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Standard-Dose Ursodeoxycholic Acid Improves Biochemical Liver Function and Fibrosis in Chronic Liver Disease: Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: This study evaluated the efficacy and safety of standard-dose ursodeoxycholic acid (UDCA; fixed daily dose of 300 mg/day) compared with placebo, in patients with chronic liver disease.

Methods: A multicenter, randomized, double-blind, placebo-controlled phase IV clinical trial was conducted in academic hospitals in South Korea. Patients with chronic liver disease and abnormal serum alanine aminotransferase (ALT) levels in at least two consecutive results

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Disclosure
The authors declare no conflicts of interest in this work. This study was sponsored by Daewoong Pharmaceutical Co., Ltd., Korea. The study protocol was designed by Jae Young Jang, and the data analysis was conducted by Young Chang in collaboration with Daewoong Pharmaceutical Co., Ltd.

prior to screening, persisting for at least 6 months, were randomly assigned to receive 100 mg UDCA or placebo three times daily for 8 weeks. The primary endpoint was the mean relative change in ALT levels from baseline. The secondary endpoints included changes in fibrosis and drug-related adverse events.
Results: A total of 262 patients were analyzed (132 in the UDCA group and 130 in the placebo group). By week 8, there was a significantly greater reduction in serum ALT levels from baseline in the UDCA-treated patients than in the placebo group (−14.70 vs. −5.51 U/L; $P = 0.010$). The ALT normalization rates were higher in the UDCA group (26.52% vs. 13.08%; odds ratio, 2.60; $P = 0.005$). Fibrosis reduction, as assessed by the FibroTest score, was greater in the UDCA group (−0.03 vs. −0.00; $P = 0.016$). The frequency of adverse events in the two groups was similar, with no serious adverse events reported in the UDCA group.
Conclusion: In patients with chronic liver disease, 100 mg UDCA three times daily for 8 weeks improved ALT levels and fibrosis, and had a favorable safety profile.

Trial Registration: ClinicalTrials.gov Identifier: NCT06272630

Keywords: Ursodeoxycholic Acid; Chronic Liver Disease; Liver Function Tests; Liver Fibrosis

INTRODUCTION

Chronic liver disease (CLD) has become a leading cause of morbidity and mortality worldwide over the past few decades.[1,2] CLD can result from various etiologies, including viral hepatitis (e.g., chronic hepatitis B or C), alcoholic liver disease, and metabolic-dysfunction-associated steatotic liver disease (MASLD). Regardless of the etiology, CLD can lead to liver fibrosis and eventually progress to liver cirrhosis, often resulting in life-threatening complications such as variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma. Because the progression of CLD significantly contributes to liver-related morbidity and mortality, effective management of patients with CLD is crucial in reducing the overall disease burden and associated healthcare costs.

Antiviral treatment with nucleot(s)ide analogues or direct-acting antivirals is the mainstay of therapy for viral hepatitis. However, indications for antiviral therapy remain limited, and economic barriers may restrict access to treatment. Effective pharmacologic options for MASLD are still scarce. Although resmetirom has recently been approved for treating metabolic-dysfunction-associated steatohepatitis with moderate to advanced liver fibrosis,[3] its use is confined to a specific subset of patients with MASLD, and its high cost may hinder broader adoption. Consequently, various readily accessible drugs with potential hepatoprotective properties, such as ursodeoxycholic acid (UDCA),[4] silymarin,[5] and biphenyl dimethyl dicarboxylate,[6] have been widely investigated and used in patients with CLD.

UDCA is a hydrophilic bile acid that is naturally present in the human body; it has mechanisms that include stabilization of cell membranes and inhibition of apoptosis, potentially mitigating the progression of liver diseases.[7] As a hydrophilic and non-toxic bile acid, UDCA competitively displaces hydrophobic toxic bile acids from cellular membranes and organelles, thereby preventing damage to hepatocytes and cholangiocytes.[8] Over the past few decades, many clinical trials have assessed whether UDCA has hepatoprotective effects in patients with CLD. However, conflicting results have been reported because of variations in inclusion and exclusion criteria and the treatment doses and durations, and the use of different drug

Data Sharing Statement

The data generated and analyzed during the current study are included in this published article and its supplementary information files. The raw datasets are not publicly available due to internal policy restrictions of the sponsor (Daewoong Pharmaceutical Co., Ltd.), but they can be available from the corresponding author upon reasonable request. Data will be shared for academic research purposes after review and approval of a formal request. Requests for data sharing should be directed to the corresponding author.

Author Contributions

Conceptualization: Jang JY, Chang Y. Data curation: Yu JM, Kim SY. Formal analysis: Yu JM, Kim SY. Funding acquisition: Yu JM, Kim SY. Investigation: Chang Y, Cho YK, Kim YS, Kim SE, Cheon GJ, Kim JH, Yang H, Kim W, Ahn SB, Yoon EL, Cheong JY, Lee JW, Kim MY, Kim HJ, Lee SH, Cho EY, Choi NR, Lee HW, Kim KM, Choe WH, Jang JY. Methodology: Yu JM. Project administration: Cho YK, Kim YS, Kim SE, Cheon GJ, Kim JH, Yang H, Ahn SB, Yoon EL, Cheong JY, Lee JW, Kim MY, Kim HJ, Lee SH, Cho EY, Choi NR, Lee HW, Kim KM, Choe WH, Yu JM, Kim SY. Resources: Yu JM, Kim SY. Software: Yu JM, Kim SY. Supervision: Cho YK, Kim YS. Validation: Jang JY, Chang Y, Yu JM, Kim SY. Visualization: Chang Y, Yu JM, Kim SY. Writing - original draft: Chang Y. Writing - review & editing: Jang JY, Chang Y.

combinations across studies. While high doses of UDCA (28–35 mg/kg/day) have demonstrated benefits in improving biochemical markers,[9,10] lower doses (13–15 mg/kg/day) have produced controversial therapeutic effects in patients with CLD.[4,11-13] In real-world clinical practice, however, UDCA is often prescribed at a much lower fixed daily dose—typically 300 mg/day (approximately 3–5 mg/kg/day)—particularly in patients without specific indications such as primary biliary cholangitis. Given these considerations, this study was performed to evaluate the efficacy and safety of standard fixed doses of UDCA (300 mg daily) in patients with CLD.

METHODS

Study design and participants

We conducted a multicenter, randomized, double-blind, placebo-controlled phase IV clinical trial in 20 academic hospitals in South Korea. Patients who voluntarily provided written informed consent to participate in the clinical trial underwent a screening test to assess their eligibility. Those who met the final eligibility criteria were enrolled and randomly assigned to either the treatment or placebo group in a 1:1 ratio. The investigated drug was administered for 8 weeks (**Supplementary Fig. 1**).

We included patients aged > 19 years with CLD and elevated serum alanine aminotransferase (ALT) levels. CLD was defined by at least one of the following two criteria: persistent elevation of serum ALT level (upper limit of normal [ULN] < ALT < 5 × ULN) observed at least twice consecutively over a minimum of 6 months, or confirmation of CLD (e.g., alcoholic liver disease, MASLD, or chronic viral hepatitis) based on ultrasound or other imaging studies conducted within the previous 6 months. The key exclusion criteria were cirrhosis, hepatocellular carcinoma, fulminant hepatitis, viral hepatitis requiring antiviral therapy, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, and IgG4-associated cholangitis. Patients who had taken medications likely to affect clinical outcomes (e.g., liver function and fatigue) or who required such medications during the trial period were excluded. Substantial alcohol consumption was defined as > 20 g/day for women and > 40 g/day for men, and individuals meeting these criteria were also excluded. Patients with uncontrolled hypertension (≥ 180/110 mmHg), diabetes mellitus (HbA1c ≥ 9.0%), or a body mass index (BMI) of ≥ 35 kg/m^2 were also excluded from the trial.

Randomization and masking

The participants were randomly assigned to either the treatment or placebo group at a 1:1 ratio using stratified block randomization, which accounted for stratification factors. The stratification factors included the ALT level (based on 2 × ULN) and the fatigue score measured at screening (based on a score of 4.0 on the Chalder Fatigue Scale [CFQ] translated into Korean [K-CFQ]). An independent randomization coordinator who was not directly involved in the study generated the randomization list and the clinical trial medication packaging list using SAS® 9.4 (SAS Institute, Cary, NC, USA). At the time of randomization, each participant who met the inclusion criteria was assigned a randomization number in order of registration. The investigated drug was then allocated to participants according to their assigned treatment group.

This clinical trial was conducted as a double-blind study, ensuring that both participants and investigators were unaware of the randomized assignment of the investigated drug. To maintain the double-blind design, placebo tablets identical in appearance and formulation to the investigated drug were used, making it impossible to distinguish between the two.

During the clinical trial period, the liver function test results of each participant were also blinded to prevent potential unblinding through indirect inference based on liver-function test outcomes. Randomization codes were employed during the allocation process, allowing participants to be identified only by their assigned codes. The allocation details for each group remained concealed until the conclusion of the clinical trial.

Measurements

Liver-function tests were conducted to assess the inclusion criteria and treatment efficacy by measuring ALT, aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels, based on results from a central laboratory. Hepatic steatosis was evaluated using abdominal ultrasound, and the diagnosis of SLD was based on these imaging findings. To evaluate liver fibrosis, noninvasive methods, including liver stiffness measurement via vibration controlled transient elastography (VCTE) and FibroTest, were performed at baseline and at the end of the study. The FibroTest is a validated tool for assessing liver fibrosis, regardless of the underlying cause of liver disease.[13] It incorporates two clinical variables (age and sex) and five biochemical markers (alpha-2-macroglobulin, apolipoprotein A1, haptoglobin, total bilirubin, and GGT), measured at a central laboratory, and calculates the degree of liver fibrosis using a specific formula.

Improvement in fatigue was assessed using the K-CFQ. The CFQ is a validated instrument for measuring physical and psychological fatigue across a range of conditions, including liver disease.[14] The K-CFQ has been specifically validated for assessing chronic fatigue in Korean populations. It comprises 11 items, with participants selecting from four response options: “less than usual,” “no more than usual,” “more than usual,” and “much more than usual.” The total scores range from 0–11, with a score ≥ 4 indicating fatigue (**Supplementary Table 1**).[15,16] The K-CFQ was administered at baseline, after 4 weeks of treatment, and after 8 weeks of treatment.

Outcomes

The primary outcome was the change in ALT level after 8 weeks of administration of the investigated drug. The secondary outcomes were the percent change in ALT level after 8 weeks of administration, the ALT change and percent change after 4 weeks of administration, the AST change and percent change after 4 and 8 weeks of administration, the GGT change and percent change after 4 and 8 weeks of administration, and the proportion of participants achieving ALT normalization after 4 and 8 weeks of administration. The ULN for ALT was defined as ≤ 41 U/L for men and ≤ 33 U/L for women, based on the reference values provided by the central laboratory.

The exploratory outcomes were the changes in K-CFQ scores at 4 and 8 weeks compared with baseline, the proportion of participants whose K-CFQ scores improved to < 4.0 after 4 and 8 weeks of administration, changes in liver stiffness by the VCTE after 8 weeks of administration, and changes in FibroTest score after 8 weeks of administration. Exploratory subgroup analyses were also conducted based on age (< 65 vs. ≥ 65 years), sex, baseline BMI (< 25, 25–< 30, 30–< 35 kg/m^2), and etiology of CLD (alcoholic liver disease, steatotic liver disease (SLD), and other liver diseases), to evaluate both primary and secondary efficacy outcomes. These subgroup analyses were performed in the full analysis set (FAS) population.

The safety outcomes were treatment-emergent adverse events (TEAEs), laboratory findings, vital signs, body weight, and physical examination results.

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Statistical analysis

Efficacy assessments were primarily analyzed using the FAS, with supplementary analyses conducted on the per-protocol set (PPS). Safety assessments were analyzed using the safety set. The FAS included all randomized participants who received at least one dose of the investigated drug and had at least one post-baseline primary efficacy assessment. Analyses for the FAS were conducted according to the randomized groups. The PPS was defined as a subset of the FAS, consisting of participants who completed the study with no major protocol violations. The safety set included all participants who received at least one dose of the investigated drug, regardless of randomization, and safety analyses were performed according to the actual treatment received.

All statistical analyses were performed using SAS® 9.4, with a two-sided test approach at a significance level of 5%. Categorical data are presented as frequencies and percentages, while continuous data are presented as means and standard deviations or as medians and ranges, depending on the data distribution. Comparisons of within-group changes or percent changes from baseline at each time point (4 and 8 weeks) were conducted using a paired t-test if the normality assumption was met, or the Wilcoxon signed rank test if the normality assumption was not met.

Analysis of covariance (ANCOVA) was performed to compare differences between the treatment and control groups in changes or percent changes from baseline at each time point (4 and 8 weeks). The model included the baseline value of the efficacy variable and stratification factors (ALT at Visit 1 as either less than or greater than or equal to 2 × ULN and the K-CFQ total score at Visit 2 as either less than or greater than or equal to 4.00 points) as covariates. The results from the ANCOVA model are presented as least-squares means and standard errors for each group, together with the least-squares mean difference (treatment group − control group), the corresponding two-sided 95% confidence intervals (CIs), and *P* values.

Sample size determination

The sample size calculation was based on the expected change in ALT levels after 8 weeks. The treatment group was anticipated to exhibit an ALT reduction of −11.87 U/L, which was derived as the weighted average of reference values from previous studies.[11,17] The placebo group was expected to show an ALT reduction of −0.78 U/L.[17] This resulted in an assumed between-group difference in the ALT change after 8 weeks of −11.09 U/L. The standard deviation of the between-group difference was estimated to be 26.28, based on pooled standard deviations from both the treatment and placebo groups.[17] Using a two-sided significance level of 0.05, 80% statistical power, and 1:1 randomization ratio, the required sample size was calculated to be 90 participants per group as determined by PASS v22.0.2. To account for a 30% dropout rate due to the recommendation of alcohol abstinence throughout the trial, the minimum required number of participants was adjusted to 129 per group, leading to a total of 258 participants for the study

Ethics statement

This trial was registered at ClinicalTrials.gov (NCT06272630) on 06/04/2024. Informed consent was obtained from all participants prior to their inclusion in the study. The study protocol and related documents were reviewed and approved by the Institutional Review Board of each participating institution (IRB approval numbers: SCHUH 2022-11-007, PC22MSDV0256, 2022-12-015, 2023GR0028, 2022-1738, 30-2022-121, 2022-12-011, SCHBC 2022-11-029, AJOUIRBCT2023037, CR122090, 4-2022-1539, 2022-12-062, 2022-11-047,

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2212-001-533, 2022-12-024, 2022-12-024, KUMC 2023-10-031, 2023-09-021, 2023-10-021, 2023-09-028; **Supplementary Table 2**). Furthermore, all methods were conducted in compliance with applicable guidelines and regulations.

RESULTS

Baseline characteristics

Of the 355 participants screened, 263 were randomized in a 1:1 ratio to either the UDCA or placebo group. Among them, 262 participants received the investigated drug, and 240 participants completed the study (UDCA group: n = 124; placebo group: n = 116) (**Supplementary Fig. 2**). The baseline characteristics were well balanced between the UDCA and placebo groups (**Table 1**). The mean age of the participants was approximately 46–47 years, and the majority were male (66.7% in the UDCA group vs. 69.2% in the placebo group). The mean BMIs of the two groups were similar (28.10 ± 3.50 kg/m^2 in the UDCA group vs. 27.85 ± 3.62 kg/m^2). Platelet counts, liver function tests (AST, ALT, and GGT), and markers of glucose metabolism (glucose and HbA1c) did not differ significantly between the two groups. Other parameters, including albumin, total bilirubin, creatinine, lipid profiles (total cholesterol and triglycerides), and liver stiffness measurements, were comparable in the two groups. The FibroTest scores were also similar (0.29 ± 0.20 vs. 0.30 ± 0.20, P = 0.678), confirming homogeneity at baseline.

Table 1. Baseline characteristics of the study population

Variables	UDCA (n = 132)	Placebo (n = 130)	*P* value
Demographic characteristics			
Age, yr	46.37 ± 13.96	47.10 ± 14.08	0.637
Male	88 (66.67)	90 (69.23)	0.657
Etiology			
Alcoholic liver disease	3 (2.27)	3 (2.31)	1.000
Steatotic liver disease	128 (96.97)	125 (96.15)	0.981
Other liver disease	33 (25.22)	30 (23.08)	0.826
Comorbidities			
Hypertension	47 (35.61)	34 (33.08)	0.763
Diabetes mellitus	28 (21.2)	25 (19.23)	0.806
Dyslipidemia	50 (37.88)	61 (46.92)	0.175
Measurements			
BMI, kg/m^2	28.10 ± 3.50	27.85 ± 3.62	0.426
Platelet, 10^3/μL	259.61 ± 71.79	255.06 ± 59.03	0.739
Total bilirubin, mg/dL	0.70 ± 0.34	0.69 ± 0.38	0.590
Albumin, g/dL	4.77 ± 0.24	4.82 ± 0.26	0.068
AST, U/L	46.46 ± 20.50	48.68 ± 22.70	0.717
ALT, U/L	77.16 ± 34.02	75.83 ± 31.90	0.782
GGT, U/L	70.28 ± 57.53	83.23 ± 83.42	0.782
Creatinine, mg/dL	0.84 ± 0.17	0.84 ± 0.16	0.979
Glucose, mg/dL	108.08 ± 17.64	105.98 ± 18.71	0.397
HbA1c, %	5.92 ± 0.72	5.85 ± 0.61	0.711
Total cholesterol, mg/dL	190.88 ± 41.76	195.13 ± 42.46	0.415
Triglyceride, mg/dL	171.66 ± 87.54	177.07 ± 131.62	0.691
K-CFQ	3.12 ± 3.15	2.85 ± 3.16	0.338
Liver stiffness measurement, kPa	6.91 ± 3.30	6.46 ± 2.49	0.494
Fibrotest	0.29 ± 0.20	0.30 ± 0.20	0.678

Data are presented as the mean ± standard deviation or the number (%).
UDCA = urodeoxycholic acid, BMI = body mass index, AST = aspartate aminotransferase, ALT = alanine aminotransferase, GGT = gamma-glutamyl transferase, HbA1c = hemoglobin A1c, K-CFQ = Chalder Fatigue Scale translated into Korean.

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Table 2. Changes in alanine aminotransferase from baseline at week 4 and week 8

Variables	UDCA (n = 132)	Placebo (n = 130)	*P* value
Baseline	77.16 (34.02)	75.83 (31.90)	
Week 4	62.78 (32.69)	73.43 (39.39)	
Week 8	61.45 (34.45)	69.85 (39.75)	
Change from baseline at week 4			
Mean ± SD, U/L	−14.24 ± 25.78	−2.64 ± 29.02	
Mean ± SD, %	−16.02 ± 35.24	−1.23 ± 37.77	
Change from baseline at week 8			
Mean ± SD, U/L	−15.71 ± 29.76	−5.98 ± 30.98	
Mean ± SD, %	−18.07 ± 37.15	−6.14 ± 36.74	
ANCOVA result at week 4			
Least square mean ± SE, U/L	−13.18 (2.44)	−1.87 (2.43)	
Least square mean difference (95% CI), U/L	−11.31 (−17.73 to −4.89)		< 0.001
Least square mean ± SE, %	−15.44 (3.37)	−0.80 (3.36)	
Least square mean difference (95% CI), %	−14.64 (−23.50 to −5.77)		0.001
ANCOVA result at week 8			
Least square mean ± SE, U/L	−14.70 ± 2.66	−5.51 ± 2.66	
Least square mean difference (95% CI), U/L	−9.19 (−16.20 to −2.18)		0.010
Least square mean ± SE, %	−17.43 ± 3.39	−5.82 (3.39)	
Least square mean difference (95% CI), %	−11.61 (−20.55 to −2.66)		0.011

UDCA = ursodeoxycholic acid, SD = standard deviation, ANCOVA = analysis of covariance, SE = standard error, CI = confidence interval.

The average drug-adherence rates for the investigated product were 95.06%, 94.25%, and 94.11% at 4 weeks, 8 weeks, and throughout the entire study period, respectively. Both the UDCA and placebo groups achieved adherence rates of > 90% at each visit (**Supplementary Table 3**).

Changes in ALT from baseline at week 8

The results of the ANCOVA analysis, adjusted for baseline ALT levels and stratification factors, indicated that the changes in ALT from baseline to week 8 were −14.70 U/L in the UDCA group and −5.51 U/L in the placebo group, a decrease in both groups. The difference in the ALT change between the UDCA and placebo groups was −9.19 U/L (95% CI, −16.20 to −2.18), indicating a significantly greater reduction in the UDCA group (*P* = 0.010) (**Table 2**, **Fig. 1**).

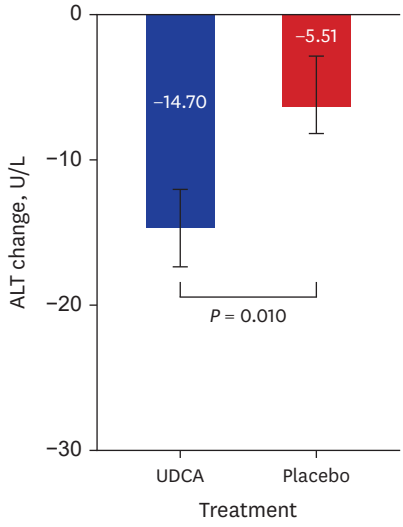

Fig. 1. Changes in ALT levels from baseline to week 8. There was a significantly greater reduction in ALT levels in the UDCA group than in the placebo group.
ALT = alanine transaminase, UDCA = ursodeoxycholic acid.

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From baseline to week 8, the percent changes in ALT were −17.43% in the UDCA group and −5.82% in the placebo group, a difference of −11.61% (95% CI, −20.55 to −2.66), again a significantly greater reduction in the UDCA group (P = 0.011) (**Table 2**). The results from the PPS analysis were consistent with those from the FAS analysis (**Supplementary Fig. 3**).

Changes in ALT from baseline at week 4

The ALT changes and percent changes at week 4 were analyzed using the same method. The changes in ALT were −13.18 U/L in the UDCA group and −1.87 U/L in the placebo group, a difference of −11.31 U/L (95% CI, −17.73 to −4.89), with a significantly greater reduction in the UDCA group than in the placebo group (P < 0.001) (**Table 2**).

The percent changes in ALT were −15.44% in the UDCA group and −0.80% in the placebo group, a difference of −14.64% (95% CI, −23.50 to −5.77), again with a significantly greater reduction in the UDCA group (P = 0.001) (**Table 2**). The results for the PPS population were consistent with those from the FAS analysis.

ALT normalization at weeks 4 and 8

At week 4, the ALT normalization rates were 22.73% (30/132) in the UDCA group and 11.54% (15/130) in the placebo group. At week 8, the rates were 26.52% (35/132) in the UDCA group and 13.08% (17/130) in the placebo group. Using a logistic regression model adjusted for stratification factors and treatment groups, the odds ratios (ORs) for ALT normalization in the UDCA and placebo groups were 2.44 (95% CI, 1.21 to 4.94) at week 4 and 2.60 (95% CI, 1.34 to 5.08) at week 8, indicating significantly higher ALT normalization rates in the UDCA group at both time points (week 4: P = 0.013, week 8: P = 0.005) (**Supplementary Table 4**, **Fig. 2**). In the PPS analysis, the OR for ALT normalization at week 8 was consistent with the findings observed in the FAS analysis.

Changes in AST and GGT from baseline at week 4 and week 8

At week 4, the changes in AST were −5.70 U/L in the UDCA group and −3.02 U/L in the placebo group, a difference of −2.68 U/L (95% CI, −6.31 to 0.96; P = 0.148). The percent

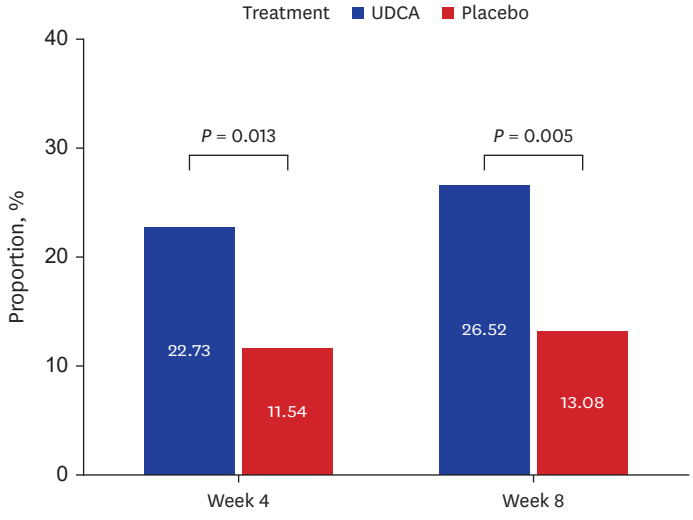

Fig. 2. Proportions of ALT normalization at week 4 and week 8. ALT normalization rates were significantly higher in the UDCA group than in the placebo group at both time points.
UDCA = ursodeoxycholic acid, ALT = alanine transaminase.

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Table 3. Changes in gamma-glutamyl transferase from baseline at week 4 and week 8

Variables	UDCA (n = 132)	Placebo (n = 130)	*P* value
Baseline	70.28 (57.53)	83.23 (83.42)	
Week 4	57.52 (50.17)	75.21 (69.27)	
Week 8	56.51 (58.53)	73.95 (68.27)	
Change from baseline at week 4			
Mean ± SD, U/L	−12.93 (21.60)	−7.97 (37.89)	
Mean ± SD, %	−15.52 (27.28)	−3.13 (30.80)	
Change from baseline at week 8			
Mean ± SD, U/L	−13.77 (26.57)	−9.28 (35.11)	
Mean ± SD, %	−18.77 (29.86)	−4.76 (30.39)	
ANCOVA result at week 4			
Least square mean ± SE, U/L	−14.66 (2.31)	−6.66 (2.33)	
Least square mean difference (95% CI), U/L	−8.00 (−14.26 to −1.73)		0.013
Least square mean ± SE, %	−16.36 (2.59)	−3.05 (2.60)	
Least square mean difference (95% CI), %	−13.31 (−20.31 to −6.31)		< 0.001
ANCOVA result at week 8			
Least square mean ± SE, U/L	−15.87 (2.48)	−8.82 (2.50)	
Least square mean difference (95% CI), U/L	−7.05 (−13.78, −0.32)		0.040
Least square mean ± SE, %	−19.86 (2.69)	−5.13 (2.71)	
Least square mean difference (95% CI), %	−14.73 (−22.03 to −7.43)		< 0.001

UDCA = ursodeoxycholic acid, SD = standard deviation, ANCOVA = analysis of covariance, SE = standard error, CI = confidence interval.

changes in AST were −8.61% in the UDCA group and −2.98% in the placebo group, a difference of −5.63% (95% CI, −13.53 to 2.26; *P* = 0.161). At week 8, the changes in AST were −7.09 U/L in the UDCA group and −3.84 U/L in the placebo group, a difference of −3.25 U/L (95% CI, −7.46 to 0.97; *P* = 0.130). The percent changes were −11.46% in the UDCA group and −4.60% in the placebo group, a difference of −6.85% (95% CI, −15.55 to 1.84; *P* = 0.122). Although the reductions in AST levels were greater in the UDCA group than in the placebo group at both week 4 and week 8, the differences did not reach statistical significance (**Supplementary Table 5**).

At week 4, the changes in GGT were −14.66 U/L in the UDCA group and −6.66 U/L in the placebo group, a difference of −8.00 U/L (95% CI, −14.26 to −1.73; *P* = 0.013). The percent changes were −16.36% in the UDCA group and −3.05% in the placebo group, a difference of −13.31% (95% CI, −20.31 to −6.31; *P* < 0.001), indicating a significantly greater reduction in the UDCA group than in the placebo group (**Table 3**). At week 8, the changes in GGT were −15.87 U/L in the UDCA group and −8.82 U/L in the placebo group, a difference of −7.05 U/L (95% CI, −13.78 to −0.32; *P* = 0.040). The percent changes were −19.86% in the UDCA group and −5.13% in the placebo group, a difference of −14.73% (95% CI, −22.03 to −7.43; *P* < 0.001), consistently demonstrating a significantly greater reduction in the UDCA group (**Table 3**).

Liver fibrosis assessed using VCTE and FibroTest

The changes in liver fibrosis, as measured by VCTE, from baseline to week 8, were −0.37 kPa in the UDCA group and 0.07 kPa in the placebo group, implying reduced liver fibrosis in the UDCA group. However, the difference between the two groups was −0.44 kPa (95% CI, −0.94 to 0.06), which was not statistically significant (*P* = 0.083) (**Fig. 3**). Among participants with a baseline liver stiffness ≥ 7 kPa, 37.5% (18/48) in the UDCA group and 34.1% (15/44) in the placebo group had a reduction to < 7 kPa following treatment with the investigated product. Conversely, among participants with a baseline liver stiffness < 7 kPa, 7.3% (6/82) in the UDCA group and 14.1% (12/85) in the placebo group showed an increase to ≥ 7 kPa after treatment.

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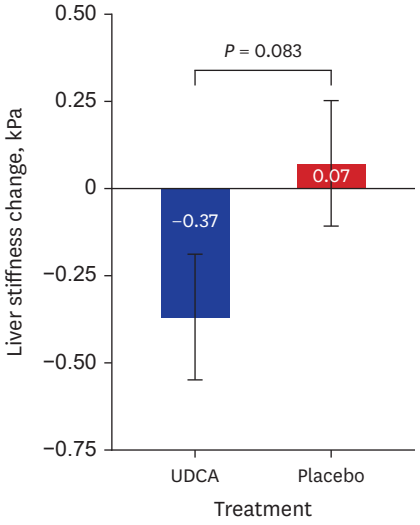

Fig. 3. Changes in liver stiffness values measured by vibration controlled transient elastography from baseline to week 8. No significant difference was observed between the groups.
UDCA = ursodeoxycholic acid.

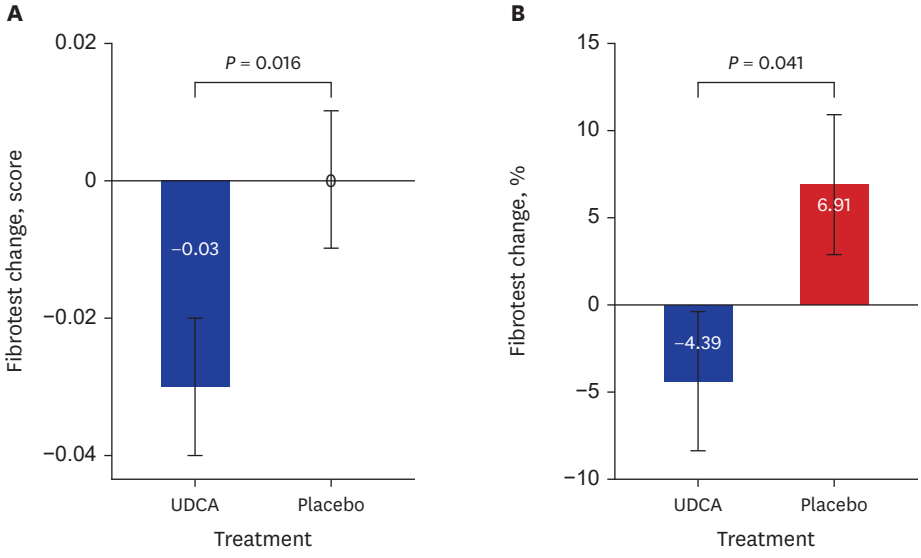

Fig. 4. FibroTest results: (**A**) changes and (**B**) percent changes from baseline to week 8. There was a significantly greater reduction in FibroTest scores in the UDCA group than in the placebo group.
UDCA = ursodeoxycholic acid.

In terms of the FibroTest results, the changes from baseline to week 8 were −0.03 in the UDCA group and 0.00 in the placebo group, a difference of −0.03 (95% CI, −0.05 to −0.01), with a significantly greater reduction in the UDCA group (P = 0.016) (**Fig. 4**). Additionally, the percent changes in the FibroTest from baseline to week 8 were −4.39% in the UDCA group and 6.91% in the placebo group, a difference of −11.30% (95% CI, −22.11 to −0.49), also with a significantly greater reduction in the UDCA group than in the placebo group (P = 0.041) (**Fig. 4**).

K-CFQ

At week 4, the changes in K-CFQ total scores (0–11, with higher scores indicating greater fatigue) compared to baseline were −2.28 points in the UDCA group and −1.87 points in the

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Table 4. Changes of total Chalder Fatigue Scale translated into Korean score from baseline at week 4 and week 8

Variables	UDCA (n = 132)	Placebo (n = 130)	*P* value
Baseline	3.12 (3.15)	2.85 (3.16)	
Week 4	0.77 (1.57)	1.14 (2.12)	
Week 8	0.59 (1.25)	1.01 (1.86)	
Change from baseline at week 4	−2.34 (3.19)	−1.73 (3.21)	
Change from baseline at week 8	−2.53 (3.09)	−1.84 (3.31)	
ANCOVA result			
Least square mean ± SE at week 4	−2.28 ± 0.17	−1.87 ± 0.17	
Least square mean difference (95% CI) at week 4	−0.41 (−0.85 to 0.03)		0.065
Least square mean ± SE at week 8	−2.45 ± 0.15	−1.99 ± 0.15	
Least square mean difference (95% CI) at week 8	−0.46 (−0.83 to −0.08)		0.018

UDCA = ursodeoxycholic acid, ANCOVA = analysis of covariance, SE = standard error, CI = confidence interval.

placebo group, a difference of −0.41 points (95% CI, −0.85 to 0.03), which was not statistically significant ($P = 0.0651$). At week 8, the changes were −2.45 points in the UDCA group and −1.99 points in the placebo group, a difference of −0.46 points (95% CI, −0.83 to −0.08) with a significantly greater reduction in the UDCA group ($P = 0.018$) (**Table 4**).

Among participants who had a baseline K-CFQ score ≥ 4.00, a greater proportion of the UDCA group improved by weeks 4 and 8 compared with the placebo group. At week 4, 83.67% (41/49) of the UDCA group and 78.72% (37/47) of the placebo group had scores < 4.00. By week 8, these proportions had increased to 95.92% (47/49) in the UDCA group and 80.85% (38/47) in the placebo group. Logistic regression analysis, adjusted for baseline score, stratification factors, and treatment groups, showed an OR of 1.41 (95% CI, 0.50 to 3.98) at week 4, which was not statistically significant ($P = 0.511$). However, by week 8, the OR had increased to 6.31 (95% CI, 1.24 to 32.21), indicating that the UDCA group had a significantly higher likelihood of improvement than the placebo group ($P = 0.027$) (**Supplementary Table 6**).

Exploratory subgroup analyses

Subgroup analyses based on age, sex, BMI, and liver-disease etiology consistently found greater reductions in ALT levels at weeks 4 and 8 in the UDCA group than in the placebo group across all subgroups (**Supplementary Table 7**). Specifically, the improvement in ALT levels was more pronounced in participants aged < 65 years of age, men, those with a high BMI (30 to < 35 kg/m^2), and those with SLD.

Among the overall study population, 253 out of 262 (95.6%) had SLD as the etiology of CLD. In subgroup analyses for participants with SLD, the changes in ALT at week 4 were −12.54 U/L in the UDCA group and −2.32 U/L in the placebo group, resulting in a difference of −10.22 U/L (95% CI, −16.81 to −3.63; $P = 0.002$). The percent changes were −14.44% in the UDCA group and −1.51% in the placebo group, with a difference of −12.93% (95% CI, −21.97 to −3.89; $P = 0.005$), indicating a significantly greater reduction in the UDCA group than in the placebo group. At week 8, ALT changes were −14.48 U/L in the UDCA group and −6.08 U/L in the placebo group, yielding a difference of −8.40 U/L (95% CI, −15.54 to −1.26; $P = 0.021$). The percent changes were −17.08% in the UDCA group and −6.46% in the placebo group, with a difference of −10.62% (95% CI, −19.71 to −1.54; $P = 0.022$). These findings consistently demonstrate a significantly greater reduction in ALT levels in the UDCA group, showing particularly notable improvements in the SLD subgroup.

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Safety analysis

The safety analysis included all 262 participants who received at least one dose of the investigated drug (UDCA group: n = 132, placebo group: n = 130). The total duration of treatment and the cumulative dose were analyzed, with mean (standard deviation) values of 54.68 (7.96) days and 15,474.81 (2,531.04) mg, respectively. The mean daily dose was 282.93 (22.98) mg/day. Among the 262 participants included in the safety analysis set, 29 (11.07%, 42 events) experienced TEAEs; by treatment group, 15 (11.36%, 21 events) were in the UDCA group and 14 (10.77%, 21 events) were in the placebo group (**Supplementary Table 8**). The difference in the incidence of TEAEs between the two treatment groups was not statistically significant (P = 0.878).

Adverse drug reactions deemed related to the investigated drug were reported in four participants (1.53%, five events). By treatment group, two participants (1.52%, three events) were in the UDCA group, and two (1.54%, two events) were in the placebo group (**Supplementary Table 9**). In the UDCA group, diarrhea (0.76%, one event), dyspepsia (0.76%, one event), and urticaria (0.76%, one event) were reported, while in the placebo group, increased creatinine phosphokinase (0.77%, one event) and decreased weight (0.77%, one event) were reported. The difference in the incidence of adverse drug reactions between the treatment groups was not statistically significant (P = 1.000). Adverse events leading to discontinuation of the investigated drug were reported in two participants in the UDCA group (1.52%, three events); the difference between the treatment groups in the incidence of adverse events leading to discontinuation was not statistically significant (P = 0.498). No serious adverse events or adverse events leading to death were reported.

DISCUSSION

In this clinical trial conducted at 20 domestic study sites, both the FAS and PPS analyses demonstrated a significantly greater reduction in ALT levels in the UDCA group than in the placebo group. In the secondary efficacy analyses, reductions in all efficacy parameters, including ALT normalization rates, were significantly greater in the UDCA group than in the placebo group, except for AST. While AST did not show statistically significant improvement, a decreasing trend was evident in the UDCA group over the study period. Unlike other biochemical markers, AST has lower specificity for liver disease because it is also present in myocardial, kidney, brain, pancreas, lung, and blood cells. Additionally, the average baseline AST levels of participants in this trial were 46–48 U/L, close to the normal range, likely limiting the potential for substantial reductions.

Previous clinical trials evaluating the efficacy of UDCA in improving biochemical markers in patients with CLD have reported mixed results. A large randomized controlled trial (RCT) involving 166 patients found that treatment with 13–15 mg/kg/day of UDCA over 2 years reduced ALT levels to a similar extent as the placebo.[4] Another trial, using a higher dose of 23–28 mg/kg/day, also failed to demonstrate significant biochemical or histological benefits compared with the placebo.[18] By contrast, a RCT involving 185 patients with biopsy-confirmed non-alcoholic steatohepatitis (NASH) observed significant improvements in GGT levels with high-dose UDCA treatment (23–28 mg/kg/day).[9] Similarly, in a separate study involving 126 patients with biopsy-proven NASH there was a significant reduction in ALT levels with high-dose UDCA treatment (28–35 mg/kg/day).[10]

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This clinical trial is the first large-scale RCT to demonstrate the efficacy of a fixed standard dose of UDCA in improving biochemical markers in patients with CLD. While a previous study reported that 300 mg/day of UDCA over 24 weeks achieved an ALT normalization rate of 34.8% and a percent reduction in ALT of −35.9%, it lacked a placebo comparison and involved a relatively small sample size.[6] In our trial, ALT normalization rates of 22.73% and 26.52%, together with percent reductions in ALT of −15.44% and −17.43%, were observed after 4 and 8 weeks of treatment, respectively. These findings imply time-dependent efficacy of UDCA, with the potential for further improvement over longer treatment periods, aligning with the results of previous studies.

In the subgroup analyses, a reduced effect of UDCA compared with placebo appeared to be evident in several subgroups. In the age-stratified analysis, the ALT-lowering effect of UDCA, relative to placebo, was less pronounced in older participants. Among individuals aged ≥ 65 years, the reduction in ALT levels following UDCA treatment was modest, whereas ALT levels in the placebo group tended to increase, possibly reflecting a natural decline in liver function with age. Although differences in trends were observed between the two groups, the small sample size of 30 participants aged ≥ 65 limited the statistical significance, warranting cautious interpretation. In the sex-stratified analysis, the ALT-lowering effect of UDCA seemed less evident in women than in men. While ALT changes and the rates of change from baseline were comparable in men and women in the UDCA group, in the placebo group there was a more pronounced ALT reduction in women than in men. This raises the possibility that non-pharmacological factors, such as lifestyle modifications following study enrollment, may have had a substantial impact on the women. Additionally, subgroup analyses based on BMI and etiology revealed that the ALT-lowering effect of UDCA was particularly pronounced in participants with a relatively high BMI (30 kg/m^2 ≤ BMI < 35 kg/m^2) and in those with SLD as the underlying condition. These findings imply that participants with a high BMI or SLD may represent subgroups in which the benefits of UDCA are maximized, indicating targeted therapeutic potential for such individuals.

In a previous study, treatment with UDCA resulted in a statistically significant improvement in fatigue after 8 weeks compared with the placebo.[17] Similarly, another study reported a statistically significant difference in fatigue improvement between UDCA and placebo groups at 4 weeks post-baseline.[19] Consistent with these findings, the present clinical trial observed a greater reduction in total K-CFQ scores after 8 weeks in the UDCA group than in the placebo group, indicating reduced fatigue. Furthermore, the proportion of participants whose fatigue levels decreased to < 4 points—meeting the definition of fatigue resolution—was higher in the treatment group than in the placebo group, with the difference reaching statistical significance.

In terms of the liver stiffness measurements using the VCTE, no statistically significant differences were observed between the UDCA and placebo groups. However, a previous study involving patients with non-alcoholic fatty liver disease reported a 52-week median change of −0.3 kPa,[20] which is comparable to the −0.3 kPa change observed in the UDCA group in the present trial after 8 weeks. In this study, most participants presented with normal to mild liver stiffness values (< 7 kPa) at baseline, likely contributing to the lack of difference between the UDCA and placebo groups in the proportion of participants showing improvement in liver stiffness. However, the proportion of participants that experienced liver stiffness progression was lower in the UDCA group, implying a tendency to slowed progression with UDCA treatment. The FibroTest results indicated that liver stiffness decreased more in the

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UDCA group than in the placebo group. The median percent change in the UDCA group at 8 weeks was −10.82%, comparable to findings from a previous study involving patients with NASH, in which high-dose UDCA administered over 12 months resulted in median reductions of −18.0% at 6 months and −10.5% at 12 months.[10] The reduction observed in the UDCA group in this study was statistically significant, aligning with the improvements reported in the previous study.

Several potential therapeutic mechanisms of UDCA have been identified in patients with CLD.[21] First, UDCA alleviates intracellular oxidative stress through multiple pathways. In rat liver, UDCA enhances hepatocellular antioxidative processes by activating nuclear factor erythroid 2-related factor 2, a key transcription factor and a crucial sensor for detoxification.[22] Additionally, UDCA increases intracellular glutathione levels, helping to normalize excessive myeloperoxidase activity and reduce reactive oxygen species production in stressed rat liver.[23] UDCA also protects hepatocytes from apoptosis by reducing endoplasmic reticulum stress, improving mitochondrial function, and enhancing several survival signaling pathways.[8,24-27] Moreover, UDCA exhibits immune-modulatory and anti-inflammatory effects in the liver.[8,28] These anti-inflammatory effects may be mediated by the glucocorticoid receptor agonist activity of UDCA, which suppresses inflammatory gene transcription in various intrahepatic cells.[29,30]

Although this study was a large-scale, multicenter RCT, several limitations should be noted. First, the treatment duration of 8 weeks was relatively short to fully evaluate long-term therapeutic outcomes. In particular, for fibrosis assessment, the 8-week treatment is likely insufficient to demonstrate histological changes in liver fibrosis. Although improvements were observed in non-invasive markers such as FibroTest and VCTE, these changes should not be interpreted as definitive evidence of fibrosis regression. Rather, they may represent early favorable signals suggesting the potential of UDCA in modulating fibrotic processes. Nonetheless, the results imply that even short-term administration yielded meaningful effects. Additionally, comparing outcomes at 4 and 8 weeks demonstrated that a longer treatment period led to greater benefits, indicating the potential for additional gains with long-term administration. Second, the use of ALT as a primary endpoint instead of liver biopsy has inherent limitations. ALT alone may not fully capture the complexity of liver injury or predict long-term outcomes. However, liver biopsy is invasive and not feasible for large-scale or short-term trials, and ALT is a non-invasive, widely available, and clinically meaningful marker of hepatocellular injury. It has been consistently associated with liver inflammation and fibrosis in various types of CLD, and its reduction has been correlated with histologic improvement in liver inflammation.[31,32] Accordingly, ALT has been adopted as a surrogate endpoint in recent randomized trials evaluating pharmacologic therapies for MASH.[33-35] Nonetheless, further studies using histological endpoints are needed to validate the therapeutic effect of UDCA. Third, there were notable differences in sample sizes among the subgroups, making it challenging to generalize the findings across all subgroups. Nevertheless, the overall trends across subgroup analyses consistently indicated that UDCA exerted hepatoprotective effects, reinforcing the general direction of the results. Finally, the subgroup analysis by etiology was based on traditional diagnostic categories. In the SLD group, the criteria did not account for cardiometabolic risk factors associated with the recently introduced concept of MASLD. However, because the previously used diagnosis of non-alcoholic fatty liver disease overlaps with MASLD in 99% of cases,[36] the two classifications largely represent the same patient population. Thus, this distinction does not significantly impact the interpretation of the results. While quantitative assessment of hepatic steatosis using controlled attenuation

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parameter (CAP) would have strengthened the analysis, CAP values were not included in the predefined data collection and thus could not be analyzed. Further studies are warranted to evaluate the impact of UDCA on hepatic steatosis.

In conclusion, in patients with CLD, compared with the placebo treatment with 100 mg UDCA three times daily for 8 weeks demonstrated superior therapeutic efficacy, improving biochemical markers and reducing fatigue, with a favorable safety profile.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Chalder Fatigue Scale translated into Korean questionnaire

Supplementary Table 2
IRB information for participating centers

Supplementary Table 3
Overall drug adherence rate to the investigational drugs of the study population

Supplementary Table 4
Proportion of ALT normalization at week 4 and week 8

Supplementary Table 5
Changes in aspartate aminotransferase from baseline at week 4 and week 8

Supplementary Table 6
Proportion of subjects whose fatigue improved from baseline at week 4 and week 8

Supplementary Table 7
Subgroup analysis of changes in ALT at week 4 and week 8

Supplementary Table 8
Incidence of treatment-emergent adverse events

Supplementary Table 9
Incidence of adverse drug reactions

Supplementary Fig. 1
Scheme of study design.

Supplementary Fig. 2

Subject disposition from the screened set.

Supplementary Fig. 3

Changes in ALT levels from baseline to week 8 (per-protocol set). There was a significantly greater reduction in ALT levels in the UDCA group than in the placebo group.

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