A study of the efficacy of Active Hexose Correlated Compound (AHCC) in the treatment of chronic Hepatitis C patients at Phramongkutklao Hospital

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ABSTRACT:

Background: Hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease, cirrhosis and hepatocellular carcinoma. Current treatment with pegalated interferon and ribavirin can achieve 54 to 61% sustained virological response. Significant number of patients does not respond to the treatment. Reported AHCC biological effects in term of immuno-modulator, anti-tumor properties, and viral suppress in chronic hepatitis C patient, this study needs to explore the effects of AHCC in chronic hepatitis C patients.

Objective: To assess the efficacy and safety of AHCC in the reduction of HCV RNA or Liver Function Test (LFT) in chronic hepatitis C patients

Method: Prospective, randomized, double-blinded placebo-control trial was conducted in 39 chronic hepatitis C patients divided into two study groups (group A - AHCC and group B - placebo). Nineteen patients under AHCC group received AHCC 6 g/ day for 24 weeks while 20 patients received placebo. All patients received HCV RNA levels and liver function tests monitoring. In addition, the reduction of HCV RNA and alanine aminotransferase (ALT) enzyme levels was observed.

Result: There was no demographic difference between 2 groups. However, the significant HCV RNA decline was noted in subgroup analysis of genotype-3 patients (p=0.008). Although the reduction of ALT levels within AHCC group was not significant, the significant difference was found between AHCC and placebo groups (p=0.01). AHCC used as monotherapy in chronic hepatitis C patients seemed to stabilize HCV RNA levels in genotype-3 chronic hepatitis C patients when comparing AHCC to placebo group. In addition, it showed efficacy in control ALT levels in all chronic hepatitis C patients. No serious side effects were found from the treatment.

Conclusion: Based on the result of this study, AHCC showed same significant HCV RNA reduction in only group B but not group A, and it could stabilize ALT levels when comparing to placebo. This may delay the disease progression, providing patients more opportunities to receive any other treatment later on.

Introduction

Hepatitis C virus (HCV) infection is now a worldwide important issue. Three percent of world population or approximate 170 million people throughout the world have infected with this virus[1]. Generally, 2 – 35% of people infected with HCV will finally develop cirrhosis[2] and hepatocellular carcinoma[3]. The treatment for chronic hepatitis C patients involves the use of pegalated interferon together with ribavirin. However, those regimens not only cause many side effects but also are expensive. Most of chronic hepatitis C patients do not respond to the standard treatment, cannot stand the side effects of the medicines, or cannot afford to pay for the medical expenses. AHCC is considered a functional food, retrieving from mycelium, which is a substance from various kinds of mushroom (*Basidio mycesles*). According to a study, AHCC can improve NK Cell macrophage function[4]. It also increases the amount of several cytokines such as γ- interferon, IL-6, and TNF-α

which have anti-tumor properties. In addition, AHCC can reduce the amount of HCV and serum ALT levels which may have an effect on the progression of the disease.[5]

To study the efficacy of AHCC in reducing the HCV RNA levels and improving the liver function tests in chronic hepatitis C patients, we conducted a randomized study comparing AHCC with placebo.

Methods

Selection of patient

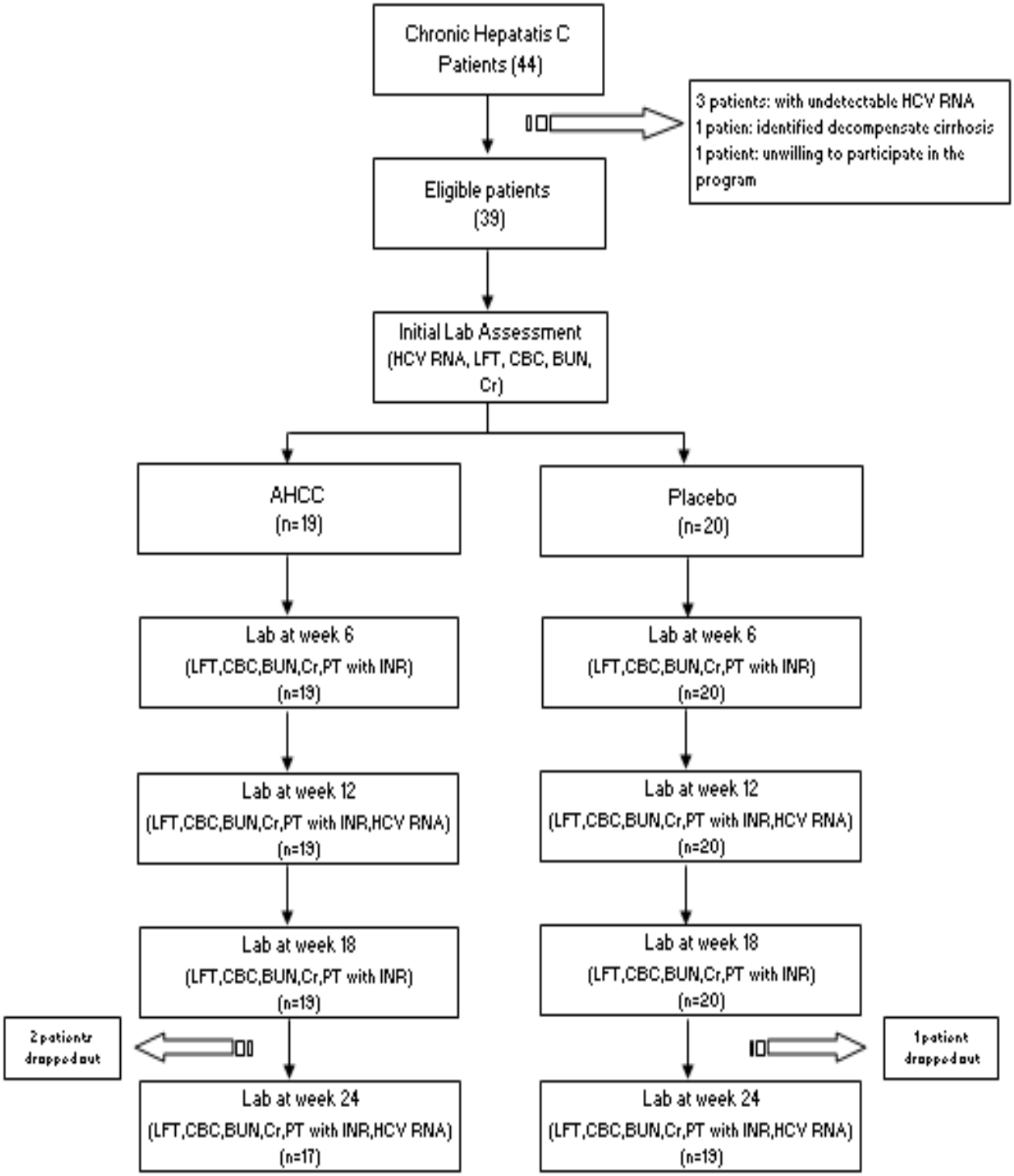
We recruited patients 15 years of age or older who had chronic hepatitis C infection (defined by positive anti-HCV and detectable HCV RNA). Patients with pregnancy, serum creatinine ≥ 1.5 mg/dL, human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co infection, and history of liver decompensation or hepatocellular carcinoma were excluded. Thirty patients fail pegalated interferon and ribavirin and there were 9 naïve patients enrolled in the study. Six out of 9 could not afford the standard treatment costs and 3 out of 9 refused to receive standard treatment.

Study design

This prospective, randomized, double-blinded placebo-controlled trial was conducted at the Liver unit of Phramongkutklao Hospital. Patients were assigned into 2 study groups (A and B), and the treatments providing to both study groups were administrative throughout 24 weeks. Patients received 2 grams of AHCC 3 times a day in group A, and same doses of placebo in group B.

Serum HCV RNA was evaluated with a quantitative HCV RNA assay (cobas amplicor HCV test, limit of detection, 50 IU/mL) in all patients prior to start the treatment at week 0, at study week 12, and week 24. Complete blood count, liver function tests, blood urea nitrogen, creatinine, and prothrombin time were assessed every 6 week from week 0 until the end of program as shown in figure 1.

Figure 1: Summary of Research Method



Statistical Analysis

Statistical analysis was performed by using Stata 10.Descriptive. Statistics indicators such as mean, standard deviation, frequency, and percentage were used to evaluate the baseline characteristics.

Statistical comparisons on categorical variables between study group A and B were performed by using Chi-square test or Fisher's exact test. Continuous variables between group A and B were compared by using student t-test. In addition, Repeated Measure ANOVA was used for comparison of similar group of patients at repeat time interval with the levels of significance at an $\alpha = 0.05$.

Results

The clinical characteristics after randomization and patient demographic data of the two study groups at baseline were similar (Table 1). Initially, 44 patients had been enrolled into the research program during April to July, 2009. After the basic screening, 5 patients were excluded because of undetectable HCV RNA in 3 out of 5 patients, decompensated cirrhosis in 1 patient, and refusing to participate in the program by 1 patient. In summary, 39 patients participated in the research.

Nineteen patients were in AHCC therapy group while the rest of them were in placebo group. Mean age was 52.82 ± 8.88 years, 21 male (53.85%) and 18 female (46.15%) patients. Mean of Body Mass Index (BMI) was 24.79 ± 3.27. In addition, there are 21 genotype-1 patients and 18 genotype-3 patients. At the end of the study, 36 patients (94.8%) fully participated in the program whereas 2 patients from AHCC group and a patient from placebo group were dropped out prior to the target completion date (week 24). At the end of 24-week treatment program, the reduction of HCV RNA was noticed in AHCC group through the decrease of mean of HCV RNA (log 6.37 ± 9.4 to log 6.29 ± 0.9) while no such change was found in placebo study group (log 6.01 ± 0.94 to log 6.01 ± 0.75). However, no statistical significance of HCV RNA reduction was identified from the test ($p = 0.32$).

Table 1: Baseline characteristics of AHCC and placebo groups

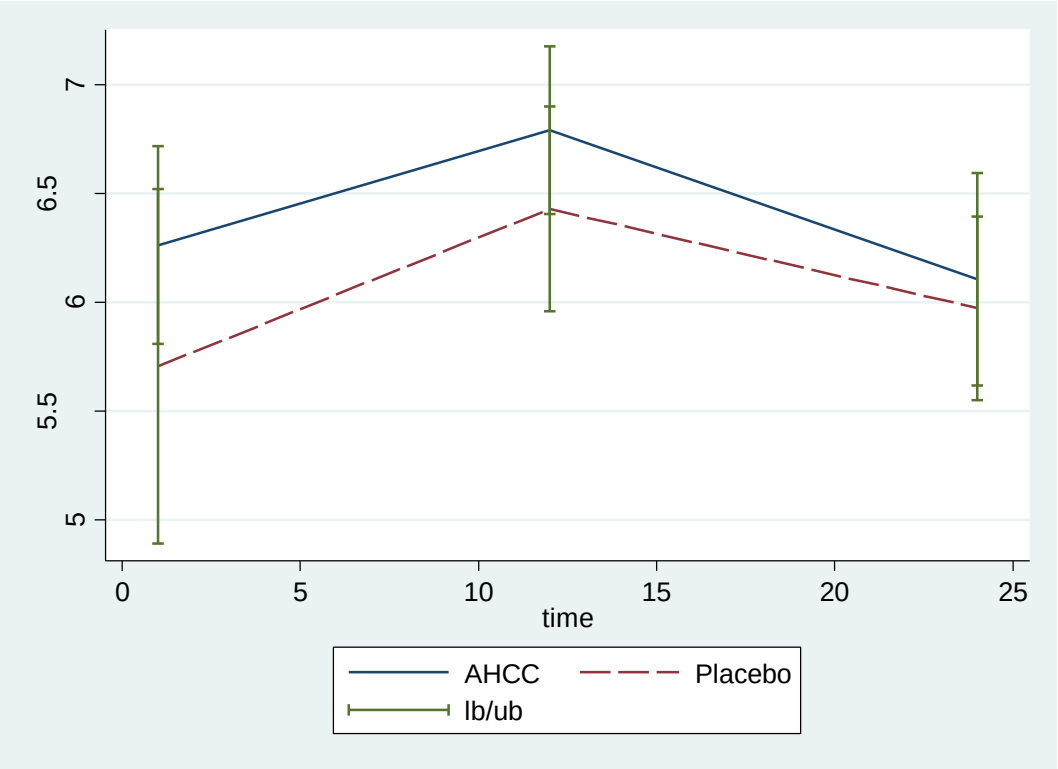
		A		B		Total		p-value
		N	%	N	%	N	%	
sex	male	12	57.14	9	42.86	21	53.85	0.256
	female	7	38.89	11	61.11	18	46.15	
age		53±7.89	51(40-68)	52.65±9.94	52.5(30-72)	52.82±8.88	52(30-72)	0.904
weight		67±12.24	65(50-95)	64.95±9.42	63.5(48-82)	65.95±10.79	65(48-95)	0.56
Hight		163.58±8.39	165(145-178)	162.4±5.07	163.5(152-170)	162.97±6.82	164(145-178)	0.596
BMI		24.91±3.26	24.22(20.31-33.2)	24.63±3.36	5.78(18.37-31.6	24.76±3.27	25.39(18.37-33.2)	0.791
Naïve		2	22.22	7	77.78	9	23.08	0.07
Non-responder		17	56.67	13	43.33	30	76.92	
Genotype	1	10	47.62	11	52.38	21	53.85	0.882
	3	9	50	9	50.00	18	46.15	
HCV RNA		6.37±0.94	6.5(3.37-7.42)	6.01±0.94	6.28(4.1-7.19)	6.19±0.95	6.46(3.37-7.42)	0.249

On the other hands, statistical significance (p=0.008) was noted when performing subgroup analysis on genotype-3 for two study groups. HCV RNA of patient receiving AHCC reduced from log 6.26 ± 0.59 at based line to 6.11 ± 0.58 at the completion date while that of placebo group increased from 5.71 ± 1.06 at based line to 5.97 ± 0.51 at the completion date. However, if focusing on the result of AHCC group only, there was no statistical significance of HCV RNA reduction within 24 weeks (p=0.126) as shown in table 2 and figure 2.

Table 2: Mean (SD) of HCV RNA levels in AHCC group (A) and placebo group (B) classified by HCV genotype.

Genotype			A	B	Total	P-value
1	HCV RNA					0.091
		Baseline	6.46(1.2)	6.27(0.79)	6.36(0.99)	
		12 wks	6.62(1.01)	6.32(0.93)	6.46(0.96)	
		24 wks	6.39(1.13)	6.04(0.92)	6.2(1)	
3	HCV RNA					0.008
		Baseline	6.26(0.59)	5.71(1.06)	5.98(0.88)	
		12 wks	6.79(0.5)	6.43(0.61)	6.61(0.57)	
		24 wks	6.11(0.58)	5.97(0.5)	6.04(0.53)	

Figure 2: Levels of HCV RNA in chronic HCV genotype-3 patients *(solid line (a) for AHCC group, dash line (b) for placebo group)*

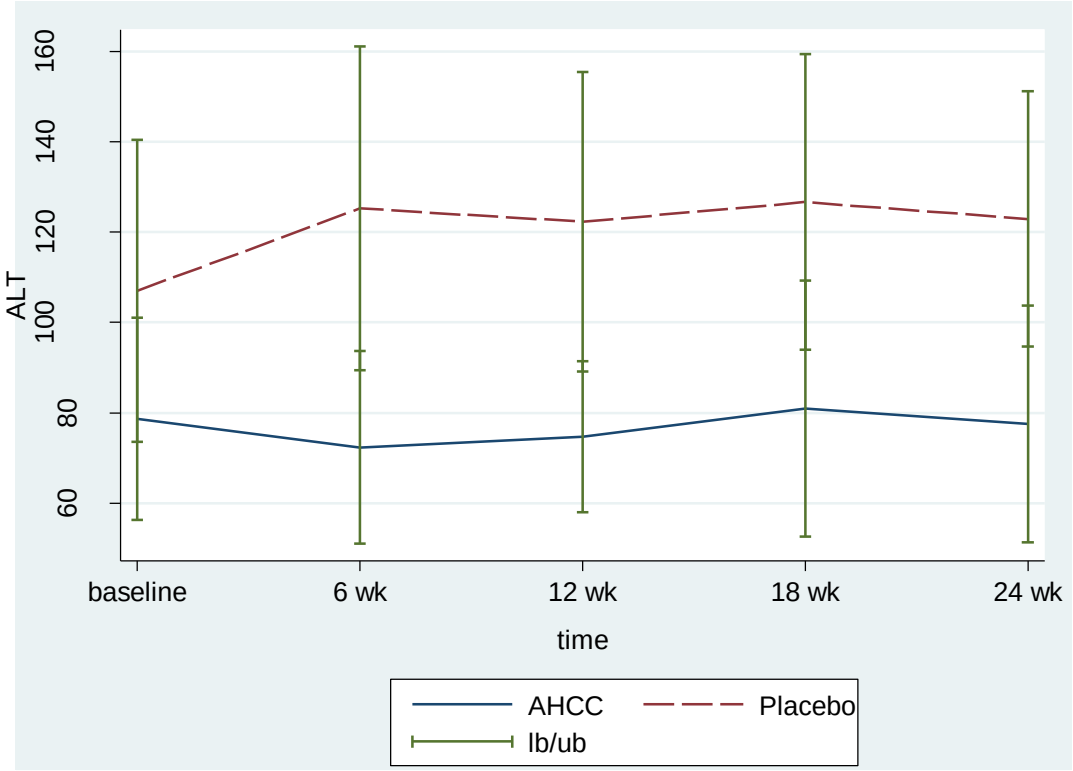


In term of the liver function tests, the differences of ALT levels were found. ALT levels of AHCC study group slightly decreased from 78.63 ± 46.44 at based line to 77.47 ± 50.98 at the end of the treatment while the ALT levels of placebo group increased from 107 ± 71.52 to 122.89 ± 58.61. As a result, statistical significance was identified (p = 0.01). The ALT levels differences had been noticed from the first 6 weeks of the follow up period.

Table 3: Mean (SD) of ALT levels in AHCC group (A) and placebo group (B)

		A		B		Total		p-value
		Mean	SD	Mean	SD	Mean	SD	
ALT								0.01
	Baseline	78.63	46.44	107	71.52	93.18	61.53	0.153
	6 wks	72.32	44.26	125.25	76.56	99.46	67.65	0.012
	12 wks	80.89	57.06	126.65	69.9	104.97	67.39	0.012
	18 wks	74.68	34.6	122.3	70.79	99.1	60.45	0.033
	24 wks	77.47	50.98	122.89	58.61	101.44	59.02	0.019

Figure 3: Levels of ALT in all patients *(solid line for AHCC group, and dash line for placebo group)*



During 24 weeks of data collection period, no severe side effects were found in patients receiving AHCC. Only one patient in AHCC study group had diarrhea in the first two weeks, but the symptom disappeared without any treatment provided.

Discussion

New drugs have been developed under researches and clinical trials for treatment of chronic hepatitis C treatment resulting in 54-61% successful rate of current standard treatment for chronic hepatitis C patients[6,7,8,9]. The important clue of the successful standard treatment would result from the correlation of complex interaction between host-virus-drug. For instance, ribavirin was used as a combination in the treatment program even though it might not be effective in the mono therapy[10]. Since some reports related to the efficacy of AHCC in the reduction of HCV RNA and ALT levels in chronic hepatitis C patients were published, this study was designed and developed.

Although no significant reduction of HCV RNA levels was noticed in patients under AHCC group comparing to those of placebo group, subgroup analysis of genotype-3 patients illustrated the significant differences between those two study groups. Within the AHCC group itself, the decrease in HCV RNA levels was not obviously identified whereas the HCV RNA levels of patients under placebo group significantly increased with the maximum value at 1.63 log.

Similar to the result of the reduction of HCV RNA levels, there was a significant difference on ALT levels between those two groups. However, the ALT levels were stable for AHCC group while ALT levels increased in placebo group, and such difference was initially noted within the first six weeks of the study. The increase of ALT levels would not have a correlation to HCV RNA levels. There might be other mechanisms of AHCC functioning to reduce the liver inflammation in chronic

hepatitis C patients which is still unknown. Based on several reports, such ALT difference would benefit chronic hepatitis C patients. There were a few studies reported that patients with normal ALT levels would have less progression of disease and fibrosis development than those with high ALT levels.[11,12]

Based on the result of this study, although no significant reduction of HCV RNA and ALT levels was identified after treatment with AHCC, the difference of HCV RNA levels of genotype-3 patients and ALT levels of all patients was found. This may serve as preliminary indicator to use AHCC as an alternative treatment for chronic hepatitis C patients not responding to current standard treatment when those patients are waiting for new drugs under researches. Longer duration or higher doses of the AHCC treatment should be taken in the consideration to confirm whether they will have significant impact on chronic hepatitis C patients this might support AHCC to be added in the standard treatment.

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