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Hepatitis B

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Which Drug Combination and Sequence Works Best Against Hepatitis B?

With the availability of several new antiviral medications and pegylated interferon, doctors are trying to define what drug or drug combinations will work best to lower the amount of virus in the body (HBV DNA), strengthen the immune system, and prevent liver damage.

Because over time patients can develop viral resistance to antivirals, which work by preventing viral reproduction, doctors must select the best drugs and the right drug se-

quence to avoid viral resistance.

According to an article in the 2005 issue of the *Journal of Antimicrobial Chemotherapy*, hepatitis B virus (HBV) that can resist lamivudine's (Epivir-HBV) antiviral effects can also resist the effects of the antiviral emtricitabine.

The good news is that the antiviral adefovir (Hepsera) is effective against these resistant HBV, as is the promising antiviral telbivudine.

However, entecavir (Baraclude) is not as effective, for example, against lamivudine-resistant HBV.

Clevudine, another antiviral under development, is not effective against the lamivudine-resistant strains, but it appears to be effective against

adefovir-resistant HBV, according to early studies.

Elvucitabine, another new antiviral, is not effective at clearing lamivudine-resistant HBV, but it is effective against adefovir-resistant strains.

Tenofovir is effective against lamivudine-resistant strains, but is only slightly effective against adefovir-resistant HBV. There are also tenofovir-resistant HBV that doctors are now studying.

"Given the cross-resistance profile of these drugs, the rationale is to combine the drugs that would inhibit the emergence of drug-resistant strains to one or the other drug. This may lead to an improved management of antiviral therapy of chronic HBV

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infection in the long term,” the author suggested.

To avoid the complexities of viral resistance, pegylated interferon therapy may be the best first-step because it requires only short-term treatment and carries the hope of a complete cure. But many patients will probably require long-term treatment with antivirals to control viral replication and liver disease. For them, clevudine and emtricitabine may be the best antiviral, according to the article. “Clevudine, with its unusual antiviral activity profile, may be the first (antiviral) to be used as a relative short-term treatment and to achieve sustained control of viral replication even after treatment withdrawal,” the researcher wrote. “On the other hand, emtricitabine, as well as other drugs in development, offers a new option for combination of nucleoside analogues that do not share the same cross-resistance profile. For instance, it may be used in combination with adefovir or tenofovir.”

Jury Still Out on Effectiveness of Lamivudine and Adefovir Combination

One study of eight hepatitis B patients who developed viral resistance to lamivudine, found that a second round of treatment using a combination of lamivudine and adefovir conferred no added benefits compared to treatment with just adefovir.

But a team of German researchers, who used a mathematical analysis to study the impact of the antiviral combination on viral load (HBV-DNA), found that the combination of adefovir and lamivudine should produce a lower viral load, even though that did not occur in this small group of patients.

The researchers, reporting in the June 2005 issue of the *Journal of Hepatology*, conclude that the combination should be used on more patients to see if is effective in clearing the virus as the model suggests.

Doctor: Start Liver Cancer Screening Earlier for African-Americans

Dr. Morris Sherman, author of a recent Medscape Seminar in Liver Disease, explored when screening for hepatocellular carcinoma (HCC or liver cancer) should begin in people with hepatitis B.

The highest rate of liver cancer occurs in chronically-infected men, at a rate of 0.5% per year. The rate starts to climb at about age 40 (when it is 0.2%) and reaches 1% at age 70. The incidence among patients with cirrhosis is higher yet, reaching 2.5% per year. The doctor recommends screening men of Asian ethnicity starting at age 40, and Asian women, who generally have a lower rate of liver cancer, at age 50. Screening should

start younger if the patient has an immediate family member with liver cancer.

“Chronic carriers who are anti-HBe-positive (have the “e” antibody) with long-term inactive disease and who do not have cirrhosis seem to have little risk for developing HCC,” he wrote. “Whether screening is worthwhile in this population is not clear. However, because 20 to 30% of such patients have reactivation of hepatitis B disease, some form of long-term monitoring is required. Africans with hepatitis B seem to contract HCC at a younger age. Whether this is true in North American blacks or blacks from the Caribbean is uncertain. Although it is not possible to define accurately an appropriate age to start surveillance in these populations, clearly surveillance should start at a younger age than for Asians.”

Lamivudine-Resistant HBV Have Mutations that Can Hide Presence of HBsAg

A group of South Korean researchers have found that HBV with the YMDD mutations that allow them to replicate even when the antiviral lamivudine is used have another mutation that changes the molecular make-up of the surface antigen (HBsAg) that allows it to escape detection.

While disappearance of HBsAg usually indicates complete clearance of the virus (and recovery from the infection), scientists reported in the June 2005 issue of *The Journal of Korean Medical Science*, that some patients with lamivudine-resistant HBV lost HBsAg, but still had HBV DNA in their bloodstream.

They found that YMDD mutations in the HBV of a patient with lamivudine resistance changed the surface antigen molecular make-up, so it could not be identified by normal HBsAg lab

tests. "Our result suggests that false HBsAg negativity can be induced by combination of overlapping gene mutations during the lamivudine therapy," they wrote.

Soy Helps Prevent or Temper Liver Disease in Patients with Hepatitis B

Hepatitis B patients who eat foods made with soybeans may reduce their risk of liver cancer, according to a report in the June 10th issue of the *International Journal of Cancer*.

Dr. Gerald B. Sharp, of the National Institute of Allergy and Infectious Diseases, monitored Japanese A-bomb survivors to see if consumption of soy foods reduced liver cancer.

The researchers compared the consumption of isoflavone-rich miso soup and tofu before diagnosis of cancer in 176 confirmed cases of liver cancer between 1964 and 1988, and 560 control subjects who died of diseases

other than liver cancer. Dietary information collected at least two years prior to diagnoses or death was examined.

Subjects who ate miso soup or tofu more than five times per week had a 50% lower risk of cancer compared with those who ate soy-containing foods no more than once per week.

The lower HCC risk with higher soy consumption, "may reflect a counteracting effect of isoflavones on estrogen and testosterone levels that reduces HCC risk," the investigators suggest.

Dynavax Starts Phase III Trial of Hepatitis B Vaccine for Older Adults

To date, older adults have had lower response rates to the hepatitis B vaccine than children and young adults. Dynavax Technologies Inc. has begun a Phase III clinical trial of a hepatitis B vaccine that may be highly effective for older adults.

The trial will enroll more than 400 adults, aged 40 to 70, in Asia with no indications of past or current hepatitis B infection. One group will get three doses of Dynavax's HBV vaccine at a dose of 20 micrograms of HBsAg co-administered with 3 mg of its proprietary immunostimulatory sequence (ISS) technology injected at zero, two, and six months. The second group will be given three doses of a competitor's vaccine.

The ISS technology uses synthetic DNA molecules designed to stimulate an immune response, and is being developed not only as part of the HBV vaccine but also in ragweed allergy and asthma studies.

Dynavax is targeting people who need an enhanced vaccine, such as hemodialysis patients, health care and emergency response personnel, people infected with HIV or hepatitis C, and those receiving multiple transfusions.

Dynavax reported significant superiority in antibody response and robustness in Phase II trials, when compared to existing hepatitis B vaccines.

Genotype Appears to Play No Role in Success or HBV Resistance to Lamivudine

Researchers followed 71 patients who received lamivudine for up to five years to see what impact genotype played in the development of HBV resistance to lamivudine. According to their report in the July 2005 issue of the *Journal of Viral Hepatitis*, genotype played no role in the treatment's success, nor did genotype affect the development of viral resistance.

However, the severity of liver disease and development of cirrhosis appeared to be impacted by genotype.

In the same journal, another published study reported on a group of 15 patients who were received a second round of lamivudine treatment. While initially patients responded to the second course of antiviral treatment within a short time, ultimately the results, including HBeAg seroconversion (disappearance of

HBeAg and development of the "e" antibody), were not durable, and ultimately HBeAg returned.

Genotype May Determine Success of Interferon Alpha Treatment

Reporting in the July 2005 issue of *Gut*, researchers followed 165 hepatitis B patients treated with conventional interferon, 144 of whom had either genotype A or D.

Sustained response six months after treatment was higher in patients with genotype A, compared with HBV genotype D (49% vs. 26%). Sustained response to interferon was 46% versus 24% in HBeAg-positive patients, and 59% versus 29% in HBeAg-negative patients with HBV genotype A compared with HBV genotype D.

HBeAg status had no negative impact on IFN response.

Researchers reported genotype A and high alanine aminotrans-

ferase (ALT) levels (twice normal) were good predictors of treatment success.

Ultimately, HBV genotype may impact which patients are treated with this interferon, researchers suggest.

Genotype C Carries Higher Risk of Hepatitis B Reactivation and Cirrhosis

Taiwanese researchers followed 202 HBeAg-positive patients (150 genotype B, 52 genotype C) with initially normal ALT levels for an average of 10 years to see what impact genotype played in progression of liver disease.

They reported in the *Journal of Hepatology*:

- Genotype B patients had significantly earlier and higher rate of HBeAg seroconversion.
- Reactivation of hepatitis B was significantly more common in genotype C patients.
- Five genotype B

and 10 genotype C patients progressed to cirrhosis.

- Genotype C and reactivation of hepatitis B (increased HBV DNA and ALT levels) were common factors in development of cirrhosis.

Genotype Plays Significant Role in Liver Transplantation Survival

Researchers compared the success of 43 liver transplant patients with HBV genotype B and 74 patients with genotype C.

The genotype B patients in their study, reported in the August 2005 issue of the *American Journal of Transplantation*, initially had more severe liver disease. The three-year survival rate was 83% for genotype B and 89% for genotype C, and the rate of HBsAg clearance was the same.

But the rate of HBV DNA rebound due to lamivudine-resistant HBV at three years was 4% for genotype B and

21% for genotype C. Liver biopsies showed recurrent hepatitis B in seven of 10 genotype C patients, and no re-infection in two genotype B patients. In conclusion, genotype C may carry a greater risk and severity of re-infection due to lamivudine-resistant mutants.

HBeAg Can Cross Placenta and Reach Babies, But Vaccine Still Confers Protection

Researchers are just beginning to identify when babies born to HBsAg-infected mothers become infected – is it before birth? Do HBV cross the placenta and infect the baby? Or, does infection occur during the birthing process?

Also of interest is the significance of hepatitis B antigens and antibodies that are present in babies after birth.

A Shanghai researcher followed 42 infants born to infected mothers (16 born to HBeAg-

positive mothers and 26 to HBeAg-negative mothers) who were immunized at birth and also given hepatitis B surface antibodies (HBIG).

Four babies born to HBeAg-positive carrier mothers became chronically infected, all other babies developed surface antibodies before 12 months of age. Among the other 12 babies born to HBeAg-positive carrier mothers, HBeAg was detected in seven infants at birth, in four at one month, and in none thereafter. No HBeAg antibodies were ever detected in the infants.

The researcher concluded that HBeAg can cross the placenta from mother to fetus and become undetectable before four months of age, but no antibody response to the transplacental HBeAg could be detected until month 24 in the babies given HBIG.

The presence of “e” antibodies before one year of age, or HBcAg (core) antibodies before two years of age in babies born to HBsAg carrier mothers may simply represent the mother’s antibodies and may not indicate an active hepatitis B infection.

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