

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Silymarin for the Treatment of Chronic Liver Disease

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G&H Do the terms silymarin and “milk thistle” refer to the same substance?

KRR Milk thistle is a colloquialism or slang term for the plant from which silymarin is extracted, and the two names are essentially synonymous.

G&H Could you describe the theoretical mechanism of silymarin, as it relates to the support of hepatic function?

KRR Silymarin is a flavonoid with alleged antioxidant properties to counteract the oxidative stress associated with certain liver diseases. Based on urinary excretion of isoprostanes, which are markers of oxidative stress, hepatitis C disease, alcoholic liver disease, and acute alcoholic hepatitis are all associated with this process. Recent work by Polyak and colleagues at the University of Washington has also demonstrated, in an in vitro replicon system, some antiviral and immunomodulatory properties of silymarin. However, the main mechanism that seems to provide a hepatoprotective effect is the free radical scavenging and related antioxidant effect.

G&H Can you discuss the aims of the ongoing SyNCH trial?

KRR The Silymarin in NASH and C Hepatitis (SyNCH) trial is a randomized, multicenter, double-blind, placebo-controlled trial funded by the National Center for Complementary and Alternative Medicine (NCCAM)

and the National Institute of Diabetes and Digestive and Kidney Diseases. The aim of the trial is to examine the impact of silymarin treatment in noncirrhotic nonresponders to standard hepatitis C therapy, as well as nonresponders to conventional therapy for nonalcoholic steatohepatitis (NASH). SyNCH is a combination phase I/II study, in which the two best-tolerated doses with optimal pharmacokinetic profiles will be identified in phase I. These two doses can then be administered in a phase II efficacy study. At this time, the phase I portion of the study is nearly complete, and we are about to commence phase II. We hope to demonstrate silymarin's antioxidant properties and ability to ameliorate the inflammatory process in these conditions. Although we are not expecting to see significant antiviral properties, we will be looking at viral markers, as well as immunologic changes that may take place as a result of silymarin therapy. The establishment of maximal therapeutic doses will be key in the use of silymarin, as current standard doses have been shown to be ineffective in many patients with chronic disease, and the safety of dose escalation has not been established, particularly in its possible variance from one disease state to another.

G&H How has the dose/potency of the silymarin used in the SyNCH trial been regulated?

KRR In SyNCH, we are using a formulation of silymarin called Legalon (140 mg milk thistle extract con-

taining 77.5% silymarin; silybum marianum; Madaus, Cologne, Germany). We are reviewing molecular stability and conducting batch-to-batch variability testing along with the pharmacokinetic and safety profiles being examined in phase I.

G&H Will this trial lead to better-controlled manufacture of silymarin/milk thistle in the United States?

KRR Currently, there is no regulation or quality control of herbal compounds like silymarin in the United States because they are not considered drugs and are not under the supervision of the US Food and Drug Administration (FDA). If the results of this trial are positive in terms of efficacy and eventually lead to an official FDA indication in chronic liver disease, silymarin will be manufactured as a pharmaceutical-grade product, which will end concerns regarding variable levels of potency and dose consistency from one formulation to another.

G&H What do you see as the ultimate role of silymarin in the treatment of chronic liver diseases like hepatitis C?

KRR This will depend largely on the results of the SyNCH trial. This may be a negative trial, which will at least put to rest any controversy surrounding the efficacy of silymarin. However, if silymarin proves to be positive

in terms of efficacy, it will most likely work as an antioxidant, in which case it will be utilized as an alternative adjunct to standard therapies for chronic liver diseases. If silymarin has an antiviral effect, it will most likely be a secondary rather than a primary mechanism that will be contributive to therapy but not as significant as the antioxidant properties.

In the event of a positive result, the next step will be to test silymarin as a cotherapy with standard treatments for chronic liver disease to be sure there are no negative drug-drug interactions. Once this safety issue is confirmed, its uses will be unlimited in helping to maintain patients with chronic liver diseases and slow their natural disease progression.

Suggested Reading

- Polyak SJ, Morishima C, Shuhart MC, et al. Inhibition of T-cell inflammatory cytokines, hepatocyte NF-kappaB signaling, and HCV infection by standardized Silymarin. *Gastroenterology*. 2007;132:1925-1936.
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