A Multicenter and Randomized Controlled Trial of Bicyclol in the Treatment of Statin-Induced Liver Injury

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABE 1 Wu Naqiong
BF 2 Wang Liansheng
BD 3 Han Zhanying
CD 1 Guo Yuanlin
F 1 Zhu Chenggang
F 1 Gao Ying
CD 1 Dong Qian
CF 2 Liu Dongchen
BCD 3 Zhou Yanjun
AE 1 Li Jianjun

1 Dyslipidemia and Cardiovascular Disease Center, Fuwai Hospital Chinese Academy of Medical Sciences, Beijing, P.R. China
2 Department of Cardiology, Jiangsu Province Hospital, Nanjing, Jiangsu, P.R. China
3 Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China

Corresponding Author: Li Jianjun, e-mail: lijianjun1957@yeah.net
Source of support: Departmental sources

Background: The aim of this study was to evaluate the efficacy and safety of bicyclol treatment in statin-induced liver injury.

Material/Methods: The study included 168 patients with liver injury caused by statins. Patients were randomized into two four-week treatment groups: bicyclol 25 mg three times daily or polyene phosphatidylcholine 456 mg three times daily as control. Serum biochemical indexes were compared before and after treatment.

Results: Significant differences in alanine transaminase (ALT) levels among the three measurements before and after treatment in the two groups at different time points were observed ($p < 0.01$). There was a significant difference ($p < 0.01$) between two weeks and four weeks after treatment compared to the baseline period. There was a significant interaction ($p = 0.003$) between the two groups and time factors. After two and four weeks of treatment, the ALT levels in the control group (68.20 ± 26.31, 50.71 ± 27.13 respectively) were higher compared to the ALT in the bicyclol group (49.33 ± 21.39, 30.36 ± 17.41 respectively) ($p < 0.01$). After four weeks of treatment, the normalization rates of bicyclol and polyene phosphatidylcholine groups were 74.68% and 46.15%, respectively. The efficacy of bicyclol was significantly better than that of polyene phosphatidylcholine ($p < 0.05$). The incidence of adverse reactions in the bicyclol and polyene phosphatidylcholine groups were 2.53% and 2.56%, respectively, with no statistically significant differences observed between the two groups ($p > 0.05$).

Conclusions: These findings suggest that trends of ALT changes in the two groups were different, and the improvement of ALT was more obvious in the bicyclol group. Bicyclol is considered to be safe and effective in the treatment of statin-induced liver injury.

MeSH Keywords: Alanine Transaminase • Drug-Induced Liver Injury • Hydroxymethylglutaryl-CoA Reductase Inhibitors

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/904090

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Background

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are among the most widely prescribed drugs for the treatment of cardiovascular diseases in recent years. This is because statins significantly reduce the level of serum low density lipoprotein cholesterol (LDL-C), which thereby effectively reduces the risk of cardiovascular events [1]. The wide use of statins has raised several concerns regarding their safety and tolerance. According to recent studies, some patients have been reported to have statin-related liver injuries and other adverse reactions [2]. A study that included 9,360 drug alert data demonstrated the risk of liver adverse events were increased three-fold in patients using statins compared to patients not using statins [3]. The reason for this might be that statins often elevate liver enzymes. A systematic review of randomized studies showed that statin-treated patients had a higher elevated transaminase risk compared to placebo treatment [4]. In October 2013, the Chinese Food and Drug Administration (CFDA) issued a circular revision of statin specifications on the safety of statins, to further help Chinese physicians and patients. In 2014, the National Lipid Association published an updated version of their expert consensus on statin safety issues [5]. In the same year, China issued its expert consensus on safety assessment of statins [6]. Thus, statins safety has become a major issue of concern to clinicians worldwide. China has about 20 million people suffering from hepatitis B, and the safety of statin use in the treatment of liver diseases is still a major concern to clinicians [7]. Chinese Adult Dyslipidemia Prevention Guidelines pointed out that when using statin drugs, examination of liver transaminases, such as alanine transaminase (ALT), aspartate aminotransferase (AST), and regular monitoring and follow-up during treatment is required. If ALT or AST exceeds three times the upper limits of normal (ULN), patients should be suspended from treatment, and an examination of liver function should be conducted weekly, until levels return to normal [8].

According to Chinese guidelines for diagnosis and treatment of drug-induced liver injury (DILI), the basic treatment principles of DILI include discontinuing the suspected culprit drugs and treatment with anti-inflammatory and hepatoprotective agents [9]. Polyene phosphatidylcholine capsule is an oral drug for auxiliary improve toxic liver damage (induced by drugs, poisons, chemicals, and so on) approved by CFDA and the Chinese pharmacopoeia, but its effect has not yet been satisfactory.

Bicyclol is an innovative chemical drug, with proprietary intellectual property rights in China, used for the treatment of hepatic inflammation. It was launched in 2001, and was registered and sold in many countries. Basic and clinical studies have shown that bicyclol is effective in improving liver function, relieving hepatic inflammation, alleviating hepatic fibrosis, and has good hepatoprotective and anti-inflammatory effects [10–12]. However,

at present, there is less information available on bicyclol use as treatment for statin-induced liver injury. Therefore, we conducted a multicenter and randomized controlled trial to explore the efficacy and safety of oral bicyclol versus polyene phosphatidylcholine in the treatment of statin-induced liver injury.

Material and Methods

Research design

This study was a multicenter, randomized, parallel-design controlled trial conducted in three tertiary hospitals of China. There were 168 statin-induced liver injury patients who were equally (1: 1) randomized to the treatment group (bicyclol group) or the control group (polyene phosphatidylcholine group). The inclusion and exclusion criteria are shown in Figure 1. The study investigations were conducted in accordance with the ethical recommendations of the Declaration of Helsinki (World Medical Association) and Good Clinical Practice (GCP). The research was performed after being discussed and proved by the ethics committees.

Case selection

Inclusion criteria were: 1) age 24–66 years with no limitation to gender; 2) in line with acute drug-induced liver injury clinical diagnosis, a RUCAM causal rating scale score of ≥6 points [13], all patients had a causality grading of probable or highly probable; 3) serum ALT 2~5 ULN, TBiL ≤2 ULN; and 4) liver biochemical abnormalities should be maintained for less than 90 days. Exclusion criteria were 1) other liver injuries such as viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, and autoimmune liver disease; 2) acute hepatic failure or decompensated liver function such as the emergence of hepatic encephalopathy, ascites, albumin ≤35 g/L, prothrombin time extended over three seconds or more than the normal control; 3) serum creatinine greater than 1.5 times the upper limit of normal; 4) severe heart, lung, brain, kidney, gastrointestinal, and systemic diseases; 5) use of other drugs that could influence the efficacy of the study; 6) patients allergic or intolerant to the study drug; 7) patients unable to express their complaints, such as those with psychosis and severe neurosis; 8) patients who cannot cooperate because of poor adherence; 9) pregnant women, lactating women, or women of childbearing age or ready to conceive; 10) patients who had participated in other clinical trials in the last three months, or one week before enrollment other hepatoprotectants were administered; and 11) any other conditions making them unsuitable for inclusion.

Methods

Drugs used included bicyclol tablets (25 mg/tablet, Beijing Union Pharmaceutical Factory) and polyene phosphatidylcholine
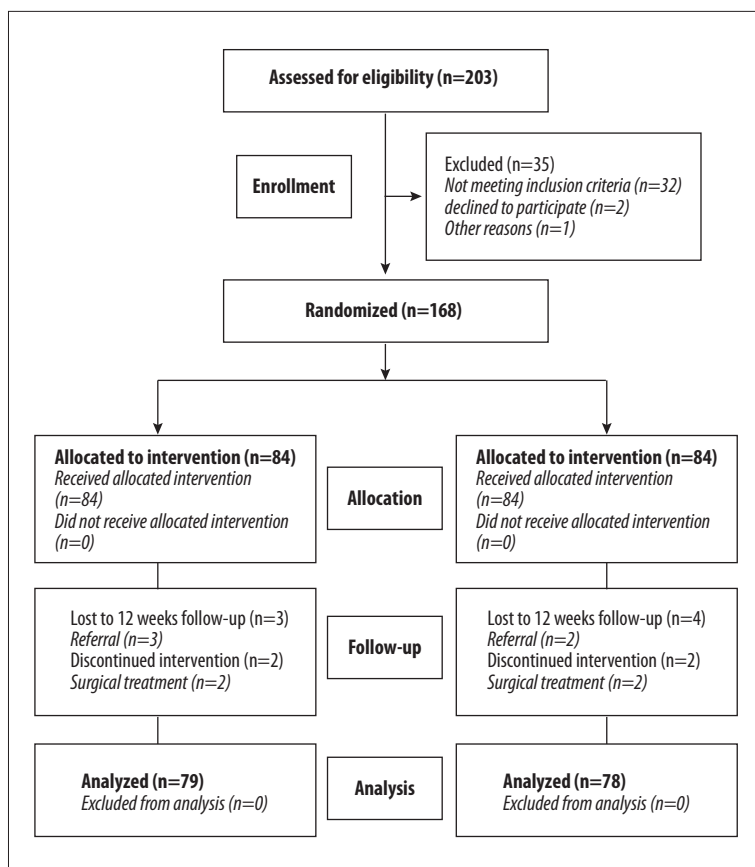
Figure 1. Flow diagram of the studies inclusion.

capsules (228 mg/tablet, Beijing Sanofi Aventis Co., Ltd.). Treatment group drugs were administered as follows: oral bicyclol tablets 75 mg (25 mg three times daily) as continuous medication for four weeks. Control group drugs were administered as follows: oral polyene phosphatidylcholine capsules 1,368 mg (456 mg three times daily) as continuous medication for four weeks. During the treatment period, the patients were followed once every two weeks. Observation indicators included general patient characteristics such as gender, age, medical history, concomitant diseases or symptoms, and concomitant medications. Biochemical tests were ALT, AST, ALP, and TBiL. Other indicators included B ultrasonic diagnosis, and adverse reaction observation according to quality management practices on drug clinical trials. Criteria for discontinuation of statins were as follows: if ALT or AST exceeds three times ULN, patients were suspended for treatment administration, and patient received a weekly review of their liver function until it returned to normal [6]. The main efficacy indicators and secondary efficacy indicators included primary efficacy indicators of decrease of serum ALT levels after four weeks of treatment, and secondary efficacy indicators of: a) normalization rate of serum ALT at two and four weeks, and b) evaluation of single efficacy and comprehensive efficacy at the end of four weeks of treatment. Single efficacy was defined using abnormal liver function indicators (ALT, AST, ALP, and TBiL)

that were calculated before the treatment, and judged based on the following definitions. "Evidently effective" was defined as normalization of liver function after treatment. "Effective" was defined as liver function indicators decreased ≥50% from baseline, but not returned to normal after treatment. "Not effective" was defined as no significant change or improvement that did not meet the aforementioned evidently effective and effective standards. "Comprehensive efficacy" was defined as abnormal liver function indicators (ALT, AST, ALP, TBiL) before treatment that were judged according to the following criteria. Evidently effective was abnormal liver function indicators (ALT, AST, ALP, and TBiL) before treatment that were all normalized. Effective was at least two abnormal liver function indicators (ALT, AST, ALP, TBiL) before treatment were decreased ≥50% from baseline; Not effective was no significant change or improvement that did not meet the aforementioned evidently effective and effective standards. For patients with only one abnormal ALT liver function indicator before treatment, we substituted a single efficacy with comprehensive efficacy.

Statistical analysis

The sample size was calculated using PASS 11 software. The sample size (multiplied by 1.2 or 1.25), β=0.1, and the bilateral test α=0.05 were estimated by the number of cases after

Table 1. Comparison of the two groups in general.

General	Treatment group (n=79)	Control group (n=78)	Statistics	P
Age (y)				
≥55	42	49	1.502	0.220
<55	37	29		
Gender				
Male	63	63	0.026	0.872
Female	16	15		
Category of statins				
Atorvastatin	48	45	0.701	0.873
Simvastatin	15	13		
Rosuvastatin	10	12		
Other	6	8		
History of alcohol intake				
Yes	23	21	0.093	0.760
No	56	57		
History of previous liver injury				
Yes	3	3	0.000	0.987
No	76	75		
Serum biochemistry				
ALT (U/L)	130.49±34.99	131.36±39.98	0.144	0.885
AST (U/L)	100.68±58.80	99.81±58.89	0.092	0.927
TBIL (μmol/L)	13.37±5.57	12.94±4.50	0.523	0.602
ALP (U/L)	83.72±30.43	86.14±50.94	0.358	0.721

entry. The random number table was generated by SPSS 22.0 statistical analysis software. Intergroup comparisons of baseline continuous variables were performed using independent sample t-test. Intergroup comparisons of categorical variables were performed using χ^2 test (Pearson method). Wilcoxon rank sum test was used for intergroup comparisons of the variables for hierarchical classification. The analysis of ALT was used ANOVA for repeated measures data. Comparison of the mean at each time point of each group was analyzed by Bonfferoni. Comparison of ALT between groups at each time point was analyzed by independent sample t-test analysis. Single-factor logistic regression was used in the subgroup analysis. ALT normalization at the end of four-week treatment was taken as the dependent variable, and the control group was used as the independent variable to compare the ALT normalization rate of each confounder in the two groups. All statistical tests were two-sided and $p<0.05/3$ (0.017) was considered to be statistically significant for pairwise comparison of ALT. A value of $p<0.05$ was considered to be statistically significant for other comparisons. The graph presenting time course of ALT changes was made by Graph Pad Prism 6.01.

Results

Selected patients

A total of 168 patients met the inclusion criteria and were enrolled in the study. There were 11 patients who withdrew from the study, seven for referral and four for surgical treatment. Thus, a total of 157 patients completed the study according to the study protocol, which included 79 patients in the treatment group and 78 patients in the control group. There were no statistically significant differences observed in age, gender, or disease characteristics between the two groups ($p>0.05$, Table 1).

The main efficacy indicators

There was a significant interaction between the two groups and time factors ($p=0.003$), suggesting that the trend of ALT changes in the two groups was different, with an improvement of ALT more obviously observed in the treatment group (Table 2, Figure 2). There were statistically significant differences among the three measurements of ALT before and after

Table 2. Analysis of results of serum ALT biochemical indicators in 2 groups (mean ± standard deviation).

Group	Patients	Indicators	Baseline period	2 weeks of treatment	4 weeks of treatment	P value		
						Time	Grouping ×time	Grouping
Treatment group	79	ALT (U/L)	130.49±34.99	49.33±21.39*#	30.36±17.41*#	0.000	0.003	0.000
Control group	78		131.36±39.98	68.20±26.31*	50.71±27.13*	0.000		

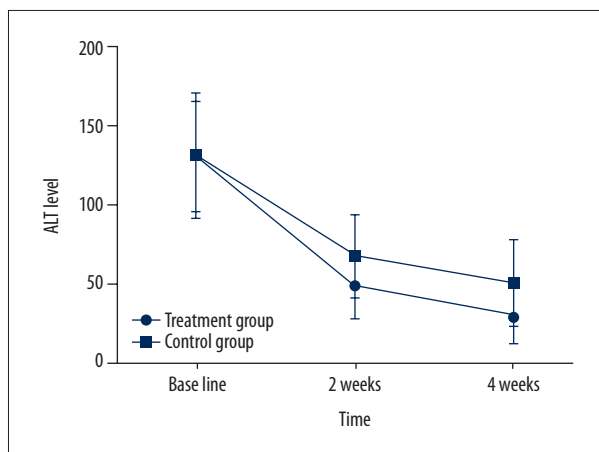* Compared with baseline, $P<0.01$; # Compared with the control group, $P<0.01$.

Figure 2. ALT changes in two groups.

treatment in the two groups at different times ($p<0.01$). There were significant differences from baseline after two weeks and four weeks of treatment ($p<0.01$).

Secondary efficacy indicators

After two weeks of treatment, serum ALT normalization rate in the treatment group and control group were 30.38% and 12.82%, respectively ($p=0.008$). After four weeks of treatment, ALT normalization rates were 74.68% and 46.15%, respectively ($p=0.000$). Efficacy of the treatment group was significantly better than the control group ($p=0.004$, Table 3).

Subgroup analysis of ALT normalization rate

Subgroup analyses were performed for each level of age, gender, history of alcohol intake, and baseline ALT levels (Table 4). For patients with baseline ALT levels greater than 120 U/L, the

male patients benefitted from bicyclol treatment and achieved a significantly higher ALT normalization rate.

Adverse reactions

There were no serious adverse events observed during the study. There were two cases with adverse reactions in the treatment group, which were characterized by abdominal distension and mild diarrhea, with incidence rates of 2.53%. Also, there were two cases of adverse reactions in the control group, which were characterized by mild abdominal distension and dizziness, with incidence rates of 2.56%. There was no significant differences observed between the two groups ($\chi^2=0.0002$, $p=0.989$). No laboratory abnormalities were associated with the investigated drug during the study.

Discussion

In recent years, the incidence of drug-induced liver injury (DILI) has been increasing year by year with a continuous launch of new drugs and demand for clinical drug combinations. Globally, the incidence of DILI is 13.9 to 24 per 100,000 population [14]. Currently, the incidence of DILI in China accounts for about 20% of acute liver injury inpatients [15–17]. The incidence and development of DILI involves factors such as genetics and drug types, with the pathogenesis closely related to oxidative stress, cytokine release, mitochondrial damage, liver cell apoptosis, and others factors [18]. DILI may lead to downregulation of enzymes that influence drug pharmacokinetics [19].

Statins are currently the most widely used drugs clinically. Because the primary target organ for statins is the liver [20], statin-related hepatotoxicity has been the most commonly

Table 3. Comparison of comprehensive efficacy in two groups.

Group	Patients	Evidently effective	Effective	Not effective	Wilcoxon W	P
Treatment group	79	45	17	17	5498.000	0.004
Control group	78	31	11	36		

Table 4. Comparison of subgroup analysis of ALT normalization rate.

Subgroup		Treatment group		Control group		Statistics	P	OR(95%CI)
		ALT normalized patients/total number of patients (%)						
Age	≥55 yrs	31/42	(73.81)	23/49	(46.94)	6.768	0.009	3.186 (1.311–7.740)
	<55yrs	28/37	(75.68)	13/29	(44.83)	6.575	0.010	3.829 (1.342–10.927)
Gender	Male	49/63	(77.78)	29/63	(46.03)	13.462	0.000	4.103 (1.893–8.893)
	Female	10/16	(62.50)	7/15	(46.67)	0.784	0.376	1.905 (0.454–7.983)
History of alcohol intake	Alcohol consumption	16/23	(69.57)	7/21	(33.33)	5.776	0.016	4.571 (1.284–16.273)
	None	43/56	(76.79)	29/57	(50.88)	8.202	0.004	3.194 (1.422–7.172)
Baseline ALT levels	<120	28/39	(71.79)	22/38	(57.89)	1.633	0.201	1.851 (0.716–4.783)
	≥120	31/40	(77.50)	14/40	(35.00)	14.679	0.000	6.397 (2.386–17.153)

reported statin-related adverse reaction [21]. Statin-induced liver injury with asymptomatically elevated transaminases often occurs within 12 weeks after the initiation of statin therapy [22]. Hence, clinicians should pay more attention to the effect of statins on liver function.

The results of the present study showed that there were significant improvements in ALT after four weeks of therapy with bicyclol or polyene phosphatidylcholine. However, bicyclol was better for improving serum biochemical parameters than polyene phosphatidylcholine.

DILI can be divided into hepatocellular, cholestatic, and mixed [23]. Bjornsson et al. [24] reported that hepatocellular liver injury alone accounts for 43% of statin-induced liver injuries. But the statin-induced liver enzyme elevation mechanism still remains unclear, probably because these drugs cause changes in the liver cell membrane which results in further leakage of liver enzymes [6]. A foreign *in vitro* study [25] confirmed that lipophilic statins significantly increased the number of annexin V-or TUNEL-stained cells, leading to DNA breakage, causing liver cell apoptosis. In addition, higher doses of statins caused liver cell oxidative stress and inflammatory responses, and promoted apoptosis of liver cells related to drug inhibition of mevalonate synthesis, which in turn lead to hepatocellular necrosis in the center belt [26].

The main active ingredient of polyene phosphatidylcholine is polyphosphatidylcholine diacylglycerol, or poly-acetyl lecithin,

which is an important part of all cell membranes and subcellular membranes. In addition to physiological phospholipids, polyene phosphatidylcholine also has demonstrated reduction in oxygen stress and lipid peroxidation, inhibited liver cell apoptosis, reduced inflammatory responses, and inhibited activation and other functions, thus protecting liver cells from injuries from several aspects [27].

Previous pharmacological studies have shown that bicyclol demonstrated a good protective effect on the liver during acute and chronic liver injuries caused by a variety of chemical poisons, alcohols, and others agents [28,29]. The metabolic interactions between drugs may cause changes in the drug concentrations in blood, which in turn affects the efficacy and toxicity. Studies have shown that bicyclol did not affect the plasma concentration and peak time of atorvastatin in rats, and there was no interaction between bicyclol and statins [30]. Therefore, bicyclol is considered safe in the treatment of statin-induced liver injury.

For asymptomatic patients with simple aminotransferase elevation (<3 ULN), the National Lipid Society of America recommends no change or discontinuation of treatment [31]. However, in clinical practice, mild to moderate abnormalities in liver test may influence the adherence of patients with atherosclerotic cardiovascular disease and their use of statins, thus reducing the potential for clinical benefit. Therefore, for patients whose ALT or AST were not exceeding three times the ULN, we did not stop using statins during treatment, and the application

of bicyclol improved liver functions which also improved the adherence of patients' long-term use of statins. On the other hand, for patients who discontinued statins due to ALT or AST of >3 times the ULN, the application of bicyclol could quickly improve the liver function tests, and thus allow for restoration of the statin treatment program (taking another category of statin with less hepatotoxicity than the original one), and ensure clinical benefit of statins to these patients.

Conclusions

The use of statins is considered to be safe and reliable; the United States, Europe, and China have relevant guidelines and

advisories, however, confusion still remains with regard to usage. This in turn affects the adherence of patients in the use of long-term medication. Proper treatment of statin-related adverse events reduces the effect caused by statins and helps patients with increased clinical benefits. In our study, bicyclol was safe and effective for the treatment of statin-induced liver injury. Considering patients' adherence problem, this study selected patients with mild liver injury (ALT 2~5 ULN, TBiL ≤2 ULN). Whether bicyclol can be benefit for severe liver injury needs further study. Due to the small sample size and short duration of treatment time in our study, it is still necessary to accumulate more scientific clinical data, especially related to bicyclol effects on statin efficacy, to further validate the impacts of bicyclol in the treatment of statin-induced liver injury.

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