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Hepatitis B

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Combination Treatment Effective in Small Group of Immune-Tolerant Children

Doctors have been unable to effectively treat children infected with hepatitis B virus (HBV) who remain in the immune-tolerant stage – during which children have normal alanine aminotransferase (ALT), are HBeAg-positive and have high viral load (HBV DNA). During this phase, the immune system appears not to notice or attack the infection.

To date, antivirals and interferon used independently of each other have not been able to lower viral load or slow viral replication in these young patients.

An article in the February 2006 issue of *The Journal of Pediatrics* reports that treatment with the antiviral lamivudine (Epivir-HBV) for eight weeks, followed by a combination treatment of lamivudine and conventional interferon for 10 months, may be effective.

British researchers treated 23 children with this drug regimen and 78% became HBV DNA negative at the end of treatment, five seroconverted and produced HBeAg antibodies (anti-Hbe), and four children (17%) cleared the infection and produced surface antibodies (anti-HBs). There was no change in these results 40 months after treatment ended.

"This pilot study suggests that lamivudine pretreatment followed by a combination of lamivudine and interferon can induce complete viral control in HBV immuno-tolerant children, hitherto considered poor responders," researchers wrote.

In the United States, only conventional interferon and lamivudine have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of hepatitis B in children.

Expert Suggests Lamivudine for Children in Immune-Tolerant Stage

Dr. William F. Balistreri, author of a *Medscape Gastroenterology* "Ask the Expert" column published in February, discussed how he would treat a child in the immune-tolerant stage of hepatitis B (with high viral load and normal ALT).

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Balistreri, director of the Liver Transplantation Program at Cincinnati Children's Hospital Medical Center, acknowledged that high viral load in young children may lead to cirrhosis and liver cancer later in life, so the pressure is on to develop a treatment to clear infection and lower viral load in these children before liver damage occurs.

"Most pediatric hepatologists would suggest that interferon-alfa treatment should be offered only to children with (elevated) ALT levels and low HBV DNA levels," he wrote.

Interferon-induced HBeAg clearance rates of 20% to 40% have been noted in children with elevated ALT levels and low viral load, however interferon is less effective in patients with normal ALT levels and high HBV DNA levels.

Lamivudine-induced HBeAg clearance rates are similar to those achieved with interferon, viral levels decrease during treatment, but often rebound when treatment stops. "The advantage here is that oral forms (of lamivudine), both tablet and liquid, are available," for children, he noted.

"A future strategy may be to combine the immune-stimulating effect of interferon-alpha (perhaps the weekly administered pegylated form) with the antiviral action of lamivudine in 'immunotolerant' children," he added. "Bottom line: … I would attempt to treat with lamivudine after two years of age, with careful monitoring for response and side effects."

Clearing HBsAg Assures Most Patients of Long-Term Liver Health

A study of 231 Japanese patients who cleared HBsAg found that six years after the virus was eradicated, nearly all of those "cured" enjoyed healthy livers with little lingering effects of liver disease.

Writing in the January 2006 issue of *The American Journal of Medicine*, Japanese researchers reported the patients were on average age 51 when they cleared the infection. They monitored their ALT levels, viral load and liver health for 6.5 years.

One year after HBsAg seroclearance, 203 patients (87.9%) had normal ALT levels, HBV DNA was detectable in only four patients (1.7%). Thirteen patients had liver biopsies that appeared normal, but only two of the 13 patients showed no signs of past liver fibrosis. There was no cirrhosis or liver cancer identified in the 164 patients who had no signs of cirrhosis when they cleared HBsAg.

Liver cancer developed in two of the 67 patients who had cirrhosis when they cleared HBsAg. During the study period, 15 patients died but none of the deaths resulted from liver disease.

"Our results suggest that HBsAg seroclearance confers favorable long-term outcomes in patients without (liver cancer) or decompensated liver cirrhosis at the time of HBsAg seroclearance," the researchers concluded.

Experimental HBV Vaccine Confers Protection in 100% After Second Dose

Available hepatitis B vaccines currently require three doses and about four to five months to confer protection from infection. The vaccines also fail to protect about 10% of those immunized, including older and obese individuals, dialysis patients, and immune-compromised people who fail to develop the necessary antibodies.

Researchers from Dalhousie University in Halifax, Canada, developed an experimental hepatitis B vaccine that uses the HBsAg antigen, plus a new immune-boosting ingredient to speed up protection.

According to a report in the Jan. 9, 2006, issue of *Vaccine*, researchers administered it to 99 people, average age 22, and 79% of those receiving the experimental vaccine developed protective antibody response within four weeks of the first dose.

One week after the second dose, 100% receiving the experimental vaccine (HBV-ISS) achieved protection, compared to 18% receiving a conventional HBV vaccine.

FDA Approves New Treatment for Those Exposed to HBV in Blood and Body Fluids

The FDA has approved Cangene's HepaGam B for treatment after exposure to HBV. HepaGam B is a hepatitis B immune globulin, which are purified antibodies that target the HBV.

HepaGam B has been approved for treatment when someone is exposed to HBV-infected body fluids, such as healthcare workers, sexual or household contacts of people infected with HBV, or infants born to HBV-infected mothers.

Antivirals Help Avoid HBV Relapse During Chemotherapy for Liver Cancer

Patients who develop liver cancer as a result of their hepatitis B infection face a 55% chance of having the virus reactivated and suffering additional liver damage during chemotherapy to treat the cancer.

A study of patients who received an antiviral drug when they underwent chemotherapy found the treatment helped prevent relapse of hepatitis B, according to a report in the February 2006 issue of *Hepatology*.

Korean researchers pretreated 36 liver cancer patients undergoing chemotherapy with lamivudine between January 2004 and February 2005. They compared the results to a control group of 37 patients who underwent the chemotherapy without receiving lamivudine.

The chemotherapy was continued every month without any limit on the number of cycles until the tumors disappeared, while treatment with lamivudine began with the chemotherapy and continued for 12 months following its completion.

Researchers reported that 43% of the control group developed hepatitis during the follow-up period, several cases were severe, compared to 17 percent of the patients who took lamivudine.

In addition to reducing HBV reactivation, the lamivudine allowed chemotherapy to continue in these cancer patients, thus increasing survival. “The beneficial effects of preemptive therapy on the severity of hepatitis most probably result from an elimination of any potential risk arising from viral reactivation,” researchers wrote.

HBeAg-Positive, Genotype A Patients Benefit Most from Pegylated Interferon

One year of pegylated interferon treatment in HBeAg-positive patients led to HBsAG loss in 7% of patients with HBV genotype A, according to a report in the February 2006 issue of *The American Journal of Gastroenterology*.

Researchers followed 266 HBeAg-positive patients treated for 52 weeks with pegylated interferon in combination with either lamivudine (100 mg/day) or a placebo, and for another 26 weeks after treatment ended.

At the end of follow-up, 95 (36%) of the patients exhibited HBeAg loss, 18 (7%) HBsAg loss, and 16 (6%) HBsAg seroconversion (production of surface antibodies or anti-HBs). The addition of lamivudine did not enhance HBeAg loss, HBsAg loss, or development of anti-HBs.

All 18 patients who showed HBsAg loss had normal ALT, and 11 (61%) had undetectable HBV DNA at the end of follow-up. Loss of HBsAg differed according to HBV genotype: 14% for genotype A, 9% for genotype B, 3% for genotype C, and 2% for genotype D.

“Our study indicates that treatment with (pegylated interferon) is the best therapy to achieve HBsAg clearance in patients with genotype A,” researchers concluded.

Pegylated Interferon Has Limited Success in Patients with Lamivudine Resistance

Dutch researchers treated 16 HBeAg-positive HBV patients with lamivudine resistance with pegylated interferon for one year, and followed them for 26 weeks, to assess the success of interferon treatment in this group.

In the January 2006 issue of the *Journal of Hepatology*, research-

ers reported that only two (12.5%) of the patients seroconverted and developed HBeAg antibodies, low viral load and normal ALT levels. Significantly, these two patients had the lowest volume of lamivudine-resistant HBV in the group.

Viral load and ALT levels rebounded after treatment ended in all 12 patients.

"Pegylated interferon-alpha therapy showed marginal efficacy in the presence of lamivudine resistance, but such therapy may be beneficial in patients with only small amounts of mutant virus," researchers concluded. "In our opinion, an analysis of the patient subgroup harboring a YMDD-mutation (lamivudine resistance) should be included in all future studies of pegylated interferon-alpha in chronic hepatitis B."

Experimental Antiviral ANA380 Effective against Lamivudine-Resistant HBV

A phase II, dose-determining clinical trial of Anadys Pharmaceuticals' antiviral ANA380 (LB80380) shows great promise in people with lamivudine-resistant HBV, according to a report scheduled to be presented at the European Association for the Study of the Liver in April 2006.

In the trial, 59 patients with lamivudine resistance received either 30 mg, 60 mg, 90 mg, 150 mg, or 240 mg of ANA380 daily by oral administration for the 12 weeks.

Patients receiving either 90 mg, 150 mg or 240 mg of ANA380 achieved dramatic viral load reductions ranging from 3.8-fold to four-fold. ALT levels also dropped substantially.

ANA380 was safe and well tolerated with no serious side effects.

"We can conclude from the clinical data that doses of 90 mg, 150 mg and 240 mg give similarly profound viral load reductions, enabling future clinical investigations of attractive dose levels," researchers reported.

Testing HBV DNA 12 Weeks After Interferon Begins Indicates Who Won't Respond

Dutch researchers may have found a way to identify which people will and won't respond to interferon treatment after just 12 weeks of treatment. Interferon is costly and fraught with side effects so an early predictor of success is useful.

In a study published in the February 2006 issue of the *Journal of Viral Hepatology*, the researchers reported comparing the amount of HBV DNA in the bloodstream of patients 8 to 12 weeks after treatment begins.

Monitoring HBV DNA changes at week 12 was most effective in identifying who will and won't respond to interferon. This study showed that quantitative HBV DNA testing before treatment begins, and again at week 12, identifies patients who have virtually no chance of reaching a sustained response from interferon. Patients who have not achieved a drop in viral load at week 12 will not respond to interferon.

HBV-HIV Coinfected Fare Worse when Hepatitis D Virus Is Present

The hepatitis D virus infects the liver and requires the surface antigen (HBsAg) from the hepatitis B virus to replicate. As a result, only chronically-infected hepatitis B people can be infected with the hepatitis D virus (HDV). To date, there has been little research on the impact of antiviral treatment on 26 people who were coinfected with HIV, HBV and HDV.

Taiwanese researchers, reporting at the 13th Conference on Retroviruses and Opportunistic Infections held in February 2006, compared the HDV-HIV-HBV coinfected patients with 78 HBV-HIV coinfected patients matched by age, sex, and degree of liver disease over a 55-month period.

HDV-coinfected patients tended to become infected through injecting drug use, and had lower HBV DNA levels. The severity of HIV infection was comparable for HDV-infected and non-HDV patients as measured by viral suppression, CD4 counts and development of AIDS-related illnesses.

Over time, HDV-infected patients were more likely to clear HBsAg and less likely

to develop viral resistance to antivirals. However, they had more hepatitis flares (periods of elevated ALT, which indicates liver damage) and were more likely to develop cirrhosis and severe liver damage. HDV infection was also associated with higher death rates.

"These data suggest that HDV infection further worsens the outcome of HBV-HIV coinfected patients, even with the use of HAART (antivirals)," researchers wrote.

HBV Genotype G Linked to More Liver Damage in HBV-HIV Coinfected Men

To learn more about the role of HBV genotypes or strains in those coinfected with both HIV and HBV, investigators from seven French HIV clinics examined the risk factors for liver damage in 104 HIV- and HBV-infected patients.

Investigators, reporting in the Feb. 14, 2006 edition of *AIDS*, compared the patients' risk factors for liver damage to the degree of fibrosis detected in liver biopsies. Risk factors included hepatitis B genotype, duration of HIV and hepatitis B coinfection, and treatments for both viruses, as well as infection with hepatitis C or D, alcohol intake and body mass index.

Seventy (67%) of the patients had extensive fibrosis. Researchers reported that the coinfected patients experienced a 12.6 times greater risk of liver damage when they were infected with HBV genotype G, compared to the more common genotype A.

They recommend that HBV genotyping should be performed on all coinfected patients who were at risk of liver damage.

While genotype G is rare, it was found in 13% of the patients in the study and reportedly occurs in Western countries and in men who have sex with men.

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