HCV ADVOCATE

HEPATITIS JOURNAL REVIEW

Volume 1, Issue 15
August 20, 2004

Hepatitis C

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Risk Factors for Ribavirin: Anemia

In many patients with hepatitis C, hemolytic anemia necessitates dose reduction or discontinuation of ribavirin, which increases the chances of HCV relapse after interferon-based therapy. In the July issue of the *Journal of Gastroenterology*, Shintaro Takaki and colleagues examined factors associated with an increased risk of developing anemia. Their study included 123 patients with chronic HCV (85 male, 38 female; mean age 50 years [range 20-70]); patients were treated with standard interferon plus 600-800 mg daily ribavirin. During the study, about 28% required ribavirin dose reduction and about 16% discontinued ribavirin. In a multivariate analysis, ribavirin dose reduction was associated with lower pretreatment hemoglobin levels (less than 14 g/dL) and age older than 55. In a univariate analysis, female sex was also linked to dose reduction, but this variable was not statistically significant in the multivariate analysis. (Women typically have lower normal hemoglobin levels than men.) According to the researchers, more careful monitoring during combination therapy is indicated for older patients and those with lower pretreatment hemoglobin levels.

Herbal Remedies for HCV Patients

Herbal remedies are being used by a growing number of people with hepatitis C, and are increasingly being studied in clinical trials. At this year's Digestive Disease Week conference in

Continued on page 2

Hepatitis Journal Review

A publication of the Hepatitis C Support Project

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Continued from page 1

May, for example, German researchers reported that an herbal combination containing mistletoe extract, green tomato extract, and Hepatodoron (extracts of *Fragaria vesca* and *Tritis vinifer) produced SVR* rates of 18% after one year of treatment and 44% after two years, as well as decreased liver inflammation and fibrosis.

In the August 1 issue of the *Journal of Hepatology,* Yukihiro Imanishi and colleagues reported on a study of a Kampo (traditional Japanese medicine) herbal preparation called inchin-ko-to (TJ-135), which is used in Japan to treat hepatitis C, cirrhosis, and cholestasis. They found that inchin-ko-to downregulates the proliferation and activity of hepatic stellate cells, which produce substances that contribute to fibrosis. Inchin-ko-to attenuated the development of fibrosis in rat livers induced by a toxic chemical. The preparation suppressed collagen and fibronectin synthesis, reduced expression of alpha-actin (a smooth muscle protein), and decreased blood levels of hyaluronic acid (a component of connective tissue). It also interfered with stellate cell signaling pathways. Among the various ingredients in inchin-ko-to, a phytochemical called emodin, derived from the rhizomes of the *Rheum palmatum* plant (Chinese rhubarb or Da Huang), was the most active. In past research, another ingredient, genipin (derived from *Gardenia jasminoides),* was shown to reduce hepatocyte apoptosis (cell death).

In the July supplement of the *Journal of Clinical Gastroenterology,* Filomena Morisco and colleagues reported that a tomato-based "functional food" reduces anemia in HCV patients taking ribavirin. The researchers created a functional food high in natural antioxidants and carotenoids. Because oxidative stress appears to play a role in ribavirin-related hemolytic anemia, they hoped the antioxidants in the food would help prevent anemia. The study included 92 patients with chronic HCV receiving pegylated interferon plus ribavirin. Half also received a daily dose of the functional food. After three months, about 9% of patients in the functional food group reduced their ribavirin dose due to side effects, compared with about 30% in the group not receiving the antioxidant product. Subjects in the functional food group had higher hemoglobin levels measured at 15, 30, and 90 days. The new product "reduces the severity of ribavirin-related anemia and improves the tolerance to the full dose of ribavirin in patients with chronic hepatitis C," the authors concluded.

Not all studies of herbal remedies have found a beneficial effect, however. In the June 28 issue of the *Archives of Internal Medicine,* Mrudula Jakkula and colleagues reported on a double-blind trial in which 45 HCV patients with fatigue were randomly assigned to receive a Chinese herbal combination or placebo for 12 weeks. The herbal preparation "had no effect on any quality-of-life variables," nor did it have a significant effect on ALT levels or HCV viral load. "Patients and practitioners should remain cautious about the use of herbal medicines for HCV, because studies have not shown a clear benefit of these agents," the authors concluded. Clearly, this is an area that requires more research.

Liver Toxicity Related to Acetaminophen

The July issue of *Hepatology* included two "point / counterpoint" articles on liver toxicity related to acetaminophen (e.g., Tylenol). Acetaminophen, like many drugs, is metabolized by the liver. If the normal processing pathway is overwhelmed, the cytochrome P450 enzyme sys-

Continued on page 3

Continued from page 2

tem comes into play, producing a toxic metabolite called NAPQI. Liver damage can be prevented by administering N-acetylcysteine, which detoxifies NAPQI. Acetaminophen overdose accounts for more than 56,000 emergency room visits and 450 deaths due to acute liver failure annually. Data from the U.S. Acute Liver Failure Study (ALFS) registry implicates acetaminophen in half of all cases of acute liver failure. Although liver toxicity usually occurs when people take too much acetaminophen, hepatotoxicity is sometimes seen at recommended doses. Emphasizing the drug's risks, ALFS principal investigator William Lee asks, "Is this amount of injury and death really acceptable for an over-the-counter pain reliever?"

Barry Rumack of the University of Colorado's Rocky Mountain Poison and Drug Center argues that normal therapeutic doses of acetaminophen are generally safe, and that alcohol consumption or fasting "do not place patients at a greater risk." He contends that most acetaminophen-related injuries and deaths are due to intentional overdose, such as suicide attempts. "Glucuronidation capacity [ability to metabolize acetaminophen] in humans is not a factor except in massively overdosed patients," Rumack concludes.

In September 2002, an FDA advisory panel recommended that acetaminophen should carry a warning about the potential for liver toxicity, and that all medications that contain acetaminophen should be clearly labeled as such. Nearly two years later, however, the agency has not yet implemented these recommendations. "For a pain reliever with only mild-to-moderate efficacy, it would seem prudent to move toward limiting these needless deaths," Lee argues. It is unclear whether people with chronic liver disease (including viral hepatitis) are at greater risk for acetominophen-related hepatotoxicity, but Lee suggests it would be prudent for such individuals to limit themselves to half the maximum recommended adult dose of 4,000 mg within a 24-hour period.

Most Common Causes of Drug-Related Liver Failures

In related news, Mark Russo and colleagues reported on liver transplantation due to acute drug-related liver failure in the August issue of *Liver Transplantation*. Analyzing data from the United Network for Organ Sharing (UNOS) liver transplant database from 1990 to 2002, the researchers identified 270 patients diagnosed with acute drug-related hepatic necrosis (tissue death). Overall, drug toxicity accounted for 15% of all transplants due to acute liver failure. Acetaminophen, alone or in combination with other drugs, accounted for 49% of all such cases. The other drugs implicated most frequently were isoniazid (for tuberculosis) at 17.5%, propylthiouracil (for hyperthyroidism) at 9.5%, and phenytoin (Dilantin) and valprioc acid (Depakene), both used for seizures, at 7.3% each. After transplantation, the overall one-year survival rate was 77%. Liver failure due to acetaminophen alone was more common among Caucasians (53%) compared with African Americans (25%), while African Americans were more likely to develop liver failure related to other drugs (75% vs 47%). Overall, 76% of the acute drug-related hepatotoxicity cases requiring transplants were seen in women. (Other research indicates that women are at greater risk for hepatotoxicity related to HIV medications.) The researchers concluded that more study is needed to explain the different rates of liver toxicity in women and people of different races.