

# HBV JOURNAL REVIEW

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## Hepatitis B

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### **Pegylated Interferon and Lamivudine More Effective Than Lamivudine Alone**

In the Feb. 15, 2005 issue of the *Annals of Internal Medicine*, Hong Kong researchers reported that a combination of pegylated interferon and lamivudine proved more effective than lamivudine alone in lowering HBV DNA (viral load), stopping liver damage, clearing the hepatitis B “e” antigen (HBeAg), and producing the “e” antibody. Researchers recruited 100 participants with HBeAg-positive hepa-

titis B and moderately elevated alanine aminotransferase (ALT) levels, an enzyme which indicates liver damage. Half were treated for 60 weeks with pegylated interferon, which boosts the immune system, and the antiviral lamivudine (EpiVir-HBV), which interferes with the virus’s genetic material so it cannot replicate easily. The other half was treated for 52 weeks with only lamivudine.

They found 60% of patients treated with interferon and lamivudine achieved lower viral load and normal ALT levels, and developed the “e” antibody (called seroconversion). This group was also less likely to develop viral resistance to lamivudine.

Only 28% of those treated with just lamivudine seroconverted and achieved undetectable viral load.

When researchers tested the patients 24 weeks after treatment ended, they found 36% of the combination group sustained their low viral load and HBeAg seroconversion, while only 14% of the lamivudine-treated group did.

About 21% of patients receiving combination treatment developed HBV that could resist lamivudine’s antiviral effect, while 40% of those receiving lamivudine developed viral resistance.

“We now need head-to-head comparisons to see whether this combination treatment leads to similar or higher

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rates of sustained response compared with either pegylated interferon alone or conventional interferon with or without lamivudine,” the researchers concluded.

### **Long-Term Lamivudine Beneficial, Despite Viral Resistance**

A historic study of 20 patients infected with the hepatitis B virus (HBV) who were treated with lamivudine for more than one year, and then followed for eight years, found these patients experienced no cirrhosis or liver cancer, and generally had a better prognosis than those who were never treated.

Reporting in the February 2005 issue of the *Journal of Medical Virology*, a team of Tokyo researchers studied the non-cirrhotic patients. At the start of treatment, 55% did not have HBeAg, 25% had undetectable HBV DNA and 20% had nor-

mal ALT levels. After about eight years, 85% had cleared HBeAg, 80% had undetectable HBV DNA and 80% had normal ALT.

The improvements in liver health occurred despite the development of lamivudine-resistant HBV (called YMDD variants) and continued treatment with lamivudine.

Viral resistance and resurgence of HBV DNA appeared in 65% and 45% respectively during follow-up, but severe breakthrough hepatitis, signaled by liver damage and high viral load, occurred in only 5%. About 80% of patients who received additional treatment for breakthrough hepatitis, regardless of continuation of lamivudine, were ALT normal level at the last visit, in contrast to 25% who were untreated.

Clearance of the surface antigen (HBsAg) occurred in two patients who had discontinued lamivudine. They were not infected at birth, and both were young. One was infected with HBV genotype C and had breakthrough hepatitis, and

the other had lamivudine resistance and had genotype D, which is rare in Japan.

“Our results suggest that long-term lamivudine therapy improves long-term prognosis, especially when additional treatment for breakthrough hepatitis is used,” the researchers reported.

### **Addition of Adefovir to Lamivudine Treatment Cleared Infection in One Patient**

One patient, who was treated with both adefovir and lamivudine after developing viral resistance to lamivudine, cleared the hepatitis B infection completely and developed surface antibodies.

French researchers, reporting in the February 2005 issue of the *Journal of Hepatology*, found that when they continued lamivudine but added adefovir to the patient’s treatment,

HBV DNA levels dropped by more than 10,000 times and surface antigen (HBsAg) disappeared after 22 months of combination antiviral therapy. The patient developed surface antibodies after 32 months of treatment.

Not only did HBV DNA dip to undetectable levels, but cccDNA declined.

This protein is associated with liver cancer. The patient’s liver condition also improved with decreased fibrosis.

“This report suggests that in patients who previously failed lamivudine therapy, proactive antiviral treatment may lead to a beneficial virological and clinical effect,” the researchers wrote.

### **Extending Lamivudine in HBeAg-Negative Patients with YMDD Mutations Ineffective**

A group of Italian researchers studied the

impact of extending lamivudine treatment in patients who have HBeAg-negative hepatitis B, an infection in which HBV do not produce the “e” antigen.

Writing in the February 2005 issue of the *Journal of Hepatology*, they reported treating half of 76 patients with lamivudine, and the other half with placebo.

Liver biopsies were performed before and after treatment to evaluate liver health.

Liver health improved, remained unchanged, and worsened in 64, 32 and 5% of patients respectively treated with lamivudine who did not have YMDD-variants HBV.

Among patients with YMDD mutations, only 15% had improved liver health, 54% had unchanged conditions, and 31% experienced additional liver damage during the study.

None of the patients without cirrhosis at beginning of treatment developed cirrhosis.

ALT levels gradually increased in patients with YMDD mutations

after two years of treatment.

“The clinical benefit of lamivudine is greatest for patients without YMDD variants over two years of extended treatment,” researchers concluded. “Additional therapies should be considered for patients with YMDD variants.”

### **T-Cell Response to HBeAg May Dictate Whether Chronic Hepatitis B Develops**

A group of California researchers delved into the function of HBeAg, an antigen found in the precore region of HBV, to find out what role this antigen played in the development of chronic or long-term hepatitis B.

This antigen is not required for new virus assembly, but some researchers suspect HBeAg promotes chronic infection by somehow affecting the immune system’s T-cells that fight infection. Researchers used mice to study the role of

HBV precore (HBeAg) and core antigen (HbcAg) proteins and T-cell response. Writing in the March 2005 issue of the *Journal of Virology*, the researchers confirmed that the HBeAg secreted by the HBV is significantly more efficient than HbcAg at getting T-cells to tolerate, and not attack, the virus.

### **Hepatitis B Vaccination of HIV-Infected Hemodialysis Patients Recommended**

The Centers for Disease Control and Prevention (CDC) recommends hepatitis B immunization for all hemodialysis patients because they are at high risk of infection, but some studies show these patients, who suffer kidney damage, often fail to respond to the vaccine and develop the necessary antibodies to fight off an HBV infection.

Researchers studied whether HIV-infected patients with serious kidney disease would

also fail to develop antibodies against hepatitis B when they were immunized.

Of 116 HIV-infected dialysis patients who received the vaccine, 62 (53.4%) developed adequate antibody protection. This was similar to the response rate of 50.4% of 220 dialysis patients who were not HIV-infected.

They reported in the March 2005 issue of the *Kidney International* journal that 70% of the HIV-infected responders maintained protective antibodies six months after vaccination. The researchers recommend that the hepatitis B vaccine should be offered to all HIV-infected hemodialysis patients because more than half will develop protective antibodies.

### **Vaccination in Prisons Help Protect the IDU Community**

A Scottish program that offered hepatitis B immunization to all prison inmates was found to

also improve the hepatitis B vaccination rate among the area's injecting drug users (IDU) community, according to a report published in the journal *Vaccine*.

In April 1999, the Scottish Prison Service began offering the vaccine to all inmates in Glasgow. Researchers then screened long-term injecting drug users for vaccine-conferred hepatitis B antibodies in the local community. They found the immunization rate was significantly higher among those surveyed in 2001-2002 (52%) than in 1993 (16%).

Of the 2001-2002 IDUs who were vaccinated, 56% had been vaccinated in prison. "Our results indicate that the universal offer of vaccination to all prisoners, within two years of the initiative's implementation, had a dramatic impact on uptake among IDUs," the researchers reported.

### HIV Type 1 Infection Hinders CD4 T-Cells That Normally Target HBV

The immune system's T-cells, which normally target and destroy hepatitis B viruses, are greatly weakened when a person is also infected with HIV, according to a report published in the March 2005 issue of the *Journal of Virology*.

When a person is infected with HBV, whether they quickly clear the infection or develop a chronic hepatitis B infection hinges on the strength of their T-cells. When individuals are infected with HIV Type 1, they are prone to developing chronic HBV infections.

To find out why, researchers studied two types of T cells, CD4 and CD8 in 34 chronic HBV carriers, including individuals never treated for HBV infection (7), HBV-infected individuals receiving anti-HBV therapy (13), and HIV and HBV coinfecting individuals

receiving hepatitis B antiviral therapy (14).

HBV-specific T-cell responses were more frequently detected and had greater strength in patients receiving hepatitis B antiviral treatment than untreated patients.

Although, the frequency and breadth of HBV-specific T-cell responses were comparable in those infected with just HBV and those coinfecting with HIV and HBV, HBV-specific CD4 T-cell responses were significantly reduced in HIV-HBV-coinfecting individuals. "Therefore, HIV-1 infection has a significant and specific effect on HBV-specific T-cell immunity," researchers concluded.

### Coffee May Help Prevent Liver Cancer

Coffee and its caffeine may help prevent the most common type of liver cancer, according to a study of more than 90,000 Japanese, published in the February 2005 issue of the *Journal*

*of the National Cancer Institute*.

A research team led by the National Cancer Center in Tokyo analyzed a 10-year public health study to compare the effects of coffee consumption in people diagnosed with liver cancer and people who did not have cancer.

They found the risk of liver cancer in people who never or almost never drank coffee was 547.2 cases per 100,000 people over 10 years while people who drank coffee daily had a risk of 214.6 cases per 100,000.

They found a protective effect from coffee in people who drank one to two cups of coffee a day, and it increased when they consumed three to four cups daily. While some studies suggest caffeine aggravates symptoms of menopause and intensifies the side effects of some antibiotics, studies have also shown that a skin cream spiked with caffeine lowers the risk of skin cancer in mice.

**Researchers Study YMDD Mutations in Patients Never Treated with Antivirals**

A team of Chinese researchers examined 104 hepatitis B patients, who had never been treated with lamivudine, to see if the YMDD viral mutation was present. Reporting in the February 2005 issue of the *World Journal of Gastroenterology*, they reported that more than one-quarter of the patients had a YMDD mutation in the HBeAg region of their virus, apparently unrelated to antiviral treatment. Treatment with lamivudine is known to promote HBV with YMDD mutations.

Researchers found the presence of YMDD mutations varied based on patients' HBV genotypes. HBV DNA level, the researchers reported, appeared not to impact development of YMDD mutations.

**Hepatitis B Virus Added to Government List of "Known" Cancer-Causing Agents**

The Department of Health and Human Services, in its 11th Edition of the *Report on Carcinogens*, added the hepatitis B virus to its list of 246 agents that cause cancer.

HBV cause liver cancer by either integrating into liver cells and causing abnormal cell growth, or by causing extensive scarring and cellular regeneration, which can also lead to tumors.

About 1.2 million Americans are chronically infected with HBV, which primarily is transmitted through sexual contact (50%) and intravenous drug use (15%).

Hepatitis C was also added to the "known" cancer-causing list for its role in causing liver cancer.

**Health Issues Can Linger Even in Those Who Clear Chronic Hepatitis B**

A team of South Korean researchers studied 49 individuals who had cleared their hepatitis B infections and had no detectable levels of HBsAg to see if the infection caused any residual health effects.

Reporting in the February 2005 issue of the *Journal of Hepatology*, the researchers followed patients for about 20 months after they cleared HBsAg. They found five of the 49 (10.2%) patients developed liver cancer even after clearing the infection.

The presence of cirrhosis, acquiring the infection at birth, and HBV infections that spanned more than 30 years all played a role in increasing liver cancer risk.

Despite an absence of HBsAg in blood, HBV DNA was detected in the liver tissues of all

15 patients who underwent liver biopsies. Inflammation of the liver declined, but fibrosis in the liver did not decrease significantly improve after HBsAg clearance, researchers noted, and actually worsened in two patients.

**Study Finds Oxymatrine Could Be a Cost-Effective Alternative to Interferon**

To date, interferon has proven to be a costly and often ineffective treatment for hepatitis B. In a study published in the 2004 *Chinese Journal of Digestive Diseases*, researchers reported that oxymatrine, made from an extract from the Chinese plant *Sophora alopecuroides*, produced treatment results similar to conventional interferon.

In one multicenter study in China, three months of oxymatrine treatment produced undetectable HBV DNA in 42.3% of patients

(compared to 40.7% treated with interferon), and HBeAg loss in 36.5% (compared to 38.9% treated with interferon).

Research also shows that oxymatine is effective in spurring the immune system to fight infection and promoting regrowth of liver cells. It reportedly causes fewer side effects than interferon.

Oxymatine is also more affordable at one-fifth the cost of interferon.

### **Body Fat Reduced When Even Moderate Cirrhosis Is Present**

Brazilian researchers discovered that even during in the early stages of cirrhosis, a person will lose substantial body fat and experience significant reduction in body cell mass, according to a report in the February 2005 issue of the *Cirrhosis Journal of Gastroenterology and Hepatology*.

While malnutrition is common in patients suffering from severe liver scarring (cirrhosis), doctors lack detailed information about how body composition changes when liver function is impaired during the early stages of cirrhosis.

Researchers examined the relationship between cirrhosis and body fat and tissue in 79 HBV-infected patients and 17 uninfected patients. They measured body water distribution, body cell mass, and fat.

They found body cell mass and body fat were significantly reduced, mainly in patients with moderate and severe disease.

In patients with early stages of cirrhosis, body fat declined. However, in more advanced stages of cirrhosis (Child-Pugh class C), patients had simultaneous loss of cell mass and fat, and redistribution of body water.

### **HepDirect Prodrugs Offer New Way to Deliver Treatment to the Liver**

HepDirect prodrugs offer a new strategy to deliver medication directly to the liver and achieve “more efficacious therapies to fight chronic liver diseases such as hepatitis B, hepatitis C and liver cancer,” according to an article in the February 2005 issue of *The Journal of Pharmacology and Experimental Therapeutics*. HepDirect prodrugs include pradefovir mesylate (previously known as remofovir or MB06866) for hepatitis B, and MB07133 for liver cancer. Both drugs are currently in clinical trials. HepDirect is developed by Metabasis Therapeutics Inc.

### **Genetics May Determine Liver Cancer Development**

Researchers in southern China studied hepatitis B genotypes to see if there was a link between genotype or viral strain and liver cancer. They studied the link between polymorphisms in T-helper 1 (Th1) and Th2 cytokine genes among a group of 250 patients with liver cancer and a group of 250 hospital controls who were matched to the cancerous individuals by age, gender, ethnicity, residence, and month of hospital admission. They found that diminished cell-mediated immune response, which is controlled genetically, appeared to play an important role in determining what individual, infected with hepatitis B, developed liver cancer, according to an article published in the January 2005 issue of *Cancer*.

## **Organ Donor Age Not an Issue for Transplanted Hepatitis B Patients Is**

Researchers studied the impact of age of organ donors among hepatitis B and C patients who received liver transplants. In the study, survival of 778 liver transplant patients infected with hepatitis B was compared to survival rates among hepatitis C patients and uninfected liver transplant patients.

In the March 2005 issue of the *American Journal of Transplantation*, researchers reported that patients with hepatitis B appeared to fare equally well as patients without viral hepatitis, no matter what age the organ donor was. However hepatitis C transplant patients did not fare well with older transplanted organs.

## **Medium- Or Long-Term Survival Possible for HIV-Hepatitis Transplant Patients**

Recently, researchers have begun conducting liver transplants on patients coinfecting with HIV and hepatitis B or C. Historically, these transplants did not occur because doctors assumed patients with HIV would not survive.

Researchers recently monitored liver transplants in five coinfecting patients and reported in the February 2005 issue of *Liver International* that medium- or even long-term survival is possible. Patients did generally well, without their HIV worsening due to antiviral therapy to control the viral hepatitis infection.

Of the five HIV-infected patients, one had hepatitis B, three had hepatitis C, and the fifth had hepatitis B, C and D coinfections. Three patients ulti-

mately died 3, 10 and 31 months after their transplants.

Despite that death rate, the researchers were optimistic and encouraged doctors to define criteria for HIV-hepatitis coinfecting patients who would survive and benefit from a liver transplant.

## **Parents Accept Vaccine, Even When Behavior Might Prevent Disease**

If a vaccine was promoted as a tool to prevent a sexually-transmitted infection such as hepatitis B, would parents accept it and get their adolescent children immunized? Yes, according to researchers writing in the February 2005 issue of the *Archives of Pediatrics & Adolescent Medicine*.

They surveyed 278 parents and found that parents did not care about how the vaccine-preventable disease

was transmitted, nor did they assume that their children's behavior would prevent the disease.

The two issues that mattered most to parents were the severity of the infection – the threat it might pose to their children's health, and the safety and effectiveness of the vaccine.

Education, income, and gender did not impact parents' decision to vaccinate.

## **Scientists Conduct First Human Trial of Plant-Derived Hepatitis B Vaccine**

Reporting in the February 2005 issue of the *Proceedings of the National Academy of Sciences*, immunologist Yasmin Thanavala of the Roswell Park Cancer Institute in Buffalo reported initial success in the first human trial of a plant-derived hepatis-

tis B vaccine.

Scientists have been working to genetically modify plants – in this case a potato – to carry the gene for HBsAg. They hoped once individuals consumed this noninfectious antigen from the HBV, that their immune systems would create surface antibodies against that single antigen and be able to ward off hepatitis B infection.

An oral vaccine is preferred to the cost and hazard of injected vaccines, especially in developing countries. Previously researchers have found potatoes can deliver vaccines that prevent intestinal pathogens such as the E. coli and Norwalk viruses. In this trial, 42 people who had already been immunized against hepatitis B by the traditional three-shot series, consumed raw, genetically-modified potatoes. About 60 percent showed signs of increased immunity.

### Are Liver Biopsies Effective in Finding Liver Cancer Early?

Writing in the *Nature of Clinical Practice: Gastroenterology & Hepatology*, German researcher Jürgen Schölmerich examined whether a liver biopsy would improve a patients' survival by finding small liver cancers when cirrhosis was present and alpha fetoprotein (AFP) levels were high. High AFP levels can indicate the presence of a tumor.

Currently, there are no guidelines on when to perform a liver biopsy when cirrhosis is present and AFP rates rise. During a liver biopsy, a small needle is inserted in the liver to withdraw a tissue sample.

Scholmerich evaluated the effectiveness of ultrasound-guided fine needle biopsy in the diagnosis of liver cancer in patients with small lesions, which might be missed by an ultrasound or other imaging diagnostic procedures.

He reported that this biopsy procedure accu-

rately diagnosed liver cancer, even small tumors, in 90% of patients when AFP levels are less than 400 ng/ml. "This is more accurate than other approaches," he wrote, which have accuracy rates of 50-80%.

"We are confident that the risks of (a biopsy) are acceptable because the rate of bleeding is low and the rate of needle-tract seeding (ed: spreading the cancerous cells) is probably overestimated," he concluded.

### A Snapshot of Hepatitis B Infection Worldwide

Kris V. Kowdley, a University of Washington medical professor, reported on hepatitis B infection rates worldwide at the 14th Biennial Conference of the Asian Pacific Association for the Study of the Liver.

Hepatitis B infects up to 2 billion people worldwide and about 400 million people are chronically infected. About 1 million die each from year from the

infection; one-third from liver cancer and the remainder from complications of liver disease.

While immunization has reduced infection and liver cancer rates in some countries, universal vaccination has not yet been implemented in Chile, Japan, some northern and central European countries and most central African countries.

Using HBsAg to indicate chronic infections in 32 countries with published data, researchers reported the infection rate varied from 0.2% in the United States to 12% to 14% in Vietnam and China. China appears to have the highest number of chronically-infected people, an estimated 100 million people.

The current prevalence of chronic hepatitis B in Bangladesh ranges from 4.4% to 7.5%, and India has 10% (40 million people) of the world's HBV-infected population with an infection rate of 0.7% to 4.2%.

The prevalence of hepatitis B in Indonesia is 5 to 10%, in Pakistan it is 3 to 5% and in Turkey it is 4 to 7%.

Researchers hope universal immunization will dramatically decrease new HBV infections and liver disease in the coming years.

