Milk Thistle and Chronic Liver Disease

Milk thistle has been used for centuries to treat acute and chronic liver diseases and, even today, is one of the most widely used herbal medications. Its active ingredients appear to be several closely related flavinoids, collectively known as silymarin. Most silymarin preparations have at least a dozen molecular components and their isomers, including silybin, isosilybin, cis-silybin, silydianin, and silychristine. It is not clear whether one, several, or all of these components are the active ingredient(s), and most commercial preparations represent rough extracts of the milk thistle plant (*Silybum Marianum)* rather than a purified subcomponent.

Results of studies in experimental animal models suggest that silymarin has a broad spectrum of hepatoprotective effects. Thus, silymarin can protect experimental animals against injury from several toxins, including amanita phalloides, carbon tetrachloride, ethanol, and galactosamine. Silymarin is partially protective even when given after exposure. The basis for this hepatoprotective activity may be the antioxidant qualities of the several flavinoids, but antifibrotic, antiinflammatory and immune modulatory actions of silymarin may also be important.

A safe and effective, broad-spectrum hepatoprotective agent would likely be very useful in the management of liver disease. Yet, despite its clear effects in experimental animal models, silymarin has yet to be proven effective in ameliorating human liver disease. Part of the problem is that silymarin has never been adequately evaluated using objective and clinically meaningful endpoints in well-characterized cohorts of patients with well-defined forms of liver disease.

Because of its safety, lack of side effects, activity in animal models, and centuries-long traditional use in liver disease, milk thistle has been introduced and is widely used as an herbal preparation in the United States. It is available in most health food stores and in many conventional grocery stores where it is advertised as beneficial for the liver or for "liver wellness." Food and Drug Administration (FDA) rules prohibit the advertisement of any agent as a specific therapy for liver disease, unless it has been proven to be safe and effective, in which case it would be regulated as a drug rather than an herbal preparation. In surveys conducted in liver disease clinics, between 10% and 15% of patients report taking milk thistle, almost entirely on the basis of advice from friends, magazine articles, or the Internet rather than on advice of a physician. Clearly, proof of the efficacy of milk thistle preparations (or lack thereof) and further documentation of its safety are critical needs in improving management of liver disease. In the recently published Action Plan for Liver Disease Research (http://liverplan.niddk.nih.gov), evaluation of nonspecific hepatoprotective agents such as silymarin was listed as an unmet and important research goal.

To address these issues, the National Center for Complementary and Alternative Medicine (NCCAM) in collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) held a research workshop entitled "Silymarin for Chronic Liver Disease" (http://www.niddk.nih.gov/federal/ddicc/meetings.htm). In this workshop, two critical first steps for development of silymarin as a therapy for liver disease were defined: (1) to identify a standard, reliable silymarin product that could be used in clinical investigation and (2) to initiate phase I/II trials of this product in liver disease. Disease conditions that were considered most appropriate for evaluation were nonalcoholic steatohepatitis (NASH) and chronic hepatitis C, with particular focus on patients who were nonresponders to conventional therapy. The goals for pilot, phase I/II studies were to define the optimal dose and dosing regimen for silymarin and to identify the appropriate patient cohorts and surrogate markers for assessment of efficacy and safety. These elements were considered critical, before expensive, definitive trials of silymarin therapy were initiated that might depend upon more long-term therapy and more critical clinical endpoints.

Accordingly, in March 2005, NCCAM published an announcement of availability of an industry collaboration for the development and evaluation of a commercial form of silymarin (http://nccam.nih.gov/research/announcements/active.htm). This announcement requested a partnership with a commercial entity that could provide a well-characterized, standard formulation of silymarin that could be evaluated in humans under an FDA-approved Investigational New Drug (IND) Application. Finally, in June 2005, NCCAM and NIDDK published a Request for Applications for a Silymarin Clinical Research Consortium. The Consortium will consist of approximately four Clinical Centers and a single Data Coordinating Center, which would be charged with the design and conduct of phase I/II clinical trials of silymarin in NASH and chronic hepatitis C. Each applicant for a Clinical Center is asked to document their experience in participating in multi-center clinical trials, experience in evaluation and follow-up of patients with liver disease, and insight and knowledge about design and conduct of phase I/II clinical trials. Applicants for the Data Coordinating Center are asked to document experience with managing multi-center clinical trials and data acquisition, management and analysis. A letter of intent is requested by August 15, 2005 and final applications by September 12, 2005. Applicants are limited to the United States. Details of the RFA are available at: http://grants.nih.gov/grants/guide/rfa-files/RFA-AT-05-006.html.

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