HCV ADVOCATE

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Leptin and Fibrosis

In recent years there has been considerable interest in leptin, a hormone produced by fat cells that helps regulate appetite and promote normal insulin activity. Leptin leads to weight loss in obese mice, and is under study as a treatment for lipodystrophy (abnormal body fat distribution) in people with HIV. Leptin also appears to play a role in liver fibrosis. In the January 2004 issue of the *Journal of Viral Hepatitis*, Dr. Thierry Piche and colleagues from Nice, France, studied the association between leptin levels and fibrosis in patients with chronic HCV. They compared 77 HCV-infected patients and 22 uninfected control subjects; 65 of the patients had minimal to moderate (stage F0-F2) fibrosis and 12 had severe (stage F3-F4) fibrosis. Overall, leptin levels were higher in the HCV-infected patients compared with the uninfected controls; in addition, leptin levels were higher in women than in men among both patients and controls. Higher leptin levels were observed in patients with fibrosis and steatosis (fatty liver), and elevated leptin was linked to higher body mass index (BMI) and blood sugar levels. The authors concluded that, "the severity of liver fibrosis is associated with serum leptin," and suggested that TNF-alpha (a cytokine, or chemical messenger, produced by immune cells) may be a possible mediating mechanism. In related research, Dr. Piche and colleagues reported in 2002 that high leptin levels were associated with greater fatigue in people with chronic HCV.

Patients with Cirrhosis Benefit from Treatment

Several recent journal articles have looked at various aspects of HCV treatment. In a study published last fall in the November/December

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2003 issue of the *Journal of Clinical Gastroenterology*, Dr. Jenny Heathcote from Toronto presented an overview of treatment of HCV patients with cirrhosis. Patients with compensated cirrhosis (the liver is damaged but can still carry out most of its normal functions) can benefit from interferon therapy. Even in this difficult-to-treat population, about 43% achieve a sustained virological response (SVR) with pegylated interferon plus ribavirin. Those who achieve an SVR have decreased fibrosis progression, and some show improvements in liver damage; sustained responders also appear to be at less risk for hepatocellular carcinoma (liver cancer). Even some patients who do not achieve an SVR may still experience histological (tissue health) improvement. Although patients with cirrhosis may be more likely to experience treatment side effects, they "have a high chance of dying from progressive liver disease," concluded Dr. Heathcote, and thus "have the most to gain from successful antiviral therapy." However, treatment of patients with decompensated cirrhosis remains potentially dangerous, and should only be undertaken in the context of a clinical trial.

Pegylated Interferon Improves Liver Health

In the February 2004 issue of *Hepatology*, Dr. Calogero Cammà from Palermo, Italy, and colleagues reported on a meta-analysis of data from three randomized clinical trials that included a total of 1,013 previously untreated chronic HCV patients, looking at the effect of treatment on liver histology. All patients had paired pre- and post-treatment liver biopsies. Knodell scores were compared before and after treatment; histological improvement was defined as a decrease of a least one point in the fibrosis score or at least two points in the histological (necroinflammatory) activity score between the two biopsies.

As expected interferon (Pegasys) monotherapy was more effective than standard interferon monotherapy (33.4% vs 17.6%). After 24-48 weeks of therapy, pegylated interferon improved liver tissue health the most in patients who achieved a sustained virological response, and to a lesser extent in relapsers. Among those with an SVR, about 81% had reduced necroinflammatory (cell inflammation and death) activity and about 33% had improved fibrosis; the rate of fibrosis improvement in the nearly 200 participants with cirrhosis was about the same as in those with less advanced liver damage. However, among nonresponders, the researchers found that therapy produced "negligible changes in necroinflammation and no significant change in fibrosis." This result conflicts those of some previous research. Dr. Cammà and colleagues suggested that the scoring method used in their study might better reflect actual changes in liver tissue health.

The authors also found that improved liver histology was more likely in those who experienced an early virological response at 12 weeks, in those with higher pre-treatment ALT levels, and in obese patients (body mass index over 30). "[I]mpressive improvements in terms of fibrosis can be achieved in patients

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with SVRs and, to a lesser degree, in patients with recurrent disease," the authors concluded, but "[n]o significant changes were observed in nonresponders."

Thymosin-alpha 1

In the January 2004 issue of the *Journal of Viral Hepatology*, Dr. Pietro Andreone and colleagues from Bologna, Italy, reported that combination therapy with standard interferon plus thymosin-alpha 1 was initially more effective than interferon alone in chronic HCV patients being treated for the first time. In this study, 22 patients received the combination, while 19 received interferon monotherapy. After **six months of therapy**, the end-of-treatment response rate was higher in the patients receiving thymosin-alpha 1, but after six months of follow-up, the sustained response rate was the same in both groups. Limitations of this study include the short treatment duration (genotype 1 HCV is usually treated for 12 months) and the use of standard interferon rather than the more effective pegylated interferon. However, the results suggest that thymosin-alpha 1 might contribute to treatment effectiveness if added to the best available therapy.

Liver Disease Research Funding

Finally, also in the February 2004 *Hepatology*, Dr. Jay Hoofnagle of the National Institute of Diabetes and Digestive and Kidney Diseases gave an overview of federal liver disease research funding. According to Dr. Hoofnagle, funding for liver disease research accounts for about 1.4% of the total National Institutes of Health (NIH) budget, spread among 16 of 27 NIH institutes and centers. During the past five years, liver disease research funding more than doubled, reaching about $377 million in 2003; total NIH funding doubles during this period. Among the 1,646 grants funded in 2002 (the last year for which complete data is available), the largest number were for viral hepatitis and liver cancer (477 and 418, respectively). Nearly 60% of the viral hepatitis grants were for HCV, and almost 20% were for HBV.