

EXTENDED REPORT

Short term efficacy and safety in glaucoma patients changed to the latanoprost 0.005%/timolol maleate 0.5% fixed combination from monotherapies and adjunctive therapies

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Aims: To evaluate efficacy and safety in patients with ocular hypertension or open angle glaucoma changed to latanoprost/timolol fixed combination (LTFC).

Methods: A prospective, multicentre, historical control in which qualified patients had their previous therapy substituted by LTFC and were followed for at least 2 months.

Results: In 1676 patients LTFC was continued in 93% throughout the observation period. In all patients LTFC reduced the intraocular pressure (IOP) from 20.6 (SD 3.8) to 17.7 (3.0) mm Hg ($p < 0.001$) compared to previous monotherapies including latanoprost, timolol, α agonists or carbonic anhydrase inhibitors (CAI). LTFC provided more efficacy after changing from adjunctive therapies including: a β blocker added to either CAI, α agonist, or pilocarpine, or CAI added to an α agonist, or latanoprost added to either CAI, α agonist, or β blocker (unfixed combination), and travoprost added to timolol ($p < 0.007$). LTFC was as effective as latanoprost used with dorzolamide/timolol fixed combination (-0.9 mm Hg, $p = 0.1792$). The most common reason to discontinue therapy was lack of efficacy ($n = 70$, 4%) and adverse event ($n = 17$, 1%).

Conclusion: In a clinical setting, patients who have their monotherapy or adjunctive therapy substituted with LTFC may experience reduced IOP, good tolerability, and continuation of therapy for the first 2–3 months of treatment.

The prospective multicentre, randomised, parallel, double masked clinical trial is an important standard in evaluating efficacy and safety of a new glaucoma agent. This type of design provides a clinical evaluation in a well controlled clinical environment. Such a design helps eliminate bias in patient and treatment selection, clinical measures, and data analysis.

However, such studies also have several limitations; firstly, they typically include patients who are sufficiently healthy, physically and psychologically, to withstand the inconvenience of a prospective comparative clinical trial. Consequently, these patients may not exhibit the true incidence of side effects that may occur outside of these studies. Secondly, the sample size is limited because of the expense of a well controlled trial. Usually around 1000 patients are treated in regulatory studies before drug approval. Consequently, the types of adverse events that might occur may be incomplete and the number of comparisons to previously available medications limited. Lastly, the manner in which therapy is initiated in a randomised, double masked trial is not typical of clinical practice. Consequently, a clinical trial may not completely reflect a doctor's experience when initiating a new medication in clinical practice.

The purpose of this trial was to prospectively evaluate intraocular pressure (IOP) changes, adverse events, and discontinuation rates over the first 9 weeks after substituting from previous monotherapy or adjunctive therapies to the latanoprost/timolol fixed combination (LTFC) in a large number of patients in order to emulate the clinical experience that might be expected in routine practice.

PATIENTS AND METHODS

Patients

This observational trial included 308 office based ophthalmologist investigators located across Germany. The trial was designed to capture observational treatment data in all glaucoma patients regardless of diagnosis or previous treatment. Appropriate patients ($n = 2199$) were entered into the study whom the physician had already decided to switch from their previous therapy to the latanoprost 0.005%/timolol maleate 0.5% fixed combination (Xalacom, Pfizer, Inc, New York, NY, USA) as part of their routine care because of inadequate IOP control, an adverse event, poor compliance, or need for greater ease of dosing.

Patients included in this specific data analysis were those with ocular hypertension or primary open angle, exfoliation, or pigment dispersion glaucoma who were previously treated with a monotherapy (β blocker, α agonist, or topical carbonic anhydrase inhibitor (CAI)) or fixed or unfixed combinations of β blockers, α agonists, pilocarpine, or topical CAI who had a follow up of at least 9 weeks with LTFC therapy as the sole treatment for elevated IOP.

Patients were excluded from the study who had contraindications to treatment with latanoprost or timolol maleate according to the summary of product characteristics—that is, known hypersensitivity to the components of latanoprost or timolol maleate, were pregnant or lactating, had uveitis in

Abbreviations: CAI, carbonic anhydrase inhibitors; IOP, intraocular pressure; LTFC, latanoprost/timolol fixed combination

Table 1 Patient characteristics* (n = 1676)

	No	Mean or number of patients	%
Age (median years)	1675	65.8 (12.4)	
Sex:			
Male	1671	733	43.9
Female		938	56.1
Duration of disorder (years)	1600	7.0 (6.3)	
Duration of observation period (weeks)	1676	27.2 (6.0)	Range (8.3–54.9)
Number of visits			
1	1676	146	8.7
2		1502	89.6
3		28	1.7
Diagnosis			
Primary open angle glaucoma	1676	1488	88.8
Exfoliation glaucoma		91	5.4
Ocular hypertension		82	4.9
Pigment dispersion glaucoma		15	0.9
Treatment eye			
Right	1664	39	2.3
Left		46	2.8
Both		1579	94.9

*Data collection was not complete in some patients.

either eye, had known cardiac conduction disease, decompensated heart failure or reactive airway disease.¹ Patients also were excluded from the current data analysis who: were in the early postoperative phase of conventional or laser ocular surgery, had acute angle closure, congenital, low tension or secondary (apart from exfoliation syndrome or pigment dispersion) glaucoma, had therapy combinations of insufficient numbers to statistically evaluate ($n \leq 15$), or were on no previous glaucoma therapy or three drug glaucoma therapy.

Procedures

Patients were changed to the LTFC as part of their routine care and underwent a typical anterior segment examination including slit lamp biomicroscopy, Goldmann applanation tonometry and Snellen visual acuity. Patients then were placed on the LTFC once each morning in the study eye(s) and re-examined generally after 3–6 months. This was an open label trial and visit times were scheduled according to patient and doctor convenience. Consequently, the time the IOP was measured was not standardised for this trial.

Statistics

Data in this study were evaluated using a two sided analysis and a 0.05 alpha level to declare significance. The primary efficacy variable, IOP, was evaluated by a Student's paired *t* test between the LTFC and the individual preparations that were substituted, as well as the study population as a whole.² An average eye analysis was used (average of the pressure response in both eyes). If an eye was not treated with the LTFC then only the opposite treated eye was used in the analysis.

Table 2 Reasons for switching to the LTFC* (more than one choice possible) (n = 1660)

Reason	No of patients	%
Simplification of pressure control	950	57.2
Improved compliance	948	57.1
Improved efficacy	866	52.2
Improved safety	398	24.0
Patient medical situation	14	0.8
Other	8	0.5
Patient desire	3	0.2

*Data collection was not complete in some patients.

RESULTS

Study sample and clinical characteristics (demographic data)

In this study data from 2199 patients were collected. Out of this total sample 1676 patients were evaluable according to the diagnostic and treatment group exclusion criteria for this study analysis. Table 1 includes the characteristics of patients included in this analysis. Table 2 shows the reason why patients were switched from previous therapy to the LTFC. A small portion of the patients, noted in the tables, had missing data points and were not evaluable for some parameters.

Intraocular pressure

The IOP across all treatment groups decreased from 20.6 (SD 3.8) to 17.7 (3.0) mm Hg after switching to the LTFC from either a monotherapy or adjunctive therapy ($p < 0.001$), which reflects an additional IOP reduction of 14.1%.

Table 3 shows the IOP change after switching to the LTFC from previous medication classes. The LTFC allowed for a further statistically significant reduction in IOP when compared to each individual previous monotherapy class ($p < 0.001$). In addition, the LTFC caused a similar statistically significant reduction when switched from most evaluated adjunctive treatment ($p \leq 0.007$). Three drug treatment with latanoprost and the dorzolamide/timolol fixed combination was the only previous therapy from which the LTFC did not provide a further reduction in pressure ($p = 0.1792$).

Table 4 shows the reduction in IOP for all medicines changed to the fixed combination for each diagnosis individually. There was a statistical decrease in pressure after beginning the fixed combination for each diagnosis ($p < 0.001$) except for pigment dispersion ($n = 15$, $p = 0.135$).

Adverse events

The incidence of ocular and systemic adverse events on the LTFC were generally low. Ocular irritation was the most common and reported in 26 (1.6%) patients. Ocular hyperaemia was reported in nine (0.5%) patients. Overall, there were 59 ocular events during the observation period. All ocular events were reported as non-serious (table 5). Suspected iris pigmentation occurred in 130 patients (8.5%). However, the iris change was called definite by the investigator in six patients (0.4%). In three patients eyelash growth was reported during the trial.

There were 13 systemic adverse events during the observation period with cardiovascular ($n = 5$, 0.3%) or

Table 3 Intraocular pressure changes after switching to the LTFC for each of the previous medication classes (mm Hg, mean (SD))

	Sample	Baseline	Treated	Difference	p Value
Monotherapy					
Latanoprost	69	20.8 (3.4)	17.8 (2.9)	-3.1 (3.6)	<0.001
Timolol	53	21.6 (4.3)	17.9 (2.3)	-3.7 (4.5)	<0.001
Dorzolamide or brinzolamide	33	22.1 (4.4)	17.4 (2.2)	-4.7 (3.5)	<0.001
Brimonidine	18	20.2 (4.2)	16.6 (2.8)	-3.6 (3.6)	<0.001
Adjunctive therapy					
Dorzolamide/timolol	505	21.1 (3.8)	17.8 (3.1)	-3.4 (3.4)	<0.001
Latanoprost + timolol	342	19.4 (3.8)	17.7 (3.1)	-1.7 (3.6)	<0.001
Pilocarpine/timolol	159	21.3 (3.3)	17.5 (2.6)	-3.8 (3.5)	<0.001
Latanoprost + β blocker	86	19.2 (3.5)	17.6 (2.5)	-1.6 (3.5)	<0.001
Brimonidine + β blocker	56	21.3 (3.7)	17.2 (2.8)	-4.1 (3.2)	<0.001
Pilocarpine + metipranolol	56	21.7 (3.7)	17.6 (2.8)	-4.0 (3.5)	<0.001
Latanoprost + brimonidine	52	20.0 (3.3)	18.2 (2.6)	-1.8 (3.0)	<0.001
Dorzolamide + timolol	50	21.1 (3.1)	18.0 (2.9)	-3.1 (3.2)	<0.001
Brinzolamide + timolol	45	20.5 (3.4)	17.9 (3.5)	-2.6 (2.9)	<0.001
Latanoprost + dorzolamide/timolol	38	19.9 (4.0)	19.0 (3.6)	-0.9 (4.1)	0.1792
Latanoprost + brinzolamide	34	19.7 (4.4)	17.0 (3.2)	-2.7 (4.1)	<0.001
Brimonidine + CAI	24	20.9 (2.9)	17.5 (2.1)	-3.3 (3.5)	<0.001
Pilocarpine + timolol	21	21.9 (2.8)	17.8 (2.6)	-4.1 (3.5)	<0.001
Latanoprost + dorzolamide	20	20.2 (3.8)	17.8 (3.3)	-2.4 (3.6)	0.007
Travoprost + timolol	15	22.0 (3.8)	16.9 (3.2)	-5.1 (5.5)	<0.001

Table 4 IOP reduction for all medicines changed to the LTFC for each diagnosis (mm Hg (SD)) (n = 1676)

Diagnosis	Baseline	Treated	Difference	p Value
Primary open angle glaucoma	20.6 (3.7)	17.6 (2.9)	-2.9 (3.6)	<0.001
Exfoliation glaucoma	21.0 (5.5)	18.1 (4.5)	-2.9 (4.3)	<0.001
Ocular hypertension	21.5 (3.0)	18.5 (2.4)	-3.1 (3.4)	<0.001
Pigment dispersion glaucoma	19.6 (3.5)	17.7 (3.4)	-1.9 (4.7)	0.1353

nervous system symptoms (n = 6, 0.4%) being the most common.

Discontinued patients

In total, 123 patients (7.3%) had the LTFC therapy discontinued or changed during the observation period. When a reason(s) was provided for changing therapy, physicians indicated most often it was because of insufficient IOP control in 70 patients (4.2%) and an adverse event in 17 patients (1.0%) (table 6).

DISCUSSION

Previous multicentre, randomised, regulatory trials have demonstrated that the LTFC (Xalacom) is more effective than either of its individual components.^{3,4} Morning dosing of the LTFC has been evaluated in several multicentre studies in Europe and the United States. In Germany, Pfeiffer and

associates have shown that the LTFC reduced the IOP further compared to timolol alone, by 1.9 mm Hg and from latanoprost alone by 1.2 mm Hg.³ In the United States the LTFC reduced the IOP compared to timolol alone by another 2.9 mm Hg and from latanoprost alone by another 1.1 mm Hg.⁴ Compared to other adjunctive treatments, Stewart and associates have noted that the LTFC dosed in the evening was more effective at 6–12 hours after dosing, and for the end of the daytime diurnal curve than brimonidine and timolol.⁵ In addition, Shin and coworkers noted that the latanoprost based fixed combination showed a mean 1.0 mm Hg further reduction than the dorzolamide based fixed combination given twice daily over a three time point diurnal curve.⁶

Few data are currently available regarding the LTFC in a clinical setting that helps the physician understand efficacy and safety after switching from other monotherapy or adjunctive therapies commonly used. Such evaluations are important because physicians may choose to use the LTFC as second line therapy when patients using latanoprost or timolol alone need further efficacy.

In this current trial we evaluated patients treated with the LTFC substituted from previous monotherapy or adjunctive therapies. We wished to evaluate the efficacy, safety, and discontinuation rates over at least the first 9 weeks of treatment in a setting in which the LTFC would typically be prescribed clinically.

This study showed that the LTFC caused a further lowering of IOP of 2.9 mm Hg (14%) at 2 months in 1676 patients when switched from other common treatments including monotherapy with timolol, α agonists, or CAIs and latanoprost; and adjunctive therapy including β blocker added to a

Table 5 Ocular adverse events with the LTFC (more than one event per patient was possible) (n = 1676)

Symptom	No of patients	%
Ocular irritation	25	1.5
Conjunctival hyperaemia	8	0.5
Conjunctivitis	5	0.3
Other	4	0.2
Vision change	1	0.06
Ocular pain	1	0.06
Chemosis	1	0.06
Eyelid rash	1	0.06
Blepharitis	1	0.06

Table 6 Reason provided for discontinuation or change of the LTFC* (n=1676)

Reason	No of patients	%
Insufficient efficacy	70	4.2
Adverse event	17	1.0
No information provided	15	0.9
Surgery	6	0.4
Other	5	0.3
Lost to follow up	4	0.2
Patient desire	3	0.2
Patient death	2	0.1
Poor compliance	1	0.06

*The physician may not have thought a relation between the drug and adverse event existed.

CAIs, α agonist, or pilocarpine, or CAIs added to an α agonist, latanoprost added to CAIs, α agonist, or a β blocker, as well as travoprost and timolol. Of special note is that the LTFC provided further reduced pressures compared to the individual components given concomitantly. The LTFC was as effective as latanoprost given with the dorzolamide/timolol fixed combination (-0.9 mm Hg, $p = 0.1792$).

The reason for the greater efficacy with the LTFC compared to most other treatments in this trial is not known completely, but several reasons may exist. Firstly, the LTFC may have provided greater efficacy than each previous monotherapy or adjunctive therapy evaluated. These findings are consistent with previous monotherapy trials versus timolol and latanoprost, and adjunctive therapy of timolol and brimonidine, and the dorzolamide/timolol fixed combination.³⁻⁶ However, previous data have indicated only equal daytime pressures versus latanoprost and brimonidine.⁷ Also, in a recent study by Diestelhorst and associates the LTFC dosed in the morning was not as effective as the medicines given separately in the evening.⁸

Secondly, the design of the experience trial may have provided several other potential explanations for a decrease in IOP that could be observed in routine practice. These effects might include any potential influence on the efficacy measures by the physician or compliance by the patient, because of the hope that a new medicine would be more effective than the previous one. In addition, the pressure increase, which caused the doctor to change medications, could have returned to the previous level on the following visit irrespective of the change in prescription (regression to the mean phenomena).

Thirdly, the greater efficacy with the fixed combination observed in this study, compared to controlled clinical trials, may have resulted from better compliance. Potentially the once daily dosing, from one bottle, within the experience trial may have allowed for improved pressure control that was not observable in previous well controlled clinical studies. However, currently there is little direct proof that once daily dosing improves compliance.

After treatment with the LTFC the incidence of side effects was low, with ocular irritation being the most common (1.5%). Iris pigmentation changes occurred in 130 (8.5%) patients, which is a lower incidence than noted in the latanoprost regulatory trials.⁹⁻¹¹ The difference may be due to the duration of this current study; usually iris pigmentation occurs following 2 months of therapy.⁹⁻¹¹ In addition, iris colour changes in the regulatory trials were determined by photographs. The incidence in the current trial may more closely resemble how often patients and doctors actually note this side effect clinically. In general, however, systemic and

ocular side effect incidence was low. These rates may not reflect actual incidence, but how frequently these side effects are noted by the physician or mentioned by the patient.

This study suggests that, in a clinical setting, patients who have their monotherapy and adjunctive therapy treatment substituted for the LTFC may, on average, experience reduced IOP, good tolerability, and continuation of therapy for the first 2-3 months of treatment.

This study did not evaluate the LTFC compared to the other medications in a double masked, randomised fashion. Importantly, adequate evidence of improved clinical efficacy can only be gained from a masked, randomised trial. In such a clinical trial, patient populations are better controlled with consistent timing of IOP readings, continuation rates, and side effect reporting. Further investigation is needed to completely understand the efficacy, safety, and persistency issues related to the LTFC and other glaucoma medicines.

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