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Hepatitis B

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Tenofovir Succeeds When Adefovir and Lamivudine Fails

Three patients coinfecting with HIV and the hepatitis B virus (HBV), who failed to respond to either lamivudine (Epivir-HBV) or adefovir (Hepsera), experienced a significant drop in viral load (HBV-DNA) when they were treated with the antiviral tenofovir (Viread). All three patients had hepatitis B genotype A.

The lack of response to adefovir surprised researchers, who hoped adefovir would be effective against

both HBV and HIV.

Historically, lamivudine has been ineffective in HBV-HIV coinfecting patients because they develop viral resistance to this drug even faster than patients infected with only HBV.

Adefovir, in contrast, has a very low rate of viral resistance of just 1 to 2% each year. Researchers hoped adefovir would work effectively against both HIV and HBV because of its low rate of viral resistance.

Surprisingly, none of the three patients showed signs of adefovir resistance when their HBV were analyzed, the drug simply proved ineffective in this coinfecting group. Studies have

found that 8 to 15% of patients infected with lamivudine-resistant HBV exhibit an initial non-response to adefovir.

However, when tenofovir was used, the three coinfecting patients experienced a significant drop in viral load, according to a report published in the November 2004 issue of *AIDS*.

The researchers suggest that a combination of HBV genotype A and lamivudine resistance may indicate a patient will not respond to adefovir.

“At this stage, we recommend tenofovir for the treatment of adefovir-non-responders, probably also in HBV-mono-infected patients,” they wrote.

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Lamivudine and Adefovir Compared in Best Practices Journal

Physicians, reporting in the 2004 supplement of *Best Practice & Research Clinical Gastroenterology*, compared the success of lamivudine to adefovir in their summary of recommended treatments for hepatitis B.

Twelve months of lamivudine treatment produces HBeAg seroconversion in 16-18% of patients and histological (liver health) improvement in 49-56% treated patients.

HBeAg seroconversion rates increase with the duration of lamivudine therapy from 17% at one year to 27, 40, 47 and 50% at two, three, four and five years, respectively.

However, some HBV develop resistance to lamivudine and over time they become the dominant HBV, causing potentially dangerous ALT (alanine transaminase) “flares” or viral breakthrough when therapy is stopped in

patients with cirrhosis. After 48 weeks of treatment with 10 or 30 mg of adefovir daily or placebo, significantly more patients with HBeAg-positive chronic hepatitis B had improved liver health (53, 59 and 25%, respectively), undetectable HBV DNA (21, 39 and 0%), normalization of ALT levels (48, 55 and 16%) and HBeAg seroconversion (12, 14 and 6%).

In HBeAg-negative patients treated with adefovir (10 mg) for 48 weeks, ALT levels normalized in 72% (29% in the placebo group), HBV DNA levels were reduced to fewer than 400copies/ml in 51% (none in the placebo group), liver health improved in 64% (33% in the placebo group).

Interferon May Delay HBV Rebound During Long-Term Lamivudine Use

Researchers added conventional interferon to long-term lamivudine treatment to see what impact interferon had

after three years of lamivudine. Half of 83 patients received just lamivudine and the other half received the lamivudine-interferon combination.

The two groups experienced similar HBV DNA clearance and HBeAg-seroconversion. The only notable difference was that the group that received the interferon experienced a lower rate (5%, 20% and 30% vs. 10%, 55% and 58%, respectively, at 12, 24 and 36 months) of viral breakthrough, and a lower rate of HBV mutations developing that could resist lamivudine’s antiviral effects.

Lamivudine, Followed by High-Dose Interferon, Effective in 55% of Children

More than half of HBV-infected children treated with lamivudine, followed by high-dose interferon alpha, experienced “e” antigen seroconversion (loss HBeAg and production of the “e” anti-

body) and undetectable HBV-DNA.

In the January 2005 issue of the *Journal of Clinical Gastroenterology*, Turkish researchers report treating 20 chronically-infected children, who had never been treated, with lamivudine (4 mg/kg per day; maximum, 100 mg). After three months, interferon-alpha (10 MU/m, thrice weekly) was added to lamivudine regimen for six more months. After interferon treatment stopped, lamivudine continued for six months.

Therapy stopped six months after HBeAg seroconversion. Every three months, children were tested for viral load, HBeAg loss, and “e” antibody appearance.

After 15 months, 11 patients (55%) achieved undetectable HBV DNA and the “e” antibody, and 12 patients (60%) cleared HBeAg. Therapy was well tolerated in all children.

“Preliminary results of our study seem to indicate that lamivudine and high-dose interferon-alpha combination therapy after a

three-month lamivudine induction may represent an effective treatment option for children with chronic hepatitis B,” they wrote.

It was not reported if the treated children had elevated ALT levels prior to treatment.

HBeAg Seroconversion Delayed in Children with Genotype C in Taiwan

Writing in the December 2004 issue of *Gastroenterology*, a team of Taiwanese researchers reported on the impact HBV genotype posed on HBeAg seroconversion and liver cancer in 460 HBV-infected children who were followed for 15 years, and 26 children with HBV-related liver cancer.

HBV genotyping and viral load was checked at enrollment, and the children were grouped by HBeAg antigen and antibody status.

Most of the children had either genotype B or C. Genotype C carriers were more prevalent in the HBeAg-positive group and had a delayed HBeAg seroconversion, compared with the genotype B carriers.

Changes of genotype during the follow-up period were rare (2.8%).

The majority of those with liver cancer had genotype B (74%).

“Although HBV genotype B dominates in children with chronic HBV infection and (liver cancer) in Taiwan, genotype C delays HBeAg seroconversion in pediatric chronic HBV infection,” the researchers reported.

Infants Immunized with Plasma-Derived HBV Vaccine May Need Boosters as Teens

There continues to be debate internationally over when and if

hepatitis B vaccine boosters are needed a decade or more after immunization.

Writing in the December 2004 issue of *Hepatology*, Taiwanese researchers asserted that, one or more vaccine booster shots may be needed if there are no surface antibodies (titers) present in the bloodstream 15 years after immunization with the plasma-derived hepatitis B vaccine.

Researchers from the National Taiwan University Hospital measured antibodies to the core antigen, the surface antigen, and the volume of antibodies before and after vaccine boosters were administered to two groups of 15-year-old children who had been vaccinated at birth with plasma-derived vaccine.

Group A consisted of 78 children who were born to HBeAg-positive, HBsAg carrier mothers and had initially developed protective levels of surface antibodies after immunization. Group B consisted of 113 apparently healthy children whose surface antibodies or titers after vaccination were unknown.

Protective antibodies were still undetectable in only 29.9% of group A and 62.4% of group B.

Core antibodies, which shows evidence of past HBV infection, were detected in 33.3% of group A, who lived with HBV-infected household members, and 4.4% in group B.

After a single booster dose of hepatitis B vaccine, 2.7% of group A and 3.3% of group B remained surface antibody negative, and lacked adequate protective antibodies.

One HBsAg carrier was detected in group A, and four were identified in group B (3.5%).

“Fifteen years after neonatal immunization with plasma-derived HB vaccine, a large proportion of children exhibited waning immunity. This poses the risk of breakthrough infection,” the researchers noted.

One vaccine booster restored immunity to hepatitis B in most, but not all children, they added.

HBV Trumps HCV in Individuals Coinfected with HIV and Viral Hepatitis

At the November 44th Interscience Conference on Antimicrobial Agents and Chemotherapy conference, Vicente Soriano, MD, PhD, evaluated what happens when HIV-infected patients are also infected with HBV or the hepatitis C virus (HCV) or both viruses. When both HBV and HCV are present, often one virus overcomes the other, “suggesting a competition for replication in the liver.” To see how that HCV /HBV coinfection played out in the HIV-infected, researchers examined 107 HIV-infected individuals (22 of whom tested positive for HBsAg), who all had HCV antibodies. Those with positive HBsAg were significantly less likely to have frequently detectable HCV-RNA than were HBsAg-negative subjects (10% vs. 68%). In another study, researchers analyzed

whether HCV might rebound after HBV was cleared due to successful lamivudine or tenofovir treatment. HCV did not rebound in these treated patients, “which suggested that HCV had been definitively cleared in these individuals.”

ICAAC Speakers Suggest New Therapies for HIV-HBV Coinfected

Chronic hepatitis B infection affects 5% to 10% of HIV-infected patients in Western countries. Historically, the treatment of HBV infection in HIV coinfecting subjects was limited to lamivudine. During the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) symposium, speakers recommended treatment of coinfecting individuals only if ALT levels were elevated.

- The combination of tenofovir and lamivudine (or emtricitabine) should be considered as the first choice, along with a

third antiretroviral agent.

- Patients who don't need HIV-related antiretroviral therapy (those with CD4+ cell counts > 350 cells/mcL), should try pegylated interferon first if they are HBeAg-positive. Adefovir (10 mg daily) is recommended for HBeAg-negative patients.

“The reason for this distinction is that HBeAg-negative patients rarely respond to interferon, which is also poorly tolerated and cannot be taken indefinitely. In contrast, adefovir is administered orally once daily and can be taken for long periods of time; it also selects resistant HBV strains in less than 5% of patients per year,” researchers explained.

When new HBV-specific antiviral medications, such as entecavir, telbivudine, or clevudine, become available, they will be recommended over adefovir. “This is because concerns have emerged about the risk of selecting the K65R mutation in HIV, even with the recommended 10-mg daily low dose of adefovir that is active against HBV but

not against HIV,” researchers noted.

Alternatives to Liver Biopsy Urged for HIV-HBV Coinfected with Normal ALTs

A researcher, speaking at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, urged doctors to use noninvasive procedures rather than a liver biopsy, which uses a needle to extract a small liver tissue sample, on HBV-HIV coinfecting patients who have normal ALTs.

He suggested doctors use biochemical serum markers, such as FibroTest, adenine phosphoribosyl transferase or FibroScan to evaluate patients for cirrhosis and liver cancer. He suggested doctors use biochemical serum markers, such as FibroTest, adenine phosphoribosyl transferase or FibroScan to evaluate patients for cirrhosis and liver cancer.

HIV-HBV coinfecting patients with cirrhosis tend to develop liver cancer at a younger age than HIV-negative individuals, and the tumors can develop in several places throughout the liver. While it is important to evaluate the health of the liver, noninvasive tests have proven to be reliable in assessing liver fibrosis in patients with hepatitis B or C.

Doctors Find HBV Viral Resistance to Tenofovir in Coinfected Patients

Doctors for the first time have found HBV mutations that were able to replicate despite treatment with tenofovir in HIV-HBV coinfecting patients in Europe.

Doctors, reporting during the 44th Inter-science Conference on Antimicrobial Agents and Chemotherapy, examined 35 HIV-positive individuals who maintained detectable HBV-DNA levels despite treatment with

tenofovir for longer than six months. All of the patients had previously been treated with lamivudine until they developed viral resistance to it. After an average of 12 months on tenofovir, three patients developed mutations at the HBV polymerase gene. Researchers found the mutation rtA194T, along with the classical lamivudine resistance changes rtL180M and M204V, caused a reduced susceptibility to tenofovir.

FDA Warns Those with Viral Hepatitis Against Remicade and Strattera

The U.S. Food and Drug Administration (FDA) had warned healthcare professionals and the public against the use of infliximab (Remicade) for arthritis and atomoxetine (Strattera) for treating attention deficit hyperactivity disorder in children and adults, in patients who have liver disease, such as HBV infection.

The FDA has determined that both drugs carry a risk of causing acute liver failure, jaundice, hepatitis and cholestasis, and therefore should be avoided by those with an existing liver infection. Infliximab is a therapy used to treat rheumatoid arthritis, Crohn's disease, and ankylosing spondylitis. Atomoxetine has been prescribed for more than 2 million patients since its approval in 2002 for the treatment of children and adults with attention deficit hyperactivity disorder (ADHD). The warning was based on reports received by the FDA of severe liver toxicity in one adult and one teen who had been receiving atomoxetine therapy for several months. Both patients recovered after discontinuation of the drug.

Pegylated Interferon for HBV Approved in Switzerland, Taiwan and Thailand

Swiss regulatory officials recently approved the pegylated

interferon drug Pegasys (peginterferon alfa-2a) for the treatment of hepatitis B. It was approved for both HBeAg-positive and HBeAg-negative patients following three large clinical trials involving more than 1,500 patients worldwide. The studies found Pegasys to be superior to either interferon alpha and lamivudine. Pegylated interferon stimulates the immune system and appears to deter viral replication. This is a major milestone for more than 90 other countries worldwide that rely on Swiss regulatory review for their own approval process. Roche, maker of Pegasys, filed for permission to sell the drug to treat hepatitis B simultaneously in Switzerland, the United States and the European Union in the summer of 2004. Approvals in the United States and EU are expected in early 2005.

Viral Load after Lamivudine Treatment Does Not Predict Relapse Rate

A team of Taiwanese researchers investigated whether viral load is a true indicator of whether a patient with either HBeAg-negative or HBeAg-positive hepatitis B, will experience a relapse, with increased viral load and high ALT levels, after lamivudine treatment.

Writing in the December 2004 issue of the *World Journal of Gastroenterology*, researchers described how they followed patients treated with lamivudine for at least nine months, and then monitored them for 12 more months.

Relapse occurred in six (50%) of HBeAg-negative patients within 12 months after treatment ended. The relapsers' viral loads at end of treatment were not significantly different than those who had a sustained response to treatment.

However, genotype C patients tended to have a lower relapse rate than genotype B pa-

tients (14.3% vs. 57.9%). "Our results suggest that end-of-treatment virologic response (viral load) cannot predict post-treatment relapse in patients with HBeAg-negative or -positive chronic hepatitis B," they concluded.

Patients with Strong T-Cells Can Clear Lamivudine-Resistant HBV

Writing in the January 2005 issue of *Gut*, a team of researchers analyzed the role of T-cells in patients who do not develop HBV resistance to lamivudine and were able to achieve a sustained response after treatment. Many hepatitis B patients have HBV with mutations, called YMDD mutations, that are able to continue to replicate despite lamivudine's antiviral effect. A team of Taiwanese researchers examined how anti-YMDD and -mutant cytotoxic T lymphocytes (CTL or T-cells) performed against these HBV mutations in a laboratory setting.

They found sustained responders had more potent CTL responses against YMDD, and other HBV mutations, than non-responders. The frequency of successful immune action and clearance of the mutant HBV increased when patients had vigorous T-cell response during lamivudine therapy.

10.4% of Chinese, Koreans and Vietnamese in U.S. Cities Have Hepatitis B

A recent study examined the HBsAg prevalence rate among Chinese, Korean, and Vietnamese immigrants living in large U.S. cities. Of 5,341 people screened, from 2001 to 2004, 558 had HBV infection, producing an active or chronic infection rate of 10.4%. In contrast, the HBV infection rate among the general U.S. population is 0.3%. The researchers recommended that primary-care providers should screen Asian-Americans for hepatitis

B, promote immunization, and ensure all infected people receive appropriate monitoring and treatment.

Health Care Costs of Hepatitis B Patients Compared Worldwide

A team of researchers reported on the average, annual cost of providing healthcare to hepatitis B patients around the world in the November/December 2004 issue of the *Journal of Clinical Gastroenterology*.

They examined the healthcare costs of patients in six disease states, including HBV-infected patients with asymptomatic chronic hepatitis B, compensated cirrhosis, decompensated cirrhosis, liver cancer, and those who received a liver transplant and the cost of their care one year after the transplant.

United States: Looking at health insurance reimbursements for year 2000, the U.S. researchers reported \$761 was

spent on asymptomatic HBV patients; \$227 was spent on patients with compensated cirrhosis; \$11,459 was spent on those with decompensated cirrhosis; \$86,552 was spent on each patient who received a liver transplant; \$12,560 was spent on transplant patients one year after the transplant; and \$7,533 was spent on patients with hepatocellular carcinoma or liver cancer.

Australia:

Researchers reported the average annual cost for each disease state (1 Australian dollar = 0.77 U.S. dollar) was \$1,233 for noncirrhotic patients; \$1,394 for compensated cirrhosis; about \$11,961 for decompensated cirrhosis; \$144,392 for a liver transplantation; \$23,160 for care one year after transplantation; and \$11,753 per year for patients with liver cancer.

Canada:

The annual per-person costs in Canadian dollars (1 Canadian dollar = 0.82 U.S. dollar) were: \$2,191 for asymptomatic patients; \$2,987 for compensated cirrhosis; \$11,228 for decompensated cirrhosis; \$13,350 for liver cancer; \$99,066 for liver transplants,

and \$38,242 for transplant care after the first year.

“The cost of treating Canadian subjects with hepatitis B-related conditions increases substantially with deteriorating liver function,” researchers noted.

“Any new therapy that proves to be more effective at slowing or preventing the course of liver disease progression would be cost-effective.”

France, Italy, Spain, and the United Kingdom:

In Euro dollars (1 Euro dollar = 1.3 U.S. dollar) the average annual cost for asymptomatic chronic hepatitis B was 1,093 to 3,396; for compensated cirrhosis it was 1,134 to 3,997; for decompensated cirrhosis it was 5,292 to 8,842; for liver cancer it was 3,731 to 9,352; and liver transplant surgery cost on average it was 25,165 to 84,568.

Taiwan:

Using national health insurance claims filed in 2000, the average annual cost (1 Taiwan dollar = 0.03 U.S. dollars) of asymptomatic HBV infection was 4,905 in Taiwan dollars; compensated cirrhosis cost 6,574; decompensated cirrhosis cost \$36,621; hepato-

cellular carcinoma cost \$95,741; and a liver transplant cost \$199,725.

The total inpatient cost for HBV infection in Taiwan for the year 2000 was almost \$800 million, which accounts for about 1% of the country’s total inpatient expenditure.

South Korea:

Korea is a hepatitis B-endemic area with 5.79% to 10.87% of males and 1.51% to 4.44% of females over 20 years of age chronically infected.

Measuring costs in Korean Won, (1 U.S. dollar = 1,035.25 Korean Won), annual treatment costs per patient ranged from 297,392 Won (U.S. \$248) for asymptomatic chronic hepatitis B to 80.6 million Won (U.S. \$67,156) for a liver transplant.

Hong Kong

Hong Kong has an HBV infection rate of about 10%. Costs were analyzed according to the five disease states and estimated in Hong Kong dollars (1 Hong Kong dollar = 0.128573 U.S. dollar). Asymptomatic chronic HBV cost 6,318 in Hong Kong; compensated cirrhosis cost 10,304; decompensated cirrhosis cost 58,428; liver cancer cost 121,822. Each

case of liver transplant was estimated to cost 514,498. Chronic hepatitis B in Hong Kong accounts for about 4% of its annual healthcare expenditures.



**HBV
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