

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

Complementary and Alternative Medicines for Hepatic Disease

Leonard B. Seeff, MD
Senior Scientist for Hepatitis Research
National Institute of Diabetes and Digestive
and Kidney Diseases
National Institutes of Health

G&H Why is there an urgent need to study the use of complementary and alternative medicines in patients with hepatic illness?

LBS Physicians need to know about complementary and alternative medicines (CAM) because of the plain fact that our patients use them. Proper investigation must be undertaken to see how these substances affect our patients because they are being utilized whether or not we recommend them.

Our group currently has a paper in press with *Hepatology* that focuses on the use of CAMs in the ongoing HALT-C (Hepatitis C Antiviral Long-term Treatment against Cirrhosis) trial, supported by The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This trial involves patients with histologically advanced chronic hepatitis C, all of whom were non-responders, sometimes on more than one occasion, to state-of-the-art antiviral therapy. For this present study, patients were randomized to receive either no treatment or antiviral therapy for a period of 3.5 years in the hope of diminishing progression of the liver disease. One would therefore conclude that these patients are committed to treating their disease with conventional drugs. At baseline, all participants completed an extensive questionnaire that included information regarding the use of herbal products or other CAMs. We found that 40% of the patients enrolled in HALT-C were either currently using or had previously used herbal products. In fact, 21–22% were using herbal products concomitant with the study medication.

G&H What are the most popular CAM substances that are in use among patients with hepatic disease?

LBS The most popular drug, by far, is silymarin (milk thistle), which was used by 72% of the patients taking CAM in the HALT-C trial. Others include glycyrrhizin (licorice root), Sho-saiko-to (TJ-9), phyllanthus amarus, picrorrhiza, and traditional Chinese herbal mixtures (CH-100, Compound 861).

G&H Have any of these agents been shown to provide sustained support of liver function?

LBS At this point, there is no evidence of real efficacy because none of these agents have been properly and rigorously studied. Silymarin and glycyrrhizin have been evaluated extensively in basic research studies, and there is evidence that they both possess antioxidant and immunomodulatory properties. They may also have an antifibrotic effect. However, studies completed to date have been in either animal or in vitro models.

Most studies have failed to identify evidence of an antiviral effect in persons infected with the hepatitis C virus (HCV). However, Polyak and associates have recently published a paper in *Gastroenterology* focused on examining the effect of silymarin in HCV-infected Huh cells. They found reasonably convincing evidence of antiviral properties associated with this substance. Additional studies are urgently needed to confirm these data and, indeed, similar studies are currently ongoing at European centers.

G&H Are there any trials planned or currently ongoing to examine the efficacy of these substances?

LBS The ongoing SyNCH (Silymarin in NASH and C Hepatitis) trial is a Phase I/II trial, in which dosing, pharmacokinetics, and, ultimately, efficacy of this substance will be measured in a rigorous, double-blind and placebo-

controlled manner. If the findings of this study are positive, silymarin will be further studied in this population in the phase III setting.

For more information on the SyNCH trial, see Reddy KR. Silymarin for the treatment of chronic liver disease. Gastroenterology and Hepatology. 2007;3(11):825-826.

G&H What are the predicted or hoped-for findings from this study?

LBS Silymarin could improve symptoms of disease and may ease the side effects of conventional hepatitis drugs, allowing more patients to take these drugs and thus improving their overall efficacy. If silymarin has a clinically significant antiviral effect, that would be a surprise and an additive mechanism to support conventional medications.

G&H What are the challenges faced in studying the efficacy of these products?

LBS Our analysis of the HALT-C trial was not a controlled study. Patients were using these substances before they came into the trial, and we studied them based on self-medication rather than any form of randomization. Although we found no difference with respect to viral load and enzyme elevations between those using and those not using CAMs, there was an impact seen on quality of life and symptom severity. Without placebo control and randomization, we cannot be sure whether these results are a function of taking CAM products or whether patients who take CAMs are generally more proactive about their disease, wealthier (as insurance does not pay for these products), or have other educational or material advantages that may encourage a better overall sense of well-being. Randomized, blinded study, such as that utilized in the SyNCH trial, is required to answer these questions.

There is also the issue of standardizing products for testing. The CAM products that our patients are taking are not controlled by the US Food and Drug Administration (FDA) and are not monitored in terms of consistency of manufacture. When pharmaceutical companies provide new drugs for evaluation, these products have been through phase I, phase II, and phase III study to examine the pharmacokinetics and to standardize the concentration of the active substance at an optimal dose. This evolution is not being performed with over-the-counter CAMs because they are not considered drugs or under US FDA jurisdiction.

Standardization is also complicated by the large number of herbal mixtures administered, particularly in the Far East. Sho-saiko-to is a mixture of 7 herbs. Compound

861 contains 10 different herbs, and CH100 contains 19 different herbs. Some herbalists take a pinch of one and a pinch of another, and nothing is formally measured. Concentration of herbals can also vary based on where the product is grown, the time of the year, and whether the root, the stem, or the leaf is harvested.

G&H How do physician attitudes regarding CAMs further complicate their administration?

LBS There is tremendous antipathy among physicians about the use of CAMs in liver disease. As a result, patients will not often tell their doctors that they are taking these products, which is a problem because side effects and adverse events cannot be monitored if physicians do not know what their patients are taking. Condemning patients who are taking these drugs does not serve their best interest, nor does it serve scientific interest.

For some patients, this is a philosophy, almost a religious zeal with which they approach the use of herbals. CAMs have a centuries-old anecdotal history that drives patients to take them. Given the terrible side effects of our current drug options, it is understandable that patients look for alternatives, and they will continue to take them, regardless of our advice. If current research can demonstrate some efficacy for some of these products, they can at least be certified and regulated by the US FDA.

G&H What are the possible consequences of ignoring patient use of CAMs?

LBS Drug-induced liver injury from herbals is a serious problem. NIDDK is currently attempting to bring some clarity to this issue. Currently, five institutions are participating in the Drug-Induced Liver Injury Network (DILIN), collecting and reporting all cases of drug-induced liver injury. What is most difficult in studying injury from herbals is that in patients taking nonstandardized mixtures, it is nearly impossible to distinguish which substance is responsible for injury. There have been reports of heavy metals, prednisone, and other drugs in these mixtures, and it is difficult to know what these patients are actually taking, let alone which substance is causing the injury.

We have thus far collected almost 400 instances of drug-induced liver injury in the DILIN study and approximately 10% of it appears to be a consequence of herbals, most of which are mixtures. There are a number of herbal products that have been implicated as causes for liver injury. These include black cohosh, chaparral, comfrey, germander, Kava, mistletoe, Pennyroyal, and several others.

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However, many reports of drug- and herbal-induced liver injury are based on single cases and were made many years ago, when the viruses of hepatitis A, B, C, and E had not been identified and may have been responsible. Nonetheless, there is no doubt that some of these products cause harm and, in some parts of the world, are the most common cause of liver injury. In Singapore, 70% of drug-induced injuries are a result of herbal administration but investigators have yet to pinpoint the herbs that are at fault. Thus, the problem continues to be that the products are not standardized.

G&H Is there currently a registry in place so that any physician in the United States can report an incidence of drug-induced liver injury?

LBS Currently, no. There is no system for general reporting. There is the FDA MedWatch system, which is helpful but often takes in so little information that cases cannot be validated to provide meaningful evidence.

The DILIN study is currently in the process of expanding the number of involved investigators who will

receive and adjudicate cases of drug-induced liver injury from conventional drugs as well as CAM products, in specific catchment areas. Also, we are currently working with the National Library of Medicine to develop a database covering all of the previously reported cases. Our hope is that this will eventually lead to a system where any physician can report information directly and include all of the necessary information to validate diagnosis.

Suggested Reading

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