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# Chronic Hepatitis B — New Goals, New Treatment

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The hepatitis B virus (HBV) causes chronic infection in approximately 400 million people in the world. Most carriers of chronic HBV, including Asians, Africans, and a proportion of persons in Mediterranean countries, acquire the infection at birth or within the first 1 to 2 years after birth.[1] It is estimated that 50% of male carriers and 14% of female carriers will eventually die of the complications of cirrhosis and hepatocellular carcinoma.[2]

The criteria and end points for the treatment of chronic HBV infection should be reevaluated in light of three important recent findings. First, more than 70% of patients with complications of cirrhosis and hepatocellular carcinoma are negative for the hepatitis B e antigen (HBeAg).[3] Therefore, although the disease may become quiescent in some patients after HBeAg seroconversion, the disease can progress, and most disease-related deaths occur in these patients. Even with clearance of the hepatitis B surface antigen (HBsAg), there is no decrease in the risk of hepatocellular carcinoma if the HBsAg is lost in patients after the age of 50 years.[4]

Second, an elevated HBV DNA level of more than 2000 IU per milliliter ($10^4$ copies per milliliter) is a strong independent predictor of the risk of complications of cirrhosis and hepatocellular carcinoma.[5,6] Prolonged, effective suppression of HBV DNA has been shown to decrease the risk of the development of cirrhosis and hepatocellular carcinoma.[7,8]

Finally, as is the case in chronic hepatitis C infection, patients with chronic HBV infection who have alanine aminotransferase levels that are near the upper limit of the normal range are at a significantly higher risk for complications of cirrhosis and hepatocellular carcinoma than patients with alanine aminotransferase levels that are less than half the upper limit of the normal range.[3] The highest risk of complications of cirrhosis and hepatocellular carcinoma occurs in patients with alanine aminotransferase levels that are one to two times the upper limit of the normal range.

The implications for the treatment of chronic HBV infection are that, other than the traditional end point of HBeAg seroconversion alone, a more important aim is the sustained suppression of HBV DNA to very low levels, preferably to below the detection limit of sensitive polymerase-chain-reaction (PCR) assays.[1] The alanine aminotransferase level should also ideally be lower than half the upper limit of the normal range.

The first licensed agent for the treatment of chronic HBV infection was the conventional form of interferon alfa, which acts mainly through immunomodulation and has the advantage of being given over a fixed period of time, although this is partly because of its often severe side effects. However, the majority of patients still have levels of HBV DNA that are detectable by means of PCR assays after treatment, and most studies show no decrease in the occurrence of hepatocellular carcinoma on long-term follow-up.[9,10] The short-term efficacy of pegylated interferon (peginterferon), licensed in 2005, is almost identical to that of conventional interferon. Data on its long-term effects on the development of cirrhosis and hepatocellular carcinoma have not yet been published.

Lamivudine, a nucleoside analogue, was licensed in 1998. Nucleoside and nucleotide analogues suppress HBV replication through inhibition of the reverse-transcriptase and DNA polymerase activities. During the past decade, four other nucleo-

side and nucleotide analogues have been licensed: adefovir (in 2002), entecavir (in 2005), telbivudine (in 2006), and, most recently, tenofovir disoproxil fumarate (DF) (in 2008).

In this issue of the *Journal*, Marcellin et al.[11] report on two studies comparing the antiviral efficacy of tenofovir DF with that of adefovir dipivoxil in both HBeAg-negative and HBeAg-positive patients; 18% of the HBeAg-negative patients had received lamivudine previously. At week 48, tenofovir DF was superior to adefovir dipivoxil in achieving the primary end point, defined as the combination of an HBV DNA level of less than 400 copies per milliliter (69 IU per milliliter) and histologic improvement (P<0.001). A total of 93% of the HBeAg-negative patients and 76% of the HBeAg-positive patients who received tenofovir DF (the intention-to-treat population) had an HBV DNA level of less than 400 copies per milliliter by week 48. The choice of this HBV DNA level as the primary end-point threshold was dictated by the detection limit of the sequencing assay used for resistance surveillance. However, the detection limit of the PCR assay used for quantification of HBV DNA in the studies was 169 copies per milliliter (29 IU per milliliter). This end-point threshold for HBV DNA would have been a better choice, because lower levels of HBV DNA measurement would allow earlier detection of viral rebound[12] and because the modern treatment end points aim at suppressing HBV DNA to as low a level as possible.[1]

Two of the most encouraging aspects of tenofovir DF in the studies reported by Marcellin et al. are its efficacy in patients with a lamivudine-resistant virus and the absence of resistant mutations up to week 48. A longer treatment period is of course required to determine the incidence of tenofovir DF resistance. The relative efficacy and resistance rates of the approved drugs are listed in Table 1.

The most obvious niche for tenofovir DF is in

**Table 1. HBV DNA Suppression and Resistance Rates Associated with Different Therapeutic Agents.***

| Variable | Pegylated Interferon | Lamivudine | Adefovir Dipivoxil | Entecavir | Telbivudine | Tenofovir DF |
|---|---|---|---|---|---|---|
| | | | *percent of patients* | | | |
| **HBeAg-positive patients** | | | | | | |
| Undetectable HBV DNA by PCR† | | | | | | |
| 1 yr | 25 | 36 | 21 | 67 | 60 | 76 |
| 2 yr | NA | NA | 40 | 80 | 56 | NA |
| 3 yr | NA | NA | 48 | 82 | NA | NA |
| Resistance | | | | | | |
| 1 yr | 0 | 24 | 0 | <1 | 4 | 0 |
| 2 yr | — | 42 | NA | <1 | 25 | NA |
| 5 yr | — | 76 | 20 | 1 | NA | NA |
| **HBeAg-negative patients** | | | | | | |
| Undetectable HBV DNA by PCR† | | | | | | |
| 1 yr | 63 | 72 | 63 | 90 | 88 | 93 |
| 2 yr | NA | NA | 71 | 94 | 82 | NA |
| 3 yr | NA | NA | 79 | NA | NA | NA |
| Resistance | | | | | | |
| 1 yr | 0 | 21 | 0 | <1 | 3 | 0 |
| 2 yr | — | 35 | 3 | <1 | 11 | NA |
| 5 yr | — | NA | 29 | 1 | NA | NA |

* Data are from Yuen et al.,[13] Marcellin et al.,[11,14] Hadziyannis et al.,[15] Tenney et al.,[16] and Liaw et al.[17] HBeAg denotes hepatitis B e antigen, HBV hepatitis B virus, NA not available, and PCR polymerase chain reaction.
† The lower limit of detection varied from 40 to less than 200 IU per milliliter (200 to <1000 copies per milliliter).

the treatment of patients with lamivudine-resistant HBV. Tenofovir DF is superior to adefovir dipivoxil and entecavir in these patients, and it has a much lower renal toxicity than adefovir dipivoxil.[18] An even greater prospect is its potential use as a first-line drug in patients who have not received treatment; these patients compose the great majority of the population of persons with chronic HBV infection in the world. One of the besetting problems with nucleoside and nucleotide analogues is the development of resistance with long-term use. Early suppression of HBV DNA (e.g., to <40 IU per milliliter [200 copies per milliliter] by week 24) has proved to be associated with low rates of resistance development.[13] Although we must await further studies to determine the long-term resistance to tenofovir DF, it is encouraging to note that 86% of HBeAg-negative patients and 50% of HBeAg-positive patients had HBV DNA levels that were less than 400 copies per milliliter at week 24. The resistance rate for adefovir dipivoxil after 5 years of treatment is 20% among HBeAg-positive patients and 29% among HBeAg-negative patients.[14,15] It is to be expected that resistance to tenofovir DF would be lower because of its greater efficacy in viral suppression.

Finally, what is the possible future role of tenofovir DF in combination therapy? In HBeAg-negative patients, long-term therapy with nucleoside and nucleotide analogues is the standard practice. However, in HBeAg-positive patients, most treatment guidelines suggest that therapy may be discontinued after a stable HBeAg seroconversion, preferably with levels of HBV DNA that are undetectable by means of PCR assays. Nevertheless, at least one study in HBeAg-positive patients shows that even with a relatively weak agent such as lamivudine, continuing drug treatment after HBeAg seroconversion results in better sustained suppression of HBV DNA and fewer alanine aminotransferase flares than discontinuing the treatment.[19] Long-term therapy in both HBeAg-positive and HBeAg-negative patients with sustained viral suppression will most likely be the trend in the future. The problem of resistance will become a major concern. Although most studies with combination therapy show no additive antiviral effects, combination therapy has resulted in a reduction of resistance development. The ideal combination may be a nucleoside analogue such as lamivudine or telbivudine with a nucleotide analogue such as adefovir dipivoxil or tenofovir DF; in this combination therapy, one group of agents will remain sensitive to the resistant mutant viruses of the other group. However, if the long-term resistance to tenofovir DF turns out to be very low, similar to the 1.2% resistance rate after 5 years of treatment with entecavir among patients who have not received treatment previously,[16] long-term monotherapy with tenofovir DF or entecavir is another possible option.

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