

Safety profile of 0.0015% tafluprost eye drops in China: a post-marketing observational study

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Abstract

• **AIM:** To investigate the treatment pattern and safety of tafluprost for glaucoma and ocular hypertension (OH) in clinical practice in China.

• **METHODS:** This post-marketing observational study included patients who received tafluprost to lower intraocular pressure (IOP) within 30d between September 2017 and March 2020 in 20 hospitals in China. Adverse drug reactions (ADRs) during tafluprost treatment and within 30d after the treatment were collected.

• **RESULTS:** A total of 2544 patients were included in this study, of them 58.5% (1488/2544) had primary open angle glaucoma (POAG), 21.9% (556/2544) had OH and 19.7% (500/2544) used tafluprost for other reasons. Of 359 ADRs occurred in 10.1% (258/2544) patients, and no serious adverse event occurred. The most common ADR was conjunctival hyperemia (128 ADRs in 124 patients, 4.9%). Totally 1670 participants (65.6%) combined tafluprost with carbonic anhydrase inhibitors (CAIs; 37.1%, 620/1670), sympathomimetics (33.5%, 559/1670), β -blockers (33.2%, 555/1670), other prostaglandin analogs (PGAs; 15.6%, 260/1670) and other eye drops (15.1%, 253/1670). The highest incidence of conjunctival hyperemia was noted in patients who received tafluprost in combination with other PGAs (23 ADRs in 23 patients, 8.8%, 23/260) and

the lowest was in combination with CAIs (16 ADRs in 16 patients, 2.6%, 16/620). Tafluprost was applied in primary angle-closure glaucoma (41.6%, 208/500), after glaucoma surgery (17.8%, 89/500) and after non-glaucoma surgery (15.8%, 79/500).

● **CONCLUSION:** Tafluprost is safe for POAG and OH, and tolerable when combined with other eye drops and under various clinical circumstances.

● **KEYWORDS:** tafluprost; glaucoma; ocular hypertension; intraocular pressure; adverse drug reactions

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INTRODUCTION

Glaucoma is a leading cause of blindness and decreased vision-related quality of life^[1]. The prevalence of glaucoma in China during 1990-2015 ranged from 2.58% to 2.59%, which account for almost half of patients with glaucoma worldwide^[2]. Elevated intraocular pressure (IOP) is deemed as the most important risk factor for progression of glaucoma and lowering IOP is the only proven treatment^[3].

The Chinese Glaucoma Guidelines and European Glaucoma Society (EGS) Glaucoma Guidelines recommended prostaglandin analogs (PGAs) as the first-line treatment for primary open angle glaucoma (POAG) and ocular hypertension (OH)^[4-5]. Among them, tafluprost is a PGA with higher affinity and selectivity^[6]. The efficacy of tafluprost in lowering IOP has been verified in many countries, even in patients who were insufficiently controlled with latanoprost, while the common safety issues involved eyelid pigmentation, ocular hyperemia, eyelash changes and eyelid hypertrichosis^[7-12].

Post-marketing studies in Japan and Philippines^[8-10] proved that safety profile of tafluprost was manageable in patients with glaucoma and OH in real-world clinical setting, alone or in combination with other eye drops. Phase III randomized controlled trial conducted at five Chinese clinical centers in 2015^[13] stated that efficacy and safety of tafluprost was comparable to latanoprost in patients with POAG and OH with major adverse reactions being conjunctival hyperemia, eye irritation, eye pain and foreign body sensation. Nevertheless, the characteristics of Chinese patients receiving tafluprost has not been well described yet. Furthermore, there is still a paucity of large-sample real-world evidence regarding treatment pattern and the safety of tafluprost in actual clinical practice.

Thus, this multicenter study aimed to investigate the safety and treatment pattern of tafluprost for glaucoma and OH in clinical practice, providing real-world evidence of safety profile of tafluprost in Chinese patients.

SUBJECTS AND METHODS

Ethical Approval The study was approved by the ethics committees of each participating center. The approval number at the leading center was No.2017022-1. The study was conducted in accordance to the Declaration of Helsinki. Informed consent was obtained from all patients or their legal guardians.

Study Design and Participants This study was a post-marketing observational study. A cross-sectional survey was conducted in patients with POAG and OH who received tafluprost at departments of ophthalmology in 20 hospitals in China between September 2017 and March 2020.

The inclusion criteria were patients who were being treated with tafluprost or had been treated with tafluprost within 30d, regardless of age. The exclusion criteria were patients who participated in other trials within 30d.

Calculation of Sample Size According to 95% statistical test efficacy analysis, data of 2996 patients ought to be collected in order to observe the occurrence of adverse drug reactions (ADRs) with incidence of 0.1%. It was planned to recruit 3000 participants to meet the requirements of regulatory agencies.

Data Collection Demographics, diagnosis, medical history, complications, previous medication, combined therapy for IOP-lowering, and other tafluprost treatment details were collected. Adverse events (AEs) occurred during tafluprost treatment and within 30d after the last administration of tafluprost were collected using a safety questionnaire filled out by patients. Patients with AEs were followed for 30d and the treatment and outcomes of AEs assessed by the investigators were recorded.

AEs was defined as any medically harmful and unfavorable signs, symptoms or diseases after the use of tafluprost, including aggravation of the original disease and abnormality of laboratory test values, whether related to tafluprost or not. AEs were classified as mild (completely tolerable without influence on daily life), moderate (leading to discomfort that affected normal activities) and severe (leading to inability in working or daily activities). If correlation with tafluprost cannot be ruled out, it is considered as an ADR. Iris pigmentation, eyelash changes, eyelid pigmentation, and eyelid hypertrichosis were ADRs of special interest.

Serious adverse events (SAEs) was defined as AEs which resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity; or was a congenital anomaly/birth defect.

Statistical Analysis Statistical analysis was conducted using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA). AEs were classified according to the International Conference on Harmonisation International Dictionary of Medical Terms. The incidence of ADRs was defined as patients with at least one ADR during treatment divided by the total number of patients in safety analysis, expressed as numbers and percentages. Subgroup analysis was carried out by patient age, by combination therapy, and by actual clinical application.

RESULTS

Baseline Characteristics of Patients Owing to the Coronavirus Disease 2019 outbreak, a total of 2544 participants were recruited, and 2544 patients were eventually included in the study. There were 1367 (53.7%) males and 1177 (46.3%) females, and the average age was 50.8±19.1y. The majority (98.6%, 2509/2544) were Chinese Han ethnicity. Tafluprost was prescribed as topical treatment of both eyes in 63.1% (1604/2544) of all cases. The reason for using tafluprost was POAG and OH in 58.5% (1488/2544) and 21.9% (556/2544) of the participants respectively, while 19.7% (500/2544) of participants had other reasons. Only 1.6% (40/2544) of the patients used contact lenses. There were 38.9% (989/2544) of the patients who had other concomitant ocular diseases, and 24.3% (618/2544) had other systematic diseases. Over half of the participants (60.2%, 1532/2544) were receiving other medications or treatments. Most patients (82.5%, 2099/2544) did not stop taking other drugs within 30d before using tafluprost. Among all participants, 65.6% (1670/2544) were prescribed with tafluprost in combination with carbonic anhydrase inhibitors (CAIs), sympathomimetics, β-blockers or other PGAs. Detailed baseline characteristics are showed in Table 1.

Adverse Drug Reactions of Tafluprost In this study, a total of 359 ADRs occurred in 258 patients, with an incidence rate of 10.1% (258/2544). Table 2 presents the ocular ADRs with incidence of over 1% and non-ocular ADRs over 0.1%. Of all participants with ADRs, 21.7% (56/258) recovered, 32.9% (85/258) were improving, and 48.1% (124/258) did not show improvement. Of the 58 patients who had 74 ADRs of special interest, 5.2% (3/58) recovered, 24.1% (14/58) were improving, and 72.4% (42/58) did not show improvement. Among the 42 patients who did not show improvement, the 55 ADRs included 21 eyelid pigmentation, 5 iris pigmentation, 25 eyelash changes and 4 eyelid hypertrichosis. In the 258 patients who had ADRs, 85.3% (220/258) continued to use tafluprost, while 2.3% (6/258) suspended tafluprost treatment due to ADRs, and 12.0% (31/258) terminated tafluprost. Among all 124 patients whose ADRs did not improve, 111 patients still continued using tafluprost. The most common ADR was conjunctival hyperemia (128

Parameters	
Age (n=2386)	Patients
<65y	1740 (72.9)
≥65y	646 (27.1)
Sex (n=2544)	
Male	1367 (53.7)
Female	1177 (46.3)
Ethnicity (n=2544)	
Han	2509 (98.6)
Others	35 (1.4)
Pregnancy (n=1177)	
No	1117 (94.9)
Unknown	60 (5.1)
Reason for using tafluprost (n=2544)	
POAG	1488 (58.5)
OH	556 (21.9)
Others	500 (19.7)
Use of contact lenses (n=2544)	
Yes	40 (1.6)
No	2504 (98.4)
Other ocular diseases (n=2544)	
Yes	989 (38.9)
No	1555 (61.1)
Systematic diseases/comorbidities (n=2544)	
Yes	618 (24.3)
No	1926 (75.7)
Other medications or treatment (n=2544)	
Yes	1532 (60.2)
No	1012 (39.8)
Stop using other drugs within 30d before using tafluprost (n=2543)	
Yes	444 (17.5)
No	2099 (82.5)
Tafluprost usage status (n=2544)	
In use	2449 (96.3)
Drug withdrawal did not exceed 30d	95 (3.7)
Treating eyes (n=2544)	
Left eye	472 (18.6)
Right eye	468 (18.4)
Both eyes	1604 (63.1)

POAG: Primary open angle glaucoma; OH: Ocular hypertension.

ADR	Events	Patients (n=2544)
Total ADRs	359	258 (10.1)
Ocular ADRs (>1%)		
Conjunctival hyperemia	128	124 (4.9)
Eyelash change	31	31 (1.2)
Dry eye	31	29 (1.1)
Eyelid pigmentation	28	28 (1.1)
Non-ocular ADRs (>0.1%)		
Hirsutism	6	6 (0.2)
Burning sensation	4	4 (0.2)
Headache	4	4 (0.2)
Dizziness	3	3 (0.1)

ADR: Adverse drug reaction.

events in 124 patients, 4.9%, 124/2544). Conjunctival hyperemia was mainly mild (91.41%, 117/128) and moderate (7.03%, 9/128). There was no severe conjunctival hyperemia reported. Furthermore, 35 (27.34%) among all 128 conjunctival hyperemia recovered, 46 (35.94%) were improving, and 43 (33.59%) did not show improvement. Additionally, 87.5% (112/128) continued to use tafluprost, while 29.69% (38/128) of which conjunctival hyperemia did not improve also continued to use tafluprost.

Safety of Tafluprost in Specific Populations The safety of tafluprost in juveniles was evaluated. A total of 120 participants were 14 years old or younger, with 70 males and 50 females. Among them, 14 juveniles reported 18 non-serious ADRs. Most of the ADRs turned out recovery (27.8%, 5/18) and improvement (22.2%, 4/18), while 22.2% (4/18) were unclear. In a one-year old infant with congenital glaucoma, tafluprost was prescribed together with brimonidine, brinzolamide/timolol, and pilocarpine. Tafluprost was administered for over 5mo and no ADR occurred. The infant was still receiving tafluprost by this report of study.

The safety of tafluprost in elderly patients was also evaluated. A total of 646 participants were 65 years old or older, with 322 males and 324 females. Among them, 7.0% (45/646) reported 65 ADRs, and all of the ADRs were non-serious. The 15.4% (10/65) of the ADRs recovered, 22.2% (15/65) improved, 1.5% (1/65) unknown, while 60.0% (39/65) did not improve.

Combined Therapy of Tafluprost and Other IOP-lowering Eye Drops A total of 65.6% (1670/2544) of participants has been found to use tafluprost as a part of combined therapy. The five most common eye drops combining tafluprost are CAIs (37.1%, 620/1670), sympathomimetics (33.5%, 559/1670), β -blockers (33.2%, 555/1670), other PGAs (15.6%, 260/1670) and other medications for ophthalmic use (46.8%, 782/1670; mainly including artificial tears, fluoroquinolones, corticosteroids and antiinfectives in combination, glucocorticoids, vitamin B, mannitol injection, and mydriatics, etc). The highest incidence of conjunctival hyperemia was noted in patients who received tafluprost in combination with other PGAs (23 ADRs in 23 patients, 8.8%, 23/260) and the lowest was in combination with CAIs (16 ADRs in 16 patients, 2.6%, 16/620). Among the 5 combination regimens, eyelash changes were reported most often in patients prescribed with combination of tafluprost and other PGAs (9 ADRs in 9 patients, 3.5%, 9/260). Detailed ADRs in relation to the different combination therapy is showed in Table 3.

Other Clinical Application In clinical practice, patients were prescribed with tafluprost in the situation other than POAG or OH. Among those 500 patients, 208 (41.6%, 208/500) were primary angle-closure glaucoma (PACG), 89 (17.8%, 89/500) received tafluprost treatment after glaucoma surgery,

Table 3 Adverse drug reactions in relation to the combination therapy of tafluprost and other IOP-lowering eye drops

ADR	Tafluprost monotherapy	Tafluprost+CAI	Tafluprost +sympathomimetics	Tafluprost+ β -blocker	Tafluprost+another PGA	Tafluprost+other medication for ophthalmic use	events/patients (%)
Total ADRs	80/61 (7.0)	62/44 (7.1)	108/77 (13.8)	64/40 (7.2)	52/41 (15.8)	144/93 (11.9)	
Ocular ADRs	73/54 (6.2)	58/40 (6.5)	104/75 (13.4)	60/37 (6.7)	51/41 (15.8)	133/90 (11.5)	
Conjunctival hyperemia	25/25 (2.9)	16/16 (2.6)	52/51 (9.1)	23/21 (3.8)	23/23 (8.8)	48/46 (5.9)	
Dry eye	13/13 (1.5)	6/5 (0.8)	7/5 (0.9)	4/3 (0.5)	3/3 (1.2)	9/8 (1.0)	
Eye pruritus	9/9 (1.0)	4/4 (0.6)	5/5 (0.9)	3/3 (0.5)	2/2 (0.8)	4/4 (0.5)	
Eyelid pigmentation	5/5 (0.6)	5/5 (0.8)	8/8 (1.4)	3/3 (0.5)	7/7 (2.7)	15/15 (1.9)	
Eyelash changes	2/2 (0.2)	4/4 (0.6)	12/12 (2.1)	4/4 (0.7)	9/9 (3.5)	13/13 (1.7)	
Non-ocular ADRs							
Headache	2/2 (0.2)	0	0	0	0	1/1 (0.1)	
Hirsutism	2/2 (0.2)	1/1 (0.2)	1/1 (0.2)	1/1 (0.2)	0	2/2 (0.3)	
Dizziness	1/1 (0.1)	1/1 (0.2)	1/1 (0.2)	1/1 (0.2)	0	0	
Burning sensation	1/1 (0.1)	0	0	0	1/1 (0.4)	2/2 (0.3)	

IOP: Intraocular pressure; ADR: Adverse drug reaction; CAI: Carbonic anhydrase inhibitors; PGA: Prostaglandin analogs.

and 79 (15.8%, 79/500) were intraocular hypertension after non-glaucoma surgery. There was no SAE or new ADR different from when used for POAG and OH under various circumstances of clinical application. Of the 89 patients receiving tafluprost after glaucoma surgery, 20 patients (22.5%, 20/89) reported 29 ADRs, while 19 ADRs occurred in 13 patients (6.3%, 13/208) who were treated with tafluprost due to PACG. No ADR was observed when tafluprost was given to patients after non-glaucoma surgery. The most common ADR related to tafluprost was also conjunctival hyperemia. Detailed ADRs of tafluprost under various situations of clinical application were displayed in Table 4.

DISCUSSION

This study was a multi-center post-marketing observational study of tafluprost focusing on its safety in real-world clinical setting in Chinese population. Tafluprost proved satisfying safety profile with merely 359 ADRs occurred in 258 patients, with an incidence rate of as low as 10.1%. This study also proved acceptable safety of tafluprost in combination with various IOP-lowering eye drops, including CAIs, sympathomimetics, β-blockers, other PGAs and other medications for ophthalmic use. In clinical practice, tafluprost was also well tolerated to lower IOP in PACG and after glaucoma and non-glaucoma surgeries apart from treating POAG and OH.

In Chinese Phase III study published by Ge *et al*^[13], the incidence of ADRs reported in patients with POAG after prescription of tafluprost was 31.7%. In this study, the incidence rate was not higher (10.1%) with 359 ADRs reported in 258 patients out of 2544. This may be explained by the 4-week washout period and 1-month follow-up in the randomized phase III study. Furthermore, the relatively older baseline age of participants in this study might also relate to the low incidence rate. Nevertheless, the main ADRs in the two studies were similar, involving conjunctival hyperemia.

Despite the number of observed patients, including 27.1% (646/2386) being 65 years or older and a total of 120 being 14 years or younger, no serious AEs were reported in this study, which was similar to other observational post-marketing studies^[14], indicating that study drug is well-tolerated in observed populations. The ADRs with relatively higher incidence (over 1%), such as eyelid pigmentation (3.94%, 168/4265) and eyelash changes (2.34%, 100/4265), described in observational study by Kuwayama *et al*^[9] were reported in 1.1% and 1.2% of the patients in this study, respectively. The slightly higher incidence might be owing to the longer observation period (2y) in the Japanese study.

The frequency of ADRs in this study is 10.1% (359 ADRs in 258 patients) which is also slightly lower than reported by Tumbocon and Macasaet^[8] (Philippines, 15% of patients) or

Table 4 Adverse drug reactions related to different circumstances of clinical application of tafluprost

Parameters	events/patients (%)					
	POAG	OH	PACG	After the surgery of glaucoma	After the surgery of non-glaucoma	Others
Total ADRs	218/153 (10.4)	75/57 (10.2)	19/13 (6.3)	29/20 (22.5)	0	18/15 (12.1)
Ocular ADRs	197/140 (9.5)	74/57 (10.2)	17/13 (6.3)	27/18 (20.2)	0	18/15 (12.1)
Conjunctival hyperemia	65/62 (4.2)	31/30 (5.4)	7/7 (3.4)	15/15 (16.9)	0	10/10 (8.1)
Dry eye	21/20 (1.4)	5/5 (0.9)	2/2 (1.0)	2/1 (1.1)	0	1/1 (0.8)
Eyelash change	20/20 (1.4)	7/7 (1.3)	0	2/2 (2.2)	0	2/2 (1.6)
Eyelid pigmentation	17/17 (1.4)	8/8 (1.4)	1/1 (0.5)	2/2 (2.2)	0	0
Eye pruritus	12/12 (0.8)	5/5 (0.9)	1/1 (0.5)	1/1 (1.1)	0	1/1 (0.8)
Ocular pain	11/11 (0.7)	6/6 (1.1)	2/2 (1.0)	1/1 (1.1)	0	0
Non-ocular ADRs						
Burning sensation	4/4 (0.3)	0	0	0	0	0
Dizziness	3/3 (0.2)	0	0	0	0	0
Headache	2/2 (0.1)	0	1/1 (0.5)	0	0	0

POAG: Primary open angle glaucoma; OH: Ocular hypertension; PACG: Primary angle-closure glaucoma; ADR: Adverse drug reaction.

Kuwayama *et al*^[9] (Japan, 18.64%). The patient age in these two studies [Philippines, 64.8 (14-94)y; Japan, 66.8±12.7y] were much older than that in this study (50.8±19.1y), which might be associated with the higher incidence of ADRs. As for the common ADRs of tafluprost, this study reported similar safety profile with the most common one of conjunctival hyperemia (128 ADRs in 124 patients, 4.9%), which was consistent with previous study^[9]. Conjunctival hyperemia is a common ADR regarding PGAs which is attributed to the ocular surface toxicity of the anti-glaucoma eye drops components, including the active ingredients, the preservatives as well as the excipients^[15] and the effect of PGAs on the retinal blood flow^[16]. Studies of bimatoprost^[17] and travoprost^[18] both reported higher incidence of conjunctival hyperemia compared with that observed in this study of tafluprost. In addition, with the fact that the majority of conjunctival hyperemia was mild and moderate, 87.5% (112/128) continued to use tafluprost, while 29.69% (38/128) continued to use tafluprost despite that conjunctival hyperemia did not improve. This indicated that the most common ADR of tafluprost, conjunctival hyperemia, might not greatly interrupt the treatment.

It is important to note that 65.6% (1670/2544) of participants used other drugs, which reflect the actual clinical practices in China. Among the patients receiving combined therapy of tafluprost and β -blockers (33.2%, 555/1670), the incidence of conjunctival hyperemia did not increase tremendously compare with that of tafluprost monotherapy (3.7% vs 2.9%), supported by previous studies which also demonstrated the relatively lower incidence of hyperemia and eye irritation under such combination^[12,19]. A Meta-analysis revealed that the fixed combination of PGAs and timolol did not increase the incidence of hyperemia comparing with PGAs monotherapy^[20]. In this study, the highest incidence of conjunctival hyperemia was observed in patients who used tafluprost in combination with other PGAs (23 ADRs in 23 patients, 8.8%) and the lowest in combination with CAIs (16 ADRs in 16 patients, 2.6%).

The safety of tafluprost in 646 patients with 65 years old or older was evaluated in this study. All 65 ADRs reported among 7.0% (45/546) of these patients were not serious, which indicated satisfying safety profile of tafluprost in the application of elderly patients. This study included a total of 120 patients who were 14 years old or younger and 14 of them (11.67%) reported 18 non-serious ADRs. Furthermore, this study observed no AE of tafluprost for lowering IOP in a one-year old infant with congenital glaucoma. Tafluprost was administered for over 5mo and the infant was still receiving tafluprost by this report of study, with no ADR occurred. Tafluprost may be another PGA option for juvenile patients.

This study proved manageable safety profile regarding the combination therapy of tafluprost and other IOP-lowering eye

drops, including CAIs, sympathomimetics, β -blockers, other PGAs and other medications for ophthalmic use. Previous studies reported similar results when tafluprost was combined with timolol^[6,21], which ADRs occurred in 5.01% patients with conjunctival hyperemia, blepharitis, and punctate keratitis^[6]. This study provided multiple options for tafluprost-based combined therapy other than timolol, widening the choices of IOP-lowering regimens for doctors in real-world clinical practice.

In this study, tafluprost could also be applied in patients with PACG and lowering the IOP after both glaucoma and non-glaucoma surgeries, indicating that tafluprost might be tolerable under various circumstances in clinical practice. Other PGAs also showed acceptable safety and tolerability in effectively lowering IOP for patients with angle-closure glaucoma^[6,21].

This study had some limitations. First, ADRs were possibly underestimated owing to loss of follow-up in some patients who stopped taking tafluprost by themselves due to ADRs. In addition, the sample size included was less than the calculated sample size. Second, patients in this study were all Asian, 98.6% of Chinese Han, and the observed frequency of AEs may be different in patients with POAG and OH in other ethnicities. Third, 65.6% (1670/2544) of patients used other drugs in our study. ADRs due to other drugs might be present, which could be a potential confounding factor. Finally, it was not sufficient to observe the long-term safety of tafluprost since AEs in this study were collected only within 30d after the treatment started.

Tafluprost is safe to be applied in patients with POAG and OH. The combination of tafluprost with CAIs, sympathetic agents, β -blockers, other PGAs or other eye drops all proved manageable safety profile. Furthermore, tafluprost can also be applied in patients with PACG and after both glaucoma and non-glaucoma surgery.

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