

The Safety Profile of Tocilizumab in Pediatric Neuroimmunological Diseases: A real-world study

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Abstract

Objectives

To evaluate the safety profile and adverse events (AEs) of short-term versus long-term tocilizumab (TCZ) administration in pediatric patients with neuroimmunological diseases.

Methods

This retrospective study enrolled 90 pediatric patients treated with TCZ at the Children's Medical Center, Xiangya Hospital of Central South University, between October 2018 and January 2026. Patients were stratified by infusion number into the long-term group (≥ 6 doses) and the short-course group (< 6 doses). Laboratory parameters and AEs were documented and graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 6.0. Statistical analysis was performed using IBM SPSS Statistics version 27.0, with a two-sided $P < 0.05$ defined as statistically significant.

Results

Median follow-up duration was 15 months [interquartile range (IQR), 7–22 months]. The overall incidence of AEs was 87.8% (79/90), including 42 patients in the long-term group and 37 in the short-course group. The most common AEs were reduced immunoglobulin levels ($n = 52$), neutropenia ($n = 38$), elevated liver transaminases ($n = 35$), dyslipidemia ($n = 33$), hypofibrinogenemia ($n = 33$), new-onset or aggravated infections ($n = 12$), and rash ($n = 2$). The incidence of neutropenia was significantly higher in the long-term group than in the short-course group (53.3% vs 31.1%; $P = 0.033$), and most cases were mild (Grade 1). In contrast, the overall severity distribution of neutropenia was significantly worse in the short-course group, with a higher proportion of Grade 2–4 cases ($P = 0.017$). At the final follow-up, laboratory abnormalities resolved in all patients who discontinued therapy, while those continuing TCZ maintained stable, mild abnormalities (CTCAE Grade 1) with appropriate management. No predefined serious adverse events (SAEs, defined as severe infection, gastrointestinal perforation or severe hypersensitivity reaction) occurred. Two patients (2.2%) permanently discontinued TCZ due to Grade 3–4 neutropenia, though these laboratory abnormalities did not meet our predefined SAE criteria.

Conclusion

Tocilizumab demonstrates a favorable safety profile in children with neuroimmunological diseases. Most adverse events are Grade 1–2 and reversible. Strengthened blood cell count monitoring and stratified management are recommended during treatment.

Introduction

Tocilizumab (TCZ) is a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor that functions as an IL-6 receptor antagonist[1]. In recent years, TCZ has been widely applied to treat various pediatric neuroimmunological and inflammatory disorders, including autoimmune encephalitis (AE)[2], febrile infection-related epilepsy syndrome (FIRES)[3, 4], myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD)[5, 6], and acute encephalopathy with biphasic seizures and late reduced diffusion (AESD)[7], among other neuroimmunological conditions. Although TCZ has been formally incorporated into several of the latest clinical guidelines and expert consensus statements[2, 3], the optimal treatment duration has not been established. Guidelines or expert consensus recommend that clinicians dynamically evaluate the duration of TCZ therapy based on the patient's therapeutic response. As the duration of medication use increases, the safety of TCZ treatment deserves attention. However, at present, safety data regarding TCZ use in pediatric neuroimmunology remain limited, especially regarding how treatment duration affects the incidence, severity, and clinical outcomes of adverse events. Accordingly, this study aimed to evaluate and summarize adverse events associated with short-course and long-term TCZ administration in pediatric patients with neuroimmunological diseases[8].

1 Materials and Methods

1.1 Study Population

This retrospective study enrolled 112 pediatric patients with neuroimmunological diseases who received treatment in the Department of Neurology at the Children's Medical Center, Xiangya Hospital, Central South University, between October 2018 and January 2026. The inclusion criteria were as follows: (a) a confirmed diagnosis of AE[9], FIRES[10], MOGAD[11], or AESD[12], (b) aged ≤ 18 years, and (c) administration of TCZ with signed informed consent from the guardian because of clinical necessity. The exclusion criteria were: (a) absence of essential clinical data, or (b) guardian-requested withdrawal from the study. Patients were stratified by the number of TCZ doses into a long-term treatment group (≥ 6 doses) and a short-course group (< 6 doses), according to relevant literature[13,14] and our center's clinical practice. This study was conducted in accordance with the ethical principles established by the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee of Xiangya Hospital, Central South University (Approval No.202310892). The legal guardians of all pediatric patients were fully informed of the study content and voluntarily provided written informed consent.

1.2 Analysis of clinical and laboratory profiles

Demographic and baseline clinical data were collected. Laboratory parameters during treatment, including peripheral blood cell counts, liver function tests, and lipid profiles, were recorded. All patients underwent at least one ECG and one plain chest CT during the treatment period. Serious adverse events (SAEs) included severe infections, gastrointestinal perforation, and hypersensitivity reactions (including allergic reactions)[1,15]. Safety evaluations were conducted throughout the entire study period, with adverse reactions classified and graded according to the Common Terminology Criteria for Adverse

Events (CTCAE), version 6.0[16]. Monthly follow-up was performed by reviewing inpatient and outpatient medical records, with the final follow-up defined as the pediatric patient's last return visit or outpatient consultation. Medication status (ongoing or discontinued) was recorded at this time. The final follow-up date was January 31, 2026.

1.3 Treatment profiles

All patients received intravenous tocilizumab (Shanghai Roche Pharmaceuticals Co., Ltd., China). The dose was 8~12 mg/kg per infusion with a maximum dose of 800 mg, administered monthly. Total treatment duration was adjusted based on clinical response and required immunosuppression duration[2,17,18]. During tocilizumab therapy, all pediatric patients continued their baseline immunomodulatory treatments as clinically indicated, including oral or intravenous glucocorticoids, plasma exchange, intravenous immunoglobulin (IVIG), and rituximab or other immunomodulatory treatments.

1.4 Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages [n (%)] and compared using the Pearson chi-square (χ^2) test or Fisher's exact test. The normality of continuous variables was tested. Normally distributed data were presented as the mean $\pm$ standard deviation (SD) and compared using the independent-samples t -test. Non-normally distributed data were presented as median and interquartile range (IQR) and compared using the Mann–Whitney U test. Multivariable logistic regression analysis was conducted on the clinical factors that might influence the occurrence of adverse reactions. A two-sided $P < 0.05$ was considered statistically significant.

For missing fibrinogen and immunoglobulin data (23.3%–33.3%), baseline characteristics (age at onset, sex, PICU admission rate) were compared between the missing and complete-data cohorts. No significant differences were observed (all $P > 0.05$), suggesting that the data were missing at random. Complete-case analysis was therefore used for these indicators.

2. Results

2.1 Clinical Characteristics

Of the initial 112 patients, 12 were excluded due to incomplete data, 6 were lost to follow-up, and 4 withdrew at the request of their guardians, resulting in a final cohort of 90 patients. These patients were categorized into a long-term treatment group ($n = 45$) and a short-course group ($n = 45$). The long-term treatment group had a median age at onset of 5.7 years (IQR 3.1–9.3), and the median number of tocilizumab doses was 8 (IQR 7–11). In the short-course group, the median age at onset was 6.5 years (IQR 4.0–10.7), and the median number of doses was 3 (IQR 2–4). Baseline clinical characteristics of both groups are presented in Table 1. The long-term and short-course groups were comparable with respect to sex ratio, age at onset, disease spectrum (including autoimmune encephalitis, FIRES, MOGAD,

and AESD), pre-existing infections prior to tocilizumab therapy (predominantly pneumonia, followed by urinary tract infection, mastoiditis, lymphadenitis, and sinusitis), and history of hepatitis B virus (HBV) infection (all $P > 0.05$). Notably, the proportion of patients admitted to the PICU in the acute phase was significantly higher in the long-term treatment group than in the short-course group ($P = 0.035$).

Table 1 Comparison of baseline characteristics between the long-term treatment group and the short-course group

Variable	Total (<i>n</i> = 90)	Long-term treatment group (<i>n</i> = 45)	Short-course group (<i>n</i> = 45)	χ^2 value	<i>P</i> value
Sex, <i>n</i> (%)					
Male	60 (66.7)	30 (66.7)	30 (66.7)	-	-
Female	30 (33.3)	15 (33.3)	15 (33.3)		
Age at onset, years, median (IQR)	5.9 (3.0– 9.3)	5.7 (2.5–9.3)	6.2 (4.0–10.8)	-	0.278*
Age group, <i>n</i> (%)					
<6 years	43 (47.8)	25 (55.6)	18 (40.0)	2.182	0.140
≥6 years	47 (52.2)	20 (44.4)	27 (60.0)		
Diagnosis, <i>n</i> (%)					
AE	56 (62.2)	29 (64.4)	27 (60.0)	-	0.657**
FIRES	24 (26.7)	11 (24.4)	13 (28.9)		
MOGAD	6 (6.7)	2 (4.4)	4 (8.9)		
AESD	4 (4.4)	3 (6.7)	1 (2.2)		
Time from onset to TCZ initiation, months, <i>n</i> (%)					
<6 months	58 (64.4)	28 (62.2)	30 (66.7)	0.203	0.652
≥6 months	32 (35.6)	17 (37.8)	15 (33.3)		
Pre-existing infection before TCZ initiation, <i>n</i> (%)	36 (40.0)	17 (37.8)	19 (42.2)	0.149	0.699
History of HBV exposure [^] , <i>n</i> (%)	6 (6.7)	3 (6.7)	3 (6.7)	-	-
PICU admission in acute phase, <i>n</i> (%)	60 (66.7)	35 (77.8)	25 (55.6)	4.440	0.035

Note: * Mann-Whitney *U* test; ** Fisher's exact test; ^ Defined as anti-HBc positivity and HBsAg negativity.

Abbreviations: AE, autoimmune encephalitis; AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; FIRES, febrile infection-related epilepsy syndrome; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; TCZ, tocilizumab.

2.2 Concomitant Immunotherapy with TCZ

Since neuroimmune diseases usually require multimodal immunotherapy, children receiving TCZ treatment often combine it with other immunomodulatory regimens. Among the 90 patients, glucocorticoids, IVIG, and rituximab were the most commonly co-administered therapies, received by 75 (83.3%), 75 (83.3%), and 43 (47.8%) patients, respectively. In addition, some children also received other immunotherapies such as plasma exchange, cyclophosphamide, and mycophenolate mofetil.

When stratified by treatment duration, combined immunotherapies in the short-course group ($n = 45$) included glucocorticoids [$n = 40$ (88.9%)], IVIG [$n = 37$ (82.2%)], rituximab [$n = 18$ (40.0%)], plasma exchange [$n = 3$ (6.7%)], cyclophosphamide [$n = 1$ (2.2%)], and mycophenolate mofetil [$n = 3$ (6.7%)]. In the long-term group ($n = 45$), the corresponding frequencies were glucocorticoids [$n = 35$ (77.8%)], IVIG [$n = 38$ (84.4%)], rituximab [$n = 25$ (55.6%)], plasma exchange [$n = 13$ (28.9%)], cyclophosphamide [$n = 3$ (6.7%)], and mycophenolate mofetil [$n = 3$ (6.7%)].

2.3 Incidence and major clinical manifestations of adverse events

The overall incidence of adverse events (AEs) in the 90 patients was 87.8% (79/90). Of those with AEs, the long-term group comprised 28 males and 14 females, and the short-course group comprised 24 males and 13 females. The median age at onset for patients with AEs was 5.9 (IQR 3.1–9.6) years in the long-term group and 7.1 (IQR 3.3–11.0) years in the short-course group. Among patients with pre-existing infection prior to TCZ administration, AEs occurred in 16 cases in the long-term group and 15 cases in the short-course group. No significant between-group differences were observed in overall AE incidence after stratification by sex, age at onset, or the occurrence of new-onset or exacerbated infection following treatment (all $P > 0.05$). A comparison of specific AE indicators between the two groups is shown in Table 2, with the main clinical characteristics summarized as follows:

(1) Neutropenia: Across the entire cohort, 38 cases were observed, with a mean nadir neutrophil count of $1.0 \pm 0.4 \times 10^9/L$. No patient developed sepsis or other severe infections due to neutropenia. The incidence in the long-term treatment group was significantly higher than in the short-course group ($P = 0.033$). Considering that the proportion of patients in the long-term treatment group who were admitted to the PICU during the acute phase was relatively high, this suggested a potential difference in disease severity. Therefore, a multivariate logistic regression model included the variable of PICU admission during the acute phase for correction. The results showed that the treatment group was still associated with the occurrence of neutropenia (OR = 2.450, 95% CI: 1.021 - 5.882, $P = 0.045$), while PICU admission during the acute phase did not show a significant impact. Subgroup analysis indicated that among patients admitted to the PICU ($n = 60$), the incidence of neutropenia in the long-term group remained significantly higher than in the short-course group (62.9% vs. 20.0%, $P = 0.001$). In addition, while

neutropenia in the long-term treatment group was predominantly mild, the short-course group exhibited a higher proportion of moderate-to-severe cases, resulting in a significantly worse overall severity distribution ($Z = -2.397$, $P = 0.017$).

(2) Liver transaminases and dyslipidemia: Elevated liver enzymes were observed in 35 patients (38.9%), with a mean peak transaminase level of 56.9 ± 18.3 U/L. Dyslipidemia was recorded in 33 cases (36.7%), with a mean peak triglyceride level of 3.0 ± 1.1 mmol/L and a mean peak cholesterol level of 6.1 ± 0.7 mmol/L. Except for one case of severe hypertriglyceridemia in the short-course group, all other liver enzyme and lipid abnormalities in both groups were of Grade 1-2 severity. There was no statistically significant difference in incidence between the two groups (all $P > 0.05$).

(3) Fibrinogen abnormalities: Fibrinogen testing was performed in 60 patients ($n = 30$ in both the long-term and short-course groups). Hypofibrinogenemia (decreased fibrinogen) was identified in 33 cases (55.0%), with a mean nadir fibrinogen value of 1.4 ± 0.4 g/L. Most cases were Grade 1-2 AEs; only three cases were Grade 3-4 (< 1.0 g/L). No spontaneous bleeding events occurred, and the incidence did not differ significantly between groups (all $P > 0.05$).

(4) New-onset or exacerbated infections: Among the 36 patients with pre-existing infections prior to TCZ initiation, all received appropriate antimicrobial therapy before starting TCZ. During the TCZ treatment period, a total of 12 patients (13.3%) experienced either exacerbation of pre-existing infections or new-onset infections. The most frequent infection was pneumonia ($n = 9$), followed by urinary tract infections and conjunctivitis (some patients experienced concurrent infectious episodes). Separately, skin rash was observed in 2 patients (2.2%). All patients with infectious complications or exacerbations were promptly treated with targeted antimicrobial agents. No patient developed sepsis or other life-threatening infectious complications during the follow-up period. There was no statistically significant difference in infection rates between the long-term and short-course groups ($P = 0.063$).

(5) Reduction in immunoglobulin levels: Post-treatment humoral immune parameters were evaluated in 69 patients. Hypogammaglobulinemia (predominantly decreased IgG levels) occurred in 52 patients (75.4%), with a mean nadir IgG level of 4.6 ± 1.3 g/L. Notably, the incidence was significantly higher in the long-term group than in the short-course group [85.0% (34/40) vs 62.1% (18/29); $P = 0.031$]. Among those with hypogammaglobulinemia, concurrent infections occurred in only 6 patients (2 long-term, 4 short-course), while the majority remained clinically asymptomatic.

Table 2 Summary and Comparison of Adverse Events (AEs) between Groups

Adverse Event, <i>n</i> (%)	Total (<i>n</i> = 90)	Long-term treatment group (<i>n</i> = 45)	Short-course group (<i>n</i> = 45)	χ^2 value	<i>P</i> value
Neutropenia	38 (42.2)	24 (53.3)	14 (31.1)	4.555	0.033
Severity distribution (Mann–Whitney U)				–2.397 ^a	0.017
Grade 1	20 (52.6) ^b	16 (66.7)	4 (28.6)	-	-
Grade 2	14 (36.8) ^b	7 (29.2)	7 (50.0)	-	-
Grade 3-4	4 (10.5) ^b	1 (4.2)	3 (21.4)	-	-
Elevated liver transaminases	35 (38.9)	18 (40.0)	17 (37.8)	0.046	0.830
Dyslipidemia	33 (36.7)	17 (37.8)	16 (35.6)	0.048	0.826
Hypertriglyceridemia	22 (24.4)	12 (26.7)	10 (22.2)	0.244	0.621
Hypercholesterolemia	23 (25.6)	12 (26.7)	11 (24.4)	0.059	0.808
Hypofibrinogenemia (<i>n</i> = 60) ^c	33 (55.0)	20 (66.7)	13 (43.3)	3.300	0.069
Grade 1-2	30 (50.0)	17 (56.7)	13 (43.3)	-	-
Grade 3-4	3 (5.0)	3 (10.0)	0 (0.0)	-	-
Hypogammaglobulinemia (<i>n</i> = 69) ^d	52 (75.4)	34 (85.0)	18 (62.1)	4.646	0.031
Infection (new-onset or exacerbation) ^e	12 (13.3)	3 (6.7)	9 (20.0)	3.462	0.063
Rash	2 (2.2)	0 (0.0)	2 (4.4)	-	0.494 ^f
Severe allergic reaction	0 (0.0)	0 (0.0)	0 (0.0)	-	-
ECG abnormality	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Other (e.g., perforation, sepsis)	0 (0.0)	0 (0.0)	0 (0.0)	-	-

Note: Bold font indicates statistical significance ($P < 0.05$).

^a Mann–Whitney U test (Z value);

^b Percentages for sub-severities (Grade 1, Grade 2, Grade 3-4) are calculated based on the total number of patients with that specific AE (Total $n = 38$; Long-term $n = 24$; Short-course $n = 14$).

^c Effective sample size for fibrinogen analysis was $n = 30$ per group due to missing data. ^d Effective sample size for hypogammaglobulinemia analysis was $n = 69$ ($n = 40$ in the long-term group and $n = 29$ in the short-course group) due to missing laboratory data.

^e A total of 12 patients experienced infectious events; individual patients may have presented with more than one infectious site.

^f Fisher's exact test.

2.4 Management of adverse events

The median follow-up period was 15 (IQR 7–22) months. Among the six patients with a history of HBV infection, three received oral entecavir, one received tenofovir alafenamide, and two were managed with clinical observation without specific antiviral treatment; no HBV reactivation was detected. TCZ treatment was postponed for one month in nine patients due to moderate or severe neutropenia and discontinued in two cases. Nine patients with Grade 1-2 neutropenia received a 50% dose reduction during that cycle, while 18 patients received the standard dose as scheduled. Eleven patients received oral glutathione and one received oral bicyclol tablets for elevated transaminase levels; liver function was reassessed during follow-up in 23 patients. No patient received lipid-lowering therapy; all cases of dyslipidemia underwent periodic reassessment. All 12 patients who experienced infection exacerbation or new-onset infection received antimicrobial therapy. Six patients with hypofibrinogenemia received fibrinogen infusion support, and 27 patients underwent follow-up coagulation monitoring. IVIG was administered to 37 patients with hypogammaglobulinemia.

At the final follow-up (defined as the patient's last visit, regardless of medication status), among the 73 patients (81.1%) who had discontinued the medication for at least three months, all baseline and newly developed infections remained stable or had resolved. In patients with a history of HBV, HBV-DNA titers remained undetectable. All cases of neutropenia, elevated transaminases, dyslipidemia, hypofibrinogenemia, and hypogammaglobulinemia had resolved. Among the 17 patients (18.9%) on ongoing therapy, laboratory parameters remained mildly abnormal (CTCAE grade 1) with dose adjustment or hepatoprotective therapy, without persistent deterioration.

3. Discussion

This is the largest real-world cohort with the longest follow-up of pediatric neuroimmunological patients treated with tocilizumab. The results demonstrate that although the overall incidence of AEs was 87.8%, the vast majority were Grade 1-2 and reversible; notably, only two patients discontinued treatment completely due to Grade 3-4 neutropenia. This suggests that TCZ has an acceptable safety profile in children, irrespective of treatment duration[13,14,19,20], providing a key reference for TCZ safety management in pediatric neuroimmunology.

In rheumatology, such as juvenile idiopathic arthritis, TCZ has a well-established weight-based dosing regimen with safety validated in long-term follow-up cohorts lasting 3–5 years[14,21,22]. However, its use in pediatric neuroimmunology remains off-label, without a standardized dosing regimen. Additionally, these patients exhibit unique characteristics, including a distinct overall immune status and an elevated risk of severe infections linked to factors such as prolonged PICU stays. In this study, the frequency of TCZ administration (typically once every four weeks) was lower than in patients with rheumatologic diseases (typically every two weeks[14]), and the median treatment duration was shorter, resulting in a lower cumulative dose. Despite these differences in dosing frequency and cumulative exposure, the adverse event profiles were similar between the two disease populations, with neutropenia, elevated transaminase levels, and dyslipidemia as the primary manifestations[22]. Nevertheless, we identified features distinct from the rheumatology literature, including a high prevalence of hypofibrinogenemia (55.0%) and hypogammaglobulinemia (75.4%). In rheumatology, decreased fibrinogen is often considered an indicator of inflammatory remission[14,19]; however, in the neuroimmunological context, its marked reduction may be primarily attributed to the direct inhibition of hepatic acute-phase protein synthesis by TCZ[1,23]. Regarding humoral immunity, previous rheumatology cohorts receiving monotherapy generally maintained stable IgG levels[13], whereas the incidence of hypogammaglobulinemia in our study (75.4%) was significantly higher than that reported in neuroimmunology cohorts treated with rituximab alone or high-dose glucocorticoids (typically 20%–40%)[24]. This variation reflects the synergistic effects of multiple potent immunotherapies: patients with neuroimmunological diseases often receive intensified immunosuppression during the acute phase—such as rituximab, glucocorticoids, IVIG, B-cell depletion therapy, and other immunomodulatory regimens—which further exacerbates the reduction in protein synthesis and humoral immunosuppression[18,20].

Furthermore, in contrast to rheumatological studies that highlight long-term cumulative risk, the present study demonstrates that severe neutropenia is more likely to occur during the early stages of treatment, typically within the first three months of initiating TCZ[25,26]. Although the overall incidence in the long-term group was higher, the AEs were generally milder. It is worth noting that children treated with TCZ for a long period usually have more complex treatment backgrounds. In this study, the proportion of the long-term treatment group that received plasma exchange and other immunomodulatory treatments such as rituximab was relatively high. Therefore, the influence of disease severity and combined immunotherapy on the changes in neutrophils cannot be completely ruled out. This phenomenon is likely linked to the pharmacological mechanism of TCZ: it disrupts the dynamic distribution of neutrophils between the circulating and marginal pools and inhibits IL-6-mediated anti-apoptotic signaling pathways, leading to a reduction in circulating neutrophil counts[1,26]. During the long-term maintenance phase, as

the inflammatory milieu of the primary disease improves and pharmacokinetics reach a steady state, this distribution typically stabilizes and presents as a controllable, mild decrease[27]. This observation indicates that during the acute dosing phase, close monitoring for rapid declines in neutrophil counts and secondary infections is imperative; dose reduction, delayed administration, or granulocyte colony-stimulating factor (G-CSF) should be considered promptly if needed. Such neutropenia is predominantly transient and reversible, generally not leading to severe infection or mortality. With timely dose adjustments and symptomatic management, most patients recovered rapidly and completed subsequent treatment, resulting in a favorable overall prognosis.

Additionally, this study identified that hypofibrinogenemia was relatively prevalent during TCZ therapy, with an overall incidence of 55.0% (33/60). Most cases involved Grade 1-2 reductions, with only three instances of Grade 3-4 deficiency (< 1.0 g/L). No serious coagulation-related AEs, such as spontaneous bleeding, were observed, indicating that TCZ treatment was clinically manageable. The clinical management of hypofibrinogenemia requires regular monitoring of coagulation function. In cases of Grade 2-4 reduction, supportive fibrinogen infusion may be considered to mitigate bleeding risks. The incidence of hypofibrinogenemia in the long-term group (66.7%) was numerically higher than in the short-course group (43.3%); however, due to the relatively high rate of missing data (approximately 33.3%) inherent to the retrospective design, the statistical power was limited, and the difference did not reach statistical significance ($P = 0.069$). Further studies with larger sample sizes are warranted to clarify the specific impact of long-term TCZ treatment on coagulation function.

In addition to the hematological and infectious systems, the incidence and severity of elevated transaminase levels (38.9%) and dyslipidemia (36.7%) observed in this study were highly consistent with those reported in previous rheumatology and immunology cohorts[13,14,23]. Most of these abnormalities were Grade 1-2, reversible pharmacological effects. Following dynamic observation, dietary intervention, or hepatoprotective management, laboratory parameters normalized in patients who discontinued the medication, while those who continued therapy remained within the range of Grade 1 abnormalities without long-term organ damage. Given that the metabolic mechanisms have been thoroughly elucidated, monthly monitoring according to standard protocols is sufficient in clinical practice. Additionally, in this cohort, no viral reactivation was observed in patients with a history of HBV infection under close monitoring, indicating a favorable safety profile.

Furthermore, this study evaluated whether baseline characteristics—such as younger age at onset (< 6 years), more severe primary disease (admission to the PICU during the acute phase), and transient neutrophil reduction following initial administration—could serve as clinical indicators for predicting AEs. None of these factors were significantly associated with the occurrence or severity of AEs. This finding is largely constrained by the single-center retrospective design, where the overall incidence of AEs was as high as 87.8%, resulting in a limited no adverse event control group (only 11 cases). Although a higher proportion of patients in the long-term group were admitted to the PICU during the acute phase (indicating more severe initial disease), the primary focus of this study was to evaluate safety throughout the entire course of TCZ therapy. At our center, all patients with neuroimmunological diseases receive

standardized adjunctive therapy during the maintenance phase—such as oral glucocorticoid tapering—irrespective of PICU admission. Furthermore, our multivariable logistic regression analysis included PICU admission during the acute phase as an independent variable; the results demonstrated that it was not an independent risk factor for AEs. This finding highlights an important clinical reality: TCZ-induced AEs occur across a wide spectrum of pediatric patients regardless of baseline characteristics. A transient, mild neutropenia after the initial dose does not necessarily predict subsequent severe AEs. Conversely, older patients or those with non-critical illness (i.e., not admitted to the PICU) remain at risk for severe neutropenia. Therefore, vigilant and continuous monitoring throughout the treatment course is essential for all pediatric patients receiving TCZ.

Nevertheless, our study has several limitations. First, the duration and dosage of combined immunotherapy (including glucocorticoids, rituximab, plasma exchange, and other immunomodulatory drugs) during tocilizumab treatment could not be further quantified. Second, due to the retrospective study design, laboratory monitoring for humoral immune parameters and fibrinogen was missing in a subset of patients. Third, as a single-center retrospective study, the present study has selection bias, which may restrict the precision and generalizability of the results. More prospective multicenter studies are expected in the future.

4. Conclusion

In conclusion, TCZ has a favorable safety profile in pediatric patients with neuroimmunological diseases, with most laboratory abnormalities being reversible. Although the overall incidence of neutropenia in the short-course group was lower than that in the long-term group, the propensity for severe AEs was notably higher in the early stages of treatment. Therefore, we recommend that patients receiving TCZ undergo stringent laboratory monitoring: during the first 3–6 months, complete blood counts may be performed every 2–4 weeks to monitor for severe neutropenia. After 6 months, monitoring can be performed monthly with the dosing schedule, with periodic reassessment of humoral immune parameters every 3–6 months.

Declarations

Author contributions

YH and YH: Investigation, Formal analysis, Data curation, Methodology, Writing—original draft. FH, LY, GW: Investigation, Data curation, Methodology. JP: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Data availability

The data used or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Ethics approval and consent to participate This study adhered to the principles of the Declaration of Helsinki. Ethical approval for this study was obtained from the Ethics Committee of Xiangya Hospital(202310892). Informed consent was obtained from all participants' guardians.

Consent for publication All informed consent forms, including consent for publication, have been obtained from the guardians of patients.

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