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Comparison of Diurnal Intraocular Pressure Control by Latanoprost versus Travoprost

Results of an Observational Survey

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Abstract

Background and objective: Intraocular pressure (IOP) is known to be subject to daily fluctuations, the occurrence of which is a risk factor for progression of glaucoma. Control of IOP during the day by drugs is an important therapeutic target. We set out to compare the IOP control of travoprost and latanoprost taking into account the time since last instillation and the time of IOP measurement.

Methods: This was a prospective, cross-sectional observational study with some retrospective data collection. Private ophthalmologists were selected to each recruit ten patients with primary open-angle glaucoma and/or ocular hypertension receiving either travoprost or latanoprost as monotherapy. Clinical endpoints included IOP measurements and percentage of patients attaining predefined target IOPs. Six patient subgroups were defined according to: (a) IOP measurement time: before 1200h, 1200h–1600h and after 1600h, and (b) time since last intake (<24 hours, >24 hours). Analyses comprised χ^2 and Wilcoxon tests, ANOVA, logistic regressions and adjustment by propensity score.

Results: In total, 2052 patients treated with travoprost (n = 1704) or latanoprost (n = 348) participated in the study. Treatment groups were comparable at baseline, except for a longer treatment duration in latanoprost-treated patients. When the interval between the last treatment instillation and IOP measurement (treatment/IOP interval) was <24 hours (n = 1241), 82% of travoprost-treated patients attained pre-defined target IOP versus 67% with latanoprost ($p < 0.0001$). This difference was greatest after 1600h, when the mean IOP was 16.5mm Hg for travoprost-treated patients and 17.7mm Hg for latanoprost-treated patients ($p = 0.0025$). When the treatment/IOP interval was >24 hours (n = 461), travoprost was superior to latanoprost, i.e. more patients using travoprost attained the predefined target IOP (78.5% vs 68.3%; $p = 0.0344$), and the mean IOP value was lower in

the travoprost group (16.8 vs 17.8mm Hg; p = 0.0016). After adjustments for confounding factors, similar results were obtained.

Conclusions: According to this observational survey, travoprost appears to reduce evening and mean diurnal IOP more effectively than latanoprost. Latanoprost IOP control appears to be more sensitive to time since the last dose.

Introduction

Prostaglandin analogues are now increasingly being used as monotherapy for first-line treatment of open-angle glaucoma and ocular hypertension.[1] The greater efficacy of prostaglandins for controlling intraocular pressure (IOP) compared with β-adrenoceptor antagonists has been established in several clinical trials[2-5] and confirmed by a meta-analysis conducted in 2005.[6] Findings reported by Nordmann et al. endorse this practice by demonstrating how it may be possible to preserve vision throughout life if the most effective glaucoma treatments are used as first-line therapy.[7]

Many clinical trials have demonstrated that the two most recently introduced prostaglandins, travoprost and bimatoprost, provide better control of IOP throughout the day and into the evening than latanoprost,[2,8-12] although Parish et al.[13] found no differences between the three prostaglandin analogues. The benefits of better control of IOP on disease progression have been evaluated in different models.[14,15] A positive association between higher IOP value and costs to the healthcare system (more visits and complementary tests) has also been reported.[16,17]

Use of health economic evaluations has dramatically increased over recent decades in an attempt to justify allocation of resources to new innovative medical strategies, a situation which applies to glaucoma therapy.[17-21] Observational data models and other experimental designs have been used to justify the use of higher cost prostaglandin analogues, and to estimate the long-term consequences (use of laser and surgery, visual field loss prevention) of use of such medications. Health economics-based recommendations in many countries agree that evaluations of clinical efficacy should ideally be based on prescribing practices and not on comparisons of clinical trial data.[22] One approach is to relate medicine reimbursement to the mean duration of unchanged treatment.[23-25] Another approach is to conduct specific, prospective studies of clinical data obtained in everyday practice. To our knowledge, few studies of this kind have been performed in France[26-28] and no observational surveys have evaluated the long-term advantages of controlling IOP with the newer prostaglandins.

The objectives of the present study were 2-fold: (1) to determine how French ophthalmologists determine thresholds for target IOPs and when current therapy should be considered no longer adequate; and (2) to compare the abilities of latanoprost and travoprost to maintain target IOPs when subjects are seen either <24 hours or >24 hours after their last instillation of a prostaglandin analogue.

Methods

This survey was conducted according to French law (Commission Nationale de l'Informatique et des Libertés Declaration, Ordre des Médecins, Ministère de la Recherche) and recommendations by the Association Des Epidémiologistes de Langue Française.[29] The rationale of the survey was explained orally and was accompanied by a short written note given to each patient. Verbal informed consent was obtained for each participating patient before inclusion in the survey.

Experimental Design

The aim of the study was to compare diurnal IOP control of travoprost and latanoprost in an observational setting. The experimental design – cross-sectional survey with retrospective data collection – was chosen to avoid influencing the patient-doctor relationship (observational bias). The time of the last instillation was obtained during the visit. Treatment duration had to be >6 weeks to obtain the full efficacy of the prostaglandin analogues, with no upper limit. Treatment was chosen by the ophthalmologists according to their usual practice.

Setting

To be included in the survey, practitioners had to: (1) be able to include ten patients receiving prostaglandin monotherapy within 4 weeks; (2) have sufficient time to report patient chart data on the case report form; and (3) have the required data on their patient medical file. Each investigator was selected from the professional list of French ophthalmologists. A phone call was undertaken to check the above criteria were applicable and to obtain practitioners' agreement to participate in the study.

Subjects

Subjects of either sex with primary open-angle glaucoma or ocular hypertension were informed about the study objectives and, after providing verbal consent, enrolled in the study if they met the following criteria: age >18 years; prostaglandin monotherapy used for ≥6 weeks; and no surgical intervention or laser therapy since the start of prostaglandin treatment. Patients who received additional therapy for primary open-angle glaucoma or ocular hypertension were excluded, as were patients with secondary glaucoma (congenital, inflammatory, neovascular, partial or complete angle closure, or induced by a cataract operation). Patients whose current treatment had been initiated in a clinical trial could not participate in the survey.

Data on sociodemographic variables (age, sex, profession), type of glaucoma, i.e. primary open-angle glaucoma or normal tension glaucoma, confounding factors (insulin- or non-insulin-dependent diabetes mellitus, dyslipidaemia, arterial hypertension or hypotension, vasomotor instability, cardiovascular disease, migraine, tobacco smoking or family history of glaucoma), presence of associated ocular pathology (strong myopia, cataract, age-related macular degeneration or dry eye syndrome), glaucoma/ocular hypertension duration, circumstances of glaucoma diagnosis (routine examination, spontaneous visit for vision problems, eye symptoms or other reasons), and previous surgical or laser treatment were collected.

Observation Procedures

IOP values at diagnosis and prior to initiation of prostaglandin treatment were documented. In this observational survey, IOP was measured by an ophthalmologist according to his/her usual rules, i.e. IOP measurements were not standardised – the number of IOP measurements and measurement of the corneal thickness were determined by the individual practitioner. The technical procedures used to measure IOP were not annotated.

The following data were collected retrospectively from the patients' charts: glaucoma risk factors, ocular co-morbidities, date of diagnosis, IOP at diagnosis and at initiation of the current treatment, previous laser treatment or surgery for glaucoma. At the time of the study visit, the ophthalmologist reported from the medical chart the target IOP that he or she set at the previous visit based upon the patient's age, visual fields, optic nerve appearance and IOP before treatment in each eye. The following data were collected prospectively during an IOP control visit: patient sociodemographics, type of glaucoma, type of prostaglandin, date and time of

last dose, IOP and exact time of measurement, the therapeutic decision, the need for either invasive intraocular surgery or laser therapy, and the date of the next visit.

Main Outcome Measure and Sample Size Justification

The main evaluation criterion was defined as the proportion of patients who did not exceed the target IOP set by ophthalmologists. Subset analyses according to the time of the IOP measurement were performed to compare the efficacy of the two drugs at different time-points in the day. Time-frames were determined *post hoc* in the absence of data recording ophthalmologists' activities at the time of writing the protocol. The α risk was fixed at 5% and the β risk at 20%. A difference of 10% required 232 patients per treatments in each time-frame.

Secondary Measures

Other evaluations included IOP measured at each visit, number of patients with IOP values <20mm Hg and <18mm Hg, glaucoma-specific examinations (e.g. perimetry), and surgery or laser referrals.

Statistical Analysis

The statistical analyses were performed with SAS® software (SAS Institute, Cary, NC, USA). Evaluations were analysed in relation to the time elapsed since last treatment to IOP measurement in one of the following consultation periods: 0–1200h, 1200–1600h and 1600–2400h. Subsequently, on examining the data, two patient populations were defined by treatment/IOP intervals <24 hours or >24 hours. Time of last dose was not fixed by the protocol. Although the reasons for having a treatment/IOP interval >24 hours were not collected, non-adherence should be suspected in these patients. Efficacy comparisons were performed on each population.

Subgroup comparisons were performed by χ^2 or Fisher's exact tests for qualitative variables, and by ANOVA for quantitative variables, after verifying the normality of residuals and homoscedasticity. When the latter assumptions did not apply, Wilcoxon's test or the Kruskal-Wallis test was substituted. The ANOVA estimated the effects of disease duration and treatment duration on IOP values after the two treatment/IOP intervals (<24h and >24h). Centre effect was not taken into account because the number of patients per centre was too small and most of the centres incorporated both treatments, i.e. treatment effect was not confounded by centre effect.

In observational surveys, large differences in the observed confounding factors between two study groups may exist because the investigator has no control over who was allocated to each treatment group; this can result in biased estimates of treatment effect. According to Newgard et al., this bias can be difficult to eliminate using conventional multivariate techniques.[30] Use of a propensity score may better adjust covariates between the groups and reduce bias. It is described as a conditional probability that a subject will be 'treated' based on an observed group of covariates.

Variables included in the propensity score were selected by a stepwise logistic regression (entry and exit p-values fixed at 0.10). The seven variables listed in table I and table II, i.e. duration of illness, vasomotor instability (as reported in the medical file), cataract, bilateral visual acuity, treatment duration, time of last dose and IOP threshold, were entered into the regression, with treatment differences being significant at $p < 0.10$. A logistic score, representing the logit of the probability of being treated by one of the two treatments, was calculated for each patient and used to adjust (regression techniques) for imbalance between the treatment groups.

Statistical tests were interpreted two-sided, with $\alpha = 5\%$.

Results

Demographics and Other Patient Characteristics

The study involved 280 ophthalmologists who enrolled 2594 patients with primary open-angle glaucoma, normal tension glaucoma or ocular hyper-tension, all treated with prostaglandins.

The average age of practitioners was 47.6 years with an approximate male : female ratio of 1 : 3. Fifty percent of practitioners worked full-time in private practice and 17% in care networks, with 48% located in urban areas housing more than 100 000 inhabitants. Their facilities were open for about 10 hours daily on work days and during an average week they saw 12.3 patients with primary open-angle glaucoma and 17.8 with ocular hypertension.

The average age of patients was 65.0 years with a male : female ratio of approximately 1 : 1. Most were retired (56.7%), but a high proportion were still working (30.9%).

Data were incomplete for 542 patients, including 350 patients without information on the treatment/IOP interval. No major differences were found between these 350 patients and patients participating in the analysis with respect to age, sex, disease duration, glaucoma risk factors, eye co-morbidity, visual acuity, IOP at diagnosis and IOP before starting the current treatment. The data analysis, therefore, was performed on 2052 patients treated with either travoprost (n = 1704) or latanoprost (n = 348). When time since last dose was taken into account, the sample sizes became 1373 and 329, respectively. The unbalanced sample size allowed better documentation of IOP control late in the afternoon by travoprost. The treatment/IOP interval was <24 hours for 1241 patients and >24 hours for 461 patients.

Table I shows that there were no significant demographic differences between the two treatment groups for either of the two treatment/IOP intervals except in the <24-hour interval group, where cataracts were more frequent (p = 0.0225) and current disease was 6 months longer (p = 0.0015) in the latanoprost-treated patients. Demographic variables for the entire population (n = 2052) may be summarised as follows: males 47%, average age 64.6 years, duration of disease 44.9 months, diabetes mellitus 15.5%, dyslipidaemia 24.7%, arterial hypertension 40.8%, arterial hypotension 1.7%, vasomotor instability 4.9%, cardiovascular disease 16.3%, migraine 9.0%, smokers 14.0%, family history of glaucoma 26.3%, other risk factors 7.4%, cataract 33.5%, myopia 6.7%, macular degeneration 5.9%, dry-eye syndrome 9.4% and other pathology 11.4%.

Observations reported by the ophthalmologists are presented in table II, and show no significant differences between treatment groups in visual acuity, IOP values, time of IOP measurement or treatment/IOP intervals of <24 hours or >24 hours. Study population (n = 2052) means were visual acuity right eye 0.09 logMAR (logarithm of the minimum angle of resolution), left eye 0.09 logMAR, bilateral 0.05 logMAR, and IOP 16.86mm Hg.

However, for patients with the treatment/IOP interval <24 hours, a significant difference (p = 0.018) was observed when the time of last medication was divided into five periods. Data in table II show that travoprost was more frequently administered early in the day and latanoprost more frequently in the evening. Differences between treatment groups in the timing of administration were not statistically significant in patients in the treatment/IOP interval >24 hours group.

Treatment duration (time since first prescription) was longer in the latanoprost-treated patient group (p < 0.0001) [table II]. Table II also shows that when the treatment/IOP interval was <24 hours, the average target IOP level was set significantly (p = 0.0264) higher for travoprost (17.64mm Hg) than

Table I. Demographic characteristics of the study population and description of glaucoma and other ocular pathologies in the different treatment groups[a]

Parameter	Time since last dose <24h			Time since last dose >24h		
	travoprost (n = 1015)	latanoprost (n = 226)	p-value	travoprost (n = 358)	latanoprost (n = 103)	p-value
Age (y) [mean ± SD]	64.62 ± 12.42	65.62 ± 11.67	0.4857	64.74 ± 11.58	62.66 ± 12.14	0.1207
Male sex	488 (48.51)	104 (46.85)	0.6571	154 (43.5)	48 (46.6)	0.5657
Disease duration (mo)	44.89 ± 54.34	50.67 ± 50.48	0.0015	50.80 ± 56.86	46.01 ± 43.24	0.8227
Glaucoma surgery	44 (4.39)	10 (4.50)	1	15 (4.23)	3 (2.91)	0.7744
Glaucoma laser treatment	50 (5.02)	13 (5.86)	0.6152	16 (4.51)	3 (2.91)	0.5857
Glaucoma risk factors						
diabetes mellitus	165 (16.52)	36 (16.90)	0.8909	49 (14.00)	12 (12.00)	0.6064
dyslipidaemia	251 (25.25)	61 (28.50)	0.324	88 (25.14)	25 (25.00)	0.9768
arterial hypertension	421 (41.85)	83 (38.07)	0.3045	150 (42.49)	40 (39.60)	0.6038
arterial hypotension	16 (1.62)	7 (3.33)	0.1026	7 (2.00)	1 (1.00)	0.691
vasomotor instability	45 (4.55)	16 (7.51)	0.074	21 (6.00)	5 (5.00)	0.7054
cardiovascular diseases	174 (17.45)	33 (15.49)	0.4906	59 (16.81)	19 (19.19)	0.5802
migraine	93 (9.41)	25 (11.74)	0.3013	33 (9.40)	12 (12.24)	0.4073
smoker	148 (14.86)	30 (14.08)	0.772	47 (13.35)	18 (17.82)	0.2587
familial glaucoma history	275 (27.98)	59 (27.19)	0.815	93 (26.65)	27 (27.55)	0.8585
other risk factors	42 (6.33)	9 (6.16)	0.9422	22 (9.48)	8 (11.27)	0.6595
Eye co-morbidity						
myopia	71 (7.14)	14 (6.48)	0.7303	27 (7.65)	7 (7.07)	0.8472
cataract	324 (32.30)	88 (40.37)	0.0225	109 (30.97)	31 (30.69)	0.9583
AMD	59 (5.98)	16 (7.51)	0.4016	17 (4.80)	5 (5.00)	1
dry eye	104 (10.66)	23 (10.80)	0.9514	25 (7.10)	9 (9.09)	0.5079
other	77 (10.35)	16 (9.30)	0.682	30 (10.75)	10 (12.66)	0.6351

a Values are no. (%) or mean ± SD, as appropriate. Percentages are calculated from the documented sample size.

AMD = age-related macular degeneration.

for latanoprost (17.55mm Hg), whereas the converse was true (17.41mm Hg vs 17.89mm Hg, respectively) when the treatment/IOP interval was >24 hours.

Treatment Responses

Raw data (prior to adjustment by propensity score) are presented in table III. Patients treated with travoprost experienced, in general, better IOP control than those treated with latanoprost, irrespective of the treatment/IOP interval.

When the treatment/IOP interval was <24 hours, overall IOP values were significantly lower (−0.66mm Hg) in travoprost-treated patients than in latanoprost-treated patients ($p = 0.0007$). Mean IOP measured at the end of the day was higher in patients treated with latanoprost (table III). Differences were significant between 1200h and 1600h ($p = 0.0503$) and after 1600h ($p = 0.0025$). Lastly, an analysis including the 350 patients ($n = 2052$) without treatment/IOP interval information yielded similar results (travoprost 16.74mm Hg [SD 2.68] vs latanoprost 17.48mm Hg [SD 2.99]; $p < 0.0001$).

Overall, more travoprost-treated patients than latanoprost-treated patients had an IOP <20mm Hg ($p = 0.0018$) if they were seen <24 hours after their last eye-drop administration. This difference was statistically significant in the subset of patients whose IOP was measured after 1600h ($p = 0.0209$). The proportion of patients with an IOP <20mm Hg in the latanoprost group remained similar at different IOP measurement times but increased as IOP

was measured later in the day in the travoprost group (from 86.85% to 92.83%) [table III].

The percentage of subjects with an IOP <18mm Hg was significantly (p = 0.0062) higher in the travoprost group (65%) than in the latanoprost group (55%), especially when the IOP measurement was done after 1600h (66% vs 46%, respectively; p = 0.0082). Patients treated with travoprost maintained an IOP <18mm Hg more consistently throughout the day compared with patients in the latanoprost group, who had a lower frequency of IOP <18mm Hg when the measurement was performed in the late afternoon (table III).

When all ophthalmologists' IOP targets were pooled in patients with a treatment/IOP interval <24 hours, the target rate attainment was significantly (p < 0.0001) greater in the travoprost group (81.85%) than in the latanoprost group (67.27%), and a significant advantage in this respect for travoprost was observed at all IOP measurement times (table III). The proportion of patients who reached the IOP targeted value with travoprost was always >80% and with latanoprost was always <70%. Complementary examinations and referrals for additional laser therapy or surgery were similar between treatments (table III).

Table III does not detail full treatment response data for patients in the treatment/IOP interval >24 hours group because there were too few patients treated with travoprost (n = 358) or latanoprost (n = 103) for a reliable analysis. In travoprost-treated patients, no difference in average IOP was found between patients whose time since last dose was <24 hours and those whose time was >24 hours (16.72mm Hg vs 16.76mm Hg, respectively). By contrast, patients treated with latanoprost whose time since last dose was >24 hours had a significantly higher (p < 0.05) IOP average (17.38mm Hg vs 17.80mm Hg, respectively).

With respect to the IOP <20mm Hg threshold, the attainment rate amongst patients in the treatment/IOP interval >24 hours group was significantly (p <

Table II. Visual acuity, glaucoma treatment and intraocular pressure (IOP) values in the different treatment groups[a]

Parameter	Time since last dose <24h			Time since last dose >24h		
	travoprost (n = 1015)	latanoprost (n = 226)	p-value	travoprost (n = 358)	latanoprost (n = 103)	p-value
Bilateral visual acuity (decimal)	8.92 ± 2.04	9.08 ± 1.75	0.084	9.10 ± 1.78	9.09 ± 1.69	0.7366
Time of last medication						
0–800h	33 (3.25)	4 (1.77)	0.018	16 (4.47)	9 (8.74)	0.559
800–1200h	141 (13.89)	21 (9.29)		127 (35.47)	35 (33.98)	
1200–1600h	72 (7.09)	7 (3.10)		70 (19.55)	18 (17.48)	
1600–2000h	118 (11.63)	26 (11.50)		74 (20.67)	20 (19.42)	
2000–2400h	651 (64.14)	168 (74.34)		71 (19.83)	21 (20.39)	
Current treatment duration (mo)	7.28 (8.40)	19.23 (14.23)	<0.0001	5.57 (7.84)	15.56 (15.25)	<0.0001
Time of IOP measure						
0–800h	15 (1.48)	3 (1.33)	0.2996	5 (1.40)	0 (0)	0.1156
800–1200h	416 (40.99)	108 (47.79)		143 (39.94)	53 (51.46)	
1200–1600h	333 (32.51)	68 (30.09)		102 (28.49)	30 (29.13)	
1600–2000h	251 (24.73)	47 (20.80)		107 (29.89)	20 (19.42)	
2000–2400h	0 (0)	0 (0)		1 (0.28)	0 (0)	
IOP (mm Hg)						
at diagnosis	24.88 ± 3.25	25.03 ± 3.15	0.7325	25.18 ± 3.47	25.02 ± 2.92	0.5387
at baseline	22.62 ± 3.78	22.86 ± 4.00	0.3853	22.36 ± 3.58	23.26 ± 3.76	0.5705
targeted value at present visit	17.64 ± 2.01	17.55 ± 1.89	0.0264	17.41 ± 1.94	17.89 ± 2.07	0.0298

a Values are no. (%) or mean ± SD, as appropriate.

Table III. Treatment responses in the different groups[a]

Parameter	Time since last dose <24h			Time since last dose >24h		
	travoprost (n = 1015)	latanoprost (n = 226)	p-value	travoprost (n = 358)	latanoprost (n = 103)	p-value
IOP (mm Hg) overall	16.72 ± 2.58	17.38 ± 2.88	0.0007	16.76 ± 2.78	17.80 ± 3.38	0.0016
−1200h	16.77 ± 2.66	17.19 ± 3.13	0.1534	na	na	na
1200–1600h	16.79 ± 2.63	17.51 ± 2.97	0.0503	na	na	na
+1600h	16.55 ± 2.35	17.67 ± 2.02	0.0025	na	na	na
IOP <20mm Hg overall	894 (88.78)	180 (81.08)	0.0018	308 (88.00)	71 (69.61)	<0.0001
−1200h	370 (86.85)	91 (81.98)	0.1896	na	na	na
1200–1600h	291 (88.18)	52 (80.00)	0.0745	na	na	na
1600h+	233 (92.83)	37 (80.43)	0.0209	na	na	na
IOP <18mm Hg overall	652 (64.75)	122 (54.95)	0.0062	227 (64.86)	55 (53.92)	0.0448
−1200h	268 (62.91)	65 (58.56)	0.4001	na	na	na
1200–1600h	218 (66.06)	36 (55.38)	0.1006	na	na	na
1600h+	166 (66.14)	21 (45.65)	0.0082	na	na	na
IOP <targeted value overall	812 (81.85)	148 (67.27)	<0.0001	267 (78.53)	69 (68.32)	0.0344
−1200h	339 (80.52)	76 (69.72)	0.0148	na	na	na
1200–1600h	264 (81.48)	44 (67.69)	0.0125	na	na	na
1600h+	209 (84.62)	28 (60.87)	0.0002	na	na	na
Complementary examinations	529 (54.09)	127 (56.70)	0.4797	166 (48.68)	51 (52.04)	0.5576
Surgery	9 (0.98)	2 (0.95)	1.00	3 (0.92)	0 (0)	1.00
Laser treatment	8 (0.87)	1 (0.48)	1.00	2 (0.62)	0 (0)	1.00

a Values are no. (%) or mean ± SD, as appropriate. Percentages are calculated from the documented sample size.

IOP = intraocular pressure; **na** = not available because sample size too small.

0.0001) higher in patients treated with travoprost (88.00%) than in those treated with latanoprost (69.61%). Similarly, with respect to achieving the IOP <18mm Hg threshold, the attainment rate was significantly ($p = 0.0448$) higher in patients treated with travoprost (64.86%) than in those treated with latanoprost (53.92%) amongst patients in the treatment/IOP interval >24 hours group.

When all ophthalmologists' thresholds were pooled for the treatment/IOP interval >24 hours group, the rate of target attainment was significantly ($p = 0.0344$) greater in travoprost-treated patients (78.53%) than in latanoprost-treated patients (68.3%) [table III].

Complementary examinations and referrals for additional laser therapy or surgery did not differ significantly between treatment groups in the treatment/IOP interval >24 hours group.

ANOVA estimates of the effects of disease duration and treatment duration on treatment efficacy (IOP values) showed that both variables accounted for very little of the variance. When the treatment/IOP interval was <24 hours, the treatment duration effect was weak ($p = 0.014$) and disease duration was without significant effect ($p < 0.20$). The corresponding effects were similar when the treatment/IOP interval was >24 hours, i.e. treatment duration ($p < 0.03$) and disease duration ($p < 0.11$). By contrast, the treatment difference (travoprost vs latanoprost) met the statistical threshold ($p = 0.0001$) after adjustment for the above factors.

Adjustment by propensity score (table IV) when the treatment/IOP interval was <24 hours also found similar differences as described above and in table III. Differences between the proportion of patients attaining the various IOP thresholds were significant at all times with a higher percentage of travoprost

subjects reaching lower IOPs, especially after 1600h (table IV). Attainment of IOP thresholds of <20mm Hg ($p = 0.0128$) and <18mm Hg ($p = 0.0038$) were more frequent with travoprost when IOP measurement was performed after 1600h.

When the treatment/IOP interval was >24 hours, mean IOP was 0.83mm Hg greater in the latanoprost group than in the travoprost group ($p = 0.0289$). Also, the proportion of patients attaining the <20mm Hg IOP threshold was higher ($p = 0.0101$) with travoprost therapy (88.19%) than with latanoprost (74.70%) [table IV].

Discussion

This cross-sectional observational survey reports results that could be interpreted in the light of the randomised clinical trial findings published by Netland et al. and Dubiner et al.[2,8] The present findings suggest that subjects using travoprost had better IOP control than those using latanoprost regardless of whether IOP was measured <24 or >24 hours after the last administration. Target IOP thresholds set by ophthalmologists were achieved more frequently with travoprost (always >80%) than with latanoprost (always <70%) when treatments were instilled 24 hours before IOP measurement, whatever the time of measurement.

Under the hypothesis that lack of IOP control is associated with treatment switches, our finding suggests that switches of therapy may be more frequent when patients are treated with latanoprost, as compared with travoprost, as predicted by Dubiner et al. and Netland et al.[2,8] We identified two populations according to the time interval between last instillation and IOP measurement and used a threshold of 24 hours. This approach should not be considered as a new standard to define good therapeutic use of prostaglandin analogues but rather as an indicator of

Table IV. Results in the different groups adjusted by propensity score

Parameter	Time since last dose <24h			Time since last dose >24h		
	travoprost (n = 1015)	latanoprost (n = 226)	p-value	travoprost (n = 358)	latanoprost (n = 103)	p-value
IOP overall (mm Hg)	16.65	17.64	<0.0001	16.71	17.54	0.0289
−1200h	16.69	17.33	0.0301	na	na	na
1200–1600h	16.74	17.75	0.0069	na	na	na
1600h+	16.51	17.85	0.0027	na	na	na
IOP <20mm Hg overall (%)	89.87	77.91	<0.0001	88.19	74.70	0.0101
−1200h	87.29	79.21	0.0569	na	na	na
1200–1600h	88.63	76.44	0.024	na	na	na
1600h+	92.88	78.00	0.0128	na	na	na
IOP <18mm Hg overall (%)	65.61	50.42	0.0004	64.50	58.07	0.3324
−1200h	63.69	56.57	0.1456	na	na	na
1200–1600h	66.00	51.82	0.1482	na	na	na
>1600h+	66.79	42.88	0.0038	na	na	na
IOP < targeted value overall (%)	82.60	63.45	<0.0001	79.20	71.80	0.1949
−1200h	80.80	68.46	0.0118	na	na	na
1200–1600h	81.79	64.53	0.0077	na	na	na
1600h+	84.99	56.97	0.0005	na	na	na
Complementary examinations (%)	53.91	55.13	0.7783	47.40	48.49	0.8711
Surgery	[a]					
Laser treatment	[a]					

a Adjustment not stable because of too few events.

IOP = intraocular pressure; **na** = not available because sample size too small.

the clinical consequences of poor treatment compliance. However, comparing our results with those reported by Dubiner et al. and Netland et al.[2,8] is not straightforward because the experimental designs used are very different. These investigators measured IOP during the day in the same patient whereas we had to conduct patient subgroup analyses to 'reproduce' IOP daily variability in our study. Our results also suggest that travoprost might provide better IOP control than latanoprost, especially in non-adherent patients taking medications at varying times of the day, and might also offer a degree of coverage for patients who occasionally forget a dose.[8]

The average IOP threshold targeted by practising ophthalmologists was 17.5mm Hg, a value close to the findings of the AGIS (Advanced Glaucoma Intervention Study).[31] Therefore, it would seem that criteria used in therapeutic clinical trials do not differ much from current everyday practice.

Treatment group comparability is always an issue when studies are conducted by field observations. It is accepted theory that treatment randomisation is the only guarantee of group comparability. Seven variables associated with significant ($p < 0.01$) treatment differences were identified. All were known to be confounding factors for glaucoma. The relatively small number observed should be set against the 54 statistical tests demonstrating group comparability. We used the generally recommended method of propensity score.[30] The seven confounding variables were selected from the ensemble of glaucoma factors on the basis of group differences within the 10% limit. Accordingly, the propensity score used adjustment factors based on logistic regressions. Other methods are possible. However, we believe that the convergence of results from our two different methods (propensity score and linear model, not presented here) consolidated the validity of our results.

A degree of imbalance between the treatment groups was found with respect to treatment duration and target IOP values. Because treatment duration was not linked to outcome measures (IOP values or responder rates), no adjustment was necessary; nevertheless, we adjusted for this factor to obtain the most unbiased results. With respect to target IOP values, it should be noted that the differences were statistically significant but clinically unimportant, i.e. 0.09mm Hg in the time since the last dose <24 hours group, and 0.48mm Hg in the time since the last dose >24 hours group. For the same level of efficacy, a higher IOP target means a higher responder rate. Consequently, the largest difference (0.48mm Hg) favoured latanoprost-treated patients.

This survey could not control the quality, homogeneity and reproducibility of data in the manner possible with a prospective clinical trial protocol. The results reported here describe the everyday practice of 280 French ophthalmologists each seeing an average of 30 patients per week for primary open-angle glaucoma/ocular hypertension follow-up treatment. As stated by virtually all health economic guidelines,[22] resource allocation is determined according to effectiveness (measures applied in daily practice) and is not based on efficacy (measurements performed in clinical trials). Consequently, the present results do not relate simply to differences of efficacy between the two prostaglandin analogues, but also encompass the contribution of medical practice.

Throughout this paper the term 'diurnal IOP' is used. This wording must be interpreted in the context of an observational survey for which the protocol cannot fix IOP measurement times. Therefore, as a proxy for repeated measurements made on the same patient at set times (i.e. the true diurnal IOP profile), we presented data for three periods per day (namely −1200h, 1200h–1600h and 1600h+). Consequently, comparisons between the results of our survey and the Dubiner et al. and Netland et al.[2,8]

clinical trials should be interpreted cautiously, bearing in mind the important differences in experimental design.

Our study has several limitations. First, an important imbalance remained between the sample sizes of the two treatment groups that allowed us, in fact, to observe 24-hour IOP variations with travoprost. Second, we were unable to demonstrate an impact of better IOP control on need for laser therapy or surgery. Such interventions are necessary only when drug treatment fails and therefore are rarely needed with prostaglandin monotherapy. Complementary examinations were seldom required and it would need a prospective study to detect a difference between travoprost and latanoprost in this regard. Indeed, long-term longitudinal studies are needed to fully describe the consequences of better IOP control.[28] Third, IOP threshold targets were a possible source of bias. Collaboration in a clinical study may encourage ophthalmologists to follow good clinical practice more assiduously. A retrospective search into medical files would probably show how the present targets were set. Also, the observers were not 'blinded' to treatment identities and made their judgement in full knowledge of the treatment administered. However, decisions to switch treatments are not made 'blindly' in routine practice and this possible internal bias is intrinsic to our experimental design (observational survey). Furthermore, our results observed with an arbitrarily fixed IOP threshold were similar to those obtained when practitioners set their targets. Fourth, a cross-sectional study design limits comparisons over time because effects are not observed 'within' individuals. This problem is usually attenuated by recruiting far more patients than are required for clinical trials. In any case, our design assumed that ophthalmologists' consultation times were independent of the IOP values measured. Accordingly, the observed variations were related to the pharmacological profiles of the products studied. Fifth, IOP measures were not standardised and corneal thickness was not documented, as would be expected in an observational survey. However, since both treatments could be prescribed by each ophthalmologist, the observed results are unbiased. Sixth, time-frame was defined *post hoc* since no information related to visit time was available.

Conclusion

According to this observational survey, travoprost appears to reduce both evening and mean diurnal IOP more effectively than does latanoprost. However, these results should be interpreted in the context of a cross-sectional study conducted in a naturalistic setting.

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