

Hepatitis C

Telaprevir for Genotype 1 Nonresponders

The HCV protease inhibitor telaprevir combined with pegylated interferon plus ribavirin significantly improved response rates in people who did not achieve a cure with prior treatment, according to a study in the April 8, 2010 *New England Journal of Medicine*. In the Phase 2 PROVE-3 trial, J. McHutchison and colleagues studied 453 genotype 1 chronic hepatitis C patients who were nonresponders (60%) or relapsers (7% with viral breakthrough during therapy, 36% with relapse after completing treatment) to a prior course of pegylated interferon plus ribavirin for at least 12 weeks.

Participants were randomly assigned to four

treatment arms. Two groups received 750 mg telaprevir three times daily plus 180 mcg/week pegylated interferon alfa-2a (Pegasys) and 1000-1200 mg/day ribavirin for either 12 or 24 weeks, followed by either 12 or 24 additional weeks of pegylated interferon/ribavirin alone. The third group received telaprevir plus pegylated interferon without ribavirin for 24 weeks, and the fourth received standard therapy for 48 weeks.

Sustained virological response (SVR) rates in the telaprevir arms were significantly higher than in the standard therapy arm. Rates were similar for the 12-week and 24-week telaprevir triple therapy arms (51% and 53%, respectively), lower in the ribavirin-sparing

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arm (24%), and lowest in the standard therapy arm (14%); response rates were higher for prior relapsers than for prior non-responders. Relapse rates were 30% and 13% in the 12-week and 24-week triple therapy arms, but considerably higher in participants who did not take ribavirin or who received standard therapy (53% for both). Treatment discontinuation due to adverse events occurred more often in the telaprevir arms than the standard therapy group (15% vs 4%), with skin rash being the most common side effect; anemia was also more frequent in the telaprevir arms.

The researchers concluded, "In HCV-infected patients in whom initial peginterferon alfa and ribavirin treatment failed, retreatment with telaprevir in combination with peginterferon alfa-2a and ribavirin was more effective than retreatment with peginterferon alfa-2a and ribavirin alone." However, they stressed, inclusion of ribavirin was necessary for optimal response. Vertex plans to request U.S. Food and Drug Administration approval of telaprevir later this year.

Milk Thistle Inhibits HCV Polymerase

With the growing emphasis on directly-targeted antiviral agents to treat hepatitis C, researchers have explored whether herbal remedies traditionally used for liver disease might have similar activity. As described in the March 2010 *Gastroenterology* A. Ahmed-Belkacem and colleagues from France and Germany used laboratory models to evaluate whether active compounds in silymarin^{3/4} derived from the milk thistle plant *Silybum marianum*^{3/4} could inhibit the HCV polymerase and protease enzymes, which play crucial roles in viral replication.

Milk thistle compounds including silibinin A, silibinin B, and Legalon SIL (a commercial intravenous silibinin preparation) inhibited the function of HCV polymerase, but not HCV protease. Silibinin A and B inhibited HCV replication in both a genotype 1b replicon model and a genotype 2a cell culture model. "Our results provide a basis for the optimization and subsequent development of members of the flavonoid family as

specific HCV antivirals," the researchers concluded.

Rifaximin for Hepatic Encephalopathy

The antibiotic rifaximin maintained remission from hepatic encephalopathy, or brain impairment related to liver dysfunction, according to a study in the March 25, 2010 *New England Journal of Medicine*. Hepatic encephalopathy is caused by build-up of toxic substances such as ammonia when the liver is unable to perform its normal filtering function (decompensated cirrhosis). Since some of these toxins are produced by bacteria in the gut, N. Bass and colleagues evaluated the efficacy of rifaximin^{3/4} a broad-spectrum antibiotic that concentrates in the gastrointestinal tract^{3/4} for preventing recurrent episodes of hepatic encephalopathy.

The Phase 3 study included 299 participants in the U.S., Canada, and Russia who had experienced at least two episodes of hepatic encephalopathy during the past six months. Patients were randomly assigned to receive either 550 mg

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twice-daily rifaximin or placebo for six months; most also took lactulose, a laxative used to reduce ammonia in the gut.

In an intent-to-treat analysis, rifaximin reduced the risk of recurrent encephalopathy by 58%, significantly more than placebo; 22% of patients in the rifaximin group experienced breakthrough episodes compared with 46% in the placebo group. Patients using rifaximin were also significantly less likely than placebo recipients to be hospitalized due to hepatic encephalopathy (14% vs 23%, respectively).

"Over a six-month period, treatment with rifaximin maintained remission from hepatic encephalopathy more effectively than did placebo," the study authors concluded. They added that because rifaximin concentrates in the gut and is minimally absorbed, it appears to cause fewer side effects and may be less likely to promote bacterial drug resistance than systemic antibiotics.

Liver Cancer Survival Disparities

Liver cancer survival varied across racial/ethnic

and socioeconomic groups despite similar treatment, according to a study in the March 1, 2010, *Cancer*. A. Artinyan and colleagues investigated outcomes among patients with hepatocellular carcinoma (HCC) stratified by race, ethnicity, and income level, hypothesizing that differences in survival might result from inequities in access to care. The analysis included 20,920 HCC patients with localized liver tumors from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database and 4735 people from the United Network for Organ Sharing (UNOS) database who received liver transplants due to HCC.

Overall, survival with HCC improved significantly over time for all racial/ethnic and income groups. Individuals diagnosed with HCC in 2000-2004 had four-fold higher survival rate than those diagnosed during the 1970s. Blacks patients, however, had the worst overall long-term survival, while Asians had the best survival. People with middle and high income levels also had significantly better odds of survival than low-income

individuals. Patients who underwent tumor resection (surgical removal), tumor ablation (destruction in the body), or liver transplantation had a significantly higher likelihood of survival than those not receiving such therapy, but blacks still had a 15% higher risk of death after controlling for type of treatment received. Among transplant recipients, blacks again had the worst graft (donor liver) survival and overall survival, while Hispanic patients had the best graft and overall survival.

"Significant racial and ethnic disparities in the outcome of patients with HCC persist despite the receipt of comparable treatment," the investigators concluded. "[O]ur study demonstrates that survival disparities by race and ethnicity cannot be explained by access issues alone, and other factors need to be considered."

HIV/HCV Coinfection and Immune Activation

HIV/HCV coinfecting women with detectable HCV viral load had greater immune activation than women with HIV alone, which was associ-

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ated with a higher risk of progression to AIDS, according to a study in the March 15, 2010 *Journal of Infectious Diseases*. A growing body of evidence indicates that increased CD4 and CD8 T-cell activation is a risk factor for HIV disease progression and non-AIDS conditions such as cardiovascular disease; having two coexisting active infections may further increase the risk.

A. Kovacs and colleagues analyzed the risk of onset of clinical AIDS and AIDS-related deaths among 813 HIV positive women without HCV, 87 HIV/HCV coinfecting women with undetectable HCV viremia, and 407 coinfecting women with detectable HCV RNA; the average CD4 cell count was 439, indicating relatively well-preserved immune function.

HIV/HCV coinfecting women with detectable HCV had a significantly higher percentage of activated CD8 T-cells than HIV monoinfecting women. Over a median five years of follow-up, coinfecting women were nearly twice as likely to progress to AIDS or die of AIDS-related causes compared with HCV negative women, even if

they never had a CD4 count below 200 (the usual risk threshold for AIDS-defining opportunistic illness). The risk of disease progression or AIDS-related death was nearly three times higher among coinfecting women (but not HIV monoinfecting women) with the largest proportion of activated CD8 cells, while CD4 T-cell activation predicted progression in both coinfecting and monoinfecting women.

"Our finding of increased incidence of

AIDS-defining conditions in relation to high levels of immune activation suggests that there is impaired T-cell function in HCV positive viremic women that may potentially put them at higher risk of HIV disease progression compared with HCV negative women," the researchers concluded, suggesting that earlier treatment of HIV and hepatitis C may be beneficial for coinfecting individuals.

A vertical poster for a hepatitis awareness rally. The top left features the NVHR logo. The main text reads: "May 19, 2010 Noon United States Capitol Washington, DC". Below this is a photograph of the US Capitol building. The headline "This is hepatitis..." is in large red letters. The text continues: "Millions of Americans are infected with a 'silent killer' that can be prevented and treated. 15,000 Americans die needlessly each year. We will be silent no more! Join us as we rally to demand that Congress fully fund hepatitis programs in the United States! For more information about the rally or to endorse this event please visit www.NVHR.org or www.facebook.com and search for This is hepatitis. For more information, contact info@nvhr.org". A vertical red bar on the left side contains the text "Save the Date!" in white.

NVHR
May 19, 2010
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United States Capitol
Washington, DC

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