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Corticosteroid plus glycyrrhizin therapy for chronic drug- or herb-induced liver injury achieves biochemical and histological improvements: a randomised open-label trial

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Summary

Background: Treatment of chronic drug-induced liver injury (DILI) or herb-induced liver injury(HILI) is an important and unresolved challenge. There is no consensus regarding the indications for corticosteroids for chronic DILI/HILI.

Aims: To investigate the efficacy and safety of corticosteroid plus glycyrrhizin for patients with chronic DILI/HILI.

Methods: This was a randomised open-label trial. Eligible patients with causality assessment using the updated RUCAM were randomly assigned (1:1) either to the steroid treatment group (48-week stepwise dose reduction of methylprednisolone plus glycyrrhizin) or control group (glycyrrhizin alone). Liver biopsies were performed at baseline and at the end of the 48-week treatment period. The primary outcome was the proportion of patients with sustained biochemical response (SBR). The secondary outcomes were improvement in liver histology, time to biochemical normalisation and safety.

Jia-Bo Wang, Ang Huang, Yijin Wang, and Dong Ji contributed equally to this work.

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Results: Of 80 participants, 70 (87.5%) completed the trial. The patients were predominantly female (77.5%), aged >40 years (77.5%) and had a hepatocellular injury pattern of DILI (71.2%). Compared to the control group, the treatment group showed a higher proportion of SBR (94.3% vs. 71.4%, $p = 0.023$), shorter biochemical normalisation time and histological improvements in both histological activity and fibrosis. The DILI and HILI subgroups, as well as the autoimmune hepatitis (AIH)-like DILI and non-AIH-like subgroups, showed comparable responses. No severe adverse events were observed during the trial.

Conclusion: This study provides the first clinical evidence that corticosteroid plus glycyrrhizin therapy for chronic DILI with or without AIH-like features can achieve both biochemical response and histological improvements with good safety. (ClinicalTrials.gov, NCT 02651350).

1 | INTRODUCTION

The incidence of drug- or herb-induced liver injury (DILI/HILI) is 19.1–23.8 per 100,000 person globally.[1] DILI can be caused by synthetic drugs, biological preparations, herbs, dietary supplements and toxins. HILI specifically indicates liver injury caused by herbs and dietary supplements.[2–4] The majority of DILIs present as acute and self-limiting episodes that resolve after withdrawal of the offending agent, although some acute DILI cases can be serious, resulting in hospitalisation and even life-threatening outcomes.[5] In a substantial proportion of patients, liver injury persists with prolonged recovery[6,7] after withdrawing the offending agents. The initial acute injury progresses to chronic DILI with the prevalence ranging from 10% to 24%.[8,9] The American College of Gastroenterology (ACG) guidelines define chronicity as evidence of continued liver injury more than 6 months after drug withdrawal following the diagnosis of acute DILI.[6] In addition to unresolved liver biochemistry, histological and/or radiological evidence of persistent liver damage can also be observed in these cases.[10] The spectrum of liver injury patterns in patients with chronic DILI is broad, ranging from autoimmune-like DILI[11] with or without autoantibodies to chronic hepatitis and resolving bile duct syndrome.[12–15] The severity spectrum ranges from mild chronic injury to cirrhosis, liver failure and death.[14,16] According to the Spanish DILI Registry study,[17] 8% of patients with DILI had sustained liver injury for >1 year, among which 64% did not show resolution even after 3 years. More importantly, 44% of patients with long-term unsolved DILI exhibited progression to cirrhosis. Collectively, withdrawal of the offending drug, a common strategy for the treatment of DILI/HILI, may not be sufficient to benefit patients with chronic DILI/HILI, and a new treatment approach is warranted.

The European Association for the Study of the Liver (EASL) guidelines suggest the use of corticosteroid therapy in patients who do not show recovery despite drug cessation, with the intention of preventing progression of persistent liver injury.[18] Steroids have been used to treat DILI in acute liver failure (ALF), although evidence does not support their use.[19] Corticosteroid treatment for suspected autoimmune hepatitis (AIH), such as DILI and immune checkpoint inhibitor-induced liver injury, is much more common in clinical practice[18,20–25]; however, its efficacy still lacks high-level clinical evidence. In the four clinical guidelines from the United States,[6] Europe,[18] Asia,[26] and China,[27] no consensus has been recommended regarding the use of steroids for the treatment and management of chronic DILI/HILI, especially for non-AIH, such as chronic DILI/HILI.

This randomised open-label trial was initiated to determine the efficacy and safety of 48-week stepwise dose reduction of corticosteroid plus glycyrrhizin therapy (48w-SRCT) for these patients.

2 | PATIENTS AND METHODS

2.1 | Study design

This study was a randomised open-label trial conducted at the Fifth Medical Center of Chinese PLA General Hospital, which aimed to evaluate the efficacy and safety of 48w-SRCT protocol with a 24-week follow-up in patients with chronic DILI (Figure 1A). The randomised open-label trial and post-trial follow-up for the participants were approved by the Ethics Committees of the Fifth Medical Center of the General Hospital, Beijing (no. 2015170D and the update on 3 December 2018). Written informed consent was obtained from all participants. This study was registered at ClinicalTrials.gov (NCT02651350).

2.2 | Participants

Patients diagnosed with DILI between 26 December 2015 and 6 December 2017 were screened. Chronic DILI was defined as failure to the return of liver enzyme or bilirubin level to pre-DILI baseline level, imaging or histology data compatible with chronicity (irrespective of laboratory data),[27] and/or other signs or symptoms of ongoing liver disease (e.g. ascites, encephalopathy, portal hypertension and

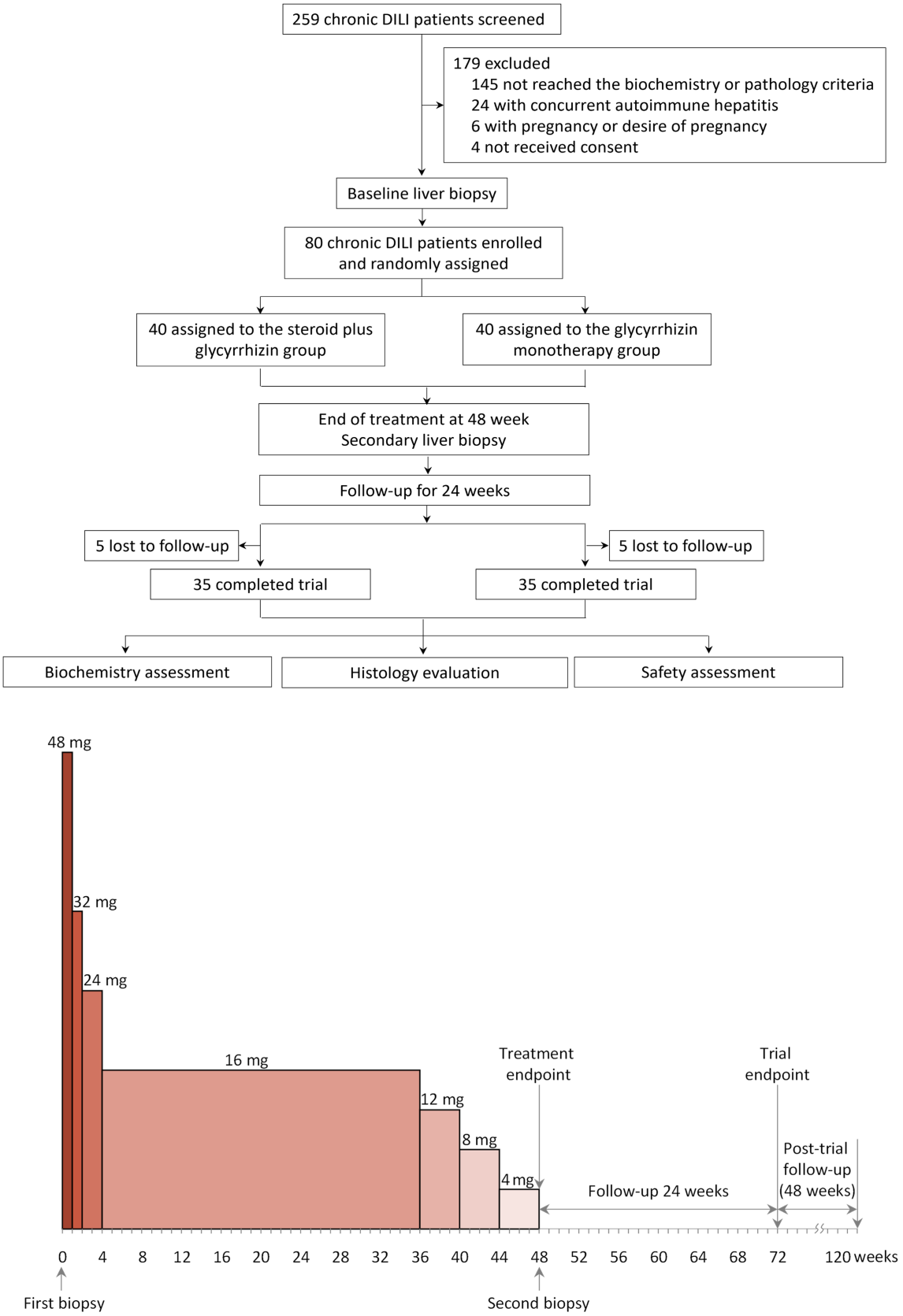

FIGURE 1 Flow diagram of the clinical trial and the steroid treatment protocol. A, The study flow chart of the trial; B, The protocol of the 48-week stepwise dose reduction corticosteroid plus glycyrrhizin therapy (48w-SRCT)

coagulopathy) 6 months after DILI onset (ACG clinical guidelines for diagnostic criteria of chronic DILI[6]).

The detailed inclusion criteria were as follows: (1) diagnosis of chronic DILI according to the ACG DILI guidelines; (2) age between 18 and 60 years; (3) updated Roussel Uclaf Causality Assessment Method (RUCAM)[28] score ≥ 6; (4) any of the following conditions: alanine aminotransferase (ALT) or AST level ≥ 10 × upper limit of normal (ULN), ALT or AST level ≥5 × ULN, and total bilirubin (TBL) level ≥2 × ULN and 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.

Patients were excluded if they had any of the following conditions: (1) serious underlying comorbidities (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 liver disease, Wilson's disease or other inherited metabolic liver diseases; (3) diagnosis of definite AIH (>15 points on the International Autoimmune Hepatitis Group Scoring System before corticosteroid therapy[21]); (4) steroid therapy within 6 months before enrolment; (5) malignancy during or prior to screening; (6) liver histological features of nodular regenerative hyperplasia, moderate to severe fatty liver, or peliosis hepatis and (7) pregnancy or breastfeeding.

2.3 | Randomisation and masking

After screening, eligible subjects were randomly assigned to the steroid plus glycyrrhizin treatment or glycyrrhizin monotherapy group according to the generated random numbers using the PROC PLAN statement (PROC PLAN seed = 151,221) of SAS software by a statistician not involved in the trial. The statistician documented the random number, and the investigators called the statistician to ask for the assignment of each eligible patient.

Two pathologists (Jingmin Zhao and Romil Saxena), who were blinded to the patients' group assignments and clinical information, assessed the liver histology. In case of discrepancies, the slides were reviewed by a third highly experienced pathologist (Tailing Wang), who was blinded to the other two pathologists' clinical information and evaluation results.

2.4 | Procedures

In the steroid plus glycyrrhizin group, patients were treated with steroid plus glycyrrhizin tablets (75 mg/dose, three times a day, Minophagen Pharmaceutical Co., Ltd., Japan) according to the DILI Guideline by the Chinese Medical Association.[27] The glycyrrhizin monotherapy group received only glycyrrhizin preparation (tablet). The protocol consisted of a gradual reduction of different doses: 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 another 2 weeks; maintenance treatment phase with 16 mg/day lasting for 32 weeks; and reduction phase using a decreasing sequence of doses from 16 to 4 mg/day by a reduction of 4 mg per 4-week period until 48 weeks (Figure 1B). The participants were monitored by assessing liver function and evaluating adverse events at 2, 4, 12, 24, 36 and 48 weeks during treatment and at 72 weeks during follow-up. After the end of the trial, we maintained the post-trial follow-up for all participants until 120 weeks (Figure 1B).

Paired liver biopsies at baseline and 48-week treatment were obtained. Inflammatory necrosis grading and fibrosis staging were determined according to the modified Ishak scoring system,[29] in addition to evaluating the typical histological characteristics. To rule out autoimmune hepatitis and IgG4-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) and fibrosis 4 score (FIB-4),[29,30] was performed based on the following formulas: APRI = ([AST/ULN]/PLT) × 100 and FIB-4 = (age × AST) / (PLT × $ALT^{0.5}$) (AST ULN = 40 U/L).

2.5 | Outcomes

The primary outcome was sustained biochemical response (SBR). The secondary outcomes were improvement in liver histology, time to normalisation of biochemical parameters, and safety. Histological improvement was defined as a decrease of at least two points in necroinflammatory activity or at least one point in fibrosis in accordance with the Ishak scoring system.

Moreover, the steroid plus glycyrrhizin treatment efficacy was also compared between autoimmune hepatitis-like DILI (AIH-like DILI) and non-AIH-like DILI subgroups. AIH-like DILI was defined as a condition with either positive serum autoantibody (antinuclear antibody and/or anti-smooth muscle antibody, ANA, and/or SMA) or elevated immunoglobulin G (IgG) level (>1.1 × ULN) but the international AIH score ≤15 points before corticosteroid therapy.[21]

Efficacy was also compared between DILI (caused by conventional pharmaceutics) and HILI (caused by herbs or multiple agents, including herbs).

The adverse events in each group were evaluated according to the Common Terminology Criteria for Adverse Events (version 5.0).[31] The types of steroid-related adverse effects were based on the AASLD[32]/EASL[33] autoimmune hepatitis guidelines. The adverse effects that occurred during both the treatment and follow-up periods were combined for the analyses.

2.6 | Statistical analysis

According to previous clinical observations of our group (data not shown), the SBR rate of patients receiving steroid plus glycyrrhizin

therapy for 48 weeks was >90%, and the SBR rate of patients receiving glycyrrhizin monotherapy was approximately 60%. Under the SAS software PROC POWER statement of 85% power to detect a rate difference of 0.3, 1:1 between groups, $\alpha = 0.05$, the total sample size was estimated to be 72 (36 cases in the steroid plus glycyrrhizin and glycyrrhizin monotherapy groups). Considering the dropout rate of 10%, the total sample size was determined to be 80 (40 cases in the steroid plus glycyrrhizin and glycyrrhizin monotherapy groups).

The trial database was locked after the 48-week treatments and 24-week follow-up. Baseline comparison, efficacy and safety were evaluated using the intention-to-treat (ITT) set and per-protocol set (PPS). Continuous variables are presented as mean ± standard deviation (SD) for normal distribution or median and range (minimum and maximum) for the non-normal distribution. Student's *t*-test (variance homogeneity) or the Satterthwaite test (variance not homogeneity) was used to compare normally distributed data, and the Wilcoxon test was used to compare non-normally distributed data. Differences between groups of classification variables were compared using chi-square or Fisher's test. We also estimated the normalisation curves of biochemistry using the Kaplan–Meier method and compared them using the log-rank test. We also performed post hoc subgroup analyses to assess treatment group and subgroup interactions using the Cochran–Mantel–Haenszel test. Safety was assessed on a per-protocol basis. The P-values for all analyses were two-sided, and the significance was set at 0.05. Analyses were performed using SAS software (version 9.4).

3 | RESULTS

3.1 | Patient flow and randomisation

From 26 December 2015 to 6 December 2017, 259 eligible patients with DILI/HILI were screened. According to inclusion and exclusion criteria, 179 patients were excluded (145 patients were ineligible based on the inclusion criteria, 24 patients had AIH, 6 patients were pregnant or planning pregnancy, and 4 patients withdrew the informed consent). Finally, 80 patients diagnosed with chronic DILI/HILI were enrolled and randomly assigned to the steroid plus glycyrrhizin or glycyrrhizin monotherapy groups in a 1:1 ratio (Figure 1A).

3.2 | Characteristics of participants

3.2.1 | Clinical features

Of the enrolled 80 patients, 62 (77.5%) were aged >40 years, and 62 (77.5%) were women. The hepatocellular type ($R \geq 5$) was the main liver injury pattern (57/80, 71.3%). Liver injury at the time of enrolment was mild in severity (41.2%) and moderate in degree (58.8%); no patients developed either severe or fatal liver injury or received liver transplantation. Moreover, 23 (28.8%) patients had positive autoantibodies (ANA and/or SMA), and 20 (25.0%) had elevated IgG levels (>1.0 × ULN), while none met the diagnostic criteria for AIH.[21]

The liver ultrasound showed that 97.5% of patients had coarsening of the liver architecture and 2.5% had a coarsening-nodular pattern. Liver biopsy results showed the activity scores of 0–6, 7–9, 10–14 and 15–18 in 23.1%, 30.8%, 33.3% and 12.8% of patients, respectively. The prevalence rates of fibrosis stages 0–1, 2, 3, 4 and 5–6 were 32.1%, 20.5%, 17.9%, 24.4% and 5.1%, respectively. Clinical characteristics were comparable between the steroid plus glycyrrhizin and glycyrrhizin monotherapy groups (Table 1).

Moreover, there were no significant differences between the non-AIH-like-DILI and AIH-like-DILI subgroups, except for positive autoantibodies and/or elevated IgG levels (Table S1).

3.2.2 | Implicated agents

In terms of causative agents of chronic DILI/HILI, the most commonly implicated agents were traditional Chinese medicine (TCM) and herbal and dietary supplements (HDS) (42/80, 52.5%), followed by synthetic drugs (27/80, 33.7%). Other causative agents were mixed agents of synthetic drugs and herbs. Eleven patients (13.8%) received both mixed synthetic drugs and TCM. The implicated TCM/HDS in this cohort was *Polygonum multiflorum* Thunb. (Heshouwu) (11 cases), *Corydalis yanhusuo* W. T. Wang (Yanhusuo) (6 cases), *Psoralea corylifolia* L. (Buguzhi) (3 cases), *Bupleurum chinense* DC. (Chaihu) (2 cases), *Dictamnus dasycarpus* Turcz. (Baixianpi) (2 cases), and *Terminalia chebula* Retz. (Hezi) (two cases). Commonly used synthetic drugs were amoxicillin (12 cases), clarithromycin (7 cases) and enalapril (2 cases).

3.2.3 | Histological features

Histologically, initial liver biopsy revealed varying degrees of inflammatory necrosis and fibrosis. Inflammatory activity >10 points occurred in 46.1% of patients, and 47.4% of patients developed significant or advanced fibrosis (fibrosis scores, 3–6) (Table 1). In cases with high activity, centrilobular necrosis, confluent necrosis and bridging necrosis were frequently noted, with ballooning and eosinophilic granular degeneration of hepatocytes surrounding necrotic areas. Central peri-venulitis and peri-sinusoidal infiltrates were also conspicuous. 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. Additionally, in chronic DILI/HILI, cholestasis with varying degrees of ductular reaction was noted. Histological features of AIH, such as predominant lymphoplasmacytic infiltrates, the formation of liver cell rosettes and emperipolesis phenomena were less common (Table 1). The baseline characteristics of subgroups with or without a second liver biopsy in the glycyrrhizin monotherapy group were also compared, and no significant differences were found (Table S2).

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

Characteristic	All patients ($n = 80$)	Steroid plus glycyrrhizin group ($n = 40$)	Glycyrrhizin monotherapy group ($n = 40$)	p value
Age (years), *n* (%)				
>40	62 (77.5)	27 (67.5)	35 (87.5)	0.059
≤40	18 (22.5)	13 (32.5)	5 (12.5)	
Female gender, *n* (%)	62 (77.5)	33 (82.5)	29 (72.5)	0.422
Class of implicated drugs, *n* (%)				
TCM or HDS	42 (52.5)	21 (52.5)	21 (52.5)	0.938
Synthetic drugs	27 (33.7)	14 (35.0)	13 (32.5)	
Mixed	11 (13.8)	5 (12.5)	6 (15.0)	
R value[a], *n* (%)				
R ≥5 (Hepatocellular)	57 (71.2)	27 (67.5)	30 (75.0)	0.486
2 < *R* <5 (Mixed)	16 (20.0)	8 (20.0)	8 (20.0)	
R ≤ 2 (Cholestatic)	7 (8.8)	5 (12.5)	2 (5.0)	
DILI severity,[b] *n* (%)				
Mild	33 (41.2)	13 (32.5)	20 (50.0)	0.115
Moderate	47 (58.8)	27 (67.5)	20 (50.0)	
Severe	0 (0.0)	0 (0.0)	0 (0.0)	
Fatal/transplantation	0 (0.0)	0 (0.0)	0 (0.0)	
WBC, $\times 10^9$/L (3.69–9.16)	4.8 ± 1.6	4.8 ± 1.9	4.8 ± 1.1	0.950
HGB, g/L (113–151)	127.0 (89.0, 167.0)	125.5 (89.0, 167.0)	128.0 (89.0, 157.0)	0.169
PLT, $\times 10^9$/L (101–320)	180.0 (60.0, 459.0)	172.0 (60.0, 368.0)	192 (70.0, 459.0)	0.203
Eosinophils,$\times 10^9$/L (0.02–0.5)	0.10 (0.00, 0.55)	0.12 (0.00, 0.55)	0.10 (0.00, 0.38)	0.580
ALT, U/L (5–35)	342.4 ± 291.5	329.0 ± 328.9	356.1 ± 250.9	0.090
AST, U/L (8–40)	320.0 (27.0, 1061.0)	329.5 (111.0, 927.0)	311.0 (27.0, 1061.0)	0.521
TBIL, μmol/L (3.3–20.5)	42.5 (6.0, 432.0)	51.3 (10.9, 328.7)	37.4 (6.0, 432.0)	0.175
ALP, U/L (40–150)	140.0 (53.7, 398.0)	135.5 (63.0–398.0)	143.0 (53.7–390.0)	0.704
GGT, U/L (7–32)	133.0 (28.0, 382.0)	132.5 (28.0–365.0)	133.0 (50.0–382.0)	0.354
Albumin, g/L (35–55)	35.0 (24.0, 44.0)	35.5 (24.0, 44.0)	35.0 (27.0, 42.0)	0.713
Cholinesterase, U/L (5000–12,000)	5348.2 ± 1618.5	5219.4 ± 1493.9	5480.4 ± 1746.8	0.472
Prothrombin time, s (10.2–14.3), *n* (%)				
Within normal range	75 (93.8)	36 (90.0)	39 (97.5)	0.359
INR (0.8–1.2), *n* (%)				
Within normal range	72 (90.0)	34 (85.0)	38 (95.0)	0.263
Autoantibodies positive, *n* (%)				
ANA and/or SMA	23 (28.8)	11 (27.5)	12 (30.0)	0.805
Others	0 (0.0)	0 (0.0)	0 (0.0)	–
IgG, g/L (7.23–16.6), *n* (%)				
>2 × ULN	1 (1.2)	1 (2.5)	0 (0.0)	0.494
1.5 × ULN–2.0 × ULN	3 (3.8)	1 (2.5)	2 (5.0)	
1.0 × ULN–1.5 × ULN	16 (20.0)	10 (25.0)	6 (15.0)	
<1.0 × ULN	60 (75.0)	28 (70.0)	32 (80.0)	
Ultrasound				
Liver, *n* (%)				
Coarsening pattern	78 (97.5)	39 (97.5)	39 (97.5)	1.000
Coarsening-nodular pattern	2 (2.5)	1 (2.5)	1 (2.5)	

TABLE 1 (Continued)

Characteristic	All patients ($n = 80$)	Steroid plus glycyrrhizin group ($n = 40$)	Glycyrrhizin monotherapy group ($n = 40$)	p value
Spleen length (mm)	107.8 ± 18.4	110.6 ± 20.0	105.0 ± 16.6	0.178
Portal vein diameter(mm)	10.6 (9.0, 13.0)	11.0 (9.0, 12.0)	10.0 (9.0, 13.0)	0.267
Liver biopsy, *n* (%)	78 (97.5)	40 (100.0)	38 (95.0)	
Activity score, *n* (%)				
0–6	18 (23.1)	5 (12.5)	13 (34.2)	0.059
7–9	24 (30.8)	13 (32.5)	11 (28.9)	
10–14	26 (33.3)	14 (35.0)	12 (31.6)	
15–18	10 (12.8)	8 (20.0)	2 (5.3)	
Fibrosis score, *n* (%)				
0–1	25 (32.1)	10 (25.0)	15 (39.5)	0.633
2	16 (20.5)	8 (20.0)	8 (21.1)	
3	14 (17.9)	8 (20.0)	6 (15.8)	
4	19 (24.4)	12 (30.0)	7 (18.4)	
5–6	4 (5.1)	2 (5.0)	2 (5.2)	
RUCAM				
6–8	74	37	37	1.000
≥ 9	6	3	3	
With or without AIH-like features				
AIH-like, *n* (%)	34 (42.5)	17 (42.5)	17 (42.5)	1.000
Non-AIH-like, *n* (%)	46 (57.5)	23 (57.5)	23 (57.5)	
AIH score[c]	7 (−2, 11)	8 (0, 11)	6(−2, 10)	0.215

[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.[4]
[c]According to the revised original scoring system (−26 to 26 points) of the International Autoimmune Hepatitis Group (21).

3.3 | Efficacy

3.3.1 | Sustained biochemical response

Five patients in each group were lost to follow-up during the treatment or follow-up period (Table S3). For the primary outcome, of the 70 patients who completed the trial (72 weeks), SBR was 94.3% (33/35) in the steroid plus glycyrrhizin group compared with 71.4% (25/35) in the glycyrrhizin monotherapy group by PPS analysis (OR, 0.15; 95% CI, 0.03–0.75; $p = 0.023$; Table 2), indicating the significant benefit of steroid treatment. The ITT analysis revealed a similar result (95.0% vs 75.0%, $p = 0.025$, ITT analysis, Table 2). Notably, the time of liver biochemical normalisation was shorter (median: ALT, 2.3 weeks; AST, 3.6 weeks; TBIL, 2.4 weeks; ALP, 0 weeks) in the steroid plus glycyrrhizin group than in the glycyrrhizin monotherapy group (median: ALT, 7.6 weeks; AST, 15.6 weeks; TBIL, 12.0 weeks; ALP, 2.9 weeks) ($p < 0.05$) (Figure 2).

We also performed a post-trial follow-up for an additional 48 weeks (Figure 1B). We found four patients with persistent abnormal biochemical indices in the glycyrrhizin monotherapy group but none in the steroid plus glycyrrhizin group, indicating that the steroid plus glycyrrhizin group achieved a much more significant benefit in terms of SBR rate within 120 weeks (including 72 weeks of trial and 48 weeks of post-trial observation) than the glycyrrhizin monotherapy group (94.3% vs 60.0%, $p = 0.001$, PPS analysis).

3.3.2 | Histological changes

Liver biopsies were obtained at baseline in all participants, except for two who withdrew consent for biopsy. At the treatment endpoint, liver biopsies were obtained from 32 patients in the steroid plus glycyrrhizin group and 12 patients in the glycyrrhizin monotherapy group. After treatment, 93.8% of patients in the steroid plus glycyrrhizin group exhibited a decrease in activity score by at least two points, whereas the frequency in the glycyrrhizin monotherapy group was 58.3% ($p = 0.011$, Table 2). The proportion of patients with different activity scores (0–6, 7–9, 10–14 and 15–18 points) significantly changed from 12.5%, 32.5%, 35.0% and 20.0% at baseline to 90.6%, 6.3%, 3.1% and 0% at week 48 in the steroid plus glycyrrhizin group ($p < 0.001$, Figure 3A), indicating an evident activity improvement in the steroid plus glycyrrhizin group. However, the proportions did not significantly change in the glycyrrhizin monotherapy group (Figure 3A). Similarly, fibrosis significantly improved (decrease in fibrosis score ≥1 point) in 53.1% of

TABLE 2 Therapeutic effects and safety of the corticosteroid treatment

Items	Steroid plus glycyrrhizin group, *n* = 40 (%)	Glycyrrhizin monotherapy group, *n* = 40 (%)	*p* value
Sustained biochemical response, n (%)	38/40 (95.0, ITT[a]) 33/35 (94.3, PPS[b])	30/40 (75.0, ITT) 25/35 (71.4, PPS)	0.025 (ITT) 0.023 (PPS)
Histology improvement at 48 weeks			
Activity score decreased ≥2 points [c], *n* (%)	30/32 (93.8)	7/12 (58.3)	0.011
Fibrosis score decreased ≥1 point [c], *n* (%)	17/32 (53.1)	0/12 (0.0)	0.001
APRI change	−4.7(−25.8, −0.8)	−2.7(−19.9, 13.7)	0.026
FIB-4 change	−5.2(−15.5, 0.7)	−1.9(−13.4, 17.4)	0.001
Adverse events during treatment (Grade I or II), *n* (%)			
Facial rounding	13/40 (32.5)	0/40	
Weight gain	10/40 (25.0)	0/40	
Impaired glucose tolerance	3/40 (7.5)	0/40	
Hypokalemia	2/40 (5.0)	1/40 (2.5)	
Acne	2/40 (5.0)	0/40	
Hypertension	1/40 (2.5)	1/40 (2.5)	
Hirsutism	1/40 (2.5)	0/40	
Dorsal hump formation	1/40 (2.5)	0/40	
Adverse events during follow-up	0	0	

Note: Data are reported as mean ± standard deviation or median (range).

[a]ITT, intention-to-treat.

[b]PPS, per-protocol set.

[c]Ishak score.

patients receiving steroid plus glycyrrhizin treatment, whereas no patients in the glycyrrhizin monotherapy group achieved improvement in fibrosis ($p = 0.001$, Table 2). Further analysis revealed that the proportion of unfavourable fibrosis status (*S* score ≥3) showed a decline from 55.0% at baseline to 40.6% at the treatment endpoint in the steroid plus glycyrrhizin group, while the proportion increased from 39.5% to 50.0% in the glycyrrhizin monotherapy group (Figure 3B). The median change in activity score was significantly higher in the steroid group than in the glycyrrhizin monotherapy group (−7.0 score vs −2.5 score, $p < 0.001$, Figure 3C). The decrease in fibrosis score was also significantly different between the steroid plus glycyrrhizin and glycyrrhizin monotherapy groups (−1.0 score vs. 1.0 score, $p = 0.005$, Figure 3D). The representative liver biopsies pre- and post-treatment from four patients in our cohort are shown in Figure 4A–D.

Fibrosis improvement was also assessed using the APRI and the FIB-4. The scores of both models were significantly lower in the steroid plus glycyrrhizin group than in the glycyrrhizin monotherapy group (APRI, −4.7 vs −2.7, $p = 0.026$; FIB-4, −5.2 vs -1.9, $p = 0.001$, respectively) (Table 2).

3.3.3 | Post hoc analyses

In the post hoc subgroup analyses of 70 patients who completed the trial, the benefit of steroid plus glycyrrhizin therapy appeared to be particularly evident in patients with fibrosis stage >3 points ($p_{interaction} = 0.015$). Factors associated with higher SBR rate in steroid plus glycyrrhizin therapy were female sex (OR, 14.0; 95% CI, 1.6–122.3; $p = 0.007$), histological activity points >6 (OR, 7.4; 95% CI, 1.3–42.3; $p = 0.038$), ALT >5 × ULN (OR, 11.5; 95% CI, 1.3–99.3; $p = 0.012$), or hepatocellular pattern of DILI (OR, 12.2; 95% CI, 1.4–105.5; $p = 0.011$) (Figure 5). We also analysed the differences in baseline clinical characteristics (Table S4) and efficacy (Table S5) between the DILI and HILI cohorts. We found no statistical difference in the efficacy between the DILI and HILI cohorts (Table S5).

Importantly, steroid plus glycyrrhizin treatment efficacy was comparable in the AIH-like and non-AIH-like chronic DILI/HILI subgroups, both biochemical response and histological improvements (Table S6).

3.4 | Safety

Regarding safety, we observed corticosteroid-related grade 1 or 2 adverse events, including facial rounding (13/40), weight gain (10/40) and impaired glucose tolerance (3/40) in the steroid plus glycyrrhizin group (Table 2). No severe adverse events (SAEs) were reported in either steroid plus glycyrrhizin or glycyrrhizin monotherapy group. All adverse events were resolved within 24 weeks of steroid withdrawal.

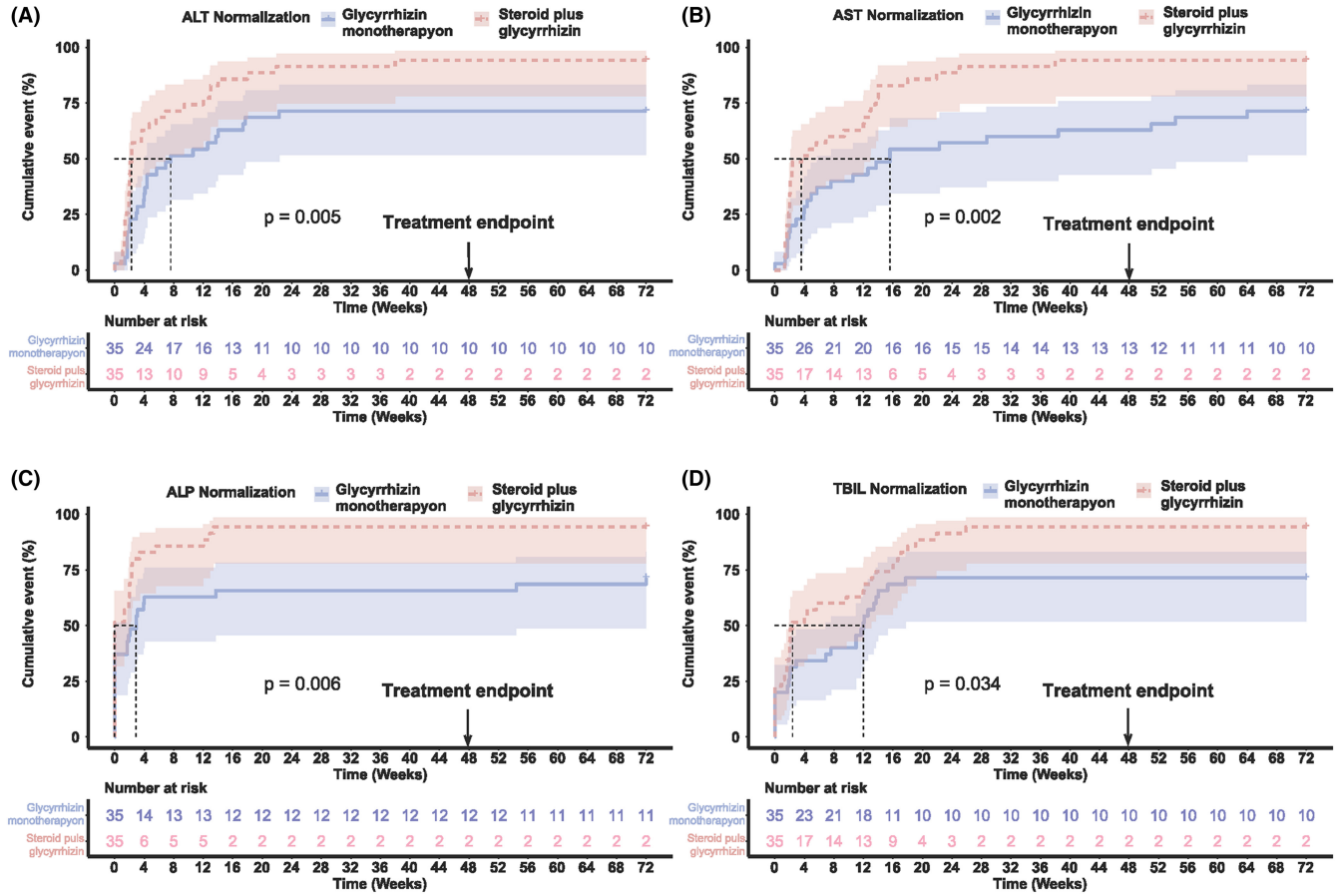

FIGURE 2 Cumulative remission curves of the liver biochemistry indices. A, Cumulative remission curve of ALT; B, Cumulative remission curve of AST; C, Cumulative remission curve of ALP; D, Cumulative remission curve of TBIL

4 | DISCUSSION

Several studies have associated idiosyncratic DILI/HILI with long-term adverse outcomes. Among those with DILI associated with histological changes, approximately one-third have been shown to have persistent biochemical or imaging abnormalities in the long-term follow-up[34] and develop chronic hepatitis, cirrhosis, liver failure and even death.[14,16] In this cohort, 47.4% of the patients had significant or advanced liver fibrosis, two had cirrhosis, and 56.1% had high necrotic inflammatory activity. These histological findings at baseline justify an intervention to arrest the progression of liver injury and reverse architectural changes, including fibrosis. Niu et al.[35] have reported the efficacy of specific drugs (silymarin, bicyclol, magnesium isoglycyrrhizinate, *N*-acetylcysteine, tiopronin, L-carnitine and TCM) is limited for acute DILI, and there are no studies on the therapy for chronic DILI/HILI. Weber et al.[36] have found that short-term (a decrease in ALT levels 1 week after the initiation of steroid therapy) response of ALT to corticosteroid therapy helps in differentiating DILI and AIH. However, the therapeutic effects of steroids on chronic DILI have not been evaluated. Sebode et al.[4] summarised the possible molecular pathogenesis of "autoimmune (–like)" DILI and HILI. However, there are no detailed corresponding steroid therapies for DILI.

Persistent liver injury, even after withdrawal of the causative agent following acute DILI/HILI, is an important clinical challenge. Therefore, we performed the first randomised open-label trial to investigate the efficacy of corticosteroid plus glycyrrhizin therapy in this setting. In a well-characterised cohort of patients with chronic DILI/HILI, we have demonstrated that corticosteroid plus glycyrrhizin therapy for 48 weeks was associated with a substantial reduction in necro-inflammatory activity and fibrosis score and a significant increase in the SBR rate. Furthermore, our post-trial follow-up indicated that the glycyrrhizin monotherapy group exhibited a decreased SBR rate from 71.4% to 60.0%, whereas the corticosteroid plus glycyrrhizin group maintained an SBR rate of 94.3%. Most importantly, similar SBRs and histological improvements were observed in the non-AIH-like and AIH-like subgroups, which implicates the rationale of the corticosteroid plus glycyrrhizin treatment for chronic DILI/HILI independent of AIH-like features.

Owing to the lack of a placebo group, we could not assess the efficacy of glycyrrhizin monotherapy. However, previous studies reported that glycyrrhizin might have a therapeutic effect, for example, only on biochemical, but not histological improvement, on drug-induced liver injury.[27,37,38] Our study showed that steroid plus glycyrrhizin therapy could significantly alleviate liver injury in patients with chronic DILI/HILI biochemically and histologically

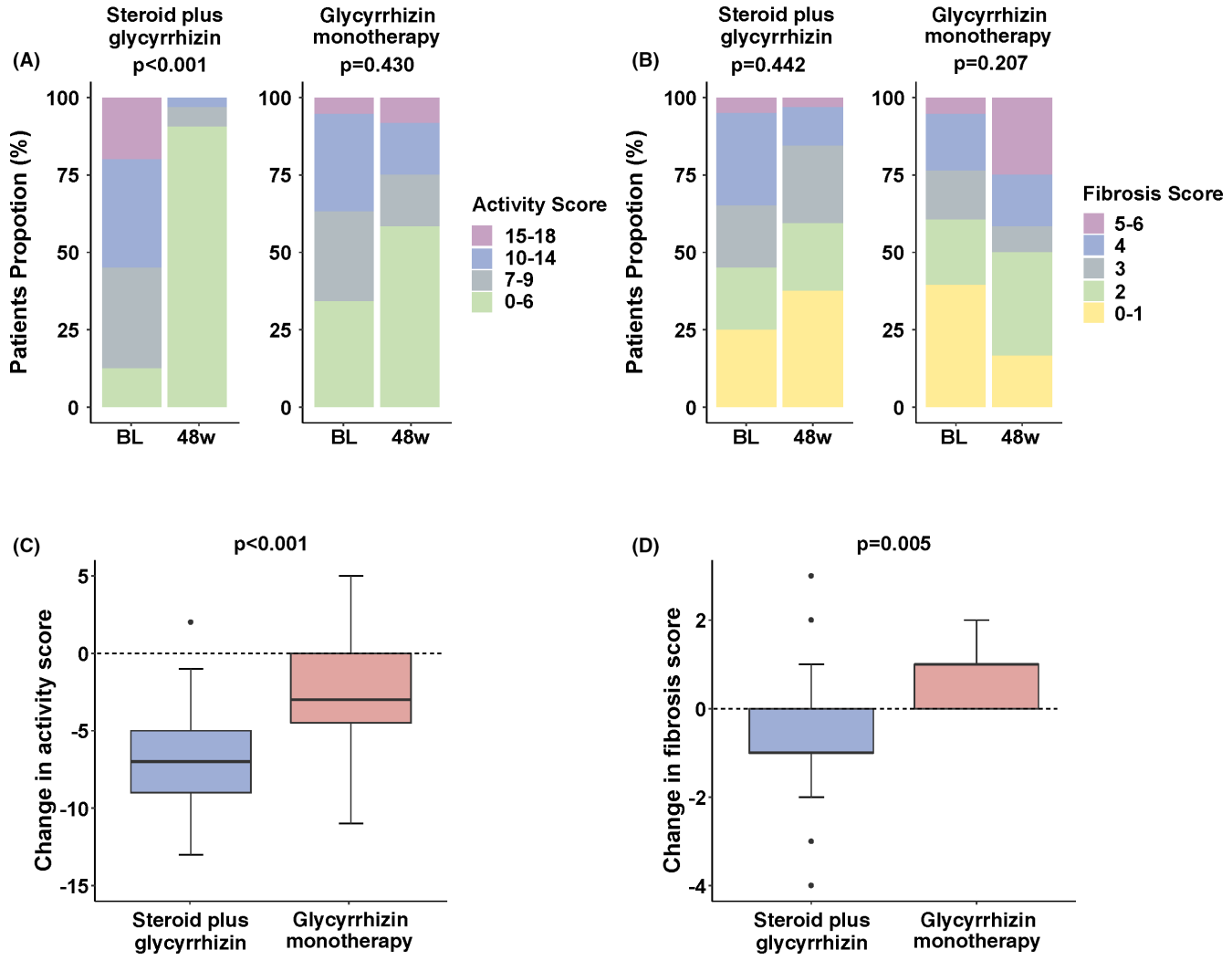

FIGURE 3 Comparisons of histological features between groups at baseline and the endpoint. Percentages of patients in different categories of inflammation activity scores (A) and fibrosis (B) at baseline (BL) and at the end point (48 weeks). Comparisons of changes in the activity (C) and fibrosis scores (D) from baseline to post-treatment in two groups

compared with glycyrrhizin monotherapy. Theoretically, these benefits are strongly suggested mainly due to steroids.

Previously, only limited data available from small, often poorly characterised cohorts[22,39] have reported the role of steroids in the treatment of chronic DILI, which remains controversial. Hu et al.[40] have pointed out that corticosteroids (potent anti-inflammatory agents) have great potential in DILI treatment. However, the effects of corticosteroids on DILI/HILI are unclear. This controversy arises because there is a lack of high-quality research on the efficacy of corticosteroids in patients with DILI/HILI. To date, most data on the beneficial effects are in the form of case reports or retrospective studies that enrolled a limited number of patients. Corticosteroids are not uniformly administered in clinical practice, making it difficult to evaluate its efficacy and thus limiting its application. A retrospective study of a small cohort of patients with severe acute DILI showed that steroid therapy had a significantly higher rate of disease resolution and shorter recovery time than non-steroid therapy.[41] Additionally, steroids were found to decrease mortality and shorten the recovery time in patients with DILI who could potentially develop ALF.[42] In contrast, two other retrospective studies suggested that steroid administration did not improve the resolution rate, recovery time or survival of patients with DILI.[43,44] Steroids have been used in clinical practice in the treatment of AIH-like DILI.[18] In this study, at the end of the 48-week treatment and 24-week post-treatment follow-up, significant SBR and histological improvement were achieved by corticosteroid plus glycyrrhizin therapy, independence of AIH-like features.

Considering DILI as either a direct cell injury or an overcompensating immune response by the drug or its metabolite with interaction to immune elements,[3,45] steroids as a major regulator of multiple cellular functions and powerful non-specific immune inhibitors are able to ameliorate immune and inflammatory responses after drug cessation at the first therapy step. Psarra et al.[46] reported that steroids could increase mitochondrial RNA synthesis, cytochrome oxidase subunit I protein expression, and mitochondrial ATP production to attenuate apoptosis. In addition, dexamethasone has been reported

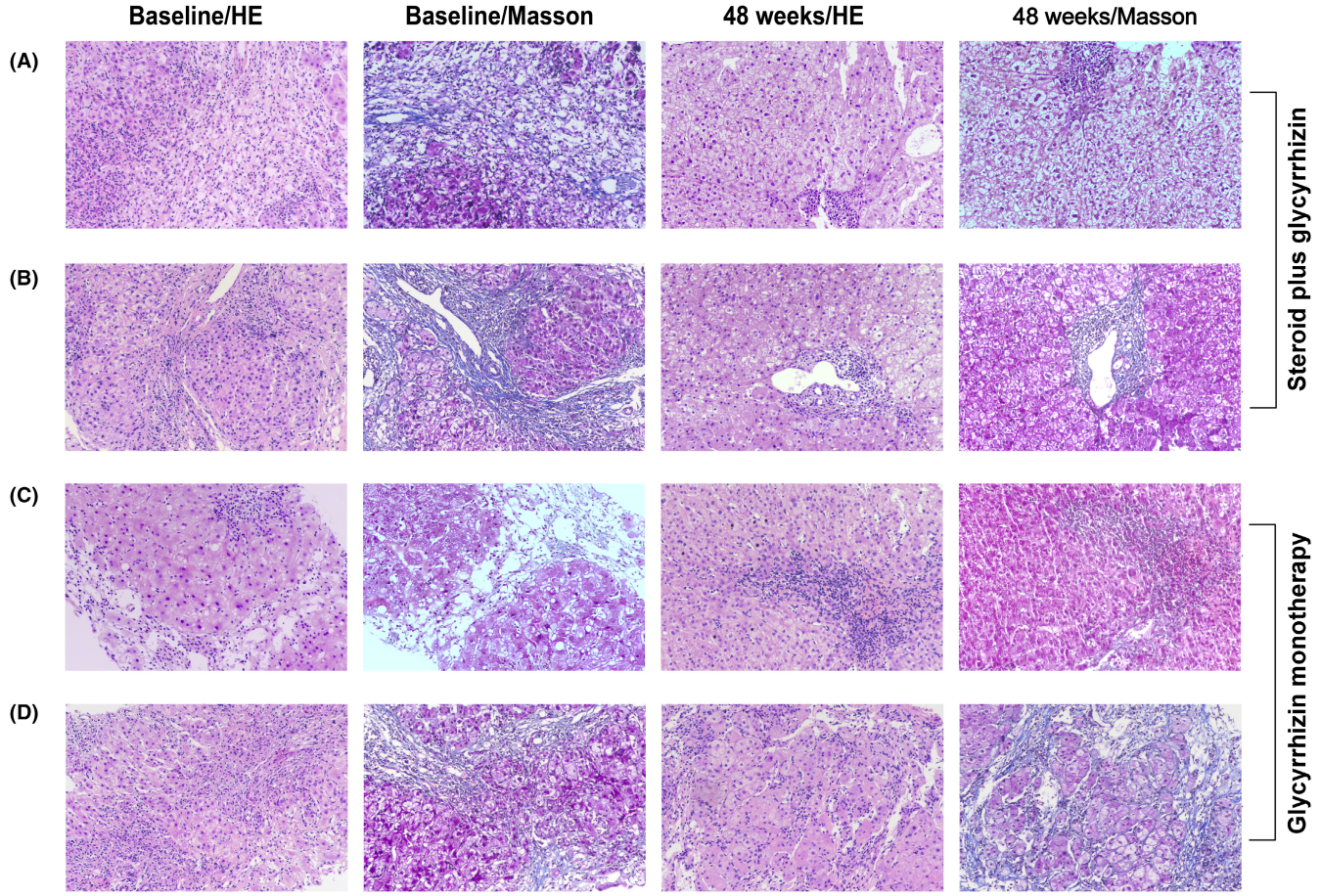

FIGURE 4 Histological assessments of pre- and post-treatment in patients receiving steroid plus glycyrrhizin treatment and glycyrrhizin monotherapy. Representative paired liver biopsies of pre-and post-treatment from four patients with two receiving steroid plus glycyrrhizin treatment (A and B) and two receiving glycyrrhizin monotherapy (C and D) are depicted. Liver biopsy of patient No. 18 (A) before steroid treatment shows massive bridging necrosis with mixed inflammatory cell infiltrates and mild fibrosis on Masson trichrome stain. After 48 weeks of steroid plus glycyrrhizin treatment, the inflammation has markedly decreased, and fibrosis has disappeared. Liver biopsy of patient No. 30 (B) at baseline from another patient treated with steroids exhibited advanced liver fibrosis and early cirrhotic nodule with lobular and portal activity. Steroid plus glycyrrhizin treatment achieved completed resolution of fibrosis with mild portal and lobular activity. In glycyrrhizin monotherapy case No. 58 (C), liver biopsy at baseline shows confluent lobular necrosis and Masson's trichrome stain displays no definite fibrosis. Marked portal inflammation and interface hepatitis with ballooning hepatocytes are still presented at the end of glycyrrhizin monotherapy, but no definite fibrosis developed. Another glycyrrhizin monotherapy case No. 14 (D) shows enlarged portal tracts with thin bridging fibrosis and focal ballooning hepatocytes at baseline. Liver tissue after glycyrrhizin monotherapy reveals significant lobular activity and advanced liver fibrosis. Haematoxylin–eosin (HE) stain and Masson trichrome stain, original magnification ×200

to prevent cellular injury and mitochondrial release of cytochrome C.[47] Our study found that both AIH-like and non-AIH-like chronic DILI responded to corticosteroid plus glycyrrhizin treatment, and no difference existed between these two subgroups. Thus, corticosteroid plus glycyrrhizin treatment might either inhibit dysfunctional autoimmunity or block the overwhelming inflammation in patients with chronic DILI/HILI. This study supports the use of corticosteroid plus glycyrrhizin therapy in chronic DILI/HILI in patients who met one of these criteria: evident increase of liver biochemistry (e.g. ALT >10 × ULN, or ALT >5 × ULN and TBIL >2 × ULN); or histological features of confluent necrosis and bridging necrosis, or portal inflammation equal or more than moderate.

Corticosteroid-related adverse events, especially severe ones, usually occur in patients with AIH after protracted therapy for >96 weeks with prednisone.[32] In contrast to patients with AIH receiving long-term steroid treatment, we used a shorter steroid treatment for 48 weeks. All steroid-related adverse effects that we observed were grade 1 or 2 according to CTCAE 5.0. Furthermore, all adverse effects disappeared at the end of the 24-week follow-up.

Hao Niu et al.,[35] Hu et al.,[40] and Sebode et al.[4] referred to RUCAM but did not use RUCAM as a differential diagnosis tool in their studies. Weber et al.[36] have used RUCAM as one of the research contents and evaluated the role of RUCAM in the differential diagnosis between DILI and AIH. The major strength of the updated RUCAM is its potential as a standard scale for DILI and HILI to assess causality by attending physicians, regulatory agencies, expert panels and the scientific community. It provides a straightforward

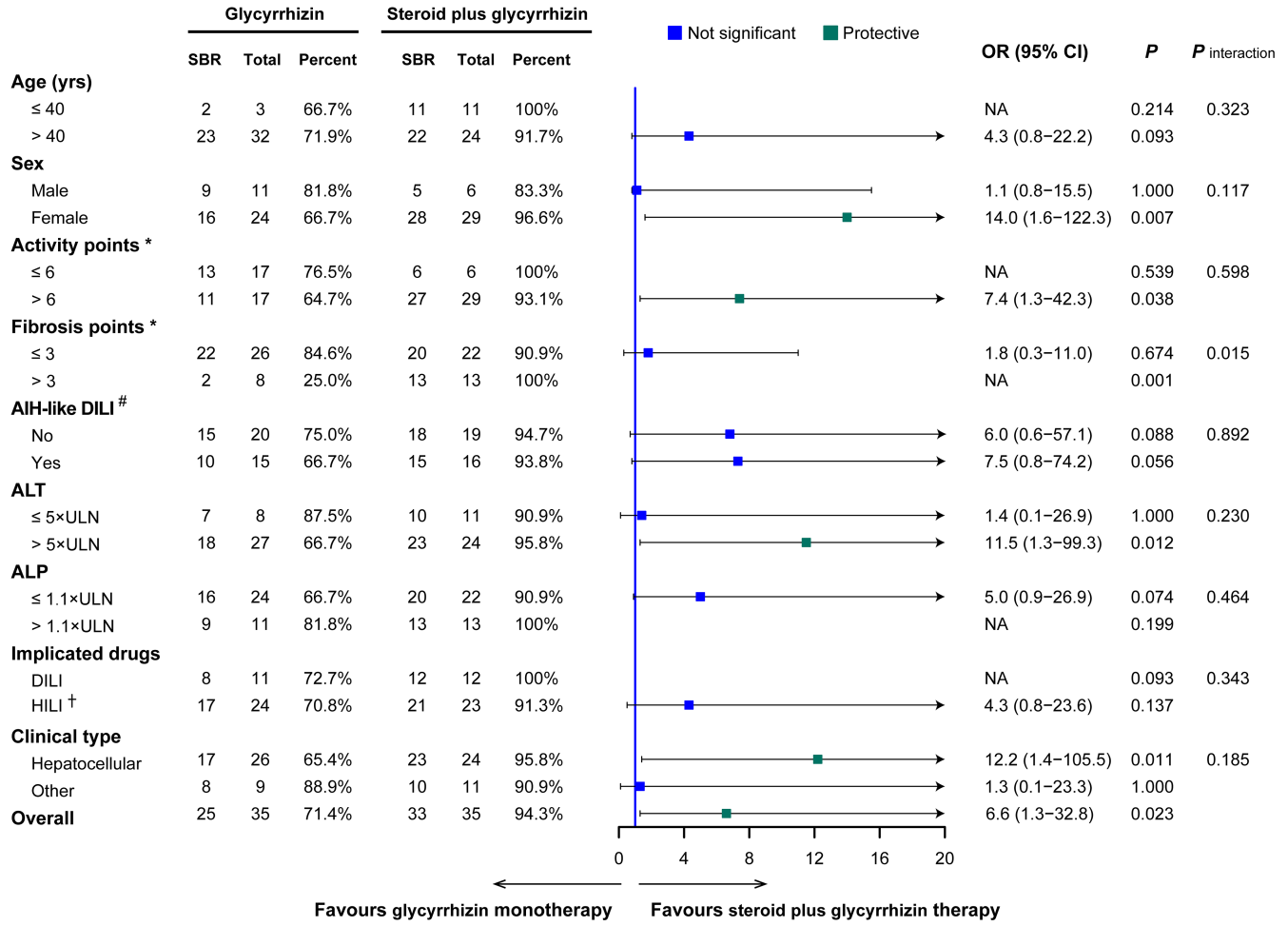

FIGURE 5 Post hoc analysis. ORs for sustained biochemical response (SBR) in the patients assigned to steroid plus glycyrrhizin therapy are shown with 95% CIs. OR = odd ratio, NA = Not available. *Data were missing for one patient in the glycyrrhizin monotherapy group. #AIH-like DILI was defined as the occurrence of either autoantibodies (ANA and/or SMA) or increased IgG (>1.1 × ULN). †Herb-induced liver injury here indicated those caused by herbs or multiple agents including herbs

application in liver and hepatotoxicity-specific domains with scored items. The updated RUCAM is improved by providing a better definition of the elements to consider and more accuracy in data elements to assist the exclusion of alternative causes.[28]

The current study has its limitations. First, this is a single centre and open-label study. The findings should be replicated in a large multicentre and randomised controlled trial. Second, the proportion of participants having a second biopsy at the end of treatment in glycyrrhizin monotherapy group was low. To overcome this issue, we used the APRI and FIB4 scores, as non-invasive assessments.

In conclusion, we have demonstrated that patients with chronic DILI/HILI with or without AIH-like features potentially benefit from steroid plus glycyrrhizin therapy, with significant biochemical response and histological improvement and good safety. Thus, we recommend corticosteroid plus glycyrrhizin preparation for the treatment of chronic DILI/HILI. A larger multicentre and randomised controlled trial should replicate our results to establish a subgroup of patients with DILI/HILI who would benefit from steroid therapy.

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REFERENCES

1. Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentat,ion, and outcomes in patients with drug-induced liver injury in the general population of Iceland, presentation. Gastroenterology. 2013;144(7):1419–25, 1425.e1-3; quiz e19-20.
2. Wang JB, Zhu Y, Bai ZF, Wang FS, Li XH, Xiao XH. Guidelines for the diagnosis and management of herb-induced liver injury. Chin J Integr Med. 2018;24(9):696–706.
3. Li C, Rao T, Chen X, Zou Z, Wei A, Tang J, et al. HLA-B*35:01 allele is a potential biomarker for predicting Polygonum multiflorum-induced liver injury in humans. Hepatology. 2019;70(1):346–57.
4. Sebode M, Schulz L, Lohse AW. 'Autoimmune(-like)' drug and herb induced liver injury: new insights into molecular pathogenesis. Int J Mol Sci. 2017;18(9):1954.
5. Ortega-Alonso A, Andrade RJ. Chronic liver injury induced by drugs and toxins. J Dig Dis. 2018;19(9):514–21.
6. Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ, et al. ACG clinical guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014;109(7):950–66. quiz 967.
7. Hisamochi A, Kage M, Ide T, Arinaga-Hino T, Amano K, Kuwahara R, et al. An analysis of drug-induced liver injury, which showed histological findings similar to autoimmune hepatitis. J Gastroenterol. 2016;51(6):597–607.
8. Wang Q, Huang A, Wang JB, Zou Z. Chronic drug-induced liver injury: updates and future challenges. Front Pharmacol. 2021;12:627133.
9. Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, et al. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015;148(7):1340–52. e7.
10. Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardisation in drug-induced liver injury. Clin Pharmacol Ther. 2011;89(6):806–15.
11. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology. 2020;72(2):671–722.
12. Stine JG, Chalasani N. Chronic liver injury induced by drugs: a systematic review. Liver Int. 2015;35(11):2343–53.
13. Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. Hepatology. 2014;59(2):661–70.
14. Andrade RJ, Lucena MI, Kaplowitz N, García-Muñoz B, Borraz Y, Pachkoria K, et al. Outcome of acute idiosyncratic drug-induced liver injury: long-term follow-up in a hepatotoxicity registry. Hepatology. 2006;44(6):1581–8.
15. Bonkovsky HL, Kleiner DE, Gu J, Odin JA, Russo MW, Navarro VM, et al. Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements. Hepatology. 2017;65(4):1267–77.
16. Björnsson E, Davidsdottir L. The long-term follow-up after idiosyncratic drug-induced liver injury with jaundice. J Hepatol. 2009;50(3):511–7.
17. Medina-Caliz I, Robles-Diaz M, Garcia-Muñoz B, Stephens C, Ortega-Alonso A, Garcia-Cortes M, et al. Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury. J Hepatol. 2016;65(3):532–42.
18. European Association for the Study of the Liver, Electronic address: easloffice@easloffice.eu, Clinical Practice Guideline Panel: Chair:, Panel members, EASL Governing Board representative: EASL Clinical Practice Guidelines. EASL clinical practice guidelines: drug-induced liver injury. J Hepatol. 2019;70(6):1222–61.
19. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52(6):2065–76.
20. Suzuki A, Brunt EM, Kleiner DE, Miquel R, Smyrk TC, Andrade RJ, et al. The use of liver biopsy evaluation in discrimination of idiopathic autoimmune hepatitis versus drug-induced liver injury. Hepatology. 2011;54(3):931–9.
21. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report. International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31(5):929–38.
22. Björnsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology. 2010;51(6):2040–8.
23. Darnell EP, Mooradian MJ, Baruch EN, Yilmaz M, Reynolds KL. Immune-related adverse events (irAEs): diagnosis, management, and clinical pearls. Curr Oncol Rep. 2020;22(4):39.
24. Czaja AJ. Drug-induced autoimmune-like hepatitis. Dig Dis Sci. 2011;56(4):958–76.
25. Nishida N, Kudo M. Liver damage related to immune checkpoint inhibitors. Hepatol Int. 2019;13(3):248–52.
26. 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):258–82.
27. Yu YC, Mao YM, Chen CW, et al. CSH guidelines for the diagnosis and treatment of drug-induced liver injury. Hepatol Int. 2017;11(3):221–41.
28. Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. Int J Mol Sci. 2015;17(1):14.
29. Ishak K, Baptista A, Bianchi L, Callea F, de Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995;22(6):696–9.
30. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple non-invasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25.
31. 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.
32. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010;51(6):2193–213.
33. European Association for the Study of the liver. EASL clinical practice guidelines. EASL clinical practice guidelines: autoimmune hepatitis. J Hepatol. 2015;63(4):971–1004.
34. Aithal PG, Day CP. The natural history of histologically proved drug-induced liver disease. Gut. 1999;44(5):731–5.

35. Niu H, Sanabria-Cabrera J, Alvarez-Alvarez I, Robles-Diaz M, Stankevičiūtė S, Aithal GP, et al. Prevention and management of idiosyncratic drug-induced liver injury: systematic review and meta-analysis of randomised clinical trials. Pharmacol Res. 2021;164:105404.
36. Weber S, Benesic A, Rotter I, Gerbes AL. Early ALT response to corticosteroid treatment distinguishes idiosyncratic drug-induced liver injury from autoimmune hepatitis. Liver Int. 2019;39(10):1906–17.
37. Akimoto M, Kimura M, Sawano A, Iwasaki H, Nakajima Y, Matano S, et al. Prevention of cancer chemotherapeutic agent-induced toxicity in postoperative breast cancer patients with glycyrrhizin (SNMC). Gan No Rinsho Japan J Cancer Clin. 1986;32(8):869–72.
38. Wang Y, Wang Z, Gao M, Zhong H, Chen C, Yao Y, et al. Efficacy and safety of magnesium isoglycyrrhizinate injection in patients with acute drug-induced liver injury: a phase II trial. Liver Int. 2019;39(11):2102–11.
39. Wree A, Dechêne A, Herzer K, Hilgard P, Syn WK, Gerken G, et al. Steroid and ursodeoxycholic acid combination therapy in severe drug-induced liver injury. Digestion. 2011;84(1):54–9.
40. Hu PF, Xie WF. Corticosteroid therapy in drug-induced liver injury: pros and cons. J Dig Dis. 2019;20(3):122–6.
41. Hou FQ, Zeng Z, Wang GQ. Hospital admissions for drug-induced liver injury: clinical features, therapy, and outcomes. Cell Biochem Biophys. 2012;64(2):77–83.
42. Hu PF, Wang PQ, Chen H, Hu XF, Xie QP, Shi J, et al. Beneficial effect of corticosteroids for patients with severe drug-induced liver injury. J Dig Dis. 2016;17(9):618–27.
43. Lee T, Lee YS, Yoon SY, Kim S, Bae YJ, Kwon HS, et al. Characteristics of liver injury in drug-induced systemic hypersensitivity reactions. J Am Acad Dermatol. 2013;69(3):407–15.
44. Pang L, Yang W, Hou F. Features and outcomes from a retrospective study of 570 hospitalised Chinese patients with drug-induced liver injury. Clin Res Hepatol Gastroenterol. 2018;42(1):48–56.
45. Kaliyaperumal K, Grove JI, Delahay RM, Griffiths WJH, Duckworth A, Aithal GP. Pharmacogenomics of drug-induced liver injury (DILI): molecular biology to clinical applications. J Hepatol. 2018;69(4):948–57.
46. Psarra AM, Sekeris CE. Glucocorticoids induce mitochondrial gene transcription in HepG2 cells: role of the mitochondrial glucocorticoid receptor. Biochim Biophys Acta. 2011;1813(10):1814–21.
47. Xu B, Strom J, Chen QM. Dexamethasone induces transcriptional activation of Bcl-xL gene and inhibits cardiac injury by myocardial ischemia. Eur J Pharmacol. 2011;668(1–2):194–200.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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