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Hepatitis B

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Tenofovir and Emtricitabine Antiviral Combination Succeeds When Adefovir Fails

While adefovir (Hepsera) generally does not cause rapid viral resistance, some patients infected with the hepatitis B virus (HBV) fail to respond to this antiviral treatment which interferes with the virus's genetic material so it can't reproduce.

Researchers at Mount Sinai School of Medicine treated seven HBV-infected patients, who had not responded to adefovir after 10 months of treatment, with a new combination of antivirals – 300 mg of tenofovir and 200 mg of emtricitabine daily. They wanted to see if these antivirals, which have

not yet been approved by the U.S. Food and Drug Administration (FDA) for treatment of hepatitis B, would be effective in lowering viral load and reducing liver damage when adefovir fails.

Each antiviral is unique and “attacks” or disrupts different areas in the virus' genetic material. Researchers wondered if this new combination would be more effective in stopping replication of HBV that were able to “resist” adefovir's antiviral effects.

Writing in the December 2006 issue of the *European Journal of Gastroenterology and Hepatology*, the researchers reported that all patients achieved undetectable HBV DNA (viral load) after a 14- to 28-month treatment period. On average, the patients'

viral load dropped 1,000-fold on the combination of antivirals. One patient lost the hepatitis B “e” antigen (HBeAg) and developed the “e” antibody (HBe-Ab).

“Tenofovir, in combination with emtricitabine, may be an alternative treatment for those with detectable HBV DNA on adefovir,” researchers noted.

YMDD Mutations, Usually Associated with Lamivudine Resistance, Are Actually Found in 18% of Healthy HBV Carriers

Because HBV has such a weak genetic blueprint, mutations in the virus's genetic make-up commonly occurs, which is why

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HBV quickly develop “resistance” to antivirals like lamivudine (Epivir-HBV). Researchers have assumed that HBV with YMDD mutations that allowed the HBV to continue to replicate despite the presence of lamivudine emerged only after treatment. Lamivudine attacks the normal or non-mutated virus, allowing HBV with the YMDD mutation to replicate and become the “majority” virus.

Researchers investigated how common HBV with YMDD mutations were in 71 healthy, HBV-infected people who had never been treated with lamivudine and who had normal alanine aminotransferase (ALT) levels for more than a year. ALT is released by liver cells when they are damaged or die so normal levels indicate a healthy liver.

Writing in the December 2006 issue of the *Journal of Gastroenterology and Hepatology*, the researchers reported that naturally-occurring YMDD mutations were detected in 13 (18.3%) of the 71 people, a surprisingly high rate. All patients in the study had tested positive for the “e” antibody (anti-HBe).

Experts Push for Decrease in “Normal” ALT Level Down to 30 IU/L

Experts are pushing for a lowering of what is considered healthy and normal for ALT levels in the bloodstream. ALT, measured in a blood test, is an enzyme released by liver cells that are damaged or dying. To date, normal has ranged from 30 to about 60 international units per liter (IU/L).

American Association for the Study of Liver Disease (AASLD) officials, who write the treatment and monitoring guidelines for doctors who treat viral hepatitis, want to “recalibrate” the normal range, based on a number of studies that show that the current upper range of ALT levels can signal liver damage even when patients feel healthy and function normally. Researchers found that patients with ALT levels that are just twice the upper limit of what is now considered normal had a high death rate of 1.63.

AASLD Chairman of Public Policy Adrian DiBisceglie, MD, chief of hepatology at St.

Louis University School of Medicine in Missouri, said, “We are setting [upper] limits lower than they have been to include people with abnormal ALT levels who feel well but who still have an increased risk of liver disease,” he said.

AASLD officials want to establish 30 IU/L as the healthy, highest level for ALT.

Early Study of Immune Stimulant Thymosin Alpha-1 Shows Promise

A group of Chinese researchers treated 62 HBV-infected patients with HBeAg and high viral load with either interferon alpha or a promising new immune stimulant called thymosin alpha-1 (Adaxin). Both drugs are synthetic versions of substances found in the body that stimulate the immune system to fight infections.

To date, interferon alpha has shown lackluster results in spurring the immune system to fight and eradicate HBV infection.

Writing in the November 2006 issue of the *Journal of Gastroenterology*, researchers

describe treating 29 patients with thymosin alpha-1 and 33 patients with interferon alpha for six months, and following them for an additional 12 months.

At the end of treatment, nine (31%) of the 29 thymosin-treated patients achieved normal ALT levels, undetectable HBV DNA and HBeAg serconversion, compared to 15 (45.5%) of the 33 interferon alpha-treated group.

However, six months after treatment ended, normal ALT, undetectable viral load and HBeAg seroconversion was observed in 14 of 29 (48.3%) patients in the thymosin alpha-1 group and in only 9 of 33 (27.3%) patients in the interferon alpha group. Additionally, the thymosin alpha-1 group experienced fewer treatment side effects than the interferon alpha group.

Despite the clear and sustained success of thymosin alpha-1, researchers noted that a “response rate of 48.3% is still less (than) ideal,” and “a more effective therapeutic approach warrants further study.”

People with HBV Genotype B Respond Better to Thymosin Alpha-1

Another study of patients treated with thymosin alpha-1 found that patients with the HBV strain or genotype B responded better to the immune stimulant than those with genotype C, according to a report in the December 2006 issue of the *Journal of Viral Hepatitis*.

Researchers treated:

- 32 HBV-infected patients for 26 weeks with two injections of 1.6 mg of thymosin alpha-1 twice a week, and
- 34 patients with the same treatment regimen but for 52 weeks.

A group of 32 HBV-infected patients served as the control group.

The researchers monitored the patients to see if HBV genotype or precore or core promoter mutations in the virus affected the outcome. A complete response to treatment (including undetectable viral load, ALT normalization) was higher in patients with genotype B compared to patients with genotype

C (52% vs 24%), and in patients with precore mutation compared to core promoter mutation.

After Surgery, Patients with HBV-Related Liver Cancer Live Longer than Those with Hepatitis C

A report in the November 2006 issue of *Annals of Surgery* journal examined the difference in survival rates among 417 patients with either hepatitis B or hepatitis C who underwent surgery for liver cancer.

The Japanese researchers examined survival as well as recurrence of cancer to see how the two infections differed in their impact.

From 1990 to 1999, the researchers followed 66 HBV-infected patients, and 351 hepatitis C-infected liver cancer patients who underwent surgery to remove liver tumors for a decade.

The 3-, 5-, and 10-year disease-free survival rates of the HCV-infected group (40%, 24%, and 12%, respectively) were significantly shorter than

those of the HBV-infected group, which were 57%, 54%, and 28%, respectively.

Five Years of Adefovir Produces Improvement, But 11% Have HBV Resurgence

Greek researchers investigated what impact five years of treatment with adefovir would have, in terms of stopping liver damage, lowering viral load and possibly causing viral resistance, on 125 HBeAg-negative patients.

According to their report in a recent issue of *Gastroenterology*, after 240 weeks of treatment:

- HBV DNA levels were less than 1,000 copies per milliliter in 67% of patients
- ALT levels normalized in 69% patients
- More than 83% had improved liver health
- About 73% experienced a decrease in liver fibrosis.
- And 20% experienced viral resistance to adefovir and 11% had increases in ALT levels.

Slight elevations in

creatinine, signaling kidney damage from the drug, were confirmed in 4 (3%)

Pegylated Interferon Succeeds in One-Third of Patients Who Don't Respond to Lamivudine or Conventional Interferon

A group of international researchers examined how successful pegylated interferon treatment was in 76 patients who had failed to respond to conventional interferon alpha or lamivudine. To date, only 10 to 40% of those treated with antivirals achieve HBeAg seroconversion (loss of "e" antigen and developing the "e" antibody). Response to conventional interferon is similarly lackluster.

The experts treated 37 patients who had been treated with interferon, 17 who had been treated with lamivudine, and 22 who had been treated with both drugs, with 52 weeks of pegylated combined with either a placebo or 100 mg of lamivudine. They were then followed for 26 weeks.

Writing in the No-

vember 2006 issue of *The American Journal of Gastroenterology*, the researchers reported that 13 (35%) nonresponders to conventional interferon, five (29%) nonresponders to lamivudine, and four (22%) nonresponders to both interferon and lamivudine responded to pegylated interferon. There was no difference between those treated with pegylated interferon alone or in combination with lamivudine.

Those with elevated ALT responded best to pegylated interferon.

Researchers Find Link Between Hepatitis B and Muscle Weakness in Small Study

Italian researchers, reporting in a recent issue of *Neurology*, found signs of myopathy (progressive muscle weakness) in two patients with chronic hepatitis B. They performed muscle biopsies, which revealed muscle cell deterioration. They also found HBV DNA and viral antigens inside the intact muscle fibers.

In one patient, muscle weakness improved

during antiviral therapy. Researchers concluded that HBV DNA and antigens can be found in muscle fibers and that when the immune system attacked the virus and viral particles in the muscle tissue, it caused muscle injury.

The Hepatitis B Virus Lives for about Four Hours in the Body

How long does HBV live in the body? Historically experts have estimated its lifespan at about one day, but a report published in the November 2006 issue of *Hepatology*, places the half-life of HBV at a brief four hours.

For the first time, Australian researchers studied the quantity of intact viruses produced by the HBV DNA in infected liver cells, instead of looking at the HBV DNA in the blood. They studied three chimpanzees that were acutely infected with HBV and found there is approximately 10-fold more total HBV DNA in infected liver cells than in the blood, and therefore the lifespan of HBV is much shorter than previously thought. The

new four-hour half-life for HBV is the same as is currently estimated for the HIV and hepatitis C virus.

“This faster turnover of HBV in blood indicates a correspondingly higher replication rate and (higher) risk of mutation against hepatitis B antiviral therapy,” researchers concluded.

A New Way to Evaluate How Fast HBV Are Replicating

Researchers are looking for new, noninvasive ways to determine if HBV are rapidly replicating, and a group of researchers, writing in the *BMC Journal of Infectious Diseases*, claim that measuring neopterin levels in the blood may indicate if HBV are rapidly replicating.

Neopterin is a natural substance found in body fluids that increases when the immune system actively fights infection. Researchers studied neopterin levels in 30 HBV patients who had signs of liver damage and high viral load, 25 inactive and healthy HBV carriers, and 30 healthy individuals.

In the inactive HBV-

infected group, all except one were HBeAg negative and “e” antibody positive. In the actively-replicating HBV group, 23 of 30 patients had HBeAg.

Neopterin concentrations were 14.5 nmol/L in replicative HBV carriers, 8.9 nmol/L in nonreplicative HBV carriers and 7.1 nmol/L in the control group. “In the hepatitis B infected carriers, elevated neopterin levels may be an indicator of the presence of (viral) replication,” researchers noted.

