

HBV JOURNAL REVIEW

Volume 3, Issue 4

April 01, 2006

Hepatitis B

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Tenofovir Effective when Adefovir Resistance and Severe Liver Damage Occur

Some hepatitis B virus (HBV) have mutations that allow them to evade antivirals, including adefovir (Hepsera), which disrupt the virus's genetic material and render it unable to reproduce. When viral resistance to adefovir occurs, some patients experience an intense rebound in their viral load (HBV DNA) and severe liver damage.

Researchers, writing in the March 2006 issue of *Comparative Hepatology*, report the experience of a man who had cirrhosis and severe HBV infection. He

had developed viral resistance to the antiviral lamivudine (Epivir-HBV), and was one of the 8% who then quickly developed viral resistance to adefovir. He recuperated when treated with the antiviral tenofovir.

“For avoiding the emergence of resistant mutants, incomplete viral response to adefovir should prompt a change in antiviral treatment,” researchers wrote. “Tenofovir appears to be an effective treatment of adefovir-resistant mutants.”

Tenofovir has been used to treat HIV infection, and has not yet been approved by the U.S. Food and Drug Administration (FDA) for the treatment of hepatitis B.

Adefovir Resistance Develops Earlier in Lamivudine-Resistant Patients

Korean researchers, writing in the February 2004 issue of the journal *Gut*, reported that viral resistance to adefovir developed more quickly in patients who have already developed viral resistance to lamivudine.

The researchers monitored 67 lamivudine-resistant patients who were then treated with adefovir. They discovered adefovir resistance developed at months 12 and 24 in 6.4% and 25.4% of patients respectively.

They concluded that adefovir mutations emerged in lamivudine-resistant patients earlier and

HBV Journal Review
A publication of the Hepatitis C
Support Project

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more frequently than in patients who had never been treated with lamivudine.

Experts: Redefine Goals of Hepatitis B Treatment and Who Should Be Treated

In a Medscape *Expert Column*, published March 10, 2006, Drs. Nancy Reau and F. Fred Poordad, encouraged doctors to re-examine the goals of hepatitis B treatment and who should be treated.

Historically, researchers assumed anyone with a low viral load (HBV DNA) and normal alanine aminotransferase (ALT) levels did not have liver damage and did not require treatment. But recently, researchers have discovered that HBV DNA persists even in patients who have normal ALT and who have seroconverted and developed the “e” (HBeAg) antibody. These people can still have liver damage and experience a rebound of HBV later in life.

One study, cited by the researchers, found that while most of 3,233 Chinese patients seroconverted at about age 35, most began developing liver complications at age 57. About 73.5% of them

had antibodies to the “e” antigen (HBeAb) when complications began.

Low viral load, achieved by antiviral treatment, is also no guarantee of health. Two recent studies reported that 24.5% to 43.6% of patients with complications had low HBV-DNA levels.

Normal liver enzyme levels are also not harbingers of health. Patients with hepatitis B with normal to slightly high ALT levels (0.5 to 1 times normal) carried the same risk for liver complications as those with highly elevated ALT levels. Yet, most clinical trials enroll only patients with elevated ALT levels, “though, these patients are not the only group likely to benefit from therapy.

“While the axiom has been that treatment is ‘ineffective’ in patients with normal ALT levels, this depends on the definition of success. If HBV-DNA suppression and reduced risk for complications such as cirrhosis and (liver cancer) are used as an endpoint, as opposed to HBeAg seroconversion and enzyme (ALT) normalization, patients with normal enzyme levels are likely to respond as well as the other patient sub-

sets,” they wrote.

Because of these assumptions, many patients have been inappropriately excluded from treatment and clinical trials.

Ultimately, drug safety and viral resistance will play increasingly important roles in assessment of antivirals, they noted.

“Finally, the paradigm shift of treating HBV infection to suppress virus over the long term will need to go hand in hand with combination therapy to reduce the risk for resistance,” they wrote. “This will certainly require revisions in what the ultimate endpoints of therapy should be.

Treat High Viral Load and Study Antiviral Combinations, Doctor Urges

A column on treating hepatitis B, written by M. Sherman and published in the April 2006 issue of the journal of *Alimentary Pharmacology & Therapeutics*, suggests doctors should consider viral load rather than elevated liver enzymes (ALT) when deciding whether to treat.

“HBeAg seroconversion can be achieved in 30-40% of treated pa-

tients whatever (antiviral) is used,” Sherman notes, “However, it takes longer for (antivirals) to achieve the same seroconversion rates as interferon. In (patients without HBeAg), long-term therapy is required for most patients because the relapse rate after withdrawal of therapy is very high, irrespective of the agent used.

“Viral resistance limits the use of lamivudine, and to a lesser extent adefovir,” Sherman adds. “Resistance to entecavir has so far only been described in pre-existing lamivudine resistance. Although therapy with combinations of nucleoside analogues has not been investigated to any extent, this is the only way to reduce the emergence or resistance, and studies are urgently needed.”

Pegylated Interferon May Help Those with Small Amounts of Lamivudine-Resistant HBV

Dutch researchers, writing in the March 2006 issue of the *Journal of Hepatology*, treated 16 HBeAg-positive patients who had developed viral resistance to lamivudine, with about 52 weeks of pegylated interferon, and

then followed them for another 26 weeks.

Only two patients seroconverted, cleared HBeAg, and achieved low viral load and normal ALT levels. These patients were the only ones with only small amounts of lamivudine-resistant HBV DNA. All others experienced lower ALT levels and viral load during treatment, but the levels quickly rebounded when treatment ended.

While the results were disappointing, “such therapy may be beneficial in patients with only small amounts of mutant virus,” researchers wrote.

Fatigue Increasingly Recognized as Symptom of Liver Disease

Many people infected with (HBV) experience fatigue, but to date there has been little scientific proof that confirms or explains the link between liver disease and fatigue.

An article in the March 2006 issue of *The Canadian Journal of Gastroenterology* affirms that fatigue, “is the most commonly encountered symptom in patients with liver disease, and it has a significant impact on their quality of life. How-

ever, . . . the understanding of the processes which may generate fatigue in general, the underlying cause(s) of liver disease-associated fatigue remain incompletely understood.”

According to the report, “experimental findings suggest that fatigue associated with liver disease likely occurs as a result of changes in neurotransmission within the brain.”

Study Finds Most HBV-Infected Caucasian Children Fare Well

A group of Italian researchers followed 99 HBV-infected Caucasian children over 29 years to monitor their health and disease progression. Most of the children had been infected after birth.

Writing in the February 2006 issue of *Hepatology*, researchers reported:

- 91 children were initially HBeAg-positive (four had cirrhosis) at the start of the study. Of them, 89 seroconverted after an average five years. Of the 85 children without cirrhosis, one developed HBeAg-negative hepatitis and the other 84 became inactive carriers. During a mean follow-up of 14.5 +/- 6.1

years after HBeAg clearance, four carriers experienced reactivation, and three had HBeAg-negative hepatitis at the last follow-up.

- Eight of the children were HBeAg negative. Of these children, two eventually developed HBeAg-negative hepatitis, and six became inactive carriers.

Of the four children with cirrhosis, two developed liver cancer and two cleared cirrhosis during adulthood. Two patients with HBeAg-negative hepatitis and one with cirrhosis experienced drug abuse.

At the end of follow-up, 15 of the 89 initially HBeAg-positive patients and two of eight initially HBeAg-negative children cleared hepatitis B surface antigen (HBsAg).

While the prognosis for horizontally-infected Caucasian children is favorable, researchers noted that some patients progress to liver cancer and the more virulent HBeAg-negative hepatitis.

Which HBeAg-Negative Patients Will and Won't Respond to Long-Term Lamivudine?

A group of Greek researchers monitored 79 patients with HBeAg-negative hepatitis B who were treated with lamivudine for 31 months to see if there were any early indications of who would or wouldn't respond well to the antiviral.

Writing in the March 2006 issue of the journal of *Alimentary Pharmacology & Therapeutics*, they reported that about 90% of the patients treated experienced a drop in viral load and ALT levels.

High levels of inflammation in the patients' liver biopsies, before treatment began, were associated with a higher response rate to treatment, while patients with high viral load, before treatment began, were three times more likely to develop viral resistance and a resurgence of viral load and liver damage.

Long-Term Lamivudine Yields Mixed Results and Viral Resistance in HBeAg-Positive Children

A group of multinational researchers followed two groups of HBeAg-positive children with elevated ALT lev-

els, to compare the impact of 12 versus 24 months of lamivudine treatment.

The group treated 276 HBeAg-positive children for one year with either placebo or lamivudine. After one year, patients were divided into two groups based on their HBeAg status; 213 HBeAg-positive children received an additional 12 months of lamivudine and 63 HBeAg-negative children were observed during the additional 12 months to monitor the durability of their HBeAg loss.

Among the children treated for another 12 months with lamivudine, 28 of 133 (21%) and 23 of 77 (30%) children who previously received placebo achieved HBeAg loss and undetectable viral load at month 24.

However, the incidence of viral resistance to lamivudine, called YMDD mutations, at month 24 was 64% (66 out of 103) in the children receiving a second year of lamivudine and 49% (34 out of 70) in those previously treated with just placebo.

At month 24, 54% who had no viral resistance to lamivudine achieved loss of HBeAg and undetectable viral load, while only 5% of children with

viral resistance achieved that goal.

The durability of response in the children who were not treated during the second 12 months was 89% (48 out of 54).

“In conclusion, further clinical response was seen over the 24-month open-label study period in children who had not initially achieved viral response (HBeAg seroconversion and undetectable viral load) after 12 months of lamivudine treatment,” researchers wrote in *Hepatology*. “However, the incidence of YMMD mutations increased over time and resulted in lower response rates. Viral response was maintained in most patients who had initially responded to lamivudine in the first 12 months.

Hepatitis B Antigens Found in Ovary and Ovum of HBV-Infected Women

A group of Chinese researchers, writing in the February 2006 issue of the *American Journal of Obstetrics and Gynecology*, report they have found hepatitis B surface antigen (HBsAg), core antigen (HBcAg), and HBV DNA in the ovary

and ovum of HBV-infected patients. This could explain why infants born to infected women become infected at a rate of more than 90%.

As a result of their research, they conclude, “HBV could infect the ovum at different stages and replicate in it. This may be an important mechanism of HBV vertical transmission.

Cirrhosis Increases Liver Cancer Risk, even after Surface Antibody Appears

Does appearance of surface antibody, signaling clearance of the virus, guarantee liver health? Not according to a group of Japanese researchers, reporting in the Jan.-Feb. 2006 issue of *Hepatology*.

The researchers followed four people who had cleared HBsAg, developed surface antibodies, and then later developed liver cancer. The four had been diagnosed with early cirrhosis or full-fledged cirrhosis more than a decade previously, but all had recently had normal ALT levels and undetectable HBV DNA before liver cancer developed.

“Our findings suggest that liver cancer due to

HBV can occur in the serologically-cured stage if progression to pre-cirrhosis or cirrhosis already has occurred, where the fibrosis level has improved considerably because of the long-term absence of active HBV viremia and inflammation,” they wrote. “Active medical intervention to prevent liver cirrhosis for chronic hepatitis B may have an important role in the inhibition of liver cancer in patients with chronic hepatitis B.”

Hepatitis B and C Coinfection Probably Increases Liver Cancer Risk

HBV and hepatitis C virus (HCV) individually increase the risk of liver cancer, but what effect does a coinfection with both viruses cause? Researchers, writing in the March issue of the *Journal of Viral Hepatitis*, suggest that because both viruses increase cirrhosis, and that dual infections probably increase cancer risk.

Studies about coinfection are few, and researchers do not understand the dynamics that occur when both viruses compete to replicate in liver cells.

“In conclusion, current information, admittedly based on imperfect analyses, supports the belief that co-infection with HBV and HCV increases the risk of (liver cancer) development over that with either virus alone,” they wrote. “The increased risk is additive rather than multiplicative. The reasons for the interaction are uncertain, although the increased incidence of cirrhosis in the presence of concurrent infection with its tumor-promoting effect, including the resulting enhanced likelihood of integration of HBV DNA into host DNA, may play a role.”

Viral Load, More Than Elevated ALT Levels, May Determine Who Develops Cirrhosis

A group of Taiwanese researchers, writing in the March 2005 issue of *Gastroenterology*, studied blood samples taken from 3,582 untreated HBV-infected patients over an 11-year period. Of the group, 365 developed cirrhosis.

The researchers reported that the rate of cirrhosis increased with the HBV DNA level and ranged from 4.5% to

36.2% for patients with a viral load of less than 300 copies/mL and 106 copies/mL or more, respectively.

They found that viral load – more so than HBeAg status or ALT levels – was a better predictor of who would develop cirrhosis.



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