Observational Study

Medicine

OPEN

Therapeutic and hepatoprotective effect of tocilizumab combined with total glycosides of peony in systemic juvenile idiopathic arthritis

Liya Gao, MM[a], Jing Xie, DSc[c], Zhongyu Ren, PhD[b], Xiaoqiong Wei, MM[a], Xuemei Tang, MD[a,*]

Abstract

This retrospective observational study aimed to evaluate the effectiveness and hepatoprotective effects of combination therapy with tocilizumab (TCZ) and total glycosides of peony (TGP) in treating systemic juvenile idiopathic arthritis (sJIA). Among the 119 sJIA patients enrolled, 49 received TCZ combined with TGP (study group) and 70 received TCZ not combined with TGP (control group). We compared clinical characteristics, 5 liver function indices (alanine aminotransferase [ALT]/aspartate aminotransferase [AST]/alkaline phosphatase/γ-glutamyltransferase/total bilirubin), transaminase (ALT/AST) Kaplan–Meier curves, and inflammatory indices between the groups. The study group showed significantly lower rates of abnormal ALT, AST, alkaline phosphatase, and γ-glutamyltransferase levels ($P < .05$). Among patients with abnormal liver function indices, transaminase abnormalities were the most common (87.50%), particularly after the first TCZ administration (44.64%). Analysis of Kaplan–Meier curves for transaminases for different treatment durations indicated significantly lower abnormal rates (ALT/AST > 1 and 3 × upper limit of normal) in the study group ($P < .05$). The Cox regression model and forest plot identified the group with the highest risk ratio (study group vs control group, hazard ratio = 3.985, 95% confidence interval: 1.997–7.952) as an independent risk factor for transaminase abnormalities. A comparison of therapeutic outcomes revealed a more obvious decrease in the number of patients with abnormal inflammation indices in the study group before and after treatment. Moreover, the erythrocyte sedimentation rate value in the study group at the last follow-up significantly lower than that in the control group ($P < .05$). The combination of TCZ and TGP effectively reduced inflammation and lowered the incidence of liver injury, suggesting it may be the preferred combination therapy for sJIA.

Abbreviations: ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CRP = C-reactive protein, DILI = drug-induced liver injury, ESR = erythrocyte sedimentation rate, GC = glucocorticoids, GTT = γ-glutamyltransferase, IL-6 = interleukin-6, IQR = inter quartile range, JIA = juvenile idiopathic arthritis, K–M curve = Kaplan–Meier curve, NSAIDs = nonsteroidal anti-inflammatory drugs, sJIA = systemic juvenile idiopathic arthritis, TBil = total bilirubin, TCZ = tocilizumab, TGP = total glucosides of peony, ULN = upper limit of normal.

Keywords: liver injury, systemic juvenile idiopathic arthritis, tocilizumab, total glycosides of peony, transaminase

1. Introduction

Systemic juvenile idiopathic arthritis (sJIA) is one of the most prevalent chronic rheumatic diseases in childhood and a subtype of juvenile idiopathic arthritis (JIA) characterized by intensified inflammation, heightened detrimental effects, and increased rates of mortality and disability.[1,2] In 2018, Ravelli et al[3] introduced the concept of a goal-directed treatment approach for JIA globally. The primary objective is to promptly control the inflammatory response to achieve clinical remission. Recent studies have indicated a substantial increase in serum interleukin-6 (IL-6) introduced the concept of a goal-directed treatment approach for JIA globally. The primary objective is to promptly control the inflammatory response to achieve

This study was supported by grants from the National Key R&D Program of China (No. 2021YFC2702003).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplemental Digital Content is available for this article.

[a] Department of Rheumatology and Immunology, Children's Hospital of Chongqing Medical University/Chongqing Key Laboratory of Child Infection and Immunity/Ministry of Education Key Laboratory of Child Development and Disorders/National Clinical Research Center for Child Health and Disorders/China International Science and Technology Cooperation Base of Child Development and Critical Disorders/ Children's Hospital of Chongqing Medical University, Chongqing, China, [b] School of Physical Education, Southwest University, Chongqing, China, [c] School of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing, China.

** Correspondence: Xuemei Tang, Department of Rheumatology and Immunology, Children's Hospital of Chongqing Medical University/Chongqing Key Laboratory of Child Infection and Immunity/Ministry of Education Key Laboratory of Child Development and Disorders/National Clinical Research Center for Child Health and Disorders/China International Science and Technology Cooperation Base of Child Development and Critical Disorders/Children's Hospital of Chongqing Medical University, Chongqing 400014, China (e-mail: tangxuemei2008@163.com).*

How to cite this article: Gao L, Xie J, Ren Z, Wei X, Tang X. Therapeutic and hepatoprotective effect of tocilizumab combined with total glycosides of peony in systemic juvenile idiopathic arthritis. Medicine 2025;104:8(e41552).

Received: 7 July 2024 / Received in final form: 5 December 2024 / Accepted: 29 January 2025

http://dx.doi.org/10.1097/MD.0000000000041552

clinical remission. Recent studies have indicated a substantial increase in serum IL-6 levels in patients with sJIA compared to healthy individuals. Elevated IL-6 levels were significantly associated with the severity of joint symptoms and increased platelet counts.[4] Tocilizumab (TCZ), a fully humanized IL-6 receptor monoclonal antibody, impedes the interaction between IL-6 and its receptors, thereby obstructing IL-6-mediated signaling pathways.[5] Consequently, TCZ is considered an optimal biological agent for sJIA treatment.[6,7] Beyond addressing the limitations of traditional drugs with suboptimal efficacy, TCZ induces fresh optimism in patients with intractable, recurrent, severe, and highly active disease.

TCZ, being the sole anti-IL-6R agent authorized for treatment in pediatric patients with sJIA aged ≥ 2 years in China, holds considerable importance. Nevertheless, its long-term effectiveness and safety are under close scrutiny owing to its limited time in the Chinese market and inadequate accumulation of dependable clinical data.[8–10]

Attention should be paid for monitoring the adverse effects such as allergies, neutropenia, and elevated liver enzymes when administering TCZ.[11] Specifically, elevation in serum concentrations of transaminases is frequently noted as an adverse reaction and has been reported multiple times.[12] Furthermore, children may be more susceptible to drug-induced liver injury (DILI) because of their underdeveloped liver, immature liver enzyme system, incomplete immune function, limited tolerance, and metabolic capacity for potential drug toxicity.[13] These adverse reactions can impede normal growth, affect vital organ function, and even lead to discontinuation of the targeted drug, presenting a significant challenge in achieving optimal therapeutic outcomes. Therefore, further research is urgently required to enhance the safety profile of TCZ.

The optimal approach for treating sJIA is the long-term concurrent use of multiple medications rather than relying solely on TCZ monotherapy because of the challenges in effectively managing the condition.[14] In addition to conventional drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs, and glucocorticoids (GC), complementary medications are commonly used. Notably, the total glucosides of peony (TGP) have demonstrated remarkable therapeutic benefits and superior safety profiles in adult patients, exerting immunomodulatory, anti-inflammatory, antioxidant, analgesic, antiviral, and hepatoprotective effects.[15] Further investigations have revealed that TGP contains a variety of active ingredients and can synergistically treat diseases through multiple pathways and targets.[16,17] It has a broad spectrum of regulatory and protective effects, making it a medicinal herb with substantial potential for development. Nevertheless, in recent years, only a limited number of Chinese researchers have reported improved efficacy and a positive safety profile of TGP in the management of JIA. Some studies have proposed that TGP combined with first-line drugs showed better effects on erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), TNF-α, and rheumatoid factor.[18,19] In addition, expert Yongsong Cai stated that in their meta-analysis, the group that incorporated TGP demonstrated a reduction in the main adverse events, including liver function abnormalities, leukopenia, rash, stomatitis, and anorexia.[20] This study aimed to provide clinicians with a scientific foundation for selecting appropriate treatment strategies by exploring the anti-inflammatory and hepatoprotective properties of TCZ in combination with TGP.

2. Methods

2.1. Study population

A total of 119 children diagnosed with sJIA and prescribed TCZ (Shanghai Roche Pharmaceutical Co., Ltd., 80 mg/4 mL) at the Children's Hospital of Chongqing Medical University between January 1, 2014, and December 31, 2023, were included in this study. The research protocol was carefully reviewed and approved by the Ethics Committee of Children's Hospital Affiliated to Chongqing Medical University.

Inclusion criteria: ① participants aged below 18 years, ② adherence to either the International League of Associations for Rheumatology classification standards (2001)[21] or the Pediatric Rheumatology International Trials Organization classification standards (2018),[22] ③ written consent obtained from all parents/legal guardians for the administration of biological agents, ④ TCZ was introduced following the conventional treatment regimen in cases of inadequate response or intolerance to NSAIDs and GC, ⑤ availability of relatively comprehensive and retrievable medical records.

Exclusion criteria: ① times of TCZ used ≤ 3, ② extremely irregular TCZ dosing intervals or intervals > 6 months between consecutive TCZ infusions, ③ extremely irregular TGP dosing intervals or not taking TGP during any consecutive TCZ infusions, ④ history of liver dysfunction or other hepatic disorders within the initial 6 months before initiating TCZ therapy, ⑤ administration of liver protective therapy or liver function indices (alanine aminotransferase [ALT]/

Table 1

Comparison of general clinical data between groups.

	n = 119	Study group (n = 49)	Control group (n = 70)	Statistical value	*P* value
Demographic characteristics					
Sex (males/females, n)	68/51	28/21	40/30	0.000	1.000
Age at medication (years)*	7.70 ± 3.18	7.90 ± 3.07	7.55 ± 3.27	0.582	.562
Nation (national minority/Han Chinese, n)	14/105	6/43	8/62	0.019	.892
Medication characteristics					
Times of TCZ used†	15 (9, 20)	14 (8.50, 19.00)	15 (8.75, 23.25)	0.450	.503
Course of treatment (Month)†	12.40 (6.10, 27.43)	12.97 (7.12, 26.44)	11.61 (5.96, 27.63)	0.003	.959
TCZ dose (mg/once)†	240 (230, 320)	240 (220, 280)	243 (222.5, 320)	1.886	.170
DILI‡					
Level 1 (mild liver injury) [n (%)]	7 (5.88)	1 (2.04)	6 (8.57)	2.415	.120
Level 2 (moderate liver injury) [n (%)]	2 (1.68)	0 (0.00)	2 (2.86)		
Level 3 (severe liver injury) [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)		
Level 4 (deadly) [n (%)]	0 (0.00)	0 (0.00)	0 (0.00)		

TCZ = tocilizumab.

* [Mean ± SD].

† [Median (IQR)]

‡ Drug-induced liver injury (DILI) is classified into 4 levels according to the Chinese Guideline for Diagnosis and Management of Drug-induced Liver Injury (2023 Version).[19]

aspartate aminotransferase [AST]/alkaline phosphatase (ALP)/γ-glutamyltransferase (GTT), and total bilirubin (TBil)) exceeding the normal limits by ≥1 item within the initial 3 months before initiating TCZ therapy.

2.2. Materials and methods

2.2.1. Materials. Employing a retrospective observational study approach, we used the clinical big data platform of the Children's Hospital of Chongqing Medical University to retrieve medical records of the selected cases. This included essential clinical information such as sex, age, ethnicity, time of TCZ use, course of treatment, use of TGP in combination, types of other concurrent medications, and laboratory data such as liver function indices (ALT, AST, ALP, GTT, and TBil) and inflammatory indices (ESR and CRP). The normal range for all indices is established based on our hospital's central laboratory standards: ALT (0.0–40.0 U/L), AST (0.0–45.0 U/L), ALP (100–300 U/L), GTT (0.0–45.0 U/L), TBil (10.0–50.0 μmol/L), ESR (0–15 mm/1 hour), CRP (<8 mg/L). Indices exceeding the upper limit of normal (ULN) were classified as abnormal.

The medication standards for TCZ and TGP in this study adhered to our hospital's central pharmacy guidelines and their respective specifications, as detailed below: ① TCZ: 12 mg/kg/time (weight <30 kg) or 8 mg/kg/time (weight ≧ 30 kg), biweekly; ② TGP: 30 mg/kg, twice a day.

2.2.2. Grouping and follow-up. Patients who consistently received TGP along with TCZ treatment were included in the study group, while the remaining patients who did not receive TGP treatment constituted the control group.

This retrospective observational study included liver function indices and treatment outcomes across different medication protocols, which require a rigorous follow-up strategy. In light of some specific factors caused by the patients that could result in loss of follow-up, we maintained our oversight via telephone or outpatient consultations after each treatment discharge until we verified the relevant indicator outcomes after the last administration of TCZ. As a result, the cumulative follow-up duration from the detection of relevant indices before the first usage of TCZ to the detection of relevant indices after the last usage of TCZ was 13.87 months (inter quartile range [IQR]: 7.50, 29.43 months).

2.2.3. Evaluation criterion. According to the "Chinese Guideline for Diagnosis and Management of Drug-induced Liver Injury (2023 Version),"[23] DILI is categorized into 4 levels: mild (ALT ≥ 5 × ULN or ALP ≥ 2 × ULN and TBil < 2 × ULN); moderate (ALT ≥ 5 × ULN or ALP ≥ 2 × ULN and TBil ≥ 2 × ULN, or symptomatic hepatitis); severe (ALT ≥ 5 × ULN or ALP ≥ 2 × ULN and TBil ≥ 2 × ULN, or symptomatic hepatitis with any one of the following conditions: ① international normalized ratio ≥ 1.5; ② ascites or hepatic encephalopathy, with a course of <26 weeks and no cirrhosis; ③ other organ failure caused by DILI); deadly (death due to DILI or need for liver transplantation to survive). As per the TCZ specification, ALT/AST > 1/3/5 × ULN was used as the basis for adjusting the sJIA treatment. According to the "Chinese expert consensus on the diagnosis and treatment of systemic juvenile idiopathic arthritis (2023 edition),"[24] the primary goal of standard treatment is to achieve clinical remission, with the reduction of the patient's inflammatory indices (ESR and CRP levels) to the normal range serving as the primary efficacy evaluation criterion in this study.

Table 2

Comparison of abnormal liver function patients.

Abnormal liver function index	n = 119	Study group (n = 49)	Control group (n = 70)	χ^2/ Fisher	*P* value
ALT [n (%)]	47 (39.50)	9 (18.37)	38 (54.29)	15.561	**.000*****
AST [n (%)]	42 (35.29)	7 (14.29)	35 (50.00)	16.098	**.000*****
ALP [n (%)]	7 (5.88)	0 (0.00)	7 (10.00)	5.206	**.040***
GTT [n (%)]	20 (16.81)	3 (6.12)	17 (24.29)	6.801	**.009****
TBil [n (%)]	10 (8.40)	2 (4.08)	8 (11.43)	1.179	.277
ALT/AST [n (%)]†	56 (47.06)	11 (22.45)	45 (64.29)	20.250	**.000*****
ALT/AST/ALP/GTT/TBil [n (%)]‡	64 (53.78)	12 (24.49)	52 (74.29)	28.753	**.000*****

Bold values represent results with statistical significance (*P* < .05).

ALT = alanine aminotransferase, ALP = alkaline phosphatase, AST = aspartate aminotransferase, GTT = γ-glutamyltransferase, TBil = total bilirubin; ALT/AST/ALP/GTT/TBil > 1 × ULN.

**P* < .05, ***P* < .01, ****P* < .001 indicate the levels of statistical significance.

† At least 1 abnormality exists in 2 transaminase indices.

‡ At least 1 abnormality exists among the 5 liver function indices.

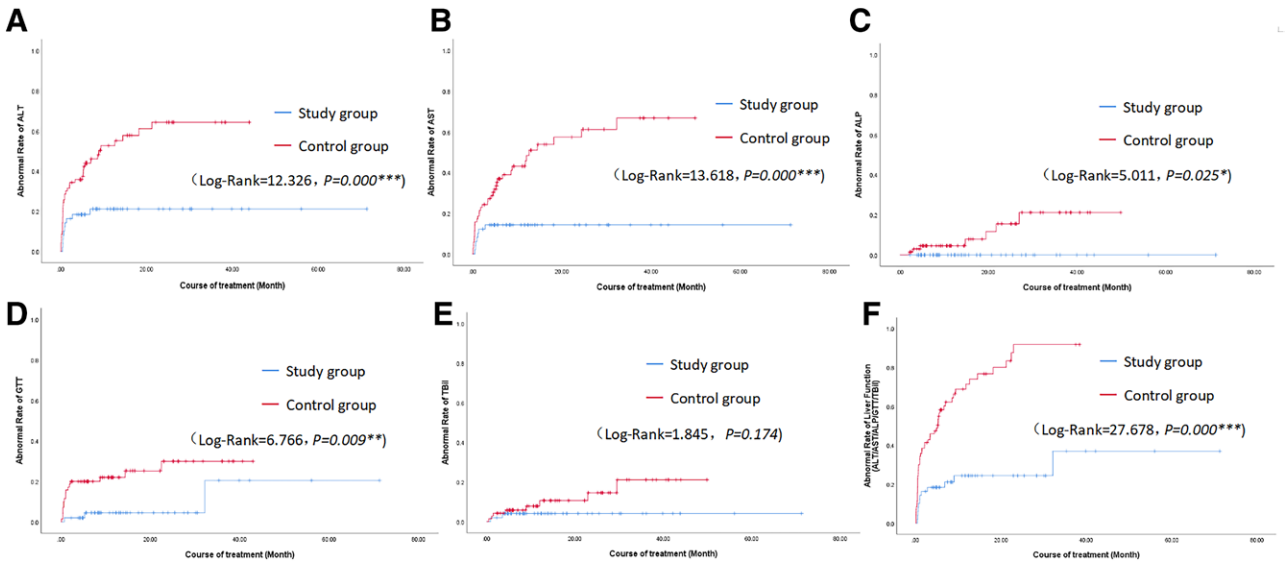

Figure 1. Kaplan–Meier curve for abnormal liver function indices. (A) K–M curve of abnormal ALT, (B) K–M curve of abnormal AST, (C) K–M curve of abnormal ALP, (D) K–M curve of abnormal GTT, (E) K–M curve of abnormal TBil, (F) K–M curve of abnormal ALT/AST/ALP/GTT/TBil (>1 × ULN).

2.2.4. Statistical methods. Measurement data: data following a normal distribution were represented by [mean ± (standard deviation [SD])] ($\bar{x}\pm s$), and comparisons of means between groups were conducted using an independent sample t test. Data not conforming to a normal distribution are represented as (median [IQR]) and compared between groups using the Kruskal–Wallis test. Counting data: data are presented as [n (%)], and intergroup comparisons were performed using the chi-square test or Fisher exact test in a 2 × 2 table. The Kaplan–Meier (K–M) method was used to generate abnormal rate curves of liver indices, and differences between the groups were compared using the log-rank test. Regression analysis of multiple factors influencing liver function was conducted using the Cox model, and the results were inputted into GraphPad Prism 9 software to construct a forest plot. Statistical analysis was performed using SPSS 26.0 software, with $P < .05$ indicating significant differences ($^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ indicating levels of significance in subsequent figures and tables).

3. Results

3.1. General clinical characteristics

Among the 119 patients diagnosed with sJIA, 58 were male and 51 were female. They received TCZ treatment for the first time at an average age of 7.70 years (±SD: 3.18 years). During the study period, the patients received TCZ treatment 15 times (IQR: 9, 20 times), with a single therapeutic dose of 240 mg (IQR: 230, 320 mg) and a treatment course of 12.40 months (IQR: 6.10, 27.43 months).

The patients were categorized into a study group of 49 patients (41.18%) and a control group of 70 patients (58.82%) based on the inclusion or exclusion of TGP in their treatment. No significant differences were observed in the general clinical characteristics of the groups ($P > .05$). Among the 9 patients who met the diagnostic criteria for DILI, only one in the study group experienced mild liver injury, whereas 8 in the control group experienced mild-to-moderate liver damage. None of the patients had severe liver injury or mortality (Table 1).

3.2. Comparison of liver function index between groups

Five key liver function indices (ALT, AST, ALP, GTT, and TBil) were analyzed using K–M curves, and the time at which each index first exceeded 1 × ULN was considered a failure event. The control group showed a significantly higher abnormal rate of ALT, AST, ALP, and GTT levels than the study group, with a statistically significant difference between the groups ($P < .05$). The proportion of patients with abnormal transaminases (ALT/AST) was 56/64 (87.50%), which was the highest abnormal rate among all liver function indices, showing the most notable difference between the groups ($P < .001$) (Table 2, Fig. 1).

3.3. Comparison of abnormal transaminase between groups

As one of the most sensitive indices of liver injury, transaminase displayed an abnormality rate of 87.50% in this study, establishing it as the primary index for comparison in subsequent analyses.

3.4. The initial transaminase abnormality and times of TCZ used

Overall, 56 patients had an ALT/AST ratio of > 1 × ULN (11 patients in the study group and 45 in the control group). Among

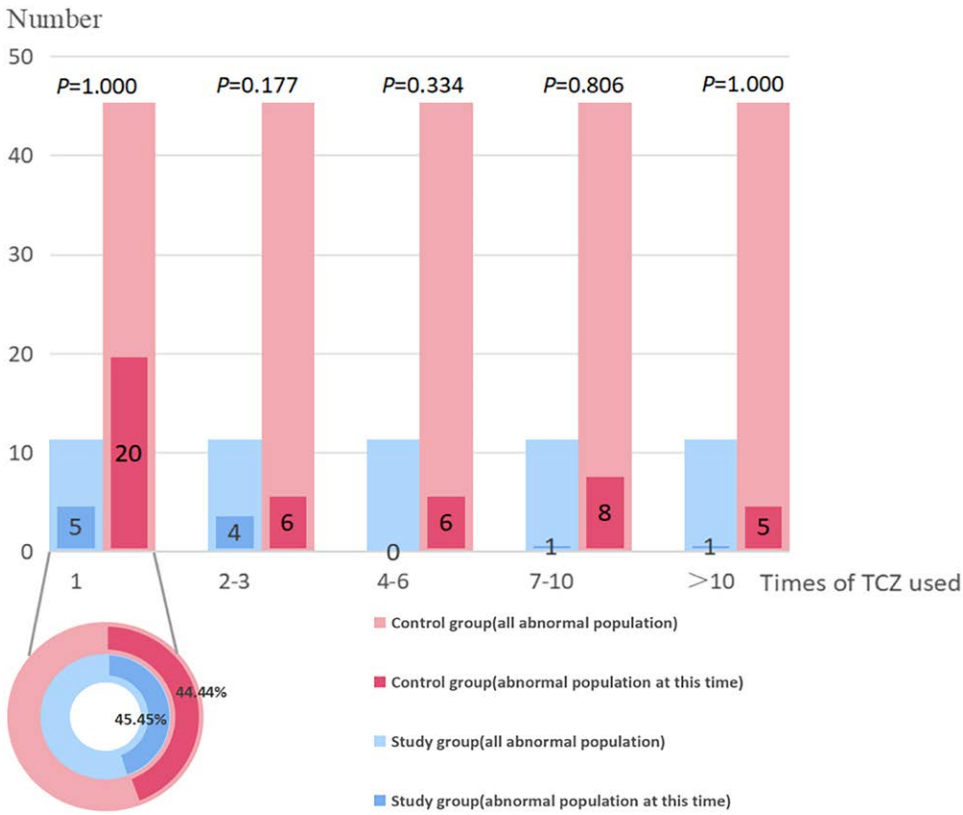

Figure 2. Comparing initial abnormal transaminase timings in patients. The Chi-square test or Fisher exact test is used for intergroup comparison. The percentage in the pie chart represents the ratio of abnormal patients after the first time of TCZ used to the total number of abnormal patients in each group.

these, 25 patients (44.64%) manifested abnormalities after the initial administration of TCZ, whereas 35 (62.5%) developed abnormalities within the first 3 TCZ administrations. No significant differences were observed between groups ($P > .05$) (Fig. 2).

3.5. Comparing K–M curves of transaminase between groups

Among the transaminase indices measured in the enrolled patients, 56 were > 1 × ULN, 20 were > 3 × ULN, and 7 were > 5 × ULN. The time when ALT/AST values first reached > 1/3/5 × ULN was considered a failure event for group comparison using the K–M curves. The incidence of abnormalities in these 3 scenarios was significantly lower in the study group than that in the control group. Significant differences were observed between the groups when ALT/AST > 1 and 3 × ULN ($P < .001$) (Table 3, Fig. 3).

3.6. Comparing the transaminase K–M curves for different courses

Among the 119 patients, 58 (48.74%) had treatment periods of ≤ 12 months, while 61 (51.26%) were treated for > 12 months. Analysis of ALT/AST > 1/3/5 × ULN differences between the groups using K–M curves indicated significantly lower abnormality rates in the study group, with significant differences noted between the groups when patients had ALT/AST > 1 and 3 × ULN in either treatment course ($P < .05$) (Table 4, Fig. 4).

3.7. Cox proportional hazards regression model

To further investigate the factors contributing to abnormal transaminase levels, 3 multifactorial Cox regression models were established, with ALT/AST > 1/3/5 × ULN as the dependent variable respectively (Tables S1–S3, Supplemental Digital Content, http://links.lww.com/MD/O388). The results indicate that when the dependent variable is ALT/AST > 1 × ULN, the findings are the most significant and representative, as shown in the forest plot. Among the 10 factors examined, Cox regression analysis revealed that the group had the highest risk ratio (hazard ratio: 3.985, 95% confidence interval: 1.997–7.952, $P < .001$), with only the group being an independent risk factor affecting ALT/AST (Fig. 5).

3.8. Efficacy evaluation of inflammatory

In this study, the normalization of inflammatory indices (ESR and CRP) was used as a criterion to assess the effectiveness of sJIA treatment. Initially, all patients had abnormal inflammatory indices (100.00%). After treatment, the total number of abnormal cases decreased to 48 (40.34%).

When comparing the number of patients with abnormal inflammatory indices before and after treatment, the study group (67.35% decrease) exhibited a slightly greater decrease than did the control group (54.29% decrease). However, intergroup differences were not statistically significant ($P > .05$). Nevertheless, a comparison of posttreatment inflammation index values showed that ESR values in the study group were significantly lower than those in the control group ($P < .05$) (Tables 5 and 6).

4. Discussion

TCZ has garnered widespread attention both domestically and internationally, as the primary biological agent for treating sJIA. Experts such as Liu et al[10] have underscored that the occurrence

Table 3

Comparison of abnormal transaminase patients.

Transaminase (ALT/AST) [1]	n = 119	Study group (n = 49)	Control group (n = 70)	χ^2/ Fisher	*P* value
>1 × ULN [n (%)]	56 (47.06)	11 (22.45)	45 (64.29)	20.250	**.000*****
>3 × ULN [n (%)]	20 (16.81)	1 (2.04)	19 (27.14)	12.990	**.000*****
>5 × ULN [n (%)]	7 (5.88)	1 (2.04)	6 (8.57)	2.220	.237

Bold values represent results with statistical significance ($P < .05$).

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.

*$P < .05$, **$P < .01$, ***$P < .001$ indicate the levels of statistical significance.

Table 4

Comparison of abnormal transaminase patients with different courses.

Treatment courses	ALT/ AST > 1 × ULN [1]	ALT/ AST > 3 × ULN [1]	ALT/ AST > 5 × ULN [1]
Courses ≤ 12 months (n = 58)			
Study group (n = 22) [n (%)]	5 (22.73)	0 (0.00)	0 (0.00)
Control group (n = 36) [n (%)]	21 (58.33)	7 (19.44)	2 (5.56)
χ^2/Fisher	7.000	4.865	1.266
P value	**.008****	**.037***	.521
Courses > 12 months (n = 61)			
Study group (n = 27) [n (%)]	6 (22.22)	1 (3.70)	1 (3.70)
Control group (n = 34) [n (%)]	23 (67.65)	12 (35.29)	4 (11.76)
χ^2/Fisher	12.451	8.956	1.300
P value	**.000*****	**.003****	.371

Bold values represent results with statistical significance ($P < .05$).

ULN = upper limit of normal.

*$P < .05$, **$P < .01$, ***$P < .001$ indicate the levels of statistical significance.

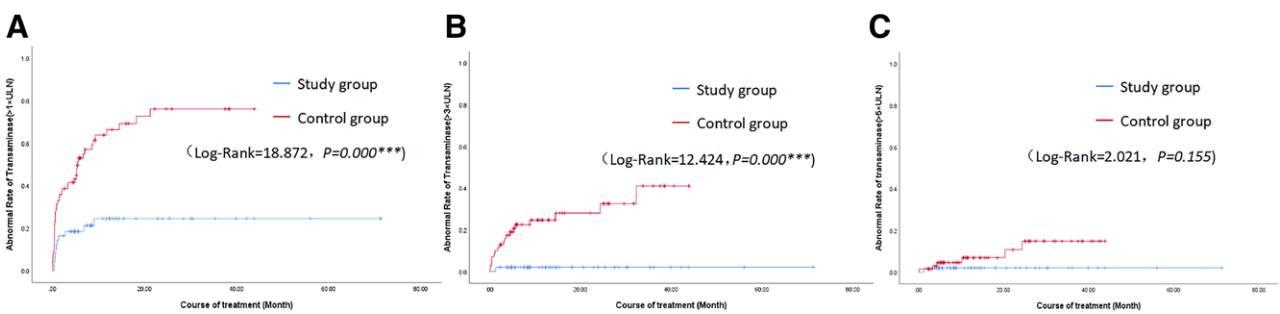

Figure 3. Kaplan–Meier curve for abnormal transaminases. (A) K–M curve of transaminase > 1 × ULN, (B) K–M curve of transaminase > 3 × ULN, (C) K–M curve of transaminase > 5 × ULN.

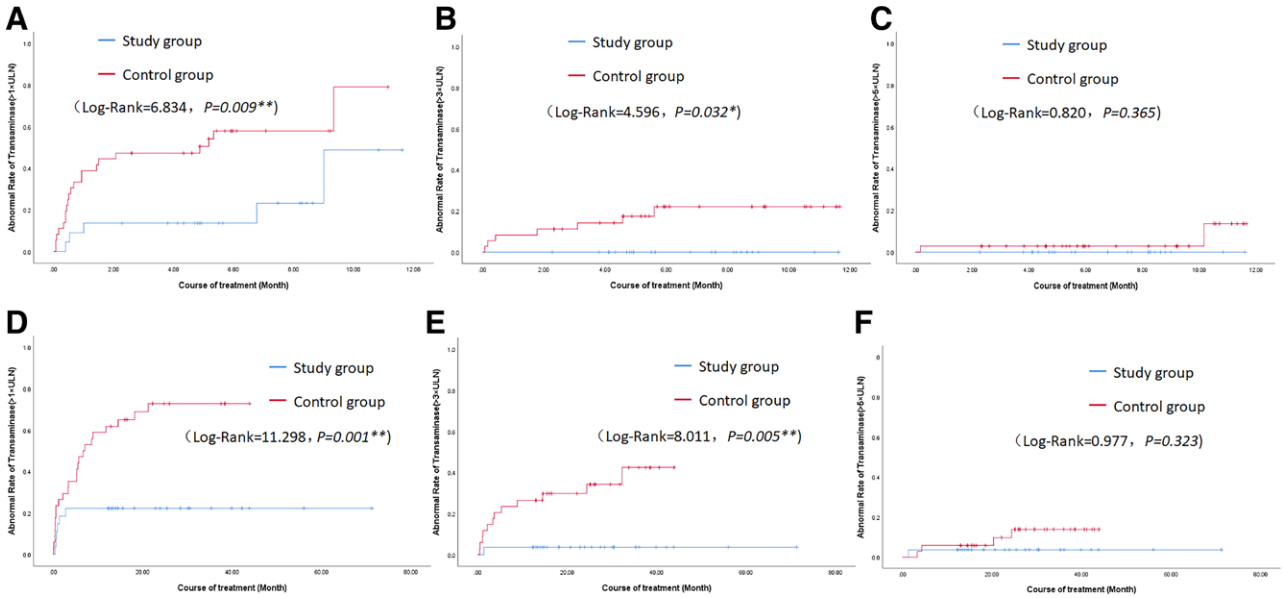

Figure 4. Kaplan–Meier curve for abnormal transaminases with different courses. Courses ≤ 12 months: (A) K–M curve of transaminase > 1 × ULN, (B) K–M curve of transaminase > 3 × ULN, (C) K–M curve of transaminase > 5 × ULN. Courses > 12 months: (D) K–M curve of transaminase > 1 × ULN, (E) K–M curve of transaminase > 3 × ULN, (F) K–M curve of transaminase > 5 × ULN.

Therapeutic and Hepatoprotective Effect of Tocilizumab Combined with Total Glycosides of Peony in Systemic Juvenile Idiopathic Arthritis

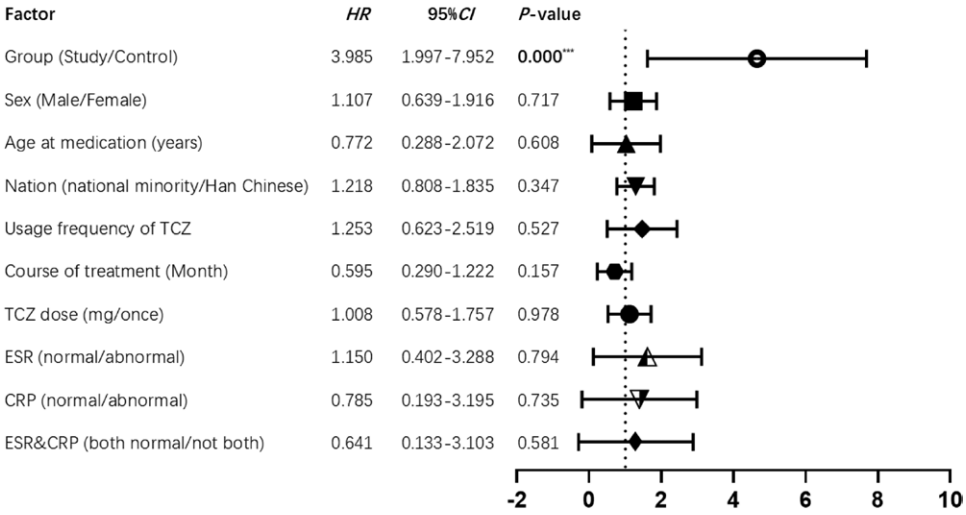

Figure 5. Cox regression models and forest plots of factors influencing transaminase. Inflammatory indicators (ESR/CRP) are all from the last follow-up. ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

of adverse events associated with TCZ use in children is relatively high, with 49% attributed to liver injury including abnormal liver indicators and even DILI. Although the resulting liver damage is generally mild, instances of severe liver injury pose life-threatening risks.[25] This study retrospectively analyzed 119 patients with sJIA treated with TCZ to investigate their hepatotoxic effects. Only 9 patients (7.56%) met the diagnostic criteria for DILI,[23] and all had mild-to-moderate cases. One major reason why the children in this study did not experience severe DILI may be the rigorous liver function monitoring protocol implemented in our research center. Additionally, the limited sample size and insufficient observation period for long-term safety could also have played a role, or it is possible that TCZ has a low likelihood of inducing severe DILI. However, the rate of abnormal liver function indices (ALT, AST, ALP, GTT, and TBil > 1 × ULN) were relatively high (53.78%). This type of liver injury is thought to be related to TCZ inhibition of the IL-6 signaling pathway, which is crucial for liver recovery,[26,27] as the pregnane X receptor is predominantly present in the liver and acts as a transcriptional regulator of the cytochrome P450 gene CYP3A4. TCZ triggers

Table 5

Comparison of abnormal inflammatory index patients.

	Pretreatment					Posttreatment				
Abnormal inflammatory index	n = 119	Study group (n = 49)	Control group (n = 70)	χ^2/Fisher	*P* value	n = 119	Study group (n = 49)	Control group (n = 70)	χ^2/Fisher	*P* value
ESR [n (%)]	115 (96.64)	46 (93.88)	69 (98.57)	0.777	.378	23 (19.33)	9 (18.37)	14 (20.00)	0.049	.824
CRP [n (%)]	115 (96.64)	48 (97.96)	67 (95.71)	0.023	.879	41 (34.45)	13 (26.53)	28 (40.00)	2.316	.128
ESR/CRP [n (%)]*	119 (100)	49 (100)	70 (100)	0.000	1.000	48 (40.34)	16 (32.65)	32 (45.71)	2.043	.153

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ESR/CRP > 1 × ULN.

* At least 1 abnormality exists in 2 inflammatory indices.

Table 6

Comparison of posttreatment inflammatory index values.

Inflammatory index	n = 119	Study group (n = 49)	Control group (n = 70)	Statistical value (H)	*P* value
ESR (mm/1 h)†	6.00 (4.00, 13.00)	6.00 (3.00, 9.00)	6.00 (5.00, 14.00)	4.664	**.031***
CRP (mg/L)†	5.00 (1.40, 8.00)	4.00 (2.00, 8.00)	5.00 (0.98, 8.00)	0.046	.830

Bold values represent results with statistical significance ($P < .05$).

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

*$P < .05$, **$P < .01$, ***$P < .001$ indicate the levels of statistical significance.

† [Median (IQR)].

pregnane X receptor by impeding the IL-6 signaling pathway and enhancing the expression of CYP3A4, leading to the accumulation of active metabolites and liver injury.[28]

Among the 64 patients with abnormal liver function indices, 56 exhibited elevated transaminase levels (87.50%), consistent with existing literature.[29,30] Transaminases, which are sensitive markers of hepatocyte damage, serve as essential parameters for adjusting treatment according to pharmaceutical monitoring institutions and TCZ guidelines,[31–33] and are also key indices for assessing hepatotoxicity levels in this study. The majority of transaminase elevations were observed after the initial treatment (44.64%). Studies by Hongxia Liu[10] and Ruperto et al[34] also noted a relatively high incidence of adverse reactions following initial TCZ use, emphasizing the necessity for vigilant scrutiny of relevant indicators and dosage adjustments during therapy. However, effective preventive measures against such liver injuries have not been reported.

To address this problem, we found that several related studies indicated that TGP can boost the activity of superoxide dismutase and glutathione peroxidase while inhibiting the production of oxygen free radicals such as malondialdehyde. Thus, TGP may exhibit a hepatoprotective effect, likely attributed to its capacity to eliminate free radicals and enhance antioxidant enzyme activity.[35,36] Therefore, as a commonly used auxiliary medication for sJIA, TGP was selected as a combination therapy in our study to prevent and mitigate TCZ-induced liver toxicity. To standardize patient cohorts and eliminate confounding variables from other potentially liver-toxic medications, this study enrolled individuals with similar medication histories (NSAIDs, disease-modifying antirheumatic drugs, and GC). Specifically adhering to the hepatotoxic drug categories outlined in the "Guideline for primary care of drug-induced liver injury (2019)," [37] any discrepancies attributable to conventional medications were discounted. K–M curves for the 5 liver function indices were analyzed. The findings revealed notable differences in 4 indices (ALT, AST, ALP, and GTT), with lower abnormality rates in the study group than in the control group ($P < .05$). The transaminases demonstrating the highest prevalence of abnormalities were used to plot the K–M curve, revealing substantial intergroup variances when ALT/AST > 1 and 3 × ULN ($P < .001$, $P < .05$). Although the lack of significance observed when ALT/AST > 5 × ULN could be ascribed to the sample size limitations, the abnormality rate in the study group remained relatively low. A Cox proportional hazards regression model and forest plot were used to investigate transaminase-related risk factors, which indicated that this group exhibited the highest risk ratio, signifying a beneficial protective effect on liver function in patients undergoing TGP combination therapy.

Previous research[38] has indicated that TGP exerts hepatoprotective effects by reducing the levels of cyclic adenosine monophosphate, cyclic guanosine monophosphate, inflammatory factors, serum ALT, and AST. It also diminishes liver tissue laminin and hyaluronic acid, thereby ameliorating pathological alterations in the liver, regulating cellular function and metabolic equilibrium, and decreasing the progression of liver fibrosis. The use of TGP in conjunction with the targeted biological agent TCZ appears to be a safer option considering TGP's mild effects, broad applicability, and minimal adverse reactions.[39]

Although TGP significantly inhibited TCZ-induced increase in transaminase levels, it is imperative to evaluate the overall therapeutic efficacy of this combination approach. Therefore, further investigations comparing intergroup inflammatory indices are necessary to assess the potential advantages of combining TGP to alleviate this condition. Analysis of abnormal inflammatory indices before and after treatment revealed a more pronounced decrease in the study group (67.35% reduction) than in the control group (54.29% reduction). Additionally, the ESR value in the study group was markedly lower than that in the control group after the final treatment ($P < .05$), indicating that the concurrent use of TGP may provide additional anti-inflammatory benefits.

5. Conclusion

In summary, this study retrospectively analyzed 119 patients with sJIA over the last decade and revealed for the first time that combining TCZ and TGP can decrease liver injury and enhance anti-inflammatory effectiveness, representing a significant advancement in sJIA combination therapy.

6. Study limitation

Inevitably, several limitations should be acknowledged in this retrospective observational study: (1) it was a single-center study with an inadequate sample size, warranting expansion of the research unit and an increase in sample size needed for robust support; (2) inadequate sample size and limited observation duration for long-term safety could be the main factors contributing to the absence of statistical significance between the groups when ALT/AST > 5 × ULN; (3) improvement in the efficacy evaluation of clinical manifestations and disease activity scores is anticipated in the future to compensate for the absence of a more comprehensive evaluation method in this article; (4) further research is imperative to elucidate the specific mechanisms of TGP's multi-component and multi-target effects of TGP.

Acknowledgments

We are very grateful to Professor Xu Xianming for his valuable feedback on the statistical analysis of the data in this study.

Author contributions

Conceptualization: Liya Gao, Xuemei Tang, Jing Xie.
Data curation: Liya Gao, Xuemei Tang, Zhongyu Ren, Xiaoqiong Wei.
Formal analysis: Liya Gao, Xuemei Tang, Jing Xie, Zhongyu Ren, Xiaoqiong Wei.
Methodology: Liya Gao, Xuemei Tang, Jing Xie.
Project administration: Liya Gao.
Resources: Liya Gao.
Supervision: Liya Gao.
Writing – original draft: Liya Gao, Xuemei Tang.
Writing – review & editing: Liya Gao, Xuemei Tang, Jing Xie, Zhongyu Ren.

References

[1] Luo X, Tang X. Progress in pathogenesis and precise diagnosis and treatment of systemic juvenile idiopathic arthritis. Chin J Pract Pediatr. 2023;38:450–5.
[2] Pardeo M, Bracaglia C, De Benedetti F. Systemic juvenile idiopathic arthritis: new insights into pathogenesis and cytokine directed therapies. Best Pract Res Clin Rheumatol. 2017;31:505–16.
[3] Ravelli A, Consolaro A, Horneff G, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2018;77:819–28.
[4] Klotsche J, Niewerth M, Haas JP, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016;75:855–61.
[5] Quartier P. Juvenile idiopathic arthritis-associated chronic uveitis: recent therapeutic approaches. J Clin Med. 2021;10:2934. doi: 10.3390/jcm10132934.
[6] Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2022;74:553–69.
[7] Onel KB, Horton DB, Lovell DJ, et al. 2021 American College of rheumatology guideline for the treatment of juvenile idiopathic arthritis: recommendations for nonpharmacologic therapies, medication monitoring, immunizations, and imaging. Arthritis Rheumatol. 2022;74:570–85.
[8] Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab for polyarticular-course juvenile idiopathic arthritis in the open-label two-year extension of a phase III Trial. Arthritis Rheumatol. 2021;73:530–41.
[9] Geng L, Miao F, Zhou Y, Li X. Efficacy and safety of tocilizumab on refractory systemic onset juvenile idiopathic arthritis: observation on 16 cases. Chin J Pract Pediatr. 2019;34:37–40.
[10] Liu H, Xie T, Zhu Y, Tan B, Yang Q, Hao S. Safety of tocilizumab in children with rheumatic immune disease. Chin J New Drugs Clin Remedies. 2024;43:426–31.
[11] Chen J, Li Q, Peng J. Efficacy and safety of tocilizumab in the treatment of refractory systemic onset juvenile idiopathic arthritis. J Pediatr Pharmacy. 2021;27:8–11.
[12] Choy EH, De Benedetti F, Takeuchi T, Hashizume M, John MR, Kishimoto T. Translating IL-6 biology into effective treatments. Nat Rev Rheumatol. 2020;16:335–45.
[13] Chen S, Xie Q, Wang H, et al. Trends and hotspots in the research on drug-induced liver injury in children: a bibliometric analysis. China Pharmaceuticals. 2024;33:50–7.
[14] t.S.o.P. The Subspecialty Group of Rheumatology, Chinese Medical Association, T.P.G.o.C.M.D.A.C.o.R.a. Immunology, T.P.G.o.R.a.I.P.C .o.C.S.M.a.H.E. Association, R.a.I.P.C.o.F.C.s.M.D.R. Center. Expert consensus on biological agents and small molecule targeted drugs for juvenile idiopathic arthritis (2022 version). Chin J Appl Clin Pediatr. 2022;37:1066–73.
[15] Liu L, Li F. Pharmacological effects and quality control management of total glycosides of peony. China Health Industry. 2018;15:62–3.
[16] Xing Q, Li S, Gong X, Hu W, Lu C. Study on the mechanism of total glucosides of paeony in the treatment of pulmonary interstitial fibrosis in rheumatoid arthritis based on network pharmacology. China Animal Husbandry Veterinary Med. 2024;51:850–63.
[17] Zhang Y, Zhu Y, Dong H. Research progress of TCM on Juvenile idiopathic arthritis. Western J Tradit Chin Med. 2023;36:129–32.
[18] Hang S, Xu D, Shen Y, et al. Evaluation of the therapeutic effect and safety of total glucosides of paeonia combined with methotrexate on juvenile idiopathic arthritis. World J Complex Med. 2024;10:83–6.
[19] Zhu S, Ye F, Gao D, Yan W. Effect of total glucosides of white paeony combined with methotrexate in the treatment of juvenile ldiopathic arthritis. Med Innovation China. 2024;21:128–32.
[20] Cai Y, Yuan Q, Xu K, et al. Assessment of the therapeutic effect of total glucosides of peony for juvenile idiopathic arthritis: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2016;2016:8292486.
[21] Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.
[22] Martini A, Ravelli A, Avcin T, et al. Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization international consensus. J Rheumatol. 2019;46:190–7.
[23] Ma S, Liu C, Liu X, et al. Chinese guideline for diagnosis and management of drug-induced liver injury (2023 Version). Chin J Gastroenterol. 2023;28:397-–431.
[24] Zhou W, Lai J, Tang X, et al. Chinese expert consensus on diagnosis and treatment of systemic juvenile idiopathic arthritis (2023 edition). Chin J Pract Pediatr. 2023;38:327–34.
[25] Genovese MC, Kremer JM, Vollenhoven R.F. van, et al. Transaminase levels and hepatic events during tocilizumab treatment: pooled analysis of long-term clinical trial safety data in rheumatoid arthritis. Arthritis Rheumatol. 2017;69:1751–61.
[26] Biehl A, Harinstein L, Brinker A, Glaser R, Muñoz M, Avigan M. A case series analysis of serious exacerbations of viral hepatitis and non-viral hepatic injuries in tocilizumab-treated patients. Liver Int. 2021;41:515–28.
[27] Ogata A, Kato Y, Higa S, Yoshizaki K. IL-6 inhibitor for the treatment of rheumatoid arthritis: a comprehensive review. Mod Rheumatol. 2019;29:258–67.
[28] Huang J, Zhang Z, Hao C, et al. Identifying drug-induced liver injury associated with inflammation-drug and drug-drug interactions in pharmacologic treatments for COVID-19 by bioinformatics and system biology analyses: the role of pregnane X Receptor. Front Pharmacol. 8041;13:89.
[29] Shu B, Jiang W, Shen A. Analysis of the literature on adverse reactions to tocilizumab. Chin J New Drugs. 2021;30:369–76.
[30] Wng L, Deng X. Mining and analysis of tocilizumab adverse reaction signals based upon real world,. Chin J Hospital Pharmacy. 2021;41:533–537+552.
[31] Gáspár Z, Szabó BG, Kiss-Dala N, Szlávik J, Vályi-Nagy I, Lakatos B. , [COVID–19-associated liver enzyme elevation is probably multifactorial]. Orv Hetil. 2022;163:1415–21.
[32] Machado SH, Xavier RM. Safety of tocilizumab in the treatment of juvenile idiopathic arthritis. Expert Opin Drug Saf. 2017;16:493–500.
[33] Zuo W, Liu R, Xu X, Hu Y, Du X, Zhang B. Research progress of tocilizumab-associated adverse reactions. Clin Medication J. 2020;18:16-–20.
[34] Ruperto N, Brunner HI, Ramanan AV, et al. Subcutaneous dosing regimens of tocilizumab in children with systemic or polyarticular juvenile idiopathic arthritis. Rheumatology (Oxford). 2021;60:4568–80.
[35] Liu L, Zhao J. Protective effects of paeoniflorin on acute liver injury induced by lipopolysaccharide in mice. Chin J Clin Pharmacol. 2016;32:433–6.
[36] Ren M, Wu S, Zhan S, Jiang N. Protective effects of total glucosides of paeony and lts main components paeoniflorin and albiflorin in carbon tetrachloride-induced acute liver injury. Chin Arch Tradit Chin Med. 2020;38:244–247+283.
[37] C.M. Association, C.M.J.P. House, C.S.o. Gastroenterology, C.S.o.G. Practice, E.B.o.C.J.o.G.P.o.C.M. Association, E.G.o.G.f.P.C.o.G. Disease. Guideline for primary care of drug-induced liver injury: practice version (2019). Chin J General Practitioners. 2020;19:876–81.
[38] Jia L, Wang L, Meng L, et al. Effect and mechanism of total glucosides of Paeoniae Radix Alba on combined model of chemical liver injury and liver yin deficiency syndrome in rats. Chin Tradit Herbal Drugs. 2020;51:1885–92.
[39] Zhang L, Wei W. Anti-inflammatory and immunoregulatory effects of paeoniflorin and total glucosides of paeony. Pharmacol Ther. 2020;207:107452.