

# Antiviral Therapy for Chronic Hepatitis B

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## Abstract

The infection rate of hepatitis B virus is approximately 1% in Japan, and about 1.5 million people are believed to be infected. After infection, some patients go into spontaneous remission and become asymptomatic carriers, while others develop cirrhosis or liver cancer due to repeated cycles of relapse and remission of hepatitis. For this reason, it is vital to determine the treatment needs based on the age, progress, and clinical status of each patient and to select the appropriate therapy method accordingly.

Antiviral treatments for chronic hepatitis B include interferon (IFN) therapy and nucleoside analogues (lamivudine, adefovir, and entecavir (tenofovir is not approved for chronic hepatitis B in Japan at this point)) therapy. Treatment strategies are decided based on the patient age, viral load, presence/absence of HBeAg, and progression of fibrosis. This paper describes the IFN and nucleoside analogue therapies with regard to the therapeutic applicability and effectiveness of each method.

**Key words** Interferon, Nucleoside analogues, Entecavir

## Introduction

In Japan, the hepatitis B virus (HBV) infection rate is approximately 1%, and about 1.5 million people are believed to be infected. Persistent HBV infection is mainly through vertical transmission during perinatal period or horizontal transmission during infancy (up to 3 years of age). After infection, some patients go into spontaneous remission and become asymptomatic carriers, while others develop hepatitis and progress to cirrhosis or liver cancer from repeated cycles of relapse and remission. For this reason, it is vital to determine the treatment needs based on the patient age, progress, and clinical status of each patient and to select the appropriate therapy method accordingly.

Antiviral treatments for chronic hepatitis B include interferon (IFN) therapy and nucleoside analogues (lamivudine, adefovir, and entecavir (tenofovir is not approved for chronic hepatitis B in Japan at this point)). This paper describes

the therapeutic applicability and effectiveness of each method.

## Treatment Strategies for Chronic Hepatitis B

The goal of treating chronic hepatitis B is to improve the condition of liver lesion and control its progression by regulating HBV proliferation. The effectiveness of treatment is determined by normalization of serum transaminase (ALT), negative HBe antigen result or seroconversion (negative result for HBeAg, plus positive result for HBeAb), and/or negative HBV-DNA result.

In the Fiscal Year (FY) 2008, Japanese Ministry of Health, Labour, and Welfare (MHLW) issued guidelines for chronic hepatitis B treatment, which stated that therapeutic strategies are to be determined based on the patient age (cutoff: 35 years old), viral load (cutoff: 7 log copies/mL), and presence/absence of HBeAg (**Tables 1 and 2**).<sup>1</sup> For patients who are 34 years old or

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**Table 1 Guidelines for the chronic hepatitis B treatment in patients aged less than 35 years**

HBe antigen test	HBV-DNA amount	
	≥7 log copies/mL	<7 log copies/mL
Positive	(1) Prolonged IFN administration (24–48 weeks) (2) Entecavir	(1) Prolonged IFN administration (24–48 weeks) (2) Entecavir
Negative	(1) Sequential therapy* (entecavir; continuous IFN therapy) (2) Entecavir	(1) Follow-up (2) Prolonged IFN administration (24 weeks)
For an advanced case with blood platelet count of less than 150,000 or at the fibrosis stage of F2 or higher, treat with entecavir from the beginning.		

The cutoff for treatment when ALT ≥ 31 IU/L:

In HBe-antigen-positive cases, when HBV-DNA amount is 5 log copies/mL or higher,

In HBe-antigen-negative cases, when HBV-DNA amount is 4 log copies/mL or higher, or

In cirrhosis cases, when HBV-DNA amount is 3 log copies/mL or higher.

\*Sequential therapy: When HBV-DNA level falls below a detectable level by the administration of nucleoside analogue(s), administer both IFN and nucleoside analogue(s) for 4 weeks followed by IFN monotherapy for 20 weeks, and then discontinue the medication.

[Extracted from Japanese Study Group of the Standard Antiviral Therapy for Viral Hepatitis (2009): p.9.<sup>1</sup>]

**Table 2 Guidelines for the chronic hepatitis B treatment in patients aged 35 years and over**

HBe antigen test	HBV-DNA amount	
	≥7 log copies/mL	<7 log copies/mL
Positive	(1) Entecavir (2) Sequential therapy* (entecavir; continuous IFN therapy)	(1) Entecavir (2) Prolonged IFN administration (24–48 weeks)
Negative	Entecavir	(1) Entecavir (2) Prolonged IFN administration (24–48 weeks)

The cutoff for treatment when ALT ≥ 31 IU/L:

In HBe-antigen-positive cases, when HBV-DNA amount is 5 log copies/mL or higher,

In HBe-antigen-negative cases, when HBV-DNA amount is 4 log copies/mL or higher, or

In cirrhosis cases, when HBV-DNA amount is 3 log copies/mL or higher.

\*Sequential therapy: When HBV-DNA level falls below a detectable level by the administration of nucleoside analogue(s), administer both IFN and nucleoside analogue(s) for 4 weeks followed by IFN monotherapy for 20 weeks, and then discontinue the medication.

[Extracted from Japanese Study Group of the Standard Antiviral Therapy for Viral Hepatitis (2009): p.10.<sup>1</sup>]

younger and can be expected to go into spontaneous remission, observing case progress through follow-ups is the standard strategy; for those who are not likely to go into spontaneous remission, IFN therapy will be the standard treatment while aiming to become drug-free eventually. For chronic hepatitis B patients aged 35 years or over, IFN therapy is not expected to be particularly effective. Thus, nucleoside analogue therapy using entecavir becomes the first therapy of choice, with the hope of sustained HBV-DNA response.

Furthermore, in cirrhosis patients, there is a

high possibility that the immunostimulatory action of IFN will induce AST/ALT rebound, compromising liver reserve even further. Therefore, regardless of the patient age or presence/absence of HBe antigens, nucleoside analogue therapy with entecavir should be actively considered.

## Antiviral Treatment

### IFN therapy

#### Characteristics of IFN therapy

INF therapy is a treatment method that controls

HBV-DNA proliferation and alleviates hepatic inflammation through immunological mechanisms or direct antiviral actions. In Japan, 24-week administration of IFN  $\alpha$  or IFN  $\beta$  to treat HBe-antigen-positive chronic active hepatitis B is covered by national health insurance. The administration method of IFN  $\alpha$  and  $\beta$  agents differ; IFN  $\alpha$  is injected intramuscularly, whereas IFN  $\beta$  is injected intravenously. In April 2008, the national insurance approved self-injection of IFN  $\alpha$  as a home therapy. Side effects include fever, headache, depression, pancytopenia, loss of appetite, and interstitial pneumonia.

#### **Timing to start IFN therapy**

When HBeAg is positive, HBV-DNA is positive, and ALT level is doubled or higher compared to the normal level, starting IFN therapy immediately after ALT level has exceeded its peak has been shown to be highly effective. A meta-analysis in overseas on IFN therapy (4–6 months) targeting HBeAg-positive chronic hepatitis B patients supports the effectiveness of IFN therapy, reporting that 33% of patients in the group administered with IFN became HBe antigen negative and 37% became HBV-DNA negative, while 12% became HBe antigen negative and 17% became HBV-DNA negative in the control (untreated) group.<sup>2</sup> Additionally, the results of IFN therapy performed in our hospital on HBeAg-positive patients over a 6-month period showed a response rate of 20% (cases in which the patient had become both HBeAg and HBV-DNA negative and also achieved normal ALT levels 6 months after the completion of treatment). Factors contributed to this successful result were the age and ALT level at the time that the therapy began (being 34 years or younger with ALT level of 200 IU/L or higher).<sup>3</sup>

#### **Future outlook**

Two possible means of further enhancing the effectiveness of IFN therapy are the extension of the treatment period (to 12 months) and the use of pegylated interferon (PEG-IFN) therapy. The 12-month administration of IFN to HBeAg-positive patients in our hospital achieved a response rate of 38%, showing a clear improvement over the results of the 6-month treatment (20%). Moreover, PEG-IFN therapy conducted for 48 weeks in overseas has achieved good results, with HBeAg seroconversion rate of 32% and HBV-DNA response rate of 32%.<sup>4</sup> The PEG-IFN therapy is under clinical trials in Japan

as well, and the results are currently awaited with interest.

### **Nucleoside analogue therapy**

#### **Characteristics of nucleoside analogue therapy**

Nucleoside analogues are oral medications. When they are absorbed into blood and enter hepatocytes, they become activated and specifically inhibit the reverse transcription step (synthesis of DNA chains from RNA chains) in hepatitis B virus replication process. Namely, lamivudine, adefovir, and entecavir, each inhibits the extension of DNA chains by resembling dCTP, a dATP, and dGTP, respectively, acting as the antiviral agents.

Compared with the IFN therapy described above, nucleoside analogue therapy is a very revolutionary treatment method. They are simpler to administer for they are oral medications, their effects to control HBV-DNA proliferation are evident, and they have few side effects. However, there are also problems; hepatitis may relapse when the treatment is discontinued, and resistant viruses can emerge as a result of prolonged administration. These problems must be considered before nucleoside analogue therapy is conducted.

#### **Lamivudine**

Lamivudine was the first medication to be approved as a nucleoside analogue agent for treating chronic hepatitis B. In clinical experiments conducted overseas on chronic hepatitis B patients, administration of 100 mg/day of lamivudine for 52 weeks was shown to be significantly effective compared with untreated control group; 73% of subjects achieved ALT normalization, 96% became HBV-DNA negative (<5.7 log copies/mL), and the HBeAg seroconversion rate was 16%.<sup>5</sup>

However, after 6 to 9 months in the course of treatment, lamivudine-resistant virus emerged in many cases, HBV-DNA began proliferating again, and hepatitis recurred. The cumulative emergence rates of lamivudine-resistant virus were 12% at 1 year, 37% at 3 years, and 61% at 5 years, which are rather high. Moreover, there were also severe cases in which the relapse of hepatitis caused by the resistant virus led to liver failure. When the resistant virus emerges, the combination therapy of lamivudine and adefovir, which is described next, must be considered.

#### **Adefovir**

Adefovir is a nucleoside analogue approved

in Japan in 2004 as an effective agent against lamivudine-resistant virus. The most effective method for treating lamivudine-resistant virus is lamivudine/adefovir combination therapy, where 10 mg/day of adefovir is administered while 100 mg/day of lamivudine is maintained. Following the start of adefovir administration, several weeks are required for the viral load to decrease and hepatitis to subside. Thus, in chronic hepatitis cases that are becoming highly fibrotic or are in the early stages of cirrhosis, it is safest to begin administering adefovir immediately if AST/ALT ratio rises even slightly. Particularly in cases with poor liver reserve or cirrhosis (Class B or C in the Child-Pugh classification), it is recommended that adefovir be administered without delay regardless of the presence/absence of hepatitis, if an increase in HBV-DNA level due to the lamivudine-resistant virus is observed.

With regard to the efficacy of lamivudine/adefovir combination therapy against lamivudine-resistant virus, the results in our hospital found 56% of cases to be HBV-DNA negative (<300 copies/mL) at 6 months, 69% at 12 months, and 81% at 24 months. Moreover, ALT normalization rate was 73% at 6 months, 85% at 12 months, and 99% at 24 months. These results confirmed the excellent therapeutic efficacy of this treatment method.<sup>6</sup>

#### Entecavir

Entecavir is a nucleoside analogue approved for insurance coverage in Japan in September 2006 to be used for nucleoside-naïve patients or against cases of lamivudine-resistant virus. In clinical testing conducted overseas on nucleoside-naïve chronic hepatitis B patients, the administration of 0.5 mg/day of entecavir for 52 weeks achieved ALT normalization in 68% of subjects and HBV-DNA response (<300 copies/mL) in 67%, which were significantly effective compared with the results of the lamivudine-administered group (100 mg/day) that showed ALT normalization rate of 60% and HBV-DNA response

rate of 35%.<sup>7</sup>

Furthermore, the results from our hospital using entecavir therapy showed the same excellent therapeutic efficacy as overseas clinical trials. HBV-DNA response rates (<300 copies/mL) were 86% at 6 months and 89% at 12 months, and ALT normalization was achieved in 87% at 6 months and 95% at 12 months. Among the nucleoside-naïve cases, there have been extremely few reports of the emergence of resistant viruses when treated with entecavir therapy as yet. According to the result of the collaborative study among multiple facilities lead by the MHLW research team in FY 2007, the emergence of entecavir-resistant virus was confirmed in 2 of the 383 nucleoside-naïve cases. The cumulative emergence rates were 0% at 1 year, 0% at 2 years, 4% at 3 years, and 8% at 4 years.<sup>8</sup> Compared with the results of lamivudine therapy that are described in earlier section, the emergence of resistant viruses is clearly less frequent in entecavir therapy, and thus entecavir is currently the first nucleoside analogue therapy of choice for nucleoside-naïve patients.

The efficacy of entecavir therapy against lamivudine-resistant virus has been reported in overseas, and it already has been approved for insurance coverage in Japan. However, unlike in nucleoside-naïve cases, entecavir-resistant virus has emerged at a comparatively high rate (53% in 4 years at our hospital) when used for the cases of lamivudine-resistant virus. Therefore, lamivudine/adefovir combination therapy is recommended for the treatment of lamivudine-resistant virus.

#### Conclusion

This paper examined IFN therapy and nucleoside analogue therapy as the treatment of chronic hepatitis B. It is imperative to fully understand the characteristics of each therapy and select the appropriate treatment method for each case.

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