Comparison of the Ocular Hypotensive Lipid AGN 192024 With Timolol

Dosing, Efficacy, and Safety Evaluation of a Novel Compound for Glaucoma Management

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Objective: To compare the safety and efficacy of the ocular hypotensive lipid AGN 192024 (Lumigan) with those of timolol.

Methods: A 30-day, randomized, investigator-masked, clinical trial involving 100 patients with elevated intraocular pressure (IOP). Study medications were instilled topically. Doses of 0.003%, 0.01%, or 0.03% AGN 192024 were given once daily for 3 weeks then twice daily for 1 week, and vehicle control or 0.5% timolol was given twice daily for 4 weeks. Mean change in IOP from baseline was the primary efficacy variable. Safety parameters included adverse events, hyperemia grading, laser flare meter analysis, heart rate, and blood pressure.

Results: Timolol and all 3 concentrations of AGN 192024 lowered IOP from baseline (P < .001). A dosage of 0.03% AGN 192024 once daily lowered IOP significantly more than timolol (P = .02) at every study visit except day 21 (P = .053) and provided better diurnal IOP control. Twice-daily dosing of AGN 192024 provided no clinically significant benefit over once-daily dosing. All treatment regimens were safe and well tolerated, with no clinically significant effects on heart rate or blood pressure and no between-group differences in the incidence of adverse events. The only significant ocular safety finding with AGN 192024 was a dose-related mild increase in conjunctival hyperemia.

Conclusions: Of the 3 concentrations tested, 0.03% AGN 192024 once daily had the best therapeutic profile. AGN 192024 was safe and well tolerated, and it provided superior ocular hypotensive efficacy and diurnal IOP control compared with timolol in patients with ocular hypertension and glaucoma.

Arch Ophthalmol. 2001;119:994-1000

ELEVATED intraocular pressure (IOP) associated with glaucoma and ocular hypertension is primarily managed with topical ocular hypotensive agents. Nonselective β-adrenergic blocking agents such as timolol have been the most commonly prescribed therapeutic option. However, a propensity for long-term drift and an association with systemic adverse effects have prompted the search for safer and more efficacious ocular hypotensive agents. Accordingly, several new agents from a diverse array of pharmacological classes have been introduced for the management of ocular hypertension and glaucoma. Among these are the topical carbonic anhydrase inhibitors, selective α2-adrenergic agonists, and ester prodrugs of prostaglandin F2α (PGF2α) analogs such as latanoprost and unoprostone isopropyl ophthalmic solution. These compounds are pharmacologically unique. They are inactive at the human PGF2α-sensitive (FP) receptor and at all other known prostanoid receptors and are devoid of several PGF2α-associated activities. Yet in preclinical evaluation it was found that they possess substantial IOP-lowering efficacy. Recent studies have elucidated the pharmacological basis of AGN 192024 to be related to the prostamides, which were recently discovered as biosynthetic products of anandamide.

To evaluate the relative therapeutic potential of AGN 19204 for glaucoma management, we conducted a 30-day, randomized, investigator-masked, parallel-group, graduated-dosing frequency clinical trial involving patients with ocular hypertension or glaucoma. The safety, tolerability, and ocular hypotensive efficacy of topically applied 0.003%, 0.01% and 0.03% concentrations of AGN 19204 were compared with those of AGN 19204 vehicle and 0.5% timolol. Doses of 0.003%, 0.01%, and 0.03% AGN 19204 were administered once in the evening for 3 weeks, then twice daily for an
SUBJECTS AND METHODS

STUDY POPULATION

This 30-day comparison trial was conducted from October 1996 through February 1997 by Eye Research Associates, Austin, Tex. The protocol was reviewed and approved by a governing institutional review board. The study was conducted according to the Declaration of Helsinki, Good Clinical Practices, and applicable Code of Federal Regulations.

Men or women (not of child-bearing potential) 21 years or older with a diagnosis of ocular hypertension (elevated IOP without evidence of visual field loss) or primary open-angle glaucoma were eligible for the study. Other primary eligibility criteria included uncontrolled (postwashout) IOP between 23 and 34 mm Hg in both eyes, between-eye asymmetry in IOP of no more than 5 mm Hg, and corrected visual acuity of at least 20/100 in each eye.

Key exclusion criteria included uncontrolled systemic disease, known allergy or sensitivity to the study medications, contraindications to β-adrenergic blocker therapy, anticipated alteration during the study of existing long-term therapy with agents that could affect IOP, anticipated use of topical or systemic steroids during the study, and history of refractive surgery within 1 year or lasik surgery within 3 months before the study.

All patients had newly diagnosed conditions and were free of medication at the time of enrollment or were taking only 1 medication, which was washed out before the study. Washout periods ranged from 4 to 30 days as follows: 4 days for parasympathomimetics and carbonic anhydrase inhibitors, 2 weeks for nonselective adrenergic agonists and topical α-agonists, and 4 weeks for β-adrenergic blocking agents and prostaglandins.

One hundred qualified patients were enrolled after obtaining written informed consent. Patients were distributed by random assignment to 1 of 5 treatment groups with 20 patients in each group. Enrolled patients could voluntarily withdraw at any time. Any patient who had an unacceptable response to treatment that affected his or her welfare, including an inappropriate IOP response (eg, an increase of 3 mm Hg or more in IOP from pretreatment baseline) was eliminated from the study.

RESULTS

DEMOGRAPHICS

The demographics of the 100 patients who were enrolled in the study are presented in Table 1. There were no significant differences in age, height, weight, sex, race, iris color, diagnosis, or medical and ophthalmic profiles among the treatment groups. All enrolled patients completed the 30-day study. Therefore, analysis of efficacy and safety was based on the results for all 100 patients.

OCULAR HYPOTENSIVE EFFICACY

AT 8 AM AND 8 PM

In a dose-dependent manner, all 3 concentrations of AGN 192024 and 0.5% timolol caused a significant (P = .001) and sustained reduction in IOP from baseline at the 8 AM time point (Figure 1). Changing the dosing regimen to twice daily from once daily had little effect on the efficacy of 0.01% or 0.03% AGN 192024 solutions (Table 2). For the 0.03% AGN 192024 treatment group, the mean change from baseline IOP ranged from −7.2 to −8.2 mm Hg during once-daily dosing and from −7.7 to −8.7 mm Hg during twice-daily dosing. Twice-daily timolol produced a mean reduction from baseline IOP at 8 AM of −3.4 to −3.9 mm Hg throughout the study.

The ocular hypotensive efficacy of the 0.01% and 0.03% concentrations of AGN 192024, instilled once daily or twice daily, was significantly greater than that of timolol taken twice daily. The 0.03% concentration of AGN 192024 lowered IOP from the 8 AM baseline significantly more than timolol (P < .02) at every study visit except day 21 (P = .03). The 0.01% AGN 192024 dose reduced IOP from baseline significantly more than timolol at every visit (P < .04) except day 3 (P = .11). The IOP-lowering efficacy of 0.003% AGN 192024 taken once daily and twice daily was comparable to that of 0.5% timolol taken twice daily.

On day 30 (48 hours following the last instillation), AGN 192024 demonstrated a prolonged IOP-lowering
was conducted), a new bottle was used each day. One bottle was used for both eyes. Patients and the investigator were asked to store study medications at room temperature.

**PRIMARY EFFICACY VARIABLE:**
**MEAN CHANGE IN IOP**

The primary efficacy variable was mean reduction of IOP from baseline as measured in millimeters of mercury using Goldmann applanation tonometry attached to a slit-lamp. Baseline IOP was established after washout and before administration of medications on day 0. The IOP of both eyes was measured and the values averaged for analyses. The IOP at 8 AM was measured at each study visit. Diurnal IOP measurements were taken at 8 AM, 12 noon, 4 PM, 8 PM, and 10 PM on days 0, 14, 21, and 28.

**PRIMARY SAFETY VARIABLES**

**Adverse Events**

The occurrence of ocular and systemic adverse events was monitored throughout the study, and each event was recorded by the investigator, with the severity (mild, moderate, or severe) and the causality of the event relative to the study medication (ie, definite, probable, possible, unlikely, unknown, or none) noted.

**Ocular Safety**

Biomicroscopy and ophthalmoscopy were performed at all study visits, and visual acuity and anterior chamber flare were evaluated. Biomicroscopy was performed using slit-lamp examination without pupil dilation and included inspection of the lids, conjunctiva, cornea, anterior chamber, lens, and vitreous. Observations were reported on a 4-point grading scale (0=none, 1=mild, 2=moderate, and 3=severe). Biomicroscopic observations of conjunctival hyperemia were reported on a 5-point scale (0=none, 0.5=trace, 1=mild, 2=moderate, and 3=severe). Best-corrected visual acuity at distance was measured using a Snellen chart. Laser flare meter readings were collected using a KOWA FM-500 Laser Flare Meter (Kowa Company Ltd, Chuo-Ku, Tokyo, Japan). The results were recorded in photon counts per millisecond. Readings were taken before the morning instillation of study medication (for the twice-daily dosing groups) and no later than 7:30 AM.

At the prestudy visit and on study day 30, cup-disc ratio and fundus pathology were assessed using direct and indirect ophthalmoscopy. Cup-disc ratio was recorded on a scale from 0.0 to 0.9 based on the Allergan Armaly Chart. Fundus examinations were done through a dilated pupil, and observations were recorded using a 4-point grading scale as above.

**Heart Rate and Blood Pressure**

Heart rate and blood pressure were measured at all study visits. Heart rate, recorded as beats per minute, was measured with the patient in a resting position for at least 5 minutes. Resting systolic and diastolic blood pressure was measured and recorded in millimeters of mercury.

**ANALYSIS**

Data were summarized with descriptive statistics (mean and SE) for continuous variables and with frequency distributions for categorical variables. Our a priori hypothesis was that a sample size of 19 per group would give us a power of 0.88 to detect a mean change of 4 mm Hg or more from baseline mean IOP.

For continuous variables, analysis of variance and the t test on rank scores were used for overall and pairwise comparisons.21 The Wilcoxon signed rank test was used to test for changes from baseline. For ordinal variables, the Kruskal-Wallis test and the Wilcoxon rank sum test were used for overall and pairwise comparisons.22 For nominal variables, the Pearson χ² test or the Fisher exact test was used for the comparisons.23 All pairwise comparisons were evaluated whenever the overall comparison was statistically significant.24 P<.05 was considered statistically significant. Statistical analysis was performed using the SAS computer package (version 6.12; SAS Institute, Cary, NC).

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**Table 1. Patient Demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vehicle</th>
<th>0.003%</th>
<th>0.01%</th>
<th>0.03%</th>
<th>0.5% Timolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>61.82 (46-90)</td>
<td>61.82</td>
<td>60.73</td>
<td>60.73</td>
<td>59.84</td>
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<tr>
<td>M/F, No.</td>
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<td>8/12</td>
<td>11/9</td>
<td>10/10</td>
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<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (65)</td>
<td>17 (85)</td>
<td>18 (90)</td>
<td>13 (65)</td>
<td>16 (80)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>7 (35)</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td>3 (75)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Iris color, No. (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blue</td>
<td>4 (20)</td>
<td>3 (15)</td>
<td>10 (50)</td>
<td>8 (40)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Brown</td>
<td>11 (55)</td>
<td>10 (50)</td>
<td>8 (40)</td>
<td>11 (65)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Hazel</td>
<td>5 (25)</td>
<td>7 (35)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>Diagnosis, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OAG</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>3 (15)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>OHT</td>
<td>17 (85)</td>
<td>19 (95)</td>
<td>17 (85)</td>
<td>15 (75)</td>
<td>19 (95)</td>
</tr>
<tr>
<td>OHT/OAG</td>
<td>1 (5)</td>
<td>0</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>0</td>
</tr>
<tr>
<td>History of eye surgery or trauma, No. (%)</td>
<td>1 (5)</td>
<td>2 (10)</td>
<td>4 (20)</td>
<td>2 (10)</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

*n = 20 for each group. OAG indicates open-angle glaucoma; OHT, ocular hypertension.*
effect at 8 AM, with a mean change from baseline IOP of −5.6 mm Hg in the 0.03% group compared with −2.1 mm Hg in the timolol group (P = .02).

The superior efficacy of AGN 192024 was also evident when considering mean percent reduction from baseline IOP at 8 AM. The mean percent IOP reduction in the 0.03% group ranged from 25.7% (on day 21) to 31.5% (on day 23), compared with a range of 12.9% (on day 14) to 15.0% (on day 3) in the timolol group. On day 14 at the 8 AM time point, the 0.03% and 0.01% AGN 192024 twice-daily groups had significantly higher mean percent reductions from baseline IOP than did timolol (Figure 2).

Because the IOP-lowering effect of topical AGN 192024 approaches maximal levels (peak) approximately 12 hours following instillation, the IOP-lowering effect on days 14 and 21 at 8 PM (24 hours following instillation of AGN 192024) was also examined. As shown in Table 3, the 0.03% AGN 192024 taken once daily produced significantly greater mean reductions of IOP than timolol taken twice daily (P = .03) at 8 PM on days 14 and 21.

DIURNAL IOP CONTROL

The 0.01% and 0.03% concentrations of AGN 192024 given once or twice daily produced a significant mean reduction in IOP from baseline throughout the day (P < .001) and provided better diurnal IOP control than timolol taken twice daily. On day 21 the mean reduction of IOP with 0.03% AGN 192024 taken once daily was significantly greater than that with timolol taken at noon, 4 PM, 8 PM, and 10 PM (P < .03; Figure 3). The 0.01% concentration of AGN 192024 administered once daily produced a significantly greater mean change in IOP than did timolol at the 8 AM and 8 PM time points (P < .02). Similar observations were made on day 14 (once-daily

Table 2. Mean Change and Mean Percent Change From Baseline Intraocular Pressure (IOP) at 8 AM During Once-Daily (Days 0-21) and Twice-Daily (Days 23-28) Study Phases

<table>
<thead>
<tr>
<th></th>
<th>Baseline IOP on Day 0, Mean ± SE, mm Hg*</th>
<th>Range of Mean Changes From Baseline IOP, mm Hg</th>
<th>Range of Mean Percent Changes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (days 0-28)</td>
<td>24.5 ± 0.2</td>
<td>+0.2 to −1.2</td>
<td>+0.8 to −4.6</td>
</tr>
<tr>
<td>0.5% Timolol twice daily (days 0-28)</td>
<td>25.1 ± 0.3</td>
<td>−3.4 to −3.9</td>
<td>−12.9 to −15.0</td>
</tr>
<tr>
<td>AGN 192024</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.003%</td>
<td>0.01%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once daily</td>
<td>24.9 ± 0.4</td>
<td>−2.0 to −3.3</td>
<td>−7.9 to −13.1</td>
</tr>
<tr>
<td>Twice daily</td>
<td>25.2 ± 0.5</td>
<td>−3.3 to −3.8</td>
<td>−13.3 to −15.2</td>
</tr>
<tr>
<td>0.01%</td>
<td>0.03%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once daily</td>
<td>25.2 ± 0.5</td>
<td>−5.4 to −6.0</td>
<td>−20.7 to −23.3</td>
</tr>
<tr>
<td>Twice daily</td>
<td>27.0 ± 0.7</td>
<td>−5.6 to −5.8</td>
<td>−21.7 to −22.5</td>
</tr>
</tbody>
</table>

*No significant between-group differences at the 8 AM baseline measurement (P = .94).
†Mean change and mean percent reduction of IOP from 8 AM baseline in the 0.01% and 0.03% AGN 192024 groups were significantly greater than those seen with timolol on most study visits (P < .04).
favorable safety profiles and were well tolerated. All patients completed the study. The overall incidence of adverse events was minimal in all treatment groups (Table 4).

There were no significant differences between active treatment groups in the incidence of any particular adverse event. The most frequent adverse event was conjunctival hyperemia, reported in 1 (5%), 3 (15%), and 1 (5%) of the 20 patients in the 0.003%, 0.01%, and 0.03% AGN 192024 groups, respectively. There were no reports of hyperemia in the AGN 192024 vehicle or timolol treatment groups. The incidence of hyperemia in the AGN 192024 groups during the once-daily and twice-daily phases combined was not significantly different from that in the timolol group (P=.23). Other adverse events reported in 2 or more patients treated with AGN 192024 included ocular dryness (5/60), foreign body sensation (2/60), dryness (5/60), foreign body sensation (2/60), ocular pruritus (2/60), diarrhea (3/60), headache (2/60), and dyspnea (2/60). None of these events was considered serious.

ADVERSE EVENTS

All 3 concentrations of AGN 192024 and timolol had favorable safety profiles and were well tolerated. All patients completed the study. The overall incidence of adverse events was minimal in all treatment groups (Table 4).

There were no significant differences between active treatment groups in the incidence of any particular adverse event. The most frequent adverse event was conjunctival hyperemia, reported in 1 (5%), 3 (15%), and 1 (5%) of the 20 patients in the 0.003%, 0.01%, and 0.03% AGN 192024 groups, respectively. There were no reports of hyperemia in the AGN 192024 vehicle or timolol treatment groups. The incidence of hyperemia in the AGN 192024 groups during the once-daily and twice-daily phases combined was not significantly different from that in the timolol group (P=.23). Other adverse events reported in 2 or more patients treated with AGN 192024 included ocular dryness (5/60), foreign body sensation (2/60), ocular pruritus (2/60), diarrhea (3/60), headache (2/60), and dyspnea (2/60). None of these events was considered serious.

**OCULAR SAFETY**

Ocular safety parameters were unaffected, other than a minor dose-related increase in the degree of conjunctival hyperemia (generally a trace to mild increase during the once-daily phase) in the AGN 192024 groups and increased laser flare meter readings in the timolol group. Although conjunctival hyperemia was observed in all treatment groups, mean grading scores of hyperemia in the 0.01% and 0.03% AGN 192024 groups were significantly higher than those in the timolol group at most study visits (P=.03). During the once-daily phase of the study, mean hyperemia scores (ranges) were as follows: timolol group, 0.35 to 0.50; vehicle group, 0.50 to 0.63; 0.003% AGN 192024 group, 0.65 to 0.78; 0.01% AGN 192024 group, 0.85-0.95; and 0.03% AGN 192024 group, 0.80 to 0.98. When the dosing schedule was changed from once to twice daily, a slight increase in mean hyperemia scores was found with the 2 highest concentrations of AGN 192024 (mean score ranges of 0.93 to 1.00 in the 0.01% AGN 192024 group and 1.03 to 1.08 in the 0.03% AGN 192024 group). There were no other significant findings with biomicroscopy.

Baseline laser flare meter readings were comparable among treatment groups (P=.12). The aqueous hu-
mor protein concentration was significantly increased from baseline at each study visit during treatment with timolol \( (P \leq .001) \). The mean increase in laser flare readings from the baseline of 7.52 ranged from 1.58 to 2.36 in the timolol group. The changes in laser flare readings in the timolol group were significantly different from those in all other treatment groups \( (P \leq .04) \).

No clinically significant changes in cup-disc ratio were seen, and visual acuity remained relatively unchanged throughout the study.

**CARDIOVASCULAR SAFETY**

All 3 concentrations of AGN 192024, whether given once or twice daily, were safe and produced no clinically significant mean changes in heart rate or blood pressure from baseline (Table 5).

In this randomized, investigator-masked clinical trial, both once- and twice-daily instillations of 0.003%, 0.01%, or 0.03% AGN 192024 were safe, well tolerated, and effective. Moreover, AGN 192024 provided superior ocular hypotensive efficacy and better diurnal IOP control than timolol.

In a sustained, dose-dependent manner, all 3 concentrations of AGN 192024, given once or twice daily, as well as timolol given twice daily produced significant mean reductions from baseline IOP at 8 AM \( (P \leq .001) \). A 31.5% maximum reduction in IOP was observed in the 0.03% AGN 192024 group compared with a 15.0% maximum reduction in the timolol group. Moreover, once-and twice-daily 0.03% AGN 192024 provided better IOP control than timolol given twice throughout the day. The IOP lowering with 0.03% AGN 192024 was substantial even at 24 hours following evening instillation, with a mean IOP reduction of approximately 5.0 mm Hg \( (P < .03) \) from baseline at the 8 PM measurement. The mean reductions from baseline IOP achieved with timolol treatment in this clinical trial were less than anticipated, possibly because patients were not excluded for previous use of timolol. However, the mean reductions of IOP in the 0.03% AGN 192024 group were greater than the reductions typically reported with timolol (approximately 20% to 25% from baseline\(^6-9,17,25,26\)), confirming the outstanding ocular hypotensive efficacy of AGN 192024 in this clinical trial.
The only significant between-group difference in ocular side effects was traz to mild conjunctival hyperemia in the AGN 192024 group. The degree of conjunctival hyperemia in the AGN 192024 groups was dosing frequency related, with lower mean grading scores seen in the 0.03% once-daily vs twice-daily regimens.

There were no biomicroscopic findings of flare in this study. Although the slitlamp can be used to detect clinically significant flare and cells in the anterior chamber, it may not be sensitive enough for evaluation of subtle disruption of the blood aqueous barrier. The most sensitive equipment available to evaluate blood aqueous barrier integrity is the laser flare meter. In this study, the KOWA FM-300 was used to quantify any effect of AGN 192024 on the blood aqueous barrier. There were no significant changes in laser flare meter readings in any of the AGN 192024 treatment groups. In the timolol treatment group, the laser flare measurements demonstrated a statistically significant increase in photon counts in the aqueous humor. This is consistent with the results of studies by Araie et al27 and Stur et al28 in which timolol caused an increase in total protein concentration in the aqueous humor. The results of these previous studies were consistent with timolol-associated reduction of aqueous humor production, without any sign of breakdown of the blood aqueous barrier.

The nonselective β-adrenergic blocking agents, although generally effective ocular hypotensive agents, can be systemically absorbed30 and cause untoward central nervous system and cardiopulmonary adverse effects.30-32 Thus, the nonselective β-adrenergic blocking agents are contraindicated in patients with, or at high risk for, cardiopulmonary disease. In this study, AGN 192024 had no consistent effects on heart rate or blood pressure, suggesting that the systemic safety profile of AGN 192024 is likely to be favorable.

Our observations in this clinical study, taken together with the unique preclinical pharmacological profile of AGN 192024, suggest that AGN 192024 has great potential as an agent for the management of glaucoma and ocular hypertension. In this short-term trial, AGN 192024 appeared to be highly efficacious, well tolerated, and systemically safe. The robust IOP lowering efficacy of AGN 192024 observed in this study suggests that future studies should be carried out to elucidate the molecular activity and aqueous flow and outflow effects of AGN 192024.

In conclusion, although all 3 concentrations and both dosing regimens tested were effective and had an acceptable safety profile, the 0.03% concentration of AGN 192024 instilled topically once in the evening had the most advantageous overall therapeutic profile. In this short-term study, 0.03% AGN 192024 given once daily provided superior ocular hypotensive efficacy and better diurnal IOP control than 0.5% timolol given twice daily and was well tolerated in patients with elevated IOP. Further clinical evaluation of 0.03% AGN 192024 given once daily for long-term management of glaucoma and ocular hypertension is warranted.

Accepted for publication December 1, 2000.
This study was supported by Allergan Inc.

REFERENCES


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