

Phase I/II Clinical Trial to Explore Silymarin in Chronic Liver Diseases

The National Center for Complementary and Alternative Medicine is sponsoring a phase I/II clinical trial to evaluate the safety, tolerability, and pharmacokinetics of orally administered silymarin in patients with noncirrhotic chronic hepatitis C virus (HCV) infection or nonalcoholic fatty liver disease (NAFLD).

The study, led by researchers from 4 institutions, includes the University of North Carolina at Chapel Hill, the University of Pennsylvania, Beth Israel Deaconess Medical Center (Boston, MA); and Thomas Jefferson University (Philadelphia, PA); with the University of Pittsburgh as the Data Coordinating Center.

Fifty percent of patients with chronic HCV infection are either ineligible or do not achieve sustained virologic response with interferon-based therapies. Currently, there are no proven treatments for patients with non-alcoholic steatohepatitis (NASH). Therefore, both of these patient populations may benefit from the use of alternative medicines. Herbal products have been used empirically for centuries as alternative medicines to treat a variety of human disorders. *Silybum marianum*, or silymarin (common name: milk thistle), is used by 30%-40% of patients with chronic liver diseases because of purported beneficial effects that include anti-inflammatory, antioxidant, and antifibrogenic activities (Figure 2).

The lack of efficacy in several clinical trials using customary doses of silymarin suggests the need to evaluate higher doses. However, there is little evidence



Figure 2. *Silybum marianum*, or silymarin (common name: milk thistle). Reprinted with permission from Dr. Ulrich Mengs.

from clinical trials to support the use of silymarin as a treatment for diseases of the liver. Several major limitations of prior clinical investigations on the hepatoprotective effects of silymarin include the following: (1) the use of nonstandardized silymarin extracts, which confounds comparisons between trials because the concentrations of the 4 potentially active isomers of silymarin are known to vary; (2) the incomplete understanding of the relationship between silymarin dose and steady-state exposures to the potentially active isomers of silymarin, confounding the evaluation of safety and efficacy; and (3) the use of

heterogeneous patient populations and variable endpoints to assess therapeutic response.

One of the investigators, Dr. K. Rajender Reddy, Professor of Medicine and Director of Hepatology at the University of Pennsylvania, points out that safe dose escalation is uncertain because the disposition of silymarin in patients with chronic liver disease is not known and may differ according to disease etiology or disease severity. Furthermore, the relative contributions of the 6 principal components (isomers) of silymarin to its safety and efficacy profile have not been previously investigated in a clinical trial, he adds.

It is proposed to study a standardized form of silymarin systematically in a randomized, multicenter, double-blind, placebo-controlled phase I trial to determine the effect of a standardized meal (35% fat and 800 kcal) on the relative oral bioavailability of the 6 principal isomers of silymarin and to determine the safety and tolerability of silymarin, as well as the pharmacokinetics for the 6 principal silymarin isomers, after single and multiple doses administered orally 3 times daily in patients with either HCV or NAFLD.

“The data obtained from this phase I study will allow for the identification of drug exposures that are both safe and dose proportional for a planned phase II study to determine the effectiveness of silymarin as a treatment for liver disease in HCV and NASH patient populations,” Reddy says.

Stories by Les Lang