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File: ■ Milk Thistle (*Silybum marianum*)
■ Silymarin
■ Chronic Hepatitis C

HC 081231-456

Date: September 14, 2012

RE: Hepatitis C Interferon Treatment Non-responder Patients also Do Not Respond to Milk Thistle (60% Silymarin) Treatment

Fried MW, Navarro VJ, Afdhal N, et al. Effect of silymarin (milk thistle) on liver disease in patients with chronic hepatitis C unsuccessfully treated with interferon therapy: a randomized controlled trial. *JAMA*. July 18, 2012;308(3):274-282.

Affecting almost 3% of the world's population, chronic hepatitis C virus (HCV) infection can lead to cirrhosis, hepatic failure, and hepatocellular carcinoma. Many patients with HCV infection do not respond well to conventional therapies (peginterferon and ribavirin) and others cannot use those therapies because of medical comorbidities. Alternative medications with disease-modifying activity may therefore be beneficial. Silymarin, an extract of milk thistle (*Silybum marianum*), is the botanical treatment most commonly used for liver disorders in the United States: 33% of patients with chronic HCV infection and cirrhosis reported current or past use of silymarin to treat their disease.[1] Clinical studies evaluating milk thistle for various liver diseases have reported inconsistent results. Because the data on dosing and pharmacokinetics of silymarin were limited, these authors conducted an earlier dose-ranging study[2] to identify silymarin doses for further study in the trial reported in this article. Two doses, 3 and 5 times higher than the customary dose, were selected based on the earlier study. The aim of the randomized, double-blind, placebo-controlled, multicenter trial reported here was to assess the safety and efficacy of silymarin for treating chronic HCV infection among patients previously unsuccessfully treated with conventional interferon (IFN)-based treatment.

Adult patients with chronic HCV infection were eligible for the trial if they had received previous IFN-based therapy without sustained virological response, had quantifiable serum HCV RNA levels, and had an alanine aminotransferase (ALT) level of ≥65 U/L at screening. Participants were recruited at 4 northeastern U.S. clinical centers. Enrollment ran from May 2008 to May 2010. Follow-up continued until March 2011.

The 154 eligible participants were randomly assigned to 1 of 3 groups to receive the following: 420 mg silymarin (n=50), 700 mg silymarin (n=52), or matching placebo (n=52) gelatin capsules administered for 24 weeks. Three times daily, the participants took 5 capsules of silymarin (420 mg); 5 capsules of silymarin (700 mg); 3 capsules of silymarin

(420 mg) plus 2 of placebo; or 5 capsules of placebo. The botanical product used was a dry extract of milk thistle fruit marketed as Legalon® 140 (Rottapharm|Madaus; Monza, Italy).

Most of the participants were men (70%); the median age was 54 years. Most participants had HCV genotype 1 infection (91%). At baseline, the median HCV RNA and serum ALT levels were similar among the groups. Participants were seen at baseline, and at 6 follow-up visits scheduled 2 to 8 weeks apart throughout the 24-week study, and subsequently at 4 and 23 weeks post-treatment.

The primary outcome measure was a serum ALT level of ≤45 U/L (considered within the normal range) or <65 U/L, provided the value was at least 50% less than the baseline value. Secondary outcomes included significant changes in ALT levels, HCV RNA levels, and quality-of-life measures.

An analysis of changes in serum ALT levels from baseline to the end of treatment revealed no statistically significant differences among the 3 groups: mean declines were -4.3 U/L for placebo; -14.4 U/L for 420 mg silymarin; and -11.3 U/L for 700 mg silymarin (P=0.75). The authors also report that there were no significant differences in HCV RNA levels: mean changes were 0.07 $\log_{10}$ IU/mL for placebo; -0.03 $\log_{10}$ IU/mL for 420 mg silymarin; and 0.04 $\log_{10}$ IU/mL for 700 mg silymarin. No significant changes were reported in the physical or mental health components of quality-of-life scores, in chronic liver disease health-related quality-of-life assessments, or in depression scores.

Frequency of adverse events reported by participants did not differ significantly among the groups. The most frequent adverse events were gastrointestinal symptoms, most of which were mild or moderate in severity.

The authors state that this trial used a well-characterized silymarin product (not described); focused on a specific liver disease; enrolled a large, representative cohort across 4 different northeastern U.S. clinical sites; included an adequate treatment duration; had excellent adherence to study medication and visits; and used well-defined outcome measures.

They conclude that oral silymarin, used in a higher than customary dose, did not significantly alter biochemical or virological markers of disease activity in patients with chronic HCV infection who had been treated previously with IFN-based regimens and had not responded to treatment. For these participants, with treatment-resistant HCV infection, silymarin did not provide a greater benefit than placebo.

—Shari Henson

References

[1]Seeff LB, Curto TM, Szabo G, et al.; HALT-C Trial Group. Herbal product use by persons enrolled in the Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis (HALT-C) Trial. *Hepatology*. 2008;47(2):605-612.

[2]Hawke RL, Schrieber SJ, Soule TA, et al.; SyNCH Trial Group. Silymarin ascending multiple oral dosing phase I study in noncirrhotic patients with chronic hepatitis C. *J Clin Pharmacol*. 2010;50(4):434-449.

Peer Reviewer's Comments:

The primary inclusion criteria for this study were that the participants FAILED to respond to "gold standard" conventional treatments. It is hardly surprising that they also did not respond to herbal therapy. To overstate the obvious, these subjects were not representative of the general U.S. HCV population.

Also, in both the result and discussion sections, the authors claimed that compliance was very good ("despite a high pill burden" – 5 capsules, three times a day); however, the methodology for assessing compliance was not reported nor was there any indication whether these unknown compliance evaluations were intended to measure medication intake or adherence to the 3 times daily dosing schedule. As the authors point out, the study medication is rapidly metabolized, so the 3 times daily dosing schedule is critical to maintain effective, steady plasma levels.

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