Prednisolone Therapy Accelerated Recovery of Severe Drug-Induced Liver Injury: A Prospective Randomized Controlled Study

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Abstract

Background Drug-induced liver injury (DILI) is one of the most serious adverse drug reactions and the incidence has been increasing rapidly. Accumulating evidence suggested that the immune activation and systemic inflammatory responses play a significant role in the progression of DILI. Corticosteroids are often used in DILI, but clinical usefulness remain controversial. We therefore conducted a prospective randomized controlled study to investigate whether corticosteroid therapy can accelerate recovery and reduce mortality in severe DILI (SDILI).

Methods SDILI patients with total bilirubin (TBIL) ≥ 171 $\mu\text{mol/L}$ presented to Fifth Medical Center of PLA General Hospital, Beijing from 1/1/2015 to 31/12/2019 were randomized into prednisolone group and control group. The primary endpoints were proportion of subjects with resolution of SDILI defined as decrease in TBIL by at least 35 $\mu\text{mol/L}$ to below 171 $\mu\text{mol/L}$ and overall survival at 6 months. Patients in prednisolone group received prednisolone 60 mg/day therapy for the first 7 days. Patients reaching the primary endpoint or achieved decrease in TBIL by more than 35 $\mu\text{mol/L}$ on day 8 would continue on tapering doses of prednisolone, otherwise prednisolone would be discontinued.

Results On day 8, 50.7% (34/67) and 26.5% (18/68) of the subjects in the prednisolone group and control group achieved the primary endpoint respectively, $p=0.002$. However, there was no significant difference in overall survival at 6 months, 95.52% (64/67) vs 91.2% (62/68), $p=0.2$. All deaths in both groups occurred in patients who failed to achieve SDILI resolution on day 8.

Conclusions Prednisolone therapy may accelerate recovery of SDILI and shorten hospitalization.

Introduction

With the improvement of socioeconomic status and universal vaccination program in China, the infection rate of hepatitis B virus (HBV) is on the decline. Meanwhile, drug-induced liver injury (DILI) is becoming one of the leading causes of acute liver injury in China. It was reported that approximately 1100 approved drugs in China had potential hepatotoxicity. Implicated drugs include prescription medications, traditional Chinese medicine (TCM), natural medicine, health product, dietary supplement, and their associated metabolites [1–4]. Two retrospective studies showed that DILI and drug-induced acute liver failure (ALF) had been increasing rapidly in China and were associated with high mortality [5, 6].

The clinical manifestations of DILI can mimic all forms of liver injury, from asymptomatic liver-function abnormalities to acute, subacute, chronic liver disease and even fulminating liver failure [7, 8]. Severe DILI (SDILI) with markedly elevated bilirubin can progress rapidly with fatal outcome. Recently, there are major advances in understanding the mechanism of liver injuries, pharmacological properties of the offending drugs and genetic risk models. However, there is little progress in the treatment of SDILI in the last 20 years [8–10]. Discontinuation of the culprit medications and supportive care remain the mainstay of management.

Accumulating evidence suggests that immune activation and systemic inflammatory responses play a significant role in the occurrence and progression of DILI [11]. Corticosteroid with its anti-inflammatory effect is often proposed as a treatment option when other managements fail, especially in SDILI with hyperbilirubinemia. Ma et al showed that corticosteroid treatment was associated with a more rapid decline of bilirubin and liver enzymes, but the overall prognosis was not improved because of worsening infectious complications [12]. Other reported trials of corticosteroid therapy demonstrated limited benefits in DILI [13]. There was reported improvement in drug-induced cholestasis, but data from large scale randomized trial were lacking [14]. Clinical practice guidelines of European Association for the Study of the Liver (EASL) and Asia Pacific Association of Study of Liver Consensus (APASL) do not give clear recommendations about corticosteroids in SDILI.

Therefore, we conducted this prospective randomized controlled study to investigate whether corticosteroid therapy can accelerate recovery and reduce mortality in SDILI treatment.

Patients And Methods

Study design

This is a randomized control study. The study protocol and procedures were in line with the ethical principles of the Declaration of Helsinki and regulation of clinical trials. The study protocol was approved by the Ethics Committee of Fifth Medical Center of Chinese PLA General Hospital. Formal written informed consent was obtained from each patient. The trial was registered at the Chinese Clinical Trial Registry with identifier ChiCTR-IOR-17010880.

Case identification and recruitment

Patients diagnosed with SDILI at Fifth Medical Center of PLA General Hospital, Beijing from 1/1/2015 to 31/12/2019 were randomly divided into two groups according to a random number table generated by a computer into prednisolone group and control group. There was no blinding. The inclusion criteria were: 1) able to provide informed consent; 2) 18 to 65 years of age; 3) diagnosis of SDILI defined as TBIL $\geq 171\mu\text{mol/L}$ with or without INR ≥ 1.5 . DILI was diagnosed according to Roussel Uclaf Causality Assessment Method (RUCAM, quantitative score ≥ 6) or Maria's criteria (quantitative score ≥ 14) which takes into account the patients recent history of drug use, the relationship between suspicious drug intake and onset of biochemical tests abnormalities, clinical presentation after excluding other causes of liver disease [15–17]. The DILI type is categorized as hepatitic, cholestatic or mixed based on R value which is defined as serum ALT/ULN divided by serum ALP/ULN according to the first laboratory tests available in relation to the clinical event. The R value of ≥ 5 indicates hepatocellular, ≤ 2 cholestatic, and 2-5 mixed injury [18, 19]. Exclusion criteria included documented infection beyond the control of antibiotics, active peptic ulcer, severe hypertension and diabetes, psychosis, epilepsy, positive serology for hepatitis B and C, heavy alcohol intake, history of chronic liver disease/cirrhosis, glaucoma and other diseases that doctors considered unsuitable for prednisolone therapy.

Treatment endpoints

The primary endpoint was: 1) resolution of SDILI defined as decrease in bilirubin by at least $35\mu\text{mol/L}$ to $<171\mu\text{mol/L}$, and 2) overall survival at 6 months.

Proportion of subjects in the prednisolone and control groups achieving the primary endpoint of resolution of SDILI at the end of week 1, 2, 4, 12 would be compared.

Treatment and follow-up protocol

All patients were given comprehensive medical treatment of liver protection drugs (such as glycyrrhizin and ademetonine). Patients in prednisolone group received prednisolone 60 mg/day therapy for the first 7 days which was called implosive therapy period. Patients reaching the primary endpoint or achieving decrease in bilirubin by more than $35\mu\text{mol/L}$ ($2\times$ ULN) on day 8 would continue on tapering doses of prednisolone, otherwise prednisolone would be discontinued.

Prednisolone would be tapered as follows: prednisolone 40mg/day for 7days (consolidation therapy period), 30mg/day for 7 days (remission therapy period), 20mg/day for 7 days (maintenance therapy period), 10 mg/day for 7 days, then off therapy. The flow chart of the study was shown as Figure 1. All patients could receive antibiotics and fresh frozen plasma treatment when indicated.

The dynamic changes of laboratory data were collected at baseline, Week 1, 2, 4 and 12. The survival rates were estimated at Week 4, 12 and 24. All adverse events would be recorded.

Sample size determination

Assuming a difference of at least 20% in the primary endpoints to be of clinical interest, we calculated the sample size of each group was 65 cases ($\alpha = 0.05$ $\beta = 0.2$, two-sided test) [20, 21].

Statistical Analyses

Data were analyzed with the Statistical Package for Social Sciences (SPSS 12.0). Variables were examined using descriptive statistics. Analysis of variance (ANOVA) was used for comparisons of groups. Nonparametric analyses (Kruskal-Wallis test) were performed when variables did not follow a normal distribution. Categorical data were expressed as proportions and analyzed by χ^2 test or the Fisher exact test. Survival curves were plotted by the Kaplan-Meier method and analyzed by the log-rank test. A p -value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

Between 1/1/2015 and 31/12/2019, 135 patients with SDILI were enrolled, 67 in the prednisolone group and 68 in the placebo group. The baseline characteristics of patients in the 2 groups were summarized in Table 1. Overall, both groups were comparable with respect to age, gender, BMI, suspected cause of liver injury, concomitant diseases, liver function indices, pattern of liver injury, artificial liver support treatment. TCM was the main suspected cause of liver injury in both prednisolone group (71.64%) and control group (50.00%). There was no significant difference in the proportion of patients receiving artificial liver treatment between the two groups ($p=0.616$). Liver biopsy is not a necessary condition for diagnose of SDILI. Although more patients in prednisolone group had pathological diagnosis by liver biopsy (62.69% vs 45.59%, $p=0.046$) (Table 1).

Table 1
Baseline characteristics of the study population

Variable	prednisolone group (n=67)	Control group (n=68)	* <i>p</i> value
Age, y	45(18-64)	46(21-63)	0.547
Male, n, %	27(40.30%)	25(36.76%)	0.673
BMI, kg/m ² #	22.63(17.44-33.2)	24.52(18.42-31.24)	0.541
Suspected cause			0.055
TCM	48(71.64%)	34(50.00%)	
Prescription drug	11(16.42%)	21(30.89%)	
Dietary supplement	4(5.97%)	6(8.83%)	
Chemical poison	4(5.97%)	1(1.47%)	
Comorbidity			
Hypertension	7(10.45%)	9(13.24%)	0.616
Diabetes mellitus	2(2.99%)	3(4.41%)	1.000
Hyperlipidemia	4(5.97%)	2(2.94%)	0.663
Thyroid disease	0(0%)	5(7.35%)	0.071
ALB (35–55 g/L) #	32.72(23-45)	32.15(23-40)	0.481
GLO (20–40 g/L) #	24.49(12-43)	24.12(12-41)	0.733
ALT (5–40 U/L) #	201.60(24-852)	218.98(7.42-705)	0.431
AST (8–40 U/L) #	252.27(33-1176)	264.85(33-965)	0.538
ALP (40-150U/L) #	219.40(66-2104)	199.41(69-607)	0.326
GGT (11-50U/L) #	151.19(18-1095)	170.40(10-1322)	0.499
TBIL (3.4-20.5μmol/L) #	322.10(171.0-724.4)	305.93(173.9-483.4)	0.355
TBA (0-10μmol/L) #	222.63(4-497.8)	249.30(59.7-512.4)	0.095
INR #	1.28(0.76-3.17)	1.32(0.85-3.41)	0.474
TC (2.8-5.2 mmol/L) #	4.2(1.08-26.41)	3.73(0.62-25.1)	0.043
TG (0.56-1.7 mmol/L) #	3.25(0.45-12.43)	2.98(0.26-6.69)	0.307
CHE (5000-12000 U/L) #	4464.64(2019-8667)	4121.87(1479-6985)	0.148
Cr (62-115mmol/L) #	69.72(33-123)	72.19(32-140)	0.438
IgG (7.23-16.6 g/L) #	14.73(5.9-34.12)	14.61(4.31-31.78)	0.912

ALB: Albumin, AFP: Alpha fetoprotein, BMI: body mass index, CHE: cholinesterase, Cr: creatinine, GGT: gamma glutamyl transferase, GLO: Globulin, IgG: immunoglobulin, TBA: total bile acids, TC: total cholesterol, TG: Triglyceride, TPE: therapeutic plasma exchange, WBC: white blood cell. * *p* by the Mann-Whitney U test or χ^2 test; # Median (range).

Variable	prednisolone group (n=67)	Control group (n=68)	* <i>p</i> value
AFP (0-10 ng/ml) [#]	91.57(0.92-1210)	159.56(1.82-1210)	0.239
WBC (3.97-9.15 10 ⁹ /L) [#]	6.57(2.76-15.57)	6.10(2.65-12.97)	0.253
R-ratio, n, %			0.831
≤2	25(37.31%)	22(32.35%)	
2-5	14(20.90%)	15(22.06%)	
≥5	28(41.79%)	31(45.59%)	
Pathological diagnosis by liver biopsy, n, %	42(62.69%)	31(45.59%)	0.046
ALB: Albumin, AFP: Alpha fetoprotein, BMI: body mass index, CHE: cholinesterase, Cr: creatinine, GGT: gamma glutamyl transferase, GLO: Globulin, IgG: immunoglobulin, TBA: total bile acids, TC: total cholesterol, TG: Triglyceride, TPE: therapeutic plasma exchange, WBC: white blood cell. * <i>p</i> by the Mann-Whitney U test or χ^2 test; [#] Median (range).			

Resolution of SDILI

After 1-week of treatment, 34/67 (50.7%) and 18/68(26.5%) of the subjects in the prednisolone group and control group achieved the primary endpoint of decrease of TBIL by at least 35 $\mu\text{mol/L}$ to less than 171 $\mu\text{mol/L}$ respectively, $p=0.002$.

The total bilirubin in the prednisolone group decreased from $324.5 \pm 117.8 \mu\text{mol/L}$ at baseline to $219.4 \pm 119.4 \mu\text{mol/L}$ by week 1, a decrease of $105.1 \pm 21.37 \mu\text{mol/L}$, while in the control group, the corresponding decrease was $56 \pm 16.23 \mu\text{mol/L}$ (from $304.9 \pm 81.7 \mu\text{mol/L}$ to $248.6 \pm 106.7 \mu\text{mol/L}$, $p=0.0013$. However, by week 2, week 4 and week 12, the proportions of subjects with resolution of SDILI in the prednisolone and control group were 61.2% vs 52.9%, 76.1% vs 77.9% and 91.0%vs 89.4% respectively, $p>0.5$ (Table 2).

Table 2

The decrease of total bilirubin and proportion of subjects achieving primary endpoint in the prednisolone and control group

	prednisolone group (n=67)	Control group (n=68)	* <i>p</i> value
TBIL ($\mu\text{mol/L}$) at baseline	324.54 ± 117.74	304.92 ± 81.68	0.265
TBIL ($\mu\text{mol/L}$) by end of Week 1	219.40 ± 129.46	248.57 ± 106.57	0.155
Decrease of TBIL from baseline by end of Week 1	105.14 ± 21.37	57.36 ± 16.23	0.001
Proportion achieving primary endpoint			
by end of Week 1	50.75% (34/67)	26.47% (18/68)	0.002
by end of Week 2	50.75% (34/67)	26.47% (18/68)	0.002
by end of Week 4	76.12% (51/67)	77.94% (53/68)	0.802
by end of Week 12	91.04% (61/67)	89.71% (61/68)	0.794
<i>The primary endpoint was resolution of severe DILI defined as decrease in bilirubin by at least 35$\mu\text{mol/L}$ to <171$\mu\text{mol/L}$.</i>			

Survival at 6 months

There was no significant difference in overall survival at 6 months between the 2 groups, 95.52% (64/67) vs 91.2% (62/68), $p=0.2$, Figure 2. All deaths occurred in patients who failed to achieve resolution of severe DILI on day 8, the death rates among such patients were 9% (3/33) and 12% (6/50) respectively in the prednisolone and control groups, Table 3.

Table 3
Deaths and transplantation in the prednisolone and control group

Characteristics	prednisolone group(n=67)	Control group (n=68)
Death*		
4 weeks	1	3
12 weeks	1	3
24 weeks	1	0
Transplantation		
4 weeks	0	1
12 weeks	0	0
24 weeks	0	0
*All deaths occurred in patients who failed to achieve resolution of severe DILI on day 8		

Adverse events

There was no significance in infectious complications, gastrointestinal bleedings and hyperglycemia between the two groups, Table 4.

Table 4
Adverse reactions of the prednisolone and control groups

	Prednisolone group (n=67)			Control group (n=68)			<i>P</i>
	Pre-treatment	By week 24	Increased cases	Pre-treatment	By week 24	Increased cases	
Pulmonary infection	0	5(7.46%)	5	0	7(10.29%)	7	<i>p</i> =0.563
Hyperglycemia	10(14.92%)	6(8.95%)	0	8(11.76%)	4(5.88%)	0	
Hypercholesterolemia	10(14.92%)	20(29.85%)	10	7(10.29%)	10(14.71%)	3	<i>p</i> =0.075
Hypertriglyceridemia	56(83.58%)	49(73.13%)	0	52(76.47%)	46(67.65%)	0	<i>p</i> =0.303
Gastrointestinal bleeding	0	0	0	0	0	0	

Discussion

DILI has become a major health and economic burden. Timely withdrawal of the offending medication is the most important treatment strategy for DILI. Currently, there is no definitive therapy or approved antidote available for idiosyncratic DILI. Empiric uses of corticosteroid are sometimes given when all other treatments fail, although it is not generally recommended due to the lack of obvious clinical benefit in previously reported studies [22–24]. A retrospective analysis of 361 patients with autoimmune ALF, indeterminate ALF and drug-induced ALF suggested that corticosteroids treatment did not improve the overall survival. In the subgroup of patients with drug-induced ALF, the rate of survival was 69% for those who received corticosteroids versus 66% for those who did not (*p*=0.82) [23]. On the other hand, Czaja et al reported that corticosteroid therapy was effective in female patients with drug induced autoimmune hepatitis [24]. Other

studies showed that corticosteroid treatment was associated with a more rapid decline of bilirubin and liver enzymes, but the overall prognosis was not improved [12–14, 25].

In our studies, about 50% of subjects given prednisolone therapy had resolution of SDILI after 1 week of treatment. All these patients continued to improve and none of them required artificial hepatic assisted device, liver transplantation or perished at 6 months followed-up. On the other hand, only about 25% of the subjects in the controlled arm had resolution of SDILI by day 8. There was no difference in survival at 6 months, but our sample size did not have the power to detect a small difference in survival. There may be some debates about our definitions of SDILI and its resolution. We chose TBIL $\geq 171 \mu\text{mol/L}$ as our cut-off point because $171 \mu\text{mol/L}$ is 10x ULN in our laboratory. In order to avoid including those cases that had only minimal decrease of TBIL from just above $171 \mu\text{mol/L}$ at baseline to just below $171 \mu\text{mol/L}$ by week 1 as achieving resolution of SDILI, we felt that the decrease must be at least $35 \mu\text{mol/L}$ ($>2x$ ULN), equivalent to at least 20% of baseline TBIL values. The mean decrease in TBIL in the prednisolone group was $105.1 \pm 21.37 \mu\text{mol/L}$. For the 34 prednisolone treated patients achieving the primary endpoint, the mean decrease in bilirubin was $128.2 \mu\text{mol/L}$, range 48.3 to $245 \mu\text{mol/L}$, 22 had decrease of more than $100 \mu\text{mol/L}$. The clinical benefits of prednisolone were observed mainly at the end of the first week. We discontinued prednisolone therapy in subjects who failed to show a significant decrease in TBIL by day 8 and for responsive subjects, and we tapered the prednisolone dosage over 6 weeks to minimize the side effects of prolonged high dose steroid therapy. Our data suggested that prednisolone therapy, may accelerate recovery of SDILI, allowing early discharge of patients who achieve SDILI resolution and cost savings. The greatest strength of the study is all subjects were managed at one center by the same team with strict adherence to study protocols, variation in supportive care, missing data, loss to follow-ups and protocol violations were not issues at all. On the other hand, one may argue that whether the experience at one center was applicable to other centers. A larger multi-center trial may address the above limitations.

Declarations

Availability of data and material

The datasets generated and analysed during the current study cannot be available for public access due to the privacy of patients, but can be obtained from the corresponding author on reasonable request approved by the Ethics Committee of Fifth Medical Center of Chinese PLA General Hospital.

Ethics approval and clinical trial registration

The study protocol was approved by the Ethics Committee of Fifth Medical Center of Chinese PLA General Hospital. The trial was registered at the Chinese Clinical Trial Registry with identifier ChiCTR-IOR-17010880.

Informed consent to participates and publish

Formal written informed consent was obtained from each patient and the work was done in accordance with the declaration of Helsinki.

Author Contributions

BZ, FS, HL, YS, TX, DL, HW, SX,SL and SY treated the patients. BZ, FS, HL, YS, TX, DL and HW collected the epidemiological and clinical data. BZ, FS, YW, GC and GL processed statistical data and drafted the manuscript. BZ, FS, SL and SY had the idea for and designed the study. SL and SY revised the final manuscript and are responsible for summarizing all the data.

Conflict of interest

The authors declared that there are no conflicts of interest.

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Figures

Figure 1

The flow chart of the study

Figure 2

Overall survival curve analysis at 24W between prednisolone and control groups. There were no significant differences in 24W survival between the two groups ($p=0.2$).