

A Randomized Trial of Chinese Herbal Medicines for the Treatment of Symptomatic Hepatitis C

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Background: Many patients with the hepatitis C virus (HCV) cannot be successfully treated with interferon-based regimens. Chinese herbal medicines have been widely prescribed for HCV in Asia, and many infected patients in the United States have used these agents. However, data to support the efficacy of these medications are limited and, to our knowledge, no published trials have been conducted in a US population.

Methods: In a double-blinded design, 45 patients with HCV and fatigue were randomized to receive a combination of Chinese herbal medications or a matched placebo for 12 weeks. The main outcome measures were changes in health-related quality of life using the role physical and vitality scale scores from the validated Hepatitis Quality of Life Questionnaire and alanine aminotransferase levels. In addition, other Hepatitis Quality of

Life Questionnaire variables, HCV load, and adverse effects were monitored.

Results: In patients with HCV, the herbal medications had no effect on any quality-of-life variables, as measured by the Hepatitis Quality of Life Questionnaire. In addition, no significant changes in alanine aminotransferase or serum HCV RNA levels were noted. No significant adverse effects were observed.

Conclusions: In this study, a regimen of Chinese herbal medicines did not improve quality of life, liver chemistry results, or viral load in a cohort of patients with HCV. Patients and practitioners should remain cautious about the use of herbal medicines for HCV, because studies have not shown a clear benefit of these agents.

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CHRONIC HEPATITIS C VIRUS (HCV) infection has become the most frequent cause of cirrhosis and hepatocellular carcinoma in the United States and western Europe.^{1,2} The prevalence of HCV is estimated to be 1.8% in the United States, with significantly higher rates in some demographic groups.³ Although the incidence of new infections is declining, estimates suggest that the number of patients with HCV-related cirrhosis and cancer will increase during the next decade.¹ Therapy of HCV involves the use of injectable interferon along with oral ribavirin, which will eradicate the infection in approximately 50% of treated patients.⁴ However, interferon-ribavirin therapy can have significant adverse effects that limit its use in some patients, particularly those with hematologic, renal, cardiac, or psychiatric disease.⁵ Thus, many HCV carriers will either fail to clear the virus or be intolerant of available therapy.

In addition to symptoms of advanced liver disease, which occur in a minority of

patients with HCV,⁶ several reports⁷⁻⁹ have found a high prevalence of fatigue and other nonspecific symptoms. As a group, patients with HCV demonstrate a lower health-related quality of life compared with either healthy patients or patients with other forms of liver disease.¹⁰⁻¹³ Aside from viral eradication using interferon-based therapy, data on treatments for reducing fatigue and enhancing quality of life in HCV patients are lacking.

The absence of reliably effective therapy for HCV, coupled with the popularity of complementary and alternative medicine (CAM), has led to increased use of botanical compounds to treat this condition.^{14,15} Because of the unregulated availability of these agents, there are no accurate data about their use among HCV patients in this country. Furthermore, data regarding the efficacy of these agents are sparse. Although a few studies¹⁶ from the Asia Pacific region suggest a possible benefit of traditional Chinese medicine compounds, to our knowledge, no controlled trials have been performed in a US popu-

lation. We, therefore, performed a short-term pilot study to examine the efficacy and safety of a combination of Chinese herbal medicines in patients with HCV and fatigue. Our results suggest no therapeutic benefit of these agents in regard to standard measures of virologic response or health-related quality of life.

METHODS

DESIGN

This was a prospective, randomized, double-blinded, placebo-controlled pilot study of a fixed combination of Chinese herbal medicines in patients with HCV and fatigue. The study was conducted at a single center. The Institutional Review Board at Hennepin County Medical Center approved the protocol and informed consent process. The Food and Drug Administration Investigational New Drug application process was completed before beginning the administration of the herbal agents.

PARTICIPANTS

Individuals with confirmed HCV who were aged 18 to 70 years were considered eligible for the study. All participants had been previously examined for HCV by their physicians and had been offered referral to specialists for interferon therapy. Participants were recruited through clinics and local advertising. After a telephone interview to assess eligibility, potential participants were asked to schedule an intake visit. During the intake visit, eligibility was established and written consent was obtained. Inclusion criteria were confirmed HCV (with detectable serum HCV RNA), an elevated alanine aminotransferase (ALT) level (≥ 57 and ≤ 350 U/L) within 6 months of enrollment, and fatigue with a perceived lower quality of life. Participants with other forms of liver disease, recent antiviral treatment (within 3 months of screening), or current alcohol consumption greater than 2 standard drinks daily (42 g [1.5 oz], 80 proof; 336 g [12 oz], 5% beer; or 140 g [5 oz], 12%-17% wine) were excluded. Forty-five eligible participants consented, and were randomized into 2 treatment arms by random number assignment and stratified by sex.

TREATMENT REGIMEN

Before initiating the study, participants stopped using all other herbs and dietary supplements for 3 weeks. Participants randomized to active treatment received a fixed combination of 10 traditional Chinese medicinal herbs, 10 g/d, that contained the following components: *Radix astragali* (6%), *Radix acanthopanax* (8%), *Radix buplei* (8%), *Radix et tuber curcumae* (10%), *Rhizoma polygonum* (10%), *Radix glycyrrhiza* (4%), *Radix isatis* (14%), *Radix paeoniae rubra* (14%), *Radix salviae* (14%), and *Herba taraxaci* (12%). Participants in the control arm consumed an equivalent amount of a similar-appearing and similar-tasting placebo. The treatment and placebo remedies were administered orally in the form of 7 tablets 2 times a day for 12 weeks. Kaiser Pharmaceuticals Company Products, Inc, Tainan, Taiwan, performed high-performance liquid chromatography of each component and the final mixture to ensure appropriate levels of constituent ingredients. Formulation Technology, Oakdale, Calif, a Food and Drug Administration-approved facility, made the herbal compound and the placebo into a tablet. All study personnel were blinded with regard to treatment assignment. The study nurse (S.M.C.) distributed bottles of medication pre-labeled with participant identification numbers by the study coordinator (T.A.B.); the study coordinator was also responsible for randomization and had no patient contact.

FOLLOW-UP AND SURVEILLANCE

After the intake visit, participants were seen by a nurse (S.M.C.) or physician (M.J.) on the day of treatment initiation (week 0), at weeks 2, 4, 8, and 12 during treatment, and at weeks 16 and 20 posttreatment. At each visit, participants were asked about tolerance and potential adverse effects, and a blood test was performed to obtain liver chemistry results, electrolyte levels, and renal function results. Blood cell counts were obtained at weeks 4 and 12 and at 8 weeks posttreatment. The prothrombin time was determined at intake and at week 8. Each participant underwent electrocardiography at intake, week 8, and 8 weeks posttreatment. Compliance was assessed by pill counts at weeks 4, 8, and 12. Participants were considered compliant if they consumed an average of 7 g/d (9.8 pills per day). Clinic physicians (M.J. and J.H.A.) reviewed participant records throughout the study. The modified World Health Organization guidelines were used in assessing abnormal laboratory results (for sodium, potassium, total carbon dioxide, glucose, urea nitrogen, creatinine, calcium, total protein, albumin, aspartate, ALT, bilirubin, and alkaline phosphatase levels),¹⁷ and participants experiencing events of grade 3 or 4 discontinued the treatment. In addition, participants discontinued the treatment if their ALT levels exceeded 350 U/L.

OUTCOME MEASURE

The principal quantitative measures in this study were Hepatitis Quality of Life Questionnaire (HQLQ) scores and ALT levels. Additional measures included HCV polymerase chain reaction and genotyping results. The HCV load was measured with a polymerase chain reaction ultraquantitative method using a commercially available kit (COBAS AMPLICOR HCV MONITOR Test, v2.0; Roche Diagnostics Corporation, Indianapolis, Ind). Viral genotypes were determined by molecular sequencing using the same kit.

Participant symptoms were measured using the standardized HQLQ. The HQLQ, based on the 36-Item Short-Form Health Survey, is a 69-item, validated, self-administered questionnaire consisting of 10 multi-item scales that measure generic functioning, well-being, and disease-specific health outcomes in participants with chronic HCV (Quality-Metric, Inc, Lincoln, RI).¹⁸ A higher score correlates with improved function or quality of life. This instrument has been used by several groups^{12,13,18} to evaluate quality of life in patients with HCV. The HQLQ was administered at weeks 0, 4, 8, and 12 and at 8 weeks posttreatment.

ANALYSIS

The primary end points in this study were as follows: (1) the HQLQ role physical and vitality scale scores at 8 weeks compared with baseline (week 0) and (2) the ALT levels at 12 weeks compared with baseline. To estimate sample size, we assumed a treatment effect δ of 25 in role physical scores and 18 in vitality scores between the placebo and herbal medicine groups, based on the response seen in previous studies¹⁰ of successful HCV treatment with interferon. Powered at 0.8 ($\beta = .2$) with a .05 α level, the calculation indicated a total sample size of 40. The secondary end points of the study were physical and mental component summary scale scores from the HQLQ at 8 weeks compared with baseline, role physical and vitality scale scores at 4 and 12 weeks compared with baseline, ALT level at 4 and 8 weeks compared with baseline, and polymerase chain reaction RNA viral load at 12 weeks compared with baseline (intake). The categorical HQLQ variables and the continuous variables of ALT level and polymerase chain reaction RNA viral load were analyzed using *t* tests and a repeated-measures analysis of vari-

Table 1. Patient Characteristics at Baseline*

Characteristic	Active Treatment Group (n = 23)	Placebo Group (n = 22)	P Value
Sex			
Female	7 (30)	7 (32)	.92
Male	16 (70)	15 (68)	
Ethnicity			
White	21 (91)	20 (91)	.96
Black	1 (4)	1 (5)	
Native American	1 (4)	0	
Other	0	1 (5)	
Genotype 1			
Yes	16 (70)	17 (77)	.56
No	7 (30)	5 (23)	
Age, y†	49.4 (±8.2)	47.8 (±8.1)	.51
ALT level, U/L†	139.4 (±73.5)	122.0 (±57.7)	.39
Viral load by quantitative PCR, log ₁₀ †	6.01 (±0.3)	6.04 (±0.3)	.81

Abbreviations: ALT, alanine aminotransferase; PCR, polymerase chain reaction.

*Data are given as number (percentage) of each group unless otherwise indicated. Percentages may not total 100 because of rounding.

†Data are given as mean (±SD).

ance. Data analysis was conducted after all the participants completed the study. All analyses were conducted using the principle of intention to treat; all participants randomized were included in the final analysis. Analysis was conducted using a commercially available software program (SPSS for Windows, version 6.0.1; SPSS Inc, Chicago, Ill). To normalize the data for statistical analysis and to simplify reporting of the viral load, the results were run as a log transformation and then geometric means were calculated.

RESULTS

PARTICIPANT CHARACTERISTICS

Of the 427 participants screened for this study, 82 met the initial eligibility criteria, and 45 of these consented and underwent randomization. Reasons for exclusion from the study included lack of HCV symptoms, such as an elevated ALT level and fatigue, and participation in other hepatitis-related clinical trials (eg, pegylated interferon). Of the 45 participants randomized, 37 completed week 12 of the study. Thirty-one participants finished both post-treatment follow-up visits. Of the 31 participants who completed the exit interview, 21 (68%) incorrectly guessed their treatment arm. Baseline participant characteristics are shown in **Table 1**.

TREATMENT EFFECTS ON LIVER TEST RESULTS

Initial mean±SE ALT values were 139.4±73.5 U/L and 122.0±57.7 U/L in the herbal medicine and placebo groups, respectively ($P=.39$). The ALT values did not significantly change during the 12-week course of the treatment, and were not different at any time between the 2 groups (**Figure 1**). The HCV load was also unchanged after 12 weeks of therapy. No significant changes were noted in other liver enzyme test results, prothrombin time, cell counts, or renal function during the study (data not shown).

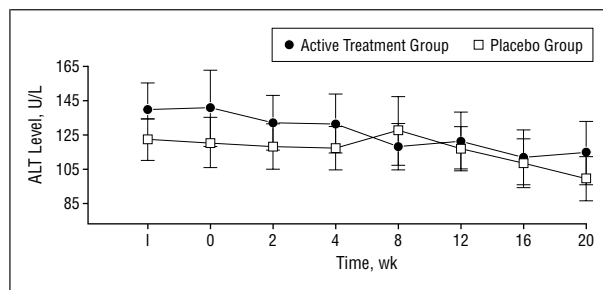


Figure 1. Mean±SE alanine aminotransferase (ALT) levels in participants treated with herbal therapy or placebo. 1 indicates initial level.

TREATMENT EFFECTS ON HQLQ SCORES

No significant differences in HQLQ scores were observed from baseline in either group (**Figure 2**). At no point did HQLQ scores improve for any single scale compared with baseline, and no differences between the placebo and treatment groups were observed. A further analysis was performed using sex as a covariate, and again no significant differences were noted.

ADVERSE EVENTS

The study nurse monitored adverse effects at each visit under the supervision of the clinic physician. The modified World Health Organization guidelines were used to evaluate adverse events.¹⁷ A self-report symptom questionnaire was administered at every visit. Although most participants did have some adverse events (19 [86%] of the 22 participants in the placebo group vs 19 [83%] of the 23 participants in the active treatment group; $P>.99$), the overall incidence of adverse events was not significantly different (29 in the placebo group vs 27 in the active treatment group; $P=.42$) between the 2 groups (**Table 2**), and events were typically mild. This was in part because of stringent criteria used to define adverse events. Gastrointestinal complaints, such as gas, bloating, and loose stools, occurred slightly more often in the treatment group, and sleep-related events, such as increased fatigue and insomnia, occurred more frequently in the placebo group. With the exception of the mild gastrointestinal complaints, the evidence does not suggest that the adverse events reported were related to the treatment regimen. Clinical reports¹⁹ suggest that mild gastrointestinal events are often attributed to the consumption of botanicals.

During the study, 3 participants discontinued because their ALT levels were elevated above 350 U/L. However, spontaneous flares of transaminase elevations are frequently observed in patients with HCV, and a review of the patients did not suggest a hepatotoxic reaction to the herbal agents (**Table 3**). The participant with the highest ALT elevation during treatment was receiving placebo. In the other 2 participants, a substantial increase in ALT level was noted between the intake visit and treatment initiation, suggesting that these participants may have experienced spontaneous flares of inflammatory activity. Of the 5 participants who voluntarily withdrew during the study, 2 stated that adverse events had influenced the decision; both participants were in the placebo group. Of the other 3 participants, one cited personal problems unrelated to the study,

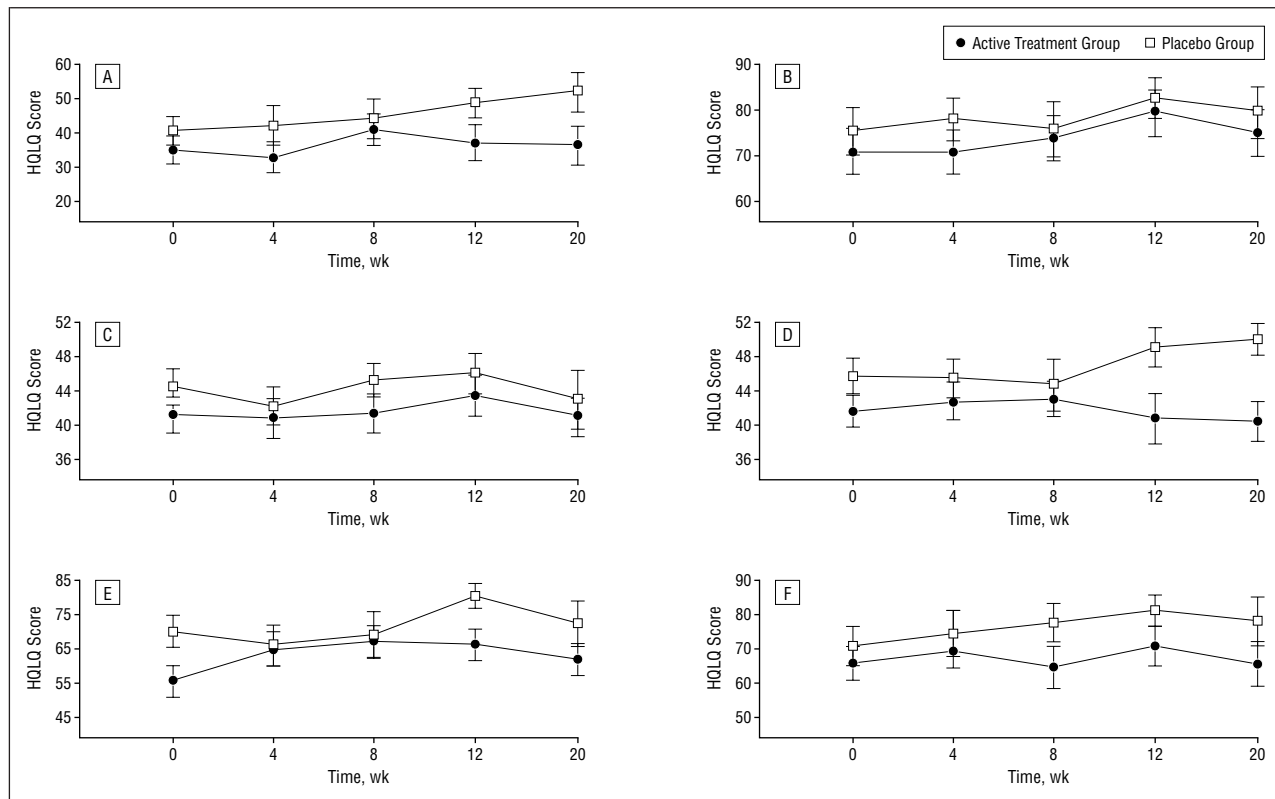


Figure 2. Mean \pm SE changes in select Hepatitis Quality of Life Questionnaire (HQLQ) component scores in participants treated with herbal therapy or placebo. All HQLQ scores are on a 0 to 100 scale, with 100 representing the best possible outcome. A, Vitality. B, Physical functioning. C, Physical summary. D, Mental summary. E, Health distress. F, Health limitations.

Table 2. Total Adverse Events in the 2 Groups*

Type of AE	Placebo Group (n = 22)	Active Treatment Group (n = 23)	P Value
GI†	4 (18)	7 (30)	.32
Hepatic‡	1 (5)	2 (9)	.61
Musculoskeletal§	5 (23)	6 (26)	.74
ENT	4 (18)	4 (17)	>.99
Sleep¶	6 (27)	1 (4)	.10
Other#	9 (41)	7 (30)	.77

Abbreviations: AE, adverse event; ENT, ears, nose, throat; GI, gastrointestinal.

*Data are given as number (percentage) of each group. Some subjects had more than 1 AE.

†Complaints such as abdominal bloating, loose stools, and nausea.

‡Hepatic-related events; all 3 events were related to elevated alanine aminotransferase levels.

§Complaints such as joint, back, neck, and knee pain.

||Complaints including respiratory tract infections.

¶Sleep-related events, such as increased fatigue or insomnia.

#The only events in this category with occurrences greater than 1 were headaches (placebo group, 4; and active treatment group, 1) and depression (placebo group, 2; and active treatment group, 0). Events of moderate severity included a low complete blood cell count (placebo group) and abnormal sinus bradycardia (active treatment group), both in subjects with histories.

another decided to begin treatment with interferon, and the third did not provide an explanation. In summary, aside from mild gastrointestinal symptoms, no significant adverse effects of the herbal treatment were observed.

COMPLIANCE

At weeks 4, 8, and 12, the number of patients who were compliant with therapy were 39 (86.7%), 37 (82.2%), and 31 (68.9%), respectively. There were no significant dif-

ferences in either overall or degree of compliance between the active treatment group and placebo.

COMMENT

The HCV epidemic has resulted in a significant disease burden in the United States, and has had a substantial impact on mortality, morbidity, quality of life, and health care costs.^{1,6} Although the success of interferon-based therapy has improved markedly since its introduction in

Table 3. Details of 3 Patients Who Discontinued the Study Because of Elevated Alanine Aminotransferase (ALT) Values

Patient	Group	ALT Level, U/L					
		Intake	Week 0	Week 2	Week 4	Week 8	Week 12
1	Active treatment	203	478*†	257	‡	‡	‡
2	Active treatment	170	279	279	384†	222	168
3	Placebo	100	105	91	127	413†	375

*Before starting medication.

†Medication was discontinued at this point because the ALT level was greater than 350 U/L.

‡This patient declined further laboratory testing.

the early 1990s, viral eradication cannot be achieved in many patients.⁴ Furthermore, these medications are costly, labor intensive, and prone to causing adverse effects.⁵ The development of additional safe, inexpensive, and effective therapies for HCV is, therefore, an important goal. The absence of fully acceptable therapy has led an unknown, but presumably large, number of patients to partake in CAM modalities, although data regarding safety and efficacy are largely lacking. To our knowledge, no studies have tested CAM therapies for HCV in a US population. Furthermore, to our knowledge, no prior reports have examined the effect of herbal medications on quality of life in the setting of HCV. In this study, we examined a combination of Chinese herbal medicines that have been used in Asia for the treatment of HCV. The results indicated no measurable benefit, and suggest that further investigation of herbal regimens is required before practitioners can recommend their use in HCV patients.

Studies²⁰ indicate that 40% or more of adults engage in some form of CAM therapy, generally without the supervision of a health care provider. Several CAM compounds have been shown to be effective in well-designed, randomized, controlled trials.^{21,22} However, for the most part, claims of efficacy or safety of botanical regimens have not been substantiated in rigorous clinical studies. This is because of several factors, including practice and education styles based on established traditions and experience, rather than a strictly evidence-based approach.^{21,23} In addition, CAM practitioners often use combinations of compounds that are frequently adjusted based on symptoms and findings, which is difficult to accommodate in the setting of a blinded and randomized trial. The lack of data supporting the use of CAM agents for chronic liver diseases has raised some concerns in the hepatologic literature.¹⁴ Given the widespread use of these agents, systematic trials in this patient population are warranted.¹⁶

In the present study, we used a combination of Chinese herbal medicines that have been used extensively for the treatment of chronic hepatitis in Asia.^{16,24} The precise formulation was based on a review of the CAM literature and the Chinese training of one of us (U.B.). The regimen in this study was similar to that used in an Australian trial,²⁴ which reported improved ALT levels in treated patients. In addition, several ingredients in the current regimen are used in popular Japanese regimens, including Sho-saiko-to (TJ-9).¹⁶ In Japan, herbal medications are prescribed frequently by physicians for HCV, particularly in patients who cannot be adequately treated with interferons.²⁵ Studies²⁶⁻²⁹ involving Sho-saiko-to have

suggested improved ALT levels and potential immunomodulatory, antifibrotic, or anticarcinogenic effects. However, a clear consensus regarding the efficacy of herbal agents in HCV patients has not emerged from the available literature.¹⁶

Studies³⁰ from Japan and Europe have suggested a possible beneficial effect of intravenous glycyrrhizin therapy in HCV patients. Several trials^{31,32} have shown a significant decrease in ALT levels, but this benefit diminished after treatment was discontinued and no effect on HCV viral replication was observed. Glycyrrhizin may have antifibrotic effects, although, to our knowledge, these have not been documented in a prospective clinical trial.³¹ A study³³ from Japan suggested that long-term intravenous glycyrrhizin therapy may diminish the risk of hepatocellular carcinoma in the setting of HCV. Each of these studies used intravenous administration, which presents logistical difficulties for some patients. In addition, at these higher doses, glycyrrhizin may have aldosteronelike effects, including sodium retention and edema.³² In the present study, we used a lower dose of glycyrrhizin in the oral formulation, and did not see a significant effect on ALT levels. However, glycyrrhizin seems to mediate intracellular pathways that control the inflammatory response and, therefore, further study of this agent may be warranted.³⁰

Numerous herbal agents have been reported to cause hepatotoxicity.³⁴ The compounds used in these studies were chosen in part because of the presumed lack of hepatic adverse effects.^{19,35} The protocol used World Health Organization criteria for hepatic adverse effects and, in addition, patients with an ALT level higher than 350 U/L were withdrawn from the study. However, marked ALT fluctuations are commonly seen in HCV patients. In both patients who were withdrawn from the herbal arm of this study, ALT elevations occurred between the screening visit and the first dosing, indicating that these were spontaneous flares of inflammatory activity. The patient with the highest ALT level during treatment received placebo. Therefore, this study does not suggest any significant hepatotoxicity of the herbal formulation. However, because hepatotoxicity from pharmaceutical or herbal agents often occurs in a sporadic and idiosyncratic manner,^{14,34} providers should remain vigilant for potential adverse effects of these and other CAM therapies for HCV.

The limitations of this study included the use of a fixed dosing regimen that is inconsistent with some traditional CAM practices.^{21,23} Furthermore, the components and doses used in this formulation differ from pre-

vious reports of HCV treatment, and the current results cannot be generalized to other herbal regimens. In addition, the individuals enrolled in this study were predominantly middle-aged white men and, thus, may not fully represent all groups of HCV patients. Finally, the small sample size in this pilot study could have only detected a large treatment effect and the stringent inclusion and exclusion criteria could have excluded patients who might have benefited from the therapy.

In summary, the present study found no significant effect of the herbal regimen in regard to quality of life, liver enzyme levels, or viral load in patients with chronic HCV. Given the widespread use of medicinal herbs among patients with HCV, and reports of benefits and adverse effects of these agents in those with liver diseases, further study is warranted. It is possible that future trials will show that herbal agents are reasonable therapeutic options for patients with HCV who are refractory to interferon-based regimens. However, given the available data,¹⁶ patients and practitioners should remain cautious about the use of herbal medications in HCV patients.

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REFERENCES

- Kim WR, Brown RS Jr, Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. *Hepatology*. 2002;36:227-242.
- Rakela J, Vargas HE. Hepatitis C: magnitude of the problem. *Liver Transpl*. 2002; 8(suppl 1):S3-S6.
- Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med*. 1999;341:556-562.
- Di Bisceglie AM, Hoofnagle JH. Optimal therapy of hepatitis C. *Hepatology*. 2002; 36(suppl 1):S121-S127.
- Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology*. 2002;36(suppl 1):S237-S244.
- Seeff LB. Natural history of chronic hepatitis C. *Hepatology*. 2002;36(suppl 1): S35-S46.
- Poynard T, Ratziu V, Benhamou Y, Opolon P, Cacoub P, Bedossa P. Natural history of HCV infection. *Baillieres Best Pract Res Clin Gastroenterol*. 2000;14:211-228.
- Poynard T, Cacoub P, Ratziu V, et al. Fatigue in patients with chronic hepatitis C. *J Viral Hepat*. 2002;9:295-303.
- Forton DM, Allsop JM, Main J, Foster GR, Thomas HC, Taylor-Robinson SD. Evidence for a cerebral effect of the hepatitis C virus. *Lancet*. 2001;358:38-39.
- Bonkovsky HL, Woolley JM, the Consensus Interferon Study Group. Reduction of health-related quality of life in chronic hepatitis C and improvement with interferon therapy. *Hepatology*. 1999;29:264-270.
- Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology*. 1998; 27:209-212.
- Ware JE Jr, Bayliss MS, Mannocchia M, Davis GL, the Interventional Therapy Group. Health-related quality of life in chronic hepatitis C: impact of disease and treatment response. *Hepatology*. 1999;30:550-555.
- Neary MP, Cort S, Bayliss MS, Ware JE Jr. Sustained virologic response is associated with improved health-related quality of life in relapsed chronic hepatitis C patients. *Semin Liver Dis*. 1999;19:77-85.
- Seeff LB, Lindsay KL, Bacon BR, Kresina TF, Hoofnagle JH. Complementary and alternative medicine in chronic liver disease. *Hepatology*. 2001;34:595-603.
- Strader DB, Bacon BR, Lindsay KL, et al. Use of complementary and alternative medicine in patients with liver disease. *Am J Gastroenterol*. 2002;97:2391-2397.
- Liu JP, Manheimer E, Tsutani K, Gluud C. Medicinal herbs for hepatitis C virus infection. *Cochrane Database Syst Rev*. 2001;(4):CD003183.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer*. 1981;47:207-214.
- Bayliss MS, Gandek B, Bungay KM, Sugano D, Hsu MA, Ware JE Jr. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. *Qual Life Res*. 1998;7:39-55.
- PDR for Herbal Medicines*. 1st ed. Montvale, NJ: Medical Economics Co Inc; 1998.
- Elder NC, Gillcrist A, Minz R. Use of alternative health care by family practice patients. *Arch Fam Med*. 1997;6:181-184.
- Vickers A, Zollman C. ABC of complementary medicine: herbal medicine. *BMJ*. 1999;319:1050-1053.
- Bensoussan A, Talley NJ, Hing M, Menzies R, Guo A, Ngu M. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. *JAMA*. 1998;280:1585-1589.
- Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava [published erratum appears in *Ann Intern Med*. 2003;138:79]. *Ann Intern Med*. 2002;136:42-53.
- Batey RG, Bensoussan A, Fan YY, Bollipo S, Hossain MA. Preliminary report of a randomized, double-blind placebo-controlled trial of a Chinese herbal medicine preparation CH-100 in the treatment of chronic hepatitis C. *J Gastroenterol Hepatol*. 1998;13:244-247.
- Kasahara A. Treatment strategies for chronic hepatitis C virus infection. *J Gastroenterol*. 2000;35:411-423.
- Shimizu I, Ma YR, Mizobuchi Y, et al. Effects of Sho-saiko-to, a Japanese herbal medicine, on hepatic fibrosis in rats. *Hepatology*. 1999;29:149-160.
- Oka H, Yamamoto S, Kuroki T, et al. Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). *Cancer*. 1995;76:743-749.
- Yamashiki M, Nishimura A, Suzuki H, Sakaguchi S, Kosaka Y. Effects of the Japanese herbal medicine "Sho-saiko-to" (TJ-9) on in vitro interleukin-10 production by peripheral blood mononuclear cells of patients with chronic hepatitis C. *Hepatology*. 1997;25:1390-1397.
- Okita K, Sakaide I, Hino K. Current strategies for chemoprevention of hepatocellular carcinoma. *Oncology*. 2002;62:24-28.
- van Rossum TG, Vulto AG, de Man RA, Brouwer JT, Schalm SW. Review article: glycyrrhizin as a potential treatment for chronic hepatitis C. *Aliment Pharmacol Ther*. 1998;12:199-205.
- van Rossum TG, Vulto AG, Hop WC, Schalm SW. Glycyrrhizin-induced reduction of ALT in European patients with chronic hepatitis C. *Am J Gastroenterol*. 2001;96:2432-2437.
- Lewis JH. Licorice for hepatitis C: yum-yum or just ho-hum [comment]? *Am J Gastroenterol*. 2001;96:2291-2292.
- Arase Y, Ikeda K, Murashima N, et al. The long term efficacy of glycyrrhizin in chronic hepatitis C patients. *Cancer*. 1997;79:1494-1500.
- Stedman C. Herbal hepatotoxicity. *Semin Liver Dis*. 2002;22:195-206.
- The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines*. Boston, Mass: Integrative Medical Communications; 1998.