Clinical adverse events to voclosporin: a real-world drug safety study based on the FDA Adverse Event Reporting System

J. Zhang[1,2], Y. Wan[1,3], L. Liu[1,3], R. Chen[4], Y. Shi[4], Y. Tang[2], P. Li[1,3], H. Huang[4]

[1]State Key Laboratory of Bioactive Substance and Function of Natural Medicines, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing; [2]Department of Pharmacy, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing; [3]Diabetes Research Center of Chinese Academy of Medical Sciences, Beijing; [4]Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China.

Abstract

Objective

Voclosporin, a novel calcineurin inhibitor, is emerging as a promising treatment for lupus nephritis (LN). It inhibits T and B cell activation with unique pharmacokinetic profile and superior safety. To optimise clinical management, a comprehensive assessment of real-world safety is urgently needed.

Methods

A retrospective observational study was performed that analysed data from the FDA adverse event reporting system (FAERS) database from 2021Q4 to 2024Q3. Advanced data mining techniques were utilised to identify safety signals associated with voclosporin. The research focused on instances where voclosporin was considered the primary suspect (PS) drug, and incidents of adverse events (AEs) were categorised utilising the Medical Dictionary for Regulatory Activities standardised preferred terms and system organ class classifications (SOCs).

Results

The analysis of FAERS database identified 11,851 reports in which voclosporin was the PS drug. The median time to onset (TTO) of AEs is 54.50 days. These reports highlighted significant safety signals across various SOCs, especially in vascular disorders, skin and subcutaneous tissue diseases, and gastrointestinal disorders. Furthermore, several previously unreported adverse events associated with voclosporin were discovered, such as hypertensive urgency (ROR: 27.96, 95%IC: 11.53, 67.81), hypertrichosis (ROR: 15.17, 95%IC:5.66, 40.65), and gingival swelling (ROR: 16.38, 95%IC: 8.78, 30.57).

Conclusion

The present research provides a significant assessment of the postmarketing safety profile of voclosporin. However, additional studies are needed to corroborate and solidify these observations. Clinicians are advised to remain highly vigilant about the potential AEs associated with voclosporin and to carefully consider the appropriate dosing regimens when utilising this medication in clinical practice.

Key words:
voclosporin, lupus nephritis, FDA adverse event reporting system, pharmacovigilance, adverse events

Jiaqi Zhang, PhD
Yanjun Wan, PhD
Liheng Liu, PhD
Ruxuan Chen, MD
Yujie Shi, MD
Yan Tang, PhD
*Pingping Li, PhD**
*Hui Huang, MD**

**Contributed equally.*

Please address correspondence to:
Hui Huang
Department of Pulmonary and Critical Care Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 1 Shuaifuyuan Street, Dongcheng District, Beijing 100730, China.
E-mail: pumchhh@126.com

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterised by the immune system mistakenly attacking the body's normal tissues (1). The aetiology involves genetic, environmental, and abnormal immune system factors (2). Lupus nephritis (LN), a prevalent and severe manifestation of SLE, which impacts nearly half of all SLE patients, posing a significant risk of irreversible kidney damage (3). It is characterised by the deposition of immune complexes, activation of the complement system, and infiltration of various innate and adaptive immune cells, presenting considerable management challenges4. The primary therapeutic objectives for LN involve several aspects: reducing proteinuria, stabilising or improving glomerular filtration rate (GFR), preventing relapses, and minimising exposure to glucocorticoids (5). Despite the availability of various treatment options for LN, patients often face suboptimal or delayed responses, relapses, chronic use of glucocorticoids, and the accumulation of both renal and extra-renal organ damage (6). Recently, newly approved combination therapies, which combine voclosporin with traditional medications like mycophenolate mofetil, have shown promising potential for enhancing disease outcomes and accelerating the reduction of glucocorticoid use (7, 8).

Voclosporin, a cutting-edge calcineurin inhibitor (CNI), offers a dual therapeutic approach for LN by inhibiting calcineurin, which halts the activation of T and B cells to mitigate inflammation, and simultaneously stabilising the podocyte cytoskeleton to reduce proteinuria and shield kidney function (9, 10). Voclosporin shows more stable pharmacokinetic profile, thus eliminating the need for drug level monitoring and making it more user-friendly in clinical settings (11). Voclosporin's superior safety profile avoids the metabolic disturbances and nephrotoxicity associated with traditional CNIs like cyclosporine A(CsA) and tacrolimus. As voclosporin could control proteinuria at an early stage, it is crucial for preventing irreversible kidney damage (12). Clinical trials, including AURA-LV, AURORA-1, and AURORA-2, have validated voclosporin's efficacy and safety. These findings highlight its potential as a valuable treatment option for improving renal response rates and reducing proteinuria in LN patients (7, 8).

However, voclosporin has been associated with adverse events including lymphoma and other malignancies, serious infections, hypertension, neurotoxicity, hyperkalaemia, QTc prolongation, pure red cell aplasia (9). To eliminate voclosporin associated potential adverse reactions, we conducted a systematic review and categorised the reported adverse events from the FAERS database.

Methods and materials

Data source

This retrospective observational study uses the FAERS database to explore voclosporin-related adverse events (AEs). Data was extracted from the drug's 2021Q4 FDA approval to 2024Q3, covering all relevant FAERS reports.

The FAERS database encompasses several sub-datasets, including DEMO (demographic data such as patient age, gender, weight), Drug (drug names), and REAC (AE information). Its terminology system is divided into system organ class (SOC) and preferred term (PT). PT is commonly employed both to indicate a particular AE and to detect pharmacovigilance signals corresponding to AEs not incorporated in the summary of product characteristics. SOC is a system for classifying AEs based on human organs or systems, such as the cardiovascular or nervous system. The primary outcomes of patients included death, life-threatening events, hospitalisation, disability, etc. In preliminary data processing, duplicate reports were removed by retaining the latest one based on date for cases with the same case id in DEMO.

The analysis focuses on reports listing voclosporin as the 'PS drug' to explore its potential role in AEs. AEs were categorised using MedDRA version 26.1 PTs and grouped into SOCs. The R platform (v. 4.3.3) was used for data preprocessing and analysis.

Data analysis

The analytical strategy employed in this study relies on an extensive array

Table I. Four grid table.

	Drug-related ADEs	Non-drug-related ADEs	Total
Voclosporin	a	b	a + b
Non-Voclosporin	c	d	c + d
Total	a + c	b + d	n = a + b + c + d

ADEs: adverse drug events.
a: The number of reports containing voclosporin and target Adverse Events (AEs). b: The number of reports detailing other Adverse Drug Events (ADEs) associated with Voclosporin. c: The number of reports mentioning the target ADEs of other drugs. d: The number of reports encompassing other drugs and their respective non-target ADEs.

of quantitative methodologies specifically tailored to assess the safety signals pertaining to voclosporin. To guarantee uniformity and accuracy in identifying reports, medication names were standardised utilising the Medex_UIMA_1.8.3 system. The methodologies utilised encompass the Reporting Odds Ratio (ROR) (13), the Proportional Reporting Ratio (PRR) and Chi-square statistic (χ^2) (14), the Bayesian Confidence Propagation Neural Network (BCPNN) (15), the multi-item gama poisson shrinker (MGPS), where empirical Bayesian geometric mean (EBGM) is an important indicator of MGPS (16). These rigorous analytical tools have been meticulously developed to provide a comprehensive and reliable evaluation of the safety profile of the medication in question.

The concurrent deployment of multiple algorithms enhances the cross-validation process, effectively mitigating the incidence of false positive outcomes. Detailed 2 × 2 contingency tables for each algorithm are presented in Table I, accompanied by comprehensive formulas and their corresponding thresholds in Table II. The decision criteria are briefly summarised as follows: For ROR, a ≥3 and ROR ≥3 with 95%CI (lower limit)>1 are considered significant. For PRR, a ≥3, PRR ≥2 and χ^2 >4 with 95%CI (lower limit) >1 are required. As for BCPNN, IC025 >0 is the threshold, for EBGM, significance is indicated by EBGM05 >2. PRR and ROR provide rapid initial screening and cross validate common signals. BCPNN enhances specificity by incorporating Bayesian uncertainty and multi-variable analysis. EGBM refines rare event detection while minimising noise.

A safety signal is deemed significant and warrants further investigation solely when it surpasses the predetermined thresholds across all five aforementioned algorithms simultaneously.

Results

Basic AE reporting for voclosporin

In the analytical process, a total of

Table II. Methods, formulas, and thresholds of four algorithms.

Method	Formula	Threshold
ROR	$\mathrm{ROR} = \frac{a/c}{b/d}$ $SE(lnROR) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%CI = e^{\ln(ROR)\pm 1.96se}$	a ≥3 ROR ≥3 95%CI (lower limit) >1
PRR	$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$ $SE(lnPRR) = \sqrt{\frac{1}{a}-\frac{1}{a+b}+\frac{1}{c}-\frac{1}{c+d}}$ $95\%CI = e^{\ln(PRR)\pm 1.96se}$	a ≥3 PRR ≥2 $\chi^2 > 4$ 95%CI (lower limit) >1
BCPNN	$\mathrm{IC} = \log_2 \frac{p(x,y)}{p(x)p(y)} = log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$ $\mathrm{E(IC)} = \log_2 \frac{(a+\gamma 11)(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+c+d+\gamma)(a+b+\alpha 1)(a+c+\beta 1)}$ $\mathrm{V(IC)} = \frac{1}{(ln2)^2}[\frac{(a+b+c+d)-a+\gamma-\gamma 11}{(a+\gamma 11)(1+a+b+c+d+\gamma)} + \frac{(a+b+c+d)-(a+b)+a-\alpha 1}{(a+b+\alpha 1)(1+a+b+c+d+\alpha)} + \frac{(a+b+c+d+\alpha)-(a+c)+\beta-\beta 1}{(a+b+\beta 1)(1+a+b+c+d+\beta)}]$ $\gamma = \gamma 11 \frac{(a+b+c+d+\alpha)(a+b+c+d+\beta)}{(a+b+\alpha 1)(a+c+\beta 1)}$ $\mathrm{IC}-2\mathrm{SD} = \mathrm{E(IC)} - 2\sqrt{\mathrm{V(IC)}}$	IC025>0
EBGM	$\mathrm{EBGM} = \frac{a(a+b+c+d)}{(a+c)(a+b)}$ $SE(lnEBGM) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$ $95\%CI = e^{\ln(EBGM)\pm 1.96se}$	EBGM05>2

5,973,976 AE reports were gathered, after deduplication resulted in 5,189,794 distinct reports. Concurrently, two additional datasets, 'DRUG' (n=27,175,129) with information on pharmaceuticals in AE reports and 'REAC' (n=15,511,259) with adverse reaction data, were merged with the refined dataset. From this integrated dataset, 4,290 AE reports where voclosporin was the PS drug were extracted, along with 11,851 PTs describing AEs potentially induced by voclosporin as the PS. Several statistical methods, including the ROR, PRR, BCPNN, and EGBM, were then applied to evaluate the data. The analyses provided insights into voclosporin's indications, the nature and incidence of outcome events, the temporal onset of these events relative to drug administration, and the associated clinical characteristics (Fig. 1).

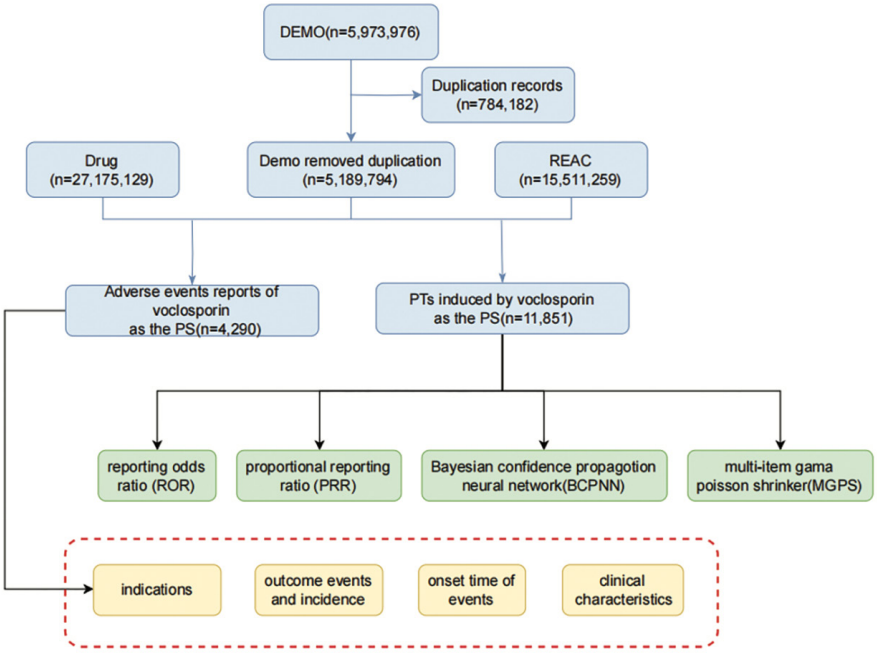

Fig. 1. The flow diagram of selecting voclosporin-related AEs from FAERS database. DEMO: demographic information; DRUG: drug information; REAC: adverse event information; PT: preferred terms; PS: major suspicion.

An analysis conducted on the FAERS database reveals an upward trend in the annual distribution of reports, with the initial three quarters of 2024 experiencing the most prominent surge, comprising 41.00% of all submissions. The years 2021, 2022 and 2023 also stand out, accounting for 7.48%, 20.61%, and 30.91% of the total reports, respectively. Regarding gender distribution, female patients constitute 83.99% of the cases, while male patients represent only 14.78%. Additionally, a substantial 1.24% of the reports do not specify the gender of the patient. The median age of the patients is 37.00 years, with an interquartile range (IQR) spanning from 28.00 to 49.00 years. The age demographic is diverse, with only 0.61% of patients aged under 18 years and 25.13% aged between 18 and 45 years. The elderly and middle-aged groups are the most prevalent, with 10.33% aged 45 to 65 years, 1.59% aged 65 to 75 years, and 0.40% aged 75 years and older. It is noteworthy that 61.96% of the reports lack complete age information. Geographically, the United States contributes the most reports, accounting for 99.84% of the total. The median time to onset of AEs is 54.50 days, with an IQR ranging from 3.00 to 210.75 days. It is worth mentioning that 10.40% of AEs occur within the first week, 3.83% between 7 and 28 days, 3.64% between 28 to 60 days, and 16.91% develop after 60 days. A significant portion of 65.22% of the reports have unspecified TTO data. The median weight of the patients is 76.90 kg, with an IQR of 63.49 to 94.33 kg (Table III).

Signal mining of voclosporin

An analysis of the FAERS database for voclosporin has uncovered a pronounced effect across 21 SOCs. In particular, the category of renal and urinary disorders stands out with a strikingly high signal, evidenced by 678 related reports, ROR of 3.37(3.12, 3.64), PRR of 3.23(2.99, 3.49), a chi-square value of 1060.87, IC of 0.96(0.79), and EBGM of 3.23(3.02). These compelling figures strongly indicate a notable correlation between voclosporin and the reported AEs in this domain. Additionally, other SOCs warranting attention include vascular disorders (573 reports); gastrointestinal disorders (1861 reports); infections and infestation (920 reports); and nervous system disorders (1050 reports). These results highlight the critical need for rigorous monitoring of AEs in patients receiving voclosporin therapy (Table IV). There is a notable variation in the signal strength rankings by gender, with females exhibiting positive signals across all 20 SOCs. In contrast, males demonstrate significant signals in only 12 SOCs, with the most pronounced response observed in the category of immune system disorders (see the online Supplementary file, Suppl. Table S1)

The analysis of the FAERS database provides a comprehensive overview of AEs associated with voclosporin. These AEs are arranged by ROR value and SOC in Table V. Similarly, all other PTs are also described according to ROR and SOC in Supplementary Table S2. The top three terms, ranked by both ROR and PRR values, such as 'absence of immediate treatment response', 'serology abnormal', 'urine protein/creatinine ratio increased' indicate a strong association with the use of voclosporin. These data provide clinicians with critical insights into the drug's safety profile. This enables clinicians to refine treatment strategies and patient management.

Discussion

The FAERS database constitutes a cornerstone of post-marketing surveillance for adverse drug reactions. It serves as a comprehensive global repository of real-world data, enabling researchers to detect and monitor safety signals as-

Table III. Basic information of AE reports related to voclosporin in the FAERS database.

Characteristics	Case number, n	Case proportion, %
Year		
2021	321	7.5
2022	884	20.6
2023	1326	30.9
2024	1759	41.0
Sex		
Female	3603	84.0
Male	634	14.8
Unknown	53	1.2
Age		
<18	26	0.6
18~45	1078	25.1
45~65	443	10.3
65~75	68	1.6
≥75	17	0.4
Unknown	2658	62.0
Reporter		
Consumer	3556	82.9
Pharmacist	394	9.2
Physician	340	7.9
Reported countries		
United States	4283	99.8
Other	7	0.2
Outcomes		
Oher serious	728	60.1
Hospitalisation	452	37.3
Death	30	2.5
Disability	1	0.1
Life threatening	1	0.1
Time to onset		
<7	369	10.4
7~28	136	3.8
28~60	129	3.6
>=60	600	16.9
Unknown	2314	65.2
Indications		
Lupus nephritis	3790	88.3
Ohers	16	0.4
Product used for unknown indication	435	10.1
Systemic lupus erythematosus	46	1.1
Unknown	3	0.1

sociated with medication use in clinical practice. By utilising this resource, the present analysis provides an extensive evaluation of voclosporin-related AEs documented to date.

Drug usage characteristics

From 2021 to 2024, there was a noticeable upward trajectory in the number of AEs reported, suggesting a rising trend in the utilisation of the medication among patients. The FDA has specifically approved this drug for adult patients suffering from moderate to severe SLE who are concurrently receiving standard treatment. In terms of gender distribution, the medication usage rate among females is 83.99%, compared to 14.78% among males, aligning with the epidemiological trends of LN (17). With 37.29% of the reports involving hospitalisation, this underscores the paramount importance of diligent patient monitoring and the adoption of preventive measures to reduce the risk of serious AEs associated with voclosporin use.

Adverse reaction signal detection

In the FAERS database, the signal strength of AEs associated with voclosporin, ranked by ROR at the PT level, shows that 'absence of immediate treatment response' has the highest ROR value of 4847.04 (95% CI: 2918.37, 8050.31). The absence of an immediate treatment response to voclosporin may be attributed to the fact that its primary use in managing of autoimmune diseases such as LN. These conditions are characterised by complex pathophysiological mechanisms and diverse clinical manifestations. In certain instances, the disease may have advanced to a more severe stage, or there may be multiple complicating factors present. This makes it challenging for a single medication to elicit a significant therapeutic effect within a short period of time (18). Clinical trials have shown that 65% of patients in the voclosporin group and 51% in the control group achieved partial renal remission, which corroborates these findings (12).

Voclosporin exerts immune modulating effects by inhibiting calcineurin, yet it may lead to acute kidney injury as it suppresses the renal detoxifying enzyme indolethylamine N-methyltransferase (INMT) (19) and follows the classic CNI induced nephrotoxicity pathway (20). While its nephrotoxicity manifestations like AKI and hypertension partly overlap with LN symptoms such as proteinuria and declining kidney function, they differ in mechanisms and acute phase characteristics (21, 22). Hence, in treatment, it is essential to balance the benefits of voclosporin in reducing LN proteinuria against its potential nephrotoxicity risks (12).

Within the SOC of vascular disorders, the PT 'hypertensive urgency' has emerged as a potential new adverse reaction with a ROR of 27.96 (95%CI: 11.53, 67.81). Hypertensive urgency refers to a situation where blood pressure is significantly elevated but is not accompanied by acute end-organ damage (23). Treatment involves gradually lowering blood pressure over several hours to balance the impact of hypertension on target organ function with the risk of over-treatment (24). While patients with hypertensive urgency face an increased long-term risk of cardiovascular events, the condition is not typically immediately life-threatening in the absence of target organ damage (25). Voclosporin, a structural analogue of CsA, shares a similar chemical structure with it (26). Calcineurin inhibitors (CNIs) induce hypertension through a multi-faceted mechanism. They inhibit calcineurin activity in the PVN (paraventricular nucleus of the hypothalamus), removing the inhibition on NMDAR (N-methyl-D-aspartate receptor) and thereby boosting

Table IV. Signal strength of reports of voclosporin at the system organ class level in the FAERS database.

System organ class (SOC)	Case Reports (N)	ROR (95% CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
Renal and urinary disorders	678	3.4 (3.1, 3.6)*	3.2 (3.0, 3.5)*	1060.9*	1.7 (1.6)*	3.2 (3.0)*
Vascular disorders	573	2.7 (2.4, 2.9)	2.6 (2.4, 2.8)*	560.5*	1.4 (1.2)*	2.6 (2.4)*
Gastrointestinal disorders	1861	2.1 (2.0, 2.2)	2.0 (1.9, 2.0)	928.4*	1.0 (0.9)*	1.9 (1.9)
Investigations	1403	2.1 (2.0, 2.2)	2.0 (1.9, 2.1)	703.8*	1.0 (0.9)*	2.0 (1.9)
Infections and infestations	920	1.3 (1.2, 1.4)	1.3 (1.2, 1.4)	64.9*	0.4 (0.3)*	1.3 (1.2)
Nervous system disorders	1050	1.2 (1.14, 1.3)	1.2 (1.1, 1.3)	37.3*	0.3 (0.2)*	1.2 (1.1)
Musculoskeletal and connective tissue disorders	747	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	22.3*	0.2 (0.1)*	1.2 (1.1)
Metabolism and nutrition disorders	257	1.1 (1.0, 1.3)	1.1 (1.0, 1.3)	2.8	0.2 (-0.1)	1.1 (1.0)
Reproductive system and breast disorders	64	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)	0.6	-0.1 (-0.5)	0.9 (0.7)
Skin and subcutaneous tissue disorders	530	0.8 (0.8, 0.9)	0.9 (0.8, 0.9)	15.8*	-0.2 (-0.4)	0.9 (0.8)
General disorders and administration site conditions	1577	0.7 (0.6, 0.7)	0.7 (0.7, 0.8)	209.0*	-0.5 (-0.6)	0.7 (0.7)
Ear and labyrinth disorders	32	0.7 (0.5, 0.9)	0.7 (0.5, 0.9)	6.18*	-0.6 (-1.1)	0.7 (0.5)
Injury, poisoning and procedural complications	1040	0.6 (0.6, 0.7)	0.7 (0.6, 0.7)	229.8*	-0.6 (-0.7)	0.7 (0.6)
Immune system disorders	81	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	22.3*	-0.7 (-1.1)	0.6 (0.5)
Respiratory, thoracic and mediastinal disorders	333	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	90.3*	-0.7 (-0.9)	0.6 (0.6)
Blood and lymphatic system disorders	124	0.6 (0.5, 0.7)	0.6 (0.5, 0.7)	38.9*	-0.8 (-1.1)	0.6 (0.5)
Eye disorders	127	0.5 (0.4, 0.6)	0.5 (0.4, 0.6)	56.5*	-0.9 (-1.2)	0.5 (0.5)
Pregnancy, puerperium and perinatal conditions	18	0.5 (0.3, 0.7)	0.5 (0.3, 0.7)	11.4*	-1.1 (-1.8)	0.5 (0.3)
Psychiatric disorders	297	0.4 (0.4, 0.5)	0.5 (0.4, 0.5)	213.5*	-1.2 (-1.3)	0.5 (0.4)
Cardiac disorders	96	0.4 (0.3, 0.5)	0.4 (0.4, 0.5)	80.7*	-1.3 (-1.6)	0.4 (0.4)
Endocrine disorders	6	0.2 (0.1, 0.4)	0.2 (0.1, 0.4)	22.2*	-2.5 (-3.5)	0.2 (0.1)
Hepatobiliary disorders	17	0.2 (0.1, 0.3)	0.020.1, 0.3)	70.7*	-2.6 (-3.2)	0.2 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	500.0*	-4.8 (-5.5)	0.1 (0.1)

*Positive signal detected.

sympathetic nerve outflow (27). Meanwhile, increased renal sodium reabsorption, often via activated NCC (sodium-chloride cotransporter), and vascular dysfunction, like endothelial disorder, can augment this process (28). Animal models, such as tacrolimus-treated rats (29), and clinical observations, like post-transplant hypertension cases (30), have broadly verified this mechanism. To manage hypertensive urgency, assess and monitor the patient's blood pressure accurately. Have them rest in a quiet, comfortable setting to avoid tension, which can elevate blood pressure (31). Administer short-acting oral antihypertensive drugs like nifedipine, but control the dose to prevent a rapid drop (32). Most of the above content is based on studies of CNI drugs, including CsA. The evidence regarding hypertensive urgency caused by Voclosporin is currently limited, and further experimental verification is required.

In the category of skin and subcutaneous tissue diseases (SOC), hypertrichosis is recognised as a potential emerging AE. Studies on cyclosporine A (CsA), a type of CNI, have revealed its potential as an effective Wnt inhibitor within human hair follicles, particularly targeting the secreted frizzled-related protein (SFRP)1. This inhibitory action may stimulate hair growth (33). CsA is used clinically for alopecia areata and other hair loss diseases, but its use is restricted due to systemic side effects (34). While they exhibit similar inhibitory effects on calcineurin, whether voclosporin shares identical mechanisms with CsA in terms of hair growth promotion remains uncertain (35). Further research is needed to explore their potential applications in hair loss treatment.

Within the SOC of gastrointestinal disorders, gingival swelling has emerged as a potential new adverse reaction. This condition is associated with pathological overgrowth of gingival tissue, which is characterised by excessive expansion of the extracellular matrix, cellular proliferation, and/or hypertrophy (36). The exact pathological mechanisms of oral hypertrophy are not fully understood, though there is a correlation between poor oral hygiene and the severity of this condition. Salivary pro-inflammatory cytokines, such as interleukin (IL)-1α, IL-8, and IL-6, have been shown to play a role in the pathogenesis of gingival hyperplasia induced by CsA (37). Additionally, immunosuppressive and genetic factors also contribute to the occurrence of this condition (38).

Limitations

The FAERS database has certain limitations. Its reliance on voluntary reporting may result in omissions and selective reporting. The accuracy of the reports could vary significantly, with issues like duplicate reporting, incomplete information, and data entry errors. These problems would affect the accuracy of data analysis. The specific analysis is as follows.

A high proportion of consumer reports are one of the major limitations. Consumer reports account for 82.89% of the data, far exceeding those from physicians (7.93%) and pharmacists (9.81%). This imbalance, combined with the large proportion of unspecified age information (65.22%), raises concerns about data accuracy and referential integrity. Consumers often lack medical expertise, leading to errors in AE reporting such as misattribution, vague descriptions, and unreliable symptom severity assessments. For example, they might mistake other health issues for drug-related reactions or provide unclear information on reaction timing and duration. In contrast, healthcare professionals, with their clinical experience and professional knowledge, can offer more precise classifications, causal assessments, and detailed

Table V. Top 30 signal strength of AEs of voclosporin ranked by ROR at the PT level in the FAERS database. All PTs showed significant differences in ROR, PRR, χ^2, IC, and EBGM.

PT	Case reports	ROR (95% CI)	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EBGM05)
General disorders and administration site conditions (SOC)						
absence of immediate treatment response	70	4847.0 (2918.4, 8050.3)	4818.4 (2894.6, 8020.9)	71976.1	10.0 (9.6)	1029.4 (673.3)
Investigations (SOC)						
serology abnormal	4	747.6 (218.8, 2554.2)	747.4 (217.4, 2569.2)	1897.3	8.9 (7.4)	476.0 (170.3)
urine protein/creatinine ratio increased	121	470.2 (381.8, 579.1)	465.4 (375.2, 577.4)	41359.4	8.4 (8.1)	343.5 (288.6)
urine protein/creatinine ratio decreased	4	402.6 (131.2, 1234.8)	402.4 (131.7, 1229.9)	1224.8	8.3 (6.8)	308.0 (120.6)
complement factor decreased	7	352.3 (152.9, 811.9)	352.1 (151.6, 817.9)	1931.0	8.1 (7.0)	277.6 (138.1)
complement factor c3 decreased	10	297.5 (149.7, 591.3)	297.2 (149.7, 590.3)	2405.7	7.9 (7.0)	242.4 (136.4)
double stranded dna antibody positive	14	197.1 (112.4, 345.8)	196.9 (111.5, 347.6)	2371.4	7.4 (6.6)	171.3 (107.0)
complement factor c4 decreased	5	176.8 (69.5, 450.0)	176.7 (69.0, 452.8)	769.7	7.3 (6.1)	155.8 (71.3)
urine protein/creatinine ratio abnormal	8	134.2 (64.8, 277.9)	134.1 (65.0, 277.0)	958.8	6.9 (5.9)	121.8 (66.2)
urine albumin/creatinine ratio increased	10	85.6 (45.1, 162.3)	85.5 (44.8, 163.2)	783.7	6.3 (5.5)	80.3 (47)
glomerular filtration rate decreased	156	57.2 (48.7, 67.3)	56.5 (48.3, 66.1)	8154.7	5.8 (5.5)	54.2 (47.4)
protein total increased	21	44.0 (28.5, 68.0)	43.9 (28.6, 67.6)	852.7	5.4 (4.8)	42.6 (29.6)
protein urine	5	32.9 (13.5, 79.9)	32.9 (13.6, 79.4)	150.7	5.0 (3.8)	32.1 (15.3)
protein urine present	34	31.5 (22.4, 44.2)	31.4 (22.5, 43.8)	976.7	4.9 (4.5)	30.7 (23.1)
glomerular filtration rate abnormal	14	29.3 (17.3, 49.8)	29.3 (17.3, 49.7)	374.3	4.8 (4.1)	28.7 (18.4)
blood albumin abnormal	3	26.2 (8.3, 82.1)	26.2 (8.4, 81.5)	71.2	4.7 (3.3)	25.7 (9.9)
glomerular filtration rate increased	6	23.9 (10.6, 53.5)	23.9 (10.7, 53.3)	129.0	4.55 (3.5)	23.4 (11.9)
blood creatinine abnormal	15	21.4 (12.9, 35.7)	21.4 (12.9, 35.7)	287.3	4.4 (3.7)	21.1 (13.8)
protein total abnormal	8	17.5 (8.7, 35.1)	17.5 (8.6, 35.4)	122.6	4.1 (3.2)	17.3 (9.6)
Renal and urinary disorders (SOC)						
proteinuria	245	65.6 (57.6, 74.7)	64.3 (57.1, 72.3)	14549.0	5.9 (5.8)	61.3 (55.0)
albuminuria	3	27.4 (8.8, 86.1)	27.4 (8.8, 85.5)	74.9	4.8 (3.3)	26.9 (10.3)
lupus nephritis	12	27.1 (15.3, 48.0)	27.1 (15.3, 47.8)	295.1	4.7 (3.9)	26.5 (16.4)
urine abnormality	26	25.8 (17.5, 38.1)	25.8 (17.4, 38.1)	606.9	4.7 (4.1)	25.3 (18.3)
Injury, poisoning and procedural complications (SOC)						
intentional underdose	30	33.0 (23.0, 47.5)	32.9 (23.2, 46.9)	906.5	5.0 (4.5)	32.2 (23.7)
Vascular disorders (SOC)						
hypertensive urgency	5	28.0 (11.5, 67.8)	28.0 (11.6, 67.5)	127.2	4.8 (3.6)	27.4 (13.1)
Skin and subcutaneous tissue disorders (SOC)						
butterfly rash	5	24.1 (10.0, 58.5)	24.1 (10.0, 58.3)	108.9	4.6 (3.4)	23.7 (11.3)
hair growth abnormal	21	19.9 (12.9, 30.7)	19.9 (12.9, 30.6)	371.1	4.3 (3.7)	19.6 (13.7)
hypertrichosis	4	15.2 (5.7, 40.7)	15.2 (5.7, 40.4)	52.31	3.91 (2.6)	15.0 (6.6)
Infections and infestations (SOC) pyuria	3	21.6 (6.9, 67.5)	21.6 (6.9, 67.2)	57.9	4.4 (3.0)	21.2 (8.2)
Gastrointestinal disorders (SOC) gingival swelling	10	16.4 (8.8, 30.6)	16.4 (8.7, 30.7)	142.5	4.0 (3.2)	16.2 (9.6)

patient backgrounds, including concomitant medications and medical histories. Their expertise allows for more accurate judgments on whether an AE is directly drug induced or related to underlying conditions or other medications.

The high proportion of missing data (61.96% of age information and 65.22% of TTO data) also poses a significant challenge to the study's comprehensiveness and accuracy. Such missing data may cause sample selection bias. For instance, missing age data may focus on patients reluctant to disclose their age or age groups overlooked during data collection. If there are significant differences in drug responses between the missing data groups and the included data groups, the findings may be skewed toward individuals who fully provided age information. This would fail to accurately reflect the drug's safety and effectiveness across the entire target population and undermine the generalisability of the study's conclusions. Additionally, the large amount of missing data can compromise the accuracy of statistical analysis. Many statistical methods require complete data, but a high proportion missing data can reduce statistical power. For example, when analysing whether there are differences in the incidence of adverse drug reactions among different age groups, the significant missing age data greatly reduces the effective sample size. Consequently, it becomes difficult to accurately detect any existing associations between age and adverse reactions, making the conclusions less reliable and leading to potential oversight of important drug safety signals. Furthermore, the missing data may result in underestimation or overestimation of drug safety. If the missing data contains numerous unanalysed adverse reaction cases or records with short TTO, which may suggest more immediate or severe drug reactions, the study might underestimate the drug's adverse reaction rate or severity. Conversely, if the missing data has more information favourable to drug safety, such as longer TTO, it could lead to an overestimation of drug safety. Both scenarios could mislead clinicians, patients, and regulatory agencies in their risk-benefit assessment of drugs, thereby affecting rational drug-use decisions and drug regulation policy formulation.

Conclusion

Common adverse reactions associated with voclosporin use include decreased glomerular filtration rate, hypertension, diarrhoea, headache, anaemia, cough, and urinary tract infections. In addition,

the study has identified some unexpected adverse reactions, such as hypertensive urgency, hypertrichosis, and gingival swelling. There is currently a need for more high-quality clinical trials to comprehensively evaluate voclosporin related reactions, thus providing more solid evidence for safe clinical use.

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