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ORIGINAL RESEARCH

Preservative-Free Tafluprost 0.0015% in the Treatment of Patients with Glaucoma and Ocular Hypertension

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ABSTRACT

Introduction: The objective of this study was to evaluate efficacy, local tolerability, and safety of this first-in-class preservative-free prostaglandin preparation in patients with ocular hypertension and glaucoma. ***Methods:*** Patients with glaucoma or ocular hypertension who required a change of medication or were naïve to treatment were included in this noninterventional and observational study. Noninterventional means that no influence was made upon the decision of the physicians to include specific patients and upon the treatment algorithm used. German law for observational studies does not allow any influence on the choice of drugs used, patient selection, masking, and comparator treatment regimens. The main aim of this observational study was to collect "real-life data" on the efficacy and safety of a new medical treatment after approval in a large patient population. Participating ophthalmologists were asked to provide anonymous patient data collected during regular visits by filling a simple data entry form. Intraocular pressure (IOP) readings were recorded at baseline (previous therapy or untreated) and 6-12 weeks after changing medical treatment to or initiating treatment with preservative-free tafluprost once daily. Changes in the IOP were evaluated over the study period for all patients as well as for specific pretreatment subgroups. Local comfort was determined using a five-point scale (very good, good, satisfactory, less satisfactory, not acceptable) before and after the change of medical treatment. All adverse events were recorded. ***Results:*** Data from 2123 patients with glaucoma or ocular hypertension were considered for the final evaluation. Medication was changed in 41.1% of patients due to tolerability issues and in 25.6% of patients due to insufficient efficacy with prior medication. In all patients preservative-free tafluprost 0.0015% lowered

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IOP from 19.5±4.4 mmHg (baseline) to 16.4±2.9 mmHg after 6-12 weeks. Preservative-free tafluprost also significantly lowered the IOP in all monotherapy subgroups: treatment-naïve patients (*n*=440): 22.6±3.9 mmHg (baseline) to 16.7±2.7 mmHg (week 6-12); beta blockers (*n*=307): 20.3±3.5 mmHg (baseline) to 16.7±2.6 mmHg (week 6-12); carbonic anhydrase inhibitors (*n*=158): 19.0±3.6 mmHg (baseline) to 16.0±2.6 mmHg (week 6-12); prostaglandin analogs (PGAs; *n*=447): 16.8±2.9 mmHg (baseline) to 15.8±2.6 mmHg (week 6-12). Local comfort was rated as "very good" or "good" by 85.6% of patients at the final visit ($P<0.001$). Only few adverse events occurred during the treatment period: 18 patients (0.8%) discontinued medical treatment with preservative-free tafluprost due to local intolerance; six patients (0.3%) due to efficacy issues; four patients complained about systemic side effects (0.2%); and two patients preferred to use a multidose treatment regimen (0.2%). ***Conclusion:*** Although this study was limited by its observational design the results demonstrate that preservative-free tafluprost 0.0015% was effective, generally well tolerated, and safe in a broad and heterogeneous patient population.

Keywords: glaucoma; ocular hypertension; ocular surface disease; preservatives; prostaglandin analogs; tafluprost

INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide: an estimated 60.5 million people will have glaucoma by 2010, increasing to 79.6 million by 2020.[1] The disease is characterized by a progressive loss of retinal ganglion cells leading to optic nerve atrophy and visual field defects. The etiology of glaucoma is probably multifactorial, however, increased intraocular pressure (IOP) is considered to be the most important risk factor and, thus far, is the only risk factor that can be modified.[2] Major outcome studies have shown that lowering IOP is beneficial for patients with primary open-angle glaucoma, normal-tension glaucoma, and ocular hypertension.[2-6] Worldwide, prostaglandins have become the major therapeutic class for medical treatment of glaucoma because of their excellent efficacy and favorable safety profile.[7] Tafluprost is a novel prostaglandin that has been approved for ophthalmic use in a number of markets worldwide. Tafluprost is highly selective for the prostaglandin FP-receptor.[8] The drug is the first and only prostaglandin that is available in a preservative-free formulation for the treatment of patients with glaucoma and ocular hypertension. In controlled clinical studies the drug lowered IOP effectively and was generally well tolerated.[9-11]

Numerous experimental and clinical studies clearly demonstrate that the long-term use of preserved topical drugs may induce side effects at the ocular surface. The most frequently used preservative, benzalkonium chloride (BAC), has consistently been shown to induce toxic effects in laboratory, experimental, and clinical studies. BAC is proapoptotic, proinflammatory and causes tear film instability and loss of goblet cells.[12-15] These changes cause irritation, ocular discomfort, and subjective visual complaints. Furthermore, more severe side effects, such as chronic inflammation or a progressive development of fibrosis, may increase the risk of failure after glaucoma filtering surgery.[16,17] Therefore, preservative-free medications may be beneficial for many glaucoma patients.

The purpose of the present study was to evaluate the efficacy, local tolerability, and safety of preservative-free tafluprost 0.0015%

in a naturalistic setting using a prospective, observational design.

MATERIALS AND METHODS

Study Design

This study was a prospective, multicenter, noninterventional, observational, open-label study conducted in Germany between July 2009 and February 2010. Patients with glaucoma or ocular hypertension who the investigators determined to require a change of medication, an add-on therapy, or who were treatment naïve were followed for 6-12 weeks after they were switched to once-daily therapy with preservative-free tafluprost 0.0015% (Taflotan®, Taflotan® sine, Tapros®, Santen Pharmaceutical Co., Ltd., Osaka, Japan, Saflutan® Merck & Co. Inc., USA) or after initiation of medical treatment (treatment-naïve patients). Six hundred and sixty-one participating ophthalmologists provided anonymous patient data using a standardized data-collection instrument.

The study treatment was based only on the decision of the physician and their reasons for prescribing the new medication were collected. German law does not require informed consent for this type of noninterventional observational studies. At baseline demographics, diagnoses and information about prior treatments were collected and IOP readings and tolerability measures were recorded. IOP measurements were made for each eye at baseline (on prior treatment or without treatment in treatment-naïve patients), and at final visit between 6 to 12 weeks after switching to or initiation of medical therapy with preservative-free tafluprost 0.0015% using Goldman applanation tonometry. Tolerability was determined using a five-point scale (very good, good, satisfactory, less satisfactory, not acceptable). For the evaluation of local tolerability the investigator asked the patients to rate the local comfort using this five-point scale. Patients' and physicians' satisfaction with preservative-free tafluprost were recorded at the final visit using a four-point scale (very satisfied, satisfied, less satisfied, not satisfied at all). For the evaluation of the overall satisfaction the investigator asked the patients to rate their degree of satisfaction on the four-point scale.

In total, datasets from 3350 patients were collected during the study period. Paired t-tests were conducted to compare IOP values at baseline with IOP values after treatment with tafluprost 0.0015%. Bowker's test of symmetry was used for statistical comparison of local tolerability at final visit versus baseline. All adverse events were recorded by the physician by asking the patient whether any unexpected events occurred after changing or initiation of medication.

RESULTS

Patient and Baseline Characteristics

In total, 1227 patients were excluded from the evaluation. These included patients for whom the time-period between the two visits was <4 or >12 weeks (n=808), patients with retrospectively collected data (n=349), patients with datasets with incomplete IOP readings (n=41), patients already treated at baseline with preservative-free tafluprost (n=17), and patients with different medical treatment for the right and left eye and with data that were not plausible (n=12). After the exclusion of these patients, 2123 patients of the initial dataset collected were eligible for the final evaluation. As shown in Table 1, the majority of the patients was female and suffered from primary open angle glaucoma. Poor local tolerance was the most common reported reason

for changing medication to preservative-free tafluprost (41.1%), followed by a lack of efficacy of the prior treatments (25.6%; Figure 1).

Table 1. Characteristics of the patient population (*n*=2123) included in the observational study with preservative-free tafluprost 0.0015%.

Patient characteristics		
Mean age (range)	65.5 (16–97)	
SD	12.1	
n.d.	37 (1.7%)	
Gender	*n*	%
Male	808	38.1
Female	1300	61.2
n.d.	15	0.7
Diagnoses		
Ocular hypertension	190	8.9
Primary open angle glaucoma	1517	71.5
Normal tension glaucoma	194	9.1
Pseudo exfoliation glaucoma	112	5.3
Other glaucomas	46	2.2
Pigment dispersion glaucoma	17	0.8
Narrow angle glaucoma	14	0.7
Multiple glaucomas	23	1.1
n.d.	10	0.5

n.d.=no data.

In patients reporting a local intolerance at baseline, irritation was the most frequent symptom (36.6%) followed by hyperemia (27.3%), allergy (17.3%), and itching (16.8%; Figure 2).

Prior Glaucoma Medication

Prior to change of medication, patients used a variety of other glaucoma products (*n*=1673; 78.8%) or were naïve to treatment (*n*=450; 21.2%). The majority of patients were treated with a monotherapy (*n*=1133; 53.4%), most frequently with a prostaglandin analog (PGA; *n*=453; 21.3%) or a beta blocker (*n*=372; 17.5%). Five-hundred and forty patients (25.4%) were treated with fixed- or nonfixed combinations (Table 2).

Effect on IOP

In the overall patient population, IOP was significantly reduced from 19.5±4.4 mmHg

Figure 1. Reasons for changing therapy to preservative-free tafluprost 0.0015%, adding preservative-free tafluprost 0.0015% to an existing medical treatment regimen, or initiating therapy with preservative-free tafluprost 0.0015%. *Multiple entries.

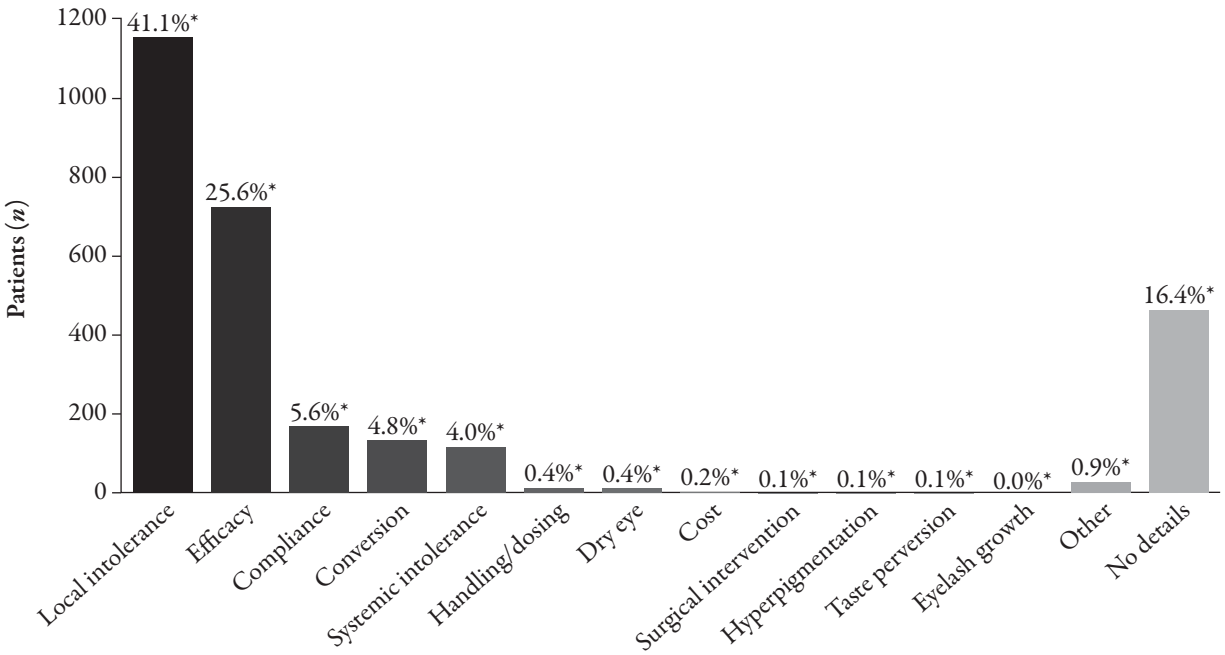


Figure 2. Local intolerances of prior medication at baseline stratified by type. Percentages refer to all patients (*n*=2123). Multiple entries were possible. *Multiple entries.

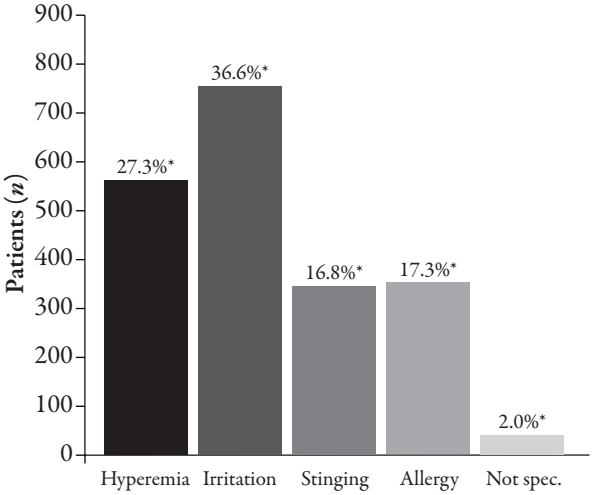


Table 2. Prior therapy used before initiating, switching, or adding preservative-free tafluprost 0.0015%.

Prior treatment (type)	*n*	%
Treatment-naïve patients	450	21.2
Monotherapy	1133	53.4
Beta blockers	372	17.5
Prostaglandins	453	21.3
Alpha-2-adrenergic receptor agonists	111	5.2
CAIs	187	8.8
Miotics	10	0.5
Combination therapy	540	25.4
Fixed combinations	307	14.5
Nonfixed combinations (2 ingredients)	104	4.9
Nonfixed combinations (≥3 ingredients)	129	6.1
Total	2123	100.0

CAI=carbonic anhydrase inhibitor.

at baseline to 16.4±2.9 mmHg (*P*<0.001) with preservative-free tafluprost therapy at the final visit (Figure 3). Among all patients, (*n*=2123) 79.4% of eyes achieved an IOP level of ≤18 mmHg, 50.9% of ≤16 mmHg, and 24.4% of ≤14 mmHg (Figure 4). Overall the IOP was lower at the final visit compared with the baseline visit in 3224 eyes (76.6%), equal in 467 eyes (11.1%), and higher in 519 eyes (12.3%; Figure 5). The mean IOP was reduced in treatment-naïve patients and in all patient subgroups with prior monotherapy that were switched to monotherapy with preservative-free tafluprost. At the final visit, 6-12 weeks after initiating medical therapy with preservative-free tafluprost or after changing medication to a monotherapy with preservative-free tafluprost, the mean IOP values were significantly lower than at baseline (*P*<0.001). Preservative-free tafluprost also lowered IOP significantly in all monotherapy-subgroups: treatment-naïve patients (*n*=440): 22.6±3.9 mmHg (baseline) to 16.7±2.7 mmHg (week 6-12); beta blockers (*n*=307): 20.3±3.5 mmHg (baseline) to 16.7±2.6 mmHg (week 6-12); carbonic anhydrase inhibitors (CAIs) (*n*=158): 19.0±3.6 mmHg (baseline) to 16.0±2.6 mmHg (week 6-12); PGAs (*n*=447): 16.8±2.9 mmHg (baseline) to 15.8±2.6 mmHg (week 6-12). In Figure 6, the mean IOP ± SD is shown for treatment-naïve patients and the subgroups of patients who had been previously treated with beta-blocker monotherapy, alpha-2-adrenergic receptor agonist monotherapy, CAI monotherapy, and PGA monotherapy and were switched to a monotherapy with preservative-free tafluprost.

In treatment-naïve patients, the mean IOP at the final visit was lowered by –5.9 mmHg, in patients with prior beta-blocker monotherapy by –3.6 mmHg, in patients with prior alpha-2-adrenergic receptor monotherapy by –3.1 mmHg, in patients with prior CAI monotherapy by –3.0 mmHg, and in patients with a PGA monotherapy by –1.0 mmHg. Preservative-free tafluprost was also used adjunctively to an existing monotherapy treatment regimen. In all subgroups of patients

Figure 3. Mean intraocular pressure (IOP) ± SD for all patients. *P<0.001 vs. corresponding baseline, paired t-test (last observation carry forward [LOCF] analysis).

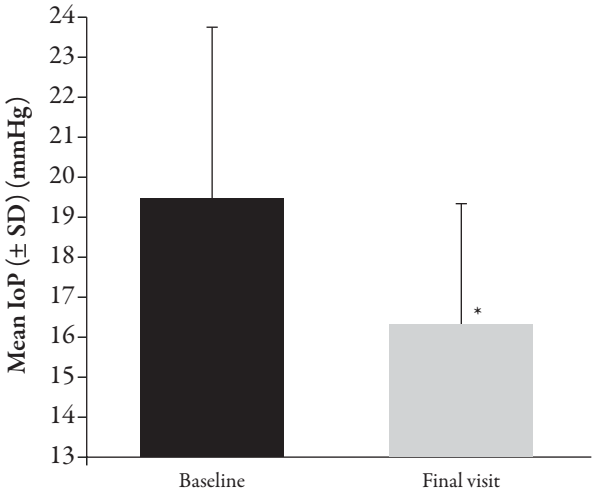
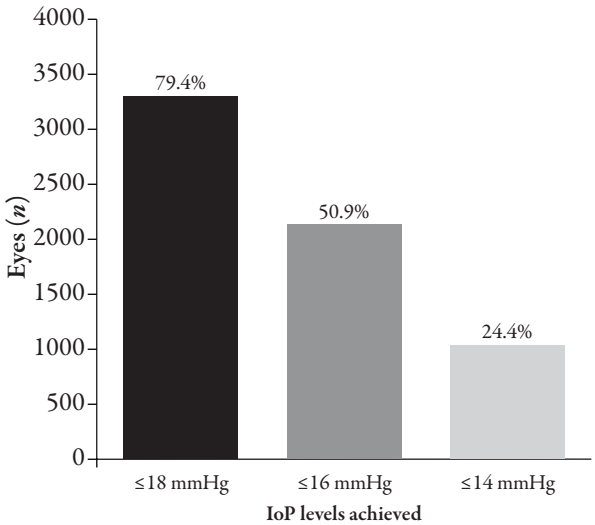
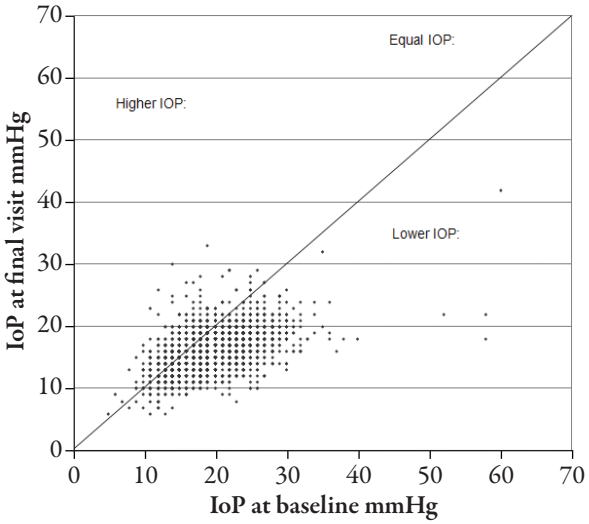


Figure 4. Intraocular pressure (IOP) levels at final visit 6-12 weeks after changing or initiation of medical therapy with tafluprost 0.0015%.



when preservative-free tafluprost was added to an existing monotherapy, the IOP was further reduced at the final visit. When given adjunctively to a prior monotherapy treatment regimen preservative-free tafluprost provided an additional IOP lowering effect: in patients with prior beta-blocker treatment the mean IOP decreased by –4.5 mmHg, in patients with prior CAI monotherapy by –3.8 mmHg, and in patients with prior alpha-2-adrenergic receptor monotherapy by –3.9 mmHg (Figure 7).

Figure 5. Comparison of intraocular pressure (IOP) of individual patients/eyes at baseline vs. final visit.



Local Tolerability and Patient Satisfaction

Tolerability improved in the majority of patients after medication was changed to preservative-free tafluprost. At baseline, tolerability of the prior treatment was rated as "very good" and "good" by only 28.3% of the patients; 38.4% of patients rated the tolerability as "less satisfactory", and 18% as "not acceptable." Tolerability improved after the change of medication to preservative-free tafluprost; a total of 85.7% of patients rated the tolerability as "very good" and "good" (Figure 8). Specifically in patients treated with prior PGA monotherapy improvement of local tolerability was evident: at baseline only 1.3% and 8.3% of patients rated the local tolerability of their prior PGA treatment regimen with "very good" or "good" respectively. After the change of medication in these patient subgroups to preservative-free tafluprost, local tolerability

Figure 6. Mean intraocular pressure (IOP) (± SD) for the different monotherapy subgroups. *P<0.001.

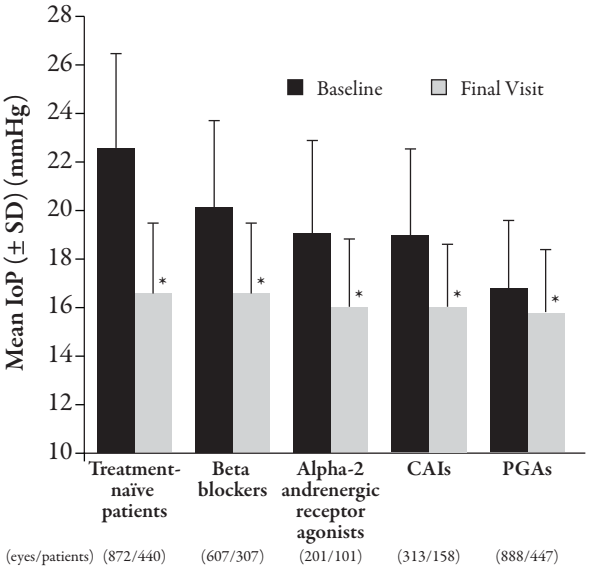


Figure 7. Mean intraocular pressure (IOP) for subgroups of patients when preservative-free tafluprost was given adjunctively to an existing monotherapy treatment regimen.

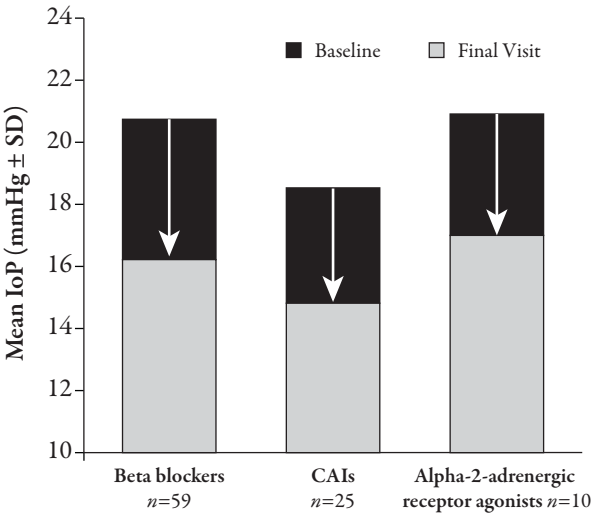


Figure 8. Tolerability rating at baseline (prior medication) and at final visit (preservative-free tafluprost). n=1741 patients with ratings at baseline and at final visit.

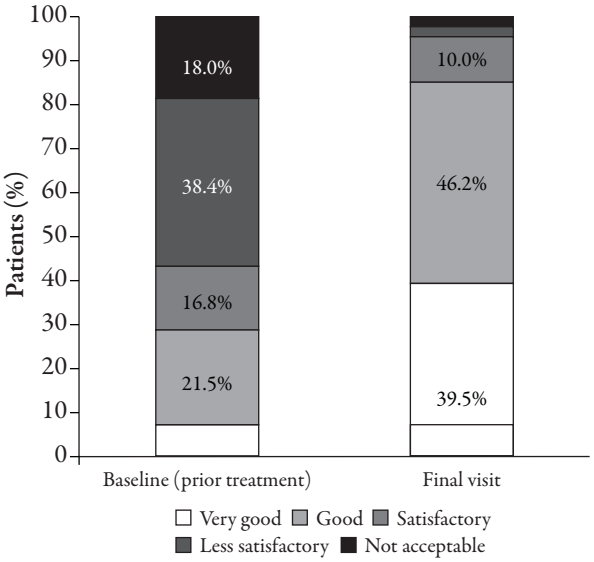
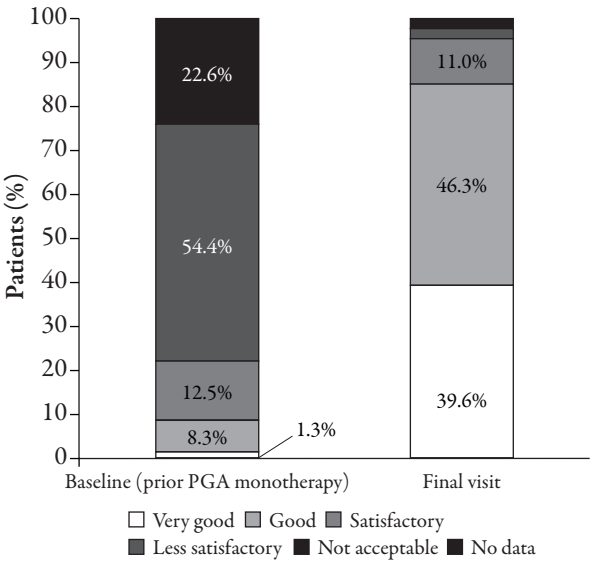


Figure 9. Tolerability rating at baseline (prior PGA monotherapy) and at final visit (preservative-free tafluprost). n=447 patients.

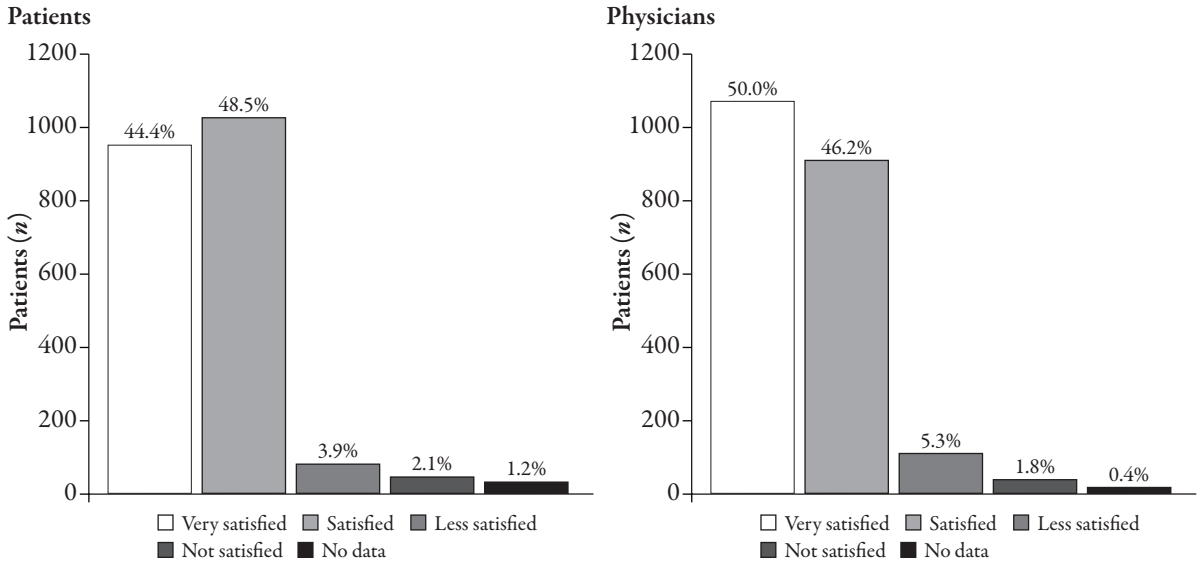


improved: local tolerability was rated as "very good" and "good" by 39.6% and 46.3% of patients, respectively (Figure 9). As shown in Figure 10, at the final visit most patients (92.9%) and physicians (92.6%) were very satisfied or satisfied with using preservative-free tafluprost.

Adverse Events and Discontinuations

Only a few adverse events occurred during the treatment period. Therapy with preservative-free tafluprost was continued after the final visit by 2077 patients (97.8%). Eighteen

Figure 10. Satisfaction of patients and physicians with preservative-free tafluprost at final visit. *n*=2123.



patients (0.8%) discontinued medical treatment with preservative-free tafluprost due to local intolerance, six patients (0.3%) due to efficacy issues, four patients complained about systemic side effects (0.2%), and two patients preferred to use a multidose treatment regimen (0.2%). Details are given in Table 3.

Table 3. Discontinuations until and after the final visit.

Reasons for termination of medical treatment	*n*	%
Allergy	2	0.1
Compliance	1	0.0
Efficacy	6	0.3
Handling	2	0.1
Local and systemic intolerance	1	0.0
Local intolerance	14	0.7
Local intolerance and allergy	1	0.0
Not medication related	1	0.0
Patient preference	6	0.3
Surgery	4	0.2
Systemic intolerance	4	0.2
Unknown	2	0.1
Total terminations	46	2.2
Therapy continued	2077	97.8

DISCUSSION

In the patient population of this noninterventional, open-label, multicenter observational study, medication was changed for two main reasons: first, many patients were switched to preservative-free tafluprost because of tolerability issues with their prior medication. Local intolerance accounted for 41.1% of changes of treatment in all patients. Second, medical treatment was changed because of lack of efficacy of prior medication in 25.6% of all patients. Irritation (36.6%), hyperemia (27.3%), allergy (17.3%), and/or stinging (16.8%) were the most common symptoms at baseline before changing medical therapy. The results demonstrate that preservative-free tafluprost can achieve good IOP control in this difficult patient population. The mean IOP in this patient cohort at baseline was relatively low, 19.5±4.4 mmHg. This may be explained by the relatively high number of patients who were treated either with a PGA monotherapy (*n*=453; 21.3%) or a fixed or nonfixed combination (*n*=540; 25.4%) at

baseline before changing medication. Regardless of the low mean baseline IOP, lower IOP values were achieved 6-12 weeks after changing medication in more than three-quarters of all eyes (*n*=3224 eyes, 76.6%). The IOP remained at the same level in 467 eyes (11.1%), and was higher in 519 eyes (12.3%) of all eyes.

There are several explanations for the higher IOP at the final visit compared with the baseline visit: first, even a relatively small increase of 1 mmHg compared with treated low baseline IOPs is counted as an increase. Second, patients with prior fixed combinations that were switched to a monotherapy with preservative-free tafluprost in order to reduce possible side effects were included in this analysis. Finally, patients whose IOPs were well-controlled by their prior PGA monotherapy who were switched to preservative-free tafluprost due to tolerability issues may also explain this finding. In 79.4% of all eyes IOP values of ≤18 mmHg were achieved at the final visit, IOP values of ≤16 mmHg were achieved in more than half of the eyes (50.9%), and IOP values of ≤14 mmHg were achieved in slightly less than a quarter of all eyes (24.4%). The change of medical treatment in patients treated with a prior monotherapy to preservative-free tafluprost provided a significant additional reduction in the mean IOP. Furthermore, when given adjunctively to an existing monotherapy with beta blockers, CAIs, or alpha-2-adrenergic receptor agonists, preservative-free tafluprost provided an additional decrease in the mean IOP. At the final visit, local tolerability increased compared with baseline. This was especially evident in the patient subgroup using preserved prostaglandins at baseline. Consequently, a high number of patients and physicians rated their satisfaction with preservative-free tafluprost at the final visit as “very satisfactory” or “satisfactory”.

Clinical studies show that a high proportion of glaucoma patients that were treated with preserved glaucoma medications developed symptoms such as burning and stinging, foreign-body sensation, dry eye, and other symptoms consistent with ocular surface irritation.[17-21] As shown in previous studies, the present results confirm that patients with irritation of the ocular surface, subjective symptoms, and clinical signs, such as hyperemia, may benefit from a change of medication to preservative-free tafluprost.[22,23] Many experimental and clinical studies have clearly demonstrated that the long-term use of topical drugs containing preservatives may induce changes in the ocular surface, tear film instability, epithelial apoptosis, conjunctival inflammation, and the loss of goblet cells.[18,24,25] After switching to preservative-free tafluprost, local tolerability improved in most patients, and the overall patient satisfaction with their glaucoma treatment increased. The present study did not reveal any causal relationship between the preservative-free nature of tafluprost and the improvement in tolerability. Beside the preservative-free nature of the drug, the low concentration of tafluprost itself may contribute to the improvement of local tolerability and patient satisfaction seen in this observational study.

The present study had both strengths and limitations. The observational design may better reflect the actual clinical practice compared with controlled clinical trials. Due to its observational nature, the study did not reveal any causal relationships. The observed reduction in IOP after switching might be ascribed to the improvement of subjective symptoms and clinical signs, and thus, a better compliance. However, regression to the mean cannot be ruled out in the present study design as a control group was not used.

It can be assumed that this patient population is representative of patients who are likely to be prescribed a preservative-free glaucoma medication. However, further studies with higher numbers of patients in the different subgroups are necessary to determine what aspects of preservative-free therapy with tafluprost account for the observed treatment effects.

CONCLUSION

Preservative-free tafluprost 0.0015% was effective, well tolerated, and associated with fewer adverse events compared with baseline medications. A change of medical therapy to preservative-free tafluprost may be beneficial, especially for patients with subjective ocular symptoms and patients with sensitive or dry eyes but also for patients who are not responding adequately to other monotherapy treatment regimens. A further reduction in the IOP was achieved in patients who were switched from other monotherapies, including beta-blockers, CAIs, and PGAs to monotherapy with preservative-free tafluprost.

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