EDITORIAL

A Major Step toward a Cure for Hepatitis B Infection

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The current treatment of chronic hepatitis B infection includes nucleoside or nucleotide analogue (NA) therapy and pegylated interferon. Both of these treatments are effective in suppressing hepatitis B virus (HBV) replication and in reducing the risk of cirrhosis and hepatocellular carcinoma.[1] However, these treatments do not eradicate HBV, and the risk of hepatocellular carcinoma is not eliminated.

NA therapy is administered orally, and entecavir and tenofovir are safe with a low risk of drug resistance. However, such therapies rarely lead to the loss of hepatitis B surface antigen (HBsAg) (i.e., a level of <0.05 IU per milliliter), which occurs in approximately 3% of patients after 8 to 10 years of therapy. Discontinuation of NA therapy before HBsAg loss is associated with virologic relapse in most patients and with hepatitis flares in some patients, but the discontinuation of NA therapy may also increase HBsAg levels in patients with low HBsAg levels (<1000 IU per milliliter in White patients and <100 IU per milliliter in Asian patients).[2] Pegylated interferon is administered as a weekly subcutaneous injection for 48 weeks. It leads to HBsAg loss in 3 to 4% of patients at the end of treatment, a percentage that increases to 8 to 11% after 3 years of follow-up. However, pegylated interferon is rarely used because it is associated with multiple side effects.

Major efforts have been devoted to the development of a functional cure for hepatitis B infection, which is defined as an undetectable HBsAg level and an unquantifiable HBV DNA level that are sustained for at least 24 weeks after the completion of a finite course of therapy.[3] Although HBV may persist in the liver and can be reactivated during immunosuppression, HBsAg loss confers several benefits, as compared with HBV DNA suppression alone, including a minimal risk of relapse after treatment discontinuation and a further decrease in the risk of hepatocellular carcinoma.[4]

Strategies for a cure for HBV infection have focused on targeting HBsAg production and restoring the immune response to HBV.[5] Small interfering RNAs (siRNAs) and antisense oligonucleotides have been the most effective in decreasing HBsAg levels but rarely result in HBsAg loss.[6,7] Immunomodulatory therapies alone have had minimal effects in decreasing serum HBsAg levels. A few phase 2 trials that evaluated a combination of three or four drugs — NA therapy and siRNA, together with pegylated interferon, toll-like receptor agonists, hepatitis B surface antibodies, or checkpoint inhibitors — have shown HBsAg loss during treatment, but the percentage of patients with a functional cure has been low (0 to 20%).[8] In addition, several of the drugs in these regimens require parenteral administration.

For these historical reasons, the results of the two B-Well trials with duplicate design now presented by Hou and colleagues in the *Journal*[9] are remarkable. Not only did these phase 3 trials aim at a cure for HBV infection, but they also had encouraging results that involved adding only one investigational agent — bepirovirsen, an antisense oligonucleotide — to NA therapy. The B-Well trials enrolled patients with noncirrhotic chronic hepatitis B with suppressed HBV DNA during receipt of NA therapy and a low HBsAg level (≤3000 IU per milliliter). A total of 1838 patients were randomly assigned in a 2:1 ratio to receive bepirovirsen or placebo administered as a weekly

subcutaneous injection for 24 weeks. The patients who had undetectable HBsAg and unquantifiable HBV DNA from week 24 to week 46 were eligible to discontinue NA therapy at week 48. The primary outcome of a functional cure was assessed at week 72.

In the bepirovirsen groups, a functional cure was reported in 20% of the patients in B-Well 1 and in 19% of those in B-Well 2, as compared with no patients in the placebo groups. The percentage of patients with a functional cure in the bepirovirsen groups was higher among those who had an HBsAg level of 1000 IU per milliliter or less at baseline (with cures in 25% in B-Well 1 and 28% in B-Well 2) than among those with an HBsAg level of 1000 to 3000 IU per milliliter (with cures of 10% and 5%, respectively). In both trials, the criteria for stopping NA therapy at week 48 were met by 24% of the patients in each bepirovirsen group, as compared with no patients in the placebo groups. Of the 62 patients who stopped NA therapy but did not have a functional cure, 5 had quantifiable HBV DNA at week 72 and none had a clinical relapse.

The overall results are impressive but cannot be generalized to patient groups that were not included in the trials — those with cirrhosis, coinfection with human immunodeficiency virus, or an HBsAg level of more than 3000 IU per milliliter. Even among the patients with an HBsAg level of 1000 to 3000 IU per milliliter, the percentage who had a functional cure was substantially lower than that among those with the lower HBsAg level. Adverse events of grade 3 or higher were more common in the bepirovirsen groups than in the placebo groups (16% vs. 3%), with an increase in alanine aminotransferase (ALT) being the most common (6%) with bepirovirsen. In addition, adverse events requiring a dose interruption or delay were reported in 16% of the patients in the bepirovirsen groups as compared with 2% in the placebo groups; adverse events resulting in permanent discontinuation occurred in 3% and less than 1%, respectively. Most, but not all, adverse events were resolved by week 48 (24 weeks after discontinuation of bepirovirsen or placebo). Several of the adverse events — an increase in the levels of ALT and creatinine and a decrease in the platelet count — can be potentially serious if stringent monitoring (every 1 to 2 weeks) and strict trial-adopted guidelines regarding the pausing of therapy are not followed.

The B-Well trials represent a major step toward a functional cure for HBV infection, and bepirovirsen is an attractive option for selected patients. The durability of HBsAg loss has to be confirmed with longer follow-up, and alternative therapies are needed for other patients, such as those with cirrhosis or a baseline HBsAg level above 3000 IU per milliliter. Ultimately, curative therapies must be simple, safe, accessible, and affordable to benefit the 240 million persons worldwide who are living with chronic HBV infection.[10]

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