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Hepatitis B

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Experts Share Their Insights Into Hepatitis B Treatment

Three hepatitis B experts shared their insights into the latest research on the treatment of hepatitis B virus (HBV) infection through the Clinical Care Options Expert Analysis Web site. The experts included Patrick Marcellin, MD, Kris V. Kowdley, MD, FACP, FACG, FASGE, AGAF, and Norah Terrault, MD, MPH. Their observations follow:

• 5% of HBeAg-Positive Patients Treated with Tenofovir Clear the Infection

The experts reviewed studies that compared the effectiveness of the antiviral adefovir (Hepsera) to tenofovir (Viread), which has been approved

in Europe and is expected to be approved soon by the U.S. Food and Drug Administration.

Patients who test negative for the hepatitis “e” antigen (HBeAg), appear to respond equally well to adefovir and tenofovir. Among HBeAg-positive patients, both treatment groups “seroconvert” (lose HBeAg and develop the “e” antibody) equally, but what surprised the experts was that 5% of HBeAg-positive patients who took tenofovir for 64 weeks lost the hepatitis B surface antigen (HBsAg), which is significant and is rarely achieved with either antivirals or the immune-boosting drug interferon.

None of the HBeAg-positive patients who were first treated with adefovir and then switched to tenofovir lost HBsAg.

Dr. Marcellin expressed surprised that the HBsAg loss was observed only in HBeAg-positive patients, who tend to be harder to treat because of their high viral loads, than HBeAg-negative patients. If these HBsAg clearance rates are confirmed in subsequent studies, it could indicate there is an advantage in using tenofovir instead of other antivirals, he noted.

“Moreover, if it transpires that tenofovir induces HBsAg loss and seroconversion through a different mechanism of action from interferon-based therapy, that may provide a rationale for studying the combination of both drugs, with the goal of inducing HBsAg loss in as many patients as possible, rather than keeping patients on therapy all their lives,” he explained.

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• ***Pegylated Interferon Is Best First Line of Treatment for Hepatitis B***

The experts reviewed response rates four years after treatment ended in 230 HBeAg-negative patients treated with pegylated interferon alone or with the antiviral lamivudine (Epivir-HBV), and 85 patients who received just lamivudine.

The study showed that significantly more patients had undetectable HBV DNA levels (less than 400 copies/mL) four years after treatment ended in the two interferon-treated groups than those treated with just lamivudine (17% vs. 7%). Also interesting, the rate of HBsAg clearance increased after treatment ended, reaching 11% in interferon-treated patients after four years, compared with 2% of lamivudine-only patients, the experts noted.

These findings indicate that in 17% of patients who respond well to pegylated interferon and achieve undetectable HBV DNA have a better chance of clearing HBsAg. The other 75% of patients do not respond well to treatment or relapse and, in those cases, should receive alternative treatment such as antivirals.

“This message supports

the continued inclusion of (pegylated interferon) treatment as a first-line option for some patients,” noted Dr. Marcellin.

“HBeAg-positive patients without cirrhosis who have genotype A, especially if associated with relatively low (viral load) and active inflammation (indicated by a) liver biopsy, may represent ideal candidates for consideration of pegylated interferon as first-line therapy,” added Dr. Kowdley. “I have also found pegylated interferon (to be) an attractive option in women of childbearing age who wish to pursue a finite course of therapy and are concerned about possible...” risk of birth defects possibly caused by antiviral treatment.”

• ***How to Predict When Pegylated Interferon Will Work***

When pegylated interferon works in patients, it can clear HBsAg in nearly half of all patients who respond, but the challenge is identifying which patients will respond as soon as possible because the drug is costly and causes side effects such as depression. Recent studies show there are two ways to predict if pegylated interferon will

work long-term in a patient: If the quantity of HBsAg is less than 10 IU/mL at end of treatment or if HBsAg levels drop by two-fold.

The three experts suggested measuring HBsAg at start of treatment and then at week 24. If there has not been a substantial decline in the antigen, the patient may consider stopping treatment. However, labs in the United States currently do not measure the quantity of HBsAg, the doctors noted, but that would change if doctors start measuring HBsAg in order to predict a patient’s response to interferon.

The doctors suggested it would be better to identify which patients will respond as early as possible so they could avoid the lengthy weeks of treatment and side effects. “It would also be particularly helpful if the ideal duration of interferon treatment in HBeAg-negative patients could be better defined as this issue is not currently clear,” Dr. Terrault added.

• ***Long-Term Treatment with Entecavir More Effective Than with Adefovir***

Several recent studies compared entecavir (Baraclude) with adefovir.

Among HBeAg-positive patients, 96 weeks of treatment with entecavir produced a 7.8-fold drop in HBV DNA, compared with a 5.9-fold drop in adefovir-treated patients. Rates of undetectable HBV DNA for entecavir vs. adefovir at year 2 were 79% and 50%, respectively. Seroconversion rates of HBeAg were similar in both treatment groups.

While the number of patients in the study was small, this head-to-head comparison shows the potency of entecavir, Dr. Marcellin noted, citing another small study that confirmed entecavir resulted in 87% of patients achieving undetectable HBV DNA after three years of treatment. Also noteworthy was a low rate of viral resistance to entecavir (1.7%) after three years of treatment, but the experts agreed that entecavir’s true resistance rate will not be known until many more people are treated long-term.

• ***How Long to Continue Antiviral Treatment After HBeAg Seroconversion?***

The experts discussed several large trials, one involving 1,211 patients, who were given the antiviral telbivudine (Tyzeka) and lamivudine over two

years. The experts focused on HBeAg-positive patients who seroconverted to see how many patients sustained their seroconversion after treatment ended. Currently, doctors don't know when it is safe to stop antiviral treatment after patients seroconvert. Doctors fear if they discontinue treatment too soon, the HBV replication rate will rebound and HBeAg will return.

These studies showed that 70% to 80% of patients treated with either lamivudine or telbivudine for an additional six months after seroconversion occurred were able to sustain their HBeAg seroconversion three years after treatment ended.

• ***Taking Antiviral as Prescribed Increases Effectiveness, Compared to Patients Who Miss Doses***

The experts discussed a study that compared tenofovir treatment with an experimental combination of tenofovir and emtricitabine (this antiviral combination comes in one pill and is now used to just treat HIV). The researchers found no improved benefit from the combined antiviral pill on hepatitis B treatment,

however another aspect of the study compared response rates in patients who took their antiviral medications as proscribed, compared to non-compliant patients.

The researchers found that patients with high medication adherence had an 87% treatment success rate, compared to non-compliant patients who had a 71% success rate.

Who Has More Side Effects from Interferon, Hepatitis B or C Patients?

A group of researchers compared the severity of side effects from pegylated interferon treatment in patients infected with either HBV or the hepatitis C virus (HCV). Pegylated interferon, injected once weekly, boosts the immune system to fight infection, but interferon can cause side effects, such as fatigue and depression.

The researchers compared side effects in 448 hepatitis B patients (HBeAg-positive and negative patients) with 791 hepatitis C patients. All received treatment for 48 weeks, and were then followed for an additional 24 weeks.

The incidence of adverse side effects was

89% in HBV patients and 98% in HCV patients. Serious side effects rates in HBV and HCV patients were 5% and 7-16% respectively, and treatment withdrawal because of side effects was 7% and about 25% respectively. The frequency of depression-related events was much lower in HBV patients than HCV patients (4% vs. 22%), according to the report published in the July 2008 issue of *Liver International*.

Study Confirms Re-activation of Hepatitis B – Even When People Have Cleared the Infection – During Chemotherapy

There are increasing reports that people who have cleared HBsAg and who may even test positive for the surface antibody (anti-HBs) often experience a return of the infection, which can be life-threatening, when they are treated with chemotherapy or immune-suppressing drugs commonly used for transplants.

This trend was recently documented by Japanese researchers in the July 2008 issue of the journal of *Clinical Infectious Diseases*. The researchers followed 1,791 patients

who tested positive for HBsAg between 2000 and 2004 in Japan, a country where 20 percent of residents have been infected by HBV. About 4 percent of these patients had resolved infections, but experienced reactivation following immune-suppressing therapy. Reactivation of hepatitis B is defined as a decreased in surface antibodies, a reappearance of HBsAg, and a three-fold increase in alanine aminotransferase (ALT) levels, which indicates liver cell damage, and detection of HBV DNA (virus in the bloodstream) during or after chemotherapy.

When acute HBV infection occurs, including through HBV reactivation, one-fourth of patients develop liver failure and die.

This large-scale study confirms that even though people may clear HBsAg and develop antibodies, small, undetectable amounts of HBV still lurk in the body and can be reactivated when the immune system is weakened. The researchers recommend that anyone treated with chemotherapy be simultaneously treated with an antiviral as a precautionary measure to prevent reactivation of the virus.

Iron (Ferritin) Levels Fall When Antiviral Treatment Succeeds

Researchers have tried to determine what role iron – called ferritin in the body – plays in HBV infection. High iron levels appear to promote HBV replication, and hepatitis B patients are encouraged to avoid high-iron diets.

Japanese researchers recently monitored ferritin levels in 30 patients treated with lamivudine for 12 months. They found that ferritin and ALT levels decreased significantly in patients who successfully responded to the antiviral. One of the patients in the study had serious liver scarring (cirrhosis), and he too improved as ferritin levels declined, according to the researchers' report in the July 2008 issue of the journal *Hepatology International*.

Identifying HBV Genotype and Viral Mutations May Help in Treating Acute HBV

Researchers know there are a variety of strains or genotypes of HBV in different regions of the world, and each has varying disease outcomes and responds differently to

treatment. Additionally, some HBV have mutations in their genetic material, which also impacts how severe HBV infection can be.

Recently, Japanese researchers studied what impact these mutations had in 139 patients who were recently diagnosed with acute hepatitis B. They reported that patients infected with HBV with basal core promoter or precore mutations were not more prone to developing chronic hepatitis B—except in patients infected with genotype C2. These patients who also had those mutations often experienced liver failure.

Knowledge of HBV genotypes and genetic mutations is useful in order to develop strategies to treat acute hepatitis B patients, the researchers wrote in the July 2008 issue of the *Journal of Gastroenterology*.

Viral Load at Week 24 of Treatment Signals Treatment Success or Failure

A patient's HBV DNA level after 24 weeks of antiviral treatment predicts whether the drug will work long-term, according to researchers reporting in the July 2008 issue of the journal

Hepatology International.

Lower HBV DNA levels after 24 weeks of treatment with lamivudine, telbivudine, or entecavir are associated with higher rates of long-term undetectable HBV DNA, normal ALT levels, HBeAg seroconversion, and a lack of viral resistance to the drug.

Patients with HBV DNA levels remaining above 10,000 copies per mL are unlikely to benefit from that particular antiviral, researchers report. Those patients should either switch to another antiviral or add another antiviral to their ongoing treatment.

“In the future, improved on-treatment monitoring should facilitate treatment strategies to optimize long-term outcomes among patients receiving oral antiviral therapy for chronic hepatitis B,” they wrote.

Eleven Percent of Liver Transplant Patients with Cancer Have Tumor Recurrence Within One Year

Turkish researchers compared 215 HBV patients who had liver transplants to 72 transplant patients with HBV-related liver cancer to see

which patients had recurring HBV infection and liver cancer.

About 24% of liver cancer patients had a recurrence of HBV infection, compared to 5.5% of transplant patients without cancer. On average, it took about 39 months for the infection to recur.

Among the 72 cancer patients, 8 patients (11%) had recurrent liver cancer and 7 of them also had HBV reinfection. It took an average 11 months for the cancer to recur in these patients, according to their report in the June 2008 issue of *Transplantation Proceedings*.

