

# HBV JOURNAL REVIEW

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## Hepatitis B

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### **11% of HBeAg-Negative Patients Clear HBsAg Within Four Years of Treatment with Pegylated Interferon**

A study presented at the European Association for the Study of the Liver (EASL) conference in Italy in April found that four years after the completion of a one-year treatment of pegylated interferon, 11% of patients tested negative for the hepatitis B surface antigen (HBsAg).

The number of patients achieving HBsAg clearance increased each year even after treatment stopped, rising from 3% at year one, 6% at year two, 8% at year three, and 11% at year four.

The long-term bene-

fits of this interferon treatment are thought to be due to the persistence of its immune system-stimulating effects even after treatment ends. Unlike antivirals, such as lamivudine (Epivir-HBV), interferon works by fighting hepatitis B virus (HBV) infection by boosting the immune system and also directly attacking the virus.

Antivirals work by hindering viral replication, but they work only during actual treatment, so the infection generally rebounds when treatment ends. Only 2% of patients who take lamivudine, for example, are able to clear HBsAg.

The study followed 537 HBeAg-negative hepatitis B patients from 54 locations worldwide. It com-

pared the success of:

- 48 weeks treatment of pegylated interferon treatment at 180 mg once a week,
- 48 weeks treatment of pegylated interferon plus 100 mg of lamivudine,
- Or lamivudine alone.

Initial results showed pegylated interferon alone was most successful in suppressing HBV DNA (viral load) and normalizing alanine transaminase (ALT) levels six months after treatment ended. ALT levels rise when liver cells are damaged or die. The study unveiled at the EASL conference, reported on what happened to the 315 patients four years after treatment ended.

In addition to clearing HBsAg, significantly more patients main-

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tained undetectable HBV DNA compared to lamivudine (17% vs. 7%), and more patients had normal ALT levels (27% vs. 18%, respectively).

### **Interferon and Adefovir Combination, Followed by 96 Weeks of Adefovir, Produces Long-Term Viral Clearance**

German researchers followed 24 patients, who initially had been treated with 48 weeks of a combination of pegylated interferon and the antiviral adefovir (Hepsera), and were then treated with an additional 96 weeks of only adefovir.

During the early combination treatment period, patients experienced a decline of 2.4-fold in viral load. After adefovir therapy, at week 144, 12 of 15 patients who initially were HBeAg-positive lost HBeAg, 23 patients achieved normal ALT levels, and HBV DNA levels on average declined 4.9-fold, and were undetectable in 11 of the 24 patients at the end of the study.

Those who achieved undetectable viral load within the first 12 weeks of treatment were more likely to achieve long-

term benefits and lose both the hepatitis “e” antigen (HBeAg) and HBsAg. Liver health, determined by liver biopsies, improved in 11 of 16 patients. Two patients developed adefovir resistance during the third year of treatment, according to the report in the April 2008 issue of *Antiviral Therapy*.

### **Older Age, Higher Viral Load and Elevated ALT Increase Risk of Severe Fibrosis**

Hong Kong researchers performed liver biopsies on 60 patients to determine the prevalence of fibrosis and cirrhosis in Asians infected with HBV. According to their report in the April 2008 issue of the *American Journal of Gastroenterology*, they determined the following:

- Severe fibrosis (inflammation, which precedes cirrhosis or severe scarring) was more common in older patients, and was identified in 20% of patients ages 65 and older.
- Severe fibrosis was also more common in patients who tested positive for HBeAg, which usually indicates higher levels of viral reproduction, and those with high

viral loads.

- Patients who received antiviral treatment had lower ALT levels, less fibrosis and lower rates of cirrhosis.

Overall, the prevalence of severe fibrosis was 34%, with higher rates seen in older age groups, males, and in patients with higher ALT levels.

### **Adefovir Resistance Risk Remains Low in Lamivudine-Resistant Patients Treated with Lamivudine and Adefovir over Two Years**

Japanese researchers studied the effect of a combination of lamivudine and adefovir treatment in 132 patients, most of whom had HBV strain or genotype C, who had developed viral resistance to lamivudine, over two years of treatment.

The combination of the two antivirals effectively suppressed HBV reproduction and generated normal ALT levels (69% at 12 months and 81% at 24 months). Five of the 132 patients developed viral resistance to adefovir during the two-year period, according to the report in the April 2008 issue of the *Journal of Hepatology*.

### **Occult HBV, Which Exists Despite Presence of Surface Antibodies, Transmits Infection in Two Blood Transfusions**

Medical experts assume that blood donors who have antibodies to HBsAg cannot be actively infected with HBV, but a study published March 2008 issue of the *Journal of Hepatology* found HBV transmission in such circumstances.

Four months after receiving blood during bypass surgery, a male patient developed acute hepatitis B, and a second patient who received a transfusion developed hepatitis B seven months after the transfusion.

Researchers discovered HBV DNA in samples of the donated blood given to the two patients, despite the presence of surface antibodies. Increasingly, scientists are finding occurrences of “occult” HBV infection – when there are surface antibodies or no HBsAg, but HBV DNA is detectable in the bloodstream.

The occult infection is thought to occur when HBV has mutations in its HBsAg, which allow it to replicate despite the presence of HBsAg antibodies.

## **Core Antibodies Strong Indicator of Possible “Occult” HBV Infection**

Given the growing awareness and recognized prevalence of “occult” HBV infection – when HBV DNA and viral replication is present despite the absence of HBsAg or the presence of surface antibodies – Italian researchers decided to determine how many people with hepatitis B core antibodies (anti-HBc), which shows past infection, have an occult HBV infection.

Researchers detected core antibodies in the blood samples from 223 people, and they identified occult infections in 9 of the samples with anti-HBc. The occult infections were most prominent in samples with HBV genotype D.

The findings, published in the April 2008 issue of the *Journal of Medical Virology*, suggest that detection of anti-HBc alone is a strong indicator of possible occult HBV infection and that physicians should conduct HBV DNA tests to determine if infection is present.

## **Scientists Identify Key Difference Between People Who Can and Cannot Fight Off HBV Infection**

Researchers from University College London analyzed thousands of genes in T cells – the immune system’s fighter cells that vanquish HBV – and found that T cells from patients who were chronically infected were triggered to “commit suicide,” which could be why these patients’ immune systems could not clear the infection.

Researcher analyzed more than 5,000 genes in T cells from both recovered and chronically-infected hepatitis B patients and discovered that instead of successfully reacting to the virus, the T cells in the chronically-infected group were programmed to commit suicide by one of the cells’ own death-inducing proteins called Bim.

Researchers speculated that if they can develop safe ways of blocking the suicidal tendency of the T cells, they may be able to prolong their survival so they could combat HBV. The findings were published in the *Journal of Clinical Investigation*.

## **HBV Infection Also Increases Risk of Bile Duct Cancer**

While HBV infection has been known to cause liver cancer, a study published in the April 2008 issue of the *International Journal of Cancer* suggests HBV infection can also contribute to bile duct cancer.

The extrahepatic bile duct collects bile from the liver, but is located outside the liver. It joins with a duct coming from the gallbladder to form the common bile duct, which carries bile to the small intestine. Cancers of this extrahepatic bile duct are unusual and very difficult to treat.

In a study of HBV- and hepatitis C virus (HCV)-infected people in Shanghai, the National Cancer Institute in Maryland examined the prevalence of biliary tract cancers in 417 patients and biliary stones in 517 patients. The rate of cancer in the HBV- and HCV-infected group was compared to that of 762 healthy subjects.

They found that patients with extrahepatic bile duct cancer were more likely to test positive for HBV (14.2 percent), and concluded that HBV infection increased the risk of extrahepatic

bile duct cancer 2.4-fold.

There was no significant association between HBV and gallbladder cancer, bile duct stones and gallbladder stones. There did not appear to be a correlation between HCV infection and increased bile duct cancer.

HBV induces liver cancer primarily by causing chronic inflammation and tissue destruction with regeneration of liver cells, researchers suggest a similar process may be involved in bile duct cancers.

## **Phase II Clinical Trial Identifies 30mg as the Optimal Dose of the Antiviral Clevudine**

Researchers, conducting a multinational phase II trial of the experimental antiviral clevudine, tried daily doses of 10 mg, 30 mg and 50 mg on 31 HBV-infected patients over 12 weeks, and then monitored the patients over an additional 24 weeks.

Reporting in the April 2008 issue of *Alimentary Pharmacology & Therapeutics*, the researchers noted that at week 12, the average viral load declines were 3.2-fold, 3.7-fold and 4.2-fold at the 10-, 30-, and 50-mg

doses. At week 12, one out of 10, five out of 11, and two out of 10 patients had undetectable viral load respectively. As a result, researchers concluded that 30 mg was the most effective dose.

Clevudine was well tolerated with no severe or serious adverse events.

### **Protein Treatment Targets Liver Cancer Recurrence**

Mayo Clinic and National Cancer Institute researchers, writing in the April 2008 issue of *Hepatology*, report that the protein sulfatase 2 (SULF2)-- may be effective in treating liver cancer, which has been historically deadly and difficult to treat.

Researchers found that if they can decrease levels of SULF2, which degrades molecules that are part sugar and part protein, it could stop the growth of cancerous tumors. They hope to identify drugs that block SULF2.

### **Genotype C and High Viral Loads Lead to Liver Cancer Recurrence**

Researchers in China followed 106 liver cancer patients for 104 weeks,

measuring their HBV DNA and documenting their HBV genotypes, to determine what factors might lead to worsening or reoccurrence of the cancer.

They reported in the April 2008 issue of the *Journal of Medical Virology* that genotype C and elevated HBV DNA levels increased the risk of cancer recurrence.

Cancer recurred in 22% who had HBV DNA levels of less than 3 log copies/ml and in 80% of those with HBV DNA levels of 5 log copies/ml or greater.

Fifty-seven (74.0%) who had genotype C and 12 (41.4%) who had genotype B had cancer recurrence or worsening.

### **Clinical Trial Determines Best Adefovir Dosing Level in Children**

A multinational research team treated 45 children and adolescents with the antiviral adefovir in one of the first clinical trials of the antiviral in children to determine safe dosing levels.

Currently, lamivudine is the only antiviral approved by the U.S. Food and Drug Administration (FDA) for treatment of hepatitis B in children, and it is associated with a very high rate of viral

resistance.

Doctors administered 0.14 mg/kg and 0.3 mg/kg of adefovir oral solution to children ages 2 to 11, and a 10 mg pill to adolescents ages 12 to 17.

Researchers, writing in the February 2008 issue of *Hepatology*, reported the 0.3-mg/kg dose in children aged 2 to 6 and the 10-mg dose in adolescents resulted in optimal results that were on par with those seen in adults treated with 10 mg. Adefovir was well tolerated at the doses evaluated in this study.

### **Conventional Interferon Largely Ineffective in HBeAg-Positive Children with High Viral Loads**

Taiwanese researchers followed 21 HBeAg-positive children, ranging in age from 2 to 21, who had been treated with conventional interferon for 24 weeks. Conventional interferon, which requires a thrice-weekly injection, is the only approved interferon for children. Researchers monitored the children, whose ALT levels were greater than 80 IU/L, over six to 12 years after treatment and compared their experiences with a similar-

aged group of untreated children with chronic hepatitis B.

One year after treatment, there was no difference between the treated and untreated group in terms of HBeAg seroconversion or decline in viral load (difference was 41% vs. 44%) or at six years (88% vs. 89%).

HBsAg became undetectable in two treated children and one untreated child. Patients who seroconverted (developing the "e" antibody), achieved undetectable viral load and normal ALT levels tended to be younger, and had a lower viral load at the start of treatment. Genotype played no role in which children responded to treatment.

The researchers, reporting in the April 2008 issue of *Liver International*, concluded that the interferon treatment was not beneficial to most children, and appeared effective only in children with low viral loads at the start of treatment.

