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A real-world pharmacovigilance study of netarsudil based on the FDA adverse event reporting system (FAERS)

Xiaomei Xiong[1], Xiuwen Zhang[1], Fengmin Tang[1] and Taomin Huang[1*]

Abstract

Background The safety information of netarsudil primarily comes from clinical trials experience. This study aimed to explore the ocular and systemic safety of netarsudil through data mining the FDA Adverse Event Reporting System (FAERS) database.

Methods Adverse event (AE) reports submitted to FAERS between January 2018 and September 2024 were extracted. The reporting odd ratio was used to identify netarsudil-related AE signals. Subgroup analysis, time to onset (TTO) analysis and sensitivity analysis were conducted to comprehensively assess the safety profile of netarsudil.

Results A total of 63 AE signals were identified. Thirty-eight were ocular AEs listed in netarsudil's label, with conjunctival hyperemia, vision blurred and eye irritation ranking the top three in reporting frequency. Twenty-one were new ocular AE signals, including allergic blepharitis, eye pruritus, dacryostenosis, myopic shift, corneal hemorrhage, etc. The rest four were unexpected systemic AE signals, including hypersensitivity, swelling face, dermatitis allergic and dermatitis contact. Subgroup analysis showed that patients ≥ 65 years were more likely to develop inflammation-related AEs, whereas the other adult patients were more prone to experience cataract subcapsular, dry eye, refraction disorder and ocular discomfort. The median TTO of netarsudil-related AEs was 1 day (IQR: 0–13 days), with the majority of AEs (82.65%) occurring within the first month of netarsudil administration. Weibull distribution analysis indicated an early failure type, indicating the incidence of AEs decreased over time.

Conclusion This pharmacovigilance study uncovered new ocular and systemic AE signals associated with netarsudil, and found netarsudil-related AEs were more likely to arise shortly after drug administration, offering valuable insights for clinical monitoring, risk identification and future research.

Keywords Adverse event, FAERS, Glaucoma, Netarsudil, Pharmacovigilance

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Introduction

Glaucoma is a group of ocular disorders characterized by intraocular pressure-associated optic neuropathy [1]. Glaucoma is the leading cause of irreversible blindness globally and was estimated to affect approximately 111.8 million people by 2040, imposing a significant economic and social burden [2, 3]. Medical therapy to reduce intraocular pressure (IOP) is the initial treatment to prevent disease progression and visual field loss [4]. Traditional medications reduce IOP primarily by either decreasing aqueous humor production or increasing aqueous humor outflow through the unconventional uveoscleral pathway [4]. Rho kinase (ROCK) inhibitors represent a new class of ocular hypotensive drugs, which can increase aqueous humor outflow through directly relaxing trabecular meshwork [5, 6]. Netarsudil is a novel ROCK inhibitor approved by the FDA in December 2017 for the treatment of glaucoma and ocular hypertension. According to the results of phase 3 clinical trials, once-daily netarsudil demonstrated non-inferior IOP-lowering efficacy compared to twice-daily timolol, providing an additional treatment option for patients with glaucoma [7–10].

The safety information of netarsudil mainly comes from clinical trials and post-marketing case reports. According to the results of phase 3 clinical trials, adverse events (AEs) of netarsudil were mostly local, mild and reversible after medication discontinuation, with conjunctival hyperemia, corneal verticillata and conjunctival hemorrhage being the most common AEs [10]. During post-marketing use, many case reports and case series reported epithelial corneal edema secondary to netarsudil use, which was subsequently added to the label of netarsudil [11–15]. Several reviews further summarized the safety profile of netarsudil based on clinical trials and post-marketing experience [16–18]. However, they also pointed out the necessity of large-sample, long-term pharmacovigilance studies to provide more comprehensive safety information of netarsudil [16–18].

The FDA Adverse Event Reporting System (FAERS) is a public database that contains numerous AE reports spontaneously reported to the FDA. It has been widely utilized to characterize the safety profile of marketed drugs. Therefore, our study aimed to explore the ocular and systemic safety of netarsudil among real-world patients through data mining the FAERS database. Additionally, we performed subgroup analysis, time to onset (TTO) analysis and sensitivity analysis to comprehensively evaluate the safety profile of netarsudil.

Methods

Data source

The FAERS is a public database designed to support the FDA's post-marketing monitoring for drugs and therapeutic biological products. It contains AE reports spontaneously submitted to the FDA by consumers, healthcare professionals and pharmaceutical manufacturers worldwide. OpenVigil 2.1 is a widely-utilized pharmacovigilance tool for data extraction, cleaning and analysis specifically for the FAERS database [19, 20]. Data for this study was extracted from the FAERS database through OpenVigil 2.1.

Data mining

In this study, we extracted AE reports submitted to the FAERS database between January 2018 and September 2024. Searches were conducted with generic name "netarsudil" or brand name "Rhopressa" as primary suspected drug. AEs were coded as preferred terms (PTs) and categorized by system organ classes (SOCs) based on MedDRA's structural hierarchy. AE reports were counted according to individual safety reports.

Statistical analysis

Disproportionality analysis

Descriptive analysis was used to summarize the characteristics of AE reports. Disproportionality analysis was performed by OpenVigil 2.1 to detect AE signals. The reporting odd ratio (ROR) and its 95% confidence interval (CI) were calculated to evaluate the association between netarsudil and AE. The calculation method was shown in Table 1. A significant safety signal was identified when the number of target AE reports ≥ 3 and the lower limit of 95% CI of ROR > 1.

$$\text{Reporting odds ratio (ROR)} = (a/c)/(b/d) = ad/bc$$

$$95\%\ \text{CI} = e^{ln\,(ROR)\,\pm\,1.96\sqrt{(1/a+1/b+1/c+1/d)}}$$

Subgroup analysis

To further evaluate the safety profile of netarsudil among different cohorts, subgroup analysis was conducted by gender (female and male) and age (0–17 years, 18–64 years, and ≥ 64 years).

Table 1 Two-by-two contingency table for disproportionality analysis

	Adverse events of interest	All other adverse events	Total
Drug of interest	a	b	a+b
All other drugs of interest	c	d	c+d
Total	a+c	b+d	a+b+c+d

TTO analysis

The TTO of netarsudil-related AEs was defined as the interval between the start of netarsudil use and the occurrence of AEs. The median and interquartile range (IQR) were used to describe the TTO. Weibull distribution analysis was performed to assess the incidence of AEs over time. When shape parameter (β) < 1 and its 95% CI < 1, it indicates an early failure type, where the incidence of AEs decreases over time; when $\beta = 1$ and its 95% CI includes 1, it suggests a random failure type, where the incidence of AEs is constant over time; and when $\beta > 1$ and its 95% CI excludes 1, it represents a wear-out failure type, where the incidence of AEs increases over time.

Sensitivity analysis

To minimize the potential impact of confounding factors and more accurately assess the safety profile of netarsudil, a stepwise sensitivity analysis was conducted. The concomitant drugs were identified from individual safety reports. And disproportionality analysis was performed again after excluding AE reports involving the top 30 co-administered drugs with netarsudil.

All analysis was performed using OpenVigil 2.1, Microsoft Excel 2016 and R (version 4.2.1).

Results

General characteristics

A total of 7,480,032 AE reports were extracted from the FAERS database between January 2018 and September 2024, including 1,295 reports with netarsudil as primary suspected drug. The characteristics of AE reports associated with netarsudil were shown in Table 2. The majority of AEs were reported from the US (1233, 95.21%). A total of 146 patients experienced serious outcomes, including death (31, 2.39%), disability (7, 0.54%), hospitalization (6, 0.46%), life-threatening events (1, 0.08%), and other serious outcomes (101, 7.80%).

Table 2 Characteristics of AE reports associated with netarsudil

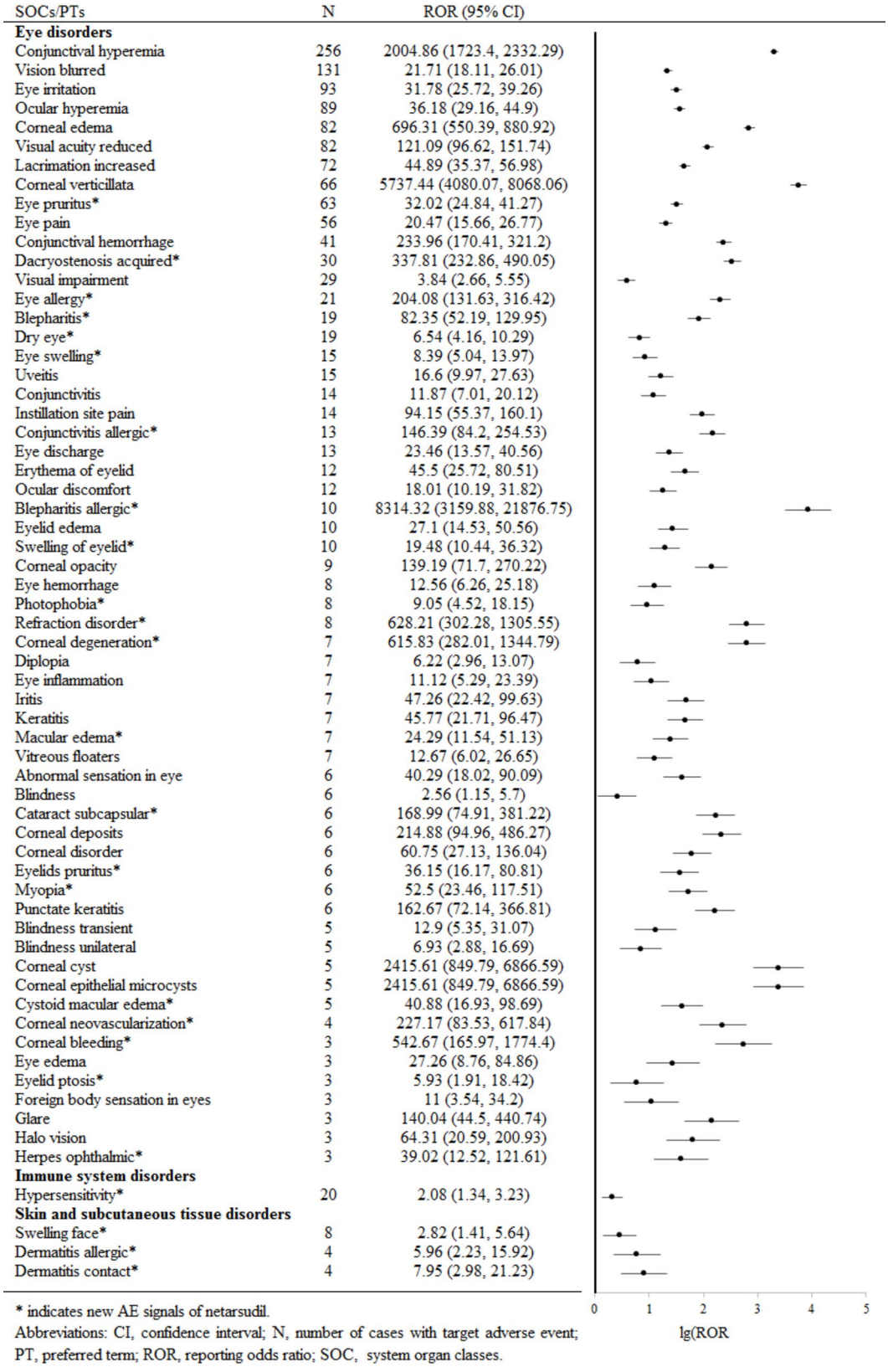
Characteristics	Case number (*n*)	Case proportion (%)
Gender		
Female	448	34.59
Male	304	23.47
Unknown	543	41.93
Age		
< 18	19	1.47
18–64	106	8.19
65–98	241	18.61
Unknown	929	71.74
Serious Outcome		
Death	31	2.39
Disability	7	0.54
Hospitalization	6	0.46
Life-threatening	1	0.08
Other serious outcomes	101	7.80
Reporter country		
United States of America	1233	95.21
Germany	7	0.54
India	4	0.31
Canada	2	0.15
Argentina	1	0.08
Denmark	1	0.08
Finland	1	0.08
Italy	1	0.08
Spain	1	0.08
Sweden	1	0.08
Country not specified	43	3.32

Disproportionality signals

A total of 63 AE signals were identified for netarsudil (Fig. 1), of which 38 (60.32%) were known AEs recorded in its label, and the rest 25 (39.68%) were new AE signals detected from the FAERS database. The majority of AEs (59, 93.65%) were categorized into the SOCs of eye disorders. Among these ocular AEs, conjunctival hyperemia (256), vision blurred (131) and eye irritation (93) ranked the top three in reporting frequency, while blepharitis allergic (10), corneal verticillata (66), corneal cyst (5) and corneal epithelial microcysts (5) showed the strongest statistical association with netarsudil based on ROR values. Systemic AE signals of netarsudil were rare and mainly involved the SOCs of immune system disorders and skin and subcutaneous tissue disorders, including hypersensitivity (20), swelling face (8), dermatitis allergic (4) and dermatitis contact (4). All these systemic AE signals were newly detected from the FAERS database.

Subgroup analysis

Subgroup analysis of netarsudil-related AE signals by gender and age was conducted, and the results were shown in Fig. 2. The number of AE signals detected in female patients (36) was higher than that in male patients (28). However, there were no apparent differences on the most frequently reported AE signals between genders. The number of AE signals in different age groups was as follows, 21 in patients aged ≥ 65 years, 18 in patients aged 18 to 64 years, and only 1 in patients under 18 years due to the limited number of pediatric AE reports. The most frequently reported AE signals were similar between patients aged ≥ 65 years and those aged 18 to 64 years. However, patients aged ≥ 65 years were more likely to develop AEs including visual impairment, eye allergy, erythema of eyelid, hypersensitivity, blepharitis allergic, eyelid edema, swelling of eyelid and uveitis. In contrast, patients aged 18 to 64 years were more prone to experience cataract subcapsular, dry eye, refraction disorder, corneal degeneration and ocular discomfort.



SOCs/PTs	N	ROR (95% CI)
Eye disorders		
Conjunctival hyperemia	256	2004.86 (1723.4, 2332.29)
Vision blurred	131	21.71 (18.11, 26.01)
Eye irritation	93	31.78 (25.72, 39.26)
Ocular hyperemia	89	36.18 (29.16, 44.9)
Corneal edema	82	696.31 (550.39, 880.92)
Visual acuity reduced	82	121.09 (96.62, 151.74)
Lacrimation increased	72	44.89 (35.37, 56.98)
Corneal verticillata	66	5737.44 (4080.07, 8068.06)
Eye pruritus*	63	32.02 (24.84, 41.27)
Eye pain	56	20.47 (15.66, 26.77)
Conjunctival hemorrhage	41	233.96 (170.41, 321.2)
Dacryostenosis acquired*	30	337.81 (232.86, 490.05)
Visual impairment	29	3.84 (2.66, 5.55)
Eye allergy*	21	204.08 (131.63, 316.42)
Blepharitis*	19	82.35 (52.19, 129.95)
Dry eye*	19	6.54 (4.16, 10.29)
Eye swelling*	15	8.39 (5.04, 13.97)
Uveitis	15	16.6 (9.97, 27.63)
Conjunctivitis	14	11.87 (7.01, 20.12)
Instillation site pain	14	94.15 (55.37, 160.1)
Conjunctivitis allergic*	13	146.39 (84.2, 254.53)
Eye discharge	13	23.46 (13.57, 40.56)
Erythema of eyelid	12	45.5 (25.72, 80.51)
Ocular discomfort	12	18.01 (10.19, 31.82)
Blepharitis allergic*	10	8314.32 (3159.88, 21876.75)
Eyelid edema	10	27.1 (14.53, 50.56)
Swelling of eyelid*	10	19.48 (10.44, 36.32)
Corneal opacity	9	139.19 (71.7, 270.22)
Eye hemorrhage	8	12.56 (6.26, 25.18)
Photophobia*	8	9.05 (4.52, 18.15)
Refraction disorder*	8	628.21 (302.28, 1305.55)
Corneal degeneration*	7	615.83 (282.01, 1344.79)
Diplopia	7	6.22 (2.96, 13.07)
Eye inflammation	7	11.12 (5.29, 23.39)
Iritis	7	47.26 (22.42, 99.63)
Keratitis	7	45.77 (21.71, 96.47)
Macular edema*	7	24.29 (11.54, 51.13)
Vitreous floaters	7	12.67 (6.02, 26.65)
Abnormal sensation in eye	6	40.29 (18.02, 90.09)
Blindness	6	2.56 (1.15, 5.7)
Cataract subcapsular*	6	168.99 (74.91, 381.22)
Corneal deposits	6	214.88 (94.96, 486.27)
Corneal disorder	6	60.75 (27.13, 136.04)
Eyelids pruritus*	6	36.15 (16.17, 80.81)
Myopia*	6	52.5 (23.46, 117.51)
Punctate keratitis	6	162.67 (72.14, 366.81)
Blindness transient	5	12.9 (5.35, 31.07)
Blindness unilateral	5	6.93 (2.88, 16.69)
Corneal cyst	5	2415.61 (849.79, 6866.59)
Corneal epithelial microcysts	5	2415.61 (849.79, 6866.59)
Cystoid macular edema*	5	40.88 (16.93, 98.69)
Corneal neovascularization*	4	227.17 (83.53, 617.84)
Corneal bleeding*	3	542.67 (165.97, 1774.4)
Eye edema	3	27.26 (8.76, 84.86)
Eyelid ptosis*	3	5.93 (1.91, 18.42)
Foreign body sensation in eyes	3	11 (3.54, 34.2)
Glare	3	140.04 (44.5, 440.74)
Halo vision	3	64.31 (20.59, 200.93)
Herpes ophthalmic*	3	39.02 (12.52, 121.61)
Immune system disorders		
Hypersensitivity*	20	2.08 (1.34, 3.23)
Skin and subcutaneous tissue disorders		
Swelling face*	8	2.82 (1.41, 5.64)
Dermatitis allergic*	4	5.96 (2.23, 15.92)
Dermatitis contact*	4	7.95 (2.98, 21.23)

* indicates new AE signals of netarsudil.

Abbreviations: CI, confidence interval; N, number of cases with target adverse event; PT, preferred term; ROR, reporting odds ratio; SOC, system organ classes.

Fig. 1 AE signals of netarsudil identified from the FAERS database

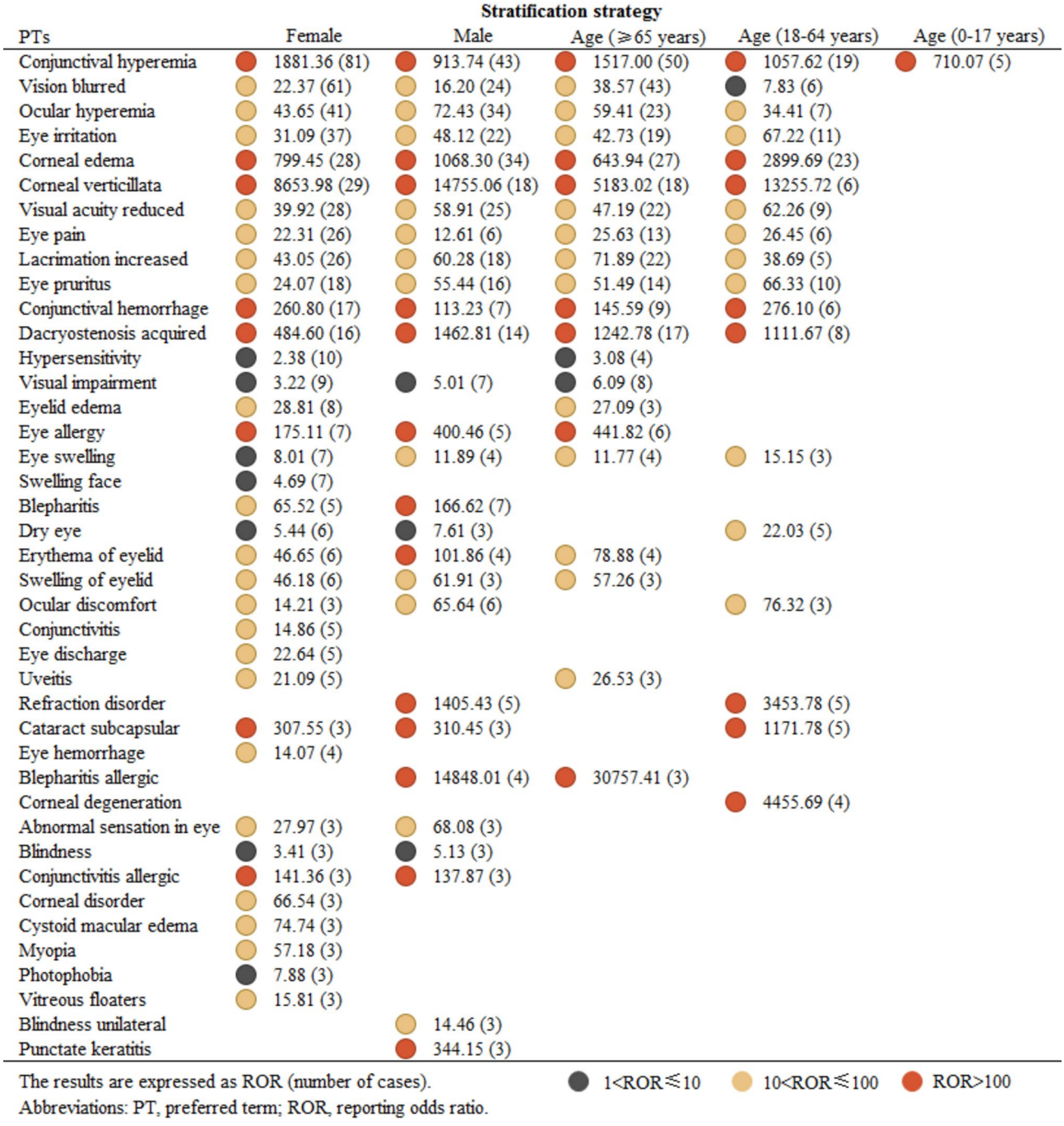


Fig. 2 Subgroup analysis of netarsudil-related AE signals by gender and age

TTO analysis

Among all the AE reports, 294 contained detailed data to calculate TTO of netarsudil-related AEs. As shown in Fig. 3, the majority of AEs (243, 82.65%) occurred within the first month of netarsudil use, with a significant proportion (204, 69.39%) occurring within 7 days. Figure 4 illustrated the cumulative incidence of netarsudil-related AEs over time. The median TTO of netarsudil-related AEs was 1 day (IQR: 0–13 days). Weibull distribution analysis indicated an early failure type, suggesting that the incidence of netarsudil-related AEs decreased over time (Table 3).

Sensitivity analysis

To minimize the influence of confounding factors, we identified the top 30 most commonly co-administered drugs with netarsudil (Supplementary Table S1). After excluding AE reports involving these drugs, 958 AE

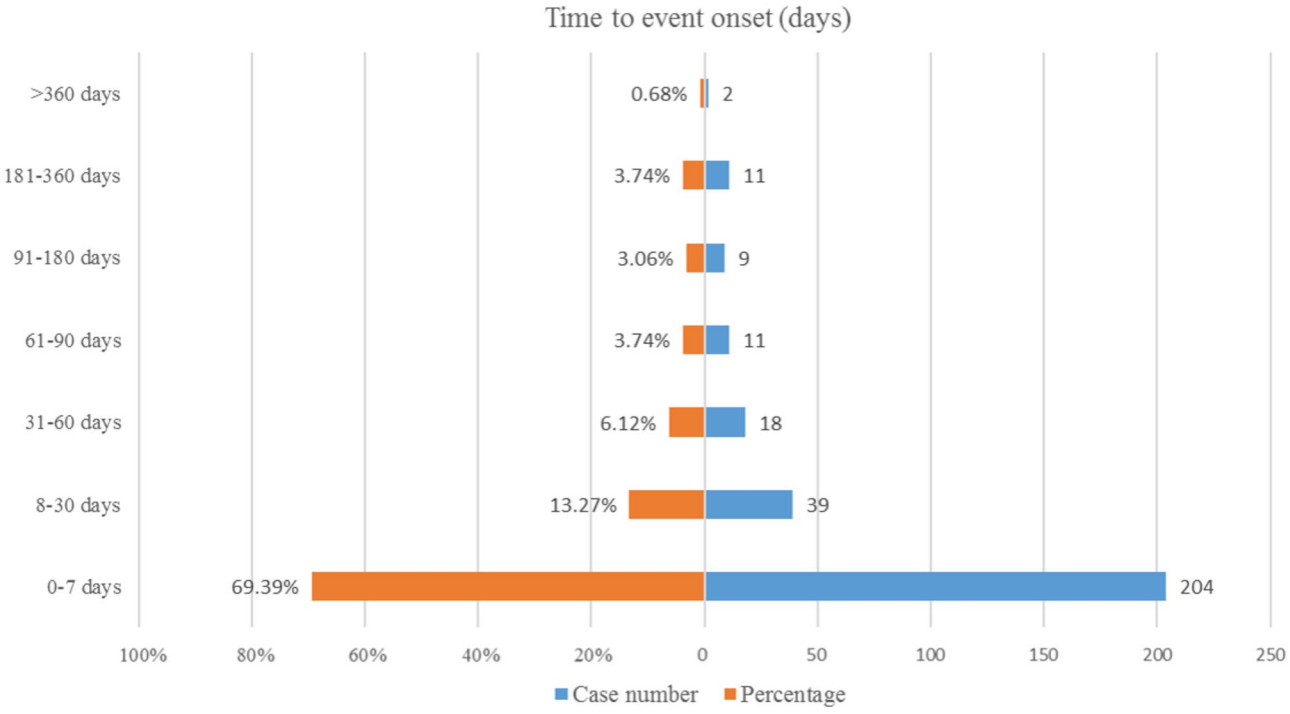


Fig. 3 The distribution of TTO of netarsudil-related AEs

reports were enrolled into sensitivity analysis, and 59 AE signals were detected. The AE signals detected in sensitivity analysis were consistent with those in the original disproportionality analysis, with conjunctival hyperemia, vision blurred and ocular hyperemia being the top three most frequently reported AEs (Supplementary Table S2).

Discussion

Netarsudil is a novel ROCK inhibitor that has demonstrated non-inferior therapeutic efficacy compared to timolol, providing another reliable treatment option for patients with glaucoma [10]. However, the safety information of netarsudil is primarily derived from clinical trials and post-marketing case reports [10]. There remains a lack of large-sample, long-term pharmacovigilance study to evaluate the safety profile of netarsudil to date. Therefore, we searched the FAERS database for a period of seven years following netarsudil's approval and for the first time comprehensively analyzed the ocular and systemic AEs associated with netarsudil in real-world settings.

Ocular AEs

Our pharmacovigilance study identified a total of 59 ocular AE signals for netarsudil, of which 38 were known AEs documented in its label. There were both similarities and differences regarding the most frequently reported ocular AEs of netarsudil between phase 3 clinical trials and our study (Table 4).

Similarly, conjunctival hyperemia ranked first in both clinical trials and real-world settings. This AE is not unexpected, as netarsudil relaxes vascular smooth muscle and dilates the conjunctival vessels through the ROCK signaling pathway [21]. Pooled data from the major clinical trials revealed that conjunctival hyperemia was mild to moderate in severity, occurred intermittently, and rarely led to medication discontinuation [10]. The reporting frequencies of vision blurred, visual acuity reduced and lacrimation increased in our study were higher than those of corneal verticillata, instillation site pain and conjunctival hemorrhage in clinical trials. This discrepancy may be due to differences in treated patients and the occupation of reporters between clinical trials and real-world practice. Notably, corneal edema was identified during post-marketing use instead of observed in phase 3 clinical trials [10, 11, 13, 14, 15]. In our study, corneal edema ranked fifth in the number of reports, which further illustrated its commonness in real-world clinical practice. According to previous case studies, this AE was transient, resolved after drug cessation, and typically presented as reticular or honeycomb-like edema accompanied by eye pain and decreased vision [12, 13]. Preexisting stromal edema, corneal transplant and decompensation, cyclophotocoagulation were major risk factors of corneal edema [13, 22, 23, 24]. Therefore, patients with the above risk factors should use netarsudil with caution and consult their physicians timely if experiencing eye pain or decreased vision during the treatment.

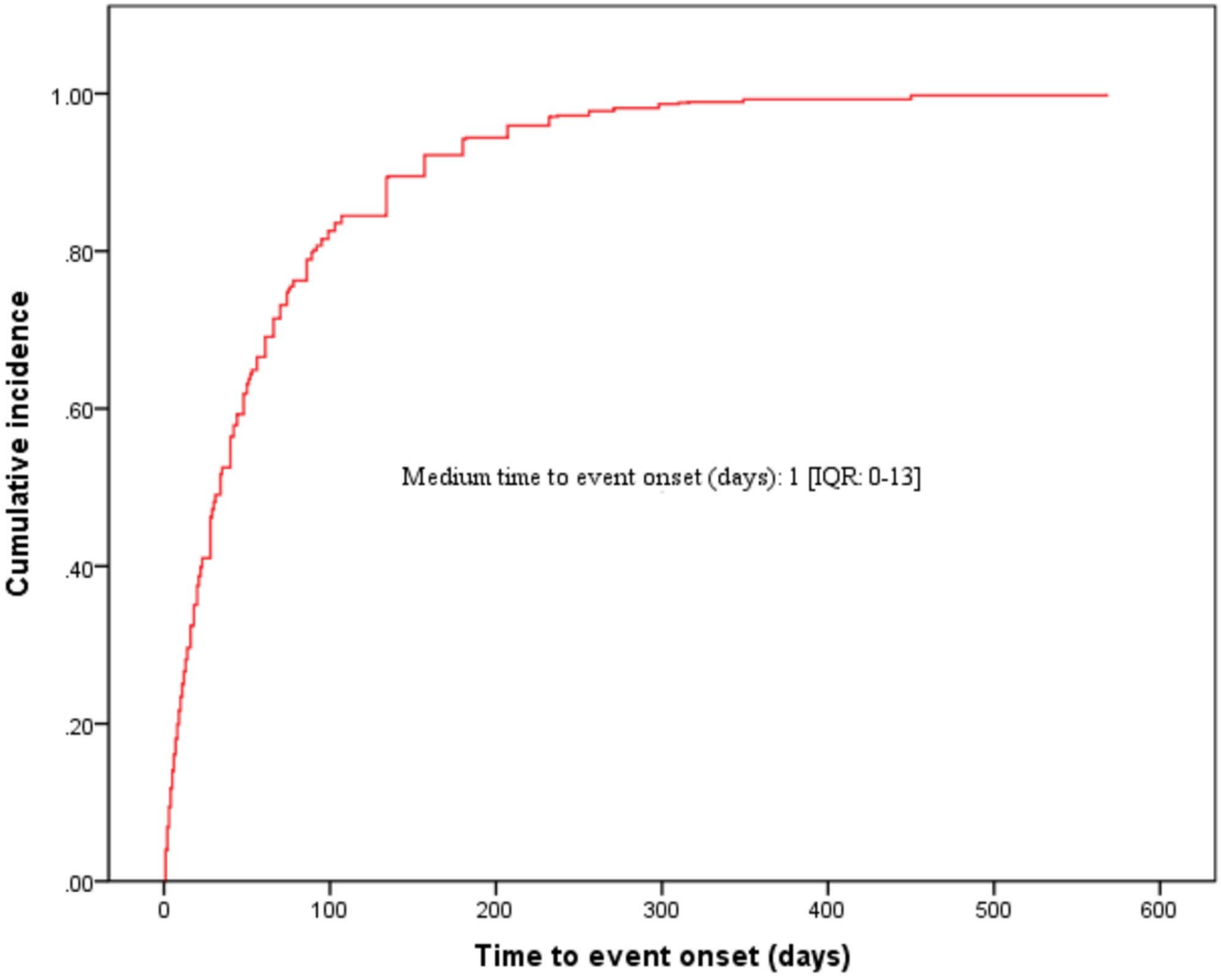


Fig. 4 Cumulative incidence of netarsudil-related AEs over time

Table 3 TTO of netarsudil-related AEs and Weibull distribution analysis

Cases number	TTO (days)	Weibull distribution				Failure type
		Scale parameter		Shape parameter		
	Median (IQR)	α	95% CI	β	95% CI	
2138	1 (0–13)	50.12	45.23–55.01	0.82	0.75–0.89	Early failure

Abbreviations: AE, adverse event; CI, confidence interval; IQR, interquartile range; TTO, time to onset

A total of 21 new ocular AE signals were identified for netarsudil in our study, which were also confirmed in sensitivity analysis. Among these AE signals, a series of PTs were related to ocular and periocular allergy, including eye pruritus, eye allergy, blepharitis, eye swelling, conjunctivitis allergic, blepharitis allergic, swelling of eyelid, and eyelids pruritus. Additionally, eye pruritus ranked first in reporting frequency among all newly-identified AE signals, and blepharitis allergic showed the strongest statistical association with netarsudil (ROR: 8314.32). Blepharitis, allergic conjunctivitis and eye pruritus are listed in the label of another ROCK inhibitor, ripasudil, as the most common AEs [25, 26]. These three AEs were also observed in phase 3 clinical trials of netarsudil, although not prominent components of netarsudil's safety profile [7, 8]. As a result, it is essential to further validate the causality between netarsudil and ocular allergy, and to consider adding these allergic AEs to its label.

Dacryostenosis acquired was the second frequently reported new AE signal and showed strong statistical association with netarsudil (ROR: 337.81) in our study. Two case series respectively reported 10 and 16 patients who developed this AE accompanied by tearing and

Table 4 Top 10 most common known ocular AEs of netarsudil in phase 3 clinical trials and in our study

AEs reported in phase 3 clinical trials [10]		AE signals detected in our study		
AEs	***N* (% of patients) †**	**AEs**	***N* (% of AE reports) ‡**	**ROR (95% CI)**
Conjunctival hyperemia	456 (54.4%)	Conjunctival hyperemia	256 (19.8%)	2004.86 (1723.4, 2332.29)
Corneal verticillata	175 (20.9%)	Vision blurred	131 (10.1%)	21.71 (18.11, 26.01)
Instillation site pain	167 (19.9%)	Eye irritation	93 (7.2%)	31.78 (25.72, 39.26)
Conjunctival hemorrhage	144 (17.2%)	Ocular hyperemia	89 (6.9%)	36.18 (29.16, 44.9)
Instillation site erythema	76 (9.1%)	Corneal edema	82 (6.3%)	696.31 (550.39, 880.92)
Corneal staining	79 (9.4%)	Visual acuity reduced	82 (6.3%)	121.09 (96.62, 151.74)
Blurred vision	62 (7.4%)	Lacrimation increased	72 (5.6%)	44.89 (35.37, 56.98)
Increased lacrimation	60 (7.2%)	Corneal verticillata	66 (5.1%)	5737.44 (4080.07, 8068.06)
Erythema of eyelid	57 (6.8%)	Eye pain	56 (4.3%)	20.47 (15.66, 26.77)
Reduced visual acuity	44 (5.2%)	Conjunctival hemorrhage	41 (3.2%)	233.96 (170.41, 321.2)

Abbreviations: AE, adverse event; CI, confidence interval; N, number of cases with target adverse event; ROR, reporting odds ratio

† Percentages represent incidence rate of specific AE among enrolled patients in phase 3 clinical trials

‡ Percentages represent proportion of specific AE among all AE reports

associated symptoms 2 ~ 35 months after netarsudil use [27, 28]. According to case series, this AE may be of sufficient severity to drug discontinuation, but could be reversed after drug cessation [27, 28]. The mechanism was thought to be inflammatory hyperemic response leading to fibrotic narrowing and obstruction of the nasolacrimal drainage pathway [29, 30]. Older age and female gender were recognized as major risk factors for this AE [29]. Notably, patients reported AE of dacryostenosis in our study were also predominantly older and female. In phase 3 clinical trials of netarsudil, increased lacrimation was reported in 7.2% of patients [10]. Given the long TTO of dacryostenosis reported in case series, it was possible that the relatively short treatment period in clinical trials did not allow for identification of this tearing related AE. All in all, there exists high correlation between netarsudil and dacryostenosis based on the strong disproportionality signal, the widely-reported downstream AE (increased lacrimation) in clinical trials, and reversal of this AE after drug cessation in case series. Therefore, it may be necessary to consider adding this possible AE to the label of netarsudil.

Two myopic related PTs, refraction disorder and myopia, were detected in our study which showed strong statistical association with netarsudil. Myopic shift was reported by two case reports. A 72-year-old patient suffered 1.5-dioptre myopic shift, reduced visual acuity and corneal flattening after using netarsudil for 1 month [31]. A 4-year-old patient developed 6.5-dioptre myopic shift and corneal flattening 4 months after using netarsdil [32]. This AE in both cases reversed after drug discontinuation, which showed a high correlation with netarsudil. As a result, myopic shift may be considered as a potential AE of netarsudil. Further well-designed studies are warranted to explore this phenomenon and its mechanism.

Conjunctival hyperemia and hemorrhage are common AEs of netarsudil in both phase 3 clinical trials and in real-world practice [10]. Our study further detected corneal neovascularization (ROR: 227.17) and corneal bleeding (ROR: 542.67) as new AE signals of netarsudil. Two case reports reported corneal neovascularization and hemorrhage that were clearly attributed to netarsudil [33, 34]. One of the patients developed corneal vascularization and hemorrhage 7 weeks after using netarsudil, which resolved 4 weeks after stopping this drug and recurred after restarting this drug [33]. The other patient developed corneal vascularization along with hemorrhage and microcystic edema 8 weeks after initiation of netarsudil, which regressed 3 months after drug cessation [34]. Similar with the mechanism of netarsudil-related conjunctival hemorrhage, the occurrence of corneal hemorrhage may be attributed to the vasodilator effect of ROCK inhibitors [21]. Therefore, netarsudil had high correlation with corneal neovascularization and hemorrhage. It may be necessary to consider adding these rare AEs to the label of netarsudil.

Systemic AEs

Pharmacokinetic studies have confirmed that systemic absorption of netarsudil is low [35]. Pooled safety analysis of phase 3 clinical trials of netarsudil showed that no systemic AE occurring in more than 2% of patients [10]. The most common systemic AEs in phase 3 clinical trials included upper respiratory tract infection, nasopharyngitis, sinusitis, urinary tract infection, headache, dermatitis contact, cough, and hypertension, most of which were not treatment-related [10]. Our study detected only 4 systemic AE signals associated with netarsudil in both original disproportionality analysis and sensitivity analysis, including hypersensitivity, swelling face, dermatitis allergic and dermatitis contact, suggesting that netarsudil has a favorable systemic safety profile and may occasionally induce hypersensitivity-related AEs.

Subgroup analysis

We conducted subgroup analysis by gender and age to further evaluate the safety profile of netarsudil in different cohorts. No apparent differences were observed in the most frequently reported AE signals between men and women, or between elderly and the other adult patients, which is consistent with the safety information described in netarsudil's label. However, we found several AE signals that were specific to certain populations.

Firstly, we found that patients aged ≥ 65 years were more likely to develop inflammation-related AEs, including eye allergy, erythema of eyelid, hypersensitivity, blepharitis allergic, eyelid edema, swelling of eyelid and uveitis, which may be attributed to age-related declines in immune function. In contrast, patients aged 18 to 64 years were more likely to experience cataract subcapsular, dry eye, refraction disorder and ocular discomfort. A case series previously reported 5 patients of cataract subcapsular after long-term use of netarsudil, with younger age identified as a risk factor [36]. The high prevalence of the other three AEs in patients aged 18 to 64 years may be associated with the high intensity of eye use in this population, potentially increasing their susceptibility to netarsudil.

Owing to the limited number of AE reports containing age information, further studies with larger sample size are needed to comprehensively evaluate the safety profile of netarsudil in different age groups.

TTO analysis

The TTO analysis was performed to elucidate the temporal distribution of netarsudil-related AEs and to identify potential patterns following drug administration. The median TTO of netarsudil-related AEs was 1 day (IQR: 0–13 days), with the majority of these AEs (243, 82.65%) occurring within the first month of netarsudil use. Additionally, Weibull distribution analysis indicated an early failure type, suggesting that netarsudil-related AEs were more likely to arise shortly after drug administration. These findings were consistent with previous literature [10, 11]. Therefore, clinicians should focus on monitoring and managing AEs during the early phase of netarsudil treatment to ensure patients' safety and adherence.

Limitations

There are some limitations of this study. First, as the FAERS database is a spontaneous reporting system, there may be underreported cases or incomplete reports, which would introduce bias into AE signal detection, subgroup analysis and TTO analysis. According to literature, only 6–10% of all AEs are reported to spontaneous reporting systems [37, 38], and one reason for healthcare professionals' underreporting is that the suspected AE is already known [39, 40]. These underreported cases may potentially lead to a skewed perception of the overall safety profile of netarsudil. The FAERS Public Dashboard also explicitly stated that many reports in the FAERS database do not contain all the necessary information, which may influence subgroup analysis and TTO analysis. Second, due to the lack of denominators and underreporting in the FAERS database, it is impossible to calculate the incidence of netarsudil-related AEs. Third, the results of disproportionality analysis could only demonstrate statistical association rather than causal relationship between suspected drug and AEs. Therefore, it is crucial to consider these limitations when interpreting the findings of our study and to encourage further investigations to validate and expand upon our observations.

Conclusion

This pharmacovigilance study for the first time comprehensively analyzed the safety profile of netarsudil in real-world patients. By data mining the FAERS database, we uncovered new ocular AEs associated with netarsudil, such as allergic blepharitis, eye pruritus, dacryostenosis acquired, myopic shift, corneal neovascularization and hemorrhage, etc. At the same time, we found that netarsudil had a favorable systemic safety profile and only occasionally induced hypersensitivity-related AEs. Through subgroup analysis, we identified population-specific AE signals, i.e., patients ≥ 65 years were more likely to develop inflammation-related AEs, while the other adult patients were more prone to experience cataract subcapsular, dry eye, refraction disorder and ocular discomfort. Through TTO analysis, we found that the median TTO of netarsudil-related AEs was 1 day (IQR: 0–13 days), and the majority of AEs (82.65%) occurring within the first month of netarsudil administration. Weibull distribution analysis indicated an early failure type, indicating the incidence of AEs decreased over time. In summary, this pharmacovigilance study enhances our understanding of netarsudil's safety profile, which provide valuable insights for future research and clinical practice.

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

All the authors were involved in the study. X. X. and T. H. contributed to the conception and study design. X. X. and F. T. were responsible for data collection. X. X. and X. Z. were responsible for data analysis. X. X. wrote the first draft of the manuscript and all authors participated in the revision of the manuscript. All authors read and approved the final version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethical approval and consent to participate was not needed for this study because FAERS is a public anonymized database.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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