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Hepatitis B

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Pegylated Interferon Recommended to Treat HBeAg-Negative Hepatitis B

Pegylated interferon, a time-release interferon administered in one weekly injection, is superior to the antiviral lamivudine (Epivir-HBV) for treating HBeAg-negative hepatitis B, which occurs when mutated hepatitis B viruses (HBV) are able to replicate without producing the "e" antigen (HBeAg).

Interestingly, even the addition of lamivudine to pegylated interferon treatment produced no additional benefits in these patients, according to researchers writing in the Sept. 16, 2004 issue of

the *New England Journal of Medicine*.

Currently, most physicians treat HBeAg-negative hepatitis B with antiviral medications, such as lamivudine, which has proven ineffective and is prone to producing viral resistance.

In this study, 177 patients with HBeAg-negative hepatitis B received pegylated interferon, 179 patients received pegylated interferon plus lamivudine, and 181 patients received just lamivudine for 48 weeks. They were then followed for 24 more weeks.

Normal ALT levels occurred in 59% of patients treated with just interferon, in 60% of those treated with interferon plus lamivudine, and in 44% of those treated with only lamivudine. HBV DNA levels decreased

below 20,000 copies/mL in 43%, 44%, and 29%.

Rates of sustained suppression of HBV DNA (to below 400 copies/mL) were 19% with just interferon, 20% with combination therapy, and 7% with lamivudine alone.

Loss of HBV B surface antigen (HBsAg) occurred in 12 patients receiving interferon alone or in combination with lamivudine, but not in any of the patients who received just lamivudine.

"Our data demonstrate the possibility of achieving HBsAg loss or seroconversion in patients with HBeAg-negative chronic hepatitis B with the use of (pegylated interferon) and therefore support the use of this agent as a first-line therapy for HBeAg-negative chronic hepatitis B," the authors wrote.

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Impact of Genotypes on Hepatitis B Disease Progression Examined

Expert hepatitis B researchers Drs. Scott Fung and Anna Lok examined the impact of HBV genotypes on disease progression and treatment in an editorial published in the October 2004 issue of *Hepatology*.

Bottom line: While HBV genotype has an impact on the severity of liver damage and success of interferon treatment, genotyping should remain a research tool for now. Researchers need more information before genotype can reliably guide treatment decisions or predict a person's risk of cirrhosis and liver cancer.

To date, most HBV genotype research has focused on genotypes B and C, the genotypes most commonly found in Asia. Compared to genotype C, genotype B is associated with spontaneous HBeAg seroconversion (loss of HBeAg and production of the "e" antibody) at a younger age, less active

liver disease, and slower rate of cirrhosis. Liver cancer is less frequent in genotype B and occurs at an older age, possibly because of a shorter duration of active HBV replication when HBeAg is present.

While no published study has compared the rate of HBeAg seroconversion, liver disease, and liver cancer among all HBV genotypes, one study of 694 patients in the United States found genotypes B and D had a lower prevalence of HBeAg than genotype A, while genotype B was associated with a lower rate of hepatic decompensation, compared to genotypes A, C, or D.

But researchers still found that ethnic background, age at infection, duration of infection, and exposure to alcohol and environmental toxins may contribute to disease progression more than HBV genotype.

When it comes to treatment, genotype does appear to affect response to standard interferon (administered in three weekly injections). Two Asian studies reported that patients with HBV genotype B had a higher rate of HBeAg seroconversion when treated with interferon compared to those with genotype C.

Another study found patients with genotype A had a higher rate of HBeAg seroconversion than those with genotype D. Although all three studies involved small numbers of patients, the findings were confirmed by a recent study of pegylated interferon. HBeAg seroconversion occurred more often in pegylated interferon-treated patients with genotypes A (47%) and B (44%), than in those with genotypes C (28%) and D (25%).

Unlike interferon, researchers have found no major difference in responses to the antiviral adefovir (Hepsera) and lamivudine between genotypes. However, two studies—one in HBeAg-positive and one in HBeAg-negative patients—found genotype B patients were more likely to sustain their response when lamivudine treatment was discontinued.

Adefovir appears to lower viral load (HBV DNA) equally among all genotypes, but its impact on HBeAg seroconversion across genotypes has not yet been determined.

The exact reasons why HBV genotype affects disease progression remains unclear, Drs. Lok and Fung noted. It is possi-

ble that some HBV genotypes replicate better than others, or are more easily targeted by the immune system. There is a clear association between HBV genotypes and development of precore and core promoter mutations.

Liver Cancer Risk High in Lamivudine-Resistant, Cirrhotic

Researchers followed 22 people for 42 months to see what long-term impact lamivudine-resistant HBV would have on patients who had cirrhosis (severe liver scarring) and who had the hepatitis B "e" antibody (anti-HBe). To their surprise, 11 patients developed liver cancer (hepatocellular carcinoma).

They found a high rate of liver cancer in 13 patients whose HBV was able to resist the antiviral effects of lamivudine. Some HBV strains are able to replicate despite lamivudine's antiviral impact, and over time these lamivudine-resistant HBV, which have YMDD muta-

tions, become the dominant HBV in a patient and viral load and liver damage rebound.

Initially, all patients responded to lamivudine, but lamivudine-resistant HBV developed in 13 patients between nine and 42 months of therapy.

During follow-up, 11 of them developed liver cancer. Of these, 10 cancers occurred soon after the emergence of aggressive, lamivudine-resistant HBV. One cancer occurred in the nine patients who appeared not to develop any viral resistance to lamivudine.

Lamivudine resistance appeared to be the only common thread among most of the patients who developed liver cancer.

The authors, writing in the September 2004 issue of the *Journal of Viral Hepatitis* concluded, “Our study suggests that the occurrence of lamivudine resistance increases the risk of hepatocellular carcinoma in anti-HBe positive cirrhosis and warrants further research.”

The study did not indicate if the patients in the study had HBeAg-negative hepatitis B, which develops when certain mutated HBV can replicate without producing HBeAg.

Those with Genotype B, HBeAg-Negative Hepatitis B Do Better on Lamivudine

A team of researchers studied the effectiveness of a two-year course of lamivudine treatment in 24 Chinese-Canadian patients with HBV genotype B and C. All patients had HBeAg-negative hepatitis B.

The researchers stopped treatment after 24 months and studied the rate of relapse in these patients.

Reporting in the September 2004 issue of the *Journal of Viral Hepatitis*, the doctors found that more patients with genotype B achieved undetectable HBV DNA (viral load) than those with genotype C (86% vs. 74% after 24 months).

About half of those with genotype C experienced a relapse – with increased HBV DNA and signs of liver damage – 18 months after treatment stopped, compared with a relapse rate of 30% in the genotype B group.

Reinstitution of lamivudine resulted in a

prompt response in both groups. The researchers concluded that “a sustained response can be achieved after a two-year course of lamivudine in a subset of patients with e-CHB.”

Lamivudine Levels in Bloodstream Vary, Based on Wild and Mutant HBV Mix

Writing in the October 2004 issue of the *Digestive and Liver Disease* journal, a group of Italian researchers carefully measured lamivudine levels in patients’ blood to see how they fluctuated when wild type (without mutations) and lamivudine-resistant HBV were present.

They found minor lamivudine fluctuations in the bloodstream over time, “with an important increase at the time of the hepatitis flare-up due to the hepatitis B virus mutant presence.”

When the wild-type HBV reappeared, mixed in with lamivudine-resistant HBV, lamivudine levels in the

serum dropped to below detectable levels.

While lamivudine levels appeared stable when the anti-viral effectiveness is fully achieved, important fluctuations are present according to the type of HBV present, the researchers concluded, “with a considerable decrease (in lamivudine in the bloodstream) possibly due to the presence of the wild-type virus.”

HBV Genotype C Increases Risk of Liver Cancer

Hong Kong researchers followed 426 chronic hepatitis B patients infected with genotypes B and C for 1,664 person years (on average four years per patient), to determine which genotype might pose a higher risk of liver cancer.

Forty-nine (11%) patients had cirrhosis. A total of 242 (57%) had genotype C and 179 (42%) had genotype B. Twenty-five patients developed liver cancer during a follow-up period that averaged 2.3 years.

The overall incidence of liver cancer was 1,502

cases per 100 000 person years. While cirrhosis increased cancer risk, having genotype C also increased a patient's risk of liver cancer.

Writing in the October 2004 issue of *Gut*, researchers reported that patient age, sex, HBeAg status, alanine aminotransferase (ALT) levels, and basal core promoter mutations did not play a role in the development of liver cancer.

However, patients infected with HBV genotype C tended to have persistently positive HBeAg or fluctuating HBeAg status and higher ALT levels during the follow up period.

Researchers reported that, "[g]enotype C HBV infection is an independent risk factor for (liver cancer) development in addition to liver cirrhosis."

The Younger the Child, the Better the Response to Interferon

When researchers examined how 22 chronically-infected children responded to standard

interferon treatment, they discovered that children age 5 or younger responded far better than older children and teens.

Writing in *The Journal of Pediatrics*, a team of U.S. and European pediatric hepatologists examined the charts of children treated with interferon who ranged in age from 17 months to 17 years, including 14 males and eight females.

Ten patients (48%) responded to interferon, achieving HBeAg conversion, undetectable HBV DNA and normal ALT and aspartate aminotransferase (AST) six months after treatment. Five cleared the infection and produced surface antibodies.

Seven of nine patients (78%) who were 5 years of age responded (five of them cleared surface antigen). Three of 13 patients (23%) who were older than age 5 responded. Younger patients clearly responded better to interferon than older children and teens.

AST, ALT, and HBV DNA at the start of

treatment were not different between responders and nonresponders. The doctors concluded interferon treatment may be more effective in younger children with chronic hepatitis B.

Hepatitis B Cited in Children's High Liver Cancer Rate in South Africa

Taiwanese researchers, reporting in the October 2004 issue of *Gut*, looked for HBV mutations in the surface antigen (HBsAg), which can result when HBV-infected children are immunized with the surface antigen derived vaccine. They wondered if these surface mutations would still be prevalent in infected children 15 years after universal immunization began in Taiwan.

They analyzed HBsAg in all HBV-DNA positive blood from 1,357 children and 219 adolescents in 1999, and

compared the prevalence and changes in the HBsAg mutations in these children from blood samples collected in 1984 (just before vaccination), 1989, and 1994.

The prevalence of HBsAg mutants in HBV-DNA positive children was 7.8% in 1984, which significantly increased to 19.6% in 1989, and peaked at 28.1% in 1994. The rate remained at 23.1% in 1999. It was higher in those fully vaccinated (with all three injections) compared with those not vaccinated. The number of HBsAg mutant-infected children in each survey was stable in the first five- to 10-year period but decreased 10 to 15 years after vaccination.

More HBsAg mutations emerged in children fully vaccinated with plasma-derived vaccine than those given recombinant vaccine. The researchers concluded that while HBsAg mutations do occur in immunized, infected children, they do not threaten Taiwan's universal vaccination program.

Children with Arthritis Respond to Hepatitis B Vaccine

Despite treatment with immune-suppressing drugs, children with juvenile idiopathic arthritis (JIA) respond well to the hepatitis B vaccine, according to a report in the September 2004 issue of the *Annals of the Rheumatic Diseases*.

As many as 300,000 children in America have JIA, a group of joint diseases. In some cases, immune-suppressing drugs have proven effective.

Researchers evaluated the safety and effectiveness of hepatitis B vaccination in 39 children with JIA and in 41 healthy children. The subjects were given the usual three doses of the vaccine when the study began.

With the exception of one JIA patient, all of the subjects displayed an appropriate hepatitis B antibody response. Antibody levels were lower in the JIA group than in the healthy group, but were still considered adequate for protection. Treatment with

immune-suppressing drugs did not influence antibody levels in the JIA group.

Hepatitis B vaccination appeared safe in the JIA group with none of the subjects experiencing a worsening of their disease.

Precore and Core Promoter Mutations Common in the United States

Increasingly, researchers are finding many chronically-infected people have precore or core promoter mutations in their HBV. This variant of HBV is often able to replicate without producing HBeAg. This variant causes HBeAg-negative hepatitis B, which is diagnosed when a patient has the “e” antibody, undetectable HBeAg, and high viral load.

Researchers, writing in the September 2003 issue of *Hepatology*, examined the prevalence of precore/core promoter HBV in the United States, and its association with HBV

genotypes, viral load and severity of liver disease.

They examined 694 chronic hepatitis B patients treated at 17 U.S. liver centers during a one-year period. Precore and core promoter variants were found in 27% and 44% respectively of patients. Precore and core promoter variants were more common in HBeAg-negative patients than in HBeAg-positive patients (precore, 38% vs. 9%; core promoter, 51% vs. 36%).

The prevalence of these variants was related to ethnicity, place of birth, and genotype. Patients with core promoter variants were more likely to have hepatic decompensation. Precore and/or core promoter variants were associated with higher viral load in HBeAg-negative but not in HBeAg-positive patients.

The researchers noted that physicians should be aware of the prevalence of HBV precore and core promoter variants and how to diagnose HBeAg-negative hepatitis B.

Risk of Flares Studied in Patients with Lamivudine Resistance

Hong Kong researchers followed 154 patients (all with HBeAg) treated long-term with lamivudine for 2.5 years to see what role genotype and lamivudine resistance (with YMDD mutations) played when patients experienced “flares” – marked by surges in ALT and elevated HBV DNA.

Writing in the September 2004 issue of the *Journal of Clinical Microbiology*, researchers reported that 43 patients with YMDD mutations experienced flares. Twenty patients (47%) had mild ALT flares and seven (16%) had severe flares. All patients recovered spontaneously.

The cumulative, annual risks of flares were 28, 47, and 58% for the first three years, respectively. Patients who experienced flares had significantly higher ALT levels before treatment began.

There were no differences in the cumulative risk of HBV DNA surges, risk, and severity of ALT flares

between patients with genotypes B and C.

Adding Interferon to Lamivudine Reduces Viral Rebound in Patients with HBeAg

South Korean researchers studied the impact of adding standard interferon to long-term lamivudine treatment to see if the drug combination would help prevent rebounding HBV DNA levels due to lamivudine-resistant HBV.

Forty-two patients received just lamivudine and 41 received lamivudine and interferon; they were followed for three years. Viral load remained undetectable over the study period in both groups, and HBeAg loss between the combination group and the lamivudine group was 49%, 61% and 67% compared to 31%, 39% and 42%, respectively, at 12, 24 and 36 months.

The rate of viral breakthrough, however, was significantly lower in the combined treatment group, compared with the lami-

vudine group (5%, 20% and 30% vs. 10%, 55% and 58%, respectively, at 12, 24 and 36 months).

YMDD mutants (which can replicate despite lamivudine's antiviral effects) were detected in 82% of the lamivudine group, compared to 56% of the combination group.

Heavy Alcohol or Diabetes plus Viral Hepatitis Boosts Liver Cancer Risk

The combinations of hepatitis B and diabetes or viral hepatitis and heavy alcohol consumption increase the risk of liver cancer 48-fold, according to a report in the September 2004 issue of *Cancer*.

Dr. Jian-Min Yuan of the University of Southern California, Los Angeles, and colleagues examined viral and non-viral risk factors for liver cancer in 295 patients with the disease, and in 435 cancer-free controls.

As expected, hepatitis B and C infections were both risk factors for liver cancer. However, the combinations of hepatitis and diabetes or hepatitis and

heavy alcohol use dramatically increased liver cancer risk.

Early Telbivudine Clinical Trials Show Promise

In the first clinical study of telbivudine, Hong Kong researchers evaluated its safety, antiviral activity, and optimal dosage in 43 adults with HBeAg-positive chronic hepatitis B.

This placebo-controlled trial assessed six daily dosing levels (25, 50, 100, 200, 400, and 800 mg per day). Treatment was given for four weeks, with a 12-week follow-up. HBV DNA levels were monitored.

Researchers, reporting in the September 2004 issue of *Hepatology*, found telbivudine was well-tolerated at all dosing levels, with no dose-related or treatment-related adverse events.

The highest level of antiviral activity was achieved in doses at or exceeding 400 mg per day. In the 800 mg per day group, the average HBV DNA reduction was 3.7-fold at week 4, producing a 99.98%

reduction in viral load. Return of viral load after treatment ended was slowest in the high-dose groups. The researchers recommend expanded clinical studies

Genotype A HBV Subtypes "a" and "e" Have Distinct Infection Features

A multinational team of researchers compared the two known subtypes of HBV genotype A against HBV genotype D to assess genotype A subtypes' unique infection features.

The genotype A subtypes have been designated genotype Aa ("a" for Africa/Asia) and genotype Ae ("e" for Europe).

In the multinational study, 78 genotype Aa carriers, 78 with Ae, and 78 with genotype D were compared. The prevalence of HBeAg was significantly lower in patients with Aa than in carriers of Ae (31% vs. 49%), with a difference more obvious in people ages 30 or younger (34% vs. 67%).

HBV DNA levels in Aa were significantly lower

than those of carriers of Ae, or of carriers of D regardless of the HBeAg status.

The most specific and frequent mutations in 54 Aa HBV samples were upstream of the precore initiation codon, which would interfere with the production of HBeAg in Aa infections. They were not detected in 57 genotype Ae or 61 D samples.

Researchers concluded that clearance of HBeAg may occur differently in Aa, Ae, and D infections.

Over Time, Lamivudine-Resistant HBV May also Resist Entecavir

During phase II clinical trials of the antiviral drug entecavir, two patients who already had developed HBV resistance to lamivudine, experienced viral breakthroughs after entecavir treatment.

One patient had been treated with lamivudine for more than a year, and then received just entecavir, followed by a combination of entecavir and lamivudine before viral breakthrough occurred, marked by rebounding HBV DNA.

The second patient, who had received a liver transplant and had failed to respond to lamivudine and other antivirals, also developed viral resistance to entecavir after 76 weeks.

The researchers, writing in the September 2004 issue of *Antimicrobial Agents and Chemotherapy*, found that “infrequent” entecavir resistance can emerge during prolonged therapy, especially in those who have already developed viral resistance to lamivudine.

Six-Fold Boost in Lamivudine Dose Reduces Infected Liver Cells in Model

Researchers, writing in the September 2004 issue of the *Journal of Viral Hepatitis*, used mathematical modeling to gauge what impact a dramatically increased daily dose of lamivudine would have on viral load.

They created a scenario in which 10 patients received 600 mg of lamivudine daily (the current recommended dose is 100 mg daily) for 48 weeks. In their model, the higher dose produced a 1.6-fold

faster decay rate in the infected cell population and a greater overall change in viral load.

“Studies using mathematical modeling of viral decay may be a useful method to evaluate single or combination therapy for HBV infection in vivo,” they recommended.

Lamivudine May Be Effective in Treating Acute Hepatitis B

Researchers treated six patients who were newly-infected with HBV with lamivudine to see if the antiviral would expedite recovery in these patients who were experiencing an acute (short-term) hepatitis B infection.

Writing in the September 2004 issue of the *Journal of Viral Hepatitis*, the researchers reported that they treated four patients who were experiencing severe liver disease, and two who were at risk of chronic or long-term hepatitis B.

HBV DNA levels in the patients ranged from 105 to 107 copies/mL prior to lamivudine treatment. The treatment produced a de-

cline in HBV DNA and appeared to reduce liver damage, as indicated by lowered ALT levels.

All but one patient survived. A 58-year-old man with fulminant hepatitis and multiple organ failure died despite antiviral treatment. When possible, HBeAg and HBsAg seroconversion was documented during follow-up.

While acute hepatitis B is not treated with any antivirals currently, these researchers suggest it might benefit patients with severe acute hepatitis B.

Study Shows Adefovir Safe for Kidneys at the 10 mg Daily Dose

Two double-blind, randomized, placebo-controlled studies found adefovir caused no problems in the kidneys of hepatitis B patients who took the 10 mg daily dose.

French researchers investigated the efficacy, safety, and the tolerability of adefovir at the 10 and 30 mg daily dose in patients with compensated liver disease who were treated for 48 weeks, and followed for

64 more weeks.

Reporting in the September 2004 issue of *Kidney International*, researchers found no overall change in creatinine or serum phosphorus levels in the 10 mg group. In the 30 mg group, there was a slight increase in creatinine levels and a decrease of phosphorus levels at week 48.

Longer, Preventive Antiviral Treatment May be Needed after Chemotherapy

Patients with resolved hepatitis B infections have experienced reactivated hepatitis B after receiving chemotherapy, which weakens the immune system. While doctors now treat these patients with lamivudine before chemotherapy begins to prevent HBV re-activation, it is not clear how long antiviral treatment should continue to prevent a recurrence of the infection.

Reporting in the August 2004 issue of the *Annals of Hematology*, researchers followed four lymphoma patients treated with rituximab-containing chemotherapy. Lamivudine ther-

apy was administered one week before chemotherapy until four weeks after chemotherapy ended.

ALT, total bilirubin, and HBV-DNA levels were monitored in three patients. The fourth patient was closely monitored for ALT.

All of the three patients studied had a relapse with HBV DNA rebounding six to eight months after completion of chemotherapy.

Two of the three patients had evidence of liver damage and one developed severe hepatitis. No lamivudine-resistant mutations were found among the three.

The fourth patient developed a hepatitis flare-up six months after completion of chemotherapy. The CD20(+) lymphocytes were totally depleted when HBV DNA started to increase.

Delayed HBV reactivation can occur in lymphoma patients receiving chemotherapy after withdrawal of pre-emptive lamivudine, the researchers concluded. A longer period of lamivudine treatment may be needed, they noted, and additional research should define the appropriate duration of post-chemotherapy antiviral therapy.

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