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Hepatitis B

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Pegylated Interferon Improves Liver Health, Adding Lamivudine Yields No Benefit

Treatment with pegylated interferon appears to decrease liver inflammation and scarring in patients with hepatitis B “e” antigen (HBeAg)-positive infection. Surprisingly, the addition of the antiviral lamivudine (Hepsera) to interferon treatment conferred no added benefits, though the antiviral reduces replication of the hepatitis B virus (HBV).

The findings, published in the May 2006 edition of *Liver International*, were reported by a group of multinational researchers. In a double-blinded, randomized study, researchers followed 110 HBeAg-positive pa-

tients treated for 52 weeks with a once-weekly injection of pegylated interferon in combination with either lamivudine or placebo. Liver biopsies were taken before and after treatment ended.

A decline in inflammation was noted in 25 patients (48%) of the combination group and in 31 patients (53%) of the interferon-only group. The fibrosis score improved in 17 patients (33%) of the combination therapy group and in 13 patients (22%) receiving just interferon.

As expected, those who lost HBeAg and developed “e” antibodies (seroconversion) showed a larger decline in inflammation and fibrosis than non-responders.

Some HBV Patients Have Natural Resistance to Both Lamivudine and Adefovir

Researchers have long thought that HBV develop resistance to the antivirals lamivudine and adefovir (Hepsera) only after prolonged treatment and a natural selection process. They assumed that during treatment, the HBV that do not have resistance to the antiviral die out and the small number of HBV with mutations that allow them to replicate despite the presence of the antiviral multiply and eventually become the majority HBV in a patient.

But an article in the April 27 issue of *The New England Journal of Medicine* reports that some patients already

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have large quantities of HBV that are naturally resistant to the two antivirals. In these patients, the antiviral tenofovir (Viread) was effective at controlling HBV. Antivirals work by meddling with the HBV' genetic material so it cannot replicate effectively.

The German researcher found the naturally-occurring resistant HBV infected three patients. "Our observations demonstrate that some naturally-occurring HBV strains are primarily resistant to adefovir," they wrote. The HBV with the mutations were present before the patients were treated with adefovir.

Whether the patients were positive or negative for HBeAg had no impact on the presence of the adefovir- and lamivudine-resistant HBV.

Some HBV Genotype Subtypes Determine Treatment Response and May Escape Blood Screening Tests

A group of researchers, writing in the 2006 issue of the *Journal of Medical Virology*, ex-

plored the impact of different strains of HBV, called genotypes, and the variety of subtypes within each genotype, on treatment, identification and prevention of hepatitis B.

The HBV genotypes that exist around the world have developed in specific regions. Genotypes, and the subtypes within each genotype, are defined by genomic sequencing, and the molecular make-up of the HBV surface antigen (HBsAg), the protein that covers the virus.

The viral subtypes are known as HBV variants, and some of them are responsible for pre-core HBV, which are much more difficult to treat.

"Viral variants displaying changes in HBsAg seem to be very common among chronic HBV carriers; and some of these variants may emerge under the pressure of the neutralizing antibody response, leading to vaccine resistance and resistance to immunotherapy," the researchers wrote.

For example, some liver transplant patients and babies born to HBV-carrier mothers still become infected,

even after treatment with an HBV vaccine and hepatitis B antibodies (HBIG) to fight infection after exposure.

Also alarming, some of the HBV with HBsAg variants are not detected by HBsAg tests used to diagnose HBV in people and blood donors. In another journal article in this issue, researchers concluded that it was possible for blood tests to miss HBV infections in people infected with genotypes E or F. Better tests for HBsAg from all HBV genotypes and subtypes are needed, scientists wrote.

Researchers: Urgent Study Needed for Drug-Resistant HBV Mutations

Australian researchers examined the impact of antiviral therapy on development of HBV mutations in the April 2006 issue of the *Journal of Medical Virology*. HBV have a weak genetic blueprint, which allows them to mutate easily to avoid the impact of attacking antibodies or antiviral therapy.

Over time, the HBV

mutants that can resist treatment or attack by the immune system become the dominant or majority HBV in a patient. The rapid rise of antiviral drug-resistant HBV mutants depend on:

- How quickly HBV mutate
- The ability of the mutation to avoid an antiviral drug
- The effectiveness of the antiviral drug
- The rate of viral replication
- The "replication fitness" of the mutant HBV
- And the availability of replication space.

Researchers express concern that, "Only a limited number of HBsAg mutations selected during antiviral treatment have been characterized (identified) and the diagnostic and public health implications of these mutations need further investigation," they wrote. "Clearly, improved treatment strategies are required urgently to prevent the continued selection of HBV drug-resistant mutants.

Mutations and Genotype Impact Viral Load in HBeAg-Negative Patients

A group of researchers, writing in the May 2006 issue of the *Journal of Viral Hepatitis*, examined the impact of mutations on HBeAg-negative patients infected with either HBV genotype B or C.

Of 79 patients, 53 (67%) were infected by HBV genotype B and 26 (33%) were infected by genotype C virus. The quantity of HBV in the bloodstream (called viral load or HBV DNA) were similar in the two groups.

However, genotype B was significantly associated with precore mutation (92.5%), and more mutations within nucleotide 1809-1817 were detected in patients infected by genotype B as compared with those infected by genotype C (18.9% vs 3.8%).

“In conclusion, minor HBV variants with mutations in the core promoter and precore region were detectable in genotypes B and C,” and appear to impact patients’ HBV DNA levels, they wrote. These HBV variants

appear to be associated with certain genotypes.

Patients with Severe Liver Disease Have More HBV Mutations

Taiwanese researchers report that hepatitis B patients with progressive liver disease may have a higher frequency of HBV mutations, according to their report published in the April 2006 issue of *Gastroenterology*.

They compared the HBV in 46 patients to the HBV in 106 age-matched patients with varying stages of liver disease.

A higher prevalence of mutations was found in carriers with progressive liver diseases. “Our data indicate that patients with progressive liver diseases have a higher frequency of pre-S deletion (a type of viral mutation),” they wrote.

Diabetes May Worsen Liver Fibrosis in Patients with Hepatitis B or C

A group of researchers evaluated the prevalence of diabetes and the severity of liver

damage in 434 patients infected with either HBV or the hepatitis C virus (HCV). Diabetes was found in 58 (13%) of the HBV- and HCV-infected patients.

The presence of diabetes was independently associated with more severe fibrosis or presence of cirrhosis, as well as the presence of hepatic steatosis and increased serum triglycerides levels.

In the noncirrhotic patients, diabetes was significantly associated with older age and higher GGT levels, but not with the extent of fibrosis.

Writing in the May 2006 issue of the *Journal of Viral Hepatitis*, the researchers concluded that diabetes is “strongly associated with more severe liver fibrosis, but such an association may be related to the high prevalence of diabetes in patients with cirrhosis.”

Lamivudine and Thymosin May Help HBV Patients with Liver Cancer

Chinese researchers treated two groups of HBV patients with liver cancer who had

liver tumors removed. One group of 17 received no treatment, while the other 16 received the antivirals lamivudine and thymosin alpha 1. Both were followed for nearly three years.

Writing in the March-April issue of *Hepato-gastroenterology*, the doctors reported that the one-year HBV-DNA suppression rate was 100% for the treated group, compared to 6% for the untreated group. The HBeAg seroconversion rate was 62.5% vs. 5.9% respectively and the average survival time was 10 vs. seven months.

Antiviral therapy using lamivudine and thymosin alpha 1 after transplantation may suppress HBV, they wrote, and prolong the survival for liver cancer patients who are HBV infected.

Lamivudine Highly Effective in Treating Severe Acute Hepatitis B

About 1% of people who suffer acute hepatitis B – a sudden onset of HBV infection with severe liver damage – require a liver trans-

plant or die. A group of German researchers treated 17 acute HBV patients with lamivudine to see if the antiviral would prevent death or the need for a transplant.

In the April 2006 issue of the *Journal of Viral Hepatitis*, the group reported that 14 of the treated 17 patients survived and experienced a full recovery without transplants. The 14 cleared HBsAg on lamivudine within six months.

The three patients who required transplantation despite lamivudine therapy had more advanced disease and liver damage upon admission to the hospital.

“Lamivudine is safe in patients with severe acute or fulminant hepatitis B, leading to fast recovery with the potential to prevent liver failure and liver transplantation when administered early enough,” researchers reported.

Viral Load and Viral Mutations Play Role in Liver Cancer Development

To date, no one knows exactly what

viral trigger causes liver cancer to develop in people infected with HBV. A group of Taiwanese doctors, writing in the May 2006 issue of the *Journal of Infectious Diseases*, compared gender, genotype, viral mutations and viral load in 160 people with HBV and 200 patients with liver cancer.

They found that male gender, advanced age, and precore and basal core promoter mutations and viral load were independently associated with the development of liver cancer. However, viral load and viral mutations appeared to play the most important role in development of liver cancer, they noted.

48 Weeks of Pegylated Interferon Better than 24 to Achieve HBeAg Seroconversion

A group of researchers found 48 weeks of pegylated interferon was more effective than limiting treatment to 24 weeks in spurring seroconversion, according to their report published in the April 2006 issue of *Alimentary Pharmacology & Therapeutics*.

They studied 53 HBeAg-positive Chinese patients, of whom 29 were treated for 48 weeks and 24 for 24 weeks to see which group lost HBeAg and developed the “e” antibody and undetectable HBV DNA.

At the end of treatment, viral load and seroconversion rates were similar in both groups, but at week 72, after treatment ended, 10 of the 29 patients (34.5%) treated for 48 weeks compared sustained their seroconversion while only two of the 24 patients (8.3%) treated for 24 weeks maintained their “e” antibody and undetectable HBV DNA.

Pegylated Interferon Produces Durable Response in HBeAg-Positive Asians

After 48 weeks of pegylated interferon, 83% of Asian patients who experienced HBeAg seroconversion maintained their “e” antibody status 12 months after treatment ended, according to a report presented at the Shanghai-Hong Kong International Liver Congress 2006.

An additional 15% of

the patients seroconverted later, six to 12 months after treatment concluded.

Researchers reported that 150 Asian patients participated in the study and 58 (39%) achieved HBeAg seroconversion by six months after treatment ended. In comparison, only 19% of patients who received only lamivudine achieved seroconversion.

Telbivudine Superior to Lamivudine Regardless of Patient ALT, Viral Load or Ethnicity

In another report presented at the Shanghai-Hong Kong International Liver Congress 2006, researchers touted the superiority of the antiviral telbivudine over lamivudine.

They found after one year of treatment, telbivudine produced:

- Greater HBV DNA suppression in HBeAg-positive patients with elevated ALT levels.
- Greater HBV DNA suppression in HBeAg-positive Asian patients, compared to North American patients
- Greater HBV DNA

suppression in HBeAg-positive and HBeAg-negative Asians compared to patients of other ethnicities.

Telbivudine is an orally L-nucleoside analogue that inhibits HBV polymerase. The study focused on 1,367 patients who received either telbivudine at 600 mg/day or lamivudine at 100 mg/day for 104 weeks.

They reported undetectable HBV DNA in 60% of HBeAg-positive patients treated with telbivudine at week 52, vs. 40% of the lamivudine-treated group.

Small Study of Immunotolerant Children Suggests Combo Treatment May Work

British researcher Giorgina Mieli-Vergani of King's College Hospital suggests that combining lamivudine with interferon alpha can help some HBV-infected children who are in the “immuno-tolerant” infection stage, when the immune system does not attack the HBV-infected liver cells.

Historically, doctors

have not treated children or young adults who have normal ALT levels, are HBeAg-positive, and have high viral load.

Mieli-Vergani treated 23 children, average age 10, with eight weeks of lamivudine, before adding alpha interferon (three injections weekly) to the treatment for ten months. At the end of the treatment, 78% of children had become HBV-DNA negative. Five children (22%) seroconverted and developed “e” antibodies and four (17%) completely cleared the virus, becoming HBsAg negative and developing surface antibodies. There were no changes in the 40-month follow-up period.

Writing in the *Journal of Pediatrics*, she encouraged more trials to see if the combination treatment would work in a larger number of children.



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