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Hepatitis B

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Pegylated Interferon May Work after Conventional Interferon or Lamivudine Fails

One-third of patients with hepatitis B "e" antigen (HBeAg-positive) hepatitis B who failed to respond to treatment with conventional interferon or the antiviral lamivudine (Epivir-HBV) may respond to pegylated interferon treatment, according to a recent report in the *American Journal of Gastroenterology*.

A team of Dutch researchers treated 76 patients who had previously failed to achieve lower HBV DNA (viral load) and HBeAg seroconversion (loss of the "e" antigen - HBeAg and appearance of "e" antibody) when treated with conventional interferon, lamivudine or a combination of the two with pegylated interferon. Pegylated interferon is thought to be more effective in combating the liver infection.

The patients received 52 weeks of pegylated interferon daily, combined with either lamivudine or a placebo. Thirteen nonresponders to conventional interferon (35%), five nonresponders to lamivudine (29%), and four nonresponders to both drugs (22%) ultimately responded to pegylated interferon treatment.

Most who responded to retreatment with pegylated interferon had high levels of alanine aminotransferase (ALT). Elevated ALT levels indicate the immune system is actively fighting the liver cells infected with the hepatitis B virus (HBV). Liver cells release ALT when they are damaged or die.

Lower Interferon Doses May Work in Young Patients with Genotype B

The high cost and significant side effects from interferon prevent it being used frequently to treat hepatitis B. Chinese researchers tried a lower dose of pegylated and conventional interferon in HBeAg-positive patients to see how effective it would be.

According to their report in the February 2007 issue of the *Journal of Clinical Infectious Diseases*, doctors treated 115 patients with 1.0 micro g/kg of pegylated interferon a week and 115 patients with 3 MIU of conventional interferon a week for 24 weeks and com-

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pared results.

A higher rate of HBeAg loss in the pegylated interferon group (23%) was the only statistically significant difference between the two groups, when evaluated 24 weeks after treatment ended.

Patients who were age 25 or younger and had HBV genotype B had higher rates of HBeAg loss.

Only 4 (1.7%) of the 230 patients discontinued therapy because of side effects.

"The choice of low-dose interferon might be a relevant clinical option to reduce the cost and adverse effects of therapy for younger patients with chronic HBV infection and genotype B infection in countries where it is prevalent," the researchers wrote.

Viral Resistance to Entecavir Rare in Patients Treated for First Time

A team of researchers, affiliated with the Bristol-Myers Squibb Pharmaceutical Research Institute, reported in the December 2006 issue of *Hepatology* that patients who had never been treated with an antiviral before (called treatment naïve) experience a very low rate of viral resistance to entecavir (Baraclude).

They monitored the HBV of 673 patients to see if and when their hepatitis B virus (HBV) would develop resistance that enabled HBV with certain mutations to continue to reproduce despite the presence of the antiviral. Antivirals work by meddling with the virus' genetic material to make it difficult for them to reproduce. However some HBV have mutations that enable the virus to "resist" the antiviral's effect.

Entecavir reduced HBV DNA levels to undetectable levels in 91% of HBeAg-positive and -negative patients by Week 96.

In contrast, 13% of lamivudine-resistant patients who were then treated with entecavir experienced a resurgence of HBV DNA within 12 months. Only 3% of treatment naïve patients treated with entecavir exhibited viral resistance and resurgence of HBV DNA by Week 96.

Researchers concluded that entecavir resistance in "treatment-naïve" patients during the first two years is rare.

Viral Mutations That Allow Lamivudine Resistance May Also Allow Entecavir Resistance

Researchers in Montreal have found that HBV with mutations that allow it to keep reproducing despite treatment with the antiviral lamivudine, can also keep replicating when the antiviral entecavir is used.

The researchers analyzed the evolution of HBV mutations from a patient who had first developed viral resistance to lamivudine, and who was then treated with entecavir.

Writing in the December 2006 issue of the *Journal of Hepatology*, the researchers reported that after the patient was switched to entecavir, the amount of HBV DNA in the patient's bloodstream (also called viral load) dropped, but the lamivudine-resistant strains continued to keep replicating despite the entecavir treatment.

"Three years later, the (patient's) viral load rose again, and a complex mixture of entecavir-resistant strains, all harboring the lamivudine-resistance signature rtL180M+M204V and the rtS202G mutation, were observed," the researchers reported.

As a result, HBV that have mutations allowing them to "resist" lamivudine may also be able to "resist" entecavir's antiviral medication.

Pegylated Interferon and Adefovir Are More Cost Effective than Lamivudine

British researchers studied the effectiveness and economics of treating hepatitis B patients with the antiviral adefovir (Hepsera) and pegylated interferon, compared to no treatment or continued lamivudine treatment, by reviewing seven randomized controlled trials.

Writing in the February 2007 issue of the *Journal of Viral Hepatitis*, the researchers reported that adefovir was significantly more effective than either a placebo (no treatment) or continued lamivudine treatment in reducing HBV DNA in patients.

Rates of HBeAg seroconversion were higher among patients receiving adefovir than either placebo or lamivudine.

Patients treated with pegylated interferon alone or in combination with lamivudine showed significantly reduced

HBV DNA levels compared to patients treated with just lamivudine.

Additionally, HBeAg seroconversion rates after treatment ended were "significantly higher for pegylated interferon patients than for those receiving lamivudine," they reported. The researchers confirmed that adefovir and pegylated interferon were much more cost effective than lamivudine treatment.

Adefovir Appears Effective in Patients with Lamivudine-Resistance and HBV Genotype C

Increasingly, researchers are focusing on which antiviral is most effective in patients with a certain strain or genotypes of HBV. In one research project reported in the February 2007 issue of *Liver International*, South Korean researchers treated 35 patients with HBV genotype C who had developed viral resistance to lamivudine with 10 mg daily of adefovir.

Their viral load, HBeAg status and ALT levels were checked every 4 to 12 weeks to evaluate adefovir's effectiveness.

Patients were treated on average for 48 weeks. Viral load became undetectable in 68.6%, 80%, 84%, and 88.2% at of patients respectively at weeks 12, 24, 36, and 48. The rate of HBeAg seroconversion was 8.3% and 14.3% at weeks 24 and 48, respectively. ALT levels came normal at week 48 in 70.6%.

Within 32 weeks of stopping adefovir, HBV DNA levels increased – sometimes dramatically – in 88.9% of patients. Researchers recommended adefovir in patients with lamivudine resistance and genotype C.

Lowering Viral Load Before Interferon Treatment Begins Improves Results

Interferon, which boosts the immune system to fight HBV infection, works best when ALT levels are elevated, which indicates the immune system is actively fighting the liver infection, and viral load is moderate.

A team of Indian researchers tried treating a group of HBV-infected patients with the antiviral lamivudine first, to lower their viral load, followed by treatment with pegylated interferon. They compared the outcomes with patients who were treated with just interferon.

Writing in the January 2007 issue of *The American Journal of Gastroenterology*, the team treated 27 HBeAg-positive patients with elevated ALT levels with a placebo for four weeks, followed by interferon. They treated a second group of 36 patients with four weeks of lamivudine, followed by interferon. The two groups were treated for 24 weeks, and then followed for an additional 24 weeks.

At week 28, undetectable HBV DNA was seen in eight (29.6%) of the interferon-only group, and in 16 (44.4%) of the lamivudine-followed-by-interferon group. HBeAg loss occurred in eight (29.6%) of the interferon-only group, and in 15 (41.7%) of the sequentially-treated group.

Six months after treatment ended, undetectable HBV DNA was seen in four (14.8%) of the interferon-only group and in 18 (50%) of the sequential group. HBeAg loss was maintained in four (14.8%) of the first group and in 14 (38.9%) of the second group.

"The strategy of using an antiviral initially to decrease HBV DNA levels before adding (interferon) leads to improved sustained virological response as compared with using (interferon) from the start," researchers wrote.

Combination of Tenofovir Plus Emtricitabine Succeeds in Adefovir-Resistant Patients

Doctors from Mount Sinai School of Medicine in New York tried switching seven patients, who no longer responded to adefovir and had probably developed adefovir-resistant HBV after a year of treatment, to an antiviral combination of tenofovir and emtricitabine.

In a study published in the December 2006 issue of the *European Journal of Gastroenterology and Hepatology*, doctors reported treating the seven patients with 300 mg daily of tenofovir, an antiviral developed originally to treat HIV infection, and emtricitabine, at a 200 mg daily dose. Neither antiviral has been approved yet by the U.S. Food and Drug Administration for hepatitis B treatment. After an average 23 months of treatment, all seven patients achieved undetectable

HBV DNA levels and one patient lost HBeAg and gained the "e" antibody.

The response of the seven patients indicates that tenofovir and emtricitabine may be effective treatment in adefovir-resistant patients.

Interferon and New Antivirals Are Improving HBV Treatment

A German researcher, writing in the January 2007 issue of the *World Journal of Gastroenterology*, summarized the current status of hepatitis B treatment in the effort to lower viral load and prevent cirrhosis and liver cancer.

To date, combination therapies employing both antivirals and interferon have not been highly successful, he noted. "Interferon plus lamivudine achieves a higher viral suppression than either treatment alone, even though HBeAg-seroconversion was not different after a one year treatment," he noted.

Increasingly, researchers are finding that HBV genotypes have an impact on treatment, with genotypes A and B responding better to interferon, achieving up to a 20% clearance rate of HBsAg in the case of genotype A.

Development of viral resistance to the antivirals adefovir and entecavir, "is somewhat slower" in patients who have never been treated before, compared to lamivudine-resistant patients.

Adefovir has a lower resistance rate of 3%, 9%, 18%, and 28% after 2, 3, 4, and 5 years of treatment, respectively, while entecavir has rarely produced resistance in treatment-naïve patients for up to three years, he noted.

HCV-HBV Co-infections: Treat the Dominant Infection and Aim for Viral Suppression

In a recent Ask the Experts about Liver Disease in *Medscape Gastroenterology*, Dr. David Bernstein, chief of the Digestive Disease Institute at North Shore University Hospital-Long Island Jewish Medical Center in New York, described how to treat patients coinfected with HBV and the hepatitis C virus (HCV).

HBV and HCV coinfections often lead to an increased risk of liver damage and cancer, he noted. However, different antivirals are used to treat each viral infection.

Often, one of the two viruses will predominate, so doctors must perform both an HBV DNA test and a hepatitis C virus (HCV) RNA. In most cases, HCV dominates over HBV.

The approach to therapy for coinfected patients is to treat the dominant viral infection, he noted. "If hepatitis C is predominant, then treatment should be initiated with a combination of pegylated interferon and ribavirin (the hepatitis C antiviral)," he wrote. Pegylated interferon may also suppress hepatitis B.

If hepatitis B is the predominant virus, then treatment should include pegylated interferon, and one of the antivirals that targets HBV.

"Care should be taken when initiating these regimens because interferons should not be used in patients with hepatitis B-related cirrhosis and lamivudine should not be used at all secondary to concerns regarding the development of antiviral mutations," he wrote.

The goals of therapy in hepatitis B patients infected without any viral resistance is HBeAg seroconversion, he noted, and the goal of therapy in patients with existing antiviral resistance should be prolonged viral suppression.

Dairy Products and Fruits Lessen Liver Cancer Risk

Certain foods, including milk and fruit, appear to reduce the risk of liver cancer, according to a report in the Dec. 15th issue of the *International Journal of Cancer*.

Vegetables did not appear to greatly decrease development of liver, but dairy products, white meat and fruit decreased the odds of cancer, according to Italian researchers.