Real-World Study on Patient Satisfaction and Tolerability After Switching to Preservative-Free Latanoprost

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Purpose: Patient satisfaction is important in the treatment of glaucoma. Suboptimal compliance and impaired long-term outcome are a likely result of poor tolerability. The present multicentre, international, transverse, epidemiological survey was conducted to assess the satisfaction of patients who had received preservative-free latanoprost (PFL) for at least 3 months.

Patients and Methods: A total of 1872 patients from 6 European countries, treated with PFL for at least 3 months, were included in this survey. Prior to PFL treatment, patients were to be treatment naïve or currently treated for their glaucoma. During a single routine consultation, patients completed a questionnaire concerning global satisfaction and satisfaction based on tolerability.

Results: In total, 76.2% had been previously treated; 69.4% had received preserved and 6.8% preservative-free (PF) topical treatment. After 3 months of PFL treatment, a large majority of patients (95.3%) were satisfied or very satisfied with their PFL treatment and were, overall, significantly (p<0.0001) more satisfied with PFL than with their previous treatment; 4.2% were either unsatisfied or very unsatisfied. Overall, 97.3% of originally treatment-naïve patients were satisfied (50.1%) or very satisfied (47.2%) with their PFL. Ocular surface disease was diagnosed in 9.2% of patients (n=173) and was mainly mild (76.9%). Patient satisfaction with PFL was very high.

Conclusion: PFL may be considered a valuable first-choice treatment in glaucoma patients.

Keywords: glaucoma, prostaglandin, preservative-free latanoprost, patient satisfaction, tolerability, tear substitutes, intra-ocular pressure, ocular surface disease, conjunctival hyperaemia

Introduction
Glaucoma is a chronic disorder that requires long-term treatment. In common with other insidious diseases such as hypertension or type-2 diabetes, obtaining patient compliance and long-term adherence with treatment is a key factor in achieving a good clinical outcome.

Whilst efficacy is a rewarding goal for both the patient and physician, many factors can impact the patient’s compliance and treatment regime. Among these factors, which include convenience, comfort and ease of use, the tolerability of the medication is a main issue.1 According to the European Glaucoma Society “A patient who complains about side effects is usually not adherent to therapy”.2 The basic problem with glaucoma patients is that in most cases they do not perceive
visual disturbances and, therefore, do not feel impaired in their daily life. However, glaucoma therapy leads to far-reaching changes on the ocular surface, which not only leads to inflammatory changes on the cellular level, but also subjectively cause discomfort for the patients, limiting their quality of life.3–7 Ocular surface toxicity is frequently associated with not only the active ingredient in the eye drops, but also with the preservative contained in the formulation, which prevents bacterial growth.8

Topically applied latanoprost has become the first line treatment for glaucoma and ocular hypertension.9 Not only is it effective and well tolerated, but patients adhere to their treatment significantly more easily with latanoprost than with bimatoprost, travoprost or timolol.10–13 The advent of a patented topical latanoprost formulation without preservative offered a higher tolerability of prostaglandin glaucoma medication, with relatively fewer symptoms of ocular surface disease that could compromise adherence to treatment.14–19

Given the importance of long-term adherence to treatment in glaucoma and the impact of tolerability upon it, surprisingly little attention has been paid to the patient’s experience of topical preservative-free (PF) glaucoma medications. The present study was conceived to determine the degree of satisfaction among treatment-naïve patients or those who had recently switched to PF latanoprost in single-use dose units (PFL, Monoprost®, Laboratoires Théa, France)

Methods
The study was conducted between 2013 and 2015, according to the principles of Good Epidemiological Practices.20 Approvals were obtained from local or National Ethics Committees in Berlin (Charité’s Ethics committee, Berlin, Germany), Bern (Inselspital Bern, Switzerland), Leuven (Université catholique Leuven, Belgium) and from the National Data Protection Committee of Spain (CNPD) Madrid, Spain,) according to the regulations at the investigational sites. According to local regulations, no ethics committee approvals were obtained for the Netherlands and Portugal. All patients provided written informed consent before participating in the study.

Eligible adult subjects had to have a documented diagnosis of glaucoma or ocular hypertension and had been treated with PFL for at least 3 months at the time of the study visit or could have been treatment-naïve.

The study was a multicentre, transverse, epidemiological survey, conducted during a single consultation with a routine clinical examination. It was performed in 337 private ophthalmological practices. Ophthalmologists were chosen from national databases on the basis of feasibility as well as geographical and national balance.

Ophthalmologists were asked to consecutively recruit 10 patients (5 in Switzerland) who had received PFL for glaucoma or ocular hypertension for at least 3 months at the time of the study visit.

Gender, age, ophthalmological and other medical history, date of glaucoma diagnosis or ocular hypertension, type and stage of glaucoma based on visual field damage were recorded, along with the patient’s intraocular pressure (IOP). The investigator also recorded the history of the patients’ previous glaucoma therapy (if applicable) and the reason for switching to PF latanoprost. Intraocular pressure, presence of ocular surface disease (OSD) and Tear-film Break-Up-Time (TBUT, classified into three groups (>10 sec, 5 to 10 sec and <5 sec) were assessed.

For patients who used tear substitutes, the investigator documented whether such use had increased, decreased or remained unchanged after the switch to PFL and whether the patient was using eye drops containing preservatives or not. Moreover, the ophthalmologists assessed ocular signs such as redness, lid swelling, lid scale or crusts, conjunctival hyperaemia, chemosis, positive corneal and conjunctival fluorescein staining on a 4-point ordinal scale from 0 (absent) to 3 (severe). In addition, the investigators were asked to answer the question: “Regarding tolerability, is the patient satisfied with his/her preservative-free latanoprost treatment?” (Very satisfied, satisfied, unsatisfied, very unsatisfied).

Figure 1 shows the questionnaire used to conduct the study. The patient’s subjective experience of tolerability to PFL was defined as the primary variable. Patients reported their subjective experience of the tolerability of their previous glaucoma treatment and of their current PFL on a Visual Analogue Scale (VAS, from 0 mm [very bad tolerance] to 100 mm [very good tolerance]). Moreover, they reported their opinion concerning the tolerability of PFL compared to their previous treatment (much better tolerated, better tolerated, identically tolerated, less well tolerated or much less well tolerated) and their experience of the ease of use of current PF latanoprost compared to their previous treatment (much easier to use/easier to use/same/less easy to use/much less easy to use).

Continuous variables were described in terms of numbers, mean, standard deviation (SD), median with minimum and maximum, as appropriate. Categorical variables
were given as absolute frequency and percentage per category. Confidence intervals at 95% were given where applicable. A logistic regression analysis was used to identify parameters associated with patients’ satisfaction with their current PFL treatment. Odds ratios and p-values were determined, as appropriate. An ad-hoc analysis was performed on treatment-naïve patients who had received no previous treatment prior to their current PFL.

Results

Patient Disposition, Demographics and Disease Characteristics

A total of 1872 patients were recruited (Spain, 1303; Germany, 213; Portugal, 168; Belgium, 104; Switzerland, 59; Netherlands, 25). Age was 66.8±12.1 years; mainly women participated (60.9%). Patients had mostly early glaucoma (41.5%) or ocular hypertension (29.9%); (Table 1).

In total, 76.2% had been treated for their glaucoma prior to their current PFL use; 69.4% had received a preservative-containing treatment and 6.8% had received PF eye drops.

On average, patients who were previously treated switched treatment 2.4 ± 1.86 times; although some had experienced up to 20 treatment switches. The most common reason for switching to PFL was local intolerance (61.8%), followed by insufficient efficacy (49.1%). Insufficient compliance, systemic intolerance, patient request and other reasons were cited by fewer than 10%.

The mean exposure to PFL was 149.5 ± 83.9 days; mean IOP was 18.4 ± 4.87 mmHg (n=3744 eyes).

Patient Satisfaction

Overall, 95.3% of the patients were satisfied (55.2%) or very satisfied (40.1%) with PFL regarding tolerability. Only 3.5% were unsatisfied and 0.7% very unsatisfied; data were missing for 0.5%. The proportion of patients satisfied with PFL was similar among patients who had previously received preserved medication (95%) and among those who were treatment-naïve (97%).

Figure 1 Questionnaire used during the study.
Table 1 Demographic and Baseline Disease Characteristics

|                        | Values            |
|------------------------|-------------------|
| **Age**                |                   |
| N                      | 1872              |
| Mean age ± SD          | 66.8 ± 12.11      |
| Range                  | [18–99]           |
| **Sex**                |                   |
| N                      | 1872              |
| Female                 | 60.9%             |
| Male                   | 38.6%             |
| Missing                | 0.5%              |
| **Intraocular pressure (mmHg)** | 17.6 ± 4.30 |
| **Glaucoma type**      |                   |
| N                      | 1872              |
| Primary                | 85.7%             |
| Secondary              | 12.1%             |
| Missing data           | 2.2%              |
| **Glaucoma stage**     |                   |
| N                      | 3744 eyes         |
| Ocular hypertension    | 29.9%             |
| Early glaucoma         | 41.5%             |
| Moderate glaucoma      | 16.7%             |
| Severe glaucoma        | 8.3%              |

Patients were significantly (p<0.0001) more satisfied with the tolerability to PFL (VAS score 83.5 ± 16.5), than with that of their previous treatment (VAS score 57.7 ± 27.2). Among patients who had previously received a preservative-containing topical glaucoma therapy, tolerability scores on the VAS increased from 56.6 ± 27.2 to 82.6 ± 16.8, corresponding to an improvement of 45.9%. For treatment-naive patients, the mean tolerance to PFL, evaluated with VAS, was even higher (86.7 ± 13.9); refer to Figure 2 for details. According to the different types of previous preserved treatments, improvement of tolerability differed.

After having switched to PFL from the most current treatments, the individual improvement of VAS score was 82% from timolol 0.3%, 70% from timolol 0.1%, 63% from latanoprost, 42% from preserved latanoprost, 35% from timolol and 38% from beta-blockers.

Tolerability Compared to Previous Treatment

The proportion of patients who provided a positive assessment of tolerance to PFL was 75.2%, with 58.7% of patients in the preserved and preservative-free subgroups. The proportion of patients who reported tolerance to PFL to be better, much better or the same as their previous treatment was therefore 95.8% for the preserved sub-group and 93.6% for the preservative-free sub-group. A lower proportion of patients in the preserved and preservative-free sub-groups considered tolerance to PFL to be less (2.7% and 4.8%, respectively) and much less (0.5% and 1.6%, respectively) than their previous treatments.

Ease of Use

In total, 48.8% of patients rated PFL to be as easy to use as their previous treatment in drop bottles, 29.4% rated it easier and 11.3% much easier to use. Only 9.3% of patients considered it to be less easy to use; for 1.2%, data were missing.

Ocular Surface Disease

OSD was diagnosed in 9.2% of patients (n=173) and was mainly mild (76.9%). Lid redness was the most
common ocular sign among patients with OSD. Lid redness, lid swelling, lid scale or crusts and chemosis showed no statistically significant difference between patients with preserved therapy and patients with PFL (Figure 3).

TBUT, Conjunctival Hyperaemia and Fluorescein Staining
TBUT was performed for 1649 eyes. It was inferior to 5 seconds for 10.8% and inferior to 10 seconds for 52.3% of the eyes.

Even though the fluorescein staining of the cornea and conjunctiva as well as the conjunctival hyperaemia showed no statistical difference between the individual therapy groups, the ocular status was slightly better in treatment naïve patients compared to that of patients who had previously been treated (Figures 4 and 5).

Use of Tear Substitutes
Overall, 45.4% of patients used tear substitutes concomitantly. This use decreased for 24.1% of these patients after they had switched to PFL.

Among patients who had previously received a preserved therapy, 28.1% reported reduced tear substitute use following the switch to PFL. A total of 30% of treatment-naïve patients used tear substitutes concomitantly with PFL.

Association of Study Parameters with Patient Satisfaction
Patient satisfaction with PFL was significantly associated with improved tolerance after use (p<0.0001), tolerability regarding the current medication (p<0.0001), ease-of-use (p<0.0001), reduction of tear substitute use after having switched to PFL (p<0.0001), absence of ocular symptoms (p<0.0004), absence of OSD (p<0.0001), use of prior treatment (p<0.05) and use of tear substitutes (p<0.02).

Discussion
Glaucoma treatment is life-long and, as with all long-term prophylactic treatments, compliance is a major issue. Preservatives in topical glaucoma medication have well-described toxic effects which trigger OSD and impact treatment compliance. A study showed that OSD are common among glaucoma patients receiving topical therapy and that it is both more common and more severe

Figure 3 Ocular signs under previous treatment, preservative-free latanoprost treatment and in naïve patients.
Abbreviations: P, previous treatment; PFL, preservative-free latanoprost; naïve, previously untreated patients.
in older patients and in those receiving multiple treatments. Moreover, the severity of OSD has been associated with low effective control of IOP.24

The majority of patients who entered the present study had switched several times from preserved monotherapy. However, the relatively high number of included treatment-naive patients allowed for an ad-hoc subgroup analysis.

Surprisingly, 6.8% of patients who switched to PFL, previously used preservative-free drops. This change may be due to tolerability issues as reported by Duru et al for preservative-free brimonidine tartrate.25 However, study results are based on a very small sample size and a comparative study may help to shade some light on the observed phenomenon.

Regarding tolerability, patients were more satisfied with PFL than with their previous preserved treatment (45.9% improvement on average on the VAS); 75.2% of patients considered the tolerability of PFL as better or much better than their previous preserved treatment, although it was changed from drop bottles to PFL.

Overall, 42% assessed the PFL as easier or much easier to use than their previous treatment. Furthermore, the use of PFL led to a lower percentage of patients using tear substitutes in the subgroup of treatment-naive patients, and a decreased use in a quarter of patients after switching from a previous treatment. Artificial tears are currently used to treat dry eye, known to be caused by preservatives...
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remained
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the
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tives
from
being
multifactorial,
the
analysis
was
not
performed
with
multiple
comparison
methods
or
used
for
adjusting
the
overall
α-level.
The
poor
tolerability
of
glaucoma
medication
may
lead
to
poor
treatment
compliance
and,
therefore,
to
treatment
failure.
Patients’
evaluation
of
their
tolerance
to
glaucoma
treatment
is
key
to
assessing
treatment
efficacy.
Moreover,
the
usability
of
the
dropper
device
is
worthy
of
consideration;
a
study
suggests
that
the
force
required
to
expel
a
drop
from
some
devices
is
beyond
the
physical
capability
of
many
patients.26

The
study
shows
that
preservative-free
latanoprost
may
be
a
valuable
choice
of
therapy
when
switching
patients
from
preserved
treatment
due
to
tolerability
issues,
and
may
be
considered
as
first
choice
in
newly
diagnosed

glaucoma
patients.29

In
conclusion,
after
at
least
3
months
of
treatment
with
PF
latanoprost,
patient
satisfaction
was
very
high
and
potentially
led
to
a
reduced
use
of
tear
substitutes.

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such
as
benzalkonium
chloride.26
Eliminating
preservatives
in
glaucoma
treatments
may,
therefore,
reduce
the
use
of
artificial
tears.

Not
surprisingly,
the
most
common
reason
for
switching
to
PFL
was
local
intolerance,
a
well-known
issue
in
the
context
of
the
local
toxicity
of
preserved
treatments
previously
used
by
a
large
majority
of
the
included
patients.
The
second
most
common
reason
was
insufficient
efficacy,
which
could
be
potentially
explained
by
poor
treatment
adherence,
due
to
local
tolerability
issues.

More
than
97%
of
treatment-naïve
patients
were
satisfied
with
PFL.
OSD
was
reported
in
less
than
7%
of
patients
and,
when
it
occurred,
severity
was
generally
mild.
 Conjunctival
hyperaemia
is
a
recognized
adverse
event
of
topical
prostaglandin
analogues,
although
it
appears
to
be
a
less
frequent
problem
with
latanoprost
than
with
other
prostaglandin
analogues,
and
its
incidence
remained
relatively
high
after
the
switch
(58.7%).27,28
The
incidence
of
conjunctival
hyperaemia
was
relatively
low
among
patients
in
this
study
and
was
rarely
severe.

Despite
despite
these
encouraging
results,
the
study
has
several
limitations
and
bias:1.
This
was
not
a
comparative,
randomised
study
making
a
direct
comparison
between
preserved
drops
and
PFL
impossible.2.
The
low
number
of
patients
in
the
subgroups
previously

treated
by
PF

glaucoma
treatment
(126
patients),
representing
only
6.8%
of
the
overall
study
population
compared
to
other
sub-groups
requires
further
investigations
in
order
to
support
the
benefits
of
PFL
in
glaucoma
for
all
different
patient
profiles.
Additional
randomised
studies
comparing
the
prevalence
in
the
preserved
and
PF

groups
or
switching
treatments
are
needed,
in
order
to
provide
unequivocal
evidence
of
an
improvement
of
signs/symptoms
and
the
long-term
benefit
of
PF
treatments.3.
Investigators
asked
their
patients
to
estimate
their
treatment
satisfaction
without
asking
for
the
reason
for
dissatisfaction.
This
may
cause
a
bias,
which
may
potentially
lead
to
an
overestimation
of
patient
satisfaction,
as
patients
might
not
have
wanted
to
contradict
their
ophthalmologist
and,
thereby,
tended
to

minimize
potential
symptoms,
which
limits
the
understanding
of
the
reasons
for
dissatisfaction.4.
A
logistic
regression
was
used
to
determine
whether
patient
satisfaction
was
related
to
other
variables.
Each
variable
was
analysed
in
a
separate
logistic
regression
model
as
a
predictor
for
being
satisfied
with
PFL.
With
satisfaction
potentially
being
multifactorial,
the
analysis
was
not
performed
with
multiple
comparison
methods
or
used
for
adjusting
the
overall
α-level.
The
poor
tolerability
of
glaucoma
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