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ORIGINAL RESEARCH

The PRAMOS Study: PRostaglandin Analogues Monotherapy—Awareness Survey on Ocular Surface Involvement

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ABSTRACT

Introduction: Even though the local tolerance of prostaglandin (PG) analogues has improved drastically since the introduction of preservative-free (PF) eye drops, prescription patterns still vary widely among practitioners and between countries and could have an impact on the ocular surface of treated patients and, in consequence, their adherence. The aim of this study is to explore the prescribing patterns of PG analogues monotherapy in France and to evaluate their impact on ocular surface status.

Methods: This was a national multicenter cross-sectional observational study that was conducted by 18 glaucoma experts in France. Patients over 18 years of age and receiving monotherapy with topical PG analogues for the treatment of ocular hypertension and/or glaucoma, with no history of prior glaucoma surgery, were consecutively selected from the

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glaucoma outpatient clinics of participating physicians and underwent an ocular surface examination.

Results: A total of 344 eyes of 344 patients were enrolled between November 2022 and November 2023. Prescribed PG monotherapy was PF in 271 (78.7%) patients. Clinical history and ocular surface evaluation indicated that 79.4% of the study population (n = 273) presented with at least one symptom or clinical sign of dry eye and that three patients out of four had an unstable tear film. Subgroup analysis comparing preserved and PF PG analogues showed a higher prevalence of conjunctival hyperemia and corneal staining in the preserved group. Multivariate analysis identified conjunctival hyperemia as consistently associated with preservative use (odds ratio = 7.654; p = 0.003 for moderate conjunctival hyperemia).

Conclusions: This study highlights the growing trend toward PF PG analogue prescriptions by specialists in France. However, ocular surface issues remain prevalent, impacting patient adherence and treatment efficacy. Comprehensive ocular surface examinations are crucial in glaucoma management to enhance long-term tolerance, compliance, and overall treatment success.

Keywords: Glaucoma; Prostaglandin analogues; Ocular surface; Drug toxicity; Prescription habits

Key Summary Points

Why carry out this study?

The first-line treatment for glaucoma is based on lowering the intraocular pressure with eye drops.

Compliance to treatment is adversely affected by ocular surface disorders, particularly induced by preservatives.

The aim of this study was to describe trends in prescribing prostaglandin analogues as a monotherapy by glaucoma specialists in France, and to assess the ocular surface of treated patients in order to assess its degree of involvement.

What was learned from the study?

There is a growing trend towards preservative-free prostaglandin analogues prescriptions in France.

The majority of patients have at least one clinical sign or symptom of ocular surface involvement, including an unstable tear film, even in preservative-free treated patients.

Glaucoma being a chronic disease requiring lifelong treatment instillation, it is important to consider the ocular surface of patients before the introduction of any topical medication and during their follow-up, in order to insure long-term tolerance, adherence, efficacy and even subsequent surgical success.

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INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy that causes progressive loss of retinal ganglion cells and retinal nerve fiber layers and can ultimately lead to blindness if left untreated. All currently available therapeutical options aim at halting or slowing the

progression of the disease by lowering intraocular pressure (IOP), and the treatment strategy relies primarily on IOP-lowering eye drops, and more recently on selective laser trabeculoplasty [1, 2]. Because glaucoma affects almost 60 million people worldwide [3], prescriptions of IOP-lowering eyedrops are common and remain the first step in glaucoma management among ophthalmologists. Patients are generally treated for many years with an estimated median duration of their disease from onset to death being 16 years [4].

The main challenge in glaucoma, as with other chronic conditions, is the adherence to treatment, which is partly correlated with local and systemic side effects [5, 6]. Maintaining local tolerance is particularly challenging in patients with glaucoma, as the prevalence of ocular surface disorders is very high in this population [7, 8]. Moreover, it is now recognized that IOP-lowering eyedrops can be responsible for chronic inflammation of the ocular surface, which can lead to dry eyes, chronic allergic keratoconjunctivitis, and dysfunction of the meibomian glands [9]. These manifestations impair the quality of life of patients undergoing treatment and compromise the efficacy of the treatment by reducing patient compliance [10, 11]. Furthermore, evidence of the involvement of preservatives contained in eye drops in the onset of these inflammatory side effects on the ocular surface is currently relatively well established [9]. Numerous studies, both experimental and clinical on humans, have demonstrated the negative impact of instilling preserved eye drops on the ocular surface without adding efficacy on IOP control [12–17]. On the contrary, the presence of preservatives appears to be an essential cofactor in the development of ocular surface disorders in glaucoma patients which can affect treatment adherence and efficacy by altering patient daily compliance. Benzalkonium chloride (BAK), in particular, was also demonstrated as a risk factor for earlier surgical failure, independent of the number of medications used [18].

Among the classes of drugs available in topical form, prostaglandin (PG) analogues are most often used as first-line treatment, due to their high efficacy in reducing IOP, their once-daily dosing, and their low systemic side effects [19]. They act primarily by increasing the elimination of the aqueous humor via the uveoscleral pathway, allowing for a 25–35% reduction in IOP [20]. Local tolerance of PG analogues has improved drastically since preservative-free (PF) eyedrops were put on the market, with many trials showing less signs and symptoms of ocular surface disease [17, 21, 22]. While one could expect all patients to be put on PF medications as a first-line therapy to maintain efficacy and local tolerance of these drugs, reality is that practices vary widely among practitioners and between countries [23, 24]. However, as stated earlier, glaucoma treatment lasts for many years and its impact on the ocular surface can drastically affect patient adherence, especially that the disease is more frequent in the elderly, who also happen to have an increased prevalence of dry eye disease [25].

The first aim of our study was to describe trends in prescribing PG analogues as a monotherapy by glaucoma specialists in France. As an awareness survey, participating physicians were also asked to assess the ocular surface of their treated patients in order to assess its degree of involvement.

METHODS

Study Design

This national multicenter cross-sectional observational study was carried out by 18 volunteer glaucoma experts in 15 ophthalmology centers throughout France. An invitation was sent out to 40 glaucoma specialists across France to take part in the study and the participation rate was 45%. All 18 participating physicians practiced in urban areas at the time of enrollment: 11 of them in private practice and seven in public university hospitals. The study was carried out as part of routine care, without modification of the medical care usually provided, and was made in accordance with the principles of the Declaration of Helsinki. All patients gave their free and informed written consent after an explanation of the study design and purpose by

their treating physician. Patients' confidentiality was ensured. The research was approved by the Rothschild Foundation Hospital review board (IRB00012801) under the study number CE_20230124_12_CBN.

Population and Study Protocol

Patients were enrolled between November 2022 and November 2023 and were consecutively selected from the glaucoma outpatient clinics of participating physicians. Eligible patients had to be over 18 years of age and receiving monotherapy with topical PG analogues for the treatment of ocular hypertension (OHT) and/or glaucoma, with no history of prior glaucoma surgery (including minimally invasive glaucoma surgery and/or laser procedures). A minimal duration of treatment before enrollment was not required. Patients with previous glaucoma surgery, those using hypotensive drops other than PG analogues, and those receiving dual or triple therapies were therefore excluded.

A short anonymous questionnaire developed by glaucoma and ocular surface experts was proposed to participating physicians (Supplementary Material). Demographics and medical/clinical history were recorded and included: age and sex; severity of glaucoma as assessed by the mean deviation (MD) of the last visual field (according to the Hodapp-Parrish-Anderson classification) [26]; duration of glaucoma treatment; current PG analogue treatment; presence or absence of burning on instillation of the current treatment; history of prior switch of hypotensive treatment; history of ocular surface disease (including dry eye disease) before initiation of hypotensive treatment; presence or absence of dry eye symptoms (burning, irritation, foreign bodies sensation, etc.); their intensity and frequency assessed in three grades (mild, moderate, severe, and occasionally, frequently, constantly, respectively) and prior treatment with artificial tears. All PG analogues containing a substance considered as a preservative in the literature (BAK, polyquaternium-1) were considered as "preserved".

All patients were then submitted to a quick ocular surface evaluation, in ascending order of invasiveness, that included: presence and severity of conjunctival hyperemia in four stages (absent, mild, moderate, or severe); tear break-up time (TBUT) in three stages (short: < 5 s, moderate: 5–10 s or long: > 10 s) after administration of a single drop of fluorescein; presence and severity of corneal fluorescein staining classified into four stages (absent, mild, moderate, or severe), and presence or absence of fluorescein staining of the nasal conjunctiva. After completion of the ocular surface examination, IOP was measured for all patients using Goldmann applanation tonometry (mmHg).

For each patient, only data from one eye were collected. If only one eye was eligible (i.e., fulfilling all inclusion criteria with no ophthalmological exclusion criteria), that eye was included. However, if both eyes were eligible, only the eye with the worse ocular surface was included and was defined as follows: the eye with the worst corneal staining, or if not applicable the one with the lowest TBUT. If both parameters were comparable, the right eye was randomly assigned as the worse eye. The anonymized data were centralized, computerized, and analyzed by a single investigator.

Statistical Analysis

Statistical analysis was performed using XLSTAT add-on software for Microsoft Excel 2016 (Addinsoft 2016, NY, USA). In the whole population, quantitative variables were described by means and standard deviations (SD), and qualitative variables were described by frequency numbers and percentages. For subgroup analyses (presence or absence of preservatives), comparisons of quantitative variables were made using the non-parametric Mann–Whitney test and qualitative variables were analyzed using the chi-square test. Factors identified as being associated with the presence of preservatives in the bivariate analysis were included in a logistic regression model in which the dependent variable was the presence or absence of preservatives. A 95% two-sided confidence interval was computed, and statistical

significance was considered in the presence of a $p < 0.05$.

RESULTS

Three hundred and forty-four eyes of 344 patients were included in the analysis, where 186 were women and 158 were men. The sociodemographic and clinical characteristics of the patients are summarized in Table 1. The mean age of participants was 68.2 ± 10.9 years, the majority of which suffered from mild glaucoma with a MD < 6 dB (288 patients, 83.7%), and mean measured IOP was 16.3 ± 3.3 mmHg.

Concerning prescription trends, the majority of patients were treated with PF PGs (271 patients, 78.7%), for a mean duration of 78.2 ± 67.3 months. Latanoprost was by far the most prescribed molecule, accounting by itself for 81.4% of PG monotherapy prescriptions. Details of the PG analogues prescribed are summarized in Table 2. Regarding the ocular surface in the overall population, 69 patients (20.1%) had prior known ocular surface diseases, and 129 patients (37.5%) were already on artificial tears at the time of the survey. The functional and clinical signs of ocular surface evaluation are summarized in Table 3. Fifty-eight patients (16.9%) complained of ocular burning upon instillation of the treatment, and 140 patients (40.7%) presented functional signs of dry eye other than during instillation. These symptoms were most often occasional (62.9%) and of mild intensity (60.7%). In terms of clinical signs, 119 patients (34.6%) had corneal staining, which was usually mild. Moreover, 88 patients (25.6%) had nasal conjunctival staining, and 135 patients (39.2%) had conjunctival hyperemia. TBUT was highly variable, with one-third of the patients (32.9%) having a TBUT < 5 s. A total of 273 patients, or 79.4% of the study population, presented with at least one symptom or clinical sign of dry eye (including symptoms of dry eye between eyedrop application, presence of conjunctival or corneal staining, presence of conjunctival hyperemia, or an unstable tear film with a TBUT < 10 s).

The results of the subgroup analysis comparing data from patients treated with preserved

Table 1 Qualitative and quantitative data of the overall population of patients with ocular hypertension or glaucoma treated with prostaglandin analogue monotherapy in France

Qualitative data, *N* (%)	
Sex	
Female	186 (54.1)
Male	158 (45.9)
Type of prostaglandin	
Preserved	73 (21.3)
Preservative-free	271 (78.7)
Glaucoma severity	
Mild (MD < 6 dB)	288 (83.7)
Moderate (6 dB ≤ MD ≤ 12 dB)	43 (12.5)
Severe (MD > 12 dB)	13 (3.8)
Modification of glaucoma treatment in the past (any reason)	122 (35.5)
Ocular surface intolerance	74 (60.6)
Loss of efficacy	30 (24.6)
Other[a]	14 (11.5)
N/A	4 (3.3)
Known concomitant ocular surface disease	69 (20.1)
Artificial tears before introduction of prostaglandin	119 (34.6)
Artificial tears concomitant with current treatment	129 (37.5)
1–2 times per day	80 (62.0)
3–4 times per day	49 (38.0)
Quantitative data, mean ± SD	
Age, years	68.2 ± 10.9
Duration of treatment, months	78.2 ± 67.3

Table 1 continued

Quantitative data, mean ± SD	
IOP, mm Hg	16.3 ± 3.2

IOP intraocular pressure, *MD* mean deviation, *N* number, *SD* standard deviation, *N/A* not available

[a]Other includes switch to a preservative-free drug for ten patients, switch to single-dose containers for one patient, switch because of posology for one patient, skin hyperpigmentation in one patient and intolerance to beta-blockers in one patient

Table 2 Distribution of current prostaglandin treatment among patients with ocular hypertension or glaucoma treated with prostaglandin analogue monotherapy in France

Current prostaglandin treatment, *N* (%)	
Preserved	
Lumigan® (bimatoprost) and generics	43 (12.5)
Xalatan® (latanoprost) and generics	15 (4.4)
Travatan® (travoprost) and generics	15 (4.4)
Total	73 (21.3)
Preservative-free	
Monoprost® (latanoprost)	249 (72.2)
Xiop® (latanoprost)	14 (4.1)
Vizitrav® (travoprost)	3 (0.9)
Sinetrav® (travoprost)	3 (0.9)
Latazed® (latanoprost)	2 (0.6)
Total	271 (78.7)

N number

(n = 73) or PF (n = 271) PG analogues are summarized in Table 4 and illustrated in Fig. 1. The proportion of women was higher in the PF group than in the group treated with preserved PG (57.2% and 42.5%, respectively; p = 0.025). In addition, the duration of treatment was greater in the preserved group (106.8 ± 75.7 months, compared with 70.5 ± 62.9 months in the PF group; $p < 0.0001$). However, the mean measured IOP did not differ between the two groups (p = 0.717) and the severity of the disease was comparable (p = 0.307). Concomitant use of artificial tears (p = 0.658) and its frequency (p = 0.081) were comparable between the two groups. There was a tendency to less stinging on instillation in the PF group, but the difference did not reach statistical significance (23.2% in the preserved group versus 15.1% in the PF group; p = 0.098). Differences in the intensity and frequency of dry eyes symptoms other than during instillation, as well as TBUT and nasal conjunctival staining were similar in patients treated with preserved or PF PG (p = 0.330, p = 0.783, p = 0.696 and p = 0.689, respectively). Conjunctival hyperemia was more frequent in the preserved group and was mostly mild ($p < 0.0001$). In addition, the intensity of corneal staining appeared to be greater in the preserved group (p = 0.047). The results of the multivariate analysis including the four parameters associated with the presence or absence of preservatives (sex, corneal staining, conjunctival hyperemia and duration of treatment) are summarized in Table 5. According to this analysis, the only clinical sign consistently associated with the presence of preservatives was conjunctival hyperemia (odds ratio (OR) = 3.966; 95% CI [2.144–7.339]; $p < 0.0001$ for mild conjunctival hyperemia; and OR = 7.654; 95% CI [1.994–29.376]; p = 0.003 for moderate conjunctival hyperemia).

DISCUSSION

This study shows that the vast majority (78.7%) of PG analogue monotherapies prescribed by glaucoma specialists in France for the treatment of OHT or glaucoma are preservative-free. Such a prescription trend is much higher than in some other European countries. In England for example, a prescription cost analyses in the public domain describing primary care prescriptions showed that the PF prescriptions increased each year from 2009 but only reached 13.9% by 2018 [23]. On the other hand, similar

Table 3 Ocular clinical findings in the overall population of patients with ocular hypertension or glaucoma treated with prostaglandin analogue monotherapy in France

Ocular clinical findings, *N* (%)	
Stinging on instillation	58 (16.9)
At least one sign of dry eye (clinical or functional)	273 (79.4)
Dry eye symptoms other than during instillation	140 (40.7)
Intensity	
Mild	85 (60.7)
Moderate	50 (35.7)
Severe	3 (2.1)
N/A	2 (1.4)
Frequency	
Occasionally	88 (62.9)
Frequently	45 (32.1)
Continuously	4 (2.9)
N/A	3 (2.1)
Tear break-up time	
> 10 s	82 (23.8)
5–10 s	149 (43.3)
< 5 s	113 (32.9)
Corneal staining	
Absent	225 (65.4)
Mild	105 (30.5)
Moderate	14 (4.1)
Severe	0 (0)
Nasal conjunctival staining	88 (25.6)
Conjunctival hyperemia	
Absent	208 (60.5)
Mild	123 (35.8)
Moderate	12 (3.5)
Severe	0 (0)
N/A	1 (0.3)

N number, *N/A* not available

Table 4 Comparison of demographic and ocular clinical findings of patients with ocular hypertension or glaucoma treated with preserved or preservative-free prostaglandin analogues as a monotherapy in France

	Preserved (*n* = 73)	**Preservative-free (*n* = 271)**	***p***
Age, years (mean ± SD)	68.2 ± 10.1	68.2 ± 11.1	0.845
Sex, *n* (%)			**0.025**
Female	31 (42.5)	155 (57.2)	
Male	42 (57.5)	116 (42.8)	
IOP, mmHg (mean ± SD)	16.3 (3.8)	16.3 (3.1)	0.717
Glaucoma severity, *n* (%)			0.307
Mild (MD < 6 dB)	65 (89.0)	223 (82.3)	
Moderate (6 dB ≤ MD ≤ 12 dB)	7 (9.6)	36 (13.3)	
Severe (MD > 12 dB)	1 (1.4)	12 (4.4)	
Known ocular surface disease, *n* (%)	13 (17.8)	56 (20.7)	0.589
Artificial tears before introduction of prostaglandin, *n* (%)	20 (27.4)	99 (36.5)	0.145
Duration of treatment, months (mean ± SD)	06.8 (75.7)	70.5 (62.9)	< **0.0001**
Artificial tears concomitant with current treatment, *n* (%)	29 (39.7)	100 (36.9)	0.658
Frequency of artificial tears			0.081
1–2 times per day	22 (75.9)	58 (58.0)	
3–4 times per day	7 (24.1)	42 (42.0)	
At least one sign of dry eye (clinical or functional), *n* (%)	61 (83.6)	212 (78.2)	0.318
Stinging on instillation, *n* (%)	17 (23.2)	41 (15.1)	0.098
Dry eye symptoms other than during instillation, *n* (%)	33 (45.2)	107 (39.3)	0.377
Intensity			0.330
Mild	24 (72.7)	61 (57.0)	
Moderate	9 (27.3)	41 (38.3)	
Severe	0	3 (2.8)	
N/A	0	2 (1.9)	
Frequency			0.783
Occasionally	22 (66.7)	66 (61.7)	
Frequently	10 (30.3)	35 (32.7)	
Continuously	1 (3.0)	3(2.8)	
N/A	0	3 (2.8)	
Tear break-up time, *n* (%)			0.696

Table 4 continued

	Preserved (n = 73)	Preservative-free (n = 271)	p
> 10 s	18 (24.7)	64 (23.6)	
5–10 s	34 (46.6)	115 (42.4)	
< 5 s	21 (28.8)	92 (33.5)	
Corneal staining, n (%)			**0.047**
Absent	44 (60.3)	180 (66.4)	
Mild	22 (30.1)	83 (30.6)	
Moderate	6 (8.2)	8 (3.0)	
Severe	1 (1.4)	0	
Nasal conjunctival staining, n (%)	20 (27.4)	68 (25.1)	0.689
Conjunctival hyperemia, n (%)			**< 0.0001**
Absent	25 (34.3)	183 (67.5)	
Mild	42 (57.5)	81 (29.9)	
Moderate	6 (8.2)	6 (2.2)	
Severe	0	0	
N/A	0	1 (0.4)	

IOP intraocular pressure, *MD* mean deviation, *n* number, *SD* standard deviation, *N/A* not available. Characters in bold are significant p values (< 0.05)

results to ours were found in a recent paper that assessed the prescribing patterns of ocular hypotensive drugs in a public hospital in Spain [24]. In their study, latanoprost was also amongst the most prescribed drugs and the prescriptions of PF PG rose from 20% in 2013 to 85% in 2020. The difference in prescription habits could be explained by different factors, including the healthcare system of each country, availability, price and reimbursement status of PF alternatives on the market, and local guidelines. In France, for example, all glaucoma eyedrops, whether preserved or not, are reimbursed at a rate of 65% by the social healthcare system; the remaining 35% are usually fully covered by private complementary insurance, which is common practice in patients with chronic conditions such as glaucoma. For some patients who may not have a complementary health coverage, what is left to pay by the patient is usually very low compared to other Western countries and is believed to have minimal effect on the observed prescription patterns. Also, only latanoprost and travoprost-based eye drops are available in PF formulations in France. Bimatoprost, which accounts for 12.5% of prescriptions, is only available in formulations that contain preservatives, and tafluprost is not currently commercialized. It is, however, important to highlight the fact that our study only included prescriptions from glaucoma specialists who could be more sensitive to iatrogenic ocular surface problems, which could also explain the high PF prescription rate. While the response rate was 45%, it was representative of both private and public practices, and we would not expect different findings from the specialists who did not volunteer to be included in the study.

In a 2009 statement, the European Medicines Agency (EMA) suggested that the use of preservatives should be avoided in patients who do

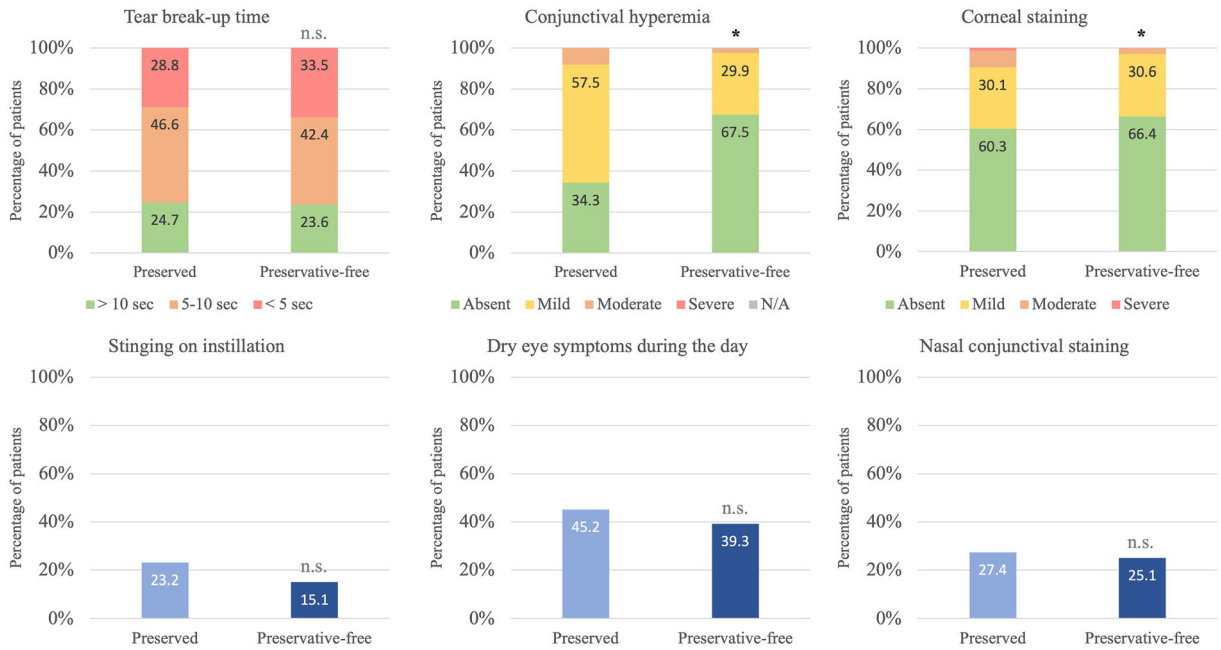

Fig. 1 Comparison of ocular clinical findings between patients treated with preserved (n = 73) and preservative-free (n = 271) prostaglandin analogues as a monotherapy. *N/A* not available, *n.s.* not significant. $^{*}p < 0.05$

not tolerate eye drops with preservatives and in those on long-term treatment. Consequently, the latest recommendations of the European Glaucoma Society advocate the use of PF eyedrops for patients with OHT or glaucoma and a pre-existing ocular surface disease [27]. In our study, prescribers largely exceeded these recommendations, with 78.7% of patients being treated with PF-PG analogues, whereas only 20% of patients had clinically significant ocular surface problems before treatment was introduced.

Another aim of this study was to spread awareness amongst glaucoma specialists on the ocular surface involvement of their treated patients. Our results seem to confirm the need for a thorough examination of the ocular surface of every glaucomatous patient prior to the initiation of treatment and during medical follow-up. In fact, almost 80% of patients had at least one sign or symptom of dry eye when treated with PG analogues, but only one out of three was using artificial tears concomitantly with their treatment. While only 40.7% of patients complained of dry eye symptoms, it should be remembered that subjective and objective clinical findings of dry eye disease do not always correlate [28], especially if the patient is treated with preserved eyedrops that can cause corneal neurotoxicity and inflammation, leading to increased damage of the ocular surface with minimal symptoms [29]. A careful clinical examination of the ocular surface along with the attention given to patients' symptoms could promote adherence to topical treatment and increase treatment efficacy [30]. A drop of fluorescein is required to measure IOP by applanation and is often sufficient to assess the ocular surface within a few minutes in clinical practice.

This observational real-life study was not designed to specifically assess the correlation between preserved treatments and ocular surface impairment, but rather to take a snapshot of the ocular surface of the treated population in order to spread awareness on this often-under-regarded topic. Our subgroup analysis seems, however, to show an equal or better tolerance profile of PF eyedrops, depending on the criterion being analyzed, but statistical significance was only reached for conjunctival hyperemia, independently of treatment

Table 5 Logistic regression of the presence of preservatives to sex, corneal staining, conjunctival hyperemia, and duration of treatment

	OR	95% CI	*p*
Sex (reference: female)			
Male	1.833	[1.015–3.309]	**0.044**
Corneal staining (reference: absent)			
Mild	0.695	[0.361–1.339]	0.277
Moderate	2.025	[0.550–7.461]	0.289
Severe	–	–	–
Conjunctival hyperemia (reference: absent)			
Mild	3.966	[2.144–7.339]	**< 0.0001**
Moderate	7.654	[1.994–29.376]	**0.003**
N/A	–	–	–
Duration of treatment (reference: short < 60 months)			
Intermediate (60–120 months)	2.356	[1.112–4.991]	**0.025**
Long (> 120 months)	3.376	[1.757–6.487]	**< 0.0001**

CI confidence interval, *OR* odds ratio. Characters in bold are significant *p* values (< 0.05)

duration, with an eightfold increase in the risk of moderate hyperemia with a preserved medication. This result is consistent with studies that have demonstrated the toxic effects of preservatives on the conjunctiva. Indeed, preservatives have an oxidative, pro-inflammatory and pro-apoptotic effect on conjunctival cells, particularly goblet cells [31, 32]. Although some of the hyperemia associated with PG analogues is linked to their vasodilatory effect which is usually transient, it does at least partly reflect inflammation of the ocular surface [33]. Moreover, this prolonged conjunctival inflammation and goblet cells loss compromises the efficacy of glaucoma filtering surgery, with a greater risk of subconjunctival fibrosis post-operatively and therefore, a poorer glaucoma prognosis [34].

However, these results comparing preserved and PF eyedrops are to be interpreted carefully because of the design of the study and the differences between the two groups regarding the sex ratio and the duration of treatment. Prevalence and complaints of dry eye disease are higher in women [35], which explains why they could have been switched more frequently to PF eyedrops. On the other hand, factors in medication adherence can be gender-related, therefore affecting clinical findings [36]. Also, patients treated with preserved eyedrops had on average 3 more years of exposure to the topical medication, even though this did not seem to impact our results on conjunctival hyperemia. It is, however, important to underline the fact that most patients receiving preserved eyedrops were treated with bimatoprost whereas the vast majority of PF treatments were latanoprost-based, keeping in mind that hyperemia is more common and more severe with bimatoprost than with latanoprost [37]. In addition, given the high prescription rate of PF PG and the fact that it was prescribed by glaucoma specialists, it is likely that the proportion of patients initially suffering from dry eyes before the introduction of treatment was greater in the PF group. Finally, it is important to mention that while cytotoxicity of preservatives and their well-known detrimental effects on the eye are well described in the literature, much less attention

is usually paid to other excipients in the formulation that can also cause a pro-inflammatory response and a detrimental effect on cells in both experimental and *ex-vivo* models and that can, at least partly, be responsible of the observed side-effects in the PF group [38, 39].

This study has some limitations. As mentioned previously, the results obtained only reflect the prescription habits of glaucoma specialists. Studies involving a wider panel of prescribers would be necessary in order to establish more precisely the overall attitude of ophthalmologists in France. Furthermore, this study was cross-sectional, so it was impossible to establish with certainty the chronological link between the onset of ocular surface disorders and the introduction of treatment with PG analogues. Also, because the aim of the study was to raise awareness on a quick way to examine the ocular surface of glaucomatous patients without lengthening the time of consultation, a complete assessment—including eyelid examination, administration of a standard quality of life questionnaire—was not made. Glaucoma type was also not collected. Finally, it is likely that patients with a good tolerance to preserved eye drops were maintained on their treatment, which enhances good tolerance results in the preserved group, whereas patients with preexisting ocular surface disease or those developing it over time, were more often treated at initiation or switched to PF eye drops, which means that an initial selection bias could have emphasized the risk of ocular surface problems in the PF group.

CONCLUSIONS

In conclusion, there is a real trend towards glaucoma specialists in France prescribing PF PG analogues as monotherapy. This should not, however, falsely reassure practitioners, as our results confirm the high prevalence of ocular surface disease and dry eye syndrome in patients with OHT or glaucoma, regardless of their preserved or PF treatment. Therefore, a careful examination of the ocular surface is recommended for all patients treated for their glaucoma before the introduction of any topical medication and during their follow-up. With glaucoma being a chronic disease requiring lifelong treatment instillation, it is important to consider the ocular surface of patients, for long-term tolerance, adherence, efficacy, and even surgical success. PG formulations with the least corneal and conjunctival toxicity are to be used when available.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Paul Bastelica received speaker honoraria and/or travel grants from Horus Pharma and Théa, outside the scope of this work. Jean Paul Renard is a consultant for Bausch & Lomb, Horus Pharma, Santen and Théa. Florent Aptel is a consultant for Alcon, Bausch & Lomb, Densmore, Elios, Eyetechcare, Glaukos, Horus Pharma and Théa. Antoine Labbé is a consultant for Alcon, AbbVie, Bausch & Lomb, Elios, Horus Pharma, Glaukos, Théa and Santen. Cédric Schweitzer is a consultant for Alcon, Bausch & Lomb, Glaukos, Horus Pharma, Nicox, Santen and Théa. Muriel Poli is a consultant for Bausch & Lomb, Horus Pharma and Théa. Antoine Rousseau is a consultant for AbbVie, Glaukos, Horus Pharma and Théa; and received speaker honoraria and/or travel grants from AbbVie, Alnylam pharmaceuticals, Bausch & Lomb, Santen and Théa, outside the scope of this work. Cédric Lamirel is a consultant for Biogen, Gensight and Horus Pharma; and received travel grants from Horus Pharma and Théa, outside the scope of this work. Christophe Baudouin is a consultant for Alcon, Glaukos, Horus Pharma, Oculis, Santen and Théa.

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