Safety and efficacy of unpreserved timolol 0.1% gel in patients controlled by preserved latanoprost with signs of ocular intolerance

Évaluation de la tolérance et de l’efficacité du gel de timolol 0,1 % sans conservateur chez des patients contrôlés par latanoprost conservé présentant des signes d’intolérance oculaire

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KEYWORDS
Glaucoma; Ocular hypertension; Unpreserved timolol gel; Signs of ocular intolerance

Summary
Purpose. — To assess the safety and efficacy of unpreserved timolol 0.1% gel in ocular hypertensive (OHT) or glaucomatous patients controlled by preserved latanoprost 0.005% but with signs of ocular intolerance.
Methods. — Patients initially treated with preserved latanoprost were randomized to receive once daily either one drop of unpreserved timolol gel in the morning or one drop of preserved latanoprost in the evening for 84 days. All patients attended three visits (D0, D28 and D84). A patient was considered as responder to primary criteria at Day 84 if the sum of the scores...
of the eight ocular symptoms and the six objective signs had decreased by at least 20% and if the effect on intra-ocular pressure (IOP) was assessed as either satisfactory or acceptable.

Results. — At D84, 91.5% of patients were responders to the primary combined efficacy/safety criteria under unpreserved timolol gel treatment versus 48.6% under preserved latanoprost treatment (P < 0.001). As early as D28, 85.3% of patients were responders in the unpreserved timolol gel group compared to 40.3% of patients in the preserved latanoprost group (P < 0.001). IOP change from baseline was not significant between treatments (P > 0.05) at D28 or D84. Both signs and symptoms were significantly improved (P < 0.001) with unpreserved timolol gel compared to preserved latanoprost.

Conclusion. — Unpreserved timolol 0.1% gel maintained the efficacy of preserved latanoprost and reduced signs and symptoms of intolerance in almost all glaucomatous/OHTT patients on preserved latanoprost.

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MOTS CLÉS
Glaucome ;
Hypertension oculaire ;
Gel de timolol non conservé ;
Signes d’intolérance oculaire

Introduction

Glaucome is generally defined as a progressive optic neuropathy involving characteristic structural damage to the optic nerve and characteristic visual field defects [1]. According to the World Health Organization (WHO), glaucoma would be responsible for 13.5% of world blindness [2,3]. Glaucome medications target the main risk factor of glaucoma progression, the elevated intraocular pressure (IOP). According to the European Glaucoma Society (EGS), the risk of having primary open-angle glaucoma for patients with IOP > 26 mmHg is 13 times higher than for those with lower IOP [4].

Lowering IOP level remains the only treatable risk factor to prevent glaucomatous progression [5–7]. The Advanced Glaucoma Intervention Study (AGIS) demonstrated that IOP fluctuations may be an important aspect of the damaging effect and that lowering IOP could reduce visual field progression [5]. These findings support the continuous use of a hypotensive drug, thus highlighting the importance of patient’s compliance. Prostaglandins/Prostamides have been approved as first-line treatment for several years [4]. However, topical beta-blockers such as timolol maleate are now approved as first choice options for medical treatment of elevated IOP [8]. Beta-blockers act to reduce IOP by inhibiting aqueous humor production [9]. Timolol maleate, a non-specific beta-blocker, is widely used worldwide as a standard medication to lower IOP and its efficacy and safety have been proven.

However, pharmacokinetic studies have shown that timolol maleate 0.5% is slightly absorbed by the systemic circulation, implying several systemic side effects leading to contraindications for patients suffering from cardiovascular or respiratory diseases [10,11]. Moreover, because of the two daily instillations required over the long term, this drug is likely to present a poor compliance. Thus, a gel-formulation of timolol maleate 0.1% was developed and was shown to be able to reduce both timolol concentration and the frequency of administration whilst maintaining efficacy [12]. As a result, systemic side effects are reduced and this one day regimen improves patient’s compliance compared to beta-blockers dosed twice daily [13].

Prostaglandin analogues (PGA) have been introduced in the late 90s and are currently prescribed as first-line therapy. They are efficient in reducing IOP by increasing uveal scleral outflow of aqueous humor with only one instillation per day. Xalatan® (latanoprost 0.005%), a prostaglandin
analogue, has shown a greater ocular hypotensive effect than timolol in glaucomatous patients [14,15]. However, as all PGA, latanoprost has notable ocular side effects: increasing iris pigmentation, mild to moderate conjunctival hyperaemia, eye irritation (burning, grittiness, itching, stinging, and foreign body sensation) [16]. Eyelashes and vellus hair changes (increased length, thickness, pigmentation and number) are also commonly described [17]. Furthermore, the commercial preparation of latanoprost Xalatan®, the mostly used PGA worldwide contains the highest concentration of benzalkonium chloride (BAK, 0.02%) among anti-glaucamotous eye drops, twice as much as in most timolol solution formulations. BAK is the most commonly used ocular preservative and is largely responsible for ocular surface toxicity and inflammation associated with the chronic use of many ophthalmic solutions, including prostaglandins [18]. BAK exerts an antimicrobial effect by its powerful detergent action on bacterial walls and membranes. This detergent effect in combination with a partial destruction of mucous cells is responsible for the induced instability of the lacrimal film, involving a decrease of the tear break-up time (BUT) and resulting in symptoms like irritation or dryness [19].

It has been demonstrated in a previous study that patients who switched from timolol to latanoprost have a further reduction in IOP but no changes in IOP were observed when patients were switched from latanoprost to timolol [20]. Moreover it has been shown that in patient with low compliance, the switch from latanoprost to timolol eye gel 0.1% increases ocular comfort without changes in efficacy [21]. The purpose of this study was to assess the safety and the efficacy of 0.1% unpreserved timolol maleate gel in glaucomatous patients initially treated and controlled by monotherapy of preserved latanoprost presenting ocular objective signs of intolerance.

Materials and methods

Study design

This was a phase IV open-labelled study, randomised in two parallel-groups conducted in 45 centres in France. A double-blind design was not feasible because of different packagings (single dose versus multidose), different formulations (gel versus aqueous solution) and different instillation time of the investigational medicinal products (morning versus evening).

Patients were randomly allocated to one of the two treatment groups and received either unpreserved timolol gel 0.1% (Gettim LP®, Laboratoires Théa), or latanoprost aqueous eye drops preserved with 0.02% BAK (Xalatan®, Pfizer). Patients were instructed to instil once daily one drop of the study medication in the conjunctival sac of each eye from Day 0 to Day 84. Regarding pharmacokinetic drug profile, unpreserved timolol gel was instilled in the morning whereas preserved latanoprost was instilled in the evening.

This study was conducted in accordance with Good Clinical Practice and all applicable guidelines as the Declaration of Helsinki (2000) and local regulations. Local Independent Ethics Committee (IEC) approval of the CPP Ile de France VIII (no. 2008-000580-41) and informed consent form were obtained prior to patient enrolment. This study was registered by www.Clinicaltrials.gov (NCT01155219).

Patients

Patients, with primary open-angle glaucoma (POAG) or ocular hypertension (OHT) controlled by preserved latanoprost and presenting signs of local intolerance were eligible for inclusion.

The study population included patients aged from 18 to 90 years old with an intraocular pressure (IOP) ≤ 18 mmHg in both eyes. Patients were eligible for inclusion if presenting local intolerance in at least one eye defined by the association of at least two ocular symptoms with a severity level ≥ 1 (mild or moderate or severe) among the following eight symptoms: irritation/burning, itching, tearing, stinging upon instillation, eye dryness sensation, foreign body sensation, photophobia, and blurred vision, and the presence of at least one mild or moderate ocular sign among the following six signs: hyperaemia, superficial punctate keratitis (SPK), interpalpebral conjunctival staining, folliculo-papillary conjunctivitis, blepharitis or BUT less than 10s.

Patients were excluded if presenting one severe ocular sign and if presenting ocular hypertension other than POAG or primary OHT (such as congenital, angle closure glaucoma, secondary glaucoma). Patients with absolute contraindications for beta-blockers or not controlled for diabetes were not eligible. Systemic antiglaucoma treatment was not allowed within the last month and during the treatment period. Patients were scheduled for three visits over 12 weeks: one inclusion visit on Day 0, a follow-up visit on Day 28±3 days and a final visit on Day 84±7 days.

Main outcome and secondary objectives

The primary evaluation was the response to the efficacy/safety criteria defined as a combination of the effect on IOP and tolerance on Day 84 in the worse eye. A responder was a patient for whom the sum of the scores of the eight ocular symptoms and the six ocular signs decreased by at least 20%, and for whom the effect on IOP was either satisfactory or acceptable, following the IOP scoring status (Table 1). The criteria “satisfactory” and “acceptable” were defined taking into account a possible loss of efficiency while maintaining a controlled IOP after the switch from latanoprost to timolol [20].

The worse eye was defined as the eligible eye with the highest total intolerance score at D0. In case of both eyes

<table>
<thead>
<tr>
<th>Table 1</th>
<th>IOP scoring.</th>
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</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>IOP (Day 84)</td>
</tr>
<tr>
<td>Satisfactory</td>
<td>≤ 18 mmHg</td>
</tr>
<tr>
<td>Acceptable (2 cases)</td>
<td>≤ 18 mmHg</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>19 mmHg</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>&gt; 19 mmHg</td>
</tr>
</tbody>
</table>
had the same intolerance score, the eye with the highest IOP was considered.

Secondary objectives
The following tolerance and efficacy criteria were evaluated: sum of the scores of signs and symptoms, assessment of both global discomfort and tolerance by the patient, assessment of both efficacy and tolerance by the investigator, adverse events, number of withdrawals, and comparison of the mean basal IOP after 28 days of treatment.

Ocular symptoms were assessed by questioning patients about each criterion, and asking patients to grade them according to a severity scale from 0 (absent) to 3 (severe). At each visit, slit lamp examination was performed to assess all criteria defined, and they were quoted judging their severity. Investigator had also to consider the global tolerance by scoring its assessment from 'very satisfactory' to 'unsatisfactory'.

Statistics
Mean IOP analyses were based on the Full Analysis Set (FAS). Descriptive statistics were performed with a 95% confidence interval. Binary variables were analysed using the Fisher exact test, the Mann-Whitney test was used for ordinal variables. Quantitative variables were assessed by independent samples t-test, and paired tests were necessary for the change from baseline. All tests were performed two-sided, at the 5% level of significance.

Results
Demography and baseline data
A total of 150 patients were included, consisting the full analysis set (FAS). Seventy-seven patients were treated with unpreserved timolol gel and 73 with preserved latanoprost. Twenty patients, six in the preserved latanoprost group and 14 in the unpreserved timolol group, had major protocol deviations (inclusion criteria not respected, treatment duration not respected…). Therefore, the Per Protocol (PP) set consisted of 130 patients. The overall mean age ± SD was 65 ± 11.7 years, ranging from 29 to 87 years old. There were more females than males in the two treatment groups (66% versus 34%). The two treatment groups were statistically similar (all P > 0.05) regarding the baseline parameters of tolerance and IOP (Table 2).

Efficacy and safety data
Primary variable
In the FAS, 91.5% of patients were responders to the primary efficacy/safety criteria under unpreserved timolol gel treatment versus 48.6% under preserved latanoprost treatment on Day 84 (P < 0.001). From Day 28, 85.3% of patients responded to the efficacy/safety criteria under unpreserved timolol gel treatment compared to 40.3% in the preserved latanoprost group (P < 0.001). The difference between treatment groups was highly statistically significant (Fisher exact test: P < 0.001). These results were confirmed in the Per Protocol set of 130 patients (Fig. 1).

Secondary variables
Efficacy variable
In the unpreserved timolol gel group, the IOP amounted on average from 15.9 mmHg (s.d. 1.9 mmHg) at baseline, to 16.1 mmHg (s.d. 2.1 mmHg) at Day 28, and to 16.2 mmHg (s.d. 2.3 mmHg) at Day 84. In the preserved latanoprost group the IOP amounted on average from 15.8 mmHg (s.d. 1.5 mmHg) at baseline, to 15.7 mmHg (s.d. 2.0 mmHg) at Day 28, and to 15.7 mmHg (s.d. 2.2 mmHg) at Day 84. The differences between groups were not significantly different (P > 0.05), and within each treatment group the changes with respect to baseline were also not significant. Thus, in both treatment groups, IOP appeared to be stable throughout the study (Table 3).

Regarding effect on IOP resulting from the IOP scoring status (Table 1), the IOP score was satisfactory or acceptable for 95.9% of patients (71.2% and 24.7%, respectively) and unsatisfactory for only 4.1% of patients in the unpreserved timolol gel group on Day 84. In the preserved latanoprost group, IOP score was satisfactory or acceptable for 94.3% of patients (88.6% and 5.7%, respectively), and unsatisfactory for 5.7% of patients on Day 84.

Tolerance variables
In both treatment groups, the global symptom scores decreased during the study, ranging for the unpreserved timolol gel group from 6.9 (s.d. 4.0) on Day 0, to 3.3 (s.d. 3.3) on Day 28, and to 2.1 (s.d. 2.1) on Day 84. Among the preserved latanoprost group, the symptom score decreased from 5.2 (s.d. 2.4) at baseline, to 4.9 (s.d. 3.1) on Day 28, and to 4.6 (s.d. 2.9) on Day 84. On Day 84 mean score change from baseline rated -4.8 (s.d. 3.4) for unpreserved timolol gel group versus -0.6 (s.d. 2.1) in the preserved latanoprost group (Fig. 2). Differences were highly significant in favour of unpreserved timolol gel group (t-test: P < 0.001).

Along the same line, in both treatment groups the global ocular sign scores decreased from baseline, with a further effect among the unpreserved timolol gel group. The global ocular sign scores decreased from 4.0 (s.d. 2.4) at baseline to 1.6 (s.d. 1.5) on Day 84 in the unpreserved timolol gel group versus 3.5 (s.d. 2.0) at baseline to 2.6 (s.d. 2.2) in the

Table 2  IOP and tolerance at baseline—Worse Eye—FAS population.

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Unpreserved timolol gel (n = 77) Mean (SD)</th>
<th>Preserved latanoprost (n = 73) Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOP (mmHg)</td>
<td>15.9 (1.9)</td>
<td>15.8 (1.5)</td>
</tr>
<tr>
<td>Global Subjective Symptom Score</td>
<td>6.7 (3.9)</td>
<td>5.6 (3.6)</td>
</tr>
<tr>
<td>Global Objective Sign Score</td>
<td>3.8 (2.4)</td>
<td>3.6 (2.0)</td>
</tr>
<tr>
<td>Total Tolerance Score</td>
<td>10.4 (5.4)</td>
<td>9.2 (5.0)</td>
</tr>
<tr>
<td>Best Far Corrected Visual Acuity (/10)</td>
<td>8.9 (1.4)</td>
<td>9.0 (1.4)</td>
</tr>
</tbody>
</table>
preserved latanoprost group. At the end of the study, mean score change from baseline ranked −2.4 (s.d. 1.9) in the unpreserved timolol gel group compared with −0.9 (s.d. 1.7) in the preserved latanoprost group (Fig. 3). The differences between groups were highly significant (t-test: P < 0.001), and within each treatment group the changes with respect to baseline was also significant.

Both symptoms and signs were significantly improved under unpreserved timolol gel treatment compared to preserved latanoprost. Table 4 presents each sign and symptom at D0 and D84 in both groups. On Day 84 the investigator assessed the global tolerance as satisfactory or very satisfactory for 96% of patients treated with unpreserved timolol gel, and for 71% of patients of the preserved latanoprost group. The difference between treatments was highly significant (Mann-Whitney test: P < 0.001).

Furthermore, after three months of treatment, 100% of the patients in the unpreserved timolol gel group versus 85.7% in the preserved latanoprost group answered “yes” at the question: How well did you tolerate the treatment? The difference between treatments was highly significant (Fisher exact test: P < 0.001). No significant adverse events occurred during the study.

**Global satisfaction**

Investigators assessed the global efficacy. The responses to treatment were quoted “very satisfactory” for 46% of the patients in the unpreserved timolol gel group and for

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**Table 3** Change from baseline regarding IOP.

<table>
<thead>
<tr>
<th></th>
<th>Unpreserved timolol gel</th>
<th>Preserved latanoprost</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 28—Day 0</td>
<td>Mean (SD), n</td>
<td>0.2 (1.9), 76</td>
<td>−0.1 (1.6), 72</td>
</tr>
<tr>
<td>Day 84—Day 0</td>
<td>Mean (SD), n</td>
<td>0.3 (2.2), 73</td>
<td>−0.2 (1.7), 70</td>
</tr>
</tbody>
</table>

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**Figure 1.** Responders to the primary criteria at D28 and D84 (%).

**Figure 2.** Global Ocular Symptom Score - Independent t-test. Global ocular symptom: irritation/burning, itching, tearing, stinging upon instillation, eye dryness sensation, foreign body sensation, photophobia, blurred vision.

Unpreserved timolol 0.1% gel and patients with signs of ocular intolerance

Figure 3. Global Ocular Sign Score - Independent t-test. Global ocular sign: hyperaemia, superficial punctuate keratitis (SPK), interpalpebral conjunctival stainings, folliculo-papillary conjunctivitis, blepharitis and BUT less than 10 s.

Table 4 Presence\(^a\) of ocular symptoms and ocular signs.

<table>
<thead>
<tr>
<th></th>
<th>Unpreserved timolol gel</th>
<th>Preserved latanoprost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Day 84</td>
</tr>
<tr>
<td><strong>Ocular symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritation/Burning</td>
<td>87.1</td>
<td>39.7</td>
</tr>
<tr>
<td>Itching</td>
<td>57.2</td>
<td>16.4</td>
</tr>
<tr>
<td>Tearing</td>
<td>45.5</td>
<td>17.8</td>
</tr>
<tr>
<td>Stinging upon instillation</td>
<td>75.4</td>
<td>27.4</td>
</tr>
<tr>
<td>Eye dryness sensation</td>
<td>53.3</td>
<td>23.3</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>55.9</td>
<td>16.5</td>
</tr>
<tr>
<td>Photophobia</td>
<td>33.8</td>
<td>16.4</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>31.2</td>
<td>21.9</td>
</tr>
<tr>
<td><strong>Ocular signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conjunctival hyperaemia</td>
<td>64.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Tear break-up time(^b)</td>
<td>53.9</td>
<td>38.0</td>
</tr>
<tr>
<td>Superficial punctuate epithelial keratitis</td>
<td>48.1</td>
<td>19.1</td>
</tr>
<tr>
<td>Interpalpebral conjunctival staining</td>
<td>44.2</td>
<td>21.9</td>
</tr>
<tr>
<td>Folliculo-papillary conjunctivitis</td>
<td>48.1</td>
<td>26.1</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>50.7</td>
<td>15.1</td>
</tr>
</tbody>
</table>

\(^a\) Presence: mild or moderate or severe.

\(^b\) Percentage of patients with BUT less than 10 s.

31% of patients in the preserved latanoprost group. However, the difference in global efficacy assessment between the two treatment groups was not statistically significant (\(P = 0.079\)).

**Discussion**

In this randomized phase IV open study, 150 ocular hypertensive or glaucomatous patients treated with BAK-preserved latanoprost 0.005% and presenting intolerance signs received either unpreserved timolol 0.1% gel or continued their BAK-preserved latanoprost treatment for 12 weeks.

Results showed that both symptoms and signs were significantly improved under unpreserved timolol gel compared to preserved latanoprost with a stable IOP throughout the study. Indeed, 91.5% of patients were responders to the primary efficacy/safety criteria under unpreserved timolol gel versus 48.6% to preserved latanoprost on Day 84 (\(P < 0.001\)). Regarding IOP, the differences between groups were not significantly different (\(P > 0.05\)), and within each treatment group the changes with respect to baseline were also not significant.

These results are in agreement with a range of other published studies. Xalatan\(^\text{®}\) contains high concentrations of BAK (0.02%) [22]. Regarding safety, this is closely linked to toxicity on the ocular surface. BAK is a detergent agent.
that is responsible for dry eye, chronic inflammation and impairment of the corneal epithelium after a long-term use. Moreover, although the number of patients with major protocol deviations was higher in the unpreserved timolol group than in the preserved latanoprost group, efficacy and safety results were similar between the FAS and the PP sets.

Several studies showed that preserved eye drops are more associated with ocular symptoms and signs of irritation compared to preserved-free eye drops, especially when patients use a long-term treatment as it is the case in glaucomatous and/or OHT patients [23]. It has been shown that BAK induces tear film instability, loss of goblet cells, conjunctival squamous metaplasia and apoptosis, disruption of the corneal epithelium barrier, and damage to deeper ocular tissues [19].

Recently, Martone et al. [24] reported ocular surface alterations in patients treated with preservative-containing antiglaucoma eye drops compared to those treated with a preservative free beta-blocker in the long term or with control eyes. Clinical data (Schirmer test, esthesiometry, and BUT) and confocal microscopy findings demonstrated better results in the preservative free group than in the preservative group. Indeed, this study showed that preservative free timolol produced significantly less surface ocular damage than agents with preservatives. Moreover, a full review of the consequences of the exposure to BAK, published recently by Baudouin et al. [19], reports the large body of evidence from experimental and clinical studies showing that the long-term use of preserved topical drugs may induce ocular surface changes.

In spite of its preservative formulation, Xalatan® is appreciated for its very good efficacy in reducing IOP [16]. In a published clinical trial, it has been shown that even if latanoprost seems more effective than timolol gel 0.5% in reducing IOP and that patients switched from timolol to latanoprost have a further reduction in IOP [20], no changes in IOP were observed when patients were switched from latanoprost to timolol gel, as also observed in our study with timolol gel 0.1%.

BAK as a penetration enhancer has been suggested to increase the amount of active product available in the anterior chamber and to enhance the product efficacy. However, results of Easty et al. [22] phase III study did not confirm such hypothesis. Indeed, results showed that the efficacy of non-preserved timolol gel was not inferior to the preserved timolol gel in OHT and glaucomatous patients after 12 weeks of treatment, confirming the hypothesis that the preservative does not interfere with the efficacy of timolol [22]. Other published studies are in agreement with these data. In a short-term comparative study of topical 2% car- teolol with and without benzalkonium chloride in healthy volunteers, the preservative free group showed better stability of the tear film, without loss of effect on IOP [25].

Another study showed that patients previously treated with a BAK-preserved prostaglandin analog who are changed to travoprost BAK-free have clinically and statistically significant improvement in their ocular surface disease symptoms, decreased hyperemia, and equal or better IOP control [26]. In equal efficiency, it therefore seems to be interesting to improve safety.

In our clinical study, most tolerance assessments were improved during the study in both treatment groups, but this improvement was more pronounced in the unpreserved timolol gel group than in the preserved latanoprost group. A possible explanation for the changes observed in the preserved latanoprost group is that the patients are followed in the context of a clinical trial, which may have increased subjective relief like a placebo effect. This is an interesting point for this study in which double blind was not feasible.

The findings of this study suggest that two factors must be taken into account for the medical management of patients with glaucoma. In choosing an IOP-lowering medication for glaucoma or ocular hypertension, a physician should consider both efficacy and tolerability. Tolerability issues are barriers to compliance with long-term treatment. As IOP-lowering was similar between preserved prostaglandin therapy and preservative free beta-blockers therapy, a switch from preserved to preservative free IOP-lowering agents should be considered in patients with ongoing glaucoma and ocular surface damage due to preservative or in previously compromised ocular surface. Moreover, in new glaucoma patients with risk of developing ocular surface damage, physician may consider preservative free beta-blockers as an interesting first choice therapy. The smallest concentration of timolol (0.1%) should be also preferred in order to decrease systemic side effects. Preservative free timolol gel 0.1% instilled once daily improved ocular tolerance, a favourable factor with respect to patient’s compliance, but also regarding surgical outcome in the most severely affected patients likely to undergo further filtration surgery. Thus, prostaglandin as first choice therapy may not be always relevant in patients with elevated ocular hypertension and all the more if they present signs of ocular intolerance.

To conclude, this study showed that the use of preservative free gel of timolol 0.1% once daily maintained the efficacy on IOP and reduced signs and symptoms in almost all glaucomatous patients treated by preserved latanoprost with signs of intolerance. On the basis of all these experimental and clinical reports, it should be recommended to use benzalkonium-free eye drops whenever possible, especially in patients with prolonged treatments, in those suffering from pre-existing or concomitant ocular surface diseases, and those experiencing side effects related to the ocular surface.

Disclosure of interest
L.D., B.V. are employees of Laboratoires Théa.
C.B. was investigator coordinator of this study.
E.A., P.G. were investigators of this study.

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