

# HBV JOURNAL REVIEW

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## Hepatitis B

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### **28-Day Treatment of Interferon Beta Is as Effective as Long-Term Treatment with Conventional and Pegylated Interferon**

Japanese researchers tried administering a daily doses of interferon beta (an interferon currently used to treat muscular sclerosis that appears promising against viral hepatitis) intravenously, to see if this short-term therapy would help patients infected with the hepatitis B virus (HBV) who tested positive for the hepatitis B “e” antigen (HBeAg) and had elevated HBV DNA (viral load).

Twenty-six patients received one to three

daily doses intravenously, for a total of 102 million international units over 28 days, and were followed for six months. Thirteen (50%) of patients became HBV DNA undetectable, and eight (31%) lost HBeAg and developed “e” antibodies (seroconverted), and eight (31%) achieved normal alanine aminotransaminase (ALT) levels. ALT levels rise above normal when liver cells are damaged or die.

This treatment was much shorter than conventional or pegylated interferon therapy treatment, which can range from four months to one year, and produced improvements similar to those achieved by longer

interferon treatment, according to a report published in the May 2008 issue of the *World Journal of Gastroenterology*. There were also fewer side effects over a shorter period of time.

### **Tenofovir Effectively Reduced Viral Load in HBeAg-Negative, Older, Male Patients**

The antiviral tenofovir (Viread) rapidly decreased HBV DNA levels in HBeAg-negative patients, and caused no viral resistance after 72 weeks of treatment, according to a research study presented during the April 2008 European Association for the Study of the Liver (EASL) conference.

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Tenofovir also worked well in patients who had never been treated as well as those who had been treated with but did not respond to 48 weeks of the antiviral adefovir (Hepsera).

Most of those who enrolled in the research study were older males with elevated ALT levels, moderate-to-high viral loads, and about 64% of the participants had HBV strain or genotype D. Among the patients, 250 received tenofovir and 125 received adefovir.

At week 48, 93% of those receiving tenofovir achieved undetectable HBV DNA, compared to 63% receiving adefovir. Both treatments, however, produced the same rate of normal ALTs. Researchers also noted that 93% of patients who did not respond to adefovir, and were switched to tenofovir, quickly achieved undetectable viral load by week 72.

Patients who did not initially respond to tenofovir by week 24 ultimately did re-

spond to the antiviral by week 72.

Tenofovir, which has been used successfully against HIV infection, is expected to be approved by the U.S. Food and Drug Administration (FDA) later this year.

### ***Tenofovir Highly Effective in HBeAg-Positive Patients Following 72 Weeks of Treatment***

Antivirals have not been found to be highly effective in HBeAg-positive patients who tend to have high viral loads. Adefovir, for example, produces an HBV DNA undetectable rate in only 13% of HBeAg-positive patients treated. But a study presented to the EASL conference revealed that 176 HBeAg-positive patients who received 72 weeks of tenofovir responded very well:

- 79% achieved undetectable viral load
- 77% achieved normal ALTs
- 26% achieved HBeAg seroconver-

sion

- And 5% cleared HBsAg.

Participants in the study had high viral loads (8.6-8.8log<sub>10</sub> copies/mL) and elevated ALT levels, with genotypes A-D represented in the study.

The study also compared the outcomes of the tenofovir-treated group to 90 patients who received 48 weeks of adefovir and were then switched to tenofovir if they did not respond to adefovir.

Tenofovir was more effective than adefovir in lowering viral load and normalizing ALT levels, and patients who did not respond to adefovir who were switched to tenofovir quickly experienced declines in viral load. Researchers reported that 76% of those who switched from adefovir to tenofovir ultimately achieved undetectable viral loads, a little less than those who were treated with only tenofovir.

Also noteworthy was that some HBeAg-positive patients did not respond immediately

to tenofovir. Their responses at week 24 did not give a true picture of their response, and many responded only after 48 to 72 weeks of treatment, including those who lost HBsAg.

Researchers reported serious adverse side effects in 4% of tenofovir patients and in 7% of adefovir-to-tenofovir switched patients, most due to ALT flares.

### ***Tenofovir Appears Safe in Previously-Treated Patients, but Is Less Effective in Patients With Adefovir Resistance***

German researchers followed 113 mostly male patients, 65% of whom were HBeAg-positive, who had been previously treated with lamivudine or adefovir to see how they fared when treated for 12 months with 300 mg daily of tenofovir.

Among the group, 93% had viral resistance to lamivudine and 85% had resistance to adefovir. All

had moderate HBV DNA levels and elevated ALT levels.

Ultimately, 85% of all patients treated achieved undetectable viral load. Specifically, researchers reported:

- 100% of patients who had no mutations achieved undetectable viral load
- 92% who had lamivudine resistance achieved undetectable viral load
- 30% who had adefovir resistance achieved undetectable viral load
- 73% of HBeAg-positive patients achieved undetectable viral load
- 92% of HBeAg-negative patients achieved undetectable viral load.

Most of the study participants had genotypes D and A.

Researchers, reporting at the EASL conference, said that the longer patients were on tenofovir, the better the outcomes. Also, those with high HBV DNA levels were also less likely to respond well to tenofovir.

### ***Tenofovir Is Equally Effective in Previously-Untreated and Lamivudine-Treated Patients***

Researchers presenting at EASL compared how 49 patients who had been treated with lamivudine responded to the antiviral tenofovir against 377 patients who had received no treatment for hepatitis B. The patients, most male, all had moderately elevated viral load and elevated ALT levels.

Most had genotype D, C and A, and 56% of those who never had been treated were HBeAg-negative, and 80% of those treated were HBeAg-negative.

At week 48, 86% of untreated patients had undetectable HBV DNA and 74% had normal ALT levels, while 88% of previously-treated patients had detectable HBV DNA and 78% had normal ALTs. There were no signs of viral resistance to tenofovir after 48 weeks.

### ***Tenofovir, and Tenofovir plus Emtricitabine Combination, both Effective in Patients with Lamivudine and Adefovir Resistance***

Researchers treated 53 patients who had developed viral resistance to adefovir and lamivudine with just tenofovir, and 52 similar patients with a combination of tenofovir and emtricitabine (FTC-an antiviral not yet approved by FDA for hepatitis B treatment, which has been used against HIV for years) for 48 weeks, and then monitored them to see how effective the two treatments were.

Researchers, reporting at the EASL conference, reported that the patients – nearly all male and half of whom were Asian or European – achieved sharp declines in viral load. Most of the patients were HBeAg-positive, had high viral loads, and moderately elevated ALT levels. Researchers noted little difference in response in

either treatment group after 48 weeks. About 81% of patients in both study arms achieved undetectable HBV DNA. About 67% of the tenofovir-only group achieved normal ALTs, and 73% of the tenofovir plus emtricitabine achieved normal ALTs, and 5.3% and 7.7% achieved HBeAg serconversion respectively.

### ***Adefovir-Emtricitabine Combination More Effective than Adefovir Alone in HBeAg-Positive Patients***

As antiviral combinations prove necessary to combat HBV infection, especially in those who have already developed resistance to one or two antiviral drugs, researchers are stepping up their efforts to find antiviral combinations that will work well against drug-resistant HBV.

A multinational research team tried treating 30 HBeAg-positive patients with either 96 weeks of just adefovir, or a

combination of adefovir and emtricitabine.

The drop in viral load was higher in the combination group (five-fold vs. 3.9-fold), and more patients in the combination group achieved both normal ALT levels and undetectable HBV DNA (79% vs. 37.5%). HBeAg seroconversion was similar in both groups (between 14% and 25%). In those with HBeAg seroconversion, half relapsed after treatment ended, researchers reported in the May 2008 issue of the *Journal of Hepatology*.

**Long-term Entecavir Treatment over Three Years Effective in Patients Who Have Never Been Treated**

A report presented at the EASL conference found treatment with 0.5 mg daily of entecavir (Baraclude) over three years was highly effective in Japanese patients in three separate studies. Most of the patients were male, had

genotype C, and the average age was 43.

After three years of treatment:

- 87% of patients achieved undetectable HBV DNA.
- 91% of patients achieved ALT normalization.
- HBeAg seroconversion occurred in 23% of 84 patients who were HBeAg-positive.
- And, fibrosis improved in 63% of patients.

After the three years of treatment, only 1.7% had developed viral resistance to the antiviral, however, nearly all had developed viral mutations that would usually be resistant to the antiviral lamivudine.

**Doctors and STD/HIV Clinics Failing to Immunize Clients against Hepatitis B**

A U.S. Centers for Disease Control and Prevention study of the prevalence of hepatitis B in 2,834 men who have sex with men, ages 23 to 29 in six metropolitan areas, published in the *American*

*Journal of Public Health*, found an overall 17.2% immunization rate. It also found:

- 21% of the men who had private physicians or who were members of health maintenance organizations were immunized.
- Among those with no source of health care, immunization rates were much lower, at 12.6%.
- Markers of past or present HBV infection were found in 20.6 percent of participants, ranging from 13.7% among the youngest men to 31% among the oldest.

Among participants susceptible to HBV, 93.5 percent had regular sources of health care, had been tested for HIV, or had been treated for an STD.

Although many young men who have sex with men have access to health care, most are not immunized against HBV, the authors concluded. To reduce HBV infection risk in this vulnerable population, health

care providers, including STD and HIV prevention clinics, should provide vaccinations or referrals for vaccination.

**Many People with Normal ALTs, or in the Immune-Tolerant Stage, Have Undetected Liver Damage**

For years, doctors have assumed that children and adults in the immune-tolerant stage of hepatitis B—with HBeAg, normal ALT levels, and high viral load—or those with persistently normal ALTs, do not have liver damage.

- A U.S. team of researchers conducted biopsies on 28 patients in the immune tolerant stage to see if they had liver fibrosis or inflammation despite the normal ALT levels. The prevalence of stage 2 fibrosis in this patient population ranged up to 32%. Researchers, writing in the May 2008 issue of the *Journal of Clinical Gastroenterology*, suggest that patients

who are older than 30 were at higher risk of fibrosis.

- In another article in the journal, researchers from Canada and the United States performed liver biopsies on 193 patients with mildly-elevated ALT levels. ALT upper normal levels are 30 for men and 19 for women. The patients in the study were divided into two groups, with ALT levels ranging 1-1.5 times the upper limit of normal, and 1.5-2 times the upper limit. Researchers reported that those with significant signs of liver damage tended to be men, older than age 35, who had mildly increased ALT levels. Liver damage tended to increase with slightly higher ALT levels and age.
- In a separate article in the May 2008 issue of *Gastroenterology*, another patient group with normal ALTs (both HBeAg-positive and -negative) were biopsied to determine the health of their livers. They discovered that numerous patients with normal ALTs and high HBV

DNA had significant fibrosis. Researchers concluded that use of ALT and HBV DNA levels – without resorting to a liver biopsy – in patients with normal ALTs may miss significant liver disease.

### ***In the Laboratory, Silver Nano-Particles Can Slow HBV Replication***

Chinese researchers, working in a laboratory, used miniscule silver nanoparticles to slow viral replication of HBV by half by having them interact with the viral DNA and particles. The particles have special properties that allow them to easily bind with small molecules and help impede viral replication.

The findings provides a new direction for developing new anti-HBV drugs, with nano-particles used as drug carriers to enhance the antiviral efficacy while minimizing the undesirable side effects. The advantage is that HBV, which can mutate rapidly,

cannot develop resistance to the nanoparticles. It may take several years before the particles can be used with current treatment, according to the researchers' report published in the journal of *Antiviral Therapy*.

### ***Some Genotypes More Sensitive to Antiviral Treatment than Others***

Spanish researchers collected blood samples from 103 HBV-infected patients, and analyzed the impact of lamivudine (Epivir-HBV) or adefovir antiviral treatment or no treatment on patients' genotype. Among the patients, 32% had genotype A, 42% had genotype D, 2% had genotype C, and 2% had genotype F. Twenty-two percent had a mixture of genotypes, primary A and D, followed by A and G.

Treatment with the antivirals lamivudine and adefovir appears to impact which genotype is the dominant strain in patients with a mix of genotypes. Geno-

type A strains appeared more sensitive to antiviral treatment than genotype D. In six patients, genotype change coincided with a decrease in HBV-DNA levels as a result of treatment.

Researchers, writing in the May 2008 issue of the *Journal of Hepatology*, also noted that patients who were not treated maintained a consistent mix of genotypes, which shows that HBV genotype remains stable without treatment.

