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RAPID COMMUNICATION

Signs and Symptoms of Ocular Surface Disease: The Reasons for Patient Dissatisfaction with Glaucoma Treatments

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On behalf of the GOAL study group

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Abstract: Ocular Surface Disease (OSD) and hyperemia are the most common adverse events of topical ocular medications. While active compounds may cause allergic reactions or irritation, preservatives, which are intended to prevent bacterial growth, are toxic as well. Therefore, the most recent glaucoma medications no longer contain preservatives. Despite this, local tolerability may still impact treatment compliance and patient quality of life. We conducted an observational, multi-center, international, cross-sectional study in 793 treated and stabilized glaucoma patients to assess patient satisfaction and local tolerability of their treatment. The vast majority (93.7%) of patients was satisfied or very satisfied with their treatment in terms of tolerability and only 6.3% were dissatisfied. However, ophthalmological examination showed a high frequency of ocular signs: conjunctival hyperemia (32%), OSD (42.5%) and positive conjunctival fluorescein staining (10.3%). Additionally, patients reported symptoms upon instillation (31.4%) and between instillations (57.3%); 25.1% of patients were using tear substitutes. All signs and symptoms were significantly ($p<0.001$) associated with patient dissatisfaction. A logistic regression model indicated that dissatisfaction was higher in patients with symptoms upon instillation and in those using tear substitutes (OR: 3.03 and 4.63, respectively). The mean patient tolerability score to treatment was 82.7 ±16.1 on a 100-point visual analogue scale. In conclusion, even if patients may be highly satisfied with their current treatment, most of them present ocular signs and symptoms. A treatment change should be considered in case of clinical signs or patient-reported symptoms.

Keywords: glaucoma, tolerance, preservatives, tear substitutes, patient satisfaction, ocular surface disease

Introduction

Patient satisfaction is important to ensure adherence to treatment and cooperation with medical practitioners.[1] To date, patient satisfaction in glaucoma treatment has not been subject to a lot of research. A prospective cohort study among 2541 subjects suggested that approximately 80% of patients were satisfied or very satisfied with their treatment.[2] Another prospective observational study identified a number of factors that were predictive of patient satisfaction with glaucoma treatment.[3] Nevertheless, reduced tolerability of glaucoma medication is common, and patients who report symptoms are less likely to be adherent to treatment.[4–6]

Ocular surface disease (OSD) and hyperemia are the most common side effects of topical medication. They are commonly associated with not only the active ingredient

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in the eye drops but also the preservative frequently added to the formulation in order to prevent bacterial growth.[7] Because preservative-containing medications are associated with OSD and hyperemia, the most recent glaucoma medical treatments do not contain preservatives. However, a significant proportion of patients still use drops containing preservatives, which might impact on local tolerability and therefore impact the patient's quality of life and his treatment compliance.

Preserved treatments are often more cost-effective than preservative-free (PF) treatment and thus preferred by health authorities. However, current guidelines recommend the evaluation of glaucoma patients for OSD and to substitute preserved medication by PF medication, whenever appropriate.[7] Prostaglandins have been recommended for many years as first-line treatment in glaucoma and ocular hypertension.[8–10]

In 2015, a survey in 164 treated and stabilized Dutch glaucoma patients showed that even if local side effects, in particular OSD, may contribute to patient dissatisfaction, only a minority of patients (11%) reported dissatisfaction.[11]

The present article provides results from 793 glaucoma patients from 3 countries about the patients' dissatisfaction with their glaucoma treatment, and reasons for dissatisfaction as well as associated factors.

Methodology

This was an observational, multi-center, international, cross-sectional study conducted between 2013 and 2018. The study was conducted in accordance with the Good Epidemiological Practice guidelines of the International Epidemiological Association.[12]

Ethical and Regulatory Issues

The study protocol was approved according to local ethic committee approval requirements by the central ethics committees of Leuven/Belgium (central IEC approval N°: B322201318662), Rotterdam/Netherlands (IEC approval N°: A13.006) and London/United Kingdom (IRAS ID: 114092) in 2013 prior to patient inclusion. All patients provided informed consent prior to inclusion.

Patient, Disease and Treatment

During the single study visit, gender, age, ophthalmological and other medical history, date of diagnosis of glaucoma or ocular hypertension, type and stage of glaucoma based on visual field damage were recorded along with the patient's intraocular pressure (IOP).

Moreover, the investigator documented the type of glaucoma treatment regimen, the number, dosing regimen, date of diagnosis and reason(s) for switching from previous treatments, whether the treatment was preserved or preservative-free, and whether tear substitutes and/or other topical ocular preparations were used. Furthermore, he recorded if the patient had experienced OSD such as blepharitis/meibomian gland dysfunction, dry eye, eczema, rosacea, allergic conjunctivitis, or other with their glaucoma treatment, and if so, what at which degree (mild, moderate, or severe). Information was obtained from patient records where possible or by direct questioning. Tolerability was evaluated on a 0–100 mm visual analogue scale (VAS: 0 mm = very poor tolerability, 100 mm = very good tolerability).

Patient Dissatisfaction

The prevalence of patients dissatisfied with their current glaucoma treatment regimen was the primary parameter. The clinician questioned the patient ("Regarding tolerance, is the patient satisfied with his/her current glaucoma treatment?") and recorded the degree of satisfaction with their current treatment; the patient chose between "very satisfied", "satisfied", "dissatisfied", "very dissatisfied". Moreover, he recorded whether the patient had experienced or presented with OSD, including blepharitis/Meibomian gland dysfunction, dry eye, eczema, rosacea, allergic conjunctivitis, or others, as well as their severity (mild, moderate, severe). Tear Break-Up-Time (TBUT from >10sec, 10 to 5sec and <5sec) was reported. Information was obtained from patient records or by direct questioning and examination.

The questionnaire used to collect investigator and patient-reported observations is provided as supplementary material.

Statistical Analysis

All statistical analyses were performed by using the SAS® software version 9.2 or later.

Quantitative variables were described in terms of mean, standard deviation and median, and range where appropriate. The χ^2 test, Fisher's exact test, Student's *t*-test, and Wilcoxon signed-rank test were used for group comparisons as appropriate. A univariate analysis was used to identify relationships between patient satisfaction and other study parameters. A multivariate logistic regression analysis was used to calculate odds ratios.

Results

In total, 793 patients (168 from the Netherlands, 253 from Belgium and 372 from the UK) were included.

Patient Demographics and Clinical Data

Overall, 71.9% of the patients were over the age of 60. Gender distribution was almost equal (51% were male). The mean time since diagnosis of glaucoma or ocular hypertension was 8.12±7.44 years. Primary open-angle glaucoma was the most frequent diagnosis (84%; angle closure 4%; secondary: pigmentary 3%, exfoliative 3% and other 6%).

In total, 42.2% of patient eyes had mild (< −6dB), 31.2% moderate (−6 to −12 dB) and 26.6% severe (> −12 dB) glaucoma; the mean IOP was 16.3±4.5 mm Hg.

At the time of the study, 91.5% of the patients received monotherapy and 8.5% combination-therapy. In total, 8.5% had PF glaucoma medication. Prior to current treatment, 66.8% of patients changed their treatment, on average, 1.56±1.98 times. Reasons for change were mainly insufficient efficacy (52.8%) and local intolerance (20.3%).

At the time the study was conducted, 25.1% reported a concomitant use of tear substitutes.

Detailed patient and clinical data are given in Table 1. Table 2 provides detailed results about treatment change and reason for change.

Patient Satisfaction

The vast majority (93.7%) of patients was satisfied or very satisfied in terms of tolerability. The remaining 6.3% rated their treatment dissatisfying or very dissatisfying.

Tolerability

The mean patient tolerability score to treatment was 82.7 ±16.1 mm on a 100-point visual analogue scale; the median score was 86.7 mm [75.2; 95.2].

In patients who were dissatisfied with their treatment, several factors were significantly ($p<0.001$) associated with their dissatisfaction including hyperemia, OSD, a positive conjunctival fluorescein staining test, symptoms upon and between instillations and the use of tear substitutes. A logistic regression model indicated that symptoms upon instillation of eye drops and the use of tear substitutes increased the proportion of patients declaring being dissatisfied with their current glaucoma treatment (OR: 3.03 and 4.63, respectively).

Table 1 Patient Demographic and Clinical Data

		Total (N=793)
Age (years)	**N**	778
18–39	n (%)	25 (3.2%)
40–49	n (%)	55 (7.1%)
50–59	n (%)	128 (16.5%)
60–69	n (%)	240 (30.8%)
70–79	n (%)	214 (27.5%)
+80	n (%)	116 (14.9%)
	Missing	15
Gender	**N**	720
Male	n (%)	367 (51.0%)
Female	n (%)	353 (49.0%)
	Missing	73
Time from glaucoma or ocular hypertension diagnosis (years)	**N**	657
	Mean (SD)	8.12 (7.44)
	Median (Q1;Q3)	6.00 (3.00;12.00)
	Min;Max	0.0;56.0
	Missing	136
Type of glaucoma - Primary	**N**	667
Open angle	n (%)	634 (95.1%)
Angle closure	n (%)	32 (4.8%)
Congenital	n (%)	1 (0.1%)
	Missing	126
Type of glaucoma - Secondary	**N**	88
Pigmentary	n (%)	22 (25.0%)
Exfoliative	n (%)	21 (23.9%)
Others	n (%)	45 (51.1%)
	Missing	705
IOP Assessment - Right Eye (mm Hg)	**N**	744
	Mean (SD)	16.34 (4.58)
	Median (Q1;Q3)	16.00 (14.00;18.00)
	Min;Max	4.0;46.0
	Missing	49
IOP Assessment - Left Eye (mm Hg)	**N**	742
	Mean (SD)	16.27 (4.45)
	Median (Q1;Q3)	16.00 (13.00;18.00)
	Min;Max	6.0;46.0
	Missing	51
Ocular Hypertension - Right Eye	n (%)	251 (31.7%)
Stage of glaucoma - Right Eye	**N**	515
Early glaucoma (< 6dB)	n (%)	268 (52.0%)
Moderate glaucoma (6–12 dB)	n (%)	139 (27.0%)
Severe glaucoma (> 12 dB)	n (%)	108 (21.0%)
	Missing	278
Ocular Hypertension - Left Eye	n (%)	243 (30.6%)
Stage of glaucoma - Left Eye	**N**	518
Early glaucoma (< 6dB)	n (%)	260 (50.2%)

(*Continued*)

Table 1 (Continued).

		Total (N=793)
Moderate glaucoma (6–12 dB)	n (%)	162 (31.3%)
Severe glaucoma (> 12 dB)	n (%)	96 (18.5%)
	Missing	275
Ocular Hypertension - Both Eye	n (%)	289 (36.5%)
	Missing	1
Stage of glaucoma - Both Eye	**N**	567
Early glaucoma (< 6dB)	n (%)	239 (42.2%)
Moderate glaucoma (6–12 dB)	n (%)	177 (31.2%)
Severe glaucoma (> 12 dB)	n (%)	151 (26.6%)
	Missing	226

Upon instillation, 31.4% of patients experienced symptoms. Pain or discomfort were reported by 21.2% and blurred vision by 7.2%.

Between instillations, one or more symptoms were reported by 57.3% of the patients. These included burning (17.4%), crusts on eyelashes (15.9%), red eye (13.1%), photophobia (12.9%), tingling (12.7%), watering (11.9%), itching (9.2%), foreign body sensation (9.0%) and dry eye sensation (5.4%).

Lid redness was observed in 21% of the patients, lid scale or crust in 22.2%, conjunctival hyperemia in 32%, corneal fluorescein positive staining in 22.6%, conjunctival fluorescein positive staining in 10.3% and chemosis in 3.1%.

About 42.5% of patients suffered from OSD with, most of the time, mild severity (71.1%); 10.3% of patients had a TBUT less than 5 sec and 60.8% less than 10 sec. After starting treatment, blepharitis/Meibomian gland disease had increased from 3.9% to 15.5% of patients, dry eye from 5.0% to 24.6%, and conjunctivitis from 2.1% to 3.9%.

Discussion

To date, patient dissatisfaction with topical glaucoma treatments has only sporadically been studied and the present study provides new insights in real-life data of glaucoma patient satisfaction regarding current topical treatment.

Even though the results from the current survey show that 93.7% of patients were satisfied or very satisfied with their glaucoma treatment, 31.4% reported symptoms upon instillation and 57.3% symptoms between instillations. In patients who were dissatisfied with their current treatment, hyperemia, OSD, symptoms on and between instillations, use of tear substitutes and a positive conjunctival fluorescein staining test were significantly associated with their dissatisfaction ($p<0.001$). These results confirm those previously reported.[11] One may hypothesize that a reason for the discrepancy between the high patient satisfaction and the high number of observed tolerance issues may reside, as already highlighted in our previous paper, in the fact that ophthalmologists insist on the importance of controlling IOP, while paying less attention to local intolerability issues.[11] Moreover, ophthalmologists and patients may consider the occurrence of such side effects as "the price to pay" for successfully controlling their glaucoma.

It is to be noted that percentage quarter of all patients using tear substitutes concomitantly to their glaucoma treatment might mask an underlying ocular tear film instability or OSD, potentially caused or increased by preserved glaucoma topical medications, since 91.5% of our study patients were using preserved eye drops, known for their local side effects and despite the availability of PF treatment options.[7] Several studies have reported on clinical tolerability issues that may have been caused by the use of preserved treatments; in addition, many side effects decreased when the preserved eye drops were discontinued.[13–18] A first real-life study showed that patients using preserved latanoprost eye drops improved their reported tolerability when they

Table 2 Treatment Change and Reason for Change

Duration of Previous Treatment (Years)	**N**	**702**
	Mean (SD)	7.83 (7.08)
	Median	6.00
	(Q1;Q3)	(3.00;12.00)
	Min;Max	0.0;46.0
	Missing	91
Number for treatment change	**N**	785
	Mean (SD)	1.56 (1.98)
	Median	1.00
	(Q1;Q3)	(0.00;2.00)
	Min;Max	0.0;15.0
	Missing	8
At least one reason for treatment change reported	n (%)	530 (66.8%)
Insufficient efficacy	n (%)	419 (52.8%)
Local intolerance	n (%)	161 (20.3%)
Systemic intolerance	n (%)	34 (4.3%)
Patient's request	n (%)	26 (3.3%)
Insufficient compliance	n (%)	18 (2.3%)
Other	n (%)	31 (3.9%)

switched to PF latanoprost. PF latanoprost was as efficacious as preserved eye drops, but better tolerated over a sustained period.[19,20] To date, almost all generic glaucoma treatments are more cost-effective than branded products. However, a majority of them is also preserved. However, they may lead to an increased use of lubricants, thus increasing initial costs for the use of preserved treatments. Thus, research is warranted to support the association between the use of PF treatments, costs and patient satisfaction. Furthermore, an additional limitation in the present study is that the patients were asked about any dissatisfaction with their treatments by their own ophthalmologists, which may have introduced a bias, since many patients were likely to belittle their symptoms.

Based on these results, we believe that it is important to question patients about any tolerance issues associated with their topical glaucoma treatment. Even if patients report to be highly satisfied, they may still have signs and symptoms of local intolerance to their therapy, possibly requiring a treatment change.

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