Current Nucleos(t)ide Analogue Therapy for Chronic Hepatitis B

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Although the prevalence of chronic hepatitis B has decreased considerably in recent years due to widespread use of the hepatitis B virus (HBV) vaccine, its prevalence still remains high in adults, and this can place a significant burden on health care in areas with endemic HBV. Since the introduction of nucleos(t)ide analogues (NUCs), there has been marked improvement in the care of patients with chronic hepatitis B, resulting in increased survival. However, the emergence of drug resistance in patients treated with NUCs is a major concern. The number of multi-drug resistant patients is increasing, and many patients may not respond to the currently available drugs. In this review, we describe the current status of NUC therapy for antiviral-naive and -resistant patients.

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Key Words: Chronic hepatitis B; Nucleos(t)ide analogue; Drug resistance; Hepatitis B virus

INTRODUCTION

Chronic hepatitis B virus (HBV) infection is an important health problem affecting approximately 400 million people worldwide. Chronic HBV infection can progress to cirrhosis, decompensated cirrhosis, hepatocellular carcinoma (HCC), and death. The prevalence of HBV infection has decreased dramatically following widespread use of HBV vaccine in Korea, an endemic area. However, chronic HBV infection is still prevalent in the population in their 20s in Korea, and has remained a significant burden to the health care system. The circulating level of HBV DNA has been proved as the most important correlating factor in the development of cirrhosis and HCC. The suppression of HBV replication can reduce necroinflammatory activity and prevent progression to cirrhosis and HCC. Several nucleos(t)ide analogues (NUCs) have been developed over the past decade, and the administration of NUCs has played a crucial role in the treatment of chronic HBV infection. Despite their potent anti-HBV effects, NUCs cannot eradicate HBV infection, and for this reason, long-term therapy is necessary. The major drawback of long-term monotherapy with NUCs is the emergence of drug resistance. The emergence of resistance limits the efficacy of the antiviral drugs, raising a serious concern in clinical practice. The prevention of drug resistance and selection of appropriate treatment options in the face of drug resistance are important for reducing morbidity and mortality of patients with chronic HBV infection.

GOALS OF TREATMENT

The goal of therapy is to improve survival by preventing progression of chronic hepatitis to cirrhosis, end-stage liver disease or HCC. Short-term goals include reduction in HBV DNA levels, persistent alanine aminotransferase (ALT) normalization, and hepatitis B e antigen (HBeAg) seroconversion. Loss of hepatitis B surface antigen (HBsAg) is an ideal end point, but this rarely occurs. NUCs can not completely eradicate HBV infection as they show little effectiveness in eliminating covalently closed circular DNA in the nucleus of infected hepatocytes. Long-term administration on NUCs is required in order to effectively treat patients with chronic HBV infection.

The European Association for the Study of the Liver (EASL) guidelines suggest that therapy must reduce HBV DNA to as low a level as possible, ideally below the lower limit of detection by the real-time PCR assay. Persistent viremia has been associated with frequent development of antiviral resistance.

DEFINITION OF FAILED RESPONSE AND VIRAL RESISTANCE

1. Primary non-response

Primary non-response is defined as less than a 1 log₁₀ IU/mL.
decrease in HBV DNA level from baseline after 3 months of therapy based on the EASL guidelines. The American Association for the Study of Liver Disease (AASLD) guidelines define primary non-response as failure to achieve a 2 log\(_{10}\) IU/mL decrease in HBV DNA after at least 6 months of therapy (Table 1). It may be due to poor compliance or low antiviral activity. A switch to a more potent drug is recommended for patients with primary non-response.

2. Partial response

The EASL guidelines propose that partial virologic response is defined as a decrease in HBV DNA of more than 1 log\(_{10}\) IU/mL but detectable HBV DNA by real time PCR at week 24 or 48, depending on the genetic barrier of anti-viral drugs (Table 1). If drugs with a high genetic barrier such as entecavir (ETV) or tenofovir (TDF) are being administered, antiviral response can be assessed at week 48. Adefovir (ADV) has delayed antiviral effect. Thus, these patients can also be assessed at week 48. A partial virologic response to antiviral drugs correlates with the risk of promoting antiviral resistance. The serum HBV DNA level at week 24 of therapy was found to be associated with the emergence of antiviral resistance in patients treated with telbivudine (LdT) or lamivudine (LAM). Patients with HBV DNA level >1,000 copies/mL at week 24 of therapy correlated with high rates of resistance when compared to those with a low HBV DNA level. A prospective cohort study of untreated hepatitis B patients showed that the risk for cirrhosis and HCC was higher in patients with HBV DNA levels >10,000 copies/mL compared to those with HBV DNA <10,000 copies/mL. International practice guidelines recommend treating chronic hepatitis B patients with HBV DNA levels >10,000 copies/mL using antiviral drugs. When partial virologic response is identified, antiviral treatment should be modified.

3. Virologic breakthrough

Virologic breakthrough is defined as an increase in serum HBV DNA by >1 log\(_{10}\) copies/mL above nadir after achieving a virologic response during treatment (Table 1). Drug-noncompliance is frequently associated with virologic breakthrough. Therefore compliance should be confirmed at the time of virologic breakthrough. If virologic breakthrough occurs, serum HBV DNA increases progressively despite continuous treatment followed by an elevation in ALT level. A test for genotypic resistance is needed to confirm the diagnosis and select appropriate treatment options. For patients presenting with mild elevation in HBV DNA and normal ALT, additional tests for HBV DNA are also necessary.

**NUCLEOS(T)IDE ANALOGUES**

A number of NUCs have been developed and used for the treatment of patients with chronic HBV infection. NUCs inhibit viral polymerase activity, thus affecting negative strand and positive strand DNA synthesis. LAM, an analogue of dideoxy-cytidine, was the first approved HBV polymerase inhibitor. LAM is the prototype of the L-nucleoside family. The triphosphate form of LAM inhibits nascent viral DNA synthesis. Other NUCs belonging to the L-nucleoside family are entecavir, LdT, and clevudine. ADV and TDF belong to the acyclic D-nucleotide, while ETV to the cyclic D-nucleoside. ADV and TDF are phosphorylated forms of nucleotide analogues. Long-term administration of drugs belonging to the L-nucleoside family is associated with the frequent development of antiviral resistance, when compared to drugs belonging to D-nucleoside analogues (Table 2).

**Table 1. Definition of a Response to Antiviral Therapy for Chronic Hepatitis B**

<table>
<thead>
<tr>
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<th>AASLD*</th>
<th>EASL†</th>
<th>APASL‡</th>
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<tbody>
<tr>
<td>Primary non-response</td>
<td>Decrease in serum HBV DNA by &lt;2 log(_{10}) IU/mL after at least 24 weeks of therapy</td>
<td>Decrease in serum HBV DNA less than 1 log(_{10}) IU/mL from baseline at 3 months of therapy</td>
<td>Reduction of serum HBV-DNA &lt;1 log IU/mL at 12 weeks of oral antiviral therapy in a compliant patient</td>
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<tr>
<td>Partial virological response</td>
<td>Decrease in serum HBV DNA of more than 1 log(_{10}) IU/mL but detectable HBV DNA by real-time PCR assay§</td>
<td>Increase in serum HBV DNA level of more than 1 log(_{10}) IU/mL compared to nadir (lowest level) HBV DNA level on therapy</td>
<td>Increase in serum HBV-DNA by &gt;1 log IU/mL increase in serum HBV-DNA from nadir of initial response during therapy as confirmed 1 month later</td>
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HBV, hepatitis B virus.