Original Article

Efficacy of Ursodeoxycholic Acid in Treatment of Non-responder or Relapser Chronic Hepatitis C or Patients with Contraindication to Standard Treatment

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ABSTRACT

Background: Ursodeoxycholic Acid (UDCA) is a highly hydrophilic bile acid, which dissolves cholesterol and fat in the intestines, and has immune modulating factor. It is an approved drug that may limit liver injury in HCV infection.

Objective: The aim of this study is to evaluate the efficacy of UDCA on serum alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and HCV-RNA level in patients with Chronic Hepatitis C (CHC) who had not responsed or had relapsed to interferon (IFN) monotherapy or IFN or pegylated interferon alpha (PEG IFN-α) plus ribavirin treatment.

Patients and Methods: Eighteen patients who had not responsed or had relapsed to IFN monotherapy or IFN or PEG IFN-α plus ribavirin treatment were randomized to receive UDCA (250 mg, tid) (n = 10) or placebo (n = 8) for 6 months.

Results: At 3-month serum ALT level was significant decrease in the UDCA group as compared with placebo and baseline (p = 0.041 and p = 0.022, respectively). There was no significant changes in the serum ALT, GGT, and HCV-RNA level at the end of the 6-month treatment period in both groups.

Conclusions: We report preliminary results of a trial using UDCA in treatment of non-responder or relapser CHC. UDCA is effective in term of ALT level but not in term of the virologic response and GGT. These results favor the hypothesis that UDCA may have direct cytoprotective effects on the hepatocyte. UDCA may be a possible alternative for patients who do not response or has relapsed after discontinuation of IFN monotherapy or IFN or PEG IFN-α plus ribavirin treatment.

Key words : Chronic hepatitis C, non-responder, relapser, ursodeoxycholic acid, retreatment

[Thai J Gastroenterol 2008; 9(1): 30-34.]

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INTRODUCTION

The prevalent of hepatitis C virus (HCV) infection has been reported around 3% of populations in the world.[1,2] Combination treatment with interferon alpha (IFN-α) plus ribavirin lead to sustain virological response (SVR) in 36-40% of patients. Currently, the treatment in naive chronic hepatitis C (CHC) with pegylated interferon alpha (PEG IFN-α) with ribavirin achieve a SVR approximately 54-63% of patients.[3-6] Retreatment with PEG IFN-α with ribavirin lead to SVR around 20% for non- responder CHC (NR-CHC) patients and 50-60% for relapser CHC (R-CHC) patients after IFN-α plus ribavirin therapy.[7]

Ursodeoxycholic acid (UDCA) is a highly hydrophilic bile acid, which dissolves cholesterol and fat in the intestines, and has immune modulating factors. It is an approved drug that may limit liver injury and the effect of HCV. The studies on efficacy of UDCA plus IFN-α in treatment of NR-CHC patients or resistant to IFN-α have recently been published and improved serum alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and the one study improved SVR (8%).[8,9] In a report UDCA monotherapy showed significant decrease in serum liver enzyme concentration in naïve CHC patients,10 but no study has yet been performed in patients who is NR-CHC or R-CHC.

Aim of our study to evaluated efficacy of UDCA in treatment of patients who is NR-CHC or R-CHC or patients with contraindication to combination treatment with IFN-α or PEG IFN-α plus ribavirin on serum ALT, GGT, and HCV-RNA viral load.

PATIENTS AND METHODS

Patients

Eighteen patients non-responder chronic hepatitis C (NR-CHC) and relapser chronic hepatitis C (R-CHC) or patients with contraindication to combination treatment with IFN-α or PEG IFN-α plus ribavirin were enrolled in this clinical trial.

Inclusion criteria

Age more than 18 years, NR-CHC (patients without end of treatment or resistant to combination treatment with IFN-α or PEG IFN-α plus ribavirin) or R-CHC (patients with returned rising of ALT and positive HCV-PCR after achieve of end of treatment or SVR) or patients with contraindication for IFN-α or PEG IFN-α plus ribavirin therapy and written informed consent form signed by the patient.

Exclusion criteria.

Co-infection with human immunodeficiency seropositivity or hepatitis B infection, pregnancy, recent using of steroid or immunosuppressive or herbal medicine, alcohol consumption more than 20 g/day.

Study design and treatment

This double-blind, placebo-controlled trial was conducted at Phramongkutklao hospital, Bangkok, Thailand. The patients were enrolled in the study between January 2006 and January 2007. Patients were randomly assigned to receive UDCA (Ursolin®, Berlin pharmaceutical, BKK,Thailand) or placebo, at a dose of 750 mg/day, in three divided doses, for 6 months.

Follow-up and laboratory testing

Initial evalution included physical examination and biochemical liver tests: serum bilirubin, serum albumin, serum globulin, serum ALT, aspartate aminotransferase (AST), GGT, and alkaline phosphatase (ALP); fasting blood sugar (FBS), serum creatinine, BUN, complete blood count, cholesterol, triglycerides, HCV-RNA level and genotypes of HCV. Patients were followed up at month 3 and 6. At month 3, serum ALT were measured. At month 6, serum ALT, GGT, and HCV- RNA level were tested. HCV-RNA level were determined by using the Cobas Amplicor HCV Monitor (Roche Diagnostics, Thailand). The Monitor assay has a sensitivity of 600 IU/ml.

Assessment of efficacy

The primary end point was decreased serum ALT activity at the 3- and 6- month. The two secondary end points were decreased serum GGT and HCV-RNA level at the end of the 6-month treatment period.

Statistical analysis

Baseline values were compared using the Mann-Whitney test. Mann-Whitney test was also used to be compare the variation of serum ALT, GGT, and HCV-RNA levels between UDCA treated and placebo treated patients. The Wilcoxon signed ranks test was used to be compare the variation of serum ALT, GGT, and HCV-RNA levels within the same group. To detect such a difference (a = 5% and b = 20%, using a two-sided test), the estimated sample size had to be 36 patients in each group. To take into account probable

losses to follow-up, it was decided to include a total of 80 patients. A p-value less than 0.05 was considered to be significant.

RESULTS

Patient characteristics

At entry the two groups were well balanced for the main characteristics, with the exception of height and serum ALP, which was higher in the UDCA group (p = 0.04 and p = 0.021) (Table 1).

Biochemical and Virological response

At 3-month treatment period ALT activity was significantly decreased in the UDCA group than in the placebo group (p = 0.041); the difference between the two groups was no more significant at 6-month (Table 2) (Figure 1). At 3-month serum ALT level was significantly decreased in the UDCA group (32.38%, p = 0.022) as compared with baseline, but not significantly decreased at the end of the 6-month treatment period (28%, p = 0.059) (Table 3) (Figure 1). No significant changes were seen in placebo group. There was no significant changes in the serum GGT and HCV-RNA level at the end of the 6-month treatment period.

Safety

All treatments were in general well tolerated. No adverse effect was seen in the UDCA and placebo groups.

DISCUSSION

The previous study, it has been reported that

Table 1 Base-line characteristics of the patients

	UDCA group (n = 10)	Placebo group (n = 8)	p-value
Sex (M:F)	3:5	5:5	0.596
Age, median (year) (min.-max.)	47.5 (42-68)	52.5 (49-77)	0.142
Weight (kg)	59.85 (48-75)	60.5 (56-84)	0.722
Height (cm)	165 (156-170)	156 (150-168)	0.04*
Hb (g/dL)	12.35 (11.10-15)	13.65 (10.9-14.9)	0.214
Hct.(%)	38.25 (33.2-44.7)	40.10 (34.2-44.9)	0.374
WBC (/ml)	4,350 (3,100-10,590)	5,800 (4,800-7,500)	0.155
Platelet count (/ml)	94,500 (50,000-301,000)	173,000 (40,000-264,000)	0.477
Albumin (g/dL)	3.75 (3.0-4.60)	3.95 (3.20-4.40)	0.893
Globulin (g/dL)	4.45 (3.50-5.50)	3.95 (3.70-5.10)	0.247
Direct bilirubin	0.30 (0.10-1.20)	0.15 (0.10-0.40)	0.13
Indirect bilirubin	0.70 (0.20-1.20)	0.50 (0.40-1.50)	0.282
AST (U/L)	58 (33-401)	63.50 (21-113)	0.722
ALT (U/L)	64 (34-399)	68.50 (32-178)	0.79
ALP (U/L)	108 (63-173)	67 (55-108)	0.021*
GGT (U/L)	52 (17-172)	42 (20-255)	0.884
FBS (mg/dL)	93 (76-142)	93.5 (84-131)	0.929
BUN (mg/dL)	11.55 (10-17)	12.95 (10-18.9)	0.689
Creatinine (mg/dL)	0.65 (0.20-1.20)	0.75 (0.5-1.0)	0.369
Cholesterol (mg/dL)	147.50 (100-243)	162 (125-200)	0.477
Triglycerides (mg/dL)	86 (41-157)	64.50 (50-122)	0.477
HCV-RNA levels (IU/ml)	661,000 (49,200-3,600,000)	201,500 (1,430-3,050,000)	0.11
Genotype, n (%)			
1	5/10 (50%)	2/8 (25%)	
3	5/10 (50%)	6/8 (75%)	

*significant p <0.05
Values as median (min.-max.)

Table 2 Comparison of laboratory test results in ursodeoxycholic acid (UDCA) and placebo groups

	Baseline	3-month	p-value	6-month	p-value
ALT (U/L)					
UDCA	64 (34-399)	43.5 (29-72)	0.041*	37 (24-78)	0.068
Placebo	68.50 (32-178)	63 (30-165)		78.5 (30-130)	
GGT (U/L)					
UDCA	52 (17-172)	-	-	43.5 (18-381)	0.625
Placebo	42 (20-255)	-	-	48.5 (23-142)	
HCV-RNA level (IU/ml)					
UDCA	661,000 (49,200-3,600,000)	-	-	1,258,500 (12,000-24,600,000)	0.214
Placebo	201,500 (1,430-3,050,000)	-	-	184,000 (45,000-2,870,000)	

*significant p <0.05
Values as median (min.-max.)

Table 3 Comparison of serum ALT levels before and after treatment in ursodeoxycholic acid (UDCA) and placebo groups

	Baseline	3-month	p-value	6-month	p-value
UDCA	64 (34-399)	43.5 (29-72)	0.022*	37 (24-78)	0.059
Placebo	68.5 (32-178)	63 (30-165)	0.624	78.5 (30-130)	0.326

*significant p <0.05
Values as median (min.-max.)

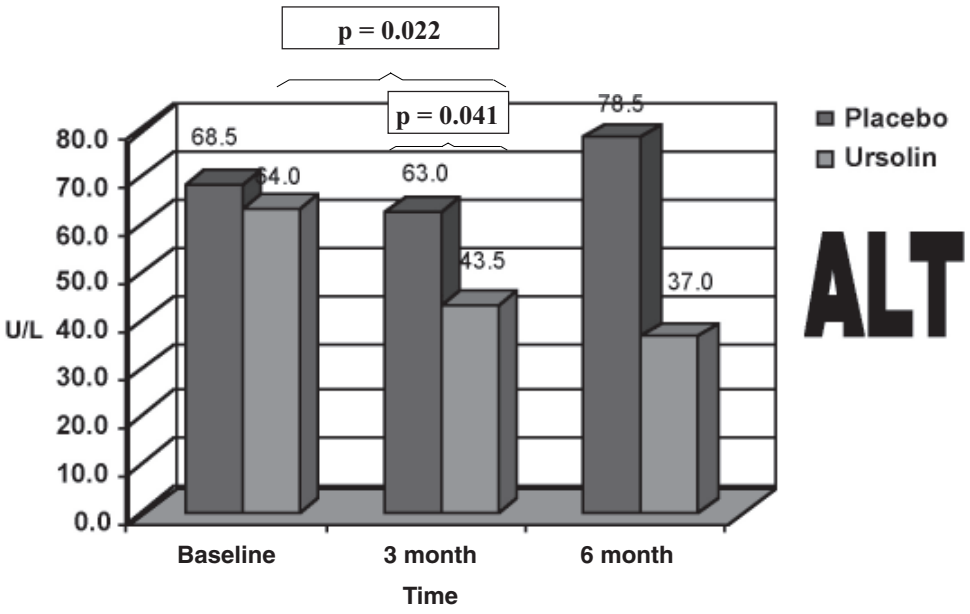

Figure 1 Comparison of serum ALT levels in ursodeoxycholic acid (UDCA) and placebo groups

UDCA might improve serum liver enzyme concentration in CHC patients. The combination of IFN plus UDCA in treatment CHC patients who not response to IFN were significant improved serum ALT activities, but no significant change in viral response.[8,9] The one study, combination of IFN plus UDCA were delay development of biochemical relapse and reduced severity, but no benefit in HCV-RNA clearance.[11] However, no clinical data its use as UDCA alone in treatment of CHC patient who do not response to IFN-α or PEG IFN-α plus ribavirin therapy or relapse after discontinuation of that treatment.

We report preliminary results of a trial designed to confirm the efficacy of UDCA in lowering serum ALT in patients with HCV-related chronic hepatitis. In our study, at the 3-month serum ALT was significant decrease in the UDCA group as compared with the placebo group and baseline (28% and 38%, respectively). The similar trend is observe in previous study that has been reported the significant decrease in serum ALT level (36.7%) after the 6-month treatment with UDCA (450 mg at bedtime) as compared with pretreatment in naïve CHC patients.[10] In our study, at the end of the 6-month treatment period serum ALT was no significant decrease in the UDCA group as compared with the placebo group and baseline ($p = 0.068$ and $p = 0.059$, respectively), but may have trend to significant changes. It is possible that these different results are due to small number of sample size at present report. So, we believe that the change of serum ALT in the UDCA group may be significant decrease when adequate sample size. No significant changes was seen in HCV-RNA level in the both groups, it is confirmed to UDCA no antiviral activity. When followed as hypothesis, UDCA may have direct cytoprotective effects on the hepatocyte.[13,14] Long-term, double-blind studies are needed to evaluate the effects of UDCA on liver histology and the ability of the drug to prevent the progression of HCV-related chronic hepatitis.

In conclusion, UDCA monotherapy may be improved serum ALT and a possible alternative for CHC patients who do not response to standart treatment or relapse after discontinuation of standard treatment.

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