

Hepatitis C

IDEAL Study

The two marketed brands of pegylated interferon alfa – Pegasys (2a) and PegIntron (2b) – are similarly effective for treating chronic hepatitis C, according to the IDEAL Study, reported in the July 22 online edition of the *New England Journal of Medicine*.

In this trial, sponsored by PegIntron manufacturer Schering-Plough, J.G. McHutchison and colleagues at 118 U.S. sites enrolled 3070 previously untreated patients with HCV genotype 1. Participants were randomly assigned to receive 1.5 (standard dose) or 1.0 (low-dose) mg/kg/week PegIntron plus 800-1400 mg/day weight-adjusted ribavirin, or else 180 mcg/week Pegasys plus 1000-1200 mg/day ribavirin for 48 weeks. Both regimens were administered according to their label direction, which allowed for a larger

range of ribavirin doses with PegIntron.

Patients receiving Pegasys had a higher end-of-treatment response rate but were also more likely to relapse, so sustained virological response (SVR) rates 24 weeks after completing treatment were similar: 40.9% with Pegasys, 39.8% with standard-dose PegIntron, and 38.0% with low-dose PegIntron. In all arms, response rates were higher among patients who achieved rapid or early virological response at weeks 4 or 12. The safety profile was similar across all three groups, with about 10% experiencing serious adverse events. The researchers concluded that, "the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon-ribavirin regimens or be-

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tween the two doses of peginterferon alfa-2b."

Kidney Disease

Interferon-based treatment is safe for chronic hepatitis C patients with end-stage renal (kidney) disease, or ESRD, according to a report in the May-June 2009 *Journal of Clinical Gastroenterology*. W. Hakim and colleagues enrolled 20 ESRD patients, mostly with HCV genotype 1, in a nonrandomized observational pilot study. Ribavirin is processed by the kidneys, so people with kidney disease may need lower doses. Study participants started on 135 mcg/week pegylated interferon (lower than the standard dose) and ribavirin was added four weeks later, beginning with 200 mg once weekly and gradually increasing to three times weekly; treatment continued for 48 weeks.

Of the 20 enrolled patients, five withdrew before starting treatment. Of the 11 who completed 12 weeks of therapy, six (55%) achieved early virological response (at least a 2-log drop in HCV viral load). Among the five patients treated for 48 weeks, however, only one achieved SVR. Treatment was generally well-tolerated, with four cases of anemia. This study, the researchers concluded, "demonstrates that combina-

tion therapy is a safe therapeutic option in the ESRD population with HCV infection which needs further testing to determine if increasing the length of treatment and/or the dose of ribavirin will affect posttreatment [response] rates."

Late ALT Increases Predict Relapse

Increases in ALT late in the course of hepatitis C treatment may predict of relapse, according to a study in the May 2009 *Hepatology*. M. Basso and colleagues from Italy looked at 173 chronic hepatitis C patients treated with pegylated interferon plus ribavirin, 58% of whom achieved SVR and 13% of whom responded but later relapsed. Overall, one-third of participants with undetectable HCV viral load had elevated ALT measured during at least one study visit.

ALT elevations during the early weeks of treatment were not associated with sustained response versus relapse, but elevations occurring between week 12 and the end of treatment were ten times more common among relapsers compared with sustained responders (90% vs. 9%). "Although ALT elevation *per se* is not associated with a greater risk of relapse, its occurrence in the later phases of therapy is more

common in relapsing patients," the researchers stated.

Consensus Interferon

Consensus interferon plus ribavirin produces a sustained response in some previous nonresponders, according to a study published in the June 2009 *Hepatology*. In the DIRECT study, B. Bacon and colleagues enrolled 487 hard-to-treat chronic hepatitis C patients. Almost all had HCV genotype 1, 80% experienced minimal response to previous treatment with pegylated interferon plus ribavirin (others responded but later relapsed), about 70% had high baseline HCV viral load, 59% had advanced liver fibrosis or cirrhosis, and about 20% were African-American. Participants were randomly assigned to receive either 9 or 15 mcg/daily consensus interferon plus ribavirin or else no further treatment. At week 24, patients with continued detectable viral load stopped treatment, early responders remained on therapy for 24 more weeks, and the initially untreated control group joined the treatment arms.

Overall sustained response rates were low, with 7% of

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patients in the 9 mcg consensus interferon group and 11% in the 15 mcg group achieving SVR. Sustained response rates were higher, however, among prior relapsers (versus those who never responded at all) and patients with lower baseline fibrosis scores. Previous partial responders without cirrhosis who had experienced at least a 2-log viral load decrease during their prior treatment reached an SVR rate of 32%. Adverse events were common, but few participants discontinued treatment for this reason.

Losartan for Liver Fibrosis

The blood pressure drug losartan may improve liver fibrosis, according to a small study published in the June 2009 *Gastroenterology*. F. Oakley and colleagues from the U.K. first performed laboratory studies to assess the effects of two natural cytokines – angiotensin II and IκB kinase (IKK) – that regulate the activity of nuclear factor kappa-B (NFκB), which promotes fibrosis. In rat liver tissue, agents that inhibited angiotensin-converting enzyme (ACE) and IKK led to fibrosis regression.

They then conducted an open-label clinical trial in

which 14 chronic hepatitis C patients with advanced liver fibrosis but no history of decompensation were treated with 50 mg/day losartan (Cozaar), an ACE inhibitor, for 18 months. Paired pre- and post-treatment biopsies showed that half the participants initially had high NFκB levels, but these fell after losartan administration. In addition, losartan was associated with reduced build-up of fibrotic scar tissue. "This early stage trial has shown that we can shrink liver scarring in some patients and shows promise for a treatment that could make a huge difference to the lives of thousands of people," study coauthor Derek Mann suggested.

HIV Treatment Reduces Liver Inflammation

Combination antiretroviral therapy (ART) is associated with reduced liver necroinflammation and lower fibrosis scores in HIV/HCV coinfecting patients with high CD4 cell counts, according to a cross-sectional study published in the May 15, 2009 *AIDS*. J.F. Pascual-Pareja and colleagues from Spain collected liver biopsy specimens from 119 coinfecting patients with relatively well-preserved immune function as indicated

by a CD4 count of at least 350, the threshold for starting ART according to current HIV treatment guidelines. Most (78%) were on combination ART, the median CD4 cell count was 549, and 40% had undetectable HIV viral load. Half had a high HCV viral load (> 800,000 copies/mL), however, and 74% had HCV genotypes 1 or 4.

Biopsies showed that 23% had advanced fibrosis and 66% had significant steatosis (fat accumulation in liver cells). In a single-factor analysis, heavy alcohol use, elevated ALT, steatosis, and high fibrosis scores were significantly associated with greater necroinflammatory activity. In a multivariate analysis, high ALT, advanced fibrosis, and not using ART were linked to greater necroinflammation. These results, the researchers said, suggest that combination ART might decrease hepatitis C activity in HIV/HCV coinfecting patients with a CD4 cell count above 350, adding to a growing body of evidence favoring earlier HIV treatment.

