

# HBV JOURNAL REVIEW

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## Hepatitis B

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### **Ask the Experts: Which Antiviral Should Be Used to Treat Lamivudine- Resistant Patients?**

In a recent *Medscape Gastroenterology* Ask the Experts column, Emmet B. Keeffe, Stanford University Medical Center's chief of hepatology and co-director of its Liver Transplant Program, reviewed which antivirals should be used to treat patients whose hepatitis B virus (HBV) had become resistant to the antiviral lamivudine (Epivir-HBV).

Because HBV mutate easily, some HBV become "lamivudine-resistant" and are able to reproduce despite treatment with this antiviral. Over time, they increase in number and viral load (HBV DNA) rises and liver damage,

evidenced by increases in alanine transferase (ALT) levels, recurs. ALT levels rise when liver cells are damaged or die.

While the antivirals adefovir (Hepsera) and entecavir (Baraclude) are both recommended for patients who have lamivudine resistance, adefovir may be better, Keeffe wrote, because recent research shows 32% of lamivudine-resistant patients develop resistance to entecavir within three years.

Whether adefovir should completely replace lamivudine, or be given in combination with continued lamivudine, may depend on the severity of the patient's liver disease. Patients with fairly healthy livers experienced only mild increases in ALT levels when switched from

lamivudine to adefovir, which may make this a safe strategy for these patients, Keeffe noted.

However, 15% to 19% of patients with advanced liver disease who switch to just adefovir develop viral resistance to adefovir within two years. In these patients, adefovir should be added to ongoing lamivudine treatment to keep all HBV under control, he recommended.

Entecavir treatment causes a dramatic five-fold reduction in HBV DNA levels in lamivudine-resistant patients, "but this potency needs to be weighed against the development of genotypic resistance and virologic breakthrough, which can develop in up to 32% of lamivudine-resistant patients within three years," Keeffe

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added.

Future treatment of lamivudine-resistant patients may involve adding the antiviral tenofovir or switching to a combination of emtricitabine and tenofovir, which appears to be promising, however neither drug has been approved by the U.S. Food and Drug Administration for hepatitis B treatment yet.

Another potential strategy may be a combination of telbivudine (Tyzeka, recently approved by the FDA) plus tenofovir, “which theoretically should be effective but has not been studied,” he concluded.

**Fine Needle Biopsy of Liver Lesions Can Inadvertently Spread Cancer**

Using a “fine needle biopsy” to retrieve tissue from a potentially cancerous liver lesion or tumor can spread cancer cells and cause new tumor growths, according to a report published in the December 2006 issue of the journal of *Digestive Diseases and Science*.

A team of Taiwanese researchers followed five patients between 1997 and 2002 who

had undergone fine needle biopsies – when doctors sampled tissue to help them diagnose liver lesions. In two patients, as the needles withdrew from the tumors, they apparently carried cancerous cells from the tumor they biopsied that “seeded” or caused new tumor outbreaks in new regions of the livers.

“Tract implantation after fine needle biopsy changed a potentially curative disease into an untreatable situation,” researchers wrote. “Because of the risk of tumor implantation in the needle tract, we support a policy of selective use of fine needle biopsy for the definitive diagnosis of liver lesions.”

The patients who do need a biopsy should be carefully followed up for early detection of an implanted tumor and its recurrence after resection, the researchers recommended.

**Hepatitis B Genotype F Linked to Higher Rate of Liver Cancer Among Alaskans**

In an effort to better understand the link between the hepatitis B genotype or strain and liver cancer, a team of

researchers studied the HBV genotype and HBV mutations in 47 HBV-infected native Alaskans who had liver cancer, and 1,129 HBV-infected Alaskans without liver cancer.

Writing in the January 2007 issue of the *Journal of Infectious Diseases*, researchers reported they identified genotype F in 68% of liver cancer patients, and in 18% without liver cancer.

Among the genotype F patients, the average age of liver cancer diagnosis was lower (age 22.5 vs. 60 years) than among patients with other genotypes.

Researchers found no significant differences in the liver cancer rates in patients with core promoter and precore region mutations between the two groups.

**Pretreatment with Prednisone, Followed by Lamivudine and Interferon, Produces Improved Liver Health**

Cuban researchers studied what difference pretreatment with the steroid prednisone would have on HBeAg-positive patients who

were next treated with lamivudine and conventional interferon alpha.

Writing in the November 2006 issue of the journal of *Gastroenterology and Hepatology*, the researchers reported that they hoped the pretreatment with the steroid that suppresses the immune system would increase the current 35% seroconversion rate (loss of HBeAg and gaining the “e” antibody).

They selected 44 HBeAg-positive patients with persistently elevated ALT levels, which indicates the immune system is attacking and killing the HBV-infected liver cells. They treated 22 patients with 40 mg of prednisone daily for four weeks, followed by two weeks without treatment. They then treated them with lamivudine 150 mg daily for four weeks; then lamivudine plus interferon (10 MIU every other day) for 24 weeks followed by continuous lamivudine 150 mg daily to complete 58 weeks.

The other 22 patients received the same treatment regimen, but without prednisone pretreatment.

HBeAg seroconversion plus a decrease of HBV DNA (viral load) of 100,000 copies/ml at 24 weeks after treatment ended was observed in 68% of the patients receiving prednisone compared with 54% of the control group. Forty-five percent of patients with prednisone priming showed improvement in liver health, compared with 23% of the control group.

“Virologic response was clinically, but not statistically, superior in the group with prednisone priming,” researchers wrote. However, liver health notably improved in the group with prednisone pretreatment.

**Female Gender, Elevated ALTs, Low Viral Load and Younger Age Produce Better Response to Pegylated Interferon with or without Lamivudine**

An international group of researchers analyzed how 518 HBeAg-negative patients responded to treatments of: pegylated interferon alone, lamivudine alone, or a combination of inter-

feron plus lamivudine.

They wanted to see if age, gender, ALT levels, viral load, HBV genotype or other characteristics played a role in identifying which patients achieved normal ALT levels and low HBV DNA levels.

Writing in the November 2006 issue of *Gut*, the researchers reported that in all three treatment groups, those who were younger and female, and had elevated ALT levels and low viral load responded best 24 weeks after treatment ended.

In the groups treated with either interferon or lamivudine, patients infected with genotypes B or C responded better than those with genotype D. But, genotype D patients responded better to combination therapy than with interferon alone.

One year after treatment ended, 19.2% of those treated with just interferon and 19% of those treated with the combination of interferon and lamivudine maintained normal ALT and low viral loads, compared to just 10% treated with only lamivudine.

“Baseline ALT and

HBV DNA levels, patient age, gender, and infecting HBV genotype significantly influenced combined response 24 weeks (after) treatment, in patients treated with peginterferon alfa-2a and/or lamivudine,” researchers wrote. One year after treatment ended, HBV genotype determined who responded best to interferon or interferon plus lamivudine.

**Improve Hepatitis B Immunization among Nursing Assistants**

A report in the November 2006 issue of the *American Journal of Infection Control* underscored the importance of immunizing healthcare workers against hepatitis B. A team of Dutch researchers studied accidental needlestick injuries, which can carry a high rate of hepatitis B infection.

They studied 144 incidents, and found that of the needlestick injuries in nursing assistants, 84% involved an insulin needle or pen. They reported that 35% of all healthcare workers and 47% of nursing assistants had not been vaccinated against

hepatitis B.

**Interferon Treatment Decreases Cirrhosis and Liver Cancer Long Term**

Researchers from Taiwan compared the long-term outcomes of 233 interferon-treated HBeAg-positive patients and 233 similar, untreated patients over an average of 6.8 years. At the end of the follow-up period, researchers reported in the October 20, 2006 online edition of the *Journal of Hepatology*:

- HBeAg seroconversion occurred in 74.6% interferon-treated patients, compared to 51.7% untreated.
- 3% of interferon patients cleared the hepatitis B surface antigen (HBsAg) clearance, compared to 0.4% untreated. 17.8% of the interferon group developed liver cirrhosis 17.8%, compared to 33.7% of the untreated group.
- And 2.7% of the treated group developed liver cancer, compared to 12.5% of the untreated group.

Interferon-treated patients who did not experience HBeAg sero-

conversion still had a slightly lower rate of cirrhosis (liver scarring). The researchers concluded that interferon therapy, HBeAg seroconversion, and infection with genotype B HBV were all indicators of better long-term outcomes.

### **Cirrhosis Causes Osteoporosis**

A team of Greek researchers studied 83 hospitalized patients with cirrhosis and a “control” group of 25 healthy people and measured bone mineral density (BMD).

Writing in the November-December 2006 issue of *Hepatology*, researchers reported, “Cirrhosis is a major cause of osteoporosis and the degree of osteopenia is related to the severity and not the etiology (cause) of the liver disease.”

### **Constant Liver Cell Death and Regeneration Causes Cancer during HBV Infection**

Does HBV cause liver cancer directly by infecting the cells and altering the cells by integrating its X protein, or does it indi-

rectly cause cancerous growths through continual liver inflammation?

Department of Molecular Microbiology and Immunology researchers at the University of Southern California, Los Angeles, studied transgenic mice infected with HBV. They reported in the January 2007 issue of *Hepatology* that HBV by itself did not cause cancer.

What caused liver cancers in these mice was not the direct alteration of liver cells, but the continual cycle of liver cell death and regeneration that occurred during infection as the immune system attacked infected liver cells.

### **Tenofovir as Effective as Tenofovir-Lamivudine Combination in HIV-HBV Infected Patients**

Is combination treatment of lamivudine plus tenofovir better than using lamivudine first, followed by tenofovir in people co-infected with hepatitis B and HIV?

Researchers, reporting in the December 2006 issue of *AIDS*, studied 25 patients who began treatment with

both tenofovir and lamivudine, and 50 patients who received just tenofovir.

A sustained undetectable viral load was achieved in 76% of the patients on tenofovir plus lamivudine and in 42 of the 50 patients (84%) on tenofovir.

HBeAg seroconversion was observed in 9 of 25 (36%) patients on tenofovir plus lamivudine and in 12 of 50 (24%) patients on tenofovir.

One patient in the combination group and three of the tenofovir group lost surface antigen.

The researchers concluded that over 116 weeks, tenofovir was as effective as tenofovir plus lamivudine.

