs, especially the cholinergic agents and the CAIs, but also because of the difficult dosing schedules. At worst, a patient would be taking 4 pills and 6 to 8 drops in each eye daily. The morning and evening dosing could take 15 minutes under the best conditions (the patient applying bilateral nasolacrimal occlusion while a family member administered drops to both eyes every 5 minutes). This would be difficult to tolerate even for our most conscientious and regimen-committed patients.

Therapeutic options were limited in the pursuit of the goal of lower intraocular pressure (IOP). Physicians and patients had few alternatives but to deal with the adverse effects associated with these agents. This situation has grown even more complex in the last few years. Rather than continuing to add medications to the regimen until the patient is overwhelmed or develops adverse effects, can we develop a strategy for simplifying medical therapy for glaucoma and making it more manageable for our patients?

Recently, we have seen the introduction of the alpha$_2$-adrenergic agonists, a topical CAI, and a prostaglandin analog. Additivity studies have shown all these to be generally additive to the topical beta-blockers as adjunctive therapy.[1-4] Information regarding additional additivity to multiple medical therapy is scarce. It is conceivable that a particular patient could be placed on treatment with these drugs in addition to the MTMT described above. This would mean 3 additional eye drops with differing durations of action and, therefore, differing dosing schedules. The worst possible scenario now has the patient taking 6 different eye drops with schedules varying from 1 to 4 times daily. Now the morning and evening routine would require the proper application of 6 different drops to each eye over a 30- to 60-minute period. The question became, "How could medical therapy

be simplified and made manageable for our patients with glaucoma ?"

When a new drug is introduced for the treatment of glaucoma, initial clinical studies usually establish efficacy as monotherapy or as an adjunct to the topical beta-blockers. However, once the drug is released we often add it to the regimen of a patient for whom multiple other drugs are not providing sufficient control of IOP. That is how we arrived at the worst-case scenario detailed above. Let's look at this in the opposite direction and consider building from initial therapy to MTMT. Market research indicates that the current drugs of choice with which to begin a therapeutic regimen (unless there are contraindications) are the beta-blockers. This does not mean that newer drugs such as the prostaglandin analogs or alpha$_2$-adrenergic agonists will not be adopted for primary therapy.[5-7] However, at present most ophthalmologists usually start therapy with a beta-blocker. If the beta-blocker does not lower the IOP sufficiently, but does have a considerable effect, we would then probably add another drug. Market studies indicate that the current practice in the United States is to add as a second drug one with additivity to the beta-blockers and a favorable therapeutic index. These currently include the topical CAI dorzolamide, the prostaglandin analog latanoprost, and possibly the alpha$_2$-adrenergic agonist brimonidine. This choice certainly has to be individualized. In certain situations the second drug might be pilocarpine. Dipivefrin is an unlikely choice because of the lack of significant additivity to the nonselective beta-blockers in most patients.[8,9] Pilocarpine suffers all the disturbing local side effects with which we and our patients are very familiar. Apraclonidine has its problems with immune allergic reactions and tolerance. These are much less common with brimonidine. A topical prostaglandin analog has been available since late last year and has the appealing feature of once-daily dosing. However, this is an entirely new class of drugs and we believe there may be some unanticipated adverse effects. As we gain more experience with this agent, it will probably move up the ladder. So, our choice has been to add the topical CAI as the first adjunct drug. If the CAI has considerable additive effect but does not lower the IOP as low as we would like, then we look for a third drug. The same arguments hold at this level also. The drug that we would probably choose as our third add-on drug would again be chosen from among dorzolamide, latanoprost, and brimonidine. At this point, we would have prescribed 3 of these 4 drugs that either decrease aqueous production (beta-blocker, dorzolamide, brimonidine) or that increase nonpressure-dependent uveal scleral outflow (latanoprost and, to some degree, brimonidine). While the addition of the third or fourth drug may have a statistically significant effect on IOP, this effect is often in the range of 1 to 2 mm which may not be clinically significant (Robert D. Fechtner, MD, and T.J.Z., unpublished data, 1997).

Our patient is now taking beta-blocker once or twice daily, topical CAI twice daily, and a topical prostaglandin once daily and/or brimonidine twice daily. We have tried to select drugs that are generally well

tolerated and that provide a relatively low likelihood of intolerable adverse effects. Should we add yet another medication?

If the IOP is still not adequately controlled, what would we do? For the topical drugs, what we have left are the cholinergic agents like pilocarpine and the adrenergic agents like dipivefrin. Not only do both of these classes have the side effects mentioned above, but we also have to carefully assess their additivity. Pilocarpine may not be substantially additive with the prostaglandin analog.[10] This question arises because of their sites of action and each drug's effect on conventional trabecular meshwork outflow and nonpressure-dependent uveal scleral outflow. Although we have substantial information about the effects of medications as monotherapy or in combination with the beta-blocker, there is very little information about the additivity of these medications as third or fourth agents.

In select patients, it could be tried and then a decision made concerning the amount of additivity vs the impact of side effects and inconvenience of an additional medication. Even when it is additive, we have to consider its side effects and its complication of the treatment regimen. So, considering all this, MTMT for the treatment of glaucoma may not be as complicated as presented in the early part of this editorial. In fact, it may even be simplified.

We believe that the core of MTMT is a beta-blocker, the topical CAI, and the prostaglandin analog and/or a brimonidine. An alpha$_2$-adrenergic agonist may move up on this list if it proves to have long-term efficacy and tolerability. These choices may be modified based on systemic health or the potential for interactions with other systemic medications. Boldly, let us suggest that while select patients receiving core MTMT might benefit from adding additional medications, laser surgery or conventional surgery should be considered for most patients who need considerable additional lowering of IOP.

For most people, core MTMT will be defined as a beta-blocker and the topical CAI plus the prostaglandin analog or brimonidine. Is there any way to further simplify this? There are plans to combine the topical CAI and timolol maleate in the same bottle,[11,12] and it has been shownthat this combination can be used twice a day with maximal effect for a full 12 hours.[13] Similarly, a beta-blocker and topical prostaglandin might be combined. Possibly then, we will move from "maximal tolerated medical therapy" to core medical therapy that, for most patients, could be as simple as 3 drops of medication in each eye daily.

Thom J. Zimmerman, MD, PhD
Robert D. Fechtner, MD
Louisville, Ky

This article was supported in part by an unrestricted departmental grant from Research to Prevent Blindness, New York, NY.

Bruce A. Ellingsen, MD, and Eric Sorensen, MD, Spokane, Wash, are acknowledged for their input into this article.

Corresponding author: Thom J. Zimmerman, MD, PhD, Department of Ophthalmology and Visual Sciences, University of Louisville, 301 E Muhammad Ali Blvd, Louisville, KY 40202.

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(Arch Ophthalmol. 1997;115:1579-1580)

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Reduction of Intraocular Pressure and Glaucoma Progression

ARCHIVES EXPRESS

Results From the Early Manifest Glaucoma Trial

Anders Heijl, MD, PhD; M. Cristina Leske, MD, MPH; Bo Bengtsson, MD, PhD; Leslie Hyman, PhD; Boel Bengtsson, PhD; Mohamed Hussein, PhD; for the Early Manifest Glaucoma Trial Group

Objective: To provide the results of the Early Manifest Glaucoma Trial, which compared the effect of immediately lowering the intraocular pressure (IOP), vs no treatment or later treatment, on the progression of newly detected open-angle glaucoma.

Design: Randomized clinical trial.

Participants: Two hundred fifty-five patients aged 50 to 80 years (median, 68 years) with early glaucoma, visual field defects (median mean deviation, −4 dB), and a median IOP of 20 mm Hg, mainly identified through a population screening. Patients with an IOP greater than 30 mm Hg or advanced visual field loss were ineligible.

Interventions: Patients were randomized to either laser trabeculoplasty plus topical betaxolol hydrochloride (n = 129) or no initial treatment (n = 126). Study visits included Humphrey Full Threshold 30-2 visual field tests and tonometry every 3 months, and optic disc photography every 6 months. Decisions regarding treatment were made jointly with the patient when progression occurred and thereafter.

Main Outcome Measures: Glaucoma progression was defined by specific visual field and optic disc outcomes. Criteria for perimetric progression were computer based and defined as the same 3 or more test point locations showing significant deterioration from baseline in glaucoma change probability maps from 3 consecutive tests. Optic disc progression was determined by masked graders using flicker chronoscopy plus side-by-side photogradings.

Results: After a median follow-up period of 6 years (range, 51-102 months), retention was excellent, with only 6 patients lost to follow-up for reasons other than death. On average, treatment reduced the IOP by 5.1 mm Hg or 25%, a reduction maintained throughout follow-up. Progression was less frequent in the treatment group (58/129; 45%) than in controls (78/126; 62%) ($P = .007$) and occurred significantly later in treated patients. Treatment effects were also evident when stratifying patients by median IOP, mean deviation, and age as well as exfoliation status. Although patients reported few systemic or ocular conditions, increases in clinical nuclear lens opacity gradings were associated with treatment ($P = .002$).

Conclusions: The Early Manifest Glaucoma Trial is the first adequately powered randomized trial with an untreated control arm to evaluate the effects of IOP reduction in patients with open-angle glaucoma who have elevated and normal IOP. Its intent-to-treat analysis showed considerable beneficial effects of treatment that significantly delayed progression. Whereas progression varied across patient categories, treatment effects were present in both older and younger patients, high- and normal-tension glaucoma, and eyes with less and greater visual field loss.

Arch Ophthalmol. 2002;120:1268-1279

From the Department of Ophthalmology, Malmö University Hospital, Malmö, Sweden (Drs Heijl, Bo Bengtsson, and Boel Bengtsson), and the Department of Preventive Medicine, State University of New York at Stony Brook (Drs Leske, Hyman, and Hussein). A list of the members of the Early Manifest Glaucoma Trial Group appears on page 1278.

STARTING IN THE 1960s, epidemiological studies demonstrated that normal-tension glaucoma was much more common than previously thought and that ocular hypertension, or elevated intraocular pressure (IOP) without glaucomatous visual field defects or optic disc cupping, was more common than glaucoma.[1-3] Subsequent studies showed that relatively few patients with ocular hypertension developed signs of glaucomatous damage during follow-up periods of up to 20 years, even if the condition was left untreated.[4-8] The earlier concept that basically equated elevated IOP with glaucoma became obsolete, resulting in uncertainty of the effects of glaucoma treatment.

For editorial comment see page 1371

Given this background, several randomized trials were initiated in the early 1980s to evaluate the relationship between glaucoma and the reduction of IOP.[9-12] The relationship was studied some-

what indirectly by investigating whether IOP reduction could reduce the incidence of glaucoma damage in patients with ocular hypertension. At that time, conducting a study to address the subject more unequivocally (ie, a carefully designed randomized trial of patients with glaucoma that included an untreated control arm) would probably have been considered unethical.

Controversy continued regarding when, how aggressively, and whether or not to treat,[13] and the uncertainty of treatment effects was outlined in a report presented to the National Leadership Commission on Health Care.[14] The development and widespread use of computerized perimetry and the improved understanding of early optic disc changes in glaucoma had demonstrated a complex relationship between IOP and glaucoma damage. Researchers and professional organizations emphasized a new glaucoma concept in which the disease was described as an optic neuropathy, with IOP as only one of several risk factors.[15,16] This view has now become the standard, and modern glaucoma definitions often do not even mention IOP.[17,18]

When our trial was planned in the early 1990s, several controlled studies using timolol maleate in patients with ocular hypertension had been in progress for many years but had not shown that such treatment effectively prevented glaucoma damage. Given the relatively low incidence of this damage in patients with ocular hypertension, the sample sizes and statistical power of these trials were probably insufficient. Only 1 controlled trial involving treated and untreated patients with glaucoma had been published, and with negative results.[19] The Collaborative Normal-Tension Glaucoma Study (CNTGS) was under way at that time.[20,21] In 1993, Rossetti et al[22] concluded in a systematic literature review that "[p]racticing ophthalmologists should be aware that the effectiveness of pressure-lowering agents in the treatment of primary open angle glaucoma is still to be determined," and that controlled trials with functional endpoints and sufficient duration were urgently needed.

Because the effectiveness of such treatment had never been shown in a randomized clinical trial, several clinical implications influenced glaucoma management: What price in terms of adverse effects, inconvenience, and cost could be considered acceptable when treatment effects were uncertain? Efforts to detect cases of glaucoma that remained undetected (approximately 50%)[2,3,23-25] could hardly be advocated because an effective treatment for a particular disease is considered a prerequisite for screening.[26-28] The need for knowledge in this area was clear. The development of improved methods for computerized visual field testing and recognition of mild glaucoma progression enhanced the feasibility of such trials. Hence, a randomized study with a control arm, in which patients underwent follow-up without treatment as long as progression did not occur, would not expose study patients to unacceptable risks.

The Early Manifest Glaucoma Trial (EMGT) began in 1992. It is a controlled clinical trial evaluating the effectiveness of reducing IOP in patients with newly detected, previously untreated glaucoma. The study design and baseline data were reported in 1999.[29]

The purpose of our article is to report the EMGT results pertaining to the primary aim of the trial, namely to compare the effect of immediate therapy to lower the IOP, vs no treatment or later treatment, on the progression of newly detected open-angle glaucoma as measured by increasing visual field loss or optic disc changes.

METHODS

Our previously published article[29] contains a detailed description of the study methods. The following is a condensed description, which should enable the reader to understand and interpret the results.

INCLUSION AND EXCLUSION CRITERIA

Study patients had newly detected, previously untreated open-angle glaucoma. All patients fulfilled the following eligibility criteria:

- A diagnosis of early manifest open-angle glaucoma, including primary open-angle glaucoma, normal-tension glaucoma, or exfoliation glaucoma.
- Reproducible glaucomatous visual field defects in at least one eye.
- Age between 50 and 80 years.

To determine eligibility, glaucomatous visual field defects were documented with computerized static perimetry using the Full Threshold 24-2 program of the Humphrey perimeter. Eligibility required a classification of "outside normal limits" involving the same visual field area at 2 initial postscreening visits using the glaucoma hemifield test [30,31] of the Statpac II program for computer-assisted visual field interpretation.[32] A "borderline" classification was acceptable only if obvious localized glaucomatous optic disc cupping was present in an area corresponding to the visual field defect.

Exclusion criteria were as follows:

- Advanced visual field defects (mean deviation [MD] worse than −16 dB)[33] or a threat to fixation, defined as differential light sensitivity of 10 dB or worse at either or both test points closest to the point of fixation in both the upper and lower hemifields. If both eyes were eligible, the MD had to be better than −10 dB in at least one eye.
- Visual acuity less than 0.5 (Monoyer-Granström), corresponding to 20/40, in any eye.
- Mean IOP greater than 30 mm Hg or any IOP greater than 35 mm Hg in at least one eye.
- Any condition precluding reliable results of perimetry or optic disc photography, the use of study interventions, or 4 years of follow-up.
- Cataractous lens changes exceeding gradings of N1, C2, or P1 according to the Lens Opacities Classification System (LOCS) II.[34]

The study was conducted according to the tenets of the Declaration of Helsinki. All subjects gave informed consent, and the study was approved by the Ethics Committee of the University of Lund (Lund, Sweden) and the Committee on Research Involving Human Subjects at the State University of New York at Stony Brook.

RANDOMIZATION, TREATMENT, AND MASKING

Eligibility was independently confirmed at the data center. Eligible patients were randomized evenly between treatment and nontreatment groups according to a permuted block randomization scheme stratified by the clinical and satellite centers. All eyes randomized to treatment received a full 360° trabeculoplasty plus betaxolol hydrochloride eye drops at a dose of 5 mg/mL (Betoptic; Alcon, Fort Worth, Tex) twice daily. Eyes

stayed in their allocation arms unless significant progression occurred. If, however, the IOP in treated eyes exceeded 25 mm Hg at 2 consecutive follow-up visits or 35 mm Hg in control eyes, latanoprost eye drops at a dose of 50 µg/mL (Xalatan; Pharmacia, Uppsala, Sweden) were given once daily. When definite progression occurred, patients were informed and options were discussed; decisions on subsequent clinical management were made with their cooperation and following the usual patterns of glaucoma treatment.

As part of the quality control protocol for the trial, all study personnel completed a training period according to the manual of procedures prior to data collection, which was followed by a formal certification process implemented by the data center. Regular site visits and data audits were conducted. Study outcomes were determined either through numerical, predetermined objective criteria (visual field tests) or by masked graders at the disc photography reading center. Study personnel measuring visual acuity, IOP, and visual fields were masked to patients' study group, but patients and treating physicians were not masked. An independent Data Safety and Monitoring Committee (DSMC), which includes members from both Sweden and the United States, has been responsible for monitoring all aspects of the trial since its inception. The DSMC meets yearly to review patient safety, evaluate data quality and the results of interim analyses, and supervise the overall conduct of the study.

PATIENT VISITS

The protocol required 2 postscreening visits preceding the 2 baseline visits. These early visits were used to substantiate the diagnosis, ascertain eligibility, minimize the effects of perimetric learning, and provide information about the trial. Both baseline examinations included visual field testing and the measurement of IOP (Goldmann applanation tonometry). After eligibility was confirmed at the second baseline visit, informed consent was obtained and patients were randomized. Patients received follow-up at 3-month intervals. A recent medical and ophthalmologic history, including adverse events and compliance, was obtained at each visit. Examinations included visual acuity testing with Monoyer-Granström standard decimal charts following subjective refraction, Goldmann applanation tonometry, computerized visual field testing (Humphrey 30-2 Full-Threshold program), ophthalmoscopy, and slitlamp examination with lens classification using the LOCS II system.[34] Optic disc photographs were obtained every 6 months.

ADDITIONS TO THE STUDY PROTOCOL

To further assess differences in nuclear clinical LOCS II gradings[34] between study groups, the DSMC approved a proposal to obtain nuclear lens photographs with slitlamp cameras specifically adapted for this purpose. After standardization and certification of the photographers, lens photographs were obtained twice: (1) between December 1999 and March 2000, and (2) between March 2001 and July 2001. The 2 sets of slitlamp photographs were evaluated concurrently, following a random order, at a reading center at the Department of Ophthalmology, University of Wisconsin–Madison. The graders were masked and applied a standardized system.[35]

Further additions to the protocol once the study began included visual function-related quality-of-life assessment with the National Eye Institute's Visual Function Questionnaire[36] and corneal pachymetry measurements.[37]

OUTCOMES

The study outcome was progression of either glaucomatous visual field defects or optic disc cupping, each according to predetermined objective criteria. For each patient, one or both eyes could be included in the study, based on eligibility at baseline. A patient was considered to have progression when the first eligible eye met progression criteria.

To determine visual field progression, all follow-up results of visual field tests were compared with an average of those from the 2 baseline tests from the same eye using glaucoma change probability maps (GCPMs). These maps differentiate between significant progression at $P<.05$ and random test-retest fluctuations at each of 74 test point locations in the visual field. The EMGT used pattern deviation GCPMs based on pointwise pattern deviations from the age-corrected normal threshold values[38] rather than the standard total deviation GCPMs. Pattern deviation maps limit the effects of increasing homogeneous loss of differential light sensitivity, such as the loss caused by progressive cataract. Definite EMGT visual field progression was defined as at least 3 test points showing significant progression, as compared with baseline, at the same locations on 3 consecutive GCPMs. These criteria have been shown to be highly sensitive indicators of early visual field progression (A.H., M.C.L., B.B., B.B., and M.H., for the EMGT Group, unpublished data, 2002).

To determine optic disc progression, baseline and follow-up photographs were compared at the disc photography reading center using flicker chronoscopy.[39,40] The protocol was designed to yield highly specific outcomes. Two graders masked to study group and photograph order independently judged each pair of photographs. If a suspected or definite change was found, a second set of photographs was judged. If a consensus was reached that flicker chronoscopy indicated change (sometimes after adjudication), a nonflicker side-by-side comparison by a third independent grader decided if definite optic disc progression was present. A previously described quality control system evaluated the validity and reproducibility of the gradings, as well as grading drift, based on a standard set of photographs.[29]

STATISTICAL ANALYSIS

The sample size calculations were based on assuming 4-year progression rates of 40% in the treatment group and 60% in the control group, a significance level of 5%, 2-tailed tests, and an attrition rate of 15%, thus providing at least 80% statistical power to detect differences in progression between trial arms. The statistical analysis plan has previously been described in detail.[29] This article includes comparisons of the primary outcome of glaucoma progression between the treatment and control groups. We followed an intent-to-treat analytic strategy, with all patients analyzed according to their original group assigned by randomization. Comparisons of glaucoma progression were based on assessing visual field or optic disc changes that met the prespecified EMGT criteria while accounting for follow-up times. Analyses were patient based; for those with 2 eligible eyes, the event time to progression was defined by the first progression in either eye. Survival analysis and life-table methods[41] were used to (1) estimate the proportion of progressions by study group, and (2) test for a significant difference in these rates between groups using the log-rank test. The estimated difference in 4-year progression rates between groups and 95% confidence intervals were derived from the life-table analyses and calculated as binomial events. Survival curves were also plotted for all patients, stratified according to the prespecified covariates of IOP (<21 mm Hg or ≥ 21 mm Hg) and exfoliation ("yes" or "no") as well as MD and age (less than median values or equal to or greater than median values).

Univariate comparisons between treatment and control groups (eg, in baseline characteristics or numbers progressing) were based on t tests for continuous variables if normality as-

sumptions were justified (otherwise, nonparametric methods were used), and on the χ^2 test or Fisher exact test for categorical variables. In addition, progression across time by study group was compared while stratifying according to the prespecified covariates mentioned previously. The generalized estimating equations method[42] was used to adjust for the correlation of lens status among different follow-up visits for the same eyes. We also compared visual field changes between the 2 study arms using linear regression analyses of both MD and number of highly significantly depressed test point locations ($P<0.5\%$) according to the pattern deviation probability maps. As reported in detail elsewhere, additional multivariate statistical analyses using Cox proportional hazards models[43,44] were performed to evaluate factors related to glaucoma progression, including treatment. These analyses estimated the magnitude of treatment effects (for each millimeter of mercury of IOP reduction) and explored possible non–IOP-related effects of treatment while controlling for other significant variables (M.C.L., A.H., M.H., B.B., L.H., and E. Komaroff, PhD, unpublished data, 2002).

RESULTS

RECRUITMENT AND RETENTION

Recruitment has previously been described in detail.[29] A large population screening of 44 243 residents aged 57 to 76 years was conducted between October 1992 and January 1997 in the cities of Malmö, Sweden, and Helsingborg, Sweden, to recruit for the trial. Most trial participants (84.7%) came from this screening, whereas a smaller number were referred from other ophthalmologists. A flowchart is shown in **Figure 1**. The randomization period began in January 1993 and ended in April 1997. Of the 255 patients randomized, 129 were allocated to treatment and 126 were controls. Only 3 patients in each group were lost to follow-up for reasons other than death (n=22); that is, 6 living patients no longer received follow-up as of September 1, 2001, the time of database closure for this study. The remaining 227 patients exceeded the originally selected minimum follow-up period of 4 years, with follow-up times comparable between study groups and ranging from 51 to 102 months (for the treatment group, mean±SD=67.0±20.4 months; median=66 months; for the control group, mean±SD=69.7±20.8 months; median=69 months). The number of patient study years was similar in the 2 groups: 720 in the treatment group and 732 in the control group.

BASELINE CHARACTERISTICS

The mean age of the patients was 68 years; 66% were women, almost all patients were white,[29] and 132 (52%) had a baseline IOP less than 21 mm Hg. The baseline characteristics of the 2 study groups (**Table 1**) were comparable, and none of the observed parameters differed significantly between groups.

IOP CHANGES AFTER BASELINE

The mean IOP in the treatment group decreased from 20.6 mm Hg at baseline (Table 1) to 15.5 mm Hg at the 3-month follow-up visit, for a reduction of 25% that was maintained throughout the follow-up period; the median change was 0.2% from 3 months until progression or the last visit (for nonprogressed eyes). The reduction was larger (29%) in eyes with a baseline IOP of 21 mm Hg or greater than in eyes with a baseline IOP less than 21 mm Hg (18%). Results were similar when considering changes in IOP from baseline to each visit until progression or the last visit. The mean±SD difference from baseline to all visits was −4.5±3.4 mm Hg in treated eyes; the corresponding values were −6.8±3.0 mm Hg for eyes with a baseline IOP of 21 mm Hg or greater and −2.7±2.4 mm Hg in eyes with a baseline IOP less than 21 mm Hg. By self-report, treated patients indicated using treatment "most of the time" at 96.8% of visits. The mean IOP reduction in the treatment group from the baseline readings (average of 2 visits) to the reading obtained just before laser trabeculoplasty a few weeks later, when patients were receiving betaxolol, was 2.7 mm Hg; the IOP reduction from that reading to the 3-month visit was 2.4 mm Hg. The protocol-defined cutoff point for extra treatment in the treated patients (>25 mm Hg) occurred infrequently (4 patients, or 3%), whereas no untreated patients reached the 35 mm Hg limit requiring topical medication before progression.

In the control group, IOP values were unchanged (20.9 and 20.8 mm Hg at baseline and the 3-month visit, respectively), with small changes thereafter (median change=0.0% from 3 months until progression or the last visit). The mean±SD difference from baseline to all visits, censored for progression, was 0.0±1.9 mm Hg.

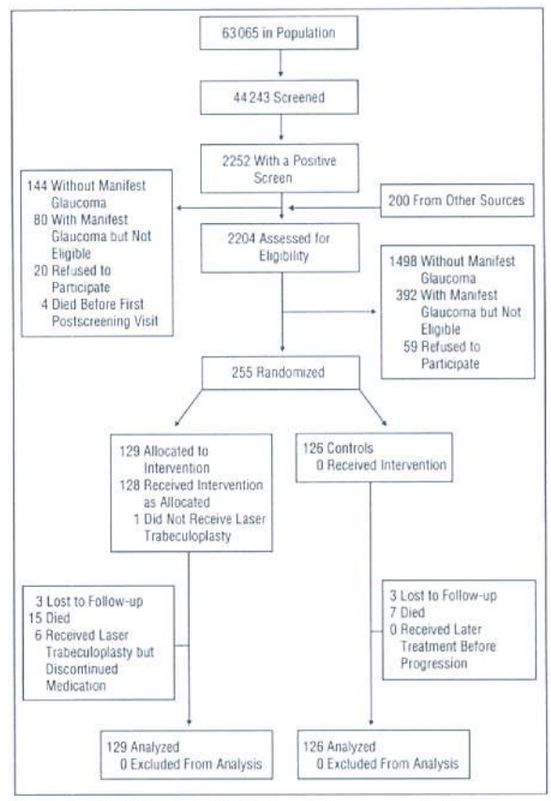

Figure 1. Patient flowchart. Most study patients were recruited from a population-based mass screening. Attrition rates were low, and follow-up is indicated as of September 2001.

Table 1. Baseline Characteristics of All Study Patients by Study Group*

Characteristic	Treatment Group (n = 129)	Control Group (n = 126)
Both eyes eligible	34 (26)	27 (21)
One eye eligible	95 (74)	99 (79)
Age		
Mean ± SD	68.2 ± 4.8	68.0 ± 5.0
Median (range)	68.0 (58.0-78.0)	68.0 (50.0-79.0)
M	47 (36)	39 (31)
F	82 (64)	87 (69)
Baseline IOP, mm Hg		
Mean ± SD	20.6 ± 4.1	20.9 (4.1)
Median (range)	20.0 (13.0-30.5)	20.5 (12.0-31.0)
IOP <21 mm Hg	69	63
Visual acuity†		
Mean ± SD	0.9 ± 0.1	1.0 ± 0.1
Median (range)	1.0 (0.6-1.0)	1.0 (0.6-1.0)
Perimetric mean deviation, dB		
Mean ± SD	−5.0 ± 3.7	−4.4 ± 3.3
Median (range)	−4.3 (1.3 to −14.7)	−3.9 (2.4 to −13.6)
Any optic disc abnormality (notching saucerization, cupping, or hemorrhages)	147 (90)	138 (90)
Exfoliation syndrome	9 (6)	16 (10)
Refraction <−1 diopter	19 (12)	23 (15)
Hypertension‡	46 (36)	52 (41)
Disease history		
Family history of glaucoma	26 (20)	24 (19)
Cardiac disease	19 (15)	14 (11)
Stroke, low blood pressure, orthostatism	12 (9)	5 (4)
General arteriosclerosis	4 (3)	5 (4)
Peripheral vasospasm and migraine	21 (16)	26 (21)
Pulmonary disease	3 (2)	0 (0)
Diabetes mellitus	3 (2)	6 (5)
Medication use		
Antihypertensives	31 (24)	31 (25)
Corticosteroids	0 (0)	4 (3)
Other (eg, insulin or estrogen)	57 (44)	55 (44)

*Data are presented as number (percentage) unless otherwise indicated. IOP indicates intraocular pressure.
†Determined according to the Monoyer-Granström system.
‡Defined as systolic pressure greater than 160 mm Hg, diastolic pressure greater than 95 mm Hg, or a history of antihypertensive treatment.

MAIN OUTCOMES

By September 1, 2001, the proportion of patients who showed definite visual field and optic disc progression was larger in the control group than the treatment group: 78 (62%) of 126 vs 58 (45%) of 129, respectively ($P=.007$) (**Table 2**). All patients with progression met the visual field outcome criteria with 1 exception, who met the optic disc criterion only. In accordance with the specific EMGT criteria to define optic disc progression, few of these outcomes were observed.

Life-table analyses show that the separation between study groups appeared early and was maintained during the entire follow-up period; they also show that progression increased considerably with time, in the treatment group as well as the control group (**Figure 2**). Progression was more common in the control group at any

Table 2. Progression by Study Group*

	Treatment Group	Control Group
Progression	58 (45)	78 (62)
Based on visual field outcome only	53 (41)	64 (51)
Based on optic disc outcome only	1 (1)	0 (0)
Based on visual field and optic disc outcomes	4 (3)	14 (11)

*Data are presented as number (percentage).

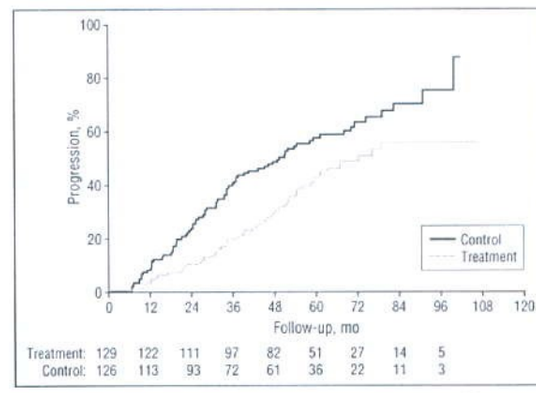

Figure 2. Progression across time of all patients by study group. The cumulative probability of patients with progression was larger in the control group than the treatment group ($P=.007$). The number of patients at risk for glaucoma progression in the treatment group and control group are shown below the x-axis.

point during follow-up; in other words, progression occurred earlier in controls than in the treatment group. Whereas the median time to progression (using the Kaplan-Meier cumulative survival function) was 48 months in controls, it was 66 months in treated patients, indicating a delay in progression caused by treatment. According to the life-table results at 48 months, which was the minimum planned period of follow-up, 62 controls (49%) had progressed compared with 39 (30%) in the treatment group (difference = 19%; 95% confidence interval, 7%-23%; $P=.004$). The differences between study groups and apparent treatment effects were also observed when stratifying according to the baseline covariates (**Figure 3**). All of these curves show a clear and persistent separation between treatment and control groups, and the covariates were significantly related to progression in multivariate analyses (M.C.L., A.H., M.H., B.B., L.H., and E. Komaroff, PhD, unpublished data, 2002). In these analyses, each millimeter of mercury of decreased IOP was related to an approximately 10% lowering of risk, and the results showed no significant treatment effects beyond those related to IOP reduction.

The regression analyses of MD and number of highly significantly depressed test point locations ($P<.5\%$) in pattern deviation probability maps yielded differences between study groups similar to those based on EMGT-defined progression criteria. Although the regression analyses may underestimate true progression because of sustained, low-grade perimetric learning, these results show significantly slower visual field deterioration in patients allocated to treatment than in control patients

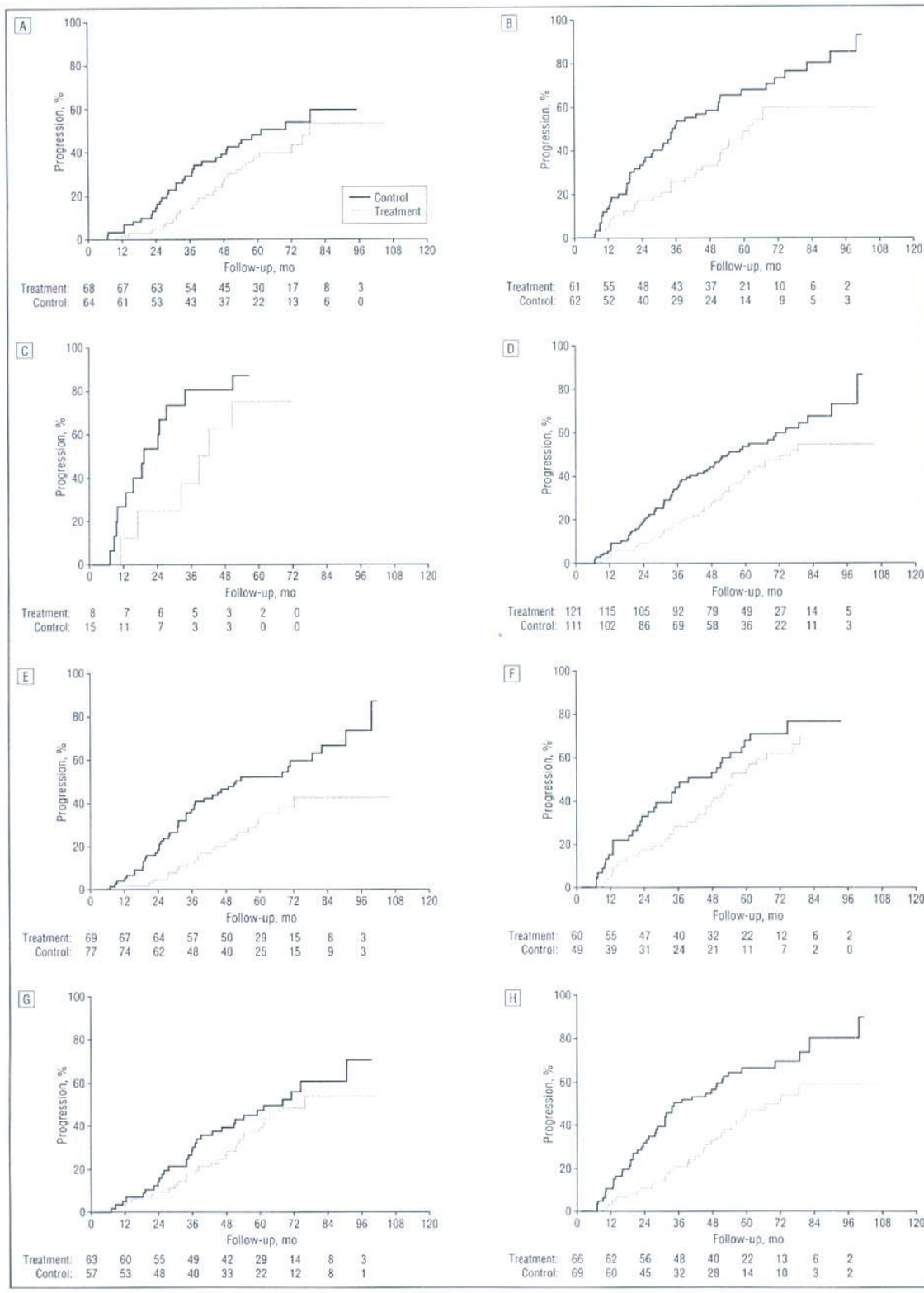

Figure 3. Progression across time stratified according to baseline covariates: patients with an intraocular pressure less than 21 mm Hg (A) and 21 mm Hg or greater (B), with exfoliation (C) and without (D), with mean deviation values better than −4.5 dB (E) and worse (F), and who are younger than 68 years (G) and 68 years or older (H). The numbers of patients at risk for glaucoma progression in the treatment group and control group are shown below the x-axes. These numbers decrease significantly with length of follow-up and were small from the beginning in the exfoliation group.

Table 3. Change of Mean Deviation Values and Number of Highly Significant Test Point Locations Until Time of Progression in Progressed Eyes or Until Last Visit in Nonprogressed Eyes, by Study Group*

	Treatment Group (n = 125)	Control Group (n = 122)	*P* Value
Mean deviation change, dB per month	−0.03 ± 0.05	−0.05 ± 0.07	.008
Median	−0.02	−0.04	...
Change in number of significant† test point locations per month	0.06 ± 0.10	0.10 ± 0.13	.006
Median	0.03	0.06	...

*Data excludes 7 treated and 4 control patients who developed nonglaucomatous damage or had insufficient follow-up. Data are presented as mean ± SD unless otherwise indicated.
†Significance was defined as $P<0.5\%$.

Table 4. Adverse Events and Self-reported Conditions by Study Group*

	Treatment Group	Control Group
Systemic		
Asthma	2	0
Bradycardia	1	0
Cardiac insufficiency	0	0
Depression	3	1
Impotence	0	0
Ocular		
Thrombosis	1	1
Cataract surgery	6	2
Trabeculectomy	1	0
Other (eg, reduction of visual acuity, floaters, or conjunctivitis)	21	16

*Data are presented as number of patients.

(**Table 3**). The mean change in visual field loss from baseline to the end of follow-up, as expressed by the MD, was a worsening by 2.24 dB in the treatment group and 3.90 dB in the control group. A separate analysis has shown that the amount of visual field deterioration needed to reach EMGT-defined visual field progression is associated with a worsening in MD by 2.26 dB (A.H., M.C.L., B.B., B.B., and M.H., for the EMGT Group, unpublished data, 2002).

ADVERSE EVENTS AND SELF-REPORTED ADVERSE EFFECTS

As seen in **Table 4**, few systemic and ocular conditions were identified; however, both occurred more commonly in the treatment group. Cataract surgery was performed in 8 patients, 6 of whom were in the treatment group. Ocular adverse effects of treatment were generally mild, with redness, dryness, and erythema reported by 11 patients, blurred vision by 8 patients, and other symptoms, mainly transient discomfort, by 12 patients. Visual acuity decreased with time and was not significantly different between study groups (visual acuity at 4 years of follow-up [Monoyer-Granstrôm]: mean ± SD = 0.87 ± 0.18 in the treatment group vs 0.90 ± 0.16 in the control group; $P=.82$).

Data-monitoring analyses indicated an unexpected increased incidence of nuclear opacities evident in the LOCS II clinical gradings. The percentages of LOCS II gradings of 2 or higher by study group during the initially planned 4-year follow-up period are shown in **Figure 4**. There was a clear and significantly more rapid development of nuclear opacities in the treatment group, without similar changes observed for cortical and posterior subcapsular lens gradings. The results of analysis using generalized estimating equations indicated a significant increase in clinical nuclear opacities with time ($P=.02$) and treatment ($P=.002$).

Lens photographs were taken to further evaluate these clinical findings, but a high percentage of controls had received treatment by that time: 34.5% (41/119) at the first round of photographs and 45.9% (50/109) at the second round. The intent-to-treat analyses of these lens photogradings were inconclusive, although more eyes in the treatment group (8) were ungradable because of cataract or cataract surgery than in controls (2). In multivariate analyses including these eyes and evaluating associations with treatment (independent of study group and controlling for age, sex, and follow-up time), lens photograding scores were related to treatment ($P=.004$).

More patients died in the treatment group than in the control group: 15 of 22 (Figure 1). This difference, although not statistically significant ($P=.08$), was observed within the first few years of follow-up. The patterns of cause-specific mortality were not unusual, with most deaths due to cardiovascular diseases (eg, myocardial infarction or stroke) or malignancies (eg, liver cancer or stomach cancer) in both trial arms; most deaths occurred in men.

DATA QUALITY

The rate of missed visits was 5.9% and was similar between study groups. Protocol deviations at follow-up were infrequent and were mainly due to the noncompletion of data items (29, or 0.5% of visits) and nonscheduling or noncompletion of additional visits according to protocol (33, or 0.6% of visits). Only 0.2% of data entries on study forms required editing. Unmasking of the technicians to study group occurred in 81 visits (1.5%) involving 31 treated patients and 17 controls. The evaluations of optic disc gradings confirmed the high specificity of the protocol, with no false-positive gradings in 12 cycles of masked readings of a quality control set of photographs. Reproducibility of flicker gradings varied throughout the quality control cycles and among graders, with most κ statistics in the "fair" to "good" range for both intragrader agreement (medians ranged from $\kappa=0.50$-0.73 among graders) and intergrader agreement (median of all comparisons of grader pairs: $\kappa=0.63$).

REVIEW BY THE DSMC

No patient safety issues were identified by the DSMC, and the trial has continued as planned. In May 2000, the results suggested favorable subclinical treatment effects, and

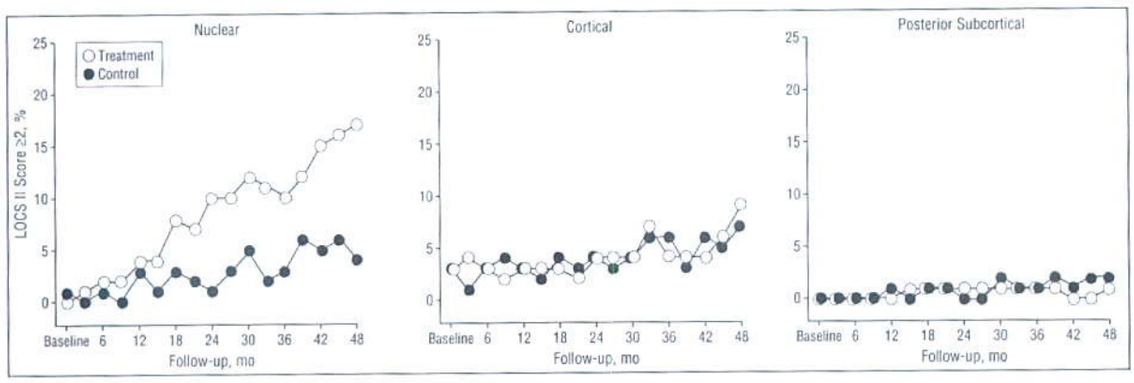

Figure 4. Lens Opacities Classification System (LOCS) II scores of 2 and higher by study group during the first 48 months of follow-up.

the DSMC recommended that the investigators share this information with enrolled patients and continue the study according to protocol until all patients had completed at least 4 years of follow-up. After receiving such information and discussing clinical management options, all patients continued follow-up in their assigned study groups.

COMMENT

Modern evidence-based medicine recognizes that the best proof of treatment effectiveness comes from randomized controlled trials that are not only well designed and executed but also thoroughly and accurately reported. Beginning in 1996, a series of statements were published by the Consolidated Standards of Reporting Trials (CONSORT) Group to increase and ensure the quality of such reports.[45] Our article follows the recently updated CONSORT guidelines.[46]

EFFECTS OF TREATMENT ON GLAUCOMA PROGRESSION

The EMGT showed clear beneficial effects of treatment on delaying the onset of progression, with lower rates of progression in the treatment group than the control group (Tables 2 and 3; Figure 2). Differences between treated and untreated patients also remained when results were further stratified according to various baseline characteristics: IOP level, degree of visual field damage, patient age, or presence of exfoliation (Figure 3). Despite these clear treatment effects, a large percentage of treated eyes showed progression during the follow-up period.

The median time to progression was 18 months longer in the treatment group than the control group. This observation should not be interpreted to mean that the only benefit of treatment (as used in the EMGT) is to delay glaucoma progression by 18 months. Instead, the finding means that the amount of disease worsening necessary to trigger the EMGT-defined progression criteria took an average of 18 months longer in treated patients than controls. This article provides data just up to the time of the initial EMGT outcome, but it is likely that the difference in glaucoma progression between study groups would have increased if the initial allocation to treatment or no treatment had remained unchanged even after this outcome.

The IOP reduction achieved by the EMGT treatment was substantial and was not associated with adverse effects as significant as those typically encountered after filtering surgery and documented in the CNTGS.[20,21] There was no difference in visual acuity loss across time between the 2 study groups, despite the fact that treatment was associated with an increased incidence of cataract in the EMGT.

Time to progression varied greatly among treated patients as well as untreated ones and was sometimes rather short. This indicates that the standardized treatment was insufficient in many rapidly progressing patients. On the other hand, many patients, even untreated ones, showed no progression after 6 or more years of follow-up. Because the EMGT visual field progression criterion is a sensitive indicator of deterioration, careful follow-up may allow treatment to be deferred in some patients, as suggested by Drance et al[47]: "[I]t might be prudent not to treat most patients with normal-tension glaucoma until the rate of the disease in the particular individual had been established over a period of observation." The EMGT thus supports today's emphasis on individualized treatment, and we expect that after further analyses, EMGT data will be found useful for tailoring follow-up and treatment to individual patients.

ADVERSE EVENTS

In our opinion, only 2 types of adverse events deserve comment: cataract and mortality. During recruitment, the EMGT used a standardized system of lens classification to ascertain lens status so that patients with cataractous changes were excluded from the trial. This design feature and the absence of glaucoma surgery in the treatment protocol resulted in a low frequency of cataract surgery at follow-up (n=8, or 3%) compared with the rates reported in other glaucoma trials. Continued monitoring of clinical lens gradings in the EMGT led to the detection of an increase in nuclear opacities in the treatment group (**Figure 4**), which was paralleled by a higher frequency of cataract surgery in that group (Table 4).

Analysis of nuclear photograding scores also showed associations with treatment, but the difference in scores

between groups was not confirmed in intent-to-treat analyses. The latter result is difficult to interpret because many of the controls were receiving treatment at the time the lens photographs were taken.

It is well known that glaucoma filtering surgery is associated with a marked rise in cataract incidence and that topical irreversible cholinesterase inhibitors caused cataract. The reports of the CNTGS have emphasized the frequent occurrence of cataract surgery in its treated group[20,21]; cataracts were also common in the Advanced Glaucoma Intervention Study (AGIS).[48,49] The CNTGS is the only other glaucoma study besides ours that permits a comparison in cataract rates between treated and untreated arms. Although it did not show a significant difference in cataract rates between the medically treated patients and untreated controls, numbers were small; the mean time to cataract development was actually lower in the medical treatment group. The use of topical IOP-lowering medications was strongly related to an increased incidence of nuclear lens opacities in the Barbados Eye Studies.[50] The Ocular Hypertension Treatment Study[51] (OHTS) reported "a slight excess of cataract surgery" in the medication group: 6.4% (52/806) vs 4.3% (35/813) in the observation group ($P=.06$), a result consistent with EMGT observations.[52]

Everything considered, we deem it likely that therapeutic IOP reduction can be linked with cataract formation.

The difference in death rate between groups is worth attention. The rate observed in the treated patients was as expected according to the population statistics of Sweden,[53] whereas the control group had a considerably lower value. Furthermore, there was no difference in cause-of-death patterns between the 2 groups. The OHTS reports similar death rates in treated and untreated patients: 3.2% and 3.5%, respectively.[52] For these reasons, it is likely that the observed mortality differences in the EMGT were caused by chance.

POSSIBLE MECHANISMS

In the EMGT, all patients received standardized treatment, and no effort was made to meet specific target IOPs. This design allowed an unbiased quantification of treatment effects related to IOP reduction, which was strongly related to glaucoma progression. The magnitude of this dependence on IOP change was impressive: an estimated 10% decrease in risk of progression with each millimeter of mercury of IOP reduction. Our results do not suggest that the outcome differences between study groups were due to non–IOP reduction effects; for example, to possible intrinsic vasoactive or neuroprotective properties of the topical medications used in this study.

Even though the EMGT clearly supports the beneficial effect of IOP reduction on open-angle glaucoma, these results do not prove that elevated IOP is the primary cause of glaucoma. The true causes of the disease may be a set of more fundamental malfunctions, some of which may lead to elevated IOP (defined as either a statistically high pressure level or a level that is not tolerated by the individual patient while falling within the normal range). However, the fact that IOP reduction slows progression indicates that IOP levels are important in the course of the disease.

COMPARISON WITH OTHER TRIALS

Since the start of the EMGT, data have become available that are of value when examining the overall evidence for the effect of IOP reduction on open-angle glaucoma.[20,21,48,51,54] In general, available results have been interpreted to indicate that all modalities of IOP reduction slow the progression of glaucomatous optic atrophy, but to an unknown extent.[20,21,52,55,56] Even recent evidence remains conflicting. A nonrandomized analysis of data from the AGIS provided evidence that effective IOP reduction is of great importance for disease progression.[55] In the Collaborative Initial Glaucoma Treatment Study[56] (CIGTS), however, aggressive medical therapy and initial surgery resulted in indistinguishable rates of visual field progression despite differences in IOP reduction, and the intent-to-treat analysis of the CNTGS showed no difference between treated and untreated arms.[21] Thus, up to now, uncertainty has remained regarding the effect of IOP reduction on glaucoma progression. Recently, researchers have agreed that conclusive evidence should come from trials specifically designed to address this issue.[55]

Most important is the CNTGS, in which 140 patients with normal-tension glaucoma were randomized either to nontreatment as controls or to have the IOP lowered by 30% from baseline. The clinical course and visual field and optic disc outcomes of both groups were then compared. Although the intent-to-treat analyses of the CNTGS found no significant differences between treated and untreated arms,[21] these negative results have largely been ignored in the ophthalmic community. Our results show that the conclusion of the CNTGS (that IOP reduction decreases glaucoma progression in normal-tension glaucoma[20]) is correct but that treatment effects can be achieved without a rigid IOP goal or serious adverse effects.

Although trials involving patients with ocular hypertension address a somewhat different subject, they deal with the same fundamental question of the relationship between IOP and glaucoma damage. It is therefore appropriate to include the results from such studies in the discussion of overall evidence. Earlier controlled studies of patients with ocular hypertension had diverging results[9-12] and together failed to demonstrate a statistically significant beneficial effect,[22] but their study power was usually low. The OHTS currently provides conclusive data showing positive effects of IOP reduction in decreasing the frequency of glaucoma damage in patients with ocular hypertension. The incidence of glaucoma damage differed significantly between treated patients and untreated controls, amounting to 4.4% and 9.5%, respectively, after 60 months of follow-up.[52] The overall evidence that lowering the IOP reduces the risk of further visual field progression in glaucoma must now be regarded as very strong.

STRENGTHS AND LIMITATIONS

Interpretation of the EMGT results must consider several methodologic strengths of the trial. That only 2.4%

of patients were lost to follow-up for reasons other than death indicates a very high motivation among patients and personnel to conduct the study according to protocol. Consequently, we are able to report the study results with few missing data items.

Data on both visual field and optic disc outcomes were obtained by masked observers following standardized and unbiased methods. Visual field criteria were defined using modern statistical programs for visual field analysis and were therefore numerical and objective. Glaucoma change probability maps provided early yet specific detection of visual field progression. These maps were based on pattern deviation rather than total deviation, strongly reducing any confounding effects of progressing lens opacities on visual field outcomes.[38] The number of significantly progressing test point locations and the reproducibility of such progressed locations required to reach a visual field endpoint were specified prior to the EMGT, based on retrospective studies of a large number of clinical visual field series. These visual field progression criteria were not changed during the study; they permitted immediate objective recognition of tentative and definite perimetric progression based on printouts that could be judged while the patient was still in the clinic. This feature allowed immediate scheduling of extra visits when tentative progression was found, as well as discussions of visual field progression and treatment alternatives with the patient when definite progression occurred and thereafter. The computer-assisted visual field analysis also obviated the need for a visual field reading center.

Because glaucoma cases were newly detected and previously untreated, no residual effects of previous drug therapy or surgery were possible. Most patients were identified through a screening of a large population group of relevant age in a designated geographical area, and the screening examination included a majority of invited citizens. This knowledge is valuable when deriving conclusions on glaucoma management from the results of this study and particularly when assessing the implications of the EMGT results on glaucoma screening.

Interpretation of the EMGT results must also consider potential limitations of the study. One such limitation is that the study involved a specific, homogeneous patient population: almost all patients were white. This certainly limits the generalizability of the study results to other populations. Patients also had relatively early glaucoma, so our study results cannot provide quantitative data pertaining to patients with high IOP levels (>30 mm Hg) or advanced visual field loss. Another necessary limitation was that the initial randomization to treatment or no treatment was maintained only as long as progression did not occur; this shortened the ascertainment period of the glaucoma's natural history, which was a secondary EMGT aim. The study, therefore, does not include long-term follow-up of untreated patients beyond EMGT progression.

The EMGT used a new criterion to define visual field progression, which was unchanged throughout the entire study. The EMGT definition allowed the detection of small amounts of progression, an important safety aspect of the trial. This criterion was based on knowledge gathered during the 1980s on the nature of random variability in glaucomatous visual fields[57] and permitted an earlier separation between treatment arms than more conventional criteria (eg, linear regression of MD values or changes in numbers of test point locations developing significant or absolute visual field loss). However, the EMGT visual field criterion is not as intuitively comprehensible as other simpler criteria. To address this issue and to provide a basis for a later article that will present clinically useful conclusions from the study results, we have compared the EMGT criterion with other criteria in a separate report (A.H., M.C L., B.B., B.B., and M.H., for the EMGT Group, unpublished data, 2002).

The EMGT's visual field progression criterion showed excellent sensitivity and specificity in a comparison of the performance of such criteria used in the EMGT, AGIS, and CIGTS. In this pilot study, the EMGT criteria detected progression in 20 of 20 series of visual fields from EMGT patients who had been deemed to have definite progression by 2 independent glaucoma experts. Progression was sustained in 90.8% of visits following the visit when definite progression was first found. Specificity was determined from another 20 series of visual fields that had been classified as stable by the same experts. It was found to be high; none of the 20 stable visual fields were falsely labeled as progressing with the EMGT's criterion (A.H., M.C.L., B.B., B.B., and M.H., for the EMGT Group, unpublished data, 2002).

IMPLICATIONS OF STUDY RESULTS

The EMGT is the first randomized study providing a long-term comparison of progression between treated and untreated patients with primary open-angle glaucoma, normal-tension glaucoma, and exfoliation glaucoma that shows a definite positive effect of IOP reduction. This information is valuable because treatment effects in chronic open-angle glaucoma have been largely unknown, and there is very little information about the natural history of glaucoma.

Although these results provide quantitative data directly applicable to most patients with glaucoma, our eligibility criteria led to a study population with earlier disease than a typical clinical glaucoma population.[58] At the population screening, 19% of patients with newly detected early manifest glaucoma were ineligible for the EMGT because their IOP exceeded the inclusion criteria (mean IOP >30 mm Hg or any IOP >35 mm Hg), and an additional 10% could not participate because the visual field damage exceeded our limits for inclusion. The EMGT results provide little information directly pertaining to patients with advanced glaucoma and high IOP levels; however, as mentioned earlier, future analyses will likely show that the current results are indeed applicable to such patients.

The EMGT data have important clinical implications. The results not only confirm previous beliefs that IOP reduction is beneficial but also provide new knowledge on rates of disease progression, with and without treatment, in patients with various characteristics. Our results therefore strengthen the rationale for current standard clinical management. In addition, they afford a basis for increased efforts to achieve earlier detection of the

Early Manifest Glaucoma Trial Group

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disease and for tailoring the clinical management of glaucoma to the needs of the individual patient. The latter issues are worth special consideration and will be addressed separately.

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SURVEY OF OPHTHALMOLOGY VOLUME 45 • SUPPLEMENT 4 • MAY 2001

Six-Month Comparison of Bimatoprost Once-Daily and Twice-Daily with Timolol Twice-Daily in Patients with Elevated Intraocular Pressure

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Abstract. The efficacy and safety of bimatoprost, a member of a new class of pharmacological agents called *prostamides*, were compared with the efficacy and safety of timolol in patients with glaucoma or ocular hypertension. Pooled 6-month results from two ongoing, multicenter, randomized, double-masked, clinical trials were analyzed. Patients were randomized in a 2:2:1 ratio to treatment with bimatoprost 0.03% once a day ([QD] n = 474), bimatoprost 0.03% twice a day ([BID] n = 483), or timolol 0.5% BID (n = 241). Scheduled visits were at prestudy, baseline, week 2, week 6, month 3, and month 6. The primary outcome measure was in diurnal intraocular pressure ([IOP] 8 AM, 10 AM, 4 PM, 8 PM). Bimatoprost QD provided significantly greater mean IOP reductions from baseline than timolol at every time of the day and at each study visit ($p \leq .05$). BID dosing of bimatoprost also provided significantly greater mean IOP reductions than timolol at most timepoints, but was not as effective as QD dosing. The IOP lowering provided by bimatoprost QD was sustained for 6 months. At month 6, the mean IOP reduction from baseline at 10 AM was 8.1 mm Hg (33%) with bimatoprost QD, 6.3 mm Hg (26%) with bimatoprost BID, and 5.6 mm Hg (23%) with timolol. Low target pressures were achieved by a significantly higher percentage of patients in the bimatoprost QD group than in the timolol group. At 10 AM (peak timolol effect) at month 6, IOP ≤ 17 mm Hg was achieved by 63.9% of bimatoprost QD patients, compared with 37.3% of timolol patients ($p < .001$). Bimatoprost was safe and well-tolerated, with few discontinuations due to adverse events. The most frequent side effect was trace-to-mild conjunctival hyperemia. Changes in iris pigmentation were reported in 1.1% of bimatoprost patients. There were no other significant findings in slit lamp examinations, ophthalmoscopy, visual acuity, or visual fields, and systemic safety parameters were also unaffected. Together these results indicate that bimatoprost QD is statistically and clinically superior to timolol in lowering IOP, and is safe and well-tolerated in patients with glaucoma or ocular hypertension. **(Surv Ophthalmol 45(Suppl 4):**S361–S368, 2001.

Key words. bimatoprost • clinical trial • intraocular pressure • ocular hypertension • prostamide • timolol

Bimatoprost is a member of a new class of pharmacologically unique intraocular pressure (IOL)-lowering agents called *prostamides*.[8] Prostamides exist naturally and demonstrate potent and highly efficacious IOP-lowering activity (Chen J, et al. British Pharmacological Society, 2000 [abstract]; Krauss AH-P, et al. Association for Ocular Pharmacology and Therapeutics, 2000 [abstract]).

In a phase II, 1-month clinical trial, bimatoprost 0.03% (Lumigan™, Allergan, Inc.) dosed once or

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twice daily was shown to be significantly more effective than timolol 0.5% dosed twice daily in lowering IOP in patients with primary open-angle glaucoma or ocular hypertension.[13] Bimatoprost 0.03% has subsequently been compared with timolol in two large, phase III clinical trials. The 3-month results of one of these studies, reported previously, showed that bimatoprost 0.03% dosed either once or twice daily was superior to timolol BID in IOP lowering.[4] Bimatoprost provided effective diurnal control of IOP over 3 months of treatment, and higher percentages of patients receiving bimatoprost reached low target pressures.

The combined 6-month results of these two large, randomized, multicenter, double-masked trials involving patients with glaucoma or ocular hypertension are summarized in this report. The IOP-lowering efficacy, safety, and tolerability of bimatoprost 0.03% ophthalmic solution, administered once or twice daily, were compared with that of timolol 0.5% given twice daily.

Materials and Methods

Two multicenter, double-masked, randomized, parallel-group, active-controlled comparison clinical trials were conducted. Both studies were extended to 1 year. The study protocols were identical, and data have been pooled here for analysis. Scheduled visits were at prestudy, baseline (day 0), week 2, week 6, month 3, and month 6.

PATIENT SELECTION

Adult patients with bilateral chronic open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma, pigmentary glaucoma, or ocular hypertension, based on the determination of the investigators, were recruited for the studies. Ocular hypotensive medications were washed out prior to baseline for 4 days (parasympathomimetics and carbonic anhydrase inhibitors), 2 weeks (sympathomimetics and topical

TABLE 1

Patient Characteristics

	Bimatoprost QD (n = 474)	Bimatoprost BID (n = 483)	Timolol (n = 241)	*p* Value
Age (years)				.742
Mean ± SEM	61.7 ± 0.6	61.6 ± 0.5	61.0 ± 0.7	
Sex				.158
Male	43.5% (206)	48.4% (234)	41.9% (101)	
Female	56.5% (268)	51.6% (249)	58.1% (140)	
Race				.282
Caucasian	76.6% (363)	76.8% (371)	71.8% (173)	
Black	18.1% (86)	17.0% (82)	19.1% (46)	
Asian	1.3% (6)	2.7% (13)	2.5% (6)	
Hispanic	4.0% (19)	3.1% (15)	6.2% (15)	
Other	0	0.4% (2)	0.4% (1)	
Iris color				.547
Blue	26.6% (126)	21.5% (104)	20.3% (49)	
Brown	35.4% (168)	35.8% (173)	39.4% (95)	
Green	3.0% (14)	3.3% (16)	6.6% (16)	
Dark Brown	10.1% (48)	10.4% (50)	10.8% (26)	
Yellow-Brown	12.7% (60)	12.8% (62)	9.1% (22)	
Gray	1.1% (5)	1.2% (6)	0.4% (1)	
Blue-Gray	4.4% (21)	5.2% (25)	4.1% (10)	
Green-Brown	2.7% (13)	3.3% (16)	4.1% (10)	
Blue/Gray-Brown	2.7% (13)	4.8% (23)	2.1% (5)	
Other	1.3% (6)	1.7% (8)	2.9% (7)	
Ophthalmic diagnosis				.892
Glaucoma	57.0% (270)	55.9% (270)	55.2% (133)	
Ocular hypertension (OHT)	41.4% (196)	41.4% (200)	44.0% (106)	
Glaucoma/OHT	1.7% (8)	2.7% (13)	0.8% (2)	
Washout required				.253
Yes	63.3% (300)	66.9% (323)	61.0% (147)	
No	36.7% (174)	33.1% (160)	39.0% (94)	
IOP at baseline (mm Hg, mean ± SEM)				
8 AM	26.0 ± 0.2	25.9 ± 0.1	25.8 ± 0.2	.739
10 AM	24.7 ± 0.2	24.6 ± 0.2	24.1 ± 0.2	.091
4 PM	23.8 ± 0.2	23.7 ± 0.2	23.2 ± 0.3	.172
8 PM*	22.1 ± 0.2	22.2 ± 0.2	22.4 ± 0.3	.619

*IOP measurements at 8 PM at selected sites only (bimatoprost QD: n = 124; bimatoprost BID: n = 123; timolol: n = 65).

adrenergic agonists), or 4 weeks (topical beta-blockers, prostaglandins, and combination therapy). Patients were required to have post-washout IOP ≥ 22 mm Hg and ≤ 34 mm Hg and best-corrected visual acuity of 20/100 or better in each eye.

Primary exclusion criteria included any contraindication to beta-blocker therapy, functionally significant visual field loss within the past year, filtering surgery within the past 6 months or other intraocular surgery within the past 3 months, required use of ocular medications other than the study medications during the trial, and pregnancy, lactation, or childbearing potential.

DRUG ADMINISTRATION

At baseline, patients were randomly assigned in a 2:2:1 ratio based on a block size of 5 to receive bimatoprost 0.03% once a day (QD), bimatoprost 0.03% twice a day (BID), or timolol 0.5% BID. The bimatoprost QD treatment group received bimatoprost in the evening and a vehicle control solution in the morning in order to maintain the study mask. Medications were self-instilled at 12-hour intervals (8 AM, 8 PM). Medications were supplied in identical-appearing masked bottles and were color coded for use in the morning or evening.

EFFICACY AND SAFETY VARIABLES

The primary outcome measure was diurnal IOP. Measurements were performed at 8 AM, immediately preceding the instillation of the morning dose of study medication, and at 10 AM and 4 PM. At selected sites, patients also had IOP recorded at 8 PM.

Secondary outcome measures included adverse events, biomicroscopy, visual acuity, visual fields, ophthalmoscopy, heart rate, blood pressure, blood chemistry, hematology, and urinalysis. The severity of adverse events was evaluated using the following definitions as guidelines: mild = awareness of sign or symptom, but easily tolerated; moderate = enough discomfort to cause interference with usual activity; severe = incapacitating with inability to work or do usual activity. To assess changes in iris pigmentation, the investigator(s) at each site compared Polaroid photographs of patients' eyes from baseline and at follow-up visits. A color calibration strip was photographed beside the eye to aid in assessing pigmentation changes. At selected sites, laser flare meter readings were recorded prior to fluorescein instillation or pupil dilation.

STATISTICAL ANALYSIS

Continuous variables were analyzed using ANOVA, and within-group changes from baseline were analyzed with paired t-tests. Comparisons of

TABLE 2

Patient Disposition

	Bimatoprost QD	Bimatoprost BID	Timolol
Enrolled	474	483	241
Completed	430	398	223
Discontinuations			
Lack of efficacy	0.4%	1.9%	2.5%
Ocular hyperemia	3.4%	5.2%	0.4%
Other ocular adverse events[a,b,c]	1.7%	6.2%	0.8%
Systemic adverse events[d,e,f]	2.7%[d]	2.9%	2.1%
Protocol violations, administrative, and other	1.9%	3.1%	1.6%
Clinical discontinuations[g]	7.4%	14.5%	5.8%

[a]In the bimatoprost QD group included: eye pruritus, irritation of eye, eye dryness, blepharal pigmentation, eye pain, foreign body sensation, allergic conjunctivitis, burning sensation in eye, photophobia, epiphora, eyelid edema, iritis, conjunctival edema, asthenopia, erythema of eyelid, eye discharge, uveitis, corneal erosion.

[b]In the bimatoprost BID group included: eye pruritus, irritation of eye, eye dryness, blepharal pigmentation, eye pain, foreign body sensation, allergic conjunctivitis, burning sensation in eye, photophobia, epiphora, eyelid edema, iritis, conjunctival edema, asthenopia, erythema of eyelid, eye discharge, uveitis, growth of eyelashes, keratitis, optic nerve (NOS), visual disturbance, visual field defect, conjunctival hemorrhage, edema periorbital, eyelid pain, eyelid pruritus, visual field worsened.

[c]In the timolol group included: irritation of eye, foreign body sensation, conjunctival edema, visual field defect.

[d]In the bimatoprost QD group included: asthenia, dizziness, facial paralysis, headache, chest pain, dyspnea, arteritis, arthralgia, asthma, lung carcinoma, coordination abnormality, glossitis, hepatic carcinoma, myocardial infarct, prostatic carcinoma.

[e]In the bimatoprost BID group included: asthenia, dizziness, facial paralysis, headache, diarrhea, anxiety, arthritis, bone fracture, breast carcinoma, coronary artery disorder, cough increased, depression, hirsutism, insomnia, nervousness, rhinitis, skin hypertrophy, tingling.

[f]In the timolol group included chest pain, dyspnea, accidental injury, infection, respiratory disorder.

[g]Clinical discontinuations were patients discontinued due to lack of efficacy or adverse events.

mean IOP reductions between the bimatoprost and timolol treatment groups were carried out using Dunnett's procedure adjusting for multiple comparisons. Nominal categorical variables were analyzed using Pearson's chi-square test, Fisher's exact test, or Cochran-Mantel-Haenszel methods. Ordinal categorical variables were analyzed using the Wilcoxon rank-sum test, with within-group changes from baseline analyzed using the Wilcoxon signed-rank test. All randomized patients were included in the analysis, and for patients who discontinued prior to the month 6 visit or who missed the month 6 visit, the last observed data were carried forward in the analysis for all subsequent timepoints. Similar results (not shown) were obtained when the analysis used the per protocol patient population and last observations were not carried forward. Analysis of IOP used only data from the eye with the higher IOP at 8 AM on day 0. For all pairwise between-group comparisons of IOP, tests of noninferiority and superiority were performed.[10] The α level for statistical significance was 0.05. Noninferiority of bimatoprost was claimed when the upper limit of the 95% confidence interval (CI) of the difference (bimatoprost − timolol) was $\leq$ 1 mm Hg. Superiority was claimed when the upper limit of the CI was $<$ 0 mm Hg.

PATIENT CHARACTERISTICS AND DISPOSITION

A total of 1198 patients were enrolled in the two studies; 474 patients received bimatoprost QD, 483 patients received bimatoprost BID, and 241 patients received timolol. There were no statistically significant among-group differences in demographic characteristics, clinical diagnosis, or mean IOP at baseline (Table 1). Most patients were Caucasian, with brown or blue irides and a diagnosis of glaucoma. Washout of a topical beta-blocker was required for 36.9% of bimatoprost QD patients, 42.4% of bimatoprost BID patients, and 39.0% of timolol patients. Six months of therapy were completed by 90.7% of bimatoprost QD patients compared with 92.5% of timolol patients and 82.4% of bimatoprost BID patients (Table 2).

Results

IOP-LOWERING EFFICACY

Once-daily bimatoprost provided significantly lower mean IOP than timolol BID at 10 AM (peak timolol effect) at every follow-up visit ($p < .001$, Fig. 1). Mean IOP at 10 AM at follow-up visits ranged from 16.4 to 16.9 mm Hg with bimatoprost QD and from 18.2 to 19.0 mm Hg with timolol. Mean IOP ranged from 18.0 to 18.3 mm Hg in the bimatoprost BID group. Similarly, bimatoprost QD provided significantly greater mean IOP reductions from baseline than timolol ($p < .001$) at 10 AM at month 6 (Fig. 2) and at every other follow-up visit. Mean IOP reductions at 10 AM ranged from 7.8 to 8.3 mm Hg (31.7–33.6%) with bimatoprost QD and from 5.1 to 5.8 mm Hg (21.1–24.2%) with timolol. Mean IOP reductions in the bimatoprost BID group ranged from 6.3 to 6.6 mm Hg (25.7–26.8%). QD dosing of bimatoprost was significantly more effective than BID dosing at 10 AM at all follow-up visits ($p < .001$).

Over the 12-hour course of diurnal IOP measurements, bimatoprost QD provided significantly lower mean IOP than timolol at every time of the day and at each follow-up visit ($p < .001$). The effects of the bimatoprost QD regimen on IOP were sustained over the course of the 6-month follow-up with no evidence of drift. The mean IOP in the bimatoprost QD group was consistently 2 to 3 mm Hg lower than that in the timolol group, and the difference be-

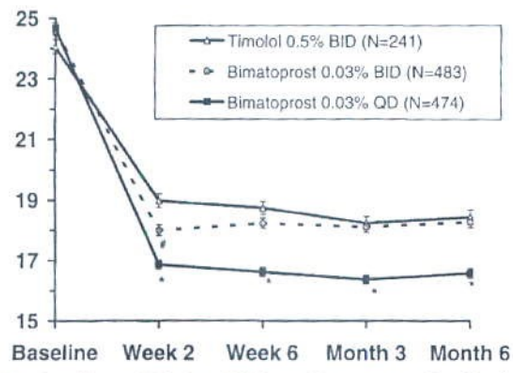

Fig. 1. Mean IOP (± SEM) at 10 AM at each scheduled study visit. Mean IOP values were statistically significantly lower in the bimatoprost QD group than in the timolol group at each follow-up visit. *$p < .001$ vs timolol and bimatoprost BID; #$p = .001$ vs timolol.

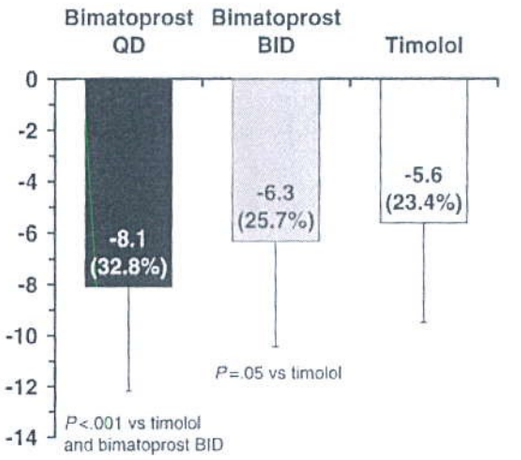

Fig. 2. Mean IOP changes from baseline at 10 AM at the month 6 visit.

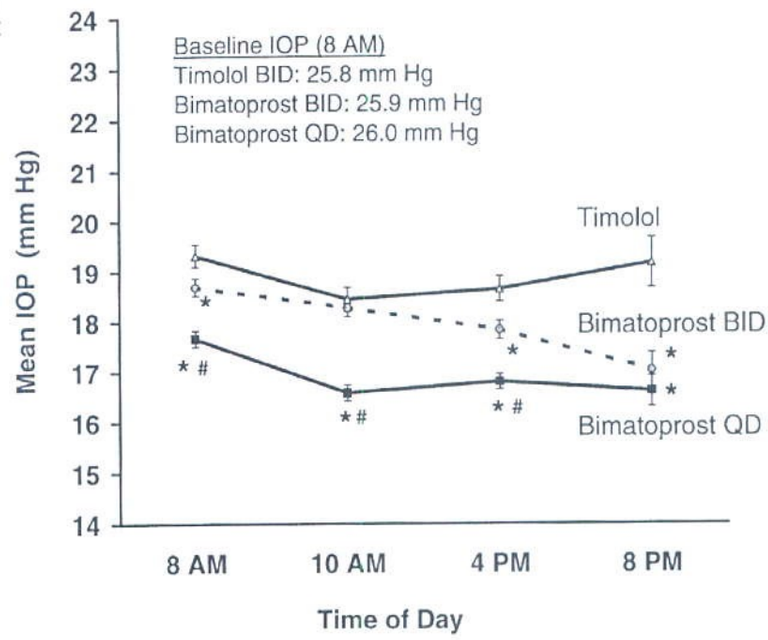

Fig. 3. Mean diurnal IOP (± SEM) at month 6. *p < .029 vs timolol; #p < .001 vs bimatoprost BID.

tween groups reached statistical significance even at the 8 PM timepoint when sample sizes were smaller. Twice-daily bimatoprost also reduced IOP significantly better than timolol at most timepoints, but was not as effective as the once-daily regimen. At month 6, mean IOP values ranged from 16.6 to 17.7 mm Hg with bimatoprost QD, compared with 18.4 to 19.3 mm Hg with timolol (Fig. 3). Mean IOP values ranged from 17.0 to 18.7 mm Hg in the bimatoprost BID treatment group.

A significantly higher percentage of patients achieved low target IOP levels with bimatoprost QD than with timolol. Fig. 4 shows the response rates of patients at month 6 at 10 AM. A target IOP of ≤ 17 mm Hg was achieved by 63.9% of bimatoprost QD patients compared with 37.3% of timolol patients ($p < .001$). In the bimatoprost BID group, 42.7% of patients achieved a target IOP of ≤ 17 mm Hg (data not shown). For a target IOP of ≤ 15 mm Hg, the response rate was 35.9% in the bimatoprost QD group compared with 20.3% in the timolol group ($p < .001$).

SAFETY AND TOLERABILITY

All treatment regimens were safe and well-tolerated. Most treatment-related adverse events were ocular or periocular and mild in severity. The only treatment-related adverse events occurring in more

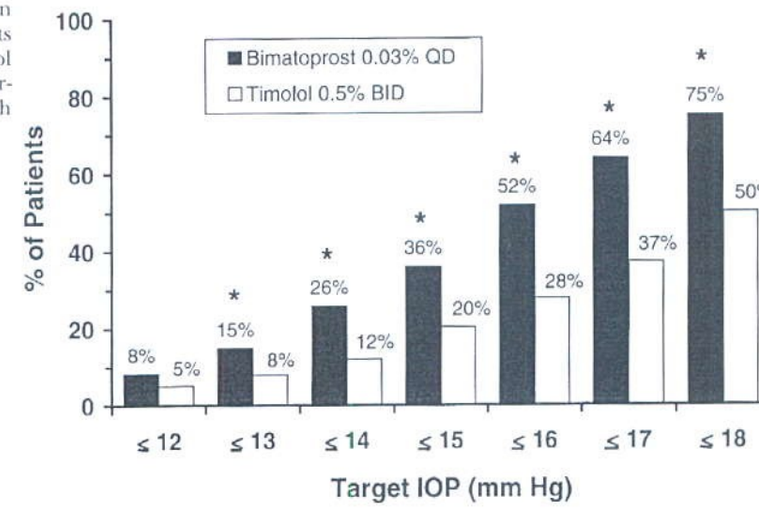

Fig. 4. Response rates. Data shown represent the percentage of patients in the bimatoprost QD and timolol treatment groups that achieved target IOP levels at 10 AM at the month 6 study visit. *p ≤ .007 vs timolol.

than 5% of bimatoprost QD patients were conjunctival hyperemia, eyelash growth, eye pruritus, eye dryness, and burning sensation in the eye. Mild conjunctival hyperemia was reported as a treatment-related adverse event in 31.2% of bimatoprost QD patients, 39.5% of bimatoprost BID patients, and 7.9% of timolol patients ($p < .001$ for bimatoprost QD or BID vs timolol). Greater than mild conjunctival hyperemia was reported as a treatment-related adverse event in 10.6% of patients receiving bimatoprost QD, 14.4% of patients receiving bimatoprost BID, and 1.7% of timolol-treated patients ($p < .001$ for bimatoprost QD or BID vs timolol). However, biomicroscopy showed a high incidence of conjunctival hyperemia at baseline in all three groups, with the greatest incidence in the bimatoprost QD group. The medication history of the patients could have contributed to the relatively high incidence of conjunctival hyperemia at baseline. Conjunctival hyperemia was present at baseline (prior to administration of study medication) in 25.1% of the bimatoprost QD patients and in 17.8% of the timolol patients (Table 3). After 6 months of therapy, greater than a mild (1 unit) increase in conjunctival hyperemia from baseline was noted in 6.2% of bimatoprost QD patients and in 0.4% of timolol patients (Table 3).

With respect to other treatment-related adverse events, eyelash growth was reported in 35.7% of bimatoprost QD patients, 48.4% of bimatoprost BID patients, and 3.7% of timolol patients ($p < .001$ for bimatoprost QD or BID vs timolol). Eye pruritus was reported in 13.9% of bimatoprost QD patients, 17.0% of bimatoprost BID patients, and 2.9% of patients receiving timolol ($p < .001$ for bimatoprost QD or BID vs timolol). Eye dryness was reported in 6.8% of bimatoprost QD patients, 9.9% of bimatoprost BID patients, and 2.1% of timolol patients ($p < .008$ for bimatoprost QD or BID vs timolol). Burning was more frequent with timolol than with either bimatoprost regimen (10% with timolol, versus 5.7% with bimatoprost QD and 5.8% with bimatoprost BID; $p = .062$).

Adverse events were not associated with sequelae and led to few discontinuations. In the bimatoprost QD treatment group, 7.0% of patients discontinued due to adverse events, compared with 3.3% of timolol patients and 12.6% of bimatoprost BID patients. Conjunctival hyperemia led to the discontinuation of 3.4% of bimatoprost QD patients, 5.2% of bimatoprost BID patients, and 0.4% of timolol patients.

Based on the determination of the masked investigators, changes in iris pigmentation were found in 5 (1.1%) of bimatoprost QD patients, in 6 (1.2%) of bimatoprost BID patients, and in no timolol patients. Seven of the 11 cases in the bimatoprost treatment groups were reported at one investigational site. There were no significant mean changes in ophthalmoscopy, laser flare meter readings, visual acuity, or visual fields, and systemic safety parameters were also unaffected in the bimatoprost treatment groups.

Discussion

Analysis of the pooled 6-month results of 2 large, phase III trials demonstrates that bimatoprost QD is superior to timolol in lowering IOP throughout the course of the day. The difference in mean IOP lowering between the bimatoprost QD and timolol treatment groups, 2 to 3 mm Hg, is statistically significant and most likely clinically relevant. Bimatoprost QD provides excellent diurnal IOP control that is sustained for 6 months with no evidence of loss of efficacy. Furthermore, significantly higher percentages of patients achieve very low target pressures with bimatoprost QD.

The 3-month results of one of these studies were previously reported.[4] Analysis of the pooled 6-month results of both studies confirms the conclusions drawn from the earlier analysis: bimatoprost is superior to timolol in IOP-lowering efficacy, and bimatoprost is a once-daily medication. This analysis further shows that the effects of bimatoprost QD on IOP are maintained over at least 6 months of treatment. Using an intent-to-treat analysis with last observation carried forward, substantial mean reductions in IOP from

TABLE 3

Biomicroscopy of Conjunctival Hyperemia[a]

	Bimatoprost QD (n = 474)	Bimatoprost BID (n = 483)	Timolol (n = 241)	*p* Value
Patients with baseline conjunctival hyperemia[b]	25.1% (119/474)	21.7% (105/483)	17.8% (43/241)	.082
Patients with more than a mild increase at month 6[c]	6.2% (27/433)	5.9% (24/405)	0.4% (1/224)	.002[d]

[a]Based on the eye with greater severity of scores. Conjunctival hyperemia was graded on a scale of 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, 3 = severe.

[b]Patients with trace or greater conjunctival hyperemia at the baseline study visit.

[c]Patients with more than a 1 unit increase from baseline in conjunctival hyperemia scores at month 6.

[d]In pairwise comparisons $p = .001$ for bimatoprost QD or BID vs timolol.

baseline (>30%) were documented with bimatoprost from week 2 through month 6.

The medication history of patients may possibly influence their responsiveness to IOP-lowering agents. However, the percentage of patients requiring washout was similar in the three treatment groups. Further, IOP lowering in the timolol group was robust and consistent with results previously reported with timolol. These findings suggest that it is unlikely that previous treatment of patients in the study population confounded our results showing greater efficacy with bimatoprost than with timolol.

The reasons for loss of efficacy with twice-daily versus once-daily dosing of bimatoprost are unknown. Twice-daily dosing of bimatoprost may give concentrations that are over the top of the dose-response curve, resulting in reduced efficacy. Regardless of the mechanism for the dosing effect, it is clear that bimatoprost should be used once daily, a dosing schedule that may enhance compliance.

There is a clear need to reduce pressures in patients with IOP higher than normal ranges and with glaucomatous optic neuropathy. Elevated IOP is the most common risk factor for open-angle glaucoma, and some studies suggest that reduction of IOP in ocular hypotensive patients decreases the risk for visual field loss.[6,7,9] The Normal Tension Glaucoma collaborative study further demonstrated that >30% reductions of IOP slow the rate of visual field deterioration in patients with IOP in normal ranges.[1] These findings have suggested a clinical strategy for glaucoma management that involves reducing pressures to individual target levels. For any given patient with glaucoma, an appropriate target IOP will be influenced by factors including the rate and extent of visual field loss, the IOP at which damage to the optic nerve occurred, patient age, etc., and typical target IOP levels may range from 12 to 18 mm Hg.[12,17] The present analysis of pooled 6-month results from two studies shows that patients treated with bimatoprost QD are almost twice as likely as patients treated with timolol to reach target IOP levels in this range. This outstanding response to bimatoprost may allow a substantially higher percentage of glaucoma patients to be controlled on a simple, once-daily, single drug regimen.

Glaucoma is a 24-hour-a-day disease, and its effective management requires IOP control throughout the day. Indeed, Asrani and colleagues have recently reported that large fluctuations in diurnal IOP are a risk factor for open-angle glaucoma.[3] Analysis of the pooled 6-month data from the bimatoprost trials has demonstrated that bimatoprost QD provides very effective diurnal IOP control. Bimatoprost therapy was associated with flat diurnal IOP curves, indicating that bimatoprost effectively controls IOP fluctuations throughout the day that could otherwise result in optic nerve damage.[11,16] Bimatoprost QD proved to have a favorable safety/tolerability profile over 6 months of treatment. Adverse events were mostly mild, were not associated with sequelae, and led to few discontinuations. More patients in the bimatoprost groups (particularly with the BID regimen) than in the timolol group reported adverse events. However, a deliberate selection bias (for safety reasons) in the study design, which excluded patients for previous intolerability to beta-blockers, likely caused an underestimation of the rate of adverse events with timolol.

Increased iris pigmentation was reported in only 1.1% of bimatoprost patients. The incidence was low, even though iris pigmentation was carefully monitored. By comparison, in the 6-month phase III studies of latanoprost,[2,5,14] increased iris pigmentation was reported in 6.6%, 3.1%, and 10.1% of patients treated with latanoprost QD in the three trials.[2,5,14] Approximately 22% of latanoprost-treated patients[15] and 16% of bimatoprost-treated patients had green-brown or yellow-brown irides which are most susceptible to changes in iris pigmentation. These results suggest that increased iris pigmentation may occur less frequently with bimatoprost 0.03% QD than with latanoprost 0.005% QD, and it will be worthwhile to compare the incidence of iris pigmentation changes in bimatoprost- and latanoprost-treated patients after 1 year of therapy.

Conclusions

Bimatoprost 0.03%, given once or twice daily, provides statistically and clinically superior IOP lowering compared with timolol 0.5% BID in patients with glaucoma or ocular hypertension. Once-daily dosing of bimatoprost is most effective and provides IOP reductions 2 to 3 mm Hg greater than those provided by timolol. Bimatoprost QD is safe and well tolerated, and significantly more patients achieve low target pressures with bimatoprost QD than with timolol BID.

Appendix

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CLINICAL SCIENCES

One-Year, Randomized Study Comparing Bimatoprost and Timolol in Glaucoma and Ocular Hypertension

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Objective: To compare bimatoprost with timolol maleate in patients with glaucoma or ocular hypertension.

Methods: In 2 identical, multicenter, randomized, double-masked, 1-year clinical trials, patients were treated with 0.03% bimatoprost once daily (QD) (n=474), 0.03% bimatoprost twice daily (BID) (n=483), or 0.5% timolol maleate BID (n=241).

Main Outcome Measures: Diurnal intraocular pressure (IOP) at 8 AM, 10 AM, and 4 PM and safety variables (IOP was also measured at 8 PM at selected sites).

Results: Bimatoprost QD provided significantly lower mean IOP than timolol at every time of the day at each study visit ($P<.001$). This was also true for bimatoprost BID at most time points, but the efficacy was not as good as that of the QD regimen. At 10 AM (peak timolol effect) at month 12, the mean reduction in IOP from baseline was 7.6 mm Hg (30%) with bimatoprost and 5.3 mm Hg (21%) with timolol ($P<.001$). A significantly higher percentage of patients receiving bimatoprost QD (58%) than timolol (37%) achieved IOPs at or below 17 mm Hg (10 AM, month 12; $P<.001$). The most common adverse effect with bimatoprost was hyperemia (significantly higher with bimatoprost QD than timolol; $P<.001$).

Conclusions: Bimatoprost QD provides sustained IOP lowering superior to timolol or bimatoprost BID and achieves low target IOPs in significantly more patients.

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BIMATOPROST IS a synthetic prostamide analogue that potently lowers intraocular pressure (IOP).[1,2] Bimatoprost has been shown to help a substantially greater percentage of patients to achieve low IOPs (≤17 mm Hg) than does timolol maleate.[3,4]

Two large-scale, double-masked, phase 3 clinical (pivotal) trials were undertaken to evaluate the safety and efficacy of once- (QD) or twice-daily (BID) regimens of 0.03% bimatoprost ophthalmic solution (Lumigan; Allergan Inc, Irvine, Calif) compared with timolol maleate BID in patients with glaucoma or ocular hypertension. Interim safety and efficacy results were evaluated at 3 and 6 months without breaking study masking for the patients or the study investigators.[3,4] These analyses demonstrated that bimatoprost QD was more effective in lowering IOP than was timolol throughout the day at all study visits through 6 months ($P\leq.001$). Moreover, a significantly higher percentage of patients treated with bimatoprost QD achieved low pressures (≤17 mm Hg) than did patients treated with timolol (the highest P value for the comparison to timolol was .007). Bimatoprost BID was also more effective than timolol at most time points, but was slightly less effective than the QD regimen.

Because glaucoma is a chronic disease, it is important to evaluate the long-term efficacy and safety of new glaucoma medications. The present report describes the pooled 12-month results from the 2 pivotal clinical trials comparing bimatoprost with timolol.

METHODS

STUDY DESIGN

Two multicenter, randomized, double-masked, parallel-group, active-controlled trials were conducted to compare the safety and efficacy of bimatoprost QD, bimatoprost BID, and timolol maleate BID. The study protocols were identical, and the data were pooled for analysis.

Both studies were conducted in accordance with the Declaration of Helsinki and the guidelines set forth by the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for

Human Use and the United States Code of Federal Regulations CFR21. All investigators obtained appropriate institutional review board or ethics committee approval before initiating the study, and all patients provided written informed consent before any study-related procedures or changes in treatment.

PATIENTS

Key inclusion criteria included a diagnosis of primary open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoexfoliative glaucoma, pigmentary glaucoma, or ocular hypertension. Washout of ocular hypotensive medications occurred before the baseline visit, and patients were required to have a postwashout IOP of at least 22 mm Hg and no greater than 34 mm Hg and a best-corrected visual acuity of 20/100 or better in each eye. Washout periods ranged from 4 days to 4 weeks, depending on the medication. Parasympathomimetics and carbonic anhydrase inhibitors were washed out for 4 days, sympathomimetics and topical α-agonists were washed out for 2 weeks, and topical β-blockers (alone or in combination) and topical prostaglandins were washed out for 4 weeks. Key exclusion criteria included any contraindication to topical β-blocker therapy, functionally significant visual field loss within the past year, filtering surgery within the past 6 months, or other intraocular surgery within the past 3 months. Women who were pregnant, nursing, planning a pregnancy, or of childbearing potential and not using a reliable form of contraception were also excluded.

TREATMENT ASSIGNMENT AND DRUG ADMINISTRATION

At baseline, patients were randomly assigned in a 2:2:1 ratio to receive 0.03% bimatoprost QD, 0.03% bimatoprost BID, or 0.5% timolol maleate BID. The study sponsor generated the allocation sequence. The bimatoprost QD group received bimatoprost in the evening and a vehicle control solution in the morning to maintain the study mask. Medications were supplied in identical-appearing bottles that were color coded for use in the morning or the evening. Patients were instructed to self-instill their medication into both eyes at approximately 8 AM and 8 PM. On study visits, the morning dose was administered by the study investigator immediately after the first examination (at approximately 8 AM). Scheduled visits occurred before the study, at baseline (day 0), weeks 2 and 6, and months 3, 6, 9, and 12.

EFFICACY AND SAFETY VARIABLES

The primary outcome measure was diurnal IOP. Measurements were performed at 8 AM, immediately preceding the instillation of the morning dose of the study medication, and at 10 AM and 4 PM. Patients at selected sites (approximately 25% of all enrolled) also had IOP recorded at 8 PM (bimatoprost QD group, n=124; bimatoprost BID group, n=123; and timolol group, n=65). At month 9, IOP was recorded only at 8 AM and (at selected sites) 8 PM.

Safety measures included adverse events, visual acuity, visual fields, blood pressure, heart rate, blood chemistry, iris pigmentation, and results of hematology, urinalysis, laser flare photometry, biomicroscopy, and ophthalmoscopy readings. The severity of adverse events was assessed using the following definitions as guidelines: mild indicates awareness of a sign or a symptom, but easily tolerated; moderate, enough discomfort to cause interference with usual activities; and severe, incapacitating, with the inability to work or to perform usual activities. Hyperemia was evaluated on the following scale: none, 0; trace, 0.5; mild, 1.0; moderate, 2.0; and severe, 3.0. To evaluate changes in iris pigmentation, investigator(s) at each site compared Polaroid photographs (Polaroid Corporation, Cambridge, Mass) of each patient's eyes from the baseline and follow-up visits. A color-calibration strip was photographed beside the eye to verify consistent photographic color processing. A reading center at the sponsor site (consisting of 2 evaluators) also evaluated all photographs in a masked fashion and obtained slightly lower but generally comparable results. At selected sites, laser-flare photometry readings (using a Kowa FM-500 photometer; Kowa Company, Ltd, Chuo-ku, Tokyo, Japan) were recorded before fluorescein instillation or pupil dilation.

ANALYSES

All randomized patients were included in the efficacy analysis (intent-to-treat population), and for patients who discontinued before the month 12 visit, the last observed data were carried forward in the analysis for all subsequent time points. An intent-to-treat analysis with the last observation carried forward is the standard analysis for clinical studies of this type and is considered the most conservative analysis. It is much more difficult for a drug to appear to perform well in an intent-to-treat analysis with the last observation carried forward than in a per-protocol analysis because data from patients who did not receive study medications or who left the study early for any reason (including lack of efficacy) were kept in the efficacy analysis. Similar results (not shown) were obtained when the analysis used the per-protocol patient population without the last observations carried forward. Analysis of IOP used only data from the eye with the higher IOP at 8 AM at baseline (worse eye). If both eyes had the same IOP at baseline, the protocol required that the right eye be used. All patients who received at least 1 dose of study medication were included in the safety analyses.

Nominal categorical variables were analyzed using the Fisher exact test, the Pearson χ^2 test, or Cochran-Mantel-Haenszel methods.[5] Ordinal categorical variables were analyzed by means of the Wilcoxon rank sum test.[6] Continuous variables were analyzed using analysis of variance (ANOVA). We compared the frequency distributions of patients who had achieved desirable target IOP levels between groups. We performed the analysis for each target IOP at a given time point using the Pearson χ^2 test.

Tests of noninferiority and superiority were performed for the pairwise between-group comparisons of IOP at each time point. The α level for statistical significance was .05. Noninferiority of bimatoprost was claimed when the upper limit of the 95% confidence interval of the difference (bimatoprost minus timolol) was no greater than 1 mm Hg. Superiority was claimed when the upper limit of the confidence interval was less than 0 mm Hg. The power of each study was at least 0.85 to claim noninferiority of bimatoprost to timolol, based on a maximum difference of 1.5 mm Hg and using an estimate of variability (SD=4.052) from a prior study.[7] To test for an interaction of drug effect with patient race, the ANOVA was performed with the main effects of treatment group, race (black vs nonblack), and treatment-by-race interaction. The α level of significance for the interaction was set at .10 to accommodate a possible low power for this test.

We used the SAS computer program package (version 6.12 and version 7 on Unix; SAS Institute Inc, Cary, NC) for computation and analysis. All the variables were analyzed using SAS procedures (version 6.12 on Unix; SAS Institute Inc) with the exception of variables of adverse events, which were analyzed using version 8.

The sample-size estimate was based on the mean change in IOP from baseline. With 200 patients in each of the bima-

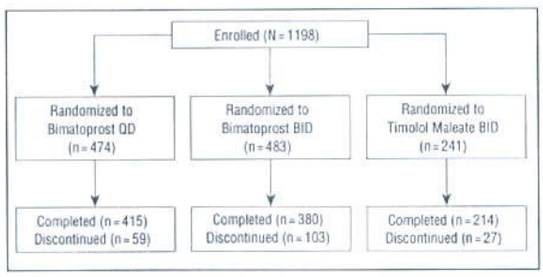

Figure 1. Trial profile. QD indicates once daily; BID, twice daily.

Table 1. Patient Disposition*

Patients	Treatment Groups, No. (%)		
	Bimatoprost QD (n = 474)	Bimatoprost BID (n = 483)	Timolol Maleate (n = 241)
Completed	415 (87.6)	380 (78.7)	214 (88.8)
Discontinued	59 (12.4)	103 (21.3)	27 (11.2)
Lack of efficacy	5 (1.1)	12 (2.5)	9 (3.7)
Adverse events†	40 (8.4)	71 (14.7)	12 (5.0)
Ocular	25 (5.3)	60 (12.4)	4 (1.7)
Nonocular	19 (4.0)	19 (3.9)	8 (3.3)
Protocol violations	2 (0.4)	1 (0.2)	0
Administrative	11 (2.3)	18 (3.7)	5 (2.1)
Other	1 (0.2)	1 (0.2)	1 (0.4)

*QD indicates once daily; BID, twice daily.
†Four patients in bimatoprost QD group, 8 in the bimatoprost BID group, and 0 in the timolol group discontinued owing to both ocular and nonocular adverse events.

toprost treatment groups and 100 patients in the timolol group, the power was 0.85 to claim that the mean IOP change from baseline with bimatoprost QD or BID was more than 1.5 mm Hg greater than that with timolol.

RESULTS

PATIENT POPULATION

A total of 1198 patients were enrolled in the 2 studies. Of these, 474 patients received bimatoprost QD, 483 received bimatoprost BID, and 241 received timolol at 61 study sites. Fifty sites were located in the United States, 4 in Canada, 5 in Australia, and 2 in New Zealand. The first patient was enrolled on November 3, 1998, and the last patient completed the 12 months of treatment on August 4, 2000. One thousand nine patients (84% of all enrolled) completed the study. Of the 189 patients who exited the study early, 123 discontinued owing to (mostly local) adverse events; 26, owing to lack of efficacy; 34, for administrative reasons; and 6, for other reasons. Patients were queried at each follow-up visit regarding use of study medication, and any changes in the study regimen were recorded. Patients or study visits could be excluded from the per-protocol analysis if significant changes in the study medication regimen were present. However, the present report is based on an analysis of the intent-to-treat population and includes all patients. Full details of patient flow through the study and exit status are given in **Figure 1** and **Table 1**.

We found no statistically significant among-group differences in demographic characteristics, clinical diagnosis, or baseline IOP (**Table 2**). We also found no among-group difference in medical history or the use of concomitant medication that could affect IOP (eg, β-blockers). Medical histories did not designate any patients as low responders to β-blockers or prostaglandin agonists. Most patients were white, with brown or blue irides and a diagnosis of glaucoma. Approximately 18% of the study population was black. None of the black patients were from the Australian or New Zealand sites, and it is consequently unlikely that any Australian aborigines (who have a very low incidence of glaucoma) were included in the black subpopulation.

IOP-LOWERING EFFICACY

Baseline IOP was similar among the treatment groups throughout the day (Table 2). Bimatoprost QD provided IOP control that was superior to that of timolol at all time points and all follow-up visits throughout the 12-month study. During all times of the day at which post-treatment measurements were obtained, mean IOP ranged from 16.2 to 18.0 mm Hg with bimatoprost QD and from 18.2 to 20.0 mm Hg with timolol. As has been reported previously, bimatoprost BID did not perform as well as bimatoprost QD.[3,4] The presentation of the efficacy results will focus on the data from the bimatoprost QD group, because this was the study regimen approved by regulatory authorities.

The peak effect for timolol typically occurs 2 hours after dosing. Therefore, in this report, the comparative response at each study visit will focus on the 10 AM IOP measurement on each follow-up visit (dosing occurred after the 8 AM examination at each visit). At 10 AM, mean ± SEM IOP ranged from 16.4±0.2 to 17.0±0.2 mm Hg with bimatoprost QD and from 18.2±0.2 to 19.0±0.2 mm Hg with timolol (**Figure 2**). The difference between the bimatoprost QD and timolol groups was statistically significant at every follow-up visit ($P<.001$). Mean IOP reductions from baseline were also significantly greater with bimatoprost QD than with timolol at this morning peak throughout the 12-month treatment period ($P<.001$). Mean IOP reductions ranged from 7.6 to 8.3 mm Hg (30.2%-32.9%) in the bimatoprost QD group and from 5.1 to 5.8 mm Hg (20.4%-23.3%) in the timolol group. The mean IOP reduction from baseline consistently ranged from 1.8 to 2.1 mm Hg greater in the bimatoprost QD group than in the timolol group at the 10 AM measurement. The decrease from baseline IOP was up to 8.8 mm Hg in the bimatoprost QD group compared with 6.5 mm Hg in the timolol group (across all times of day and all study visits).

Significantly higher percentages of patients achieved low IOP levels with bimatoprost QD than with timolol (**Figure 3**). The 10 AM measurement at month 12 revealed that target IOPs at or below 17 mm Hg were achieved by 57.6% of the bimatoprost QD group compared with 36.5% of the timolol group ($P<.001$). Pressures at or below 15 mm Hg were achieved by 30.6% of the bimatoprost QD group and 15.8% of the timolol group ($P<.001$). Patients in the bimatoprost QD group were up to 2½ times more likely than those in the timolol group

Table 2. Patient Characteristics*

	Treatment Groups			
	Bimatoprost QD (n = 474)	Bimatoprost BID (n = 483)	Timolol Maleate (n = 241)	*P* Value
Age, mean ± SD, y	61.7 ± 12.5	61.6 ± 12.0	61.0 ± 11.4	.74
Sex				
Male	206 (43.5)	234 (48.4)	101 (41.9)	.16
Female	268 (56.5)	249 (51.6)	140 (58.1)	
Race				
White	363 (76.6)	371 (76.8)	173 (71.8)	.77
Black	86 (18.1)	82 (17.0)	46 (19.1)	
Asian	6 (1.3)	13 (2.7)	6 (2.5)	
Hispanic	19 (4.0)	15 (3.1)	15 (6.2)	
Other	0	2 (0.4)	1 (0.4)	
Iris color				
Blue	126 (26.6)	104 (21.5)	49 (20.3)	.48†
Brown	168 (35.4)	173 (35.8)	95 (39.4)	
Green	14 (3.0)	16 (3.3)	16 (6.6)	
Dark brown	48 (10.1)	50 (10.4)	26 (10.8)	
Yellow-brown	60 (12.7)	62 (12.8)	22 (9.1)	
Gray	5 (1.1)	6 (1.2)	1 (0.4)	
Blue-gray	21 (4.4)	25 (5.2)	10 (4.1)	
Green-brown	13 (2.7)	16 (3.3)	10 (4.1)	
Blue/gray-brown	13 (2.7)	23 (4.8)	5 (2.1)	
Other	6 (1.3)	8 (1.7)	7 (2.9)	
Ophthalmic diagnosis				
Glaucoma	270 (57.0)	270 (55.9)	133 (55.2)	.47
OHT	196 (41.4)	200 (41.4)	106 (44.0)	
Glaucoma and OHT‡	8 (1.7)	13 (2.7)	2 (0.8)	
Washout required				
Yes	300 (63.3)	323 (66.9)	147 (61.0)	.25
No	174 (36.7)	160 (33.1)	94 (39.0)	
IOP at baseline, mean ± SD, mm Hg				
8 AM	26.0 ± 3.2	25.9 ± 3.1	25.8 ± 3.0	.81
10 AM	24.7 ± 3.7	24.6 ± 3.7	24.1 ± 3.5	.09
4 PM	23.8 ± 3.9	23.7 ± 4.0	23.2 ± 3.9	.17
8 PM§	22.1 ± 3.8	22.2 ± 4.1	22.4 ± 4.4	.62

*Unless otherwise indicated, data are given as number (percentage). Percentages have been rounded and may not sum 100. QD indicates once daily; BID, twice daily; OHT, ocular hypertension; and IOP, intraocular pressure.

†The between-group statistical comparison for iris color is for the distribution of dark vs light irides.

‡Indicates one eye with glaucoma and the fellow eye with OHT.

§Measurements were obtained at 8 PM at selected sites only (bimatoprost QD group, n = 124; bimatoprost BID group, n = 123; timolol group, n = 65).

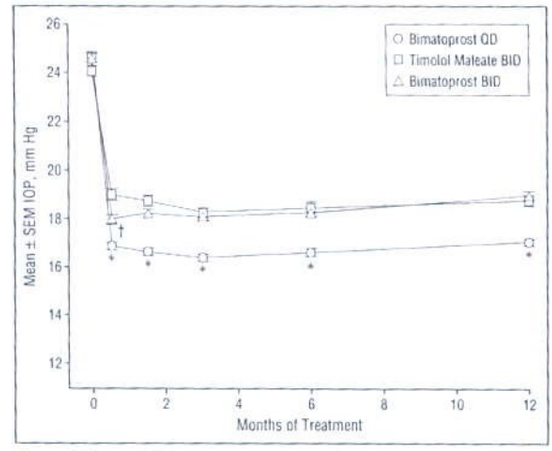

Figure 2. Mean±SEM intraocular pressure (IOP) at 10 AM (peak timolol effect) at each study visit. Asterisk indicates $P<.001$ vs timolol and bimatoprost twice daily (BID); dagger, $P=.001$ vs timolol. QD indicates once daily.

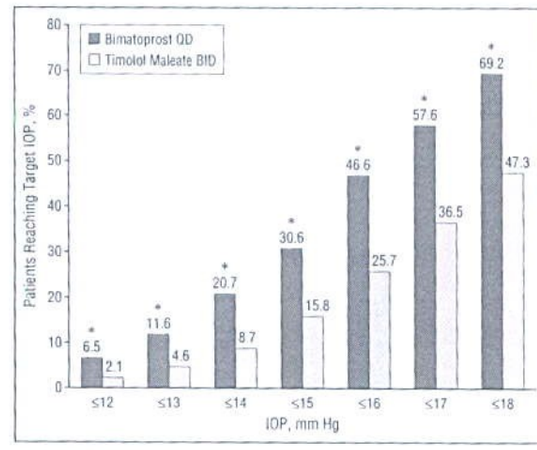

Figure 3. The percentage of patients achieving specific low intraocular pressures (IOPs) at 10 AM (peak timolol effect) after 12 months of therapy. Asterisk indicates $P\leq.001$ vs timolol. QD indicates once daily; BID, twice daily.

to achieve low pressures that were at or below 12, 13, 14, 15, 16, or 17 mm Hg.

Bimatoprost QD was also superior to timolol in maintaining a low IOP throughout the day. As mentioned in the two preceding paragraphs, bimatoprost QD produced significantly lower mean IOPs than did timolol at every time of the day at each follow-up visit throughout the 12-month treatment period ($P\leq.001$). The overall diurnal mean IOP (average of all measurements at a given time from all follow-up visits) was significantly lower in the bimatoprost QD group than the timolol group at each time of day. Throughout the day, overall mean IOP in the bimatoprost QD group was approximately 2 mm lower than the overall mean IOP in the timolol group ($P<.001$; **Figure 4**). The IOP-lowering efficacy of the single evening dose of bimatoprost was still profound 24 hours after dosing. At the 8 PM measurements, mean±SEM IOP ranged from 16.2±0.3 to 17.2±0.3 mm Hg with bimatoprost QD (n=124) compared with 18.2±0.5 to 20.0±0.6 mm Hg with timolol BID (n=65).

A subgroup analysis by race demonstrated that bimatoprost was significantly more effective than timolol in lowering IOP in both black and nonblack patients. Bimatoprost lowered IOP to the same extent in both black and nonblack patients, while timolol was notably less effective in blacks than in nonblacks (by up to approximately 2 mm). The statistical validity of this was identified from the significant treatment-by-race interaction based on the analysis of variance model for repeated measures with the fixed effects of treatment, time, race (black and nonblack), and treatment-by-race interaction. When either mean IOP or mean change from baseline IOP was analyzed for each time of day across all study visits the difference between blacks and nonblacks was statistically significant at $P=.01$.

For each analysis of pooled data from both phase 3 trials, similar results were obtained when data from the

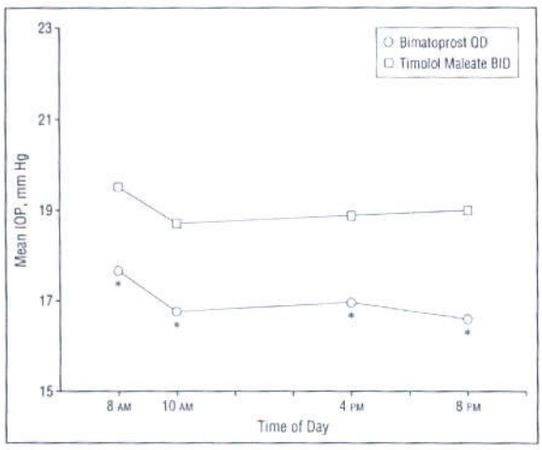

Figure 4. Overall diurnal mean intraocular pressure (IOP). The overall mean diurnal IOP is the average of all measurements at a given time from all follow-up visits. Asterisk indicates $P<.001$ vs timolol. QD indicates once daily; BID, twice daily.

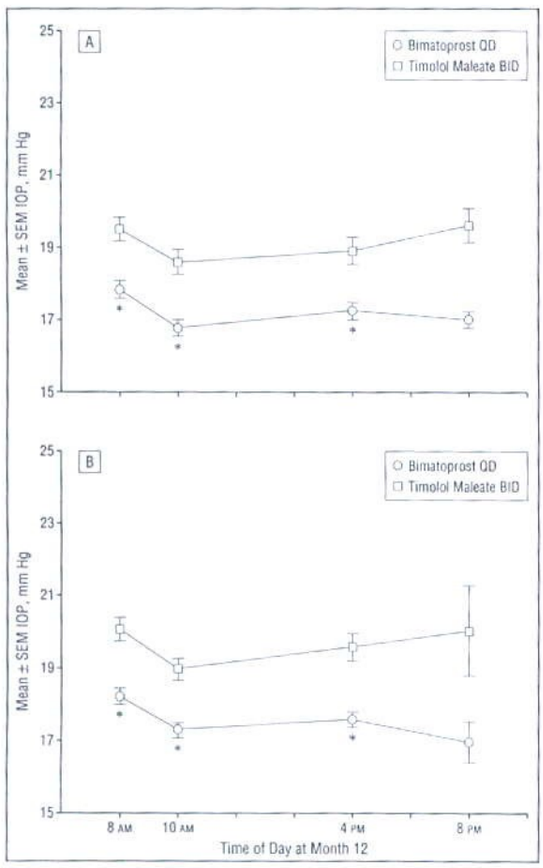

Figure 5. Diurnal mean intraocular pressure (IOP) at month 12 for trials 1 (A) and 2 (B) separately. There was inadequate power for pairwise comparisons at 8 PM because the sample sizes were too small at this time. Asterisk indicates $P\leq.001$ vs timolol. BID indicates twice daily; QD, once daily.

individual trials were evaluated separately. For example, in each trial and in the pooled data, diurnal mean IOP at month 12 was consistently 2 to 3 mm Hg lower with bimatoprost QD than with timolol throughout the day (**Figure 5**).

Table 3. Treatment-Related Adverse Events*

Event	Treatment Groups, No. (%)			*P* Value, Bimatoprost QD vs Timolol
	Bimatoprost QD (n = 474)	Bimatoprost BID (n = 483)	Timolol Maleate (n = 241)	
Conjunctival hyperemia	212 (44.7)	271 (56.1)	32 (13.3)	<.001
Eyelash growth	202 (42.6)	259 (53.6)	12 (5.0)	<.001
Eye pruritus	69 (14.6)	85 (17.6)	8 (3.3)	<.001
Eye dryness	38 (8.0)	56 (11.6)	5 (2.1)	.002
Burning sensation in the eye	33 (7.0)	32 (6.6)	25 (10.4)	.17
Eyelid pigmentation	26 (5.5)	55 (11.4)	1 (0.4)	<.001
Foreign body sensation	26 (5.5)	48 (9.9)	5 (2.1)	.03
Eye pain	24 (5.1)	45 (9.3)	8 (3.3)	.29
Visual disturbance	24 (5.1)	37 (7.7)	11 (4.6)	.14

*QD indicates once daily; BID, twice daily.

SAFETY AND TOLERABILITY

We found a low rate of discontinuations due to adverse events. All 3 treatment regimens were safe and well tolerated. The most common adverse effects associated with bimatoprost were conjunctival hyperemia and eyelash growth.

Other potentially treatment-related adverse events that occurred in more than 5% of the bimatoprost QD group are listed in **Table 3** and included eye pruritus, eye dryness, eye burning, eyelid pigmentation, foreign-body sensation, eye pain, and visual disturbance. For some of these adverse events, we found a significantly higher incidence in the bimatoprost QD group than in the timolol group. However, no statistically significant difference was found between the bimatoprost QD and timolol groups in the number of reports of eye pain, visual disturbance, and burning sensation in the eye. Patients in the bimatoprost BID group had a higher incidence of hyperemia, eyelash growth, eyelid pigmentation, and eye pain than did patients in the bimatoprost QD group ($P<.01$). Most treatment-related adverse events were mild in severity.

Assessment of the hyperemia findings were confounded by the fact that trace or greater conjunctival hyperemia was present at baseline (before the initial administration of the study medication) in 25.1% of the patients in the bimatoprost QD group and in 17.8% of the patients in the timolol group. Mean scores of conjunctival hyperemia (worse severity of the eyes) were low (in the trace range) in the bimatoprost QD treatment group and remained low throughout the study (**Figure 6**). Only 5.3% of patients experienced greater than a 1-U (mild) increase in hyperemia during this 12-month study. Only 3.4% of the patients in the bimatoprost QD group, 5.6% of those in the bimatoprost BID group, and 0.4% of those in the timolol group discontinued from the study owing to hyperemia ($P=.01$; bi-

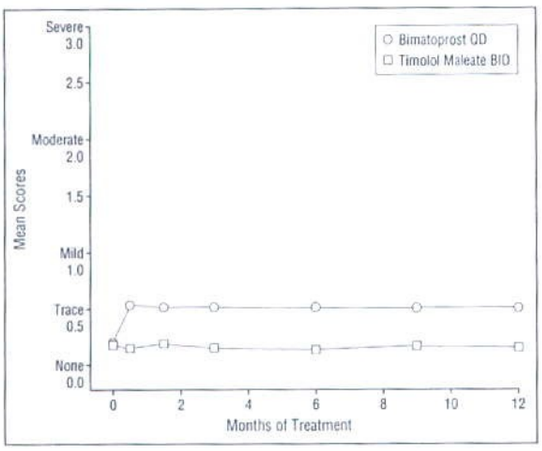

Figure 6. Mean conjunctival hyperemia scores (obtained in the worse eyes). The scale for evaluating hyperemia is explained in the "Efficacy and Safety Variables" subsection of the "Methods" section. QD indicates once daily; BID, twice daily.

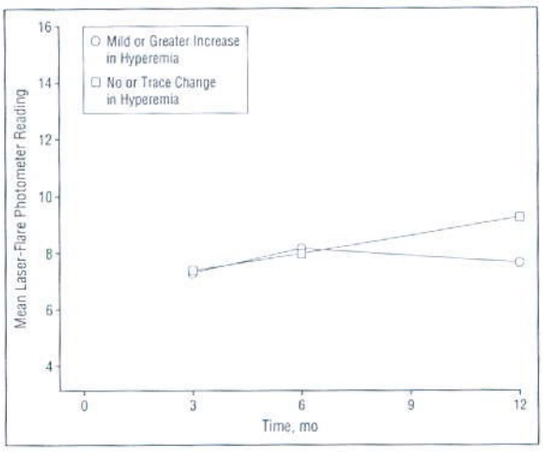

Figure 7. Mean laser-flare photometer readings in patients with greater or lesser changes in hyperemia. Readings are given in photon counts per millisecond.

matoprost QD vs timolol). The median time to onset of hyperemia was 14 days after the initiation of therapy, and in most cases it began within the first 6 weeks. No patients receiving bimatoprost QD discontinued the study because of conjunctival hyperemia after month 6.

Laser-flare photometry measurements (a common measure of ocular inflammation) of a subset of 310 patients (124 in the bimatoprost QD group, 123 in the bimatoprost BID group, and 63 in the timolol group) demonstrated that there were no significant differences among the treatment groups in mean laser-flare photometry readings or in mean changes from baseline. In addition, we found no increase in flare readings in those patients in whom conjunctival hyperemia developed. In fact, after 12 months of bimatoprost QD treatment, mean laser-flare photometry readings were lower in patients who had a mild or greater increase in conjunctival hyperemia (7.67 photon counts/ms) compared with those in patients who had no change, a trace increase, or a decrease in hyperemia (9.26 photon counts/ms) (**Figure 7**); however, this difference was not statistically significant ($P=.37$).

Changes in iris pigmentation, determined by the results of the masked investigators' evaluation of the photographs, were reported in 7 (1.5%) of the 474 patients in the bimatoprost QD group, 9 (1.9%) of the 483 patients in the bimatoprost BID group, and no patients in the timolol group. Generally comparable findings were obtained by the sponsor's reading center.

The incidence of adverse events leading to discontinuation was comparably low in the bimatoprost QD and timolol groups. In the bimatoprost QD treatment group, 8.4% of patients discontinued owing to adverse events, compared with 5.0% in the timolol group ($P=.09$). The discontinuation rate due to ocular adverse events was 5.3% in the bimatoprost QD group and 1.7% in the timolol group. This difference was statistically significant ($P=.02$), exclusively because of the statistically significant difference in the number of patients who discontinued owing to hyperemia (3.4% in the bimatoprost QD group and 0.4% in the timolol group; $P=.01$). We found no between-group difference in the number of patients who discontinued because of any other adverse event. In the bimatoprost BID treatment group, 14.7% of patients discontinued because of adverse events ($P=.003$ compared with bimatoprost QD).

No clinically significant changes in results of ophthalmoscopy, laser-flare photometry readings, visual acuity, visual fields, or systemic safety variables were found with any treatment regimen.

COMMENT

The pooled 1-year results of the 2 pivotal phase 3 trials clearly demonstrated that bimatoprost QD was superior to timolol in long-term IOP reduction. Significantly higher percentages of patients achieved low pressures with bimatoprost QD, and IOP was controlled throughout the day. The efficacy of bimatoprost QD was sustained throughout the 1-year study. The mean reduction from baseline IOP in the bimatoprost QD group was very consistent (range, 30%-33%) at follow-up visits through 1 year of treatment.

Controlling IOP is critical to slowing the progression of glaucomatous damage in patients with glaucoma or ocular hypertension. Elevated IOP is the single most important risk factor for open-angle glaucoma, and numerous studies[8-12] have found that reducing IOP decreases the risk for visual field loss in patients with glaucoma. A recent analysis by the Advanced Glaucoma Intervention Study group demonstrated that after surgery to reduce IOP, patients who consistently had IOPs less than 18 mm Hg at every clinic visit during the 6-year follow-up showed mean changes in visual fields close to 0.[12] In these patients, the mean IOP was very low (12.3 mm Hg), suggesting that lower IOPs result in greater patient benefit. Reductions in IOP of 30% or greater have also been shown to significantly reduce the rate of glaucomatous progression in patients with normal-tension glaucoma.[8] Even in patients without evidence of optic disc cupping, reduction of an elevated IOP can be beneficial in delaying the onset of early glaucomatous damage.[9,10] Therefore, a goal of glaucoma therapy should be the

achievement and maintenance of target IOPs that are low enough to minimize glaucomatous progression.[13] On the basis of the superior IOP-lowering efficacy of bimatoprost QD demonstrated in the present study, long-term bimatoprost QD treatment may reasonably be assumed to provide greater protection for the visual field than does timolol in patients with glaucoma or ocular hypertension. The greater ability of bimatoprost to help patients reach IOP levels more consistently below 18 mm Hg should prove particularly beneficial.[8,12]

A recent study by Asrani and colleagues[14] reported that large fluctuations in diurnal IOP are an independent risk factor for the progression of glaucomatous damage. The results of the present study show that bimatoprost QD effectively controls IOP fluctuations throughout the day that could otherwise increase the risk for further optic nerve damage.[15,16]

Numerous studies have reported significant differences between black and nonblack populations in the prevalence of glaucoma[17,18] and the response to treatment.[18] Population-based studies have reported that glaucoma is 4 to 6 times more prevalent in black than in nonblack populations and that glaucoma is 6 to 8 times more likely to lead to blindness in black than in nonblack populations.[17] The reasons for the greater prevalence and visual field loss in black populations are not yet known. The results of the present study demonstrated that bimatoprost QD reduces IOP as effectively in black as in nonblack patients, and that bimatoprost QD provides IOP lowering superior to that of timolol across both of these patient populations.

Throughout 1 year of treatment, bimatoprost QD was safe and well tolerated. The most common adverse effect, conjunctival hyperemia, was generally well tolerated and mild in severity. In our experience, hyperemia can resolve after 2 to 4 weeks of treatment. The lack of any correlation between hyperemia and laser-flare photometry readings indicates that there was no association with intraocular inflammation and confirms the general finding that this adverse effect does not represent a significant clinical safety concern. The investigating physicians reported an increase in iris pigmentation in only 1.5% of the patients in the bimatoprost group treated for 12 months. By comparison, in the phase 3 clinical trials of latanoprost in which iris pigmentation changes were evaluated at a reading center, the incidence of increased iris pigmentation ranged from 10.9% to 22.9% of patients treated with latanoprost QD for 12 months.[19] These results suggest that iris pigmentation changes may occur less frequently with bimatoprost than with latanoprost. However, given the different techniques used in the studies of these 2 drugs and the variation in the ability of investigators to detect iris pigment changes, a long-term comparison of bimatoprost with latanoprost using a single method will be needed to evaluate this issue more thoroughly.

Bimatoprost BID was associated with a significantly higher incidence of certain adverse events than was bimatoprost QD. This, along with the greater efficacy of the QD regimen, supports the once-daily use of this drug.

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CONCLUSIONS

We found 0.03% bimatoprost QD to be clinically and statistically superior to 0.5% timolol maleate BID in lowering IOPs in patients with glaucoma or ocular hypertension. Significantly more patients achieve very low target pressures with bimatoprost QD than with timolol maleate BID. Bimatoprost QD provides potent IOP control throughout the day and is safe and well tolerated. The efficacy of bimatoprost QD is sustained through at least 1 year of treatment.

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