Prostaglandin Efficacy and Safety Study Undertaken by Race (The PRESSURE Study)

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Purpose: Latanoprost, travoprost, and bimatoprost are prostaglandin or prostamide-type ocular hypotensive medications, all of which are effective and safe for lowering intraocular pressure (IOP). Most studies with these types of drugs have included patients mainly from European or white ethnic backgrounds; however, some reports have suggested that there is a difference in response between patients of white and African racial heritage. On account of the possibility that drugs may act differently in people of different ethnic background, we decided to study the effectiveness and safety of all 3 drugs in people from various ethnic heritages. Our hypothesis was that there might be a possible ethnic-based difference in IOP-lowering effectiveness between the 3 medications.

Method: This was a prospective randomized investigator-masked multicenter study. Patients newly diagnosed with open-angle glaucoma (primary, pseudoexfoliative, or pigmentary), or whose pressure became elevated after a washout period, were randomized to receive 1 of 3 prostaglandin/prostamide drugs. Assignment of drug was balanced by racial group and study site, and the investigator was masked to the drug used. The patients were requested to self-identify their racial group as White, African, East Indian, Asian, or Hispanic; to minimize the possibility of heterogeneity, all 4 grandparents had to be known to originate from the same group. However, for purposes of analysis, the patients were divided into 2 groups—White or Other. Patients were followed at 2, 6, 12, and 24 weeks; IOP and local side effects were assessed at each visit.

Results: Eighty-three patients were recruited from 9 sites. The mean age of the patients was 61.5 ± 10.5 years. There were no differences in mean age or the distribution of sex between the patients whether examined by the 2 racial groups or the 3 drug groups. There was a highly statistically significant decrease in IOP from baseline to 12 weeks and from baseline to 24 weeks ($F = 439.3$, $P < 0.0001$; $F = 305.94$, $P < 0.0001$). There were no differences in treatment effect between the 3 drugs or between the 2 ethnic groups, ($P > 0.05$ for all comparisons) and there was no interaction between race and drug.

Conclusions: All 3 prostaglandin/amide drugs are highly effective at lowering IOP. No differences in effect between the drugs or between members of different racial groups were detected, although the study sample size was too small to be certain to detect differences, if they existed.

Key Words: glaucoma, prostaglandin, ethnicity

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The major risk factor for the development of glaucomatous optic neuropathy, a significant cause of irreversible blindness in the world, is elevated intraocular pressure (IOP).[1,2] The management of elevated IOP is usually initiated with medical therapy. Drugs of several classes can be used, including the β-blockers, carbonic anhydrase inhibitors, α-agonists, miotics, and prostaglandin analogs. Latanoprost (Xalatan, Pfizer Inc), travoprost (Travatan, Alcon Laboratories Inc), and bimatoprost (Lumigan, Allergan Inc) are drugs in the prostaglandin class, although bimatoprost is also referred to as a prostamide. For simplicity, this paper will refer to them collectively as prostaglandin analogs. These drugs affect a hitherto unused mechanism for pressure lowering—augmentation of uveoscleral outflow[3] and all the 3 drugs have been shown to be effective and safe for lowering elevated IOP.[4–11] The first drug in the class was latanoprost, and it was quickly evident that the drug had a strong pressure-lowering effect, and a good safety profile.[12–15] Travoprost was developed subsequently,[16] and similarly proved to be an effective pressure-lowering agent.[17–19] The third agent currently available in North America is bimatoprost.[20]

The reported range of IOP lowering varies between drugs and between different published studies. Latanoprost has been shown to lower IOP by between 31% and 35%[21] or around 9 mm Hg.[5] Netland et al[17] and the Travoprost Study Group reported a large 12-month prospective study that showed mean IOP decreases in the travoprost-treated group that ranged from 6.9 to 8.9 mm Hg. The Bimatoprost/Latanoprost Study Group reported a 6-month multicenter randomized investigator-masked study comparing bimatoprost to latanoprost. Their results showed statistically more IOP lowering for bimatoprost, with diurnal measurements ranging between 16.5 and 17.4 mm Hg for bimatoprost and 17.6 to 18.9 mm Hg for latanoprost. There was also a higher responder rate for reaching various target pressures in the bimatoprost patients. Safety evaluation showed no significant differences between the groups other than conjunctival hyperemia, which was more evident in the bimatoprost-treated patients.[22]

A second study that evaluated a smaller number of patients but that performed a 24-hour diurnal measurement

was reported by Konstas et al.[23] This study also showed a small advantage for bimatoprost in IOP lowering, with a 0.6 mm Hg lower IOP produced by bimatoprost, a difference that reached statistical significance. There was also a statistically more frequent presence of conjunctival hyperemia with bimatoprost (34%) than with latanoprost (14%). Cantor et al[24] performed a head-to-head comparison of travoprost and bimatoprost and found no significant differences between the 2 drugs, although the trend was for lower IOP and a larger proportion of responders reaching low target pressures with bimatoprost.

Most studies with these types of drugs have been performed with patients mainly from European or white ethnic backgrounds. One report, however, suggested that there was a difference in response between patients of white and African racial heritage. Netland et al[17] and the Travoprost Study Group had reported that travoprost was more effective by 2.4 mm Hg than latanoprost in lowering IOP in black patients. Netland et al[25] later published a reanalysis of 2 studies, pooling the data to examine the response to travoprost in black and nonblack patients. These data showed that travoprost lowered mean IOP further in black patients than in nonblack patients by an average of 8.1 mm Hg compared with 7.0 mm Hg. respectively. This conclusion has been challenged, with Camras[26] suggesting that the difference is because of differences in baseline IOP. Netland et al[27] responded that only 1 of 3 baseline measurements was significantly different, and that the trend for lower IOP with travoprost was present at most time points. They conclude their rebuttal by suggesting that a comparative trial of the prostaglandins with an analysis of race would be helpful to clinicians.

Although race is not a scientifically well-defined concept, it continues to have a role in clinical decision-making. On account of the possibility that drugs may act differently in people of different ethnic background, we decided to compare the effectiveness and safety of all 3 drugs in individuals from different ethnic heritages. Certain side effects have been reported to occur with this class of medications, particularly increased conjunctival hyperemia and darker iris pigmentation, eyelash growth, periocular skin pigmentation, and cystoid macular edema in pseudophakic patients.[28–34] We therefore also attempted to assess whether there were any differences in these outcomes among patients from different ethnic groups.

The null hypothesis stated that there is no ethnic-based difference in IOP-lowering effectiveness, and/or safety profile, between the 3 medications; the alternative hypothesis was that such a difference existed.

METHODS

The study design was a prospective randomized investigator-masked multicenter study and had been approved by the Research Ethics Boards of Sunnybrook and Women's College Health Sciences Centre and the University Health Network. Patients were eligible if they were newly diagnosed with ocular hypertension or open-angle glaucoma (primary, pseudoexfoliative, or pigmentary) or if they were suitable for a washout of an earlier prescribed medication and their pressure became elevated after a defined period of time. To be eligible, the IOP in at least 1 eye had to be greater than 23 mm Hg and less than 36 mm Hg at 10 AM. Patients were requested to self-identify

their racial group as white, African, South Asian, East Asian, or Hispanic; to minimize the possibility of heterogeneity all 4 grandparents had to be known to originate from the same group. Exclusion criteria are listed in Table 1.

After informed consent was obtained, the participants were randomized to receive 1 of the 3 prostaglandin drugs. A randomization schedule, balanced for ethnicity and drug assignment, was produced for each participating site by the biostatistician. The investigator was masked to the drug used. Drugs were supplied to the patients, courtesy of the manufacturers who provided sufficient samples to the participating sites for the duration of the study. The patients were instructed to take their dose once daily at 8 PM.

The patients were followed for a maximum of 24 weeks. Assessments were performed at baseline, 2, 6, 12, and 24 weeks, and were scheduled at 10 AM, with an allowable variation of 1 hour on either side and included measurement of best-corrected visual acuity, IOP measured by Goldmann applanation tonometry using a calibrated tonometer, slit-lamp examination at each visit, and fundoscopy on the first and last visits. Corneal thickness was recorded at baseline. Baseline demographics were also recorded. Local and systemic side effects were specifically assessed at each visit. These included hyperemia of the conjunctiva and lid margin, rated from 0 to 3 using standardized photographs; changes from recorded baseline iris color; eyelash growth; periocular skin pigmentation if reported by the patient; presence of anterior chamber flare and/or cells; and cystoid macular edema in pseudophakic patients. Systemic complaints of headache or myalgia were also solicited and, if present, recorded.

The main outcome measure was IOP. A difference of 1.5 mm Hg for both the drug effect and the race effect was selected for the power calculation, approximately at the midrange of effects reported earlier. Responses of less than 3 mm Hg are not usually considered clinically significant, as discussed by Netland et al[17]; however, the differences between drugs found in that study were approximately 1.2 mm Hg. The original power calculation had suggested

TABLE 1. Exclusion Criteria

IOP < 24 mm Hg in both eyes or > 35 mm Hg in 1 eye
Angle grade < 2 (Shaffer classification)
Abnormalities preventing use of applanation tonometry
Cup:disc ration greater than 0.80
Severe central visual field loss (sensitivity < 10 dB in at least 2 of 4 visual field test points closest to point of fixation)
Pregnant women or those women of child bearing potential not using contraception
Chronic or recutting inflammatory eye disease
History of ocular trauma or intraocular surgery within 6 mo
Laser surgery within 3 mo
History of ocular infection or inflammation within past 3 mo
History of progressive retinal disease
Aphakia
Use of glucocorticoid during eligibility phase or use of topical NSAIDs during course of the study
Use of adjunctive IOP lowering medications in study eye or fellow eye during study
History of severe or serious hypersensitivity to prostaglandins
Significant hepatic, hematologic, electrolyte, or renal abnormalities contraindicating treatment with a prostaglandin

IOP indicates intraocular pressure; NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 2. Demographic Data by Drug Assignment

	Total	Bimatoprost	Travoprost	Latanoprost
Sex, n (%)				
Male	45 (54.2)	16 (59.3)	13 (50.0)	16 (53.3)
Female	38 (45.8)	11 (40.7)	13 (50.0)	14 (46.7)
Race, n (%)				
White	50 (60.2)	15 (55.5)	17 (65.4)	18 (60.0)
Other	38 (39.8)	12 (44.5)	9 (34.6)	12 (40.0)
Eye color, n (%)				
Blue	11 (13.3)	3 (11.1)	3 (11.5)	6 (20.0)
Brown	57 (68.6)	20 (74.1)	19 (73.1)	19 (63.3)
Mixed	15 (18.1)	4 (14.8)	4 (15.4)	5 (16.7)
Pachymetry (µm ± SD)	562.0 ± 42.2	561.2 ± 42.4	565.1 ± 36.4	559.5 ± 48.6
Age (y ± SD)	61.7 ± 10.8	60.6 ± 10.8	62.2 ± 10.6	62.3 ± 10.4

that for a design with 3 drugs and 5 racial groups (15 cells), and an expected difference of 1.5 mm Hg between drugs, a total of 300 patients would be required to provide 20 participants per cell. This would have achieved a 41% power for finding a drug effect, 46% power for finding a racial effect, and 97% for the interaction of drug by race, with an analysis of variance used to test at a 5% significance level. Unfortunately, our recruitment was inadequate to reach the intended sample size of 300 in the time available. It had been originally estimated that recruitment would take 18 months, with each of the 15 sites recruiting 20 patients. In the event, only 9 sites participated, and after a 1-year extension recruitment was closed. We therefore decided to combine the non-white subjects into 1 group and test for differences between this group and the whites. This resulted in a 3×2 design, with approximately 15 patients per cell (range, 9-18). The post hoc calculation of the power of this sample was 0.21 for the drug effect, 0.31 for the race effect, and 0.12 for the interaction, with α set at 0.05. Secondary outcomes were local and systemic side effects including conjunctival hyperemia and lid and lash changes. The main analysis was performed on a per protocol basis using the analysis of variance, with the Fisher exact test used for categorical variables.

RESULTS

Eighty-three patients were recruited from 9 sites. Thirty-eight were female and 45 were male. The mean age of the patients was 61.5 ± 10.5 years. There were no statistically significant differences in age, sex, eye color, or racial group between the 3 drug groups (Table 2) and there were no statistically significant differences in demographics or drug group among the racial groups (Table 3). The majority of the recruited patients were white (50/83, 60.2%) with the remaining 33 patients (39.8%) being African (18, 21.7%), South Asian (7, 8.4%) East Asian (7, 8.4%), and Hispanic (1, 1.2%).

The balancing of recruitment among the 3 drugs was successful, with 30 (36.2%) receiving latanoprost, 26 (31.3%) receiving travoprost, and 27 (32.5%) receiving bimatoprost.

The overall baseline IOP was 27.8 ± 3.4 mm Hg, with no statistically significant difference among the 3 groups. There was a highly statistically significant decrease in IOP from baseline to 12 weeks and from baseline to 24 weeks ($F = 439.3$, $P < 0.0001$; $F = 305.94$, $P < 0.0001$). There were no differences in treatment effect among the 3 drugs

($F = 0.94$, $P = 0.40$) or between the 2 ethnic groups, ($F = 2.20$, $P = 0.14$) and there was also no interaction between race and drug ($F = 0.47$, $P = 0.63$). Table 4 shows the IOP results at baseline, 12, and 24 weeks, subdivided by ethnic group and drug type. Figure 1A shows the IOP at all the study intervals for the 3 drugs; Figure 1B shows the results grouped for the 2 ethnic groups, and Figure 1C shows the results at baseline, 12, and 24 weeks for the 3 drugs and 2 ethnic groups separately.

Another useful way of examining the relative pressure-lowering efficacy of the drugs is to examine the percentage of patients who reached a given target pressure, rather than examining the mean IOP achieved. As expected, the lower the target pressure, the fewer the number of patients who achieved it. The targets examined were ≤ 21, ≤ 18, and ≤ 14 mm Hg, based on the recommendations of Damji et al.[35] After 6, 12, or 24 weeks of follow-up, there were no significant differences among the 3 drugs, or the 2 ethnic groupings, in the distribution of patients who reached each of these levels of pressure. The results for the 24 week data are shown graphically, by drug class in Figure 2 and by race in Figure 3.

The protocol also included the assessment of various possible side effects. At enrollment, eye color was described as blue in 11 of the 83 patients (13.3%), brown in 57 (68.6%), and hazel in 15 (18.1%). At the exit visit, eye color was listed in 77 patients, with 11 described as blue (14.3%), 53 as brown (68.8%), and 13 as hazel (16.9%). Not surprisingly, all the blue and hazel irides were found in the white population; 100% of the Other group had brown irides. The brown and hazel eye colors were evenly

TABLE 3. Demographic Data by Ethnic Group

	Total	White	Other
Sex, n (%)			
Male	45 (54.2)	27 (54.0)	18 (54.5)
Female	38 (45.8)	23 (46.0)	15 (45.5)
Drug, n (%)			
Bimatoprost	27 (32.5)	15 (30.0)	12 (36.3)
Travoprost	26 (31.3)	17 (34.0)	9 (27.3)
Latanoprost	30 (36.2)	18 (36.0)	12 (36.3)
Eye color, n (%)			
Blue	11 (13.3)	11 (22.0)	33 (100)
Brown	57 (68.6)	24 (48.0)	
Mixed	15 (18.1)	15 (30.0)	
Pachymetry (µm ± SD)	562.0 ± 42.2	573.2 ± 41.9	541.9 ± 35.4
Age (y ± SD)	61.7 ± 10.5	63.2 ± 10.3	59.6 ± 10.6

TABLE 4. IOP Results by Drug and White Versus Other Ethnic Groups

Drug	Ethnic Group (n)	IOP ± SD (95% Confidence Limits)		
		Baseline	12 wk	24 wk
Bimatoprost	All (27)	27.2 ± 2.8 (26.1-28.3)	17.2 ± 3.7*** (15.6-18.8)	17.9 ± 5.2*** (15.5-20.3)
	White (15)	28.3 ± 2.8 (26.7-29.9)	17.8 ± 4.2*** (15.3-20.3)	18.7 ± 1.9*** (14.9-22.5)
	Other (12)	259 ± 2.5 (24.3-27.5)	16.5 ± 3.2*** (14.4-18.6)	17.0 ± 4.7*** (13.4-20.6)
Travoprost	All (26)	28.3 ± 3.3 (26.1-29.5)	18.8 ± 4.1*** (17.1-20.5)	18.2 ± 3.8*** (16.5-19.9)
	White (17)	27.8 ± 3.3 (26.1-29.5)	19.1 ± 4.7*** (16.7-21.5)	18.3 ± 4.6*** (15.7-20.9)
	Other (9)	29.2 ± 4.6 (25.7-32.7)	18.3 ± 2.7*** (16.2-20.4)	18.2 ± 1.9*** (16.6-19.8)
Latanoprost	All (30)	28.3 ± 3.6 (27.0-29.6)	17.3 ± 3.2*** (16.1-18.5)	17.7 ± 3.4*** (16.3-19.1)
	White (18)	29.0 ± 3.7 (27.2-30.8)	17.2 ± 3.4*** (15.5-18.9)	17.0 ± 3.8*** (15.0-19.0)
	Other (12)	27.2 ± 3.4 (25.2-29.2)	17.4 ± 2.9*** (15.4-19.4)	19.0 ± 2.3*** (17.1-20.9)

*$P < 0.05$ compared with baseline IOP measurement.
**$P < 0.001$ compared with baseline IOP measurement.
***$P < 0.0001$ compared with baseline IOP measurement.
IOP indicates intraocular pressure.

distributed between the 3 drug groups, however, there were more blue eyes (6) in the latanoprost group than in either of the other 2 drug groups (3 each) (Table 2). No statistical significant difference was found in this distribution of the eye colors ($P = 0.85$). No patient in any group was documented as having a significant change in color, for example from hazel to brown. Hyperemia was assessed by comparison to a photographic comparator with standardized grading levels of 0, 0.5, 1, 2, 3, and 4. The highest rating given during the study was 3, and over half the patients in each drug assignment group was graded as having zero hyperemia at 6 months. The single patient assessed as having grade 3 hyperemia at 2 and 6 weeks was an African patient on latanoprost, and by 12 weeks the grading for this patient had decreased to 0.5, and to 0 by 24 weeks. Hyperemia, of any level, was reported in 17 (34%) of the white and 14 (42%) of the Other group ($P = 0.49$). Figure 4 shows the distribution of hyperemia scores for the 3 drugs at 24 weeks. Lash growth and/or periocular skin darkening were reported at any point in the study in 20 bimatoprost patients, 12 travoprost patients, and 10 latanoprost patients; these data are shown graphically in Figure 5. Sixteen (32%) of the white patients had either lash or skin changes, or both, as did 12 (36%) of the patients in the Other group ($P = 0.81$). The differences between groups in the incidence of either hyperemia, or skin, and lid changes were not statistically significant, whether tested by racial group or drug assignment. There were no findings of any anterior chamber cell or flare reaction, or cystoid macular edema, nor did any patient report headache or myalgia during the course of the study.

DISCUSSION

The development of the prostaglandin analogs represented a major advance in the medical management of glaucoma. Once all 3 medications became part of the standard clinical regimen, it was logically necessary to compare their effectiveness to help determine which drug, if any, had the advantage either in terms of IOP-lowering or side-effect profile. Relatively few studies have directly compared all the 3 drugs in this class. The first of these was the study by Parrish et al[36] and the XLT Study Group that enrolled 411 patients and evaluated IOP change at 8 AM between baseline and week 12 of follow-up. The study results showed comparable IOP-lowering effectiveness for all 3 drugs and greater ocular tolerability for latanoprost. They also analyzed patients by race, categorized as white, Black, and Other, and found no differences in response, but their study was not powered to detect subgroup differences.[36] A smaller study was reported by Orzalesi et al,[37] which also compared the IOP lowering of the 3 drugs in 44 patients using a cross-over design and a full diurnal evaluation of pressure. Although race was not a factor in their study, the IOP-lowering outcome showed statistically similar effectiveness for all 3 medications. A meta-analysis of 27 articles (reporting on 28 clinical trials) allowed the results from nearly 7000 patients to be evaluated. The results indicated that all 3 prostaglandin drugs, as well as timolol, are the most effective pressure lowering agents among the various glaucoma medications currently available.[38]

Target pressure is a useful concept, recommended by the American Academy of Ophthalmology Preferred Practice Patterns in the management of open-angle glaucoma. Once a target pressure has been chosen for a given individual, it is desirable to attain and maintain the pressure with the minimum of medical therapy.[39] The knowledge, therefore, of the likelihood of a given drug reaching the target pressure is clinically important. Unlike some earlier studies, we did not find statistically significant differences between the 3 drugs, or the 2 ethnic groups. As is usual, the lower target pressures were obtained less frequently. Noecker et al[22] found a statistically significantly
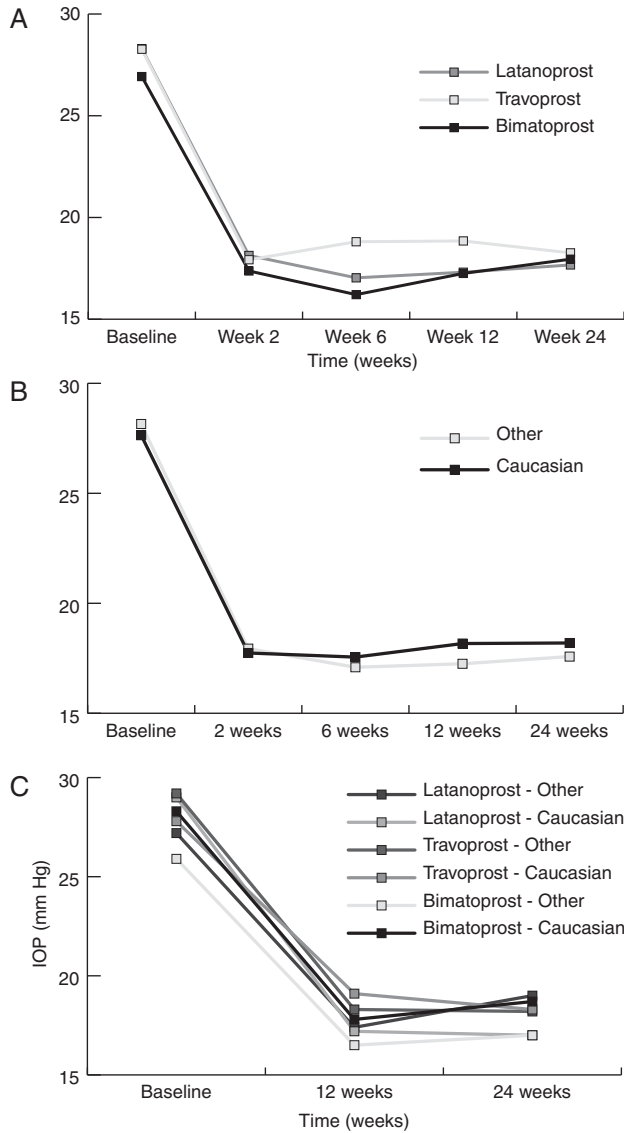
FIGURE 1. A, IOP response by drug class. B, IOP response by ethnic group. C, IOP response by drug and ethnic group. IOP indicates intraocular pressure.
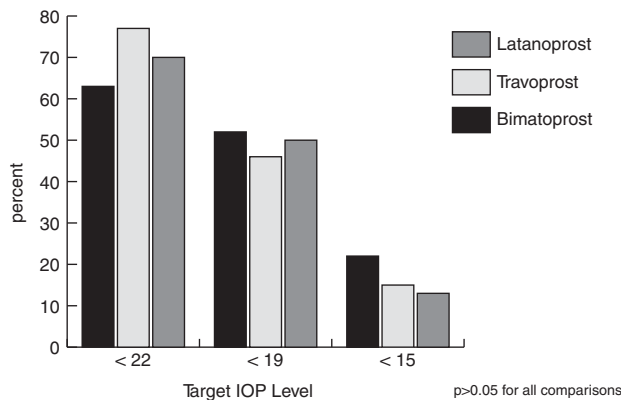

FIGURE 2. Percent of all patients reaching target IOP at 24 weeks by drug class. IOP indicates intraocular pressure.
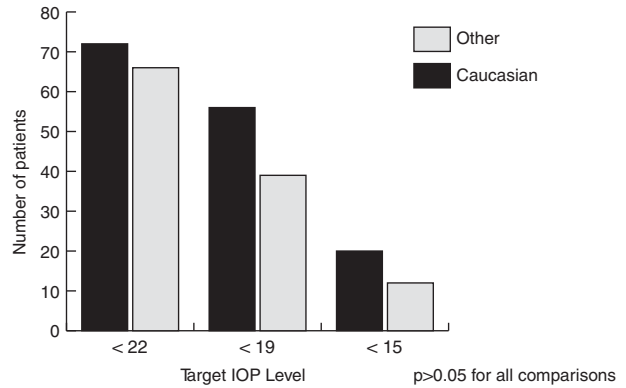

FIGURE 3. Percent of all patients reaching target IOP at 24 weeks by race. IOP indicates intraocular pressure.

higher responder rate for bimatoprost at all 3 time points tested compared with latanoprost, and Cantor et al found a nonsignificant superiority of bimatoprost over travoprost in reaching target pressures.[22,24] Parrish et al did not find differences in pressure lowering between the 3 prostaglandin analog drugs, though that report did not include a specific analysis of target pressure attainment.[36] Our findings suggest that any therapy in this class is likely to be of benefit, with no clear evidence that 1 drug is more likely than another to result in a particular level of IOP.

It is axiomatic that all drugs have side effects. The art of therapy is to find the drug that combines maximum effect with minimum undesirable consequences. The introduction of the prostaglandin agonist drugs was followed shortly thereafter by reports of hitherto unknown side effects, including iris heterochromia,[31] hypertrichiasis,[32] and periocular skin pigmentation.[33] Hyperemia of the conjunctiva,[28] and cystoid macular edema[34] were also reported, although these side effects are not unique to this drug class. Most studies report fairly high rates of fairly mild amounts of conjunctival hyperemia. Reported rates of hyperemia range between 25%[24] and 55.4%,[17] with latanoprost usually
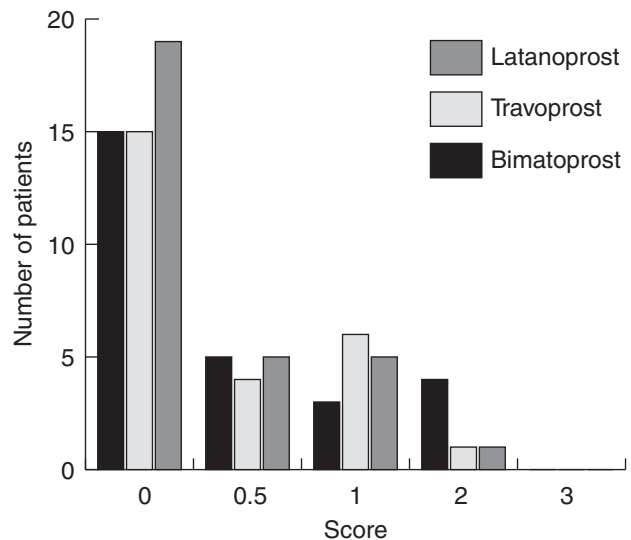

FIGURE 4. Distribution of hyperemia scores at 24 weeks, by drug.

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