Selected Highlights on Hepatitis B at DDW

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Several presentations and posters at the Digestive Disease Week conference held May 19-22 in San Francisco addressed hepatitis B virus (HBV) infection. Numerous additional reports dealt with other topics of interest to people with chronic viral hepatitis, including liver fibrosis, treatment of hepatocellular carcinoma (HCC), alternative therapies for liver disease, and liver transplantation.

Robert Perillo, MD, of the Ochsner Clinic in New Orleans presented a state-of-the-art lecture on hepatitis B treatment on Tuesday afternoon, and Jenny Heathcote, MD, of the University of Toronto spoke about HBV at a lunchtime session the same day. Dr. Perillo noted that while HBV is sometimes given little attention compared to HCV, it remains a serious disease, with an estimated 1.5 million carriers in the U.S. and many times more in parts of the world such as Asia and Africa. Noting the complexity of HBV diagnosis, pathogenesis, and treatment, Dr. Heachcote opened that HCV is a “piece of cake” compared to HBV. She suggested that as physicians have become familiar with HCV, they have a tendency to want to treat HBV and HCV similarly, but they are “totally different diseases.”

While the primary goal of HBV treatment is to diminish viral replication, a small amount of HBV DNA almost always remains detectable using the most sensitive viral load tests. As Dr. Heathcote noted, before the current generation of viral load tests became available, people with very low HBV DNA levels would have been considered healthy carriers, and such carriers tend to fare well. At a topic forum on Sunday devoted to hepatitis B pathogenesis and treatment, Mauro Manno and colleagues from Italy presented results from a natural history study of asymptomatic HBV carriers (abstract #85). They found a 30-year death rate of 10% among 296 HBV surface antigen (HBsAg) positive persons (including four liver-related deaths) compared to a death rate of 9% in 157 HBsAg negative controls (including one liver-related death). The liver-related death rate among the asymptomatic carriers was only 1%, and the overall death rates among HBV antigen positive and negative persons did not significantly differ. The researchers concluded that, “HBV carrier status is not associated with an increased risk of development of liver disease and HCC.”

In the light of this, use of more sensitive PCR tests that reveal extremely low viral load levels may actually be detrimental in some cases, by prompting physicians to treat people who do not need therapy. Whether to treat patients with low HBV viral loads, normal ALT levels, and no biopsy results showing liver damage remains controversial. Dr. Perillo said it may be a “disservice” to treat people who are likely to be inactive carriers, and suggested that the less sensitive bDNA viral load test may be more useful in indicating which patients truly have active disease. Even the necessity for biopsies in people with low ALT and HBV DNA levels remains a matter of debate. While Dr. Heathcote acknowledged that biopsy is “an integral part” of HBV management, both she and Dr. Perillo suggested that biopsy may be unnecessary if there is no plan for treatment. On the other hand—as with HCV—ALT levels are not always a reliable indicator of liver damage; some people have biopsies that show serious liver damage despite normal or modestly elevated liver enzymes.

The currently approved treatments for HBV are interferon-alpha and the nucleoside analog drug lamivudine (also known as 3TC and Epivir). AASLD practice guidelines for the treatment of chronic hepatitis B were published in the December 2001 issue of *Hepatology*.

Many physicians have moved away from using interferon to treat chronic HBV because it is often ineffective,

has numerous side effects, and can cause increased liver inflammation. But today, interferon appears to be coming back into favor. Dr. Heathcote pointed out that in many of the early studies that showed less than impressive results, patients were treated with interferon only for short intervals, and that early versions of interferon were less effective than those available today. Dr. Perillo agreed that the drug still has a role in the treatment of chronic HBV. People with high baseline ALT levels and moderate HBV DNA levels tend to respond best to interferon therapy, with a 30-35% virological response rate after 4-6 months. Dr. Heathcote suggested that longer interferon treatment (as is common in Europe) may be more beneficial. Study results presented at a recent European Association for the Study of the Liver (EASL) conference indicate that pegylated interferon may be more effective than standard interferon in treating HBV.

Nucleoside analog drugs are less expensive, have fewer side effects, and are easier to administer than interferon. However, drug resistance can be a problem. Lamivudine-resistant YMDD mutants typically develop after 2-3 years of therapy (sometimes sooner). Study results have been inconsistent concerning whether people with such mutations may still benefit from continued lamivudine therapy or whether continued treatment actually might be harmful. Yun-Fan Liaw and colleagues from Taiwan reported at DDW that they found no significant difference in the occurrence of ALT “flares” or decompensated cirrhosis in people who continued or stopped lamivudine after the emergence of YMDD mutants, and concluded that there was no benefit to continuing such therapy (abstract #88).

Researchers are studying several new nucleoside analog drugs and combination regimens that may provide better, longer-lasting virological control of HBV. Adefovir dipivoxil (Preveon) is a nucleotide analog, which requires one less processing step in the body than a nucleoside analog. Adefovir is active against both wild-type and lamivudine-resistant HBV, and does not appear to trigger resistance itself. The drug is currently under review by the FDA and may be licensed later this year. Promising results for adefovir were presented at the Retroviruses conference in February, and more followed at DDW. Patrick Marcellin and a multinational group of colleagues presented results from a randomized trial of 10mg adefovir versus placebo (abstract #T1366). Persons taking adefovir had significant histological (reduced liver inflammation and damage), biochemical (normalized ALT level), and virological (reduced HBV DNA) responses. Adverse side effects in people taking adefovir were minimal and were similar to those seen in the placebo group.

Other drugs under study for HBV treatment include entecavir (also effective against both wild-type and lamivudine-resistant HBV), emtricitabine, clevudine, BLFd4C, LdT, and val-LdC. At Sunday’s HBV topic forum, Seng Gee Lim and colleagues presented results of a study of val-LdC (abstract #87). Val-LdC is a prodrug of LdC, a nucleoside analog that has shown *in vitro* activity against HBV. Early results from this ongoing, randomized Phase I/II trial show the first evidence of viral suppression in humans after 28 days. In this dose-escalating study, the three lowest doses (50, 100, and 200mg) have been tested to date The safety profile of the drug looks promising, with no serious adverse events or dose-related toxicities so far; researchers plan to test doses up to 1,200mg. Like val-LdC, LdT also has shown good antiviral activity and minimal toxicity in early human trials. A trial of val-LdC plus LdT is planned for 2003, since the two drugs show synergistic activity *in vitro* and in woodchucks. In the only other DDW presentation on an early pipeline drug, Stephen Wise and colleagues offered a poster with results of a dose-ranging and safety study of Ly582563 (MCC-478), another new nucleoside analog (abstract #T1360).

Difficult issues in HBV mangement include treatment of people with decompensated cirrhosis, immunocompromised patients, and post-transplant patients. Use of lamivudine may help stabilize HBV positive people with liver failure while they await a transplant, but many transplant surgeons discourage use of the drug, and Dr. Perillo said it was unclear how often improvement is substantial enough to make transplantation unnecessary. Whether to use interferon in people with decompensated cirrhosis also remains controversial. Most experts discourage this potentially dangerous practice, but some studies have shown that the drug may be beneficial. Marion Peters and colleagues analyzed results from four clinical studies of adefovir, including three hard-to-treat populations: those with decompensated liver disease, those with HBV/HIV coinfection, and those who had received a liver transplant (abstract #T1367). Overall, adefovir was well tolerated and led to significant virological, histological, and clinical benefit—perhaps providing a good therapy option for difficult-to-treat patients.Dr. Heathcote concluded that “the jury is still out” on treatment in these situations, and clinical trials, if available, may be the best option for such patients.

Another issue is the emergence of HBV ‘e’ antigen (HBeAg) negative chronic hepatitis B. Traditionally, the presence of HBeAg signaled active HBV infection; loss of the ‘e’ antigen (seroconversion) was used as an indicator that treatment was effective. Increasingly, however, people are being seen who have active disease despite being ‘e’ negative. This is due to the emergence of so-called “precore” mutant HBV, which is unable to produce the ‘e’ antigen. This type of HBV is still uncommon in the U.S. (an estimated 0-20% of cases), but is prevalent in Asia and the Mediterranean. People with ‘e’ negative chronic active hepatitis tend to have poor long-term prognosis, a high relapse rate, and rapid progression. The ‘e’ negative variant is more difficult to treat, and response to treatment is less well predicted by baseline ALT or HBV DNA levels. According to Dr. Heathcote, ‘e’ negative disease is perhaps the biggest problem on the horizon in hepatitis B management.

As with HCV, HBV has several different genotypes (lettered rather than numbered, A through G), which have different geographic distributions. Previous studies have suggested that different HBV genotypes are associated with varying levels of viral replication, liver disease progression, and treatment response. Chi-Jen Chu and a large team of researchers studied the distribution of HBV genotypes among patients at 17 U.S. liver centers (abstract #86). They found all seven known HBV genotypes, although genotypes E, F, and G were rare (at 1% each). Overall, 33% had genotype A, 21% had genotype B, 34% had genotype C, and 9% had genotype D. Genotype A was more common in whites, Asian-Americans, those born in the U.S., and those with sexually acquired HBV. Genotypes B and C were more common in Asians, people born outside the U.S., and those with perinatally acquired HBV. In this study, genotype D was associated with development of “precore” HBV mutants and with decompensated cirrhosis. Hideki Watanabe and colleagues presented a poster on the association between HBV genotype and HCC. Rong-Nan Chien and colleagues presented a poster showing that HBV genotype is related to durable response to lamivudine. Fortunately, the most common HBV genotypes in the U.S. do *not* appear more difficult to treat or more likely to cause disease progression.

In summary, Dr. Perillo concluded that HBV treatment in the future likely would follow the HIV paradigm of multiple-drug regimens. Because interferon works by a different mechanism than nucleoside analogs, Dr. Heathcote and Dr. Perillo agreed that combination treatment with both drug classes—and possibly with multiple nucleoside analogs—may well prove to be the most effective approach. Asymptomatic HBV carriers generally do not need treatment, but still should be made aware that they have a chronic and potentially serious disease; they should have regular ALT tests, be screened for HCC every six months, and receive periodic HBV antigen screening (since HBV may reactivate if a carrier becomes immunocompromised, for example, due to the use of steroids). And HBV—unlike HCV—can be prevented with a vaccine. Dr. Heathcote suggested that many more lives could be saved by getting everybody vaccinated than by improving HBV treatment. She believes vaccination as a teenager is too late, and supports current U.S. recommendations that all infants receive the HBV vaccine within their first few months after birth.