

Hepatitis C

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HCV/HIV Coinfection Results Published

In Roche's APRICOT trial, Francesca Torriani and colleagues randomly assigned 868 HCV/HIV coinfecting patients to receive standard interferon plus ribavirin, pegylated interferon (Pegasys) monotherapy, or Pegasys plus ribavirin for 48 weeks. After 72 weeks, 40% of patients treated with Pegasys/ribavirin achieved a sustained virological response (SVR), compared with 20% of those receiving Pegasys monotherapy and 12% of those receiving standard interferon/ribavirin. Among patients with genotype 1 HCV (about two-thirds), the corre-

sponding rates were 29%, 14%, and 7%; for those with genotypes 2 or 3, the rates were 62%, 36%, and 20%. These Pegasys/ribavirin SVR rates are the highest yet seen in a coinfecting population.

In study ACTG 5071, (*New England Journal of Medicine* July 29, 2004, Vol 351) Raymond Chung and colleagues randomly assigned 133 participants to receive standard interferon or Pegasys, both with escalating doses of ribavirin. After 72 weeks, the overall SVR rates were 27% for Pegasys/ribavirin and 12% for standard interferon/ribavirin. Among subjects with genotype 1 (about three-quarters), SVR rates were 14% in the Pegasys arm and 6%

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Hepatitis Journal Review

*A publication of the Hepatitis C
Support Project*

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in the standard interferon arm; for those with genotypes 2 or 3, the rates were 73% and 33%, respectively. Upon liver biopsy, 35% of patients without virological clearance still showed evidence of histological response. It is unclear why the SVR rates were lower for ACTG 5071 compared with APRICOT. In ACTG 5071, the relapse rate during the post-treatment follow-up period was high in the Pegasys arm, perhaps due to the low initial ribavirin dose. Also, ACTG 5071 included more African Americans (about 33%) than APRICOT (about 10%), a group that responds less well to HCV treatment.

In an editorial in the same issue, Jean-Michel Pawlotsky discussed the treatment of hepatitis C in “difficult to treat” patients including those with HIV. The studies by Torriani and Chung, he wrote, “show that a sustained virologic response can be achieved with pegylated interferon alfa and ribavirin therapy in a

substantial proportion of coinfecting patients.” Although SVR rates for HCV/HIV coinfecting patients remain lower than those for patients with HCV alone, “[t]hese results, together with the poor prognosis for HIV-positive patients with HCV infection, justify broad use of antiviral therapy in the treatment of coinfecting patients.” Pawlotsky suggested that the availability of new classes of hepatitis C drug—including HCV polymerase, helicase, and protease inhibitor—could provide renewed hope for patients who do not respond to current therapies.

BILN 2061 and Genotype

Research clearly shows that genotype 1 HCV is harder to treat with interferon-based therapy, and that sustained response rates are high—twice as high in some studies—in people with genotypes 2 or 3. But a new HCV protease inhibitor may help reverse this imbalance. In the July 2004 issue of the *Journal of Virology*, Diane Thibeault and col-

leagues from Boehringer Ingelheim reported on a study of the sensitivity of the NS3 serine proteases from different genotypes of HCV to the experimental protease inhibitor BILN 2061. Laboratory sensitivity studies showed that BILN 2061 has less affinity for (in other words, is less likely to bind to and deactivate) proteases from genotype 2 and 3 HCV compared with genotype 1. The researchers substituted residues near the inhibitor-binding site of genotype 1b protease with residues from genotype 2b or 3a, to determine which residues account for the difference. They found that five residues (at positions 78, 79, 80, 122, and 132) account for most of the reduced sensitivity of genotype 2b, while a single residue (168) accounts for the reduced sensitivity of genotype 3a. Despite this lower sensitivity, however, the researchers concluded that BILN 2061 “remains a potent inhibitor of these non-genotype-1 NS3-NS4A proteins,” suggesting that “there is potential for BILN 2061 as an antiviral agent for individuals in-

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ected with non-genotype-1 HCV.”

Normal-Protein Diet for Hepatic Encephalopathy

Traditionally, restriction of protein in the diet has been recommended for the management of hepatic encephalopathy (HE). This condition occurs in patients with cirrhosis whose livers can no longer filter out neurotoxic substances such as ammonia. Symptoms range from mild cognitive impairment to lethargy, personality changes, and coma. (Note: the “brain fog” often described by people with HCV is not a sign of HE). Ammonia is produced in the intestines when amino acid—the building blocks of protein—are broken down, and thus it was thought that limiting the amount of dietary protein could improve encephalopathy. However, protein restriction has fallen out of favor for patients with chronic HE because it can worsen the malnutrition and muscle wasting often seen in individuals with advanced liver disease.

Protein restriction during intermittent encephalopathy episodes or flare-ups remains controversial, and there has been surprisingly little clinical research on the subject. In the July issue of the *Journal of Hepatology*, Juan Córdoba and colleagues from Barcelona reported results from a study of dietary protein in patients with episodic HE. Thirty cirrhotic patients hospitalized for episodes of encephalopathy were randomly assigned to receive either a normal-protein diet (1.2gm/kg/day) or a low-protein diet for 14 days. The patients were also treated with other standard measures (e.g., lactulose enemas, antibiotics) to reduce the amount of ammonia in the blood. The researchers found that HE outcomes did not differ significantly between the two groups. During the study period, the two arms had similar levels of protein synthesis (muscle building), but the low-protein group had greater protein breakdown (muscle wasting). “Diets with a normal content of protein, which are

metabolically more adequate, can be administered safely to cirrhotic patients with episodic hepatic encephalopathy,” the researchers concluded. “Restriction of the content of protein of the diet does not appear to have any beneficial effect for cirrhotic patients during an episode of encephalopathy.”

In an editorial in the same issue, Kevin Mullen and Srinivasan Dasarathy lauded Córdoba and colleagues for undertaking this challenging study. “We now have for the first time some data that suggests that early introduction of oral protein at levels of 1.2gm/kg/day along with adequate oral calories does not delay recovery from HE,” they wrote. “The rationale for low protein diets in the short and long-term management of HE seems questionable based on the data presented in this manuscript....Not only do expert opinions indicate protein restriction should not be employed in the management of HE, but some data also supports these opinions.”

