

Figure 1 The incidence of tyrosine-methionine-aspartate-aspartate (YMDD) motif mutant and breakthrough hepatitis was noted in patients with alanine aminotransferase level of  $\leq 20$  (IU/L) (a) Incidence of YMDD mutants over time ( $P=0.0017$ ). (b) Incidence of break through hepatitis over time ( $P<0.0001$ ).

patients in group B, and 80% in 37 patients in group C ( $P=0.002$ ), and that of BTH in the corresponding groups was 7%, 14%, and 57% ( $P<0.001$ ) (Fig. 3a,b).

In patients treated with lamivudine for  $\geq 3$  years, the increased incidence of YMDD motif mutant by HBV DNA (log copies/mL) level was 65% in patients maintaining an HBV DNA level of  $< 2.6$ , 78% in patients maintaining an HBV DNA level of 2.6–5.0, and 92% in patients maintaining an HBV DNA level of  $\geq 5.1$ , and that of BTH in the corresponding groups was 10%, 18%, and 77% ( $P<0.001$ ) (Fig. 4a,b).

The incidence of YMDD motif mutant in  $\geq 3$  years treatment with lamivudine in patients by both ALT

(IU/L) and HBV DNA (log copies/mL) levels during the course of lamivudine treatment was also analyzed (Table 4).

In patients maintaining HBV DNA  $< 2.6$  and ALT  $\leq 20$ , the incidence of YMDD motif mutant and BTH was 38% and 7%, respectively. At the same HBV DNA level of  $< 2.6$  and ALT 21–30, the incidence of YMDD motif mutant was 48% and BTH was 8%; whereas at ALT 31–40, YMDD motif mutant was 36% and BTH was 9%.

In patients maintaining HBV DNA 2.6–5.0 and ALT  $\leq 20$ , the incidence of YMDD motif mutant and BTH was 60% and 4%, respectively. At the same HBV DNA

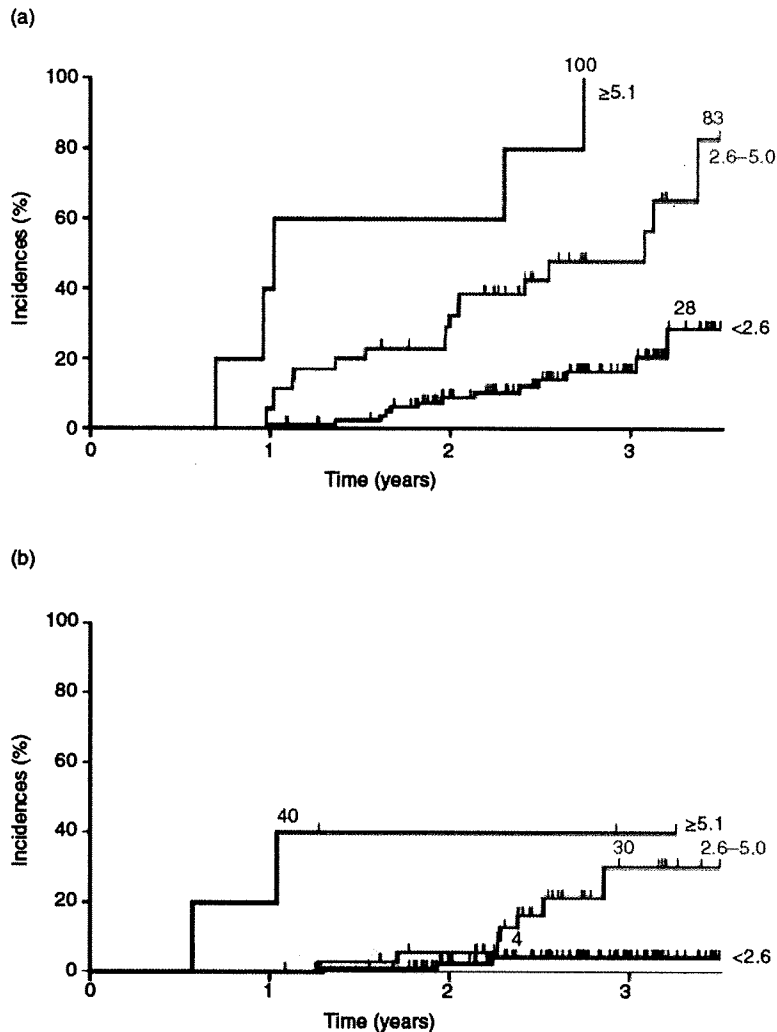


Figure 2 incidence of BTH was 4%, 30%, and 40%, respectively, in patients with HBV DNA level of  $< 2.6$ , 2.6–5.0, and  $\geq 5.1$  log copies/mL ( $P = 0.004$ ). (a) Incidence of YMDD mutants over time ( $P = 0.0001$ ). (b) Incidence of breakthrough hepatitis over time ( $P < 0.0037$ ).

level, 2.6–5.0 and ALT 21–30, the incidence of YMDD motif mutant was 86% and BTH was 18%; whereas at ALT 31–40, YMDD motif mutant was 92% and BTH was 42%.

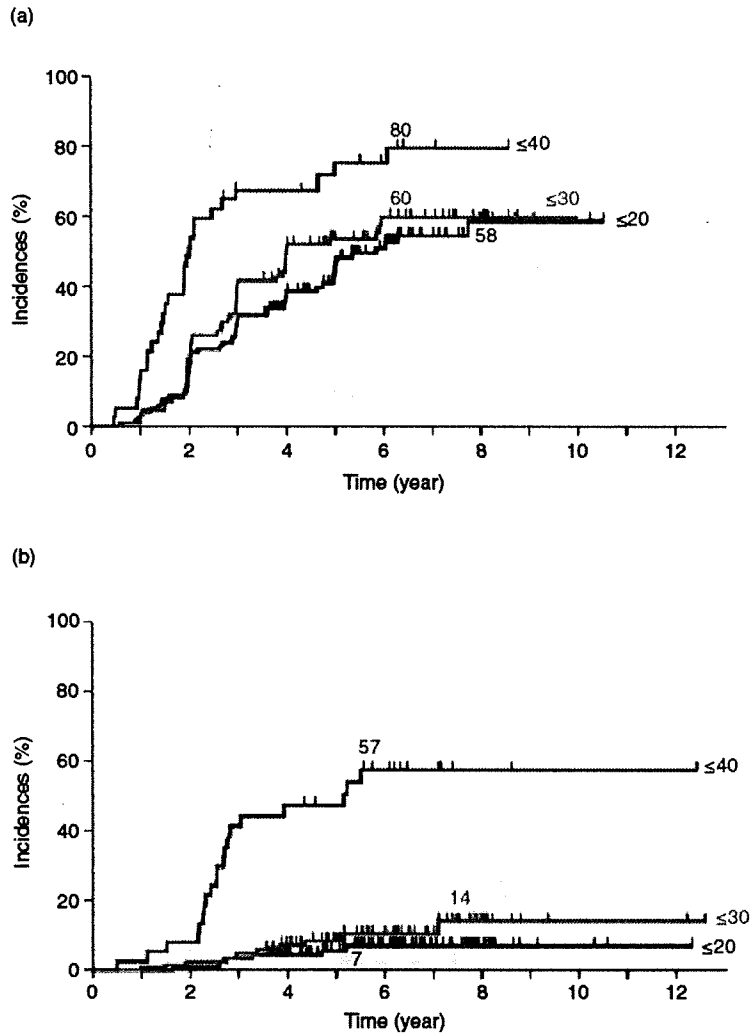
In patients maintaining HBV DNA  $\geq 5.1$  and ALT 31–40, YMDD motif mutant was 93% and BTH was 86%.

## DISCUSSION

LONG-TERM THERAPY for CHBV can lead to the development of HBV drug-resistant mutants. Early detection of the YMDD motif mutants in lamivudine-

treated patients and timely switch to other nucleoside analogues with low viral resistance is crucial to prevent viral and biochemical flares and ineffective therapeutic response. Although development of YMDD mutants results in decreased viral susceptibility to lamivudine, viral replication rate is lower in mutant strains than in wild type.<sup>6</sup>

Among the 359 patients who received lamivudine for  $> 1$  year and maintained an ALT level of  $\leq 40$  IU/L, the rate of YMDD motif mutant was 11% (1 year), 29% (2 year), 42% (3 year), 49% (4 year) and 61% (5 year). BTH occurrences were 3% (1 year), 8% (2 year), 13% (3 year), 15% (4 year) and 19% (5 year). The rate of

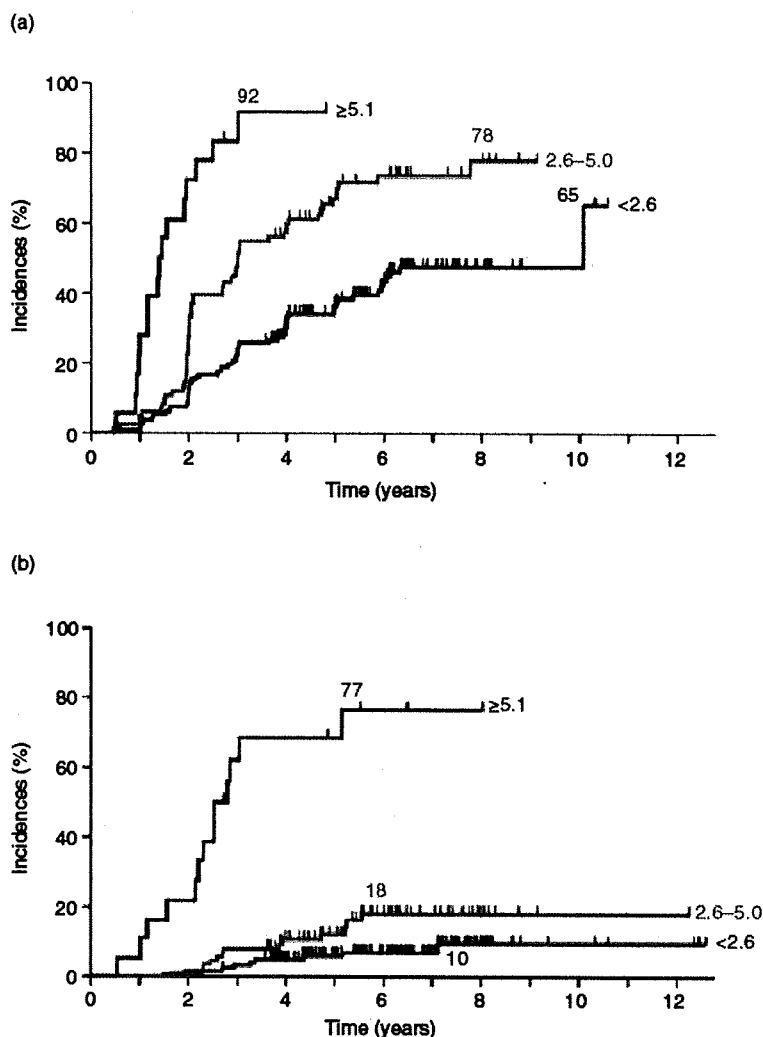


**Figure 3** In patients treated with lamivudine for 3 years or more, the incidence of tyrosine-methionine-aspartate-aspartate (YMDD) motif mutant by alanine aminotransferase (IU/L) level was 58% in 113 patients in group A, 60% in 84 patients in group B, and 80% in 37 patients in group C ( $P=0.002$ ), and that of BTH in the corresponding groups was 7%, 14%, and 57% ( $P<0.001$ ). (a) Incidence of YMDD mutants over time ( $P=0.0015$ ). (b) Incidence of breakthrough hepatitis over time ( $P<0.0001$ ).

YMDD motif mutant and BTH were low after 3 or more years of treatment with lamivudine. Therefore, the year of switching treatment from lamivudine to other nucleic acid analogue will be at 3 years. Accordingly, in this study, we examined patients treated with lamivudine for  $< 3$  and  $\geq 3$  years.

Among the patients treated with lamivudine for  $< 3$  years, the lowest incidence of YMDD motif mutant and BTH was seen in patients with ALT  $< 20$  IU/L maintaining HBV DNA level of 2.6-5.0. The other category for lowest incidence was in patients with ALT 21-30 IU/L and HBV DNA level of  $< 2.6$  log copies/mL. In this study, within 3 years of treatment with lamivu-

dine, the group of patients with the recommended HBV DNA ( $< 2.6$  log copies/mL) and ALT maintained at 21-30 IU/L may be considered eligible to be switched to entecavir therapy as per Japanese guidelines. We, however, believe it is important to consider the prognosis for patients who are switched from lamivudine to entecavir. Similarly, in patients maintaining HBV DNA level in the range of 2.6-5.0 log copies/mL and ALT  $< 20$  IU/L, switching to dual therapy with adefovir in combination with lamivudine depends on the related viral breakthrough. In a study by Li Zhou *et al.*,<sup>16</sup> some patients with YMDD motif mutants had significantly lower HBV DNA and ALT levels compared with baseline



**Figure 4** In patients treated with lamivudine for  $\geq 3$  years, the increased incidence of tyrosine-methionine-aspartate-aspartate (YMDD) motif mutant by hepatitis B virus (HBV) DNA (log copies/mL) level was 65% in patients maintaining an HBV DNA level of  $< 2.6$ , 78% in patients maintaining an HBV DNA level of 2.6–5.0, and 92% in patients maintaining an HBV DNA level of  $\geq 5.1$ , and that of BTH in the corresponding groups was 10%, 18%, and 77% ( $P < 0.001$ ). (a) Incidence of YMDD mutants over time ( $P = 0.0001$ ). (b) Incidence of breakthrough hepatitis over time ( $P < 0.0001$ ).

values, which might be due to decreased replication efficiency of the HBV mutants.

HBeAg, severe liver disease, high HBV DNA, and low ALT levels at the baseline were factors accelerating the development of BTH. This was in confirmation of previous results.<sup>17–19</sup> Development of BTH, however, was not influenced by HBV genotypes. This is probably due to the response in HBeAg-positive patients, which was comparable among those with different genotypes though it differed among HBeAg-negative patients.<sup>20</sup>

In a study of Japanese adult patients treated with lamivudine for  $> 12$  months, the YMDD motif mutation was detected in 26% patients, with 23, 16, and 21 patients

correspondingly positive for YIDD, YVDD, and YIDD + YVDD mutants. The occurrence of mutations steadily increased and two, five, and 52 patients with genotypes A, B, and C, respectively developed resistance.<sup>21</sup> Lamivudine retreatment could induce rapid re-emergence of YMDD motif mutants with associated viral and hepatic flares<sup>22</sup> and should be avoided. Next, we were interested to know if any difference in sensitivity existed in detecting YMDD mutants by the two different methods used in this study, PCR-RFLP and PCR-ELMA. We studied the rate of detection of YMDD motif mutant by both methods in 20 patients who received lamivudine for more than two years. The detection rate

Table 4 Incidences of tyrosine-methionine-aspartate-aspartate (YMDD) mutant and breakthrough hepatitis (BTH) by hepatitis B virus (HBV) DNA and alanine transaminase (ALT) level in patients during lamivudine treatment for  $\geq 3$  years (234 patients)

HBV DNA† (Amplicor: log copies/mL)	ALT level (IU/L)†					
	$\leq 20$		21-30		31-40	
	YMDD	BTH	YMDD	BTH	YMDD	BTH
< 2.6	23/60 (38%)	4/60 (7%)	29/61 (48%)	5/61 (8%)	4/11 (36%)	1/11 (9%)
2.6-5.0	30/50 (60%)	2/50 (4%)	19/22 (86%)	4/22 (18%)	11/12 (92%)	5/12 (42%)
$\geq 5.1$	3/3 (100%)	1/3 (33%)	0/1 (0%)	0/1 (0%)	13/14 (93%)	12/14 (86%)

†The HBV DNA and ALT levels are shown based on the treatment duration of lamivudine.

between PCR-RFLP and PCR-ELMA was similar; eight patients (40%) and nine patients (45%), respectively.<sup>23</sup>

## CONCLUSION

CORRELATION OF ALT and HBV DNA levels with YMDD motif mutant and viral breakthrough can be used as an indirect method of estimating susceptibility to develop lamivudine resistance. The low incidence of YMDD motif mutant and BTH associated with an HBV DNA level of < 2.6 log copies/mL and ALT level of  $\leq 30$  IU/L and an HBV DNA level of 2.6-5.0 log copies/mL and ALT level of  $\leq 20$  IU/L during only less than 3 year-treatments can be utilized as a clinically relevant tool to monitor patients' criteria in switching to other nucleoside analogue drugs. Using these simple methods, which can be easily pursued in clinical practice, it may be feasible in the future to switch from lamivudine to other nucleoside analogue drugs with low rates of inducing resistant mutants in CHBV patients. This is important considering the risk of continuous lamivudine treatment causing YMDD motif mutant and BTH.

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## Review Article

## Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis B virus infection for the fiscal year 2008 in Japan

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In the 2008 guidelines for the treatment of patients with cirrhosis, who are infected with hepatitis B virus (HBV), the main goal is to normalize levels of alanine and aspartate aminotransferases by eliminating HBV or reducing viral loads. In patients with compensated cirrhosis, the clearance of HBV from serum is aimed for by entecavir, as the main resort, for histological improvement toward the prevention of hepatocellular carcinoma (HCC). In patients with decompensated cirrhosis, by contrast, meticulous therapeutic strategies are adopted for the reversal to compensation, toward the eventual goal of decreasing the risk of HCC. For maintaining liver function and preventing HCC, branched chain amino acids and nutrient supplements are applied, in addition to conventional liver supportive therapies. For patients with chronic hepatitis B, separate guidelines are applied to those younger than 35 years and those aged 35 years or older. Even for patients

with chronic hepatitis who are negative for hepatitis e antigen (HBeAg), but who harbor HBV DNA in titers of 7 log copies/mL or more, a “drug-free state” is aimed for by sequential treatment with interferon (IFN) plus entecavir as the first line. For patients with chronic hepatitis B aged 35 years or older, who are HBeAg-negative and carry HBV DNA in titers of less than 7 log copies/mL, long-term IFN for 24–48 weeks is adopted anew. To HBeAg-negative patients who have either or both platelet counts of less than  $150 \times 10^3/\text{mm}^3$  and less than 7 log copies of HBV DNA, also, long-term IFN for 24–48 weeks is indicated.

**Key words:** chronic hepatitis, cirrhosis, hepatitis B virus, hepatocellular carcinoma, interferon, liver supportive therapies, nucleos(t)ide analogs

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## INTRODUCTION

SINCE THE FISCAL year 2002, guidelines for the treatment of patients with viral hepatitis have been compiled annually by the Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis, under the auspice of the Ministry of Health, Labor and Welfare of Japan, supported by enduring efforts of many specialists recruited from all over the nation. Guidelines have been improved every year with many supplementary issues, which had surfaced as our understanding of many facets of viral hepatitis deepened and treatment options widened increasingly with time. For the fiscal year 2008, guidelines have been worked out for a comprehensive standardization of the treatment of chronic hepatitis and cirrhosis due to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in Japan. These guidelines have been observed by more than 70% of practicing hepatologists treating patients with viral liver disease in Japan. It is hoped that these guidelines will continue being widely accepted and implemented to help as many patients as possible who are suffering from sequelae of persistent hepatitis virus infections.

Here, we relate excerpts of the 2008 guidelines for the treatment of patients with liver disease due to HBV, covering a wide range from those with chronic hepatitis to those with decompensated cirrhosis. The 2008 guidelines for the treatment of liver disease due to HCV are reported in an accompanying paper.

## GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS B

PATIENTS WITH CHRONIC hepatitis B can stabilize the activity of liver disease in their natural course, after they have seroconverted from hepatitis B e antigen (HBeAg) to the corresponding antibody (anti-HBe), accompanied by decrease in HBV DNA titers. For that reason, treatment guidelines were constructed separately for the patients younger than 35 years and those aged 35 years or older.

## GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS B YOUNGER THAN 35 YEARS

PATIENTS WITH CHRONIC hepatitis B younger than 35 years are treated in accordance with the guidelines summarized in Table 1. Criteria for the treatment eligibility are: (i) serum levels of alanine aminotransferase (ALT) of 31 IU/L or more; and (ii) HBV DNA titers of 5 log copies of more in HBeAg-positive patients and 4 log copies or more in HBeAg-negative patients. In the 2008 guidelines, the indication of treatment is extended to the patients with cirrhosis due to HBV who carry HBV DNA in titers of 3 log copies/mL or more.

In Japan, most HBeAg-positive patients with 7 log copies or more of HBV DNA have been infected with HBV of genotype C by perinatal infection at birth;

**Table 1** Guidelines for the treatment of patients with chronic hepatitis B younger than 35 years

Eligibility criteria	ALT	≥31 IU/L
	HBV DNA	HBeAg-positive patients: ≥5 log copies/mL HBeAg-negative patients: ≥4 log copies/mL Patients with cirrhosis: ≥3 log copies/mL
HBV DNA	≥7 log copies/mL	<7 log copies/mL
HBeAg-positive	(1) Long-term IFN for 24–48 weeks (2) Entecavir	(1) Long-term IFN for 24–48 weeks (2) Entecavir
HBeAg-negative	(1) Sequential treatment† (entecavir plus IFN) (2) Entecavir Start with entecavir in HBeAg-negative patients who have platelet counts <15 × 10 <sup>3</sup> /mm <sup>3</sup> and in those with advanced liver disease of stage F2 or higher.	(1) Regular follow up (2) Long-term IFN for 24 weeks

†Sequential treatment: patients who have lost hepatitis B virus (HBV) DNA after treatment with nucleos(t)ide analogs receive combined interferon (IFN) for 4 weeks, and then IFN monotherapy is continued for 20 weeks, and lifted thereafter. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen.

**Table 2** Guidelines for the treatment of patients with chronic hepatitis B aged 35 years or older

Eligibility criteria	ALT	≥31 IU/L
	HBV DNA	HBeAg-positive patients: ≥5 log copies/mL HBeAg-negative patients: ≥4 log copies/mL Patients with cirrhosis: ≥3 log copies/mL
HBV DNA	≥7 log copies/mL	<7 log copies/mL
HBeAg-positive	(1) Entecavir (2) Sequential treatment† (entecavir plus IFN)	(1) Entecavir (2) Long-term IFN for 24–48 weeks
HBeAg-negative	Entecavir	(1) Entecavir (2) Long-term IFN for 24–48 weeks

†Sequential treatment: patients who have lost hepatitis B virus (HBV) DNA after treatment with nucleos(t)ide analog receive combined interferon (IFN) for 4 weeks, and then IFN monotherapy is continued for 20 weeks, and lifted thereafter. ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen.

accordingly, they would be resistant to interferon (IFN) therapy. Should they receive nucleos(t)ide analogs, however, the duration would become inevitably longer, because they start the treatment when younger than 35 years old. Hence, IFN for 24–48 weeks is the first choice in their treatment. The standard treatment of 3 months is favored, which can be extended to the maximum of 6 months. Non-pegylated (standard) IFN- $\alpha$  is recommended to them, because self-injection at home is approved for preparations of IFN- $\alpha$ ; it helps improve their quality of life (QOL). There are many patients who are refractory to IFN and in whom improvement of ALT levels and/or decrease in HBV DNA titers are hardly achievable. Therefore, as another option, monotherapy with entecavir can be applied for the purpose of clearing HBeAg from serum and lowering HBV DNA titers. For HBeAg-positive patients with lower HBV DNA titers (<7 log copies/mL), also, long-term IFN is endorsed as a rule.

There are HBeAg-negative patients in whom ALT levels increase to 31 IU/mL or more repeatedly. In the 2008 guidelines, sequential treatment with IFN and entecavir is introduced as a new arm of therapeutic options for such patients.<sup>1</sup>

For HBeAg-negative patients with less than 7 copies/mL of HBV DNA, in general, regular follow up without therapeutic intervention is deemed to suffice for the majority. For those of them in whom ALT levels flare to 31 IU/mL or more time after time, long-term IFN for 24 weeks is indicated. Because liver disease progresses in many HBeAg-negative patients, for those with platelet counts of less than  $150 \times 10^3/\text{mm}^3$  or in fibrosis stage F2 or higher, treatment with entecavir is indicated.

### GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS B AGED 35 YEARS OR OLDER

**T**ABLE 2 SUMS up treatment modalities for patients with chronic hepatitis B who are aged 35 years or older. HBeAg-positive patients in this age range who carry HBV DNA in titers of 7 log copies/mL or more rarely, if ever, seroconvert to the loss of HBeAg by IFN-based therapies. Hence, entecavir is the first choice in their treatment.<sup>2,3</sup> Because HBV mutants resistant to entecavir can be elicited by it, sequential treatment with IFN plus entecavir is amended in the 2008 guidelines.<sup>1</sup> In view of low viral loads in patients who possess HBV DNA in titers of less than 7 log copies/mL, entecavir is selected as the first choice, followed by long-term IFN as the second choice of treatment in these patients. HBeAg-negative patients who have high viral loads (≥7 log copies/mL), on the other hand, can normalize ALT levels by monotherapy with entecavir. Therefore, entecavir becomes their first choice, and this is the case even in patients with HBV DNA titers less than 7 copies/mL.

### GUIDELINES FOR THE TREATMENT WITH NUCLEOS(T)IDE ANALOGS OF PATIENTS WITH CHRONIC HEPATITIS B WHO ARE RECEIVING LAMIVUDINE

**T**ABLE 3 DETAILS guidelines for the treatment with nucleos(t)ide analogs of patients with chronic hepatitis B who are receiving lamivudine. Because a number of drug-resistant HBV mutants emerge increasingly with time in patients on long-term treatment with lamivudine, the fundamental rule is to switch them to ente-

**Table 3** Guidelines for the treatment with nucleos(t)ide analogs in patients with chronic hepatitis who are receiving lamivudine

Lamivudine	Less than 3 years	3 years or longer
HBV DNA		
<1.8 log copies/mL persistently	May be switched to entecavir 0.5 mg daily	Continued on lamivudine
≥1.8 log copies/mL	VBT (-) May be switched to entecavir 0.5 mg daily VBT (+) Adefovir 10 mg daily add-on lamivudine	100 mg daily Adefovir 10 mg daily add-on lamivudine

HBV, hepatitis B virus; VBT, virological breakthrough.

cavir. For this reason, patients are stratified by the duration of lamivudine treatment, less than 3 years and 3 years or more, as well as HBV DNA titers persistently below 1.8 log copies/mL and 1.8 log copies/mL or more, and separate treatment strategies have been worked out for the patients in each category. Because by far the majority of patients with a duration of lamivudine treatment of less than 3 years and HBV DNA titers of less than 1.8 log copies/mL possess drug-resistant mutants in low frequencies, they are recommended to switch to entecavir 0.5 mg daily as soon as possible. Likewise, patients who have received lamivudine for 3 years or longer, but in whom drug-resistant mutants have never developed, are recommended to switch to entecavir 0.5 mg daily. By contrast, for patients in whom drug-resistant mutants have emerged already and who have undergone virological breakthroughs,<sup>4</sup> adefovir 10 mg daily add-on lamivudine is started for the purpose of stabilizing liver function.<sup>5</sup> In regard of the patients who have received lamivudine for 3 years or longer, those without drug-resistant mutants can stay on lamivudine 100 mg daily.

#### SUPPLEMENTS TO GUIDELINES FOR THE TREATMENT OF CHRONIC HEPATITIS B (PART I)

FOR THE FISCAL year 2008, the following three items have been added to previous guidelines for the treatment of chronic hepatitis B (Table 4).

1 In the treatment of patients with chronic hepatitis B, IFN is the first resort for those younger than 35 years, toward the eventual goal of gaining a "drug-free state". For the patients aged 35 years or older, persistently negative HBV DNA is the aim of nucleos(t)ide analogs, with the first choice being entecavir in their primary treatment. On the other hand, for patients with HBV mutants resistant to lamivudine and/or entecavir, combined treatment with adefovir and lamivudine is the principal rule (Table 3).<sup>6-8</sup>

2 Therapeutic responses to antiviral treatment are much different in patients with chronic hepatitis B who are infected with HBV of distinct genotypes. It is recommended therefore to determine HBV genotypes before making a decision on the treatment choice. In particular, the patients infected with HBV of genotype A or B respond to IFN in high rates, even if they are aged 35 years or older. For these reasons, IFN becomes the first choice in their antiviral treatment.

3 The duration of IFN treatment is 24 weeks basically. In the patients in whom the efficacy of IFN has been achieved with decrease in HBV DNA titers and normalization of ALT, the treatment duration is better extended to 48 weeks.

**Table 4** Supplements to guidelines for the treatment of patients with chronic hepatitis B (part I)

- 1 Treatment of patients with chronic hepatitis B aims at a "drug-free state" by IFN-based therapies in those younger than 35 years, and at persistently negative HBV DNA in those aged 35 years or older, with entecavir as the first choice in the primary therapy. Lamivudine plus adefovir forms the basis for the treatment of HBV mutants resistant to lamivudine or entecavir.
- 2 In view of antiviral response much different in patients infected with HBV of distinct genotypes, it is desired to make treatment choices based on genotypes. In particular, because genotypes A and B respond to IFN with high efficacy, even in patients aged 35 years or older, IFN is recommended as the first treatment choice in these patients.
- 3 The duration of IFN is for 24 weeks basically, but extension to 48 weeks is recommended in patients who respond to IFN with decrease in HBV DNA titers and normalization of ALT levels.

ALT, alanine aminotransferase; HBV, hepatitis B virus; IFN, interferon.

**Table 5** Supplements to guidelines for the treatment of patients with chronic hepatitis B (part II)

- Self-injection of IFN at home is recommended to patients, who are eligible to do it, for improving their quality of life.
- Treatment with nucleos(t)ide analogs should be continued in patients in whom cirrhosis or HCC has been cured.
- Antiviral treatment is considered in patients with ALT levels of  $\geq 31$  IU/L. To patients aged 35 years or older in whom viral replication persists, even to those with normal ALT levels, antiviral treatments are indicated. It is possible, however, to follow for outcomes in patients who are elderly or HBeAg-negative and in whom antiviral treatments are difficult, while they receive liver supportive therapy (e.g. SNMC, UDCA).
- In patients co-infected with HBV and HIV, entecavir cannot be used due to the possibility for emergence of HIV variants resistant to antiretroviral therapies.
- Immunosuppressive and anticancer drugs should be used with utmost caution, even in patients with low HBV DNA titers and normal ALT levels, because they can induce severe liver damage along with elevation in HBV DNA titers.

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN, interferon; SNMC, stronger neo-minophagen C; UDCA, ursodeoxycholic acid.

### SUPPLEMENTS TO GUIDELINES FOR THE TREATMENT OF CHRONIC HEPATITIS B (PART II)

FURTHER, THE FOLLOWING five supplements have been added to the 2008 guidelines (Table 5).

To patients who are eligible, self-injection of IFN at home is recommended, taking into consideration their QOL. Because IFN-based therapies are not recommended for patients in whom HBV has been transmitted by perinatal infection, sequential treatment with IFN plus entecavir serves as another option in their antiviral treatment.

Treatment with nucleos(t)ide analogs should be extended to patients in whom cirrhosis or hepatocellular carcinoma (HCC) has been cured after successful therapies.

Antiviral treatment has to be considered in patients with ALT levels of 31 IU/L or more. Patients aged 35 years or older with normal ALT levels but in whom HBV replication persists, need to be considered for antiviral treatments. Elderly and HBeAg-negative patients, as well as those to whom the administration of antiviral drugs is difficult, can be followed regularly while they

receive liver supportive therapy (e.g. stronger neo-minophagen C,<sup>9</sup> ursodeoxycholic acid [UDCA]<sup>10</sup>).

Patients co-infected with HBV and HIV type 1 cannot receive entecavir due to the possibility of emergence of HIV mutants resistant to antiretroviral drugs.

Even in patients with low HBV DNA titers and normal ALT levels, HBV DNA loads can increase massively to induce severe liver damages in them, while they receive immunosuppressive or anticancer drugs. Hence, utmost caution should be exercised if they are to undergo antiviral treatments.

### GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CIRRHOSIS DUE TO HBV

TABLE 6 SUMMARIZES guidelines for the treatment of patients with type B cirrhosis. Patients with compensated or decompensated cirrhosis, who are infected with HBV, receive entecavir for persistent clearance of HBV DNA detectable by the real-time polymerase chain reaction and normalization of aspartate aminotransferase as well as ALT levels. Combined lamivudine plus adefovir therapy are indicated for patients in whom HBV mutants resistant to lamivudine or entecavir have developed. Guidelines for maintaining liver function, for preventing the development of HCC, include liver supportive therapy with glycyrrhizin and UDCA, either alone or in combination. For treatment toward sup-

**Table 6** Guidelines for treatment of type B cirrhosis

#### Principles

Compensated: termination of HBV infection by antiviral treatment with entecavir as the mainstay.

Decompensated: reversal to compensation and prevention of HCC.

#### Methods

- (1) Eradication of HBV and normalization of ALT/AST (compensated and decompensated cirrhosis).
  - a) Entecavir.
  - b) Combined lamivudine and adefovir (for patients with HBV mutants resistant to lamivudine or entecavir).
- (2) Maintenance of liver function (improvement of ALT/AST and albumin) for preventing HCC.
  - a) Liver supportive therapy such as SNMC or UDCA.
  - b) Branched chain amino acids (Livact).
- (3) Supplementation with nutrients (for stabilizing liver function in decompensated cirrhosis).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; SNMC, stronger neo-minophagen C; UDCA, ursodeoxycholic acid.

pressing the development of HCC, branched chain amino acids (BCAA)<sup>11</sup> are implemented. Also, nutrient supplements are utilized for stabilizing liver function.

## DISCUSSION AND CONCLUSION

THE STUDY GROUP for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis, organized by the Ministry of Health, Labor and Welfare of Japan, has compiled a series of guidelines for the treatment of liver disease due to HBV and HCV ranging from chronic hepatitis to cirrhosis of various severities annually, since the fiscal year 2002. The principal aim of these guidelines is to decrease the incidence of HCC due to hepatitis virus infections in Japan. In accordance with this principle, supplements have been added to previous guidelines for the standardization of treatment of chronic viral liver disease every fiscal year. This article summarizes guidelines for the treatment of liver disease due to HBV. Guidelines for the treatment of liver disease due to HCV for the fiscal year 2008 are reported in the accompanying paper. They are formulated on evidence-based data that have been accumulated by members and cooperators of the study group. It will be necessary to improve these guidelines in the next fiscal year and henceforth, in accordance with many pieces of new evidence that are expected to evolve through enduring efforts and keen insights of members and cooperators of the study group.

In the treatment of chronic hepatitis B, novel therapeutic strategies have continued to evolve in previous guidelines. In guidelines of the fiscal year 2008, diverse new treatment arms are introduced for gaining the eventual goal of the "drug-free state".

The Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis has been drafted and displayed on the web site ([www.jsh.or.jp/medical/index.html](http://www.jsh.or.jp/medical/index.html) [in Japanese]) as well, guidelines for the treatment of a spectrum of liver diseases due to HBV, ranging from chronic hepatitis to cirrhosis of various severities for the fiscal year 2008. In view of the eventual goal of decreasing the incidence of HCC due to HBV infection, supplementation and adjustment are appended to previous guidelines, and new guidelines have been introduced to the treatment of cirrhosis due to HBV infection. As a general rule, antiviral treatments are the mainstay in guidelines for the treatment of chronic hepatitis B. In addition to them, it is necessary to always keep in mind the fundamental concepts of these guidelines. It is our sincere hope that, for the treatment of each patient, readers will conduct their

clinical practice on the basis of these concepts, and then refer to appropriate individual guidelines, when they make decisions regarding treatment strategy, on a case-by-case basis. With respect to guidelines for the treatment of patients with cirrhosis, above all, expected achievable outcomes have to be taken into account in making treatment choices.

We can foretell that there is no end to the treatment of patients with chronic hepatitis and cirrhosis due to HBV, as it will keep evolving and improving in future guidelines. The enduring efforts of doctors and scientists, in pursuit of this goal, will fill in wide social and economic gaps in medical practices being served to the nation, and produce substantial and efficient interest in the medical economy on a national basis. In conducting treatment of patients with liver disease due to HBV infection, according to these guidelines, many new and unforeseen facets may surface that will require further improvements. Hence, it will be necessary to evaluate the therapeutic efficacy of these guidelines, and revise or add necessary supplements to them as required in the future.

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Review Article

## Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan

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In the 2008 guidelines for the treatment of patients with chronic hepatitis C, pegylated interferon (Peg-IFN) combined with ribavirin for 48 weeks are indicated for treatment-naïve patients infected with hepatitis C virus (HCV) of genotype 1. Treatment is continued for an additional 24 weeks (72 weeks total) in the patients who have remained positive for HCV RNA detectable by the real-time polymerase chain reaction at 12 weeks after the start of treatment, but who turn negative for HCV RNA during 13–36 weeks on treatment. Re-treatment is aimed to either eradicate HCV or normalize transaminase levels for preventing the development of hepatocellular carcinoma (HCC). For patients with compensated cirrhosis, the clearance of HCV RNA is aimed toward improving histological damages and decreasing the development of HCC. The recommended therapeutic regimen is the initial daily dose of 6 million international units (MIU) IFN continued for 2–8 weeks

that is extended to longer than 48 weeks, if possible. IFN dose is reduced to 3 MIU daily in patients who fail to clear HCV RNA by 12 weeks for preventing the development of HCC. Splenectomy or embolization of the splenic artery is recommended to patients with platelet counts of less than  $50 \times 10^3/\text{mm}^3$  prior to the commencement of IFN treatment. When the prevention of HCC is at issue, not only IFN, but also liver supportive therapy such as stronger neo-minophagen C, ursodeoxycholic acid, phlebotomy, branched chain amino acids (BCAA), either alone or in combination, are given. In patients with decompensated cirrhosis, by contrast, reversal to compensation is attempted.

**Key words:** chronic hepatitis, cirrhosis, hepatocellular carcinoma, hepatitis C virus, interferon, liver supportive therapy, pegylated interferon, ribavirin

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## INTRODUCTION

SINCE THE FISCAL year 2002, guidelines for the treatment of patients with viral hepatitis have been compiled annually by the Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis, under the auspice of the Ministry of Health Labor and Welfare of Japan, recruiting many specialists from all over the nation. They have been improved every year with many supplementary issues that have evolved, as our understanding of various aspects of viral hepatitis deepens and treatment options widen with time. For the fiscal year 2008, guidelines have been worked out for a comprehensive standardization of the treatment of chronic hepatitis and cirrhosis due to infection with hepatitis C virus (HCV) in Japan. It is hoped that these guidelines will be accepted widely and implemented for helping as many patients as possible who suffer from sequelae of persistent HCV infection.

Here, we relate excerpts of the 2008 guidelines for the treatment of patients with HCV-induced liver disease covering a wide range from those with normal aminotransferase levels to those with decompensated cirrhosis.

## GUIDELINES FOR THE PRIMARY TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS C

TABLE 1 SUMMARIZES the antiviral therapy of treatment-naive patients with chronic hepatitis C. In comparison with previous guidelines, the duration of combined treatment with pegylated interferon (Peg-IFN) and ribavirin is extended to 48–72 weeks for patients infected with HCV of genotype 1 in high viral loads (HVL:  $\geq 5$  log IU/mL by the Japanese criteria).<sup>1,2</sup> For patients infected with HCV of genotype 2 in HVL, Peg-IFN- $\alpha 2b$  and ribavirin for 24 weeks are indicated.

To patients with HCV-1 in low viral loads (LVL:  $< 5$  log IU/mL), either the standard IFN (not conjugated with polyethylene glycol) for 24 weeks, or the weekly monotherapy with Peg-IFN- $\alpha 2a$  for 24–48 weeks, is given.<sup>3</sup> Patients with HCV-2 in LVL receive either the standard IFN for 8–24 weeks, or the weekly monotherapy with Peg-IFN- $\alpha 2a$  for 24–48 weeks.

## GUIDELINES FOR THE RE-TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS C

FOR PATIENTS WHO receive re-treatment, first, it is imperatively prerequisite to: (i) identify factors for non-response to previous treatments; and (ii) decide whether to aim for clearance of HCV or to prevent the progression of hepatitis that can accelerate the development of hepatocellular carcinoma (HCC), and this can be monitored by alanine aminotransferase (ALT) and  $\alpha$ -fetoprotein (AFP) levels toward normalizing or stabilizing their levels (Table 2).<sup>4</sup> Second, IFN combined with ribavirin is the mainstay of re-treatment of patients with chronic hepatitis C. Third, long-term IFN monotherapy is recommended to patients who are not indicated to IFN/ribavirin or who have failed to respond to the combination therapy. However, some patients do not tolerate IFN due to side-effects or their complicating morbidities. In addition, IFN monotherapy does not always improve ALT levels. Such patients need to receive liver supportive therapy including stronger neominophagen C (SNMC)<sup>5</sup> and ursodeoxycholic acid (UDCA),<sup>6</sup> as well as phlebotomy, either alone or in combination. Therapeutic target ALT levels are: (i) within  $\times 1.5$  the upper limit of normal (ULN) for patients in fibrosis stage 1 (F1); and (ii) less than 30 IU/L in those in fibrosis stages 2 or 3 (F2/F3), as far as possible.

Table 1 Guidelines for the primary treatment of patients with chronic hepatitis C

Genotypes	Genotype 1	Genotype 2
Viral loads		
High viral load $\geq 5.0$ log IU/mL $\geq 300$ fmol/L $\geq 1$ Meq/mL	<ul style="list-style-type: none"> <li>• Peg-IFN-<math>\alpha 2b</math> (Peg-Intron) + ribavirin (Rebetol) for 48–72 weeks</li> <li>• Peg-IFN-<math>\alpha 2a</math> (Pegasys) + ribavirin (Copegus) for 48–72 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Peg-IFN-<math>\alpha 2b</math> (Peg-Intron) + ribavirin (Rebetol) for 24 weeks</li> </ul>
Low viral load $< 5.0$ log IU/mL $< 300$ fmol/L $< 1$ Meq/mL	<ul style="list-style-type: none"> <li>• Standard IFN for 24 weeks</li> <li>• Peg-IFN-<math>\alpha 2a</math> (Pegasys) for 24–48 weeks</li> </ul>	<ul style="list-style-type: none"> <li>• Standard IFN for 8–24 weeks</li> <li>• Peg-IFN-<math>\alpha 2a</math> (Pegasys) for 24–48 weeks</li> </ul>

Peg-IFN, pegylated interferon.

**Table 2** Guidelines for re-treatment of chronic hepatitis C**Principles**

Selection has to be made between termination of HCV infection and normalization/stabilization of ALT as well as AFP levels (toward preventing aggravation of liver disease and development of HCC), after evaluating factors for non-response in the primary IFN treatment.

- 1 "IFN plus ribavirin" is the mainstay of re-treatment of patients who have failed to respond to the primary IFN therapy.
- 2 Long-term IFN is recommended to patients in whom ribavirin is not indicated or who have failed to respond to IFN/ribavirin; self-injection at home is approved for IFN- $\alpha$  (not for Peg-IFN).
- 3 Patients who are not indicated to IFN or have failed to improve ALT and AFP levels, in response to IFN, receive liver supportive therapy (SNMC, UDCA) and phlebotomy, either alone or in combination.
- 4 For preventing aggravation of liver disease (and development of HCC), ALT levels need to be controlled within  $1.5 \times \text{ULN}$  in patients in stage 1 fibrosis (F1), and as far as possible, 30 IU/L or lower in those in fibrosis stages 2–3 (F2/F3).
- 5 In treatment combined with ribavirin, dose and mode need to be selected, taking into consideration factors contributing to the response, such as age, sex, progression of liver disease, mutations in the HCV genome (amino acid substitutions in the core protein [aa70/aa91] and ISDR) and HCV RNA titers determined by the real-time PCR.

AFP,  $\alpha$ -fetoprotein; ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ISDR, interferon sensitivity determining region; PCR, polymerase chain reaction; Peg-IFN, pegylated interferon; SNMC, stronger neo-minophagen C; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

### SUPPLEMENTS TO GUIDELINES FOR THE TREATMENT OF CHRONIC HEPATITIS C

FOR THE FISCAL year 2008, the following items were supplemented to the treatment of chronic hepatitis C (Table 3).

- 1 The treatment of patients infected with HCV-1 in HVL with Peg-IFN/ribavirin for 72 weeks is modified by the early virological response (EVR) within 12 weeks after the start. Patients who have remained positive for HCV RNA detectable by the real-time polymerase chain reaction at 12 weeks after the start of treatment, but who turn negative for HCV RNA till 13–36 weeks on treatment.<sup>1,2</sup>
- 2 Patients with HCV-1 in HVL who fail to clear HCV RNA detectable by real-time PCR but in whom

ALT levels normalize are continued on Peg-IFN/ribavirin until 48 weeks, so that normalized ALT levels endure longer after the completion of therapy.<sup>7</sup>

- 3 Patients who are not indicated to Peg-IFN/ribavirin, or who have failed to respond to previous treatments, receive long-term IFN monotherapy. During the first 2 weeks, IFN in the conventional dose is given daily or three times a week. Patients who do not clear HCV RNA during the maximal treatment period of 8 weeks receive half the conventional dose of IFN indefinitely.<sup>8</sup>

### GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS C IN NORMAL ALT LEVELS

AS IN PREVIOUS guidelines, patients with chronic hepatitis C having normal ALT levels are stratified into four groups by ALT levels and platelet counts (Table 4). Patients with chronic hepatitis C who have normal ALT levels are reported to gain the sustained virological response (SVR) to antiviral treatments comparably frequently as those having elevated ALT levels. Taking this into consideration, patients with ALT levels of 30 IU/L or less and platelet counts of  $150 \times 10^3/\text{mm}^3$  or more are followed for ALT every

**Table 3** Supplements to guidelines for chronic hepatitis C

- 1 Criteria for extending the duration of Peg-IFN/ribavirin (to 72 weeks) in patients infected with HCV-1b in HVL: patients who have remained positive for HCV RNA detectable by the real-time polymerase chain reaction at 12 weeks after the start of treatment, but who turn negative for HCV RNA till 13–36 weeks on treatment.<sup>1,2</sup>
- 2 Patients with HCV-1b in HVL who fail to lose HCV RNA detectable by real-time PCR, but in whom ALT levels normalize by 36 weeks, Peg-IFN/ribavirin is given till 48 weeks for maintaining normalized ALT levels long after the completion of treatment.
- 3 Long-term IFN monotherapy in patients who are not indicated to Peg-IFN/ribavirin, or have failed to respond to it: the usual dose of IFN daily or three times in week is given for the first 2 weeks, and when HCV RNA does not disappear within the maximal duration of 8 weeks, long-term treatment with half the usual dose of IFN is continued indefinitely.

ALT, alanine aminotransferase; HCV, hepatitis C virus; HVL, high viral loads; PCR, polymerase chain reaction; Peg-IFN, pegylated interferon.

**Table 4** Guidelines for the treatment of patients with normal ALT levels toward preventing the development of HCC

Platelets	$\geq 150 \times 10^3/\text{mm}^3$	$< 150 \times 10^3/\text{mm}^3$
ALT		
$\leq 30$ IU/L	<ul style="list-style-type: none"> <li>Follow for ALT every 2–4 months.</li> <li>If ALT levels elevate, start antiviral treatments taking into consideration the possibility of SVR and risk for HCC.</li> </ul>	<ul style="list-style-type: none"> <li>Liver biopsy, if possible, and consider antiviral treatments for patients in A2/F2.</li> <li>Follow for ALT every 2–4 months, and consider antiviral treatments when ALT levels elevate, for patients without biopsy.</li> </ul>
31–40 IU/L	<ul style="list-style-type: none"> <li>Consider antiviral treatments for patients younger than 65 years.</li> </ul>	<ul style="list-style-type: none"> <li>Start treatments for chronic hepatitis C.</li> <li>Select treatments according to genotypes, viral load, age of patients, etc.</li> </ul>

ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; SVR, sustained virological response.

2–4 months. If ALT levels increase in them, antiviral treatments are considered based on the possibility of resolving HCV infection and the risk for developing HCC. In view of significant fibrosis present in patients with platelet counts of less than  $150 \times 10^3/\text{mm}^3$ , they are recommended to receive liver biopsy, if this is possible. Patients in fibrosis stage F2 or higher are evaluated for the indication to antiviral treatments. Patients with ALT levels between 31 and 40 IU/L are classified by platelet counts. Antiviral treatments are considered in those aged younger than 65 years who have platelet counts of  $150 \times 10^3/\text{mm}^3$  or more, while guidelines for patients with chronic hepatitis are applied to those with platelet counts of less than  $150 \times 10^3/\text{mm}^3$ .<sup>9,10</sup>

#### GUIDELINES FOR THE TREATMENT OF PATIENTS WITH CIRRHOSIS DUE TO HCV

PATIENTS WITH COMPENSATED cirrhosis who are not infected with HCV-1 in HVL receive either IFN- $\beta$  or IFN- $\alpha$  (Table 5). Since the fiscal year 2008, IFN- $\alpha$  has been approved for the treatment of patients infected with HCV-1 in HVL, with the aim of resolving infection and normalizing ALT as well as AFP levels by long-term therapy. Treatment duration was set at 1 year or longer, and because the longer the treatment duration the higher the SVR rate, 36 weeks has been recommended as the optimal treatment duration. Because the normalization of ALT/AST is important, even in patients who fail to clear HCV infection by these therapeutic regimens, treatment is better conducted for maintaining normal ALT/AST levels. Guidelines for maintaining liver function for preventing the development of HCC include liver supportive therapy with glycyrrhizin<sup>5</sup> and UDCA,<sup>6</sup> either alone or in combination. For treatment toward suppressing the

development of HCC, branched chain amino acids (BCAA)<sup>11</sup> or phlebotomy are adopted. Also, nutrient supplements are applied for stabilizing liver function.

#### SUPPLEMENTS TO GUIDELINES FOR THE TREATMENT OF CIRRHOSIS DUE TO HCV

THE FOLLOWING ITEMS have been appended to supplement guidelines for the treatment of type C cirrhosis (Table 6).

**Table 5** Guidelines for treatment of type C cirrhosis

Principles	Compensated: termination of HCV infection Decompensated: reversal to compensation and prevention of HCC
Methods	<ol style="list-style-type: none"> <li>Eradication of HCV and normalization of ALT/AST (for patients with compensated cirrhosis). <ol style="list-style-type: none"> <li>HCV-1b in HVL (<math>\geq 5</math> log IU/mL) <ul style="list-style-type: none"> <li>IFN-<math>\alpha</math> (Sumiferon)</li> </ul> </li> <li>Others <ul style="list-style-type: none"> <li>IFN-<math>\alpha</math> (Sumiferon)</li> <li>IFN-<math>\beta</math> (Feron)</li> </ul> </li> </ol> </li> <li>Maintenance of liver function (improvement of ALT/AST and albumin) for preventing HCC. <ol style="list-style-type: none"> <li>Liver supportive therapy <ul style="list-style-type: none"> <li>Stronger neo-minophagen C (SNMC), ursodeoxycholic acid (UDCA), etc.</li> </ul> </li> <li>Branched chain amino acids (BCAA [Livact])</li> <li>Phlebotomy</li> </ol> </li> <li>Supplementation with nutrients (for stabilizing liver function in decompensated cirrhosis).</li> </ol>

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HVL, high viral loads; IFN, interferon.

**Table 6** Supplements to guidelines for type C cirrhosis

- 1 To start with, IFN for compensated cirrhosis is desired at 6 MIU daily for 2–8 weeks, as far as possible, and to continue for 48 weeks or longer, as for chronic hepatitis C.
- 2 In patients with compensated cirrhosis who fail to clear HCV RNA within 12 weeks on IFN, long-term therapy at 3 MIU should be considered for preventing HCC.
- 3 In patients with platelet counts  $<50 \times 10^3/\text{mm}^3$ , splenectomy or embolization of splenic artery is recommended before re-treatment, and after thorough evaluation has been made on the response to IFN to be expected.
- 4 For the prevention of HCC, not only IFN, but also liver supportive therapy (SNMC, UDCA, etc.), phlebotomy and branched chain amino acids, either alone or in combination, are recommended for improving ALT/AST and AFP levels.

AFP,  $\alpha$ -fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; MIU, million international units; SNMC, stronger neo-minophagen C; UDCA, ursodeoxycholic acid.

- 1 For treatment of type C cirrhosis with IFN, the initial dose of 6 million international units (MIU) daily is continued as long as possible (2–8 weeks). Thereafter, long-term IFN for 48 weeks or longer is desired as in the treatment of chronic hepatitis C.
- 2 In the treatment of type C cirrhosis, patients who fail to achieve EVR with the clearance of HCV RNA from serum within 12 weeks should receive long-term IFN at a dose of 3 MIU.
- 3 For patients with type C cirrhosis who have platelet counts of less than  $50 \times 10^3/\text{mm}^3$ , splenectomy or embolization of the splenic artery is desirable before commencing IFN therapy, after the efficacy of IFN has been evaluated thoroughly.<sup>12</sup>
- 4 For preventing the development of HCC, improvement in ALT, AST and AFP levels are aimed. Toward this end, not only IFN, but also liver supportive therapy (SNMC and UDCA), phlebotomy and BCAA are used, either alone or in combination.

## DISCUSSION AND CONCLUSION

THE STUDY GROUP for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis, organized by the Ministry of Health, Labor and Welfare of Japan, has compiled a series of guidelines for the treatment of liver disease due to HCV ranging from chronic hepatitis to cirrhosis of various severities for the fiscal

year 2008. The principal aim of these guidelines is to decrease the incidence of HCC due to HCV infection in Japan. In accord with this principle, supplements have been added to previous guidelines for the standardization of treatment of chronic hepatitis C. They are prepared on evidence-based data that have been accumulated by members and cooperators of the study group. It is necessary to improve these guidelines in the next fiscal year and thereafter, in accordance with many pieces of new evidence that are expected to emerge through enduring efforts of members and cooperators of the study group.

In the treatment of chronic hepatitis C, the duration of antiviral treatments is extended to 72 weeks, which has been approved as of the fiscal year 2008, and criteria for the eligibility of extended treatment duration are clearly defined. Long-term antiviral treatments, extended up to 72 weeks, are hoped to increase the SVR even further. In addition, comprehensive guidelines for the treatment of cirrhosis have been improved with substantial additions, and their criteria for the indication made explicit.

The Study Group for the Standardization of Treatment of Viral Hepatitis Including Cirrhosis has drafted, and also displayed online ([www.jsh.or.jp/medical/index.html](http://www.jsh.or.jp/medical/index.html) [in Japanese]), guidelines for a spectrum of liver diseases due to HCV, from chronic hepatitis to cirrhosis of various severities. In view of the eventual goal of decreasing the incidence of HCC due to HCV infection, supplementation and adjustment are appended to previous guidelines, and new guidelines have been constructed for the treatment of cirrhosis due to HCV infection. As a general rule, antiviral treatments constitute the main body of guidelines for the treatment of chronic hepatitis C. Furthermore, the fundamental concept of these guidelines would need to be kept in mind always. It is our sincere hope that, for the treatment of each patient, readers will base their clinical practice on these guidelines, and refer to appropriate individual guidelines, when they make a decision on the treatment strategy, on a case-by-case basis. With respect to guidelines for the treatment of patients with cirrhosis, above all, expected achievable outcomes have to be taken into account in treatment choice.

It is our sincere desire that treatment of patients with chronic hepatitis and cirrhosis due to HCV will proceed following these guidelines. Efforts along these lines will rectify a wide gap in medical treatment served to the nation and raise substantial and efficient interest in the medical economy on the national basis. In practicing treatment according to these guidelines, it will be nec-

essary to evaluate their therapeutic efficacy, and revise or add necessary supplements to them as required in the future.

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# A Matched Case-Controlled Study of 48 and 72 Weeks of Peginterferon Plus Ribavirin Combination Therapy in Patients Infected With HCV Genotype 1b in Japan: Amino Acid Substitutions in HCV Core Region as Predictor of Sustained Virological Response

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Substitution of amino acid (aa) 70 and 91 in the core region of HCV genotype 1b is a useful pretreatment predictor of efficacy of 48-week peginterferon (PEG-IFN) plus ribavirin (RBV) therapy. Here, we determined the efficacy of 72-week PEG-IFN/RBV and the predictive factors to such therapy in a case-control study matched for sex, age, and periods from the start of treatment to initial point of HCV RNA-negative. We compared the treatment efficacy of 72-week regimen in 65 patients with that of 48-week in 130 patients, who were infected with HCV genotype 1b and treated with PEG-IFN/RBV. They consisted mainly of late virological responders (LVR) (HCV RNA-positive at 12 weeks and negative at 24 weeks after start of treatment). Sustained virological response (SVR) was achieved by 61.5% and 32.3% of patients of the 72- and 48-week groups, respectively, while non-virological response was noted in 9.2% and 29.2% of the respective groups. Multivariate analysis identified substitution of aa 70 and 91 (Arg70 and/or Leu91) and duration of treatment (72-week) as independent parameters that significantly influenced SVR. For Arg70 and/or Leu91 of core region, SVR rate was significantly higher in 72- (68.0%) than 48-week group (37.8%). For wild-type of ISDR, SVR rate was significantly higher in 72- (61.2%) than in 48-week group (29.3%). We conclude that 72-week PEG-IFN/RBV improves SVR rate for LVR, especially those with Arg70 and/or Leu91 of core region or wild-type of ISDR. Substitution of aa 70 and 91 is also a useful pretreatment predictor of response

to 72-week PEG-IFN/RBV. *J. Med. Virol.* **81:452–458, 2009.** © 2009 Wiley-Liss, Inc.

**KEY WORDS:** HCV; core region; NS5A-ISDR; peginterferon; ribavirin; 72-week; case-control study; LVR

## INTRODUCTION

Hepatitis C virus (HCV) usually causes chronic infection that can result in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) [Dusheiko, 1998; Ikeda et al., 1998; Niederau et al., 1998; Kenny-Walsh, 1999; Akuta et al., 2001]. In patients with HCV-chronic hepatitis, treatment with interferon (IFN) can induce viral clearance and marked biochemical and histological improvement [Davis et al., 1989; Di Bisceglie et al., 1989]. Especially, peginterferon (PEG-IFN) plus ribavirin (RBV) combination therapy for 48 weeks can achieve a high sustained virological response (SVR) [Manns et al., 2001; Fried et al., 2002].

Although treatment of genotype 1-infected patients typically extends over 48 weeks, there has been interest in prolongation of therapy, particularly in late

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