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Hepatitis B

Telbivudine More Effective than Lamivudine among HBeAg-Positive Patients

In an international, double-blind Phase III clinical trial, the antiviral telbivudine (LT) outperformed lamivudine (Epivir-HBV) in patients with “e” (HBeAg)-positive hepatitis B and HBeAg-negative patients, according to a report presented at the American Association for the Study of Liver Disease (AASLD) conference held in early November.

The two-year study compared telbivudine at 600 mg per day with lamivudine at 100 mg per day in 1,367 adults.

All patients had a high viral load (HBV DNA) or quantity of hepatitis B virus (HBV) in their bloodstreams and elevated

alanine aminotransferase levels (ALT), which indicate liver cell damage.

Among HBeAg-positive patients, researcher reported a 6.5-fold reduction in HBV DNA in telbivudine patients, compared to a 5.5-fold drop in lamivudine patients. HBeAg-negative patients on telbivudine had a 5.2-fold drop in viral load, compared to a 4.4-fold drop in lamivudine patients.

More striking, about 60% of HBeAg-positive patients lost the HBeAg antigen and developed “e” antibodies, compared with 40% on lamivudine. Researchers concluded that 75% of HBeAg-positive patients achieved an overall response, compared with 67% of those on lamivudine.

Adverse events from both drugs were similar, and included upper respiratory infections and headache in about 12% in each group, and fatigue and

nasopharyngitis in about 11% in each group.

To Prevent Flares, Use Adefovir ASAP When Lamivudine Resistance Develops

A team of Italian researchers, reporting in the December 2005 issue of *Hepatology*, examined when was the best time to start administering the antiviral adefovir (Hepsera) in patients who begin to develop viral resistance to the commonly-used antiviral lamivudine.

They treated 46 HBeAg-negative, lamivudine-resistant patients who had developed elevated ALTs and increased viral load due to the declining effectiveness of lamivudine. They also treated 28 other HBeAg-negative patients with adefovir, who had just begun to experience

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viral resistance to lamivudine without any increases in viral load or ALT levels.

Within three months, the group who had not yet developed a “flare” with increased viral load or ALT before beginning adefovir all tested negative for HBV DNA. In contrast, only 46% of the belatedly-treated group had undetectable viral load.

After two years, the group treated early with adefovir had undetectable viral load, while only 78% of the belatedly-treated group had low viral load.

“To optimize antiviral treatment in HBeAg-negative patients selecting resistant strains to lamivudine, adefovir should be added to lamivudine as soon as genotypic resistance is detected,” the researchers recommended.

Researchers Find More Liver Damage than Expected in Infected Children

According to a report at the AASLD conference and published in *Hepatology*, children who are infected with HBV at birth or during early infancy may face a higher risk of liver damage during childhood than previously thought, based on a study

of 76 HBeAg-positive children with elevated ALTs who underwent liver biopsies.

The general theory is that the majority of HBV-infected children do not experience much liver damage until later in life, when the immune system recognizes the infection and attacks infected liver cells. But these researchers report that more than 35% of the children had either bridging fibrosis with lobular distortion or cirrhosis. Older children and those with higher ALT levels tended to have greater degrees of fibrosis.

These observations suggest a less optimistic outcome than that traditionally associated with chronic HBV infection in children.

Immune Response and Viral Mutations Key to Success When Kids Get Lamivudine and Interferon Combo

Another AASLD report from London followed 23 HBeAg-positive children who were treated with lamivudine for 52 weeks, and conventional interferon from week 9 for 44 weeks. Five of the children responded to treatment, 18 did not.

Researchers examined the children’s immune response, including their T-cells, as well as whether the children’s HBV mutated in order to avoid the combined treatment punch of the antiviral and interferon.

They scientists concluded that the children’s sustained viral response was associated with a, “broad and strong HBV core-specific T-cell reactivity (response),” and a lower rate of viral mutations within the HBV core gene.”

Bottom line: The higher the viral mutation rate, the lower the effectiveness of the treatment.

“The strong correlation between HBV DNA levels and the number of mutations within the HBV core gene suggests that variant strains contribute to virus control failure,” the researchers concluded.

Entecavir Appears to Have a Low Rate of Viral Resistance or Rebound

Long-term treatment with entecavir (Baraclude) appears effective, even in patients who have developed viral resistance to lamivudine, according to a study presented at

AASLD.

Researchers examined five clinical trials, involving 679 patients who used the drug for one year, and 310 patients who continued the drug for two years. However, 11 patients showed evidence of viral rebound, demonstrated by an increase in viral load, during the first year, and another seven patients rebounded during the second year.

Of 192 other lamivudine-resistant patients who were treated with entecavir, two (1%) became resistant to entecavir during the first year, and five more showed evidence of viral rebound. Of the 154 lamivudine-resistant patients treated for a second year with entecavir, 14 (9%) developed resistance and an additional 20 experienced viral rebound.

Because entecavir reduces viral load quickly, researchers said, there are fewer virus available to develop mutations to evade the antiviral.

Antiviral Clevudine Shows Promise in Early Clinical Trials

Several reports on the antiviral clevudine (L-FMAU) presented at the AASLD conference

shows the antiviral reduces viral load rapidly and may be especially adept at eradicating the virus' covalently closed circular (ccc) DNA, which is the genetic blueprint that integrates into liver cells and can lead to liver damage and cancer.

The reports on clevudine were based on clinical studies in labs and on more than 600 HBV patients.

The studies followed HBeAg-negative and – positive patients, and found that a daily dose of 30 mg for 24 weeks was safe, reduced ALT levels to normal, and that the four-fold decline in HBV DNA levels continued at a three-fold rate for 24 weeks after treatment stopped.

Twenty-four weeks after treatment ended, 75% of the clevudine-treated group continued to have normal ALT, compared to 33% of the placebo-treated group. The ALT normalization rates in the clevudine group increased to 86.7% at week 34 and then slightly decreased thereafter to 70.5% at week 48.

The drug worked best in patients with elevated ALTs and high viral load.

Adefovir May Be Safe for HBV-HIV Coinfected Patients

Researchers treated seven HIV-HBV coinfecting individuals with adefovir for more than six months to see if the antiviral caused any viral resistance in the HIV virus. The patients had never been treated with any antiviral for either their HIV or hepatitis B infections.

Writing in the November 2005 issue of *AIDS*, researchers concluded that adefovir caused no HIV mutations in these patients, and appeared to be safe to use to control HBV.

In a separate study, researchers looked for any occurrence of adefovir-resistance in 29 HIV-HBV coinfecting patients who have been treated for up to five years with a combination of adefovir and lamivudine after their HBV developed resistance to lamivudine.

At year 4 of the dual antiviral treatment, 14 had undetectable viral load. Of the remaining 15, 14 had extremely low viral load with no resurgence of liver damage.

Adefovir Improves Liver Health After Five Years in HBeAg-Negative Patients

In another report on adefovir at AASLD, researchers followed 125 patients treated with adefovir during their fourth and fifth year of treatment. Liver biopsies were performed on 46 of the patients.

Among 12 patients with bridging fibrosis or cirrhosis, seven improved at year four or five, six patients (5%) lost the surface antigen (HBsAg) and of them five developed surface antibodies, which indicates a cure.

The percentage of patients with undetectable HBV DNA was 65% at year four and 67% at year five. ALT levels normalized in about 70% by year five.

The rate of adefovir resistance was 0%, 3%, 11%, 18%, and 28% at weeks 48, 96, 144, 192, and 240, respectively.

“Treatment with adefovir for five years produced significant and increasing improvement in hepatic fibrosis confirming that durable viral suppression impacts fibrosis over time,” researchers concluded.

Adefovir Is Most Cost Effective Treatment for HBV Patients with Cirrhosis

Researchers at the Greater Los Angeles Healthcare System and Mount Sinai Medical School in New York City performed an economic analysis to identify the most cost effectiveness treatment for a hypothetical 50-year old patient with cirrhosis and high viral load. They considered doing nothing, treating with just lamivudine, treating with just adefovir, treating with entecavir, or treating with lamivudine until viral resistance develops, then switching to adefovir (called salvage therapy).

They concluded:

- The do-nothing strategy was least effective, yet least expensive.
- Compared with doing nothing, using adefovir cost an incremental \$20,011 per quality of life year gained.
- Lamivudine by itself was more expensive, yet less effective than adefovir.
- Using adefovir as salvage therapy after lamivudine resistance develops costs \$107,165.

Treating with entecavir produced “diminishing returns” compared to adefovir because the drug currently costs 22% more than adefovir.

These data indicate that adefovir may be the most cost-effective strategy in patients with HBV cirrhosis, regardless of the stage of liver disease.

When Lamivudine and Adefovir Fail, Tenofovir May Save the Day

German researchers at the AASLD conference reported that the antiviral tenofovir can help patients who no longer respond to lamivudine, or who fail to respond to adefovir.

They treated 14 patients who had failed to improve or lower their viral load on adefovir, with a daily dose of 300 mg of tenofovir for up to 14 months. Ten of the patients had elevated ALT levels. Tenofovir has not yet been approved by the U.S. Food and Drug Administration for treatment of hepatitis B.

At month 3 and month 6, there was a three-fold nearly a four-fold drop in viral load, respectively. Thirteen patients ultimately achieved undetectable HBV DNA levels and five patients with elevated ALT reached normal liver

enzymes after four months.

Two patients achieved HBeAg seroconversion after 3 and 5 months.

“Because of its high antiviral activity, tenofovir might become a highly effective rescue drug for patients with suboptimal response to adefovir,” the researchers concluded.

HBV Infection Increases Health Risks in Pregnant Women

Hong Kong researchers, writing in the November 2005 issue of the *Journal of Hepatology*, found that pregnant women chronically infected with HBV experienced higher rates of premature labor, diabetes and bleeding.

They followed 253 pregnant women who tested positive for HBsAg, and 253 pregnant uninfected women.

HBsAg carriers had a high rate of premature labor (11.9% vs. 6.3%) and births (4.7% vs. 1.2%), and diabetes and bleeding during pregnancy.

The increase in health risks during pregnancy, “... may be related to the chronic inflammatory state in these subjects.” The role of HBV infection in pregnancy complications should be further investi-

gated, the researchers recommend.

Lamivudine Helps HBV Patients with Liver Cancer

A group of Japanese researchers studied what impact the antiviral lamivudine would have on the liver health and survival of hepatitis B patients with liver cancer. They treated 30 such cancer patients with lamivudine, and had an untreated, control group of 40 patients who also had hepatitis B-related liver cancer.

The lamivudine group experienced a significant improvement in liver health and function after 24 months of treatment, based on biopsies, compared to the untreated group. There was no significant difference in the recurrence of cancer or survival between the two groups.

“These results suggest that lamivudine treatment for patients with cancer may prevent death due to liver failure,” observed researchers, who called for additional research into treating liver cancer with antivirals.

Occult Hepatitis B, Without HBsAg, Is Found in Family Members of HBV Carriers

A group of Indian researchers tested 72 family members of 28 HBV B carriers to see if the people who tested negative for HBsAg might actually be infected with “occult” hepatitis B.

Occult hepatitis B occurs when a person tests negative for HBsAg, but positive for HBV DNA. Writing in the January 2005 issue of the *Journal of Medical Virology*, they reported that HBV DNA was detected in 15 HBsAg negative family members of 10 patients.

Some of the occult-infected family members had mutations in their HBsAg that allowed the antigen to evade detection by lab tests. Several family members had high viral load, despite the absence of HBsAg, and were capable of infecting others.

These cases are especially notable given that blood banks and transplantation services screen for HBsAg when accepting donations or organs.

Skin Reactions to Pegylated Interferon May Be Treated So Therapy Can Continue

Researchers, writing in the November 2005 issue of *The Canadian Journal of Gastroenterology*, report that pegylated interferon may cause skin reactions in hepatitis B patients, as has already been documented in hepatitis C patients receiving the drug.

However, the doctors report they successfully treated a patient with topical steroids and antihistamines, so interferon treatment could continue.

The doctors suggest that, "... despite the severity of reaction, withdrawal of pegylated interferon may not always be required because this particular skin reaction responded well to symptomatic treatment. This is important, because discontinuation of interferon may decrease the chance of achieving a sustained virological response in patients with viral hepatitis."

Transplant Patients with Lamivudine Resistance Run Higher Risk of Adefovir Resistance

A study presented at the AASLD found adefovir resistance in hepatitis B patients who had already developed viral resistance to lamivudine ranges from 2.9% after 12 months of treatment to 7.5% after two years. However, lamivudine-resistant patients who receive liver transplants experience a higher adefovir resistance rate, reaching 15.4% after two years.

Researchers studied 115 lamivudine-resistant patients who received adefovir for one to five years. Seventy-nine patients continued lamivudine, and 36 received adefovir alone. Thirteen subjects were liver transplant recipients, with five receiving the transplant before starting adefovir and eight after transplantation. A total of 74 patients were HBeAg positive.

The investigators concluded that liver transplant recipients with lamivudine-resistant disease undergoing treatment with adefovir should be carefully monitored for the development of adefovir resistance and the risk of decompensation.

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