

# HBV JOURNAL REVIEW

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## Hepatitis B

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### **Global Hepatitis B Study Finds Telbivudine Superior to Lamivudine**

A global study of 1,367 adults infected with the hepatitis B virus (HBV) found 52 weeks of treatment with the oral antiviral telbivudine reduced viral load (HBV DNA) more dramatically than treatment with the antiviral lamivudine (Epivir HBV). The study was presented at the Digestive Diseases Week 2006 in Los Angeles in May 2006.

The decline in viral load was seen in patients regardless of their hepatitis B “e” antigen (HBeAg) status. In HBeAg-positive patients taking telbivudine, HBV DNA rates dropped 6.5-fold compared to 5.5-fold in lamivudine patients. HBeAg-negative patients taking telbivudine achieved a 5.2-fold de-

cline in HBV circulating in their bloodstream, compared to a 4.4-fold decline in the lamivudine-treated patients.

The findings are from Phase 3 of the GLOBE study, which monitors overall therapeutic response to antivirals, including HBV DNA levels, alanine aminotransferase (ALT) levels (elevated ALT levels indicates liver cell damage) and loss of HBeAg in patients.

HBeAg-positive patients achieved a higher overall response rate (76%) after one year of telbivudine, compared to 67% who responded to lamivudine. HBeAg-negative patients had similar responses to telbivudine and lamivudine (75% vs. 77% respectively).

Researchers reported significantly less viral resistance to telbivudine

than lamivudine.

Telbivudine was associated with fewer and less severe flares or sudden increases in ALT levels than lamivudine.

A final report from the GLOBE trial is expected later this year. The study includes patients from 20 countries, and is the largest hepatitis B trial ever conducted.

The U.S. Food and Drug Administration (FDA) has not yet approved telbivudine for treatment of hepatitis B.

**Telbivudine Also More Effective than Adefovir at Week 24 in HBeAg-Positive Patients**

### **Telbivudine proved more effective than the antiviral adefovir**

(Hepsera) after 24 weeks of treatment in HBeAg-positive patients,

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according to a report presented at the 41<sup>st</sup> Annual Meeting of the European Association for the Study of the Liver (EASL) in Vienna.

In the study, 90 patients received adefovir and 45 received telbivudine (600 mg/day). At Week 24, half of the adefovir group was switched to telbivudine and the other half remained on adefovir. Patients who originally started on telbivudine remained on the antiviral.

Telbivudine proved to be superior to adefovir in lowering viral load at Week 24 (6.3-fold vs 4.9-fold respectively). The percentage of patients with undetectable HBV DNA was 38.6% vs 12.4% for telbivudine and adefovir respectively. In addition, more patients responded to telbivudine than adefovir.

The proportion of patients who achieved normal ALT was not significantly different between the groups at Week 24. However, a greater percentage lost HBeAg with telbivudine (16%) compared to adefovir (10%) at Week 24.

### **Patients with Lamivudine Resistance Develop Adefovir Resistance Faster**

South Korean researchers, writing in the May 2006 issue of *Hepatology*, report that patients with lamivudine-resistant HBV may develop viral resistance to adefovir faster than those without lamivudine resistance. This is significant because many with lamivudine resistance are often switched to adefovir before other antivirals are tried.

The researchers examined the genetic make-up of HBV in 57 lamivudine-resistant patients and 38 patients who had never been treated before during 48 weeks of adefovir treatment. They monitored the patients for increases in HBV DNA, which would indicate that the HBV were able to resist adefovir and replicate. Antivirals muddle with the virus' genetic material to prevent viral replication.

"The emergence of ... [viral] mutations was more common in lamivudine-resistant patients than in treatment-naive patients after 48 weeks of adefovir therapy and was associated with reduced antiviral efficacy to drug treatment," they reported.

### **Pegylated Interferon Benefits Increase Even After Treatment Stops**

Researchers have reported that 48 weeks of pegylated interferon treatment tends to produce higher rates of HBeAg seroconversion and lower viral load in HBeAg-positive patients than does lamivudine treatment alone. Hong Kong doctors decided to extend this study to see how these patients fared one year after pegylated interferon treatment ended.

Researchers, reporting at the EASL conference, monitored 172 patients (most were male and Asian). Six months after treatment ended, 32% of patients treated with interferon achieved HBeAg seroconversion or undetectable HBV DNA. After one year, 45% achieved HBeAg seroconversion, and 37% had undetectable viral load.

Of patients achieving HBeAg seroconversion during treatment or in the early days after treatment ended, 91% sustained this response one year later and 15% of patients developed late HBeAg seroconversion.

"A slightly higher HBeAg seroconversion rate was noted for geno-

type A compared with other genotypes," Dr. George Lau noted during his presentation. "In addition, declines in HBV DNA levels were greater in patients with early sustained HBV seroconversion," he added.

### **Entecavir Reduces HBV DNA and ALT in Lamivudine-Resistant Patients over Two Years**

A two-year study of the antiviral entecavir (Baraclude) found it achieved long-term reduction of viral load and normalization of ALT levels in patients who had failed to respond to lamivudine, according to a report presented at the Digestive Diseases Week conference.

The study monitored 286 HBeAg-positive patients over 96 weeks. Some received 1.0 mg/day of entecavir while others continued on lamivudine 100 mg/daily and then followed for 96 weeks. Eighty patients who responded but had still not seroconverted (produced the "e" antibody) continued on treatment after the first year (77 in the entecavir group and 3 in the lamivudine group).

Those who completely

cleared the virus and those who did not respond sufficiently to entecavir within the first year were discontinued from the drug.

During the second year, 30% of the entecavir group achieved undetectable HBV DNA, compared to only 1% of the lamivudine group. Seroconversion occurred in significantly more patients in the entecavir group than the lamivudine group (16% vs 4%).

Normalization of ALT levels was attained by 85% of the entecavir group compared to 29% of the lamivudine group.

Those who continued on entecavir a second year reaped additional benefits. At week 48, 21% of the 77 entecavir-treated patients achieved viral response compared to 40% at week 96. ALT normalization was achieved by about an additional 20% of patients in the second year.

Viral resistance developed in 9% of entecavir patients during the second year.

**Entecavir Better than Lamivudine in Patients Treated with an Antiviral for the First Time**

Another report presented at the EASL conference determined that entecavir was more effective than lamivudine in patients who had never been treated with antivirals before.

Researchers in Shanghai treated 258 patients with entecavir and 261 patients with lamivudine for at least 52 weeks.

About 86% of the patients were HBeAg positive, and all had high viral loads and elevated ALT levels. Ultimately, low viral load and normal ALT was achieved in 90% of the entecavir group and 67% of the lamivudine group.

HBV DNA declines by Week 48 were 5.9-fold for entecavir and 4.3-fold for lamivudine. At Week 48, HBeAg seroconversion was similar for entecavir (15%) and lamivudine (18%).

**Adefovir Resistance Surfaces in 29% of HBeAg-Negative Patients after Five Years**

Another report presented at the EASL con-

ference found that only 29% of 123 HBeAg-negative patients developed viral resistance to adefovir after five years of treatment.

After five years, HBV resistance to adefovir developed in 29% of patients and 16% had a surge in HBV DNA and 11% experienced an increase in ALT levels.

**Patient Develops Dual Viral Resistance to Both Adefovir and Lamivudine**

South Korean researchers attending the EASL conference reported on a case of a 58 year-old man with HBeAg-positive hepatitis B who had been treated with lamivudine for 23 months. He developed viral resistance and doctors stopped lamivudine and switched him to adefovir.

Within 16 months, he developed adefovir resistance so doctors added back lamivudine with poor results. Researchers discovered his HBV had mutations that could resist both antivirals. Doctors finally treated him with tenofovir, which suppressed his viral load.

“The multiple drug resistant mutation will be a troublesome question in the anti-viral therapy for

hepatitis B,” the researchers reported. A combination of antivirals or switching to a single, potent antiviral will be required in patients who develop multiple-drug resistance.

**New Antiviral LB80380 Appears Promising in HBeAg-positive, Lamivudine-Resistant Patients**

The experimental antiviral LB80380 (ANA380) appears to be safe and effective in HBeAg-positive patients with lamivudine-resistant HBV, according to the findings presented at the EASL conference.

After administration, LB80380 is converted to LB80317, a novel guanosine phosphonate nucleotide analogue (antiviral) that appears effective against lamivudine-resistant HBV.

The researchers investigated the drug’s safety and effectiveness in 65 Asian HBeAg-positive patients with lamivudine-resistant HBV, high viral loads and elevated ALT levels in this dose-ranging study.

The researchers reported HBV DNA reduction in the dose groups above 90 mg were higher

than those in the 30 and 60 mg groups, indicating a dose-response effect for LB80380.

**MMWR Study Finds 24% of Asian Emigrants in New York Infected with HBV**

A report in the May 12 issue of the U.S. Centers for Disease Control and Prevention's *Morbidity and Mortality Weekly Report* revealed an alarmingly high rate of chronic HBV infection in emigrants from Asian countries living in New York City.

The article, entitled "Screening for Chronic Hepatitis B Among Asian/Pacific Islander Populations-New York City, 2005," details a study by New York University School of Medicine researchers who screened 1,836 people for HBV. Of the 1,633 persons who had complete demographic information, 1,614 (98.8%) identified a country in Asia or the western Pacific as their place of birth. Researchers found 392 of 1,633 (24%) had chronic hepatitis B infection, 791 (48.4%) had resolved HBV infections, and 450 (27.6%) had no sign of past or present infection.

The prevalence of chronic HBV was higher in males, those ages 20 to 39, and residents who had been living in the United States for less than five years.

**Lamivudine Resistance Common in HIV-HBV Coinfected Patients**

Patients coinfecting with HBV and HIV commonly develop HBV with mutations that can resist lamivudine. Researchers, reporting in the April 4th issue of *AIDS*, examined HBV in a large population of coinfecting patients who had been treated with lamivudine for many months or years.

Those with detectable HBV had weaker immune systems, and higher rates of HIV RNA and ALT levels. Lamivudine-resistant HBV was present in 75% of the patients, and after four years of treatment.

The researchers stressed the importance of developing HBV antiviral therapy that reduces HBV DNA rapidly without allowing viral resistance to develop.

Patients with HIV and HBV coinfection who require treatment for both viruses should receive a combination of either

lamivudine plus tenofovir, or emtricitabine plus tenofovir, the researchers recommended. Patients who require treatment for HBV but not HIV, should receive either pegylated interferon or entecavir alone.

**Health Impact of Infection with Multiple HBV Genotypes Studied**

Researchers know little about the impact of infection with more than one genotype or strain of HBV. German researchers, reporting in the May 2006 issue of *Hepatology*, studied patients in Vietnam, Europe and Africa to analyze the impact of HBV genotypes, and multi-genotype infections, on liver disease.

They found genotype mixtures were more frequent in African than in Asian and European patients. In Asian patients, the predominant genotype mixtures included A/C and C/D, compared to C/D in European and A/D in African patients.

Genotype A was more frequent in asymptomatic hepatitis B patients, compared with patients with symptoms of liver disease. Genotype C was more frequent in patients with liver cancer.

Infection with more than one genotype was seen in more patients with chronic hepatitis, compared to those with acute or short-lived hepatitis B. Viral loads in patients infected with genotype mixtures were also significantly higher in comparison to patients with a single genotype.

**Diabetes May Worsen Liver Fibrosis in People with Hepatitis B**

Researchers examined 434 patients with either HBeAg-negative hepatitis B or hepatitis C to see if diabetes had an impact on their liver infection. Writing in the May 2006 issue of the *Journal of Viral Hepatitis*, researchers reported that diabetes was present in 58 (13%) of the patients, equally shared by HBV and hepatitis C patients.

Hepatitis patients with diabetes had a higher rate of liver damage, including fibrosis and cirrhosis. "The presence of 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," the researchers noted.

**After Five Years, Children Treated with Corticosteroid and Interferon Fared Best**

A group of British researchers revisited 44 children, all infected with HBV at birth, 20 of whom had been treated first with six weeks of prednisolone (a corticosteroid with anti-inflammatory properties) and then with 16 weeks of interferon alpha during the early 1990s.

The researchers compared the combination-treated children with children who received either no treatment or just interferon. At the time of treatment, all children had detectable HBV DNA and HBeAg.

Initially, researchers found the addition of the prednisolone produced no significant benefits, nor did the interferon treatment, according to their report published in the July 2006 issue of the *Journal of Medical Virology*.

However, after five years, the seroconversion rates were 54% for the prednisolone plus interferon-treated group, and 22% for the group treated with just interferon. Only 12% of the untreated children achieved seroconversion (loss of

HBeAg, and production of the “e” antibody.)

The average time to seroconversion was 3.9 years and was shortest in those treated with prednisolone plus interferon.

Children who had elevated ALT levels prior to treatment or during prednisolone “priming” before interferon began had a better response. None of the children lost hepatitis B surface antigen (HBsAg) or produced surface antibodies.

Treatment with prednisolone first, followed by interferon, improved both the time and rate of seroconversion compared to no treatment or interferon alone, the researchers concluded.



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