ADVANCES IN HEPATOLOGY

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Discontinuation of Nucleoside Analogues in Hepatitis B Virus Infection

Pietro Lampertico, MD, PhD
Assistant Professor
1st Division of Gastroenterology
Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico
Università degli Studi di Milano
Milan, Italy

G&H What are the prospects for eradication of hepatitis B virus infection?

PL Eradication of hepatitis B virus (HBV) is not an achievable endpoint with the current available anti-HBV therapeutic regimens. Even the closest outcome to a cure, hepatitis B surface antigen (HBsAg) seroconversion, is not associated with HBV eradication, as clearly shown by the significant risk of HBsAg seroreversion on drug- or disease-induced immunosuppression. Because HBV is a covalently closed circular DNA (cccDNA) virus, it is only marginally affected by long-term nucleotide or nucleoside analogue (NA) therapy. That HBV can integrate into the host genome makes eradication of it a dream that will never come true. To shed some optimism on this issue, clinicians should be aware that eradication of HBV is really not necessary to improve patient survival or prevent progression to cirrhosis or clinical decompensation, although HBV may play a significant role in the residual risk of hepatocellular carcinoma (HCC) that patients face despite successful long-term viral suppression.

G&H Which patients are the best candidates for NA therapy?

PL The great advantage of a NA-based antiviral therapy with third-generation drugs, such as entecavir (Baraclude, Bristol-Myers Squibb) and tenofovir, is that this strategy can be used to efficiently suppress HBV replication and prevent disease progression in any patient with chronic HBV infection, independently of age, serology, HBV DNA and/or alanine aminotransferase (ALT) levels, disease severity, concomitant diseases, and so on. The only disadvantage of this therapeutic approach is the need for antiviral therapy lasting many years—more than 10 to 20 years in most of these patients. Overall, any patient with clinical or histologic evidence of progressive chronic HBV infection or family history of HCC, untreatable with or not responding to peginterferon, is an ideal candidate for long-term NA therapy.

G&H Which patients would do better, in the long term, with peginterferon therapy, and why?

PL Peginterferon remains a valuable therapeutic option for both hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients, as indicated by all international HBV infection management guidelines, including the recently published National Institute for Health and Care Excellence recommendations. The main advantage of peginterferon therapy is to induce a sustained, off-therapy, immune-control status (defined as HBV DNA less than 2000 IU/mL and HBeAg negativity) in approximately 30% of treated patients after a finite duration of therapy, generally 48 weeks. Young to middle-aged patients with mild to moderate liver disease are the best candidates for peginterferon therapy. However, selection of the patients based on pretreatment predictors of response, such as viremia, ALT levels, and viral genotype, is very useful to optimize this therapy. Host genetics also have been suggested to play a major role in chronic HBV infection, but more data are needed before this information can be translated into clinical practice. The cost-effectiveness of peginterferon therapy has been recently improved by the

development and validation of a response-guided therapy based on quantification of HBsAg levels to predict sustained response. Approximately 20% of HBeAg-positive and HBeAg-negative patients treated with peginterferon can stop therapy at Week 12 because their probability of achieving a sustained response is close to zero. The development and validation of Week 12 to Week 24 stopping rules based on HBsAg levels has made an interferon-based strategy more attractive for both patients and payers.

G&H How should selection of specific NAs for a given patient with HBV infection be approached?

PL Entecavir and tenofovir are the only third-generation NAs on the market. Guidelines do not provide any specific indication for which drug should be used in which patient, but given the drug properties and the vast real-life experience with these 2 products in the past 5 years, I do not foresee any specific setting where 1 drug would be preferred to the other among treatment-naive patients, with the exception of kidney transplant recipients with chronic HBV infection or other patients with a significant baseline renal impairment for whom entecavir may be preferred. In contrast, for patients in whom drug-resistant strains have emerged, specific rescue strategies have been developed. For patients resistant to nucleosides (eg, lamivudine, telbivudine [Tyzeka, Novartis], or entecavir), tenofovir monotherapy is the preferred choice, whereas entecavir is recommended for patients who are lamivudine-naive and whose infection is resistant to adefovir. The best initial approach for difficult-to-treat patients with both lamivudine- and adefovir-resistant strains is still under discussion, but combination entecavir and tenofovir has been shown to be effective as well as safe. Finally, to prevent nephrotoxicity, lamivudine-experienced or -resistant patients on adefovir combination or monotherapy should be switched to tenofovir monotherapy. Nowadays, there is not a single clinical situation I can think of where antiviral therapy based on lamivudine, adefovir, or telbivudine is indicated.

G&H Why would discontinuation of NA therapy be attempted?

PL The best and most solid stopping rule is HBsAg seroconversion, an endpoint that can be achieved in up to 20% of the patients with chronic HBV infection treated with long-term NA therapy. This is indeed a safe stopping rule even for patients with severe liver disease such as cirrhosis, independent of the initial HBeAg status. A second stopping rule has been suggested for HBeAg-positive patients without cirrhosis. For these patients, analogues also can be discontinued if undetectable HBV DNA and HBeAg seroconversion have been achieved and consolidated for at least 12 to 18 months. However, strict virologic and biochemical monitoring off therapy is mandatory in these patients because viremia and hepatitis will relapse in approximately 50% of them, requiring urgent restart of antiviral therapy.

G&H Are there markers or predictors of which patients might be the best candidates for discontinuation of NA therapy?

PL The most challenging issue today for patients on long-term, effective NA therapy is whether drugs can be stopped before HBsAg seroconversion. In the 30% of the patients who clear HBsAg during therapy without HBsAg antibody (anti-HBs) seroconversion despite prolonged NA therapy, therapy can be safely discontinued after 12 to 18 months of consolidation. Recent retrospective studies suggest that Asian patients infected with a non-D genotype who achieve low HBsAg levels (ie, <100 IU) during long-term NA may safely stop therapy. However, although HBsAg levels are the most likely candidate markers to guide NA discontinuation, these data are very preliminary and not confirmed, making a full clinical validation mandatory before these stopping rules can enter into clinical practice.

G&H What is the rate of HBV DNA rebound after withdrawal of NA therapy? How is rebound disease managed?

PL The risk of HBV DNA rebound is negligible if NAs are withdrawn after anti-HBs seroconversion. The risk of virologic relapse ranges from 50% to 100% if a patient is still HBsAg-positive. An HBV DNA rebound after NA has been withdrawn should be always considered as a serious event in general and a life-threatening situation in patients with cirrhosis. In patients without cirrhosis, the first ALT flare can be monitored and tolerated while the second requires retreatment. In patients with cirrhosis, antiviral therapy should be resumed at the first HBV DNA rebound to avoid a hepatitis flare, which can drive hepatic decompensation and liver failure. The risk of resistance with retreatment is negligible if entecavir or tenofovir is used to re-treat patients who experience posttreatment relapse.

G&H How should a patient in whom NA therapy has been withdrawn be monitored and managed?

PL Virologic markers and biochemical tests should be monitored every month for the first 6 months and every 3 months thereafter up to Year 1. If no relapse has occurred in the first year after NA therapy has been withdrawn, monitoring should be continued every 4 to 6 months.

G&H How close are we to clinical guidelines about whether and when to discontinue NA therapy in patients with HBV infection?

PL Most of the recent data suggest that the measurement of serum HBsAg levels may help in defining new stopping rules for patients on NA therapy. This is sound on biologic and clinical grounds, given the relationship between serum HBsAg levels and cccDNA activity and all the clinical studies that associate serum HBsAg levels with the natural history of HBV in patients treated with peginterferon and long-term NA therapy. In addition, recent immunologic studies have clearly shown that, during successful long-term NA therapy, peripheral T-cell functions are recovered to an extent similar to that in inactive carriers, at least in a subset of patients. These serologic and immunologic findings do suggest that, for at least a subset of patients, long-term NA therapy can be stopped before HBsAg seroconversion is achieved, but more studies are needed before these new rules can be safely applied to everyday clinical practice. In other words, we are getting close to developing new HBsAg-based stopping rules for NA-treated patients, but we are not there yet.

Dr Lampertico has served on the advisory boards and/or speaker bureaus for Bristol-Myers Squibb, Roche, Gilead, GlaxoSmithKline, and MSD.

Suggested Reading

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