

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Advances in the Management of Hepatitis B Virus Infection



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G&H How are the statistics for hepatitis B virus infection changing with advances in detection and care?

HH Currently, there are 400 million people infected with hepatitis B virus (HBV). Seventy-five percent of that population lives in Asia. The encouraging news is that, among younger generations, the carrier rate has significantly decreased after implementation of childhood HBV vaccination.

The results of such vaccination are especially impressive in the Asian countries that have implemented a nationwide childhood vaccination program. In these countries, the overall HBV carrier rate in children has decreased to less than 2%. For example, in Indonesia, where the carrier rate was once more than 6%, it is now 1.9%. As for China, in Shanghai, the carrier rate has dropped from 8.8% to 0.5%, and, in Taiwan, it decreased from 9.7% to 0.7%. In Thailand, the carrier rate was reduced to 0.8% from 6.4%. These results give us hope that HBV infection can be eradicated in the future.

Nonetheless, while the carrier rates may decrease over time, the reduction in HBV-related morbidity and mortality rates among the already infected may take more time to bear out. This is because the history of antiviral therapy is fairly short, having begun in 1998 with the first oral anti-HBV drug, lamivudine.

Injectable interferon appeared earlier in 1992, but with its severe adverse effects, interferon has not been well tolerated by most patients with HBV infection, especially Asian patients who have been infected since birth. Now,

with the advent of oral anti-HBV drugs (nucleos[t]ide analogues [NAs]), which produce very few adverse effects, more patients are receiving treatment.

Although more time is needed to see a significant change in statistics, I personally have observed a significant decrease in the number of patients who progress to advanced cirrhosis and terminal liver cancer since the introduction of anti-HBV drugs compared with my experience with patients before 1998. Moreover, screening and educational initiatives over the past 30 years have had an impact on HBV statistics. These initiatives were given a boost with the introduction of antiviral therapy, which has enabled infected persons to receive proper treatment.

Recently published data from the National Cancer Institute note a rise in liver cancer among black, Hispanic, and white men age 50 years and older. This rise is likely due to undiagnosed or late-diagnosed HBV infection and, more significantly, an increase in hepatitis C virus (HCV) infection.

G&H In what percentage of the HBV-infected population do life-threatening sequelae develop?

HH Significant clinical sequelae, including cirrhosis, liver failure, and hepatocellular carcinoma (HCC), will develop in up to 40% of patients with chronic HBV infection (CHB) who are not receiving antiviral treatment. Also, 25% of such patients may die of liver failure or HCC. Again, with appropriate antiviral treatment, these figures are expected to decline.

G&H What is the impact of travel and immigration on HBV infection prevalence in the United States?

HH Americans traveling to HBV-endemic regions may be at risk for adult-acquired HBV infection via sexual transmission, tattooing, and other high-risk behaviors. However, I trust that the majority of American adults already are vaccinated against HBV. My advice to Americans traveling to endemic areas is to make sure, prior to such travel, that they get vaccinated if they have not been and that they refrain from high-risk behavior that could lead to HCV infection, for which there is no vaccine.

As to the impact of immigration on HBV infection in the United States, there are now 2 million people who are infected in this country. Of these, 1.5 million are foreign born: 863,000 from Asia, 291,000 from Latin America and the Caribbean, 196,000 from Africa, and 173,000 from Eastern Europe and elsewhere. Of the 2 million people infected, 600,000 are aware of their infection, but only 50,000 are on treatment. We have a huge task ahead to educate undiagnosed and untreated persons and exhort them to receive medical care at an early stage of infection.

G&H What defines treatment response in patients with HBV infection?

HH Treatment response would include suppression of HBV replication (ie, achieving undetectable HBV DNA in serum), normalization of liver enzymes and liver functions, reversal of fibrosis/cirrhosis, and prevention of progression of liver disease, such as cirrhosis and HCC.

The ultimate goal would be prevention of HCC. The final point of stopping the antiviral treatment would be when the patient becomes hepatitis B surface antigen (HBsAg)-negative. Nonetheless, these patients should be followed at regular intervals due to risk of relapse. Sometimes, even after HBsAg seroconversion, HCC develops in some patients.

G&H With the introduction of NAs, are we at the point where HBV infection is a chronic but manageable disease?

HH My answer is yes. NAs have been a game changer. We can stabilize the disease, normalize liver function, reverse fibrosis/cirrhosis, and even reverse some decompensated cirrhosis. For example, ascites recedes with antiviral therapy along with improvement of liver function. NA treatment also has shown promise in delaying or preventing the development of HCC. Furthermore, NA treatment may well prevent new/recurrent HCC

after the initial tumor ablation. Prior to the NA era, even after successful tumor resection or ablation, recurrent or new HCC in the remaining liver led to poor survival of affected patients.

The value of NA therapy is apparent in clinical practice. Before 1998, I was treating a large number of patients with CHB. Sadly, I had a cabinet filled with medical charts of patients who died of liver failure or liver cancer. Now, my cabinet is still brimming with medical charts, but they belong to patients who are alive and active, thanks to oral antiviral therapy. This contrast gives me great hope.

G&H How is therapy being optimized?

HH Optimization is to follow the treatment guidelines. Both the clinician and the patient must be dedicated to a long treatment course and be utterly compliant. Moreover, the choice of antiviral therapy is important. For example, if the baseline viral load is very low, then the patient's drug resistance rate is usually lower than that of a patient who has a high baseline HBV DNA level, and the therapeutic options to choose from are broader. If the baseline viral load is high, a more potent agent with a low resistance profile should be selected. No doubt, treatment needs to be individualized, and patients have to be closely monitored following their response to therapy to catch emergence of drug resistance and observe disease progression or regression.

G&H What is the protocol for those patients who ultimately test HBsAg-negative?

HH Treatment can be stopped if a patient becomes HBsAg-negative because HBsAg-negative status is considered the endpoint of treatment. However, patients need to be followed at regular intervals for signs of recurrence, as the virus will not be completely eradicated. There still are covalently closed circular DNAs in the liver, which are not targeted by current therapies. There also is a possibility of occult HBV infection. Although not common, occult HBV infection with HCC is well documented. Also, when a patient loses HBsAg without antibody (anti-HBs) development, that patient needs vaccination. In my experience, such patients who lost HBsAg without development of anti-HBs were vaccinated successfully.

Nowadays, HCV infection is curable. My hope is that we should be able to eradicate HBV infection in the near future. Active research for the eradication of HBV infection is in progress. Examples of such research include blocking the virus entry to hepatocytes, inhibiting the secretion of HBsAg, and inhibiting viral nucleocapsid formation among others.

G&H How is therapy for HBV infection impacting outcomes of HCC?

HH Antiviral therapy can prevent or reduce the development as well as recurrence of HCC. This is encouraging news, and we are very excited. In the past, the recurrence of HCC was associated with poor survival in patients who had experienced successful resection or ablation of the initial tumor. Recently, several controlled studies showed an improved survival in these patients when they received antiviral therapy after initial tumor resection. These were observed in Japan, Hong Kong, Taiwan, and China.

In a historical placebo-controlled, prospective study of 651 patients with CHB, published in the *New England Journal of Medicine* in 2004, Liaw and colleagues clearly showed a reduction in the development of HCC in patients with CHB who received lamivudine therapy compared with patients who received placebo. Retrospective studies, including those of Eun and colleagues, in the *Journal of Hepatology* in 2010, also showed a reduction in the development of HCC in lamivudine-treated patients. Similar results with entecavir were also seen in a more recent study by Hosaka and colleagues that was published in the July 2013 issue of *Hepatology*.

Our team at Thomas Jefferson University Hospital has made similar observations, which were recently published in the April 2014 issue of *Cancer Medicine*. This was the first report from the United States, and the study represented the longest follow-up in the world. With anti-HBV treatment, we have been able to prevent recurrent HCC in patients whose initial tumor was ablated or resected. In our series, we observed patient survival with maintenance of undetectable HBV DNA and no recurrence of tumor in patients who continued anti-HBV therapy. These patients need to be maintained on therapy indefinitely, though, because they remain HBsAg-positive while their viral loads remain undetectable.

In our study, we followed 25 patients with a single HCC of 7 cm or less from 1991 to 2013. The patients had not received anti-HBV therapy prior to diagnosis of HCC, and all underwent successful tumor ablation. Nine patients did not receive anti-HBV therapy after diagnosis of HBV-associated HCC because anti-HBV drugs were not yet available. Sixteen patients received anti-HBV therapy immediately after diagnosis of HCC. The tumor recurred in all of the untreated patients, who all ultimately died of multiple tumor recurrences and had a median survival of 12.5 months. By contrast, 14 of the 16 treated patients are alive and well, with a median survival of 80 months

(6.7 years). Of these, the 2 longest surviving patients have thrived for more than 13 years since diagnosis and treatment initiation and have remained cancer-free. I believe the remaining patients in the treated cohort will do the same as long as they continue anti-HBV therapy.

I believe that this novel treatment strategy offers an alternative to liver transplantation in patients with HBV-associated HCC. Of note is a report, published in *Gastroenterology* in 2009, in which Kim and colleagues showed a decline in the need for liver transplantation for HBV-related end-stage liver disease in the United States.

G&H What are your thoughts about optimization of screening initiatives?

HH I think we need an active education campaign that utilizes all types of media outlets: radio, television, newspaper, and especially local initiatives in many ethnic languages. The Hepatitis B Foundation has used media and done very well in educating immigrants from endemic regions and physicians alike about the importance of HBV screening and early treatment. Screening initiatives have picked up, but more needs to be done. Although awareness of the disease has increased, with many persons becoming aware that they are infected, many infected persons still are not getting treatment. Primary care physicians need to be informed that effective therapies are available for HBV infection, and they need to take on the responsibility of not only screening for HBV infection but offering treatment to patients.

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Suggested Reading

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