Herbal Product Use by Persons Enrolled in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial

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Herbal products, used for centuries in Far Eastern countries, are gaining popularity in western countries. Surveys indicate that persons with chronic hepatitis C (CHC) often use herbals, especially silymarin (milk thistle extract), hoping to improve the modest response to antiviral therapy and reduce side effects. The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial, involving persons with advanced CHC, nonresponders to prior antiviral therapy but still willing to participate in long-term pegylated interferon treatment, offered the opportunity to examine the use and potential effects of silymarin. Among 1145 study participants, 56% had never taken herbals, 21% admitted past use, and 23% were using them at enrollment. Silymarin constituted 72% of 60 herbals used at enrollment. Among all participants, 67% had never used silymarin, 16% used it in the past, and 17% used it at baseline. Silymarin use varied widely among the 10 participating study centers; men were more frequent users than women, as were non-Hispanic whites than African Americans and Hispanics. Silymarin use correlated strongly with higher education. No beneficial effect of silymarin was found on serum alanine aminotransferase or hepatitis C virus (HCV) RNA levels. Univariate analysis showed significantly fewer liver-related symptoms and better quality-of-life parameters in users than nonusers, but after reanalysis adjusted for covariates of age, race, education, alcohol consumption, exercise, body mass index, and smoking, only fatigue, nausea, liver pain, anorexia, muscle and joint pain, and general health remained significantly better in silymarin users. *Conclusion:* Silymarin users had similar alanine aminotransferase and HCV levels to those of nonusers but fewer symptoms and somewhat better quality-of-life indices. Because its use among these HALT-C participants was self-motivated and uncontrolled, however, only a well-designed prospective study can determine whether silymarin provides benefit to persons with chronic hepatitis C. (HEPATOLOGY 2008;47:605-612.)

Abbreviations: CAM, complementary and alternative medications; HALT-C, Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis; HCV, hepatitis C virus; QOL, quality of life.

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Received August 16, 2007; accepted September 12, 2007.

Supported by the National Institute of Diabetes & Digestive & Kidney Diseases (contract numbers are listed below). Additional support was provided by the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, the National Center for Minority Health and Health Disparities, the National Center for Research Resources (grant numbers are listed below), and National Institute on Alcohol Abuse and Alcoholism grant K24 AA13736. Additional funding to conduct this study was supplied by Hoffmann-La Roche, Inc., through a Cooperative Research and Development Agreement (CRADA) with the National Institutes of Health.

This is publication number 27 from the HALT-C Trial Group.

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The current recommended treatment for chronic hepatitis C virus (HCV) infection is the combination of pegylated interferon and ribavirin.[1] This regimen leads to a sustained virologic response rate of a little over 50%, but the rates differ according to the infecting genotype, being lower among those with HCV genotype 1 infection (45%) than among those with genotype 2 and 3 infections (80%).[2-4] Because of the high rate of nonresponse in persons infected with genotype 1, the predominating strain in the United States, and because antiviral treatment causes frequent, unpleasant and sometimes serious adverse effects, many HCV-infected persons choose either to supplement antiviral medications with 1 or more herbal products or to reject conventional therapy altogether and instead rely solely on herbals as an alternative form of therapy.[5,6]

Herbals have been used for centuries in China and other Far East countries and have recently become increasingly popular in western countries.[7] Surveys in the United States demonstrate that use of complementary and alternative medications (CAM) has increased from 34% of the population in 1990 to 48% in 2004.[8,9] The basis for this increasing interest is the thus far unfounded belief that, because herbals have been used for hundreds of years and are "natural" products, they must be effective and safe.[10] Their use is especially prevalent in persons with chronic diseases, and therefore the fact that those with chronic liver disease seek primary or adjunctive herbal treatment is not surprising.[5,11] In the United States, silymarin (an extract of milk thistle) is the most popular product taken by those with liver disease.[6,12]

An opportunity was provided to explore the frequency of use of herbal supplements and their potential effects in a large cohort of persons with chronic liver disease by interviewing all participants in the Hepatitis C Antiviral Long-Term Treatment against Cirrhosis (HALT-C) Trial[13] for this purpose. Eligibility for the trial included a diagnosis of chronic hepatitis C together with histological evidence of marked fibrosis or cirrhosis and failure to have responded to previous therapy for chronic hepatitis C. These treatment nonresponders, some of whom had been treated on more than 1 occasion, proved their commitment to conventional therapy by volunteering to participate in this randomized, controlled trial of long-term pegylated interferon versus observation for 3.5 years to determine whether such maintenance therapy could reduce progression of the chronic liver disease.

The data collected at baseline indicate that herbal use was indeed common. Silymarin was found to be the most frequently used herbal supplement, and its use was associated with fewer and milder symptoms of liver disease and better overall quality of life but no difference in biochemical or virologic markers of chronic hepatitis C.

Patients and Methods

Patient Selection. Patients enrolled at all 10 clinical centers participated in the study. To enter the trial, participants had to have chronic hepatitis C with HCV RNA detected in serum by the central laboratory at the time of screening, to have failed to respond previously to at least 12 weeks of interferon-based therapy, and to have undergone a liver biopsy that demonstrated bridging fibrosis (Ishak fibrosis score, 3 or 4) or cirrhosis (Ishak fibrosis score, 5 or 6).[14] Reasons for exclusion were evidence of hepatic decompensation, other coexistent liver diseases, serious medical disorders that would preclude treatment with interferon, previous interferon intolerance, active use of illicit drugs, active alcohol abuse, a suicide attempt or hospitalization for depression within the past 5 years, and a history of a severe or uncontrolled psychiatric condition within the preceding 6 months.

Details of the treatment protocol have been reported previously.[13] Briefly, persons with chronic hepatitis C, defined by the presence of HCV RNA and histological evidence of either marked fibrosis or cirrhosis, who had failed previous treatment that had not consisted of the now standard pegylated interferon and ribavirin, were

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22044

Potential conflict of interest: Financial relationships of the authors with Hoffmann-La Roche Inc., are as follows: G. Szabo receives research support; G.T. Everson is a consultant, on the speaker's bureau, and receives research support; M.L. Shiffman is a consultant, on the speaker's bureau, and receives research support; K.L. Lindsay is a consultant and receives research support; A.S.F. Lok is a consultant and receives research support; A.M. Di Bisceglie is a consultant, on the speaker's bureau, and receives research support; and W.M. Lee receives research support. Authors with no financial relationships with Hoffmann-La Roche Inc. to disclose are: L.B. Seeff, T.M. Curto, H.L. Bonkovsky, J.L. Dienstag, and M.G. Ghany. Dr. Lee is a consultant for Lilly AstraZeneca. Dr. Lok is a consultant for and received grants from Schering-Plough. Dr. Lindsay is a consultant for and received grants from Valeant Pharmaceuticals. She received grants from Vertex Pharmaceuticals, Human Genome Sciences. She is also a consultant for Zymogenetics, Kendle International, and King Pharmaceuticals, Inc. Dr. Shiffman received grants from Schering-Plough and Vertex. He advises and received grants from Valeant, Wyeth, and Novartis. Dr. Dienstag advises GlaxoSmithKline, Bristol-Myers Squibb, Idenix Pharmaceuticals, Achillion Pharmaceuticals, Metabasis Therapeutics, SciClone, Nucleonics, and Valeant. She is a consultant for Oxxon Therapeutics, ComninatoRx, and Pharmasset. She also advises and received grants from Vertex.

then treated with this therapeutic combination, referred to as the "lead-in" phase of the trial. If HCV RNA was no longer detected at week 20, the study subjects continued the combination treatment for a full 48 weeks. If HCV RNA was still present, they were randomized at week 24 to receive either pegylated interferon alfa-2a treatment alone for 3.5 years or to be monitored for the same period without treatment. Persons who were previous nonresponders to the combination treatment of pegylated interferon and ribavirin were immediately entered into the 3.5-year maintenance phase without passing through lead-in. Standard demographic, clinical, medication, laboratory, and radiological data were obtained during baseline visits at all clinical centers. The data were entered into a central database maintained by the Data Coordinating Center (New England Research Institutes, Watertown, MA).

Medication Interview. Study coordinators at all clinical sites were trained to conduct uniform interviews. Data collected at the baseline visit included not only clinical information relevant for the treatment trial, but also information on past and current use of all prescription and nonprescription drugs, including herbal medications, dietary supplements, and other botanical products. The patients were given a card displaying 37 examples of herbal products listed in alphabetical order and were asked whether they had ever taken any of them or any other herbal product at least once a week for 1 month or longer. The information obtained was entered into the trial database. At each subsequent study visit, patients were asked whether they had stopped any of the medications since the last visit or whether they were taking any new herbals.

Patients who reported no past or current use of herbals at the baseline visit were considered to be "never users"; those who reported past but no current use were considered "past users only" and those who admitted using herbals at baseline were counted as "baseline users," regardless of past use. No information was obtained on the length of time that the baseline users had been taking herbals.

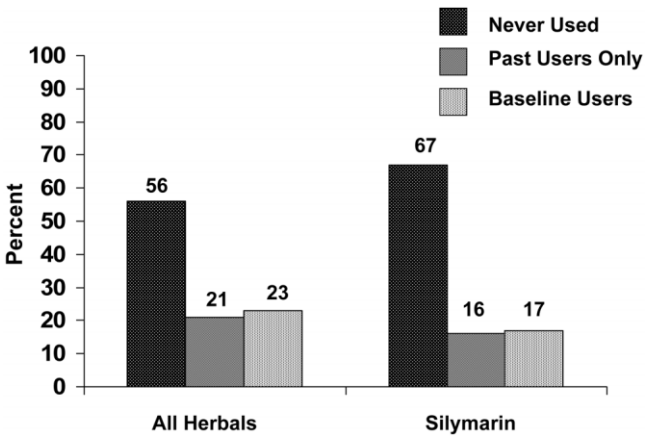

Fig. 1. Percentages of non-users, past users, and baseline users of all herbals and silymarin.

Table 1. List of the Top 24 Herbals Used at Baseline

Herbal Product	No. of Users	Herbal Product	No. of Users
1. Silymarin	195	13. Flaxseed	9
2. Green Tea	37	14. Dandelion	7
3. Garlic	29	15. Evening Primrose	7
4. Ginseng	25	16. Licorice	7
5. Ginko	24	17. Olive Leaf Extracts	5
6. Echinacea	22	18. Thymus Extracts	5
7. Grape Seed	19	19. Bilberry	4
8. Melatonin	13	20. Kava Kava	4
9. St. John's Wort	12	21. Pine Bark	4
10. Saw Palmetto	11	22. Chamomile	3
11. Aloe Vera	10	23. Goldenseal	3
12. Psyllium	10	24. Valerian	3

The numbers do not add up to the 269 baseline users of herbals because many study participants used more than one product.

Data Analysis. Data were analyzed with SAS (Statistical Analysis Software, version 9.1, SAS Institute, Cary, NC) software. Chi-squared and *t* tests were used to calculate the significance of differences in variables among the 2 categories of herbal product use (never and baseline). Multivariable associations of herbal use with selected outcomes were evaluated by analysis of variance.

Results

Among the 1145 study participants who were questioned, 641 (56%) reported that they had never used herbals, 235 (21%) stated that they had used them in the past only, and 269 (23%) admitted to current use at the time of the baseline evaluation (Fig. 1). Although patients reported using 60 different herbals, many in combinations, 195 (72%) of the 269 baseline herbal users reported taking silymarin, by far the most common single herbal used (Table 1). Focusing on silymarin, 772 (67%) indicated they had never used it, 178 (16%) admitted to taking it in the past, and 195 (17%) used it at the baseline visit (Fig. 1). The frequency of use of all herbal products as well as of silymarin varied widely among the different participating centers. As shown in Fig. 2, baseline use of all herbals ranged from 12% and 13% at the Bethesda, Maryland, and Boston, Massachusetts, sites to 29% and 42% at the Los Angeles, California, and Denver, Colorado, sites. Similarly, silymarin use ranged from 8% and 9% at the Bethesda and Boston locations to 22% and 33% at the Ann Arbor, Michigan, and Denver sites.

Among the 195 patients who were using silymarin at baseline, their mean age was 50.8 years, not significantly

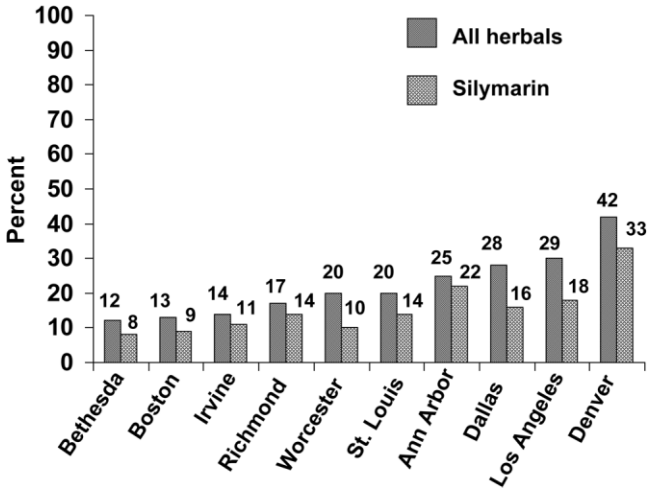

Fig. 2. Comparison among 10 clinical centers of use of all herbals and of silymarin at baseline

Table 3. Comparison Between Baseline Users and Nonusers of Silymarin
Laboratory Values

Variable	Never Used n = 772		Baseline Users n = 195		
	Mean	SD	Mean	SD	*P*
Log_{10} HCV RNA	6.4	0.5	6.5	0.5	0.08
ALT U/L	109.5	71.1	124.5	96.2	0.04
AST U/L	87.4	58.9	91.6	66.7	0.42
Alk. Phos U/L	99.7	43.1	88.5	38.3	0.0004
Tot. Bil mg/dL	0.8	0.4	0.8	0.4	098
Albumin g/dL	3.9	0.4	3.9	0.4	0.85
INR	1.0	0.1	1.0	0.1	0.57
WBC mm^3	6.0	2.0	5.6	1.8	0.03
Hemoglobin g/dL	15.0	1.4	15.4	1.3	<0.0001

Abbreviations: Alk.Phos, alkaline phosphatase; SD, standard deviation; Tot.Bil, total bilirubin; INR, international normalized ratio; WBC, white blood count.

different from those who never used this herbal. Silymarin was used more frequently by men than women (18.4% versus 13.5%; $P = 0.05$) and by non-Hispanic whites than both African Americans and Hispanics (19.4% versus 8.6% and 10.4%, respectively; $P = 0.0005$) (Table 2). The highest formal education received was significantly greater among those who were using silymarin at baseline than among those who had never used silymarin ($P < 0.0001$) as well as among the users of the other herbal products combined when compared with the never users (0.0024); higher education was also associated strongly with white race ($P < 0.0001$).

Statistical comparisons presented are between persons using silymarin at the baseline (enrollment) visit and those who had never used herbals. The levels of HCV RNA were not significantly different between silymarin users and non-users; the mean HCV RNA levels were 6.5 log_{10} IU/mL in silymarin users at baseline compared with 6.4 log_{10} IU/mL in those who had never used silymarin (Table 3). Similarly, no significant difference between baseline silymarin users and non-users was noted for mean aspartate aminotransferase (91.6 U/L versus 87.4 U/L) or total serum bilirubin levels (0.8 mg/dL for both). The mean serum alanine aminotransferase level was significantly *higher* in silymarin users than nonusers (124.5 U/L versus 109.5 U/L; $P = 0.04$), whereas the mean serum alkaline phosphatase level was significantly ($P = 0.0004$) *lower* in users than in non-users (88.5 U/L versus 99.7 U/L); both, however, were in the normal range. Measures of hepatic synthetic function (serum albumin and prothrombin time) did not differ between the 2 groups. Baseline silymarin users had lower white blood cell counts ($5.6 \times 10^3/mm^3$ versus $6.0 \times 10^3/mm^3$; $P = 0.03$) and higher hemoglobin levels (15.4 g/dL versus 15.0 g/dL; $P < 0.0001$) than nonusers; however, the level of statistical significance in the hemoglobin level was lowered after excluding the Denver site from the analysis ($P = 0.01$), presumably a consequence of the low oxygen tension present at the high altitude of the Denver site.

Table 2. Demographic Characteristics of Users of Silymarin at Baseline

Variable	Total Number	Silymarin Users	Percent	*P*
Male	827	152	18.4	
Female	318	43	13.5	
				0.0502
Non-Hispanic White	844	164	19.4	
African American	175	15	8.6	
Hispanic	96	10	10.4	
				0.0005

Excluded from the racial categories are 30 persons whose race was listed as "other"; 6 (20%) of them were using silymarin at baseline.

Univariate analysis of symptoms at baseline between silymarin users and non-users revealed a significantly lower frequency among silymarin users of fatigue ($P = 0.004$), nausea ($P < 0.0001$), pain over the liver ($P = 0.002$), anorexia ($P < 0.0001$), headaches ($P = 0.05$), muscle and joint pains ($P \leq 0.0001$), pruritus ($P = 0.03$), depression ($P = 0.02$), and general wellness ($P = 0.05$) (Table 4). Also, the Beck BDI Depression Score was significantly lower in those using silymarin compared with those who had never used it ($P = 0.003$). However, when the analysis was adjusted for the covariates of age, race, education, total alcohol consumed, exercise, body mass index, and smoking, the only symptoms that remained significantly less frequent in users of silymarin were fatigue ($P = 0.01$), nausea ($P = 0.02$), liver pain ($P =$

Table 4. Univariate Analysis Comparing Baseline Users of Silymarin to Those Who Had Never Used Silymarin
Symptoms

	Never Used		Baseline Users		
	n = 772		n = 195		
Variable	Mean	SD	Mean	SD	*P*
Fatigue	3.4	2.6	2.9	2.3	0.004
Nausea	1.0	1.7	0.6	1.0	<0.0001
Liver pain	1.8	2.4	1.4	1.8	0.002
Anorexia	1.3	2.0	0.8	1.3	<0.0001
Headaches	1.9	2.2	1.5	2.1	0.05
Muscle/joint pain	3.3	2.9	2.4	2.3	<0.0001
Pruritus	1.8	2.4	1.4	2.1	0.03
Depression	1.5	2.1	1.2	1.7	0.02
Gen. wellness	2.8	2.3	2.5	1.9	0.05
BDI Dep.Sc.	7.6	7.6	6.1	6.2	0.003

Higher scores denote worse symptom. Abbreviations: Dep, depression; Gen, general; Sc, score; SD, standard deviation.

0.02), anorexia ($P = 0.01$), and muscle and joint pain ($P = 0.003$) (Table 5).

Similarly, quality-of-life (QOL) domains were measured and compared between silymarin users and nonusers. Significantly higher QOL scores among silymarin users were found for 6 of 8 QOL domains and 2 of 3 summary scales: physical functioning ($P = 0.002$), body pain ($P = 0.005$), general health ($P = 0.002$), vitality ($P = 0.03$), social functioning ($P = 0.0004$), mental health ($P = 0.04$), physical summary scale ($P = 0.003$), and the sexual summary scale ($P = 0.05$) (Table 6). All of these items became nonsignificant, however, except general health ($P = 0.04$) when adjusted for the same covariates of age, race, education, total alcohol consumed, exercise, body mass index, and smoking.

Discussion

The data in this survey of a population of study subjects who volunteered to participate in a trial of long-term interferon-based therapy for histologically advanced hepatitis C reveal that levels neither of HCV RNA nor of serum alanine aminotransferase—virological and biochemical markers of virus activity and hepatic inflammation—were improved in those taking herbals, particularly silymarin, when compared with those who had never used herbal products. The absence of an identified positive relationship between silymarin and the virological and biochemical parameters of chronic HCV infection is consistent with the prevailing belief about these products, but is not surprising in view of the uncertainty of the product purity, the dose used, and the duration of use among those questioned at baseline, coupled with the fact that this particular cohort, nonresponders to accepted standard antiviral therapy, are a group especially difficult to cure. Nevertheless, those who were using silymarin did have findings of lower frequencies of a limited number of non–liver-specific symptoms.

Interest in the use of CAM and especially in the use of herbal products has grown considerably in the United States in recent years. In a national survey conducted in 1999, an estimated 9.6% of the U.S. population stated that they had used herbals.[15] A similar analysis of data in the 2002 National Health Interview Survey revealed that 18.6% of 31,044 adult respondents (double the 1999 figure) had used herbs or supplements in the previous 12 months.[16] Based on this figure, 38.2 million adults in the United States were estimated to have used herbals for the treatment of various health-related conditions.[16] Most reported that herbals were important to their health and well-being, and many were reluctant to inform their physicians of this use.[16]

Herbals are often used simply in an effort to improve well-being and QOL, but they are also commonly em-

Table 5. Multivariate Analysis Comparing Baseline Users of Silymarin to Those Who Had Never Used Silymarin*
Symptoms and Quality of Life

	Never Used		Baseline Users		
	n = 731		n = 182		
Variable	Adj. Mean	SD	Adj. Mean	SD	*P*
Fatigue	3.4	0.1	2.9	0.2	0.01
Nausea	1.0	0.1	0.7	0.1	0.02
Liver Pain	1.8	0.1	1.4	0.2	0.02
Anorexia	1.3	0.1	0.9	0.1	0.01
Muscle/joint pains	3.2	0.1	2.5	0.2	0.003
General Health	58.8	0.8	62.4	1.6	0.04

*Adjusted for covariates of age, race, education, total number of alcoholic drinks, exercise, BMI, and smoking. Abbreviation: SD, standard deviation.

Table 6. Univariate Analysis Comparing Baseline Users of Silymarin to Those Who Had Never Used Silymarin
Quality of Life

	Never Used		Baseline Users		
	n = 772		n = 195		
Variable	Mean	SD	Mean	SD	*P*
Phys. Func	75.0	26.7	81.1	23.4	0.002
Body pain	68.6	26.1	74.3	23.5	0.005
Gen. Health	58.2	22.4	63.7	21.6	0.002
Vitality	53.1	24.6	57.4	22.8	0.03
Soc. Func.	78.9	24.6	85.0	20.3	0.0004
Mental Health	75.9	16.8	78.3	14.3	0.04
Phys Summ Sc	44.0	11.8	46.8	10.9	0.003
Sex Summ Sc	71.0	30.9	75.9	29.1	0.05

Higher scores denote higher quality of life. Abbreviations: SD, standard deviation; Phys.Func, physical functioning; Gen.Health, general; health; Soc.Func, social functioning; Phys.Summ.Sc, physical summary score; Sex.Summ.Sc, sexual summary score.

ployed to treat medical ailments, particularly for chronic diseases.[16,17-24] Not surprisingly, therefore, herbals are used commonly by persons with chronic liver diseases, especially those with chronic viral hepatitis B and C.[11,12,25-27] Indeed, clinic-based surveys suggest that the frequency of CAM use among persons with chronic liver disease ranges between 40% and 50%.[5,6]

Thus, the results of the current survey are in close agreement with previously reported experiences; 44% of the study participants had either previous or current experience with herbals; 23% continued to take a variety of herbals even at the time of enrollment; and 17% were using silymarin either on its own or together with other herbals. Reliance on herbal remedies might have been unexpected in this selected study population who had received conventional antiviral therapy previously—some more than once—and now were prepared to commit themselves to an additional 31/2 to 4 years of conventional pegylated interferon–based antiviral therapy.

In keeping with past reports,[15,28-30] sex and racial/ethnic differences in the use of herbals were observed in this study population. Also noted was a wide disparity in silymarin use among patients enrolled at the 10 different centers, ranging from a low of 8% to a high of 33%; silymarin use was reported most frequently among patients in Colorado, Michigan, and Southern California and least frequently among those in Maryland and Massachusetts. The reason for these regional differences and those reported by others[5] is unknown; demographic differences in herbal use across the centers in sex, race, or education did not explain the wide regional disparities in herbal use (data not shown). Conceivably, local and cultural differences among the populations might have accounted for the variations in the use of alternative medications, as might the influence of the medical staff across sites whose attitudes toward CAM practices might have differed.

Study participants reported using 60 or more herbal preparations, but silymarin was by far the most commonly used herbal. The popularity of silymarin among patients with liver disease may derive from the belief that it has a protective effect in liver injury resulting from *Amanita phalloides* poisoning.[31,32] Also, despite failure of clinical trials to demonstrate silymarin efficacy in any type of liver disease,[33,34] silymarin has been postulated to have numerous metabolic effects that might be hepatoprotective.[35-46] Comprehensive analyses of published data on CAM in general[5,6,12,47,48] and silymarin in particular[49,50] for the treatment of liver diseases including viral hepatitis,[51-53] however, provide little convincing support for the efficacy of such therapies in chronic viral hepatitis, with the exception of a recent study undertaken in humans[54] as well as an *in vitro* study using hepatoma Huh 7 cells.[55] A possible reason for the absence of demonstrable silymarin efficacy in viral hepatitis and other liver disorders is that silymarin formulations studied have not been standardized and that doses administered may have been inadequate. To address these issues, a multicenter group of investigators is conducting a clinical trial with standardized formulations and doses of silymarin to assess its efficacy in chronic hepatitis C and nonalcoholic steatohepatitis (ClinicalTrials.gov Identifier NCT000389376).

An association was noted was between symptoms and measures of QOL among the silymarin users, who, after adjustment for the covariates of age, race, education, exercise, body mass index, and smoking, had lower symptom scores for fatigue, nausea, liver pain, anorexia, and muscle and joint pains and a higher QOL general health domain, 1 of 8 domains analyzed. Because these observations do not represent a prospective and randomized analysis of CAM use in the study subjects, a definitive conclusion cannot be reached that the differences encountered in these symptom scores between silymarin users and non-users reflect a clinically meaningful impact of silymarin.

An issue not explored in this survey is whether liver injury might have occurred as a result of use of the herbals. Rich literature exists in regard to herbal hepatotoxicity,[10,56] and indeed, 1 of the herbal products claimed to have been used by a small number of study participants, kava kava, has been clearly implicated as a cause of drug-induced liver injury.[57] The HALT-C trial was, however, not designed to detect evidence of hepatotoxicity. Moreover, there is great difficulty in establishing a diagnosis of drug-induced liver injury when the biochemical abnormalities of chronic liver disease already exist.

In conclusion, in the HALT-C trial, involving persons with chronic HCV infection and advanced liver disease who had failed to respond previously to 1 or more episodes of antiviral therapy and were now willing to embark on a new long-term antiviral treatment trial, approximately one fifth chose also to use herbals concomitantly. There was no evidence, however, that silymarin showed antiviral activity against HCV infection. Moreover, the observation of better scores in a small number of symptoms among silymarin users than in non-users is insufficient to support the value of this alternative therapy. Currently in progress, therefore, is a properly designed prospective, randomized, controlled trial in which a fully characterized, purified, and standardized silymarin formulation is being evaluated.

Acknowledgment: In addition to the authors of this manuscript, the following individuals were instrumental in the planning, conduct, or care of patients enrolled in

this study at each of the participating institutions as follows:

University of Massachusetts Medical Center, Worcester, MA: (Contract N01-DK-9-2326) Maureen Cormier, RN; Donna Giansiracusa, RN

University of Connecticut Health Center, Farmington, CT: (Grant M01RR-06192) Michelle Kelley, RN, ANP

Saint Louis University School of Medicine, St. Louis, MO: (Contract N01-DK-9-2324) Bruce Bacon, MD; Brent Neuschwander-Tetri, MD; Debra King, RN

Massachusetts General Hospital, Boston, MA: (Contract N01-DK-9-2319, Grant M01RR-01066) Raymond T. Chung, MD; Andrea E. Reid, MD; Wallis A. Molchen

University of Colorado School of Medicine, Denver, CO: (Contract N01-DK-9-2327, Grant M01RR-00051) Jennifer DeSanto, RN; Carol McKinley, RN

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