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Intraocular Pressure Control with Latanoprost/Timolol and Travoprost/Timolol Fixed Combinations

A Retrospective, Multicentre, Cross-Sectional Study

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Abstract

Objective: The aim of this study was to confirm randomized clinical trial results showing that a fixed timolol/travoprost combination (TT; DuoTrav®) controls intraocular pressure (IOP) better than a fixed timolol/latanoprost combination (TL; Xalacom®) in everyday ophthalmic practice, when measured in the morning and >24 hours after instillation.

Methods: Patients with ocular hypertension or primary open angle glaucoma stabilized on TT or TL were included in this retrospective cross-sectional study. Data on demographics, medical history and previous treatments were extracted from the patients' medical records. Last treatment instillation times and IOP values were recorded at clinic visits. Treatments were compared by analyses of variance, logistic regressions and propensity scores adjusted for confounding factors.

Results: Out of 316 patients included, 124 instilled TT, 192 instilled TL and 266 (84.2%) overall had instilled their eye drops within 24 hours. The patients' mean age was 64.5 years and 51.6% were female. Treatment groups were comparable except for longer disease and treatment durations in TL recipients. Worse eye mean IOPs were 25.8 mmHg at diagnosis and 21.9 mmHg on starting their designated fixed combination treatment. The best IOP control was provided by TT instillations (mean IOP 17.1 and 19.0 mmHg in the TT and TL groups, respectively; $p < 0.001$). This difference was reinforced by results in the subgroup of patients who instilled treatment >24 hours prior to IOP measurement (mean IOP 17.0 and 20.3 mmHg in the TT and TL groups, respectively; $p < 0.004$). Also, 82.6% of TT patients satisfied their ophthalmologists' IOP targets versus 51.1% of TL patients ($p < 0.001$). All significant differences persisted after adjustment for confounding factors.

Conclusion: This study, conducted in routine ophthalmic practice, confirmed published clinical trial results showing that TT provides better IOP control than TL when measured in the morning, and that travoprost has longer-lasting residual effects than latanoprost when IOP is measured >24 hours after instillation. However, readers should interpret these findings in the context of a cross-sectional observational study conducted in a naturalistic setting.

Background

Glaucoma remains a major cause of vision loss worldwide.[1-3] Treatments for glaucoma are aimed at reducing intraocular pressure (IOP) to a defined level that arrests optic nerve damage.[4,5]

Current glaucoma medications encompass five therapeutic classes, i.e. α-adrenergic agonists, β-adrenergic antagonists (β-blockers), carbonic anhydrase inhibitors, cholinergic receptor agonists and prostaglandin analogues. For many years β-blockers enjoyed great success as first-line glaucoma therapy, but recently they have been superseded by prostaglandin analogues as initial treatment for most patients.[6] In addition, more than one medication is frequently required to achieve adequate IOP control.[7] Although more medicines can mean more bottles, and more complex treatment regimens for patients, these inconveniences may be overcome with use of fixed treatment combinations. Such combinations offer several advantages over separate instillations, including a reduction in the total number of drops and excipient instilled per day, cost savings, improved tolerability and compliance, and obviation of prior treatment washout resulting from rapid, successive instillations.[8,9]

Attempts to develop effective fixed combinations of glaucoma medication date back several decades. In recent years, fixed combinations of commonly paired drugs have been approved by various regulatory bodies and are accepted in many countries.[10,11] Currently available drug pairs include the topical β-blocker timolol 0.5% combined with a prostaglandin analogue.[12] While there is no uniformity of design between trials for drug registration, most published studies compare the efficacy of fixed combinations with their components administered separately in succession.[13]

Fixed combinations of prostaglandin analogues and β-blockers have rarely been compared directly. Recently, however, a well controlled randomized clinical trial by Topouzis et al.[14] found that the fixed timolol/travoprost combination (TT) [DuoTrav®; Alcon Laboratories, Fort Worth, TX, USA][1] controlled IOP better than the fixed timolol/latanoprost combination (TL) [Xalacom®; Pfizer Inc., New York, NY, USA]. Also, several previous trials[15-17] demonstrated sustained IOP control after administration of travoprost (up to 84 hours[15]) that was not observed after administration of latanoprost. Whether or not a sustained action occurs with TT has yet to be determined. Furthermore, it would be useful to demonstrate such an effect in everyday clinical practice, as this setting might not reflect the findings of randomized controlled trials.

In order to confirm the foregoing clinical trial results, a dedicated study was performed on glaucoma treatment in routine clinical practice. The objectives were, first, to address whether TT would provide better IOP control than TL and, second, to evaluate the possibility of a more sustained control of IOP with TT.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Patients and Methods

The study was performed in accordance with French law (Commission Nationale de l'Informatique et des Libertés, Conseil National de l'Ordre des Médecins, Ministère de l'Enseignement Supérieur et de la Recherche) and the recommendations of the Association Des Epidémiologistes de Langue Française,[18] and adhered to the principles of the Declaration of Helsinki. The rationale of the research was explained to patients both verbally and in writing. Oral informed consent was obtained from each participating patient before inclusion in the study.

Study Design

The design was cross-sectional with retrospective data collection. This design was chosen in order to avoid influencing the doctor-patient relationship and possible observational bias. Treatments were prescribed by ophthalmologists according to their usual practice.

A sample of ophthalmologists who were willing to provide information on the current treatment of their glaucoma patients was recruited. Ophthalmologists were selected randomly from a professional list and were required to enrol the first five consenting patients diagnosed with primary open angle glaucoma or ocular hypertension (OHT) and already treated with one of the designated fixed combinations for ≥4 weeks.

Patients

In order to be included, patients were required to satisfy the following inclusion criteria: (i) age ≥18 years; (ii) primary open angle glaucoma or OHT treated for ≥6 weeks; (iii) not a participant in another phase III or IV clinical trial, or any other epidemiological investigation; (iv) informed about the objectives of the study and consenting to participate. Patients were excluded if any of the following criteria applied: (i) age <18 years; (ii) secondary glaucoma (e.g. congenital, inflammatory, neovascular, closed or narrow angle after cataract surgery, pseudoexfoliative glaucoma); (iii) retrospective data unavailable; (iv) previously included in the study; (v) unwilling to participate.

Methods

Sociodemographic data were collected for the following variables: age, sex, type of glaucoma (primary open angle glaucoma or normal tension glaucoma), confounding factors (diabetes mellitus, dyslipidaemia, arterial hypertension or hypotension, vasomotor instability, cardiovascular disease, migraine, tobacco smoking, family history of glaucoma), presence of associated ocular pathology (severe myopia, cataract, age-related macular degeneration, dry eye syndrome), glaucoma/OHT duration, and previous surgical or laser treatment.

The following data were collected retrospectively from the patients' medical records: glaucoma risk factors, ocular co-morbidities, diagnosis date, IOP measured at diagnosis and upon current treatment initiation, and previous laser therapy or surgery for glaucoma. At the study enrolment visit, ophthalmologists recorded the patient's target IOP based on visual fields, optic nerve appearance and IOP in each eye. The following data were collected prospectively at each IOP visit: patient sociodemographics, type of glaucoma, the timolol/prostaglandin treatment prescribed, date and time of last dose, IOP (with exact time of measurement), the therapy chosen and need for invasive intraocular surgery or laser therapy, and the next visit date. Data on ocular adverse events (stinging, redness, etc.) were not collected systematically, but reasons for switching included safety.

Details on the specific technical procedures used to measure IOP were not collected for this observational study and IOP measurements were not standardized. Instead, the IOP measurement procedure,

number of IOP evaluations, and measurements of corneal thickness were performed according to the ophthalmologist's usual practice. IOP values at diagnosis and prior to initiating the timolol/prostaglandin treatments were documented.

The following clinical endpoints were evaluated for each treatment group: (i) the proportion of patients who did not exceed the ophthalmologists' target IOPs; (ii) the mean IOP of the worst eye; and (iii) the proportion of patients with IOP values <18 mmHg in the worse eye or both eyes. Analyses were performed on the following data sets: (i) the intent-to-treat (ITT) population, and (ii) hours since the last treatment instillation (≤24 hours or >24 hours). The primary analysis concerned the proportion of patients in the ITT population who did not exceed their target IOP.

Statistical Analyses

Statistical analyses were performed with SAS® software version 9.1 (SAS Institute, Cary, NC, USA). All statistical tests were interpreted two-sided with $\alpha = 5\%$. No correction was made for multiplicity.

With observational studies large differences may exist between confounding factors applying to each study group; treatment allocation is not controlled and may bias the estimates of treatment effects. Accordingly, for qualitative variables, treatment groups were compared by the chi-square (χ^2) test or Fisher's exact test, whereas quantitative variables were assessed by analysis of variance (ANOVA) after verifying the normality of residuals and homoscedasticity. When the latter assumptions did not apply, Wilcoxon's test or the Kruskal-Wallis test was applied.

Several methods were used to deal with unbalanced risk factors between the two treatment groups:

- Multivariate analyses with linear and logistic regression models were performed to assess treatment (TT vs TL) effects on IOP measurements: (i) a linear regression model assessed the effect of treatments on IOP values (mmHg); and (ii) logistic regression models assessed the effects of treatments on responder rates as determined by both the 18 mmHg criterion and IOP target values declared by ophthalmologists.
- According to Newgard et al.,[19] bias due to unbalanced risk factors can be difficult to eliminate with the preceding multivariate techniques and, instead, the propensity score may be used to adjust between-group covariates more effectively. This score represents the conditional probability that a subject will need to be 'treated', as determined by an observed group of covariates. The propensity score was calculated by logistic regression and included in the models as a fitting variable. Quintiles of the estimated propensity score were created and included in the multivariate models (similar to those above) in order to obtain adjusted estimates of treatment effects.

Lastly, a 'centre effect' was not required as the number of patients per centre was too small and most centres prescribed both treatment combinations. Thus, treatment effects were not confounded by centre effects.

Results

A total of 2712 patients enrolled by 583 French ophthalmologists included 316 patients prescribed TT or TL as sole treatments for ≥4 weeks.

Patient characteristics are shown in table I. The average age was 64.5 years and the sex ratio was almost equal. The rates of co-morbidities and risk factors for the entire population of enrolled patients were: arterial hypertension 39.6%, family history of glaucoma 31.3%, cataract 29.7%, dyslipidaemia 28.1%, smoking 16.9%, cardiovascular disease 15.3%, diabetes mellitus 14.7%, dry-eye syndrome 11.2%, migraine 7.7%, myopia 7.3%, vasomotor instability 6.7%, macular degeneration 4.2%, arteri-

Table I. Demographic and medical history of patients by treatment group[a]

Variable	TT (n = 124)	TL (n = 192)	p-Value
Age (y)	64.0 (12.1)	64.8 (11.5)	0.56
Sex: female [no. (%)]	71 (57.3)	92 (47.9)	0.11
Type of glaucoma [no. (%)]			0.10
POAG	89 (71.8)	145 (75.5)	
normal pressure POAG	–	5 (2.6)	
ocular hypertension	35 (28.2)	42 (21.9)	
Disease duration (mo)	67.4 (53.0)	95.5 (71.2)	<0.001
Studied treatment duration (mo)	3.3 (7.5)	25.0 (15.2)	<0.001
Age at diagnosis (y)	58.3 (11.8)	56.9 (11.3)	0.29
IOP at diagnosis right eye (mmHg)	24.7 (4.5)	24.8 (3.9)	0.90
IOP at diagnosis left eye (mmHg)	24.8 (4.5)	24.7 (4.1)	0.85
IOP at initiation of treatment right eye (mmHg)	21.0 (3.9)	20.8 (4.1)	0.73
IOP at initiation of treatment left eye (mmHg)	21.4 (4.5)	20.9 (4.4)	0.38
Target IOP (mmHg)	16.3 (2.0)	16.6 (2.2)	0.26
Last instillation [no. (%)]			0.90
≤24 hours	105 (84.7)	161 (85.2)	
>24 hours	19 (15.3)	28 (14.8)	
IOP measurement time [no. (%)]			0.93
before 12:00h	63 (50.8)	94 (49.0)	
12:00–16:00h	34 (27.4)	53 (27.6)	
after 16:00h	27 (21.8)	45 (23.4)	

a Data are given as mean (SD) unless otherwise specified.

IOP = intraocular pressure; **POAG** = primary open angle glaucoma; **TL** = timolol/latanoprost fixed combination; **TT** = timolol/travoprost fixed combination.

al hypotension 3.2%, other pathology 10.9%, and other risk factors 5.8%.

Most patients (74.1%) had primary open angle glaucoma. Treatment duration was longer for TL than for TT patients, which may be explained by the earlier market authorizations for both latanoprost and TL, as compared with travoprost and TT. Of the two variables, only treatment duration was associated with IOP during treatment (moderate correlation; Pearson correlation coefficient: $r = 0.165$). Mean IOP values at diagnosis were 24.8 mmHg for the right eye and 24.8 mmHg for the left eye. Mean IOP values remained comparable at initiation of the designated treatments (20.9 mmHg for the right eye; 21.1 mmHg for the left eye). Most importantly, the IOP target set by ophthalmologists was similar for both treatment groups (mean 16.5 mmHg). Most patients (85.0%) instilled their treatment combination ≤24 hours before the clinic visit, which was in the morning for about 50% of patients.

Table II shows the mean IOP values for ITT patients receiving each fixed drug combination. Patients instilling the TT combination achieved lower mean IOP values (differences ranging from −1.5 to −1.9 mmHg) than TL patients and all differences were statistically significant ($p < 0.001$). Consequently, the difference between patients attaining an IOP value <18 mmHg was 22.0% in favour of TT ($p < 0.001$). In other words, one of every five patients treated with TL experienced an IOP control failure that might have been avoided had TT been instilled. According to ophthalmologists, IOP was controlled in 82.6% of TT patients compared with 51.1% of TL patients ($p < 0.001$). Switches to another treatment for tolerability reasons occurred in 2.4% of TT patients and 3.6% of LT patients.

Table II. Intraocular pressure (IOP) measurement and response rates by treatment group[a]

Intent-to-treat population	TT	TL	p-Value
IOP right eye (mmHg)	16.3 (3.3)	18.0 (4.1)	<0.001
IOP left eye (mmHg)	16.7 (3.4)	18.2 (4.0)	<0.001
IOP worse eye (mmHg)	17.1 (3.4)	19.0 (4.5)	<0.001
IOP worse eye ≥18 mmHg (%)	36.3	58.3	<0.001
Target IOPs reached[b](%)	82.6	51.1	<0.001

a Data are given as mean (SD) unless otherwise specified.

b As defined by ophthalmologists.

TL = timolol/latanoprost fixed-dose combination; **TT** = timolol/travoprost fixed-dose combination.

Figure 1 shows the distribution of patients achieving IOP results and the mean IOP achieved by treatment group.

Table III compares two populations, i.e. patients who instilled their treatment ≤24 hours before IOP measurement and those who instilled their treatment >24 hours before IOP measurement. It should be noted that no major differences in IOP were found between these two populations amongst those instilling TT, whereas significant differences were observed with TL patients. In terms of mean IOP values, TL patients whose last dose was instilled >24 hours prior to IOP measurement experienced an increase of 1.3 to 1.9 mmHg, as compared with a change of –0.4 to 0.1 mmHg in the TT group. Figure 2 illustrates the sustained IOP effect of TT in the worst eye.

Table IV presents the foregoing results after linear adjustment and after adjustment for propensity scores. Although the magnitudes of the differences between the two groups were modified by these adjustments, the differences remained statistically significant regardless of the statistical method applied.

Discussion

The results of this cross-sectional observational study can be interpreted by reference to the randomized clinical trial observations published by Topouzis et al.,[14] Dubiner et al.,[15] and Garcia-Feijoo et al.[17] The present findings suggest that patients prescribed TT eye drops experienced better IOP control than patients given TL when measured either within or later than 24 hours after administration. During the 24 hours before IOP measurement, target

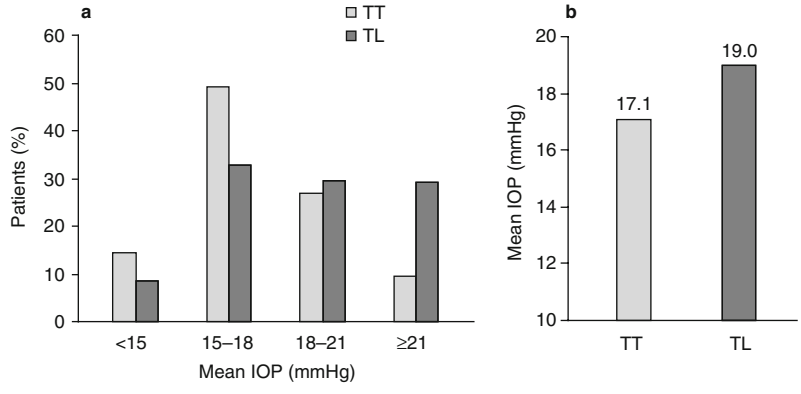

Fig. 1. Comparative efficacy of treatment with timolol/travoprost fixed-dose combination (TT) or timolol/latanoprost fixed-dose combination (TL) in patients with ocular hypertension or primary open angle glaucoma (intent-to-treat population): (**a**) distribution of intraocular pressure (IOP) values by treatment group ($p < 0.001$), and (**b**) mean IOP value by treatment group ($p < 0.001$).

Table III. Intraocular pressure (IOP) measurement and response rates by treatment group and time since instillation[a]

IOP measurement	TT	TL	p-Value
Last instillation ≤24 hours			
IOP right eye (mmHg)	16.3 (3.4)	17.8 (4.1)	0.002
IOP left eye (mmHg)	16.7 (3.6)	18.1 (3.8)	0.004
IOP worse eye (mmHg)	17.1 (3.6)	18.9 (4.5)	0.001
IOP worse eye ≥18 mmHg (%)	37.1	57.8	0.001
Target IOPs reached (%)[b]	83.5	52.8	<0.001
Last instillation >24 hours			
IOP right eye (mmHg)	16.4 (2.4)	19.7 (3.9)	0.002
IOP left eye (mmHg)	16.3 (1.7)	19.4 (4.3)	0.005
IOP worse eye (mmHg)	17.0 (1.8)	20.3 (4.4)	0.004
IOP worse eye ≥18 mmHg (%)	31.6	67.9	0.019
Target IOPs reached (%)[b]	77.8	39.3	0.011

a Data are given as mean (SD) unless otherwise specified.

b As defined by ophthalmologists.

TL = timolol/latanoprost fixed-dose combination; **TT** = timolol/travoprost fixed-dose combination.

IOP thresholds set by ophthalmologists were achieved significantly more frequently following TT instillations (>80%) than TL instillations (<60%), irrespective of the precise measurement time. When eye drops were instilled >24 hours prior to IOP measurements, mean IOP values of TT patients were comparable to those just cited, whereas TL patients exhibited a much higher failure rate.

The better IOP control in TT treated patients reported in this study was slightly greater than that (0.6 mmHg) reported by Topouzis et al.[14] This could be explained by several factors. First, 15% of patients in this study had their last instillation >24 hours before IOP measurement, while this delay was strictly controlled in the clinical trial protocol. Therefore, the longer duration of effect of travoprost probably contributed to the difference in IOP between the two groups in this study. In addition, LT demonstrates better IOP control when instilled in the morning,[20] but half the patients instilled their drops in the evening in this study.

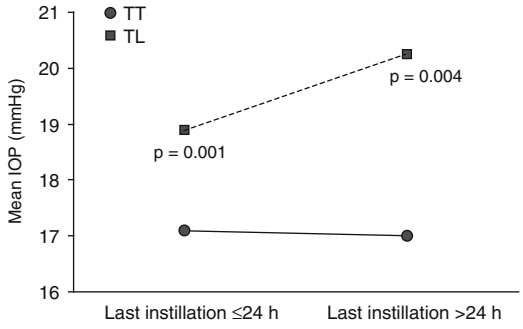

Fig. 2. Mean intraocular pressure (IOP) in the worst eye by time between last instillation of timolol/travoprost fixed-dose combination (TT) or timolol/latanoprost fixed-dose combination (TL) and IOP measurement.

The average IOP target set by practising ophthalmologists was 16.5 mmHg, which was slightly lower than that reported in AGIS (Advanced Glaucoma Intervention Study)[4] and lower than reported by similar studies comparing travoprost and latanoprost as monotherapies.[21,22] These differences may be explained by the fact that combination therapies are used for patients who have already experienced a treatment failure, i.e. patients with more severe glaucoma.

Results reported in randomized clinical trials are difficult to confirm in daily clinical practice, especially for chronic conditions where treatment compliance becomes a major stumbling block. Because randomized clinical trials are planned to measure a specific effect, they are designed to restrict variance and minimize confounding factors. The real world is more complex and treatments selected by a physi-

Table IV. Results of multivariate analyses[a]

Variable	Effect of treatment	Adjustment method		
		without adjustment	linear regression	propensity score
IOP worse eye (mmHg)	Difference TT–TL[b] (p-value)	−1.9 (<0.001)	−1.8 (0.005)	−1.9 (0.002)
Both eyes <18 mmHg (ITT population)	Odds ratio[c] (95% CI)	2.46 (1.54, 3.91)	2.65 (1.44, 4.90)	2.92 (1.60, 5.33)
Both eyes <18 mmHg (last instilliation ≤24h previously)	Odds ratio[c] (95% CI)	2.31 (1.40, 3.83)	2.31 (1.20, 4.44)	2.27 (1.1, 4.36)

a Covariables: time since diagnosis, treatment duration, sex, age, type of glaucoma.

b Negative difference means better IOP control with TT.

c Odds ratio >1 indicates fewer failures with TT.

IOP = intraocular pressure; **ITT** = intent-to-treat; **TL** = timolol/latanoprost fixed combination; **TT** = timolol/travoprost fixed combination.

cian are founded on many objective and subjective factors. Thus the best strategy for detecting a therapeutic effect in routine practice is to increase the number of subjects and limit known confounding factors. That is why we adopted a retrospective design that would not allow physicians to select patients *a priori*.

Many studies have evaluated and compared treatment effects in everyday clinical practice, but in the case of glaucoma these have been restricted to follow-up of patient cohorts treated by a single agent and without head-to-head treatment comparisons.[23-25] Treatment group comparability is always in question when studies are based on field observations. It is accepted theory that treatment randomization is the best way to seek group comparability. Given our design, we used the generally recommended propensity score method.[19] Confounding variables were selected from the totality of known glaucoma factors using a stepwise algorithm with an entry and exit p-value fixed at 0.10. 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, i.e. propensity score and linear model (not detailed here), support the validity of our results.

We could have measured IOP after the first treatment instillation in all patients. However, in keeping with our objectives, we wanted to estimate the impact on IOP of time from the last instillation, which is very rarely documented in patients' records. Hence, the decision was whether or not to measure IOP during a visit. An IOP measurement after the first treatment instillation would have included patients undergoing a treatment switch. Hypothesizing that the average duration of first-line treatment is about 36 months and that visits occur every 6 months, it follows that one of every six visits would be associated with a treatment switch. Consequently, the time needed to recruit more patients, or more participating practitioners, would have been multiplied by six, requiring more project resources. Instead, we decided to select all patients and adjust for confounding variables.

Some imbalance was observed between groups with regard to both treatment and disease duration. Disease duration was not correlated with IOP ($r = 0.09$, $p = 0.08$) and therefore no adjustment was required. Treatment duration was weakly linked to two related outcome measures (IOP values and responder rates); hence, an adjustment for this variable was necessary. Although we did not collect data on glaucoma severity such as perimetry and cup/disc ratio, the two treatment groups were similar in terms of glaucoma type (primary open angle glaucoma, OHT, normal pressure primary open angle glaucoma, age at diagnosis, IOP at diagnosis, IOP at current treatment initiation and target IOP), suggesting that our findings are unlikely to have been con-

founded by disease severity. Lastly, instillation and IOP measurement times were similar for the two groups, suggesting that efficacy differences were not confounded by patient or practitioner treatment management.

Most participants in this survey were private practice ophthalmologists who recruited few patients. Consequently, there is no guarantee that each investigator included at least one patient receiving each treatment. Therefore, to a certain extent, treatment differences could have been confounded by practitioner practices. However, in France, a country with 62 million inhabitants, most of the 5000 ophthalmologists practice alone, in outpatient settings, and only the most severe glaucoma patients are followed-up at clinics. Thus, it would be impossible to obtain a 'representative sample' of glaucoma patients if practitioners with few glaucoma patients were excluded. This is one of the reasons we decided to study glaucoma treatment in everyday practice. Lastly, as IOP management in Europe is heavily standardized by European Glaucoma Society guidelines, practitioner variability in France is expected to be very low and comparable for two similar fixed-treatment combinations.

Study Limitations

Our study has several limitations. First, the main limitation of retrospective designs is that treatments selected by physicians could involve confounding factors that would not be taken into account by the analysis. Second, IOP threshold targets were a possible source of bias, as collaboration in a clinical study might encourage ophthalmologists to follow good clinical practice more assiduously. A retrospective search through the medical files would probably show how the present targets were set. However, results observed with an arbitrarily fixed IOP threshold were similar to those obtained when ophthalmologists set their own targets. Third, ophthalmologists made their assessments in full knowledge of the treatment administered. However, decisions to switch treatments are never made 'blindly' in routine practice and this possible internal bias is necessarily intrinsic to our experimental design (observational study). Fourth, a cross-sectional study design limits comparisons over time because treatment effects are not observed 'within' individuals. This problem is usually attenuated by recruiting many more patients than are required for clinical trials. In addition, our design assumed that ophthalmologists' appointment times were independent of the IOP values measured. Accordingly, the observed IOP variations resulted from the pharmacological profiles of the products studied. Fifth, IOP measures were not standardized and corneal thickness was not documented, as would be expected in an observational study.

Conclusion

The results of this observational study suggest that TT reduces mean diurnal IOP levels more effectively than TL. However, readers should interpret the findings in the context of a retrospective study conducted in a naturalistic setting.

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