ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

An optimized short-term steroid therapy for chronic drug-induced liver injury: A prospective randomized clinical trial

Ang Huang[1,2] | Yun Zhu[1] | Shuhong Liu[3] | Ying Sun[1] | Zherui Liu[4] |
Qing-sheng Liang[1] | Jun Zhao[1] | Bin-xia Chang[1] | Jing-feng Bi[5] | Jiang-tao Liu[6] |
Xing-ran Zhai[4] | Huan Xie[1] | Ning Li[1] | Hui Tian[1] | Lin Han[1] | Yingjie Zhuang[7] |
Hongbin Ma[8] | Guang-ju Teng[1] | Wei Zhang[1] | Guruprasad P. Aithal[9] | Dong Ji[1,4] |
Jingmin Zhao[3] | Zhengsheng Zou[1,4]

[1]Senior Department of Hepatology, the Fifth Medical Center of PLA General Hospital, Beijing, China

[2]Department of Gastroenterology and Hepatology, the First Medical Center of PLA General Hospital, Beijing, China

[3]Department of Pathology and Hepatology, the Fifth Medical Center of PLA General Hospital, Beijing, China

[4]Peking University 302 Clinical Medical School, Beijing, China

[5]Epidemiology Department, the Fifth Medical Center of PLA General Hospital, Beijing, China

[6]Department of Gastroenterology, Hainan Hospital of Chinese PLA General Hospital, Hainan, China

[7]Department for Disease Control and Prevention, the Fifth Medical Center of PLA General Hospital, Beijing, China

[8]Department of Clinical Diagnostic Center, the Fifth Medical Center of PLA General Hospital, Beijing, China

[9]NIHR Nottingham Biomedical Research Center, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK

Correspondence
Zhengsheng Zou and Dong Ji, Senior Department of Hepatology, the Fifth Medical Center of PLA General Hospital, Beijing, China.
Email: zszou302@163.com and jidg302@126.com

Jingmin Zhao, Department of Pathology and Hepatology, the Fifth Medical Center of PLA General Hospital, Beijing, China.
Email: jmzhao302@163.com

Guruprasad P. Aithal, NIHR Nottingham Biomedical Research Center, Nottingham University Hospitals NHS Trust and the University of Nottingham, Nottingham, UK.
Email: guru.aithal@nottingham.ac.uk

Abstract

Background and Aims: The use of corticosteroids in chronic drug-induced liver injury (DILI) is an important issue. Our previous randomized controlled trial showed that patients with chronic DILI benefited from a 48-week steroid stepwise reduction (SSR) regimen. However, it remains unclear whether a shorter course of therapy can achieve similar efficacy. In this study, we aimed to assess whether a 36-week SSR can achieve efficacy similar to that of 48-week SSR.

Methods: A randomized open-label trial was performed. Eligible patients were randomly assigned to the 36- or 48-week (1:1) SSR group. Liver biopsies were performed at baseline and at the end of treatment. The primary outcome was the proportion of patients with relapse rate (RR). The secondary outcomes were improvement in liver histology and safety.

Results: Of the 90 participants enrolled, 84 (87.5%) completed the trial, and 62 patients (68.9%) were women. Hepatocellular damage was observed in 53.4% of the

cohort. The RR was 7.1% in the 36-week SSR group but 4.8% in the 48-week SSR group, as determined by per-protocol set analysis ($p = 1.000$). Significant histological improvements in histological activity (93.1% vs. 92.9%, $p = 1.000$) and fibrosis (41.4% vs. 46.4%, $p = .701$) were observed in both the groups. Biochemical normalization time did not differ between the two groups. No severe adverse events were observed.

Conclusions: Both the 36- and 48-week SSR regimens demonstrated similar biochemical response and histological improvements with good safety, supporting 36-week SSR as a preferable therapeutic choice (ClinicalTrials.gov, NCT03266146).

KEYWORDS
corticosteroids, drug-induced liver injury, liver biopsy, randomized controlled trial, Roussel Uclaf causality assessment method (RUCAM)

1 | INTRODUCTION

The global estimated annual incidence of idiosyncratic drug-induced liver injury (DILI) is 19.1–23.8 per 100 000 individuals in the general population,[1] whereas it is 1.4% in hospitalized patients.[2,3] Many drugs and herbal and dietary supplements (HDS) have been implicated as causes of DILI.[3] Most patients with acute idiosyncratic DILI recover biochemically with the spontaneous normalization of liver enzymes upon discontinuation of the causative agents. However, in some patients, DILI persists even after stopping the suspected drug. Up to 24% of patients develop chronic DILI,[3,4] which is typically defined as persistent elevation in serum liver biochemistry values or the presence of radiological or histological evidence of ongoing injury at 6–12 months after DILI onset.[3] Patients with long-term unresolved DILI may develop cirrhosis.[5–7] Additionally, the serious consequences of chronic DILI may cause a loss of working hours and an increase in health care expenditure owing to repeated hospitalization.[7] Therefore, developing therapies to halt the progression of chronicity is necessary if the patient does not recover from liver injuries after discontinuing the suspected drug.

In the past, specific therapies, apart from corticosteroid administration, have been provided for idiosyncratic DILI in patients with severe hypersensitivity features, drug reaction with eosinophilia and systemic symptoms, or autoimmune features.[3,8] Corticosteroids have also been used to treat acute DILI cases, with conflicting results.[9] In a multi-centre propensity score-matched analysis, corticosteroid administration was associated with a greater rate of normalization of liver enzymes in patients with serious DILI.[10] However, the optimal dose and duration are unknown because of the lack of controlled clinical trials. Recently, we completed the first randomized open-label clinical trial to investigate the efficacy of corticosteroids in the treatment and management of chronic DILI cases. The study provided the first clinical evidence that patients with chronic DILI with

Key points

We should pay more attention to chronic drug-induced liver injury (DILI) patients with relapse or cannot achieve a sustained biochemical response. Corticosteroid therapy can be used in patients with chronic DILI meeting one of the following criteria: (1) evident increase in liver biochemistry parameters (e.g. ALT or AST >10×ULN, upper limit normal, or ALT or AST >5×ULN and TBIL >2×ULN), (2) histological features of confluent necrosis and bridging necrosis. Thirty-six-week steroid stepwise reduction (SSR) regimen may be a rational therapeutic choice for above chronic DILI patients and can achieve sustained biochemical response and histological improvements with good safety.

or without autoimmune features potentially benefit from a 48-week steroid stepwise reduction (SSR) therapy, with significant biochemical response, histological improvement and good safety.[11]

To decrease the risk of possible adverse effects and increase compliance of patients with DILI during steroid treatment, we initiated this randomized prospective open-label trial to determine whether a short-term (36-week) SSR can achieve similar efficacy and safety to those of the established 48-week SSR regimen for patients with chronic DILI. Additionally, in our previous clinical trial,[11] 42.5% of patients with chronic DILI exhibited autoimmune features, and the standardization in treatment regimen and timing of withdrawal remain unclear. While the initial clinical trial explored an effective steroid treatment regimen for chronic DILI cases. By expanding the sample size, we aimed to further validate the steroid therapy regimen for chronic DILI, especially drug-induced autoimmune-like hepatitis (DI-ALH) cases.[12]

2 | PATIENTS AND METHODS

2.1 | Study design

The study was performed as a randomized open-label trial conducted at the Fifth Medical Center of Chinese PLA General Hospital. We aimed to evaluate whether a short-term (36-week) SSR for patients with chronic DILI can achieve similar efficacy and safety to those of 48-week SSR (Figure 1A). The randomized open-label trial for the participants was approved by the Ethics Committee of the Fifth Medical Center of the General Hospital, Beijing (no. 2017106D). This study was conducted in accordance with the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. This study was registered at ClinicalTrials.gov (NCT03266146).

2.2 | Participants

Patients diagnosed with DILI between 7 September 2017 and 28 August 2021 were screened. Chronic DILI was defined as the failure to return liver enzyme or bilirubin levels to pre-DILI baseline (BL) levels, imaging or histology data compatible with chronicity (irrespective of laboratory data), and/or other signs or symptoms of ongoing liver disease (e.g. ascites, encephalopathy, portal hypertension and coagulopathy) at 6 months after DILI onset despite withdrawal of the offending agent (American College of Gastroenterology [ACG] clinical guidelines for diagnostic criteria of chronic DILI[13]).

The detailed inclusion criteria were as follows: (1) diagnosis of chronic DILI according to the ACG DILI guidelines; (2) age of 18–60 years; (3) updated Roussel Uclaf causality assessment method (RUCAM) score ≥6 points[14]; (4) any of the following conditions: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level ≥10 times the upper limit of normal (ULN), ALT or AST level ≥5 times the ULN and total bilirubin level (TBIL) ≥2 times the ULN, or liver histopathological findings of active necrotic inflammation, including confluent necrosis, bridging necrosis, multiacinar necrosis and portal inflammation and (5) voluntary participation with an ability to understand and provide written informed consent.
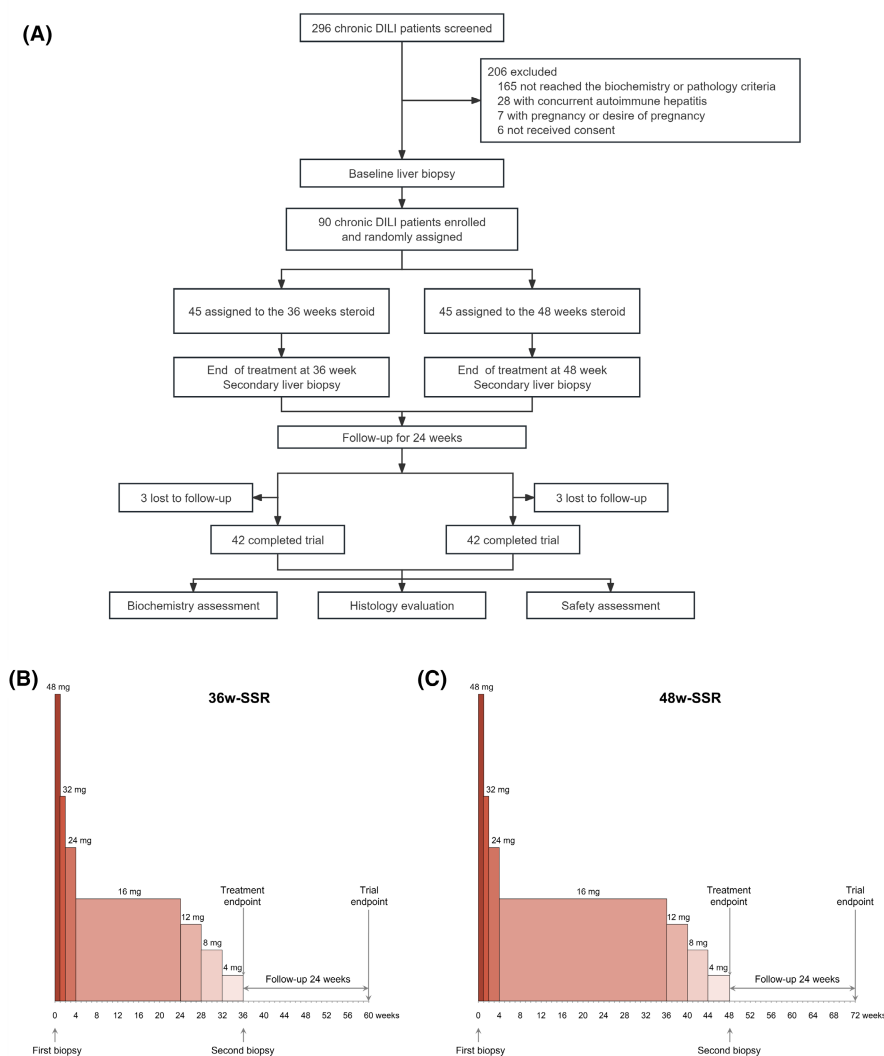

FIGURE 1 Flow diagram of the clinical trial and steroid treatment protocol. (A) The flow chart of the trial; (B) The protocol of the 36-week steroid stepwise reduction (36w-SSR); (C), The protocol of the 48-week steroid stepwise reduction (48w-SSR).

Patients were excluded if they had any of the following conditions: (1) serious underlying comorbidities (e.g. psychosis, active peptic ulcer, brittle diabetes and uncontrolled hypertension); (2) concomitant non-drug aetiologies, including viral hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis E, Epstein–Barr virus infection, cytomegalovirus infection and herpes virus infection), alcoholic or non-alcoholic fatty liver disease, Wilson's disease or other inherited metabolic liver diseases; (3) diagnosis of definite autoimmune hepatitis (AIH; >15 points on the International Autoimmune Hepatitis Group Scoring System before corticosteroid therapy[15]); (4) steroid therapy within 6 months before enrollment; (5) malignancy during or prior to screening; (6) liver histological features of nodular regenerative hyperplasia, moderate to severe fatty liver or peliosis hepatis or (7) pregnancy or breastfeeding.

2.3 | Randomization and masking

After screening, eligible participants were randomly assigned to the 36- or 48-week SSR group according to the random numbers generated using the PROC PLAN statement (PROC PLAN seed = 20170903) of SAS software (SAS Corp., Cary, NC, USA) by the statistician (Jing-Feng Bi). The statistician documented the random numbers, and the investigators called the statistician to ask for the assignment of each eligible patient.

The pathologist (Jingmin Zhao), who was blinded to the patients' group assignments and clinical information, assessed liver histology.

2.4 | Procedures

In both the 36- and 48-week SSR groups, patients were treated with steroids. The protocol of the 36-week SSR was as follows: induction phase with oral methylprednisolone administration at a dose of 48 mg/day for the first week, 32 mg/day for the second week and 24 mg/day for the next 2 weeks; maintenance treatment phase with 16 mg/day lasting for 20 weeks; and reduction phase using a decreasing sequence of doses from 16 to 4 mg/day, with a reduction of 4 mg per 4-week period until 36 weeks (Figure 1B). The participants were monitored by assessing liver function and evaluating adverse events at 2, 4, 12, 24 and 36 weeks during treatment and at 60 weeks during the follow-up period. The protocol of the 48-week SSR was similar to that of the 36-week SSR, with the key distinction being the maintenance treatment phase involving a daily dose of 16 mg lasting for 32 weeks (Figure 1C).

Paired liver biopsies were obtained at BL and at the end of steroid treatment. Inflammatory necrosis grading and fibrosis staging were determined according to the modified Ishak scoring system,[16] in addition to evaluating the typical histological characteristics. To rule out AIH and immunoglobulin G (IgG)4-related diseases, the rosette arrangement of hepatocytes and emperipolesis of lymphocytes, plasma cells and IgG4-positive cells were assessed. Non-invasive assessment of liver fibrosis, including the AST-to-platelet ratio index

(APRI)[17] and fibrosis 4 score (FIB-4),[18] was performed based on the following formulae: APRI = ([AST/ULN]/platelet [PLT]) × 100 and FIB-4 = (age × AST)/(PLT × ALT$^{0.5}$) (AST ULN = 40 U/L).

Our previous study found that AST and TBL, PLTs, prothrombin time (PT), sex and age were associated with biochemical non-resolution (BNR) and incorporated these parameters to construct a nomogram model (BNR-6).[19] We categorized patients into those having low, medium and high risk of BNR-6 (0–28, 28–50, >50 points respectively).[19]

2.5 | Outcomes

The primary outcome was the relapse rate (RR), defined as an elevation in the AST or ALT level by more than fivefold the ULN or being two times higher than before. The secondary outcomes were improvement in liver histology, time to normalization of biochemical parameters and safety. Histological improvement was defined as a decrease of at least 2 points in necroinflammatory activity or at least 1 point in fibrosis, as per the Ishak scoring system.

Moreover, the efficacies of both 36- and 48-week SSR treatments for chronic DILI cases were assessed and compared between the DI-ALH and non-DI-ALH subgroups. DI-ALH was defined as a condition presenting with either positive serum autoantibodies (antinuclear antibody and/or anti-smooth muscle antibody [ANA] and/or smooth muscle antibody [SMA]) or elevated IgG levels (>1.1× ULN), while maintaining an international AIH score of ≤15 points before corticosteroid therapy.[10,12,15]

The adverse events in each group were evaluated according to the Common Terminology Criteria for Adverse Events (version 5.0).[20] The types of steroid-related adverse effects were based on the AASLD[21]/EASL[22] AIH guidelines. The adverse effects that occurred during both the treatment and follow-up periods were combined for the analyses.

2.6 | Statistical analysis

We hypothesized that the effective rate at 36 weeks of SSR would be similar to that at 48 weeks of SSR. Based on our previous clinical observations, the RR of patients receiving 48-week SSR was 7% (2%–13%). Employing SAS software (version 9.4) with a 1:1 allocation between the groups, the proposed non-inferiority margin was 10%, α = .05, β = .2, and the total sample size was estimated to be 81. Considering a dropout rate of 10%, the total sample size was determined to be 90 (45 patients each for the 36- and 48-week SSR groups).

Baseline characteristics, efficacy and safety were evaluated using the intention-to-treat (ITT) set and per-protocol set (PPS). All continuous variables conforming to normal distribution are presented as means ± SDs, while non-normally distributed variables are presented as medians (interquartile ranges). Continuous variables with normal distribution were compared using unpaired

Student's t tests (for equal variances) or the Satterthwaite test (for unequal variances); the Mann–Whitney U test was used for non-normally distributed variables, and the Wilcoxon rank sum test was used for comparison between two groups. Comparisons of categorical variables between the groups were conducted using Chi square or Fisher's exact tests. The p-values for all analyses were two-sided, and the significance was set at $p < .05$. Analyses and graph plotting were performed using SPSS software (version 25.0; IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 8.4.2; La Jolla, CA, USA).

3 | RESULTS

3.1 | Patient flow and randomization

From 7 September 2017 to 28 August 2021, 296 patients with chronic DILI were screened. According to the inclusion and exclusion criteria, 206 patients were excluded (165 patients were ineligible based on the inclusion criteria, 28 patients had AIH, seven patients were pregnant or planning pregnancy and six patients withdrew informed consent). Ultimately, 90 patients diagnosed with chronic DILI were enrolled in the ITT population and randomly assigned to the 36- or 48-week SSR groups in a 1:1 ratio (Figure 1A). Eighty-four (93.3%) of 90 patients were included in the PPS analysis at the trial endpoint.

3.2 | Characteristics of participants

3.2.1 | Clinical features

In the ITT population, the median age of patients was 49.5 years, and 62 (68.9%) of the 90 patients were women. The leading cause of chronic DILI was the use of traditional Chinese medicine (TCM) or HDS (51.1%), followed by synthetic drugs (27.8%). The hepatocellular type ($R \geq 5$) was the main liver injury pattern (48/90, 53.4%). Liver injury at the time of enrollment[23] was mild (57.8%), moderate (41.1%), or severe (2.2%); no patients developed fatal liver injury or received liver transplantation. In total, 21 (23.3%), 57 (63.3%) and 12 (13.3%) participants showed high, medium and low risk of BNR[19] at the time of enrollment respectively. Moreover, although none met the diagnostic criteria for AIH, 40 (44.4%) patients had positive autoantibodies (ANA and/or SMA) or elevated IgG levels ($>1.1 \times$ ULN).[15] Liver ultrasound showed that 94.4% of patients had coarsening of the liver architecture, and 5.6% displayed a coarsening-nodular pattern. Liver biopsy results showed that 11.4%, 39.8%, 47.7% and 1.1% of patients had activity scores of 0–6, 7–9, 10–14 and 15–18 points respectively. The prevalence rates of fibrosis stages 0–1, 2, 3, 4 and 5–6 were 15.9%, 20.4%, 30.7%, 27.3% and 5.7% respectively.

Clinical characteristics were comparable between the 36- and 48-week SSR groups in the ITT population or per-protocol population (Table 1, Table S1). Moreover, there were no significant differences between the DI-ALH or non-DI-ALH subgroups (Table S2).

3.2.2 | Implicated agents

Of the 90 patients with chronic DILI, 21 (23.3%) were administered for healthy purposes, 18 (20.0%) for gastrointestinal diseases, 13 (14.4%) for bone and joint diseases, seven (7.8%) for skin diseases and four (4.4%) for hyperlipidaemia. In terms of implicated agents, TCM and HDS were implicated in 46 patients (51.1%), followed by synthetic drugs (27.8%). Moreover, 19 patients (21.1%) received a combination of synthetic drugs and TCM/HDS. The major Chinese herbs associated with chronic DILI in this cohort were *Polygonum multiflorum Thunb.* (Heshouwu) ($n = 12$), *Corydalis yanhusuo W. T. Wang* (Yanhusuo) ($n = 7$), *Psoralea corylifolia L.* (Buguzhi) ($n = 3$), *Dictamnus dasycarpus Turcz.* (Baixianpi) ($n = 3$) and *Cassia obtusifolia L.* (Juemingzi) ($n = 2$). The most implicated synthetic drugs were ibuprofen ($n = 6$), omeprazole ($n = 5$), clarithromycin ($n = 4$), amoxicillin ($n = 3$) and atorvastatin ($n = 3$). In this cohort, the single-used implicated agents related to DI-ALH were Shu-shen-ling capsules (containing *Polygonum multiflorum Thunb.* and 10 other Chinese herbs without hepatotoxicity reports [$n = 1$]), Ding-kun-dan pill (containing *Corydalis yanhusuo W. T. Wang* and 29 other herbs [$n = 1$]) and Niu-huang-jie-du tablet (containing *Rheum palmatum L.* and seven other herbs [$n = 1$]).

Additionally, we analysed the relationship between the effects of steroid treatment and the implicated agents. Excluding six patients who were lost to follow-up during the treatment period, there were five non-responders to steroid therapy in the remaining 84 patients. Among them, four participants were using TCM/HDS (80.0%), one was using combined synthetic drugs and TCM/HDS (20.0%), and no patient was using synthetic drugs only (0.0%). However, 79 patients responded to steroid treatment, among which 23 (29.1%), 38 (48.1%) and 18 (22.8%) patients used synthetic drugs, TCM/HDS and a combination of both respectively (Table S3).

3.2.3 | Histological features

Histologically, varying degrees of inflammatory necrosis and fibrosis were observed in the BL liver biopsy. Inflammatory activity >10 points occurred in 48.8% of patients, and 63.7% of patients developed significant or advanced fibrosis (fibrosis scores from 3 to 6 points; Table 1). Confluent necrosis and bridging necrosis were frequently noted in patients with high activity. Moderate-to-severe portal inflammation and variable interface hepatitis were histological hallmarks. Lobular and portal infiltrates consisted primarily of mixed inflammatory cells dominated by lymphocytes with only a few plasma cells. Histological features of AIH, such as predominant lymphoplasmacytic infiltrates, the formation of liver cell rosettes and emperipolesis phenomena, were less common (Figure 2).

TABLE 1 Demographic, clinical and histological characteristics of the patients at baseline.

Characteristic	All patients (n = 90)	36w-SSR group (n = 45)	48 w-SSR group (n = 45)	p value
Age (years), n (%)	49.5 (41.0, 54.0)	50.0 (41.5, 54.0)	48.0 (40.5, 54.0)	.390
Female gender, n (%)	62 (68.9)	31 (68.9)	31 (68.9)	1.000
From DILI onset to enrollment, month	7.0 (6.0, 15.5)	7.0 (6.0, 17.0)	7.0 (6.0, 14.0)	.737
Class of implicated drugs, n (%)				
TCM or HDS	46 (51.1)	24 (53.3)	22 (48.9)	.914
Synthetic drugs	25 (27.8)	12 (26.7)	13 (28.9)	
Combination	19 (21.1)	9 (20.0)	10 (22.2)	
R value[a], n (%)				
R ≥ 5 (Hepatocellular)	48 (53.4)	23 (51.1)	25 (55.6)	.914
2 < R < 5 (Mixed)	40 (44.4)	21 (46.7)	19 (42.2)	
R ≤ 2 (Cholestatic)	2 (2.2)	1 (2.2)	1 (2.2)	
DILI severity[b], n (%)				
Mild	52 (57.8)	25 (55.6)	27 (60.0)	.831
Moderate	37 (41.1)	19 (42.2)	18 (40.0)	
Severe	1 (1.1)	1 (2.2)	0 (0.0)	
Fatal/transplantation	0 (0.0)	0 (0.0)	0 (0.0)	
BNR risk[c]				
Low	12 (13.3)	4 (8.9)	8 (17.8)	.417
Medium	57 (63.3)	29 (64.4)	28 (62.2)	
High	21 (23.3)	12 (26.7)	9 (20.0)	
WBC, ×10^9/L (3.69–9.16)	4.73 ± 0.95	4.76 ± 0.97	4.70 ± 0.95	.775
HGB, g/L (113–151)	123.2 ± 14.0	123.7 ± 14.9	122.6 ± 13.1	.717
PLT, ×10^9/L (101–320)	185.2 ± 75.5	183.8 ± 79.2	186.6 ± 72.6	.858
Eosinophils, ×10^9/L (0.02–0.5)	0.08 (0.05, 0.14)	0.08 (0.05, 0.14)	0.10 (0.05, 0.16)	.374
ALT, U/L (5–35)	187.0 (146.0, 251.0)	200.0 (154.3, 270.0)	170.0 (139.0, 235.5)	.268
AST, U/L (8–40)	205.0 (141.0, 300.0)	201.0 (147.5, 290.3)	205.0 (119.0, 364.5)	.933
TBIL, μmol/L (3.3–20.5)	31.4 (16.8, 68.3)	30.7 (16.7, 76.3)	31.4 (16.8, 64.3)	.752
ALP, U/L (40–150)	126.5 (96.8, 170.5)	124.1 (103.0, 180.0)	129.0 (95.0, 164.5)	.688
GGT, U/L (7–32)	117.0 (59.3, 169.0)	112.0 (54.0, 210.0)	122.0 (60.0, 167.0)	.933
Albumin, g/L (35–55)	34.5 (32.0, 37.0)	35.0 (33.0, 37.0)	34.0 (31.5, 38.0)	.802
Cholinesterase, U/L (5000–12000)	5213.0 (3805.5, 6047.5)	5142.0 (3666.0, 5994.5)	5285.0 (3882.0, 6083.0)	.900
Prothrombin time, s (10.2–14.3), n (%)				
Within normal range	79 (87.8)	38 (84.4)	41 (91.1)	.266
INR (0.8–1.2), n (%)				
Within normal range	77 (85.6)	37 (82.2)	40 (88.9)	.368
Autoantibodies positive, n (%)				
ANA and/or SMA	35 (38.9)	15 (33.3)	20 (44.4)	.280
Others	0 (0.00)	0 (0.00)	0 (0.00)	
IgG, g/L (7.23–16.6), n (%)				
>2×ULN	0 (0.0)	0 (0.0)	0 (0.0)	.155
1.5×ULN–2.0×ULN	4 (4.4)	3 (6.7)	1 (2.2)	
1.0×ULN–1.5×ULN	17 (18.9)	5 (11.1)	12 (26.7)	
<1.0×ULN	69 (76.7)	37 (82.2)	32 (71.1)	

TABLE 1 (Continued)

Characteristic	All patients (n = 90)	36w-SSR group (n = 45)	48 w-SSR group (n = 45)	p value
Ultrasound				
Liver, n (%)				
Coarsening pattern	85 (94.4)	43 (95.6)	42 (93.3)	1.000
Coarsening-nodular pattern	5 (5.6)	2 (4.4)	3 (6.7)	
Spleen length (mm)	111.1 ± 18.2	110.1 ± 19.8	112.1 ± 16.7	.618
Portal vein diameter (mm)	11.0 (10.0, 11.0)	11.0 (10.0, 11.0)	11.0 (10.0, 11.0)	.882
Liver biopsy, n (%)	88 (97.8)	44 (97.8)	44 (97.8)	1.000
Activity score, n (%)				
0–6	10 (11.4)	6 (13.6)	4 (9.1)	.829
7–9	35 (39.8)	18 (40.9)	17 (38.6)	
10–14	42 (47.7)	20 (45.5)	22 (50.0)	
15–18	1 (1.1)	0 (0.0)	1 (2.3)	
Fibrosis score, n (%)				
0–1	14 (15.9)	9 (20.4)	5 (11.4)	.766
2	18 (20.4)	8 (18.2)	10 (22.7)	
3	27 (30.7)	12 (27.3)	15 (34.1)	
4	24 (27.3)	12 (27.3)	12 (27.3)	
5–6	5 (5.7)	3 (6.8)	2 (4.5)	
RUCAM				
6–8	79 (87.8)	40 (88.9)	39 (86.7)	.748
≥9	11 (12.2)	5 (11.1)	6 (13.3)	
With or without autoimmune-like hepatitis				
DI-ALH, n (%)	40 (44.4)	18 (40.0)	22 (48.9)	.396
Non-DI-ALH, n (%)	50 (55.6)	27 (60.0)	23 (51.1)	
AIH score[d]	8.00 (7.00, 9.00)	8.00 (6.25, 9.00)	8.00 (7.00, 9.00)	.434

Note: Data reported as mean ± SD or median (quartile 1, quartile 3).

Abbreviations: DI-ALH: drug-induced autoimmune-like hepatitis; HGB, hemoglobin; INR, international normalized ratio; PLT, platelet; SSR, steroid stepwise reduction; WBC, white blood cell.

[a]R-value was used to define the injury patterns of DILI, which is calculated as the ratio of ALT/ULN between ALP/ULN.

[b]The severity of DILI was evaluated according to the International DILI Expert Working Group's severity criteria.[23]

[c]BNR (biochemical non-resolution) risk was used to predict the outcome of patients with chronic DILI.[19]

[d]According to the revised original scoring system (−26 to 26 points) of the International Autoimmune Hepatitis Group.[15] Not involved the HLA-DR3 and DR in the calculation of AIH score.

3.3 | Efficacy

3.3.1 | Relapse rate

Three patients in each group were lost to follow-up during the treatment period (Table S4). ITT analysis revealed a similar result (6.7% vs. 4.4%; Table 2) for the primary outcome. The between-group difference was 2.3% (95% confidence interval [CI], −7.1%–11.7%; p = 1.000), indicating non-inferiority. In the PPS analysis, three (7.1%) and two (4.8%) of the 42 patients in the 36- and 48-week SSR group, respectively, exhibited relapse, with a between-group difference of 2.3% (95% CI, −7.8% to 12.4%; p = 1.000; Table 2), indicating non-inferiority. No difference was observed in the time of liver biochemical normalization between the 36-week (median: ALT, 3.0 weeks; AST, 3.0 weeks; alkaline phosphatase [ALP], 2.0 weeks; TBIL, 4.0 weeks) and 48-week

SSR groups (median: ALT, 3.0 weeks; AST, 2.0 weeks; ALP, 2.0 weeks; TBIL, 2.0 weeks; all p > .05; Figure 3, Table S5).

Briefly, during the ITT analysis, the 36-week SSR revealed a comparable RR between the DI-ALH (5.6%) and non-DI-ALH (7.4%) subgroups; the 48-week SSR also achieved a comparable RR between the DI-ALH (4.5%) and non-DI-ALH (4.3%) subgroups (Table S6).

In both the 36- and 48-week SSR, the RR of patients with low-risk BNR-6 was zero, which was lower than that of patients with medium/high-risk BNR-6 (Table S7).

3.3.2 | Histological changes

Liver biopsies of all participants were obtained at BL, except for two who withdrew consent for biopsy. At the treatment endpoint,
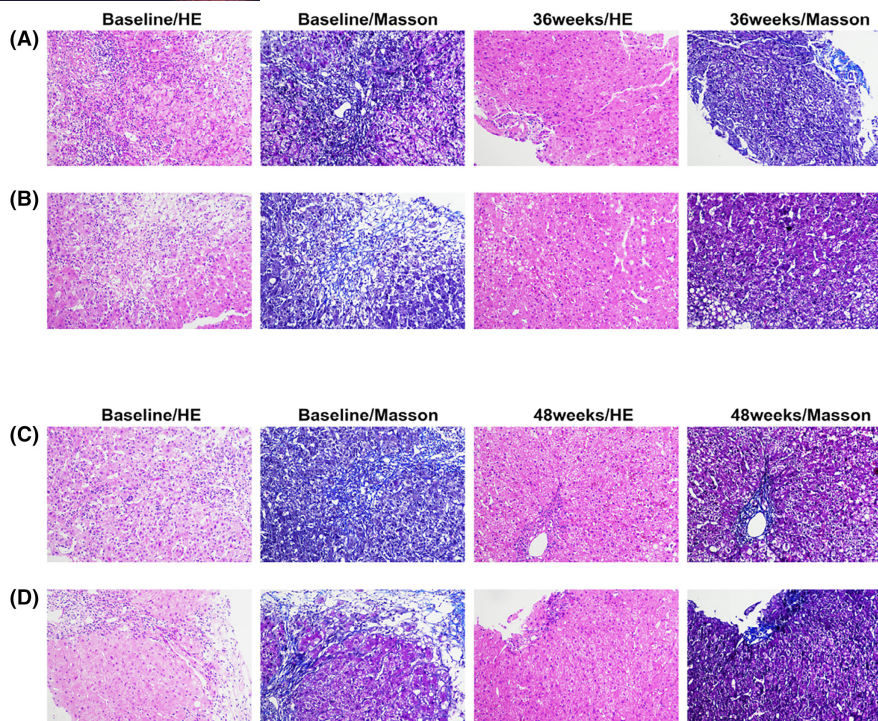
FIGURE 2 Histological improvement assessment of pre- and post-treatment in patients with chronic drug-induced liver injury (DILI) receiving steroid treatment. Patient no. 25 represented in (A), who received a 36-week steroid treatment, initially presented with extensive lobular necroinflammatory activity, moderate portal inflammatory infiltration and significant fibrosis as indicated by Haematoxylin–eosin (HE) and Masson trichrome stains (patient no. 25). Post 36-week steroid treatment, the liver biopsy showed mild histological activity and an absence of fibrosis. Patient no. 17 represented in (B) exhibited confluent necrosis and lobular inflammation before treatment. Notably, lobular necroinflammation and fibrosis reversal were noted during the liver biopsy of patient no. 17 after the 36-week steroid treatment. Patient no. 10 represented in (C), who received the 48-week steroid treatment, demonstrated obvious lobular and portal inflammatory activity with interface hepatitis on HE staining. Masson trichrome stain revealed advanced liver fibrosis and distorted lobular structure at baseline (patient no. 10). Post-treatment liver biopsy indicated a return to normal lobular structure and mild portal inflammation. Patient no. 14 represented in (D) also received the 48-week steroid treatment and initially showed a few lobular confluent necrosis and mild portal inflammatory infiltrate. Masson trichrome stain indicated bridging fibrosis. After 48 weeks of steroid treatment, lobular histological activity and liver fibrosis were absent in the post-treatment biopsy (patient no. 14). HE stain and Masson trichrome stain, original magnification ×200.

liver biopsies were obtained from 29 (29/42, 69.0%) patients in the 36-week SSR group and 28 (28/42, 66.7%) patients in the 48-week SSR group. After treatment, 93.1% of patients in the 36-week SSR group exhibited a decrease in activity score by at least 2 points, and the frequency in the 48-week SSR was 92.9%. The between-group difference was 0.2% (95% CI, −0.7–1.1%; $p = 1.000$), indicating non-inferiority (Table 2). The proportions of patients with different activity scores (0–6, 7–9, 10–14 and 15–18 points) significantly changed in both the 36- and 48-week SSR groups (Figure 4A), indicating an evident activity improvement in the two groups. Similarly, 41.4% of patients in the 36-week SSR group exhibited a decrease in fibrosis score by at least one point, and the frequency in the 48-week SSR group was 46.4%, with a between-group difference of −5.0% (95% CI, −8.4% to 1.6%; $p = .701$), indicating non-inferiority (Table 2).

Further analysis revealed that the proportion of unfavourable fibrosis status (S score ≥3 points) showed a decline from 61.4% (95% CI, 47.0%–75.8%) at BL to 44.8% (95% CI, 32.5%–57.1%) at the

treatment endpoint in the 36-week SSR group, and the proportion also decreased from 65.9% (95% CI, 51.0%–80.8%) to 48.3% (95% CI, 35.5%–61.1%) in the 48-week SSR group (Figure 4B), indicating non-inferiority ($p = .684$). There was no difference between the changes in the activity score (Figure 4C) or fibrosis score (Figure 4D) between the 36- and 48-week SSR groups. The pre- and post-treatment representative liver biopsies from four patients in our cohort are shown in Figure 2A–D.

Importantly, steroid treatment efficacy for chronic DILI was comparable between the DI-ALH and non-DI-ALH subgroups in terms of histological improvements, whether in the 36- or 48-week SSR group (Table S4).

Fibrosis improvement was also assessed using the APRI and FIB-4. The scores of both models decreased in the 36- and 48-week SSR groups (APRI, −2.70 [95% CI, −3.11 to 1.42] vs. −2.52 [95% CI, −4.08 to 0.89], $p = .536$; FIB-4, −3.23 [95% CI, −3.24 to 0.39] vs. −2.655 [95% CI, −2.99 to 0.06], $p = .511$ respectively), indicating non-inferiority (Table 2).

TABLE 2 Therapeutic effects and safety of the corticosteroid treatment.

Items	36w-SSR group (n = 45)	48 w-SSR group (n = 45)	p value
Relapse rate (RR), n (%)	3/45 (6.7%, ITT)	2/45 (4.4%, ITT)	1.000 (ITT)
	3/42 (7.1%, PPS)	2/42 (4.8%, PPS)	1.000 (PPS)
Histology improvement			
Activity score decreased ≥2 points[a], n (%)	27/29 (93.1)	26/28 (92.9)	1.000
Mean decline in activity score	5.6 ± 2.8	5.5 ± 3.1	.949
Fibrosis score decreased ≥1 point[a], n (%)	12/29 (41.4)	13/28 (46.4)	.701
Mean decline in fibrosis score	−0.4 ± 0.9	−0.6 ± 1.1	.632
APRI[b] change	−2.7 (−5.5, −1.5)	−2.5 (−5.1, −0.9)	.536
FIB-4[c] change	−3.2 (−5.4, −1.7)	−2.6 (−6.7, −0.8)	.511
Adverse effects during treatment (Grade I or II), n (%)			
Facial rounding	7/45 (15.6%)	9/45 (20.0%)	.581
Weight gain	3/45 (6.7%)	5/45 (11.1%)	.714
Impaired glucose tolerance	2/45 (4.4%)	2/45 (4.4%)	1.000
Hypokalaemia	3/45 (6.7%)	4/45 (8.9%)	1.000
Acne	1/45 (2.2%)	4/45 (8.9%)	.361
Hypertension	2/45 (4.4%)	2/45 (4.4%)	1.000
Hirsutism	1/45 (2.2%)	3/45 (6.7%)	.616
Dorsal hump formation	1/45 (2.2%)	1/45 (2.2%)	1.000
Adverse events during follow-up	0	0	

Note: Data reported as mean ± SD or median (range).

Abbreviations: ITT, intention-to-treat; PPS, per-protocol set; SSR, steroid stepwise reduction.

[a]Ishak score.[16]

[b]The formula of APRI calculation is $AST/ULN \times 100/PLT$ ($\times 10^9$/L).[17]

[c]The formula of FIB-4 calculation is $Age \times AST/PLT$ ($\times 10^9$/L) $\times$ Square root of ALT.[18]
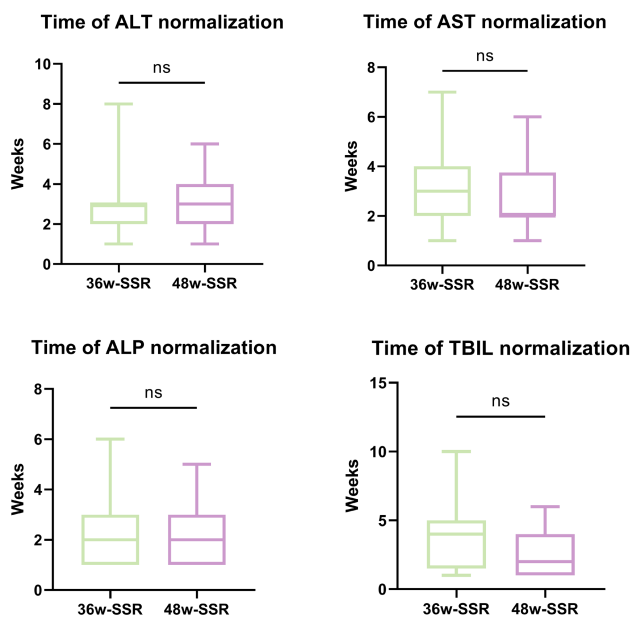

FIGURE 3 Time of liver biochemistry (ALT, AST, ALP and TBIL) normalization between the 36w-SSR and 48w-SSR groups. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SSR, Steroid stepwise reduction; TBIL, total bilirubin.

3.4 | Safety

We observed corticosteroid-related grade 1 or 2 adverse events, including facial rounding, weight gain, impaired glucose tolerance, hypokalaemia and acne, in both the groups (Table 2). However, no difference was observed in adverse events during treatment between the 36- and 48-week SSR groups. No severe adverse events were reported in either the 36- or 48-week SSR group. All adverse events resolved within 24 weeks of steroid withdrawal.

4 | DISCUSSION

Currently, an effective treatment for chronic idiosyncratic DILI cases is lacking. The prevailing consensus suggests that immunological mechanisms play an important role in the pathogenesis of idiosyncratic DILI.[24] Therefore, as immunosuppressant drugs, corticosteroids might represent an opportunity to confine the damage caused by inflammatory responses. While corticosteroid therapy is not a standard treatment for DILI cases, it is commonly used in patients with idiosyncratic DILI, especially in those exhibiting autoimmune features.[3,8,25–28] Short-term use of corticosteroids was strongly recommended for patients with severe DILI with hyperbilirubinaemia
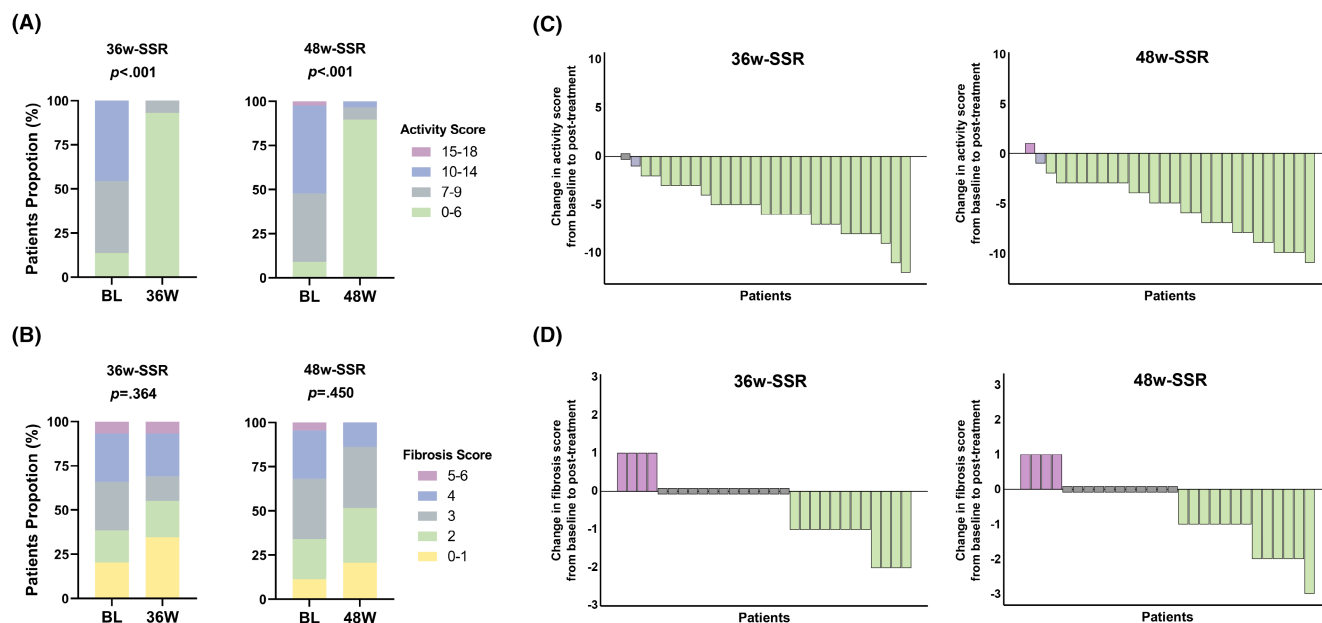
FIGURE 4 Comparisons of histological features between groups at baseline and the endpoint. Percentages of patients in different categories of inflammation activity scores. Inflammatory activity (A) and fibrosis (B) at baseline (BL) and at the end of treatment (36 or 48 weeks). Waterfall plots of the changes in activity scores (C) and fibrosis scores (D) from baseline to post-treatment in patients in the two groups (36-w SSR or 48-w SSR). SSR, steroid stepwise reduction.

in a retrospective study.[29] Moreover, rapid responses to corticosteroids were reported in two well-characterized patients of DILI without autoimmune features as observed by serology or histology.[8] In contrast, steroid therapy was not associated with an improved recovery time or survival in patients with acute severe DILI in another retrospective study.[30] An analysis from the Spanish DILI Registry indicated that patients receiving corticosteroids had a higher rate of death/liver transplantation than those who were not treated with steroids.[31] The benefit–risk ratio of corticosteroid administration is controversial owing to significant differences and mismatches in DILI characteristics between the steroid and non-steroid groups. Niu et al.[10] examined the relationship between corticosteroid therapy and the risk of acute liver failure in patients with idiosyncratic DILI in a rigorous propensity score-matched analysis. This approach could remove the effects of confounding factors when estimating the effects of steroid treatment on idiosyncratic DILI, and corticosteroid therapy did not increase the risk of mortality in patients with idiosyncratic DILI but exhibited a beneficial effect in terms of the rate of normalization of liver enzymes.

Many studies on the therapeutic effects of steroids have focused on acute idiosyncratic DILI. The therapeutic effects of steroids on chronic DILI have not been fully evaluated. Retrospective studies[32,33] without liver histological evaluation have reported the role of steroids in the treatment of chronic DILI, which remains controversial. Persistent liver injury, even after withdrawal of the causative agent following acute DILI remains a clinical challenge.

In our previous study, we showed that a 48-week SSR leads to significantly decreased necro-inflammatory activity, fibrosis score and RR, independent of autoimmune features, in patients with

chronic DILI.[11] Although corticosteroid-related side effects occur mostly at doses >20 mg daily for >18 months,[21,34] concerns persist regarding severe side effects of steroids during the 48-week SSR treatment period.

To decrease the risk of potential adverse effects and increase compliance of patients with DILI during steroid treatment, we performed a randomized prospective open-label trial to investigate the efficacy of 36-week SSR for patients with chronic DILI. In a well-characterized cohort of patients with chronic DILI, both 36- and 48-week SSR achieved similar efficacy in biochemical response and histological improvements with good safety. These data support the concept that the 36-week SSR was non-inferior to the 48-week SSR in patients with chronic DILI.

DI-ALH was defined as a liver injury with laboratory and/or histological features that may be indistinguishable from those of AIH.[12] Corticosteroids may be of benefit in selected patients with DI-ALH. However, the optimal dose and duration are unknown because of the lack of controlled clinical trials. In our study, >40% of patients were diagnosed with DI-ALH. Consistent with our previously reported results,[11] in this study, both 36- and 48-week SSR achieved a biochemical response and histological improvements in patients with DI-ALH. Our research results provide an effective treatment regimen for patients with DI-ALH, particularly in those where ongoing injury persists beyond 6 months.

We found that similar RRs and histological improvements were observed in the DI-ALH and non-DI-ALH subgroups, whether in the 36- or 48-week SSR group, indicating the rationale of corticosteroid treatment for chronic DILI independent of autoimmune features. DI-ALH is considered a liver injury with laboratory and/

or histological features that may be indistinguishable from those of AIH.[12] Distinguishing DI-ALH from AIH is crucial as patients with DI-ALH rarely require long-term immunosuppression, and approximately 70% (based on our data) experience spontaneous resolution after discontinuing the implicated drug. The absence of relapse during long-term follow-up, such as the 36-week period, without immunosuppressive therapy is an important feature of DI-ALH. We believe that DI-ALH is a special type of chronic DILI and may not conform to the classical definition of AIH. We need to pay more attention to this situation. We also found that approximately 93% of enrolled patients who underwent steroid treatment (approximately 41% with DI-ALH) did not relapse, further confirming that these patients have chronic DILI rather than AIH. The remaining 7% of patients might develop classical AIH and may require long-term follow-up.

Clinical practice guidelines in DILI discourage routine corticosteroid use or recommend limiting their use to specific patients with autoimmune features.[3,26,27] Niu et al.[10] found that corticosteroid administration was associated with a greater rate of normalization of liver enzymes in patients with more severe DILI and/or features suggesting autoimmune hepatitis-like DILI. However, in line with our previous research findings,[11] we found in the current study that similar RRs and histological improvements were observed in the DI-ALH and non-DI-ALH subgroups, whether in the 36- or 48-week SSR group, indicating the possible rationale of corticosteroid treatment for chronic DILI independent of autoimmune features. Additionally, there have been reports of two cases of DILI that improved with corticosteroid therapy despite the lack of autoimmune features by serology or histology.[8] To overcome this issue, a larger multi-centre and randomized controlled trial should be performed to evaluate whether corticosteroid-treated patients with DI-ALH would have a better outcome.

Further, we performed a post hoc analysis, focusing on risk stratification management and thus evaluating the efficacy of steroid therapy. There is an urgent unmet clinical need to develop tools for risk assessment and stratification in treating patients with DILI. Our previous BNR-6 score (consisting of age, sex, AST, TBIL, PLT and PT), measured on the date of chronic DILI diagnosis, exhibited physician-friendly performance for predicting the risk of BNR in chronic DILI.[19] Considering the observed zero RRs in the low-risk category for BNR-6 (<28 points) in both treatment groups, we had previously suggested that for those with medium/high BNR-6 scores (≥28 points), corticosteroid treatment should be considered with an intention to avoid progression of liver injury. For low risk of BNR-6 (<28 points), steroid therapy is not required. In the present study, we showed that steroid therapy could decrease the RRs to 4.9% (36-week) and 5.4% (48-week) in medium–/high-risk patients respectively. The BNR-6 score might fulfil clinicians' expectations concerning precise identification for treatment; therefore, we suggest that the BNR-6 score might be incorporated into future clinical practice to initiate timely steroid therapy for patients with chronic DILI.

The findings from this study support the use of 36-week SSR in patients with chronic DILI meeting one of the following criteria: (1)

evident increase in liver biochemistry parameters (e.g. ALT or AST >10×ULN, or ALT or AST >5×ULN and TBIL >2×ULN), (2) histological features of confluent necrosis and bridging necrosis, or portal inflammation equal to or more than moderate, even with or without autoimmune features or (3) medium/high BNR risk (BNR-6 ≥28 points).

Corticosteroid-related side effects, especially severe complications, usually occur in patients with AIH after protracted therapy with prednisone (20 mg daily) for >18 months.[21,34] In this study, 36- and 48-week treatments were compared. All observed steroid-related adverse effects were of grade 1 or 2 according to CTCAE 5.0. Furthermore, all adverse effects disappeared prior to the end of the 24-week follow-up period.

Furthermore, we conducted a subgroup analysis on the implicated agents for patients based on the efficacy of steroid treatment. Among the patients who did not respond to steroid treatment, the implicated agents included partially or entirely TCM/HDS. In contrast, nearly 30% of the patients who responded to steroid treatment had implicated agents consisting solely of synthetic drugs. Although there was no significant difference in the implicated agents between the two groups, our results indicate that TCM/HDS could be an underlying agent affecting the efficacy of steroid treatment. This also suggests that more attention should be paid to the clinical assessment and treatment strategies of patients with chronic DILI caused by TCM/HDS in future clinical practices.

The current study has some limitations. First, this was a single-centre and open-label study. The findings should be replicated in a large multi-centre and randomized controlled trial. Second, the proportion of participants in the two groups who underwent a second biopsy at the treatment endpoint was <70%. To overcome this issue, we used the APRI and FIB4 scores for non-invasive assessment.

In conclusion, this study provides high-quality evidence that both 36- and 48-week SSR demonstrate similar efficacy in biochemical response and histological improvements with good safety, supporting 36-week SSR as a preferable therapeutic choice for patients with chronic DILI with or without autoimmune features. Thus, we recommend 36-week SSR therapy for the treatment of chronic DILI cases. A larger multi-centre and randomized controlled clinical trial should be performed to replicate our results and establish a subgroup of patients with DILI who would benefit from steroid therapy.

AUTHOR CONTRIBUTIONS

CONFLICT OF INTEREST STATEMENT
None.

DATA AVAILABILITY STATEMENT
Deidentified individual participant data that underlie the reported results will be made available 3 months after publication for 5 years after the publication date. The study protocol has been included as supplementary data available with the online version of this article. Individual participant data will not be shared. For request of data, analysis methods, and study materials, please contact the corresponding author (ZSZ) via email: zszou302@163.com.

TRIAL REGISTRATION
NCT03266146 (ClinicalTrials.gov).

ETHICS STATEMENT
This study was approved by the Ethics Committees of the Fifth Medical Center of Chinese PLA General Hospital (no. 2017106D).

PATIENT CONSENT STATEMENT
Written informed consent was obtained from all participants.

ORCID
Bin-xia Chang https://orcid.org/0000-0002-7954-7230
Jiang-tao Liu https://orcid.org/0000-0003-4506-6102
Xing-ran Zhai https://orcid.org/0000-0002-4655-7109
Guruprasad P. Aithal https://orcid.org/0000-0003-3924-4830
Dong Ji https://orcid.org/0000-0001-8214-462X
Jingmin Zhao https://orcid.org/0000-0003-4345-2149
Zhengsheng Zou https://orcid.org/0000-0002-1778-269X

REFERENCES
1. Li X, Tang J, Mao Y. Incidence and risk factors of drug-induced liver injury. *Liver Int*. 2022;42(9):1999-2014.
2. Bjornsson HK, Olafsson S, Bergmann OM, Bjornsson ES. A prospective study on the causes of notably raised alanine aminotransferase (ALT). *Scand J Gastroenterol*. 2016;51(5):594-600.
3. Fontana RJ, Liou I, Reuben A, et al. AASLD practice guidance on drug, herbal, and dietary supplement-induced liver injury. *Hepatology*. 2023;77(3):1036-1065.
4. Chalasani N, Bonkovsky HL, Fontana R, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology*. 2015;148(7):1340-1352.
5. Medina-Caliz I, Robles-Diaz M, Garcia-Munoz B, et al. Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury. *J Hepatol*. 2016;65(3):532-542.
6. Devarbhavi H, Aithal G, Treeprasertsuk S, et al. Drug-induced liver injury: Asia Pacific Association of Study of liver consensus guidelines. *Hepatol Int*. 2021;15(2):258-282.
7. Bjornsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. *J Hepatol*. 2009;50(3):511-517.
8. Sundaram S, Vuppalanchi R, Saxena R, Chalasani N. Treatment of idiosyncratic drug-induced liver injury using steroids. *ACG Case Rep J*. 2020;7(2):e00319.
9. Karkhanis J, Verna EC, Chang MS, et al. Steroid use in acute liver failure. *Hepatology*. 2014;59(2):612-621.
10. Niu H, Ma J, Medina-Caliz I, et al. Potential benefit and lack of serious risk from corticosteroids in drug-induced liver injury: an international, multicentre, propensity score-matched analysis. *Aliment Pharmacol Ther*. 2023;57(8):886-896.
11. Wang JB, Huang A, Wang Y, et al. Corticosteroid plus glycyrrhizin therapy for chronic drug- or herb-induced liver injury achieves biochemical and histological improvements: a randomised open-label trial. *Aliment Pharmacol Ther*. 2022;55(10):1297-1310.
12. Andrade RJ, Aithal GP, de Boer YS, et al. Nomenclature, diagnosis and management of drug-induced autoimmune-like hepatitis (DI-ALH): an expert opinion meeting report. *J Hepatol*. 2023;79(3):853-866.
13. Chalasani NP, Hayashi PH, Bonkovsky HL, et al. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2014;109(7):950-966.
14. Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci*. 2015;17(1):14.
15. Alvarez F, Berg PA, Bianchi FB, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol*. 1999;31(5):929-938.
16. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. *J Hepatol*. 1995;22(6):696-699.
17. Carvalho-Filho RJ, Schiavon LL, Narciso-Schiavon JL, et al. Optimized cutoffs improve performance of the aspartate aminotransferase to platelet ratio index for predicting significant liver fibrosis in human immunodeficiency virus/hepatitis C virus co-infection. *Liver Int*. 2008;28(4):486-493.
18. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology*. 2006;43(6):1317-1325.
19. Wang CY, Deng Y, Li P, et al. Prediction of biochemical nonresolution in patients with chronic drug-induced liver injury: a large multicenter study. *Hepatology*. 2022;75(6):1373-1385.
20. Common Terminology Criteria for Adverse Events. (CTCAE, version 5.0). https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf
21. Manns MP, Czaja AJ, Gorham JD, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology*. 2010;51(6):2193-2213.
22. European Association for the Study of the L. EASL clinical practice guidelines: autoimmune hepatitis. *J Hepatol*. 2015;63(4):971-1004.
23. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther*. 2011;89(6):806-815.
24. Andrade RJ, Chalasani N, Bjornsson ES, et al. Drug-induced liver injury. *Nat Rev Dis Primers*. 2019;5(1):58.

25. Fontana RJ, Hayashi PH, Gu J, et al. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. *Gastroenterology.* 2014;147(1):96-108.

26. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. Practice Parameters Committee of the American College of G. ACG clinical guideline: diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol.* 2021;116(5):878-898.

27. European Association for the Study of the Liver. Electronic address eee, Clinical Practice Guideline Panel C, Panel m, representative EGB. EASL Clinical Practice Guidelines: drug-induced liver injury. *J Hepatol.* 2019;70(6):1222-1261.

28. Björnsson ES, Vucic V, Stirnimann G, Robles-Díaz M. Role of corticosteroids in drug-induced liver injury. A systematic review. *Front Pharmacol.* 2022;13:820724.

29. Hu PF, Wang PQ, Chen H, et al. Beneficial effect of corticosteroids for patients with severe drug-induced liver injury. *J Dig Dis.* 2016;17(9):618-627.

30. Pang L, Yang W, Hou F. Features and outcomes from a retrospective study of 570 hospitalized Chinese patients with drug-induced liver injury. *Clin Res Hepatol Gastroenterol.* 2018;42(1):48-56.

31. Stephens C, Robles-Diaz M, Medina-Caliz I, et al. Comprehensive analysis and insights gained from long-term experience of the Spanish DILI registry. *J Hepatol.* 2021;75(1):86-97.

32. Bjornsson E, Talwalkar J, Treeprasertsuk S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology.* 2010;51(6):2040-2048.

33. Wree A, Dechene A, Herzer K, et al. Steroid and ursodesoxycholic acid combination therapy in severe drug-induced liver injury. *Digestion.* 2011;84(1):54-59.

34. Wang G, Tanaka A, Zhao H, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidance: the diagnosis and management of patients with autoimmune hepatitis. *Hepatol Int.* 2021;15(2):223-257.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.