Table 2
The rate of biochemical and virological response

	At treatment completion	3 months after treatment completion	6 months after treatment completion	12 months after treatment completion
ALT normalized	4.3%	34.8%	39.1%	36.8%
	1/23	8/23	9/23	7/19
HBeAg lost[a]	38.9%	29.4%	31.3%	50.0%
	7/18	5/17	5/16	7/14
HBV DNA cleared[b]	47.6%	40.0%	42.1%	41.2%
	10/21	8/20	8/19	7/17

Reduction of the number of patients during the follow-up is caused by without patient's consent.
[a] Five patients were excluded because negative at study initiation.
[b] Two patients were excluded because undetectable at study initiation.

became negative for HBeAg was 38.9% (7/18) at treatment completion, 31.3% (5/16) at 6 months after completion, and 50.0% (7/14) at 12 months after completion. Thus, the highest negative rate was at 12 months after the treatment completion. The rate of patients who became undetectable for HBV DNA (bDNA probe assay) was 47.6% (10/21) at treatment completion, 42.1% (8/19) at 6 months after completion, and 41.2% (7/17) at 12 months after completion. A rate of more than 40% undetectable was maintained after the treatment completion. The inability to obtain consent resulted in a reduction in the number of patients followed (Table 2).

3.2. *Efficacy according to patient baseline characteristics*

Examination of baseline patient characteristics, ALT normalization, and loss of HBeAg and HBV DNA at 6 months after treatment completion revealed a trend toward greater efficacy with respect to the rate of ALT normalization and

Table 3
Efficacy according to baseline characteristics of patients

Features			6 Months after treatment completion		
		n	ALT normalized ($n = 23$)	HBeAg lost[a] ($n = 16$)	HBV DNA cleared[b] ($n = 19$)
Sex	Male	16	25.0% (4/16)	20.0% (2/10)	38.5% (5/13)
	Female	7	71.4% (5/7)	50.0% (3/6)	50.0% (3/6)
Age	<40	15	40.0% (6/15)	25.0% (3/12)	38.5% (5/13)
	40≦	8	37.5% (3/8)	50.0% (2/4)	50.0% (3/6)
Prior IFN therapy	Yes	14	35.7% (5/14)	40.0% (4/10)	53.8% (7/13)
	No	9	44.4% (4/9)	16.7% (1/6)	16.7% (1/6)
Staging	F0,F1	10	50.0% (5/10)	28.6% (2/7)	25.0% (2/8)
	F2,F3	8	37.5% (3/8)	20.0% (1/5)	66.7% (4/6)
	Non-perform	5	20.0% (1/5)	50.0% (2/4)	40.0% (2/5)
ALT (IU/ml)	67≦	20	35.0% (7/20)	33.3% (5/15)	37.5% (6/16)
	34–66	3	66.7% (2/3)	0% (0/1)	66.7% (2/3)
HbeAg (index)	100–1000	11	27.3% (3/11)	22.2% (2/9)	33.3% (3/9)
	2.1–100	7	42.9% (3/7)	42.9% (3/7)	50.0% (3/6)
	<2.1	5	60.0% (3/5)	–	50.0% (2/4)
HBeAb (%)	50–100	8	62.5% (5/8)	50.0% (2/4)	42.9% (3/7)
	0–50	15	26.7% (4/15)	25.0% (3/12)	41.7% (5/12)
HBV DNA (Meq./ml)	100≦	11	27.3% (3/11)	25.0% (2/8)	33.3% (3/9)
	0.7–100	10	40.0% (4/10)	42.9% (3/7)	50.0% (5/10)
	<0.7	2	100% (2/2)	0% (0/1)	–
HBV DNA (copies/ml)	10^7–10^9	16	31.3% (5/16)	27.3% (3/11)	35.7% (5/14)
	10^2–10^7	7	57.1% (4/7)	40.0% (2/5)	60.0% (3/5)
	$<10^2$	0	–	–	–
Precore mutant (copies/ml)	10^7–10^9	12	41.7% (5/12)	37.5% (3/8)	45.5% (5/11)
	10^2–10^7	10	30.0% (3/10)	25.0% (2/8)	37.5% (3/8)
	$<10^2$	1	100% (1/1)	–	–

[a] Five patients were excluded because negative at study initiation.
[b] Two patients were excluded because undetectable at study initiation.

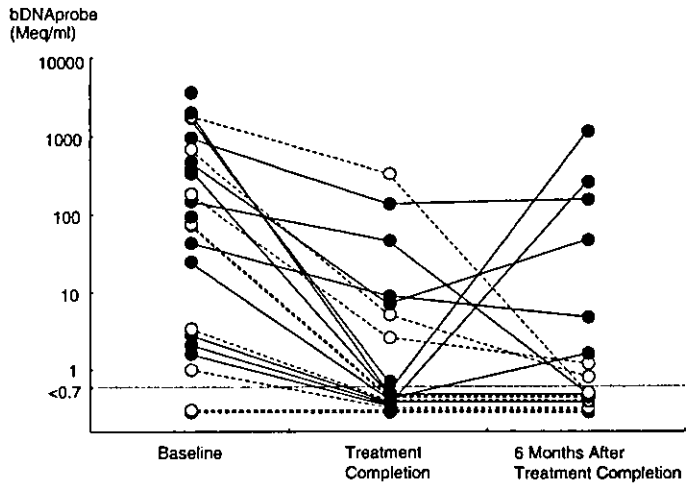

Fig. 1. Changes in Serum HBV DNA levels on interferon (IFN) therapy. And normalization of ALT in each patients at 6 months after the treatment completion. HBV DNA levels were significantly lower in patients with normalized ALT than with abnormal ALT at 6 months after the treatment completion. Open circles with dotted lines showed the changes in serum HBV DNA levels in normalized alanine transaminase (ALT) at 6 months after treatment completion, and closed circles with solid lines showed the abnormal alanine transaminase (ALT) at the same time. It was performed by the bDNA probe assay, since the changes in total hepatitis B virus (HBV) DNA levels were clearer than by the polymerase chain reaction (PCR) assay.

loss of HBeAg and HBV DNA in female patients than in male patients. Moreover, patients who had undergone previous IFN therapy showed greater efficacy, as indicated by the negative rate for HBeAg and HBV DNA, than patients who had not undergone previous therapy. In addition, the lower the baseline viral load, the greater was the efficacy with respect to the rate of ALT normalization and loss of HBeAg and HBV DNA. However, there were no significant differences between baseline characteristics and efficacy (Table 3).

3.3. *Efficacy based on changes in viral markers*

Regardless of its level at baseline, HBV DNA tended to decrease from the initiation of IFN therapy to its completion. After treatment completion, this decrease continued in five patients, while HBV DNA levels increased in the remaining patients. Two of the patients who exhibited more than 100 Meq/ml of the virus at treatment completion had ALT normalization at 6 months after treatment completion; conversely, seven patients who had less than 100 Meq/ml of the virus or were undetectable for the virus at treatment completion did not show ALT normalization at 6 months after treatment completion. Thus, there was no relation between the virus level at treatment completion and efficacy at 6 months after completion. However, HBV DNA levels at 6 months after treatment completion were significantly lower in patients with normalized ALT than with abnormal ALT at the same time (the ALT normalization rate of positive HBV

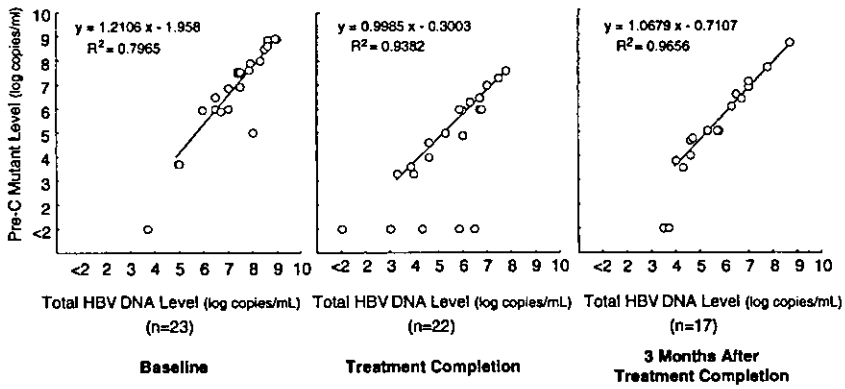

Fig. 2. Total HBV DNA Levels and Precore Mutant Levels on interferon (IFN) Therapy. Total hepatitis B virus (HBV) DNA and precore mutant were measured in: 23 patients at baseline, 22 patients at the treatment completion and 17 patients at 3 months after the treatment completion. Correlation coefficients are shown at each point. From the point of sensitivity of detection limit during the treatment, hepatitis B virus (HBV) DNA was performed by the polymerase chain reaction (PCR) assay.

DNA patients was 25%, and 70% for negative HBV DNA patients; $P = 0.0359$). It performed by the bDNA probe assay, since the changes in total HBV DNA levels were clearer than by the PCR assay (Fig. 1).

At baseline, only one patient had a precore mutant level of less than 10^2 copies/ml and was thus considered to have the wild-type virus. A correlation was seen between the total HBV DNA level and the precore mutant level at baseline, with no consistent trend seen between the proportion of precore mutant in relation to total HBV DNA. A correlation between total HBV DNA and precore mutant level was also seen at treatment completion and 3 months after completion, with no trend seen between the proportion of precore mutant at these timepoints. At all timepoints, the slope of the curve was equal, and no change was seen in the mutant proportion. However, there were exceptions in four patients: only the precore mutant level decreased to the limit of detection at treatment completion, indicating that inhibition of precore mutant growth exceeded inhibition of wild-type growth. From the point of sensitivity of detection limit during the treatment, HBV DNA was performed by the PCR assay (Fig. 2).

4. Discussion

Although no drugs have shown adequate efficacy in chronic hepatitis B, lamivudine has recently been introduced. Lamivudine has potent anti-HBV activity, but long-term lamivudine treatment frequently produces the YMDD mutation and increases HBV DNA and ALT levels [7]. As treatment discontinuation in this case may produce a rebound effect and result in acute exacerbation of the hepatitis, strategies such as continued lamivudine therapy with concurrent IFN use have been adopted [8]. Combined therapy with lamivudine and IFN reportedly increases the negative rate for HBeAg [9].

The first results of 4 weeks of IFN monotherapy in Japan were reported in 1983 by Matsumura et al. [10]. Since then, there have been occasional reports on topics such as the virological and immunological changes seen during IFN monotherapy, but there have been few reports on the efficacy of IFN therapy. The criteria for evaluating the efficacy of IFN therapy are not clearly defined. Generally, negative response for HBeAg, seroconversion to HBeAb, and normalization of ALT are assessed. Recently, however, the results of clinical studies using liver carcinogenesis or survival as the endpoint have been reported. Factors such as IFN therapy, age, histological progression in the liver, and post-treatment negative for HBeAg, HBV DNA, and HBsAg and normalization of ALT, play significant roles in efficacy after treatment completion [11–13].

In the present study, treatment with rIFN alfa-2a for 4 weeks resulted in, at 6 months and 12 months after treatment completion, normalization of ALT and almost the same undetectable HBV DNA rate, however the negative HBeAg rate rose from about 30 to 50%. Thus, in this study, treatment with rIFN alfa-2a did not show its effectiveness at each timepoint. It will be necessary to perform long-term follow-up observations of these patients, using liver carcinogenesis or survival as the endpoint.

The close relation between HBV mutation and disease type has been shown, and there have been numerous studies on this topic. Mutation at nucleotide 1896 of the precore region is considered particularly important, because it is thought to be related to the pathophysiology of fulminant and other hepatitis. In this study, we evaluated the frequency of the occurrence of precore mutants using MSSA for the detection of point mutations at the 83rd base in the precore region for the mutant HBV genome. MSSA can be used for the detection of 10^2 copies/ml of precore mutants in the presence of 10^7 copies/ml of wild-types, its sensitivity is considered to be at least 0.001%. With the use of this MSSA, even if only wild-type genomes are present, precore mutant-type can be identified on electrophoresis [4]. There have been numerous reports in the US and Europe indicating that this precore mutant is resistant to IFN [14,15]. In Japan, however, IFN efficacy in patients positive for HBeAb was first reported by Muraoka et al. [16], and since then other groups have also reported inhibition of HBV growth and ALT normalization with IFN therapy [17,18]. Possible factors in this discrepancy include the fact that, in the US and Europe, negative responses, not only for HBeAg and HBV DNA, but also for HBsAg, are the objectives of treatment and baseline characteristics such as the period of infection and HBV genotype differ greatly. Therefore, an examination of the response to IFN in which there is uniformity with respect to these factors is needed. In the present study, the total HBV DNA level and precore mutant level were correlated before and after IFN treatment. Among the 18 patients who were positive for HBeAg at baseline, none was negative for the precore mutant. Thus, in chronic hepatitis B, the precore mutation occurred at a constant proportion beginning from the HBeAg-positive phase, and IFN therapy inhibited growth of the wild-type virus and the precore mutant virus equally in most of the patients. In some patients, inhibition of the precore mutant growth exceeded inhibition of the wild-type growth; there were no cases in which wild-type growth was inhibited. Shindo et al. [19] reported that the precore wild-type and mutant have similar sensitivities to IFN. However, because they used the restriction fragment length polymorphism (RFLP) assay [20] to determine mutant virus levels and did not perform a quantitative examination, and because the IFN was administered intermittently (three times per week for 17 weeks) and the efficacy rate was 26.1% (6/23 patients; defined as showing seroconversion to HBeAb, loss of HBV DNA and normalization of ALT), the results of their study cannot be adequately compared with those of our investigation.

In an investigation in patients with type B cirrhosis, Ikeda et al. [21] reported high rates of carcinogenesis when the precore mutant is present at high concentrations. They

further report that high precore mutant concentrations correlate with a high total HBV DNA level in such patients, indicating that the inflammation associated with the hepatitis is severe, and acts to indirectly promote carcinogenesis. In addition, it is reported that a primary infection by HBV with a gene mutation contributes to the infection becoming fulminant and severe [22]. However, it is also reported that mutation of the precore region during the natural course of chronic hepatitis B is related to quiescence of the hepatitis and a decrease in the virus level [23].

The time required to reach the true endpoint of the present study, carcinogenesis or survival, makes it difficult to provide conclusions regarding whether the hepatic lesions in patients will progress or whether the hepatitis will become quiescent and the patients will become asymptomatic carriers. However, it is already evident that IFN treatment inhibits the growth of both the wild-type and precore mutant viruses seen in chronic hepatitis B and that it is also effective in patients who are positive for HBeAg and have a predominance of the wild-type virus.

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The significance of interferon and ribavirin combination therapy followed by interferon monotherapy for patients with chronic hepatitis C in Japan

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Received 26 December 2003; received in revised form 16 March 2004; accepted 25 March 2004

Abstract

One hundred seventy-one patients with chronic hepatitis C were included in this study (genotype1 and high viral loads (1H), $n = 130$; non-1H, $n = 37$; N.D., $n = 4$). The combination therapy of interferon and ribavirin for 24 weeks with an additional 24 weeks of interferon monotherapy (48-week treatment) was undergone by 42 1H patients and 5 non-1H patients. The combination therapy of interferon and ribavirin was administered for 24 weeks in 67 1H patients and 22 non-1H patients. Among the 1H patients, the HCV relapse rate was significantly higher in those receiving 24-week combination treatment than in those receiving 48-week treatment (78% versus 42%, $P = 0.003$). Among the non-1H patients, no significant difference was found between them. Sustained virological response (SVR) rates were observed to decrease as the timing of HCV RNA disappearance was delayed. In spite of the small rate (16%), SVR was obtained from the patients who became negative for HCV RNA by week 24 (beyond week 12) only in those receiving 48-week treatment. In 1H patients, 24-week combination treatment followed by interferon monotherapy for 24 weeks was concluded to be the treatment offering the most hope among those that the medical insurance can be applied in Japan.

Keywords: Chronic hepatitis C; Interferon and ribavirin combination therapy; Combination therapy followed by IFN monotherapy

1. Introduction

Interferon is the only available treatment for patients with chronic hepatitis C since HCV was discovered in 1989 [1–4]. Thirty percent of patients with chronic hepatitis C achieved SVR by interferon therapy but the efficacy was not satisfactory. Furthermore, in the patients considered to be the most treatment-resistant, that is, the 1H patients, only 5–8% showed SVR. In Japan, 40–50% of the patients with chronic hepatitis C belong to the 1H group. Therefore, finding how to eradicate the HCV RNA

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1386-6346/$ – see front matter © 2004 Published by Elsevier B.V.
doi:10.1016/j.hepres.2004.03.008

of 1H patients is most important for the treatment of chronic hepatitis C.

Recently, ribavirin, a nucleic acid analogue, exhibiting in vitro activity against various kinds of DNA and RNA viruses has been developed. The combination therapy of ribavirin and interferon has been shown to be very useful in the eradication of HCV in patients with chronic hepatitis C [5–7], although the mechanism of action of ribavirin remains speculative and ribavirin monotherapy led to no significant decrease of the amount of HCV RNA in the patients with chronic hepatitis C [8]. Most recent studies, performed with large numbers of naïve patients, have shown that the combination therapy of interferon and ribavirin can increase the SVR rate two-fold compared with interferon monotherapy for patients with chronic hepatitis C [9–12]. Especially, in the 1H patients, the combination therapy of interferon and ribavirin was more useful than in the other patients. Furthermore, Poynard et al. [10] showed that 1H patients treated by combination therapy for 48 weeks had a higher SVR rate than those treated for 24 weeks (28% versus 8%). Therefore, the combination therapy of interferon and ribavirin for 48 weeks is recommended as the standard therapy for 1H patients in Europe and the United States [13,14].

In Japan, the combination therapy of interferon and ribavirin was approved in 2001. However, the duration of the combination therapy is limited to 24 weeks in the medical insurance. As mentioned above, the SVR rate in 1H patients treated by the combination therapy for 24 weeks was clearly lower than those treated for 48 weeks. Furthermore, prolonged interferon monotherapy was reported to suppress relapse after cessation of therapy and to achieve a higher SVR rate in patients with chronic hepatitis C [15]. This study assessed the efficacy of the combination therapy of interferon and ribavirin for 24 weeks with an additional 24 weeks of interferon monotherapy compared with that of the combination therapy for 24 weeks.

2. Patients and methods

2.1. Patients

The current study was conducted at Osaka University Hospital and the institutions of the Osaka Liver Disease Study Group. The 171 patients included in this study had HCV RNA detectable in serum by the polymerase chain reaction (PCR) method, had elevated ALT (above the upper limit of the normal) and had been histologically proven to have chronic hepatitis. No patients were positive for hepatitis B surface antigen and anti-human immunodeficiency virus antibody or had other forms of liver disease (such as alcoholic liver disease and autoimmune liver disease). This study protocol was carried out according to the ethical guidelines of the 1975 Declaration of Helsinki and informed consent was obtained from each patient.

2.2. Determination of HCV RNA levels and HCV genotype

Serum HCV RNA levels were quantified using branched DNA (bDNA) probe assay (version 2; Chiron, Dai-ichi Kagaku, Tokyo) [16,17] or combined PCR assay (Amplicor-HCV monitor assay) [18]. In this study, a high viral load, as described previously [16,18,19], was designated as the condition of a serum HCV RNA level of more than 10^6 equivalents/ml by bDNA assay or more than 10^5 copies/ml serum by Amplicor-HCV monitor assay. HCV genome typing was classified by serological genotyping assay [20].

2.3. Treatment schedule

Of the 171 patients with chronic hepatitis C enrolled in this study, 130 had HCV RNA with genotype 1 and high viral loads (1H group), which were difficult to eradicate by anti-viral therapy. Of the remaining 41 patients, 37 had HCV RNA with genotype 2 or low viral loads (non-1H group); genotype or viral levels could not be determined for four. One hundred thirty-six patients in whom treatment had been done without the discontinuation of interferon till the end of the scheduled duration were studied (1H, $n = 109$; non-1H, $n = 27$).

The combination therapy of interferon-α-2b and ribavirin was administered for 24 weeks in 67 patients of the 1H group and 22 patients of the non-1H group. In this protocol, interferon-α-2b was given intramuscularly every day for the first 2 weeks and then three times a week for the following 22 weeks in combination with ribavirin at a daily dose of 600 or 800 mg, depending on body weight (<60 or ≥60 kg, respectively). The combination therapy of interferon-α-2b and ribavirin for 24 weeks, followed by interferon-α-2b monotherapy three times a week for a further 24 weeks, was administered to 42 patients of the 1H group and 5 patients of the non-1H group. The pretreatment characteristics of the patients were similar (Table 1).

The starting doses of interferon-α-2b were 10 MU per day for 38, 6 MU per day for 127, and 3 MU per day for 6 patients. With ribavirin, 800 mg per day was started in 92, 600 mg per day in 77, and 400 mg per day in 2 patients. Among the 171 patients, the interferon dose was decreased in six patients during the treatment, and the interferon was stopped along with ribavirin in 33 patients (19%) due to side effects. The ribavirin dose was decreased in 43 patients (25%) during the treatment, and stopped without discontinuance of interferon in six patients. Eighty-seven patients (51%) completed treatment without discontinuance or dosage decrease of both drugs.

After the sufficient informed consent at the end of the combination therapy of interferon and ribavirin, the patients themselves decided whether to be treated for 24 or 48 weeks. The information included the results of clinical trials of the combination therapy for 24 and 48 weeks in other countries, such as the SVR rate, HCV relapse rate.

Table 1
Baseline characteristics of patients according to therapeutic protocol

	24-week treatment		48-week treatment
	1H group	Non-1H group	1H group
	67	22	42
Age (yo)	55.8 ± 10.9	55.7 ± 12.8	54.0 ± 11.7
M/F	40/27	15/7	28/14
ALT (IU/L)	107 ± 71	102 ± 45	103 ± 58
Fibrosis	1.9 ± 0.9	1.9 ± 1.2	1.8 ± 1.1
History of IFN treatment			
Naïve	34	11	17
Relapser	21	7	17
Non-responder	11	4	8
Unknown	1	0	0

Note: All comparisons are not significant. Twenty-four-week treatment, interferon plus ribavirin treatment for 24 weeks; 48-week treatment, interferon plus ribavirin treatment for 24 weeks followed by interferon monotherapy for 24 weeks. 1H group, patients with genotype 1 and high viral load; non-1H group, patients other than 1H group. Fibrosis, Knodell's histological score (category 4).

Also, side effects were presented and the combination therapy of interferon-α-2b and ribavirin for 48 weeks was explained as not being covered by medical insurance in Japan. In the 47 patients who agreed to receive the additional 24 weeks of interferon monotherapy, the starting doses of interferon-α-2b were 10 MU per day for 10, 6 MU per day for 35, and 3 MU per day for 2 patients. All patients completed the additional treatment although interferon was decreased only in one patient from 10 to 6 MU per day.

2.4. Statistical analysis

Age, histological scores before interferon therapy, and serum ALT levels are expressed as mean ± S.D. The chi-squared test was used for statistical analysis of the comparison between group frequencies. When appropriate, the clinical and laboratory features of the two groups were compared by Student's *t*-test. Histological evaluation was substituted as a variable for Knodell's histological scores [21].

3. Results

3.1. Results of interferon and ribavirin combination therapy

Seventy-five percent of all of the patients of 1H group (82/109), including not only patients who received 24-week treatment but also those who received 48-week treatment, had no detectable HCV RNA at 24 weeks after the beginning of combination therapy of interferon and ribavirin. This was also the case for 100% of the non-1H patients (27/27). In patients given 24-week treatment of combined interferon and ribavirin, 45 out of 67 of the 1H group were negative for HCV RNA at the end of therapy, but only 22% of the patients (10/45) showed no detectable HCV RNA at 24 weeks after cessation of therapy. On the other hand, HCV RNA was negative in all non-1H patients at the end of the 24-week treatment, and the SVR rate was 86% (19/22) (Fig. 1). In patients with 48-week treatment (24-week combination treatment, followed by 24-week interferon monotherapy), HCV RNA reappeared during interferon monotherapy (break through) in 11 out of 37 patients (30%) who were negative for HCV RNA at the end of 24-week combination therapy: SVR was finally reached in 15 out of 26 patients who continued to be sero-negative for HCV RNA at the end of 48-week treatment. On the other hand, HCV RNA was not cleared even by 48-week treatment in all five patients who were positive for HCV RNA at the end of 24-week treatment (Fig. 2). In the non-1H patients who received 48-week treatment, HCV RNA was negative in all five patients at the end of the 24-week treatment, and SVR was attained by 80% (4/5).

The HCV RNA relapse rate after treatment was compared according to the duration of treatment. In all patients, 57% of those receiving 24-week treatment (38/67) had HCV RNA relapse, as compared with 39% of those receiving 48-week treatment (12/31). Among the 1H patients, a significant dif-

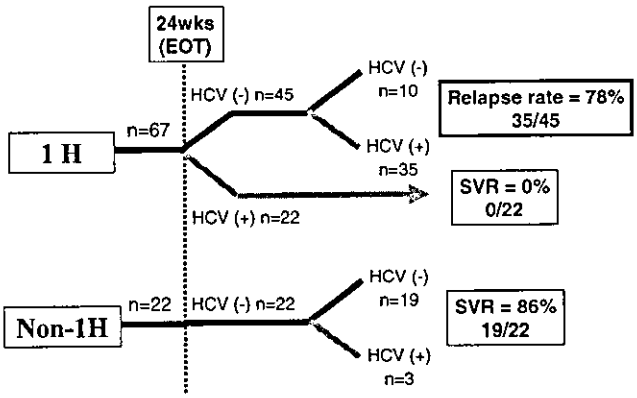

Fig. 1. Efficacy of the combination therapy (24-week treatment). 1H group, patients with genotype 1 and high viral load; non-1H group, patients other than those of the 1H group. EOT, end of treatment. HCV, serum HCV RNA positivity by polymerase chain reaction.

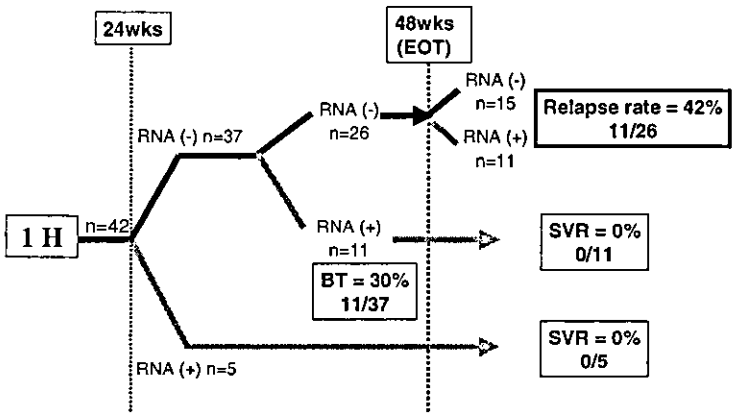

Fig. 2. Efficacy of the combination therapy followed by interferon monotherapy (48-week treatment). 1H group, patients with genotype 1 and high viral load; non-1H group, patients other than those of the 1H group. EOT, end of treatment. HCV, serum HCV RNA positivity by polymerase chain reaction. BT, break through.

ference was found in HCV relapse rate between those receiving 24-week treatment and those receiving 48-week treatment (78% versus 42%, $P = 0.003$). Among the non-1H patients, HCV RNA relapsed in 14% (3/22) of those receiving 24-week treatment (Fig. 1) and 20% (1/5) of those receiving 48-week treatment.

3.2. *Timing of HCV RNA disappearance and efficacy of treatment*

The relationship between the timing of HCV RNA disappearance and SVR rate according to the duration of treatment was evaluated. As shown in Fig. 3A, in all patients receiving 24-week treatment, 71% (12/17) of the patients who had no detectable HCV RNA by week 4, 61% (11/18) by week 8 (beyond week 4), and 21% (4/19) by week 12 (beyond week 8) had SVR. Although 11 patients became negative for HCV RNA by week 24 (beyond week 12), none of them attained SVR. A tendency for a decrease in the SVR rate was observed as the timing of the HCV RNA disappearance was delayed. In the patients receiving 48-week treatment, 86% (6/7) of those who had no detectable HCV RNA by week 4, 100% (6/6) by week 8 (beyond week 4), 40% (4/10) by week 12 (beyond week 8), and 16% (3/19) by week 24 (beyond week 12) attained SVR.

Among the 1H patients, the same tendency was also observed (Fig. 3B). In the patients receiving 24-week treatment, 50% (3/6) of those who had no detectable HCV RNA by week 4, 40% (4/10) by week 8 (beyond week 4), and 18% (3/17) by week 12 (beyond week 8) attained SVR. None of the 10 patients who became negative for HCV RNA by week 24 (beyond week 12) showed SVR. In the patients receiving 48-week treatment, 80% (4/5) of those who had no detectable HCV RNA by week 4, 100% (5/5) by week 8 (beyond week 4), 38% (3/8) by week 12 (beyond week 8), and 16% (3/19) by week 24 (beyond week 12) had SVR. In spite of the small rate (16%), SVR was obtained from the patients who became negative for HCV RNA by week 24 (beyond week 12) only in those receiving 48-week treatment.

Fig. 4 shows the relationship between the timing of HCV RNA disappearance and the prediction value in 1H patients who received the combination therapy of interferon and ribavirin for 24 weeks. As the timing of the HCV RNA disappearance was late, the positive prediction value decreases and the negative prediction value increases. In particular, the negative prediction value at week 12 was 100%, that is, none

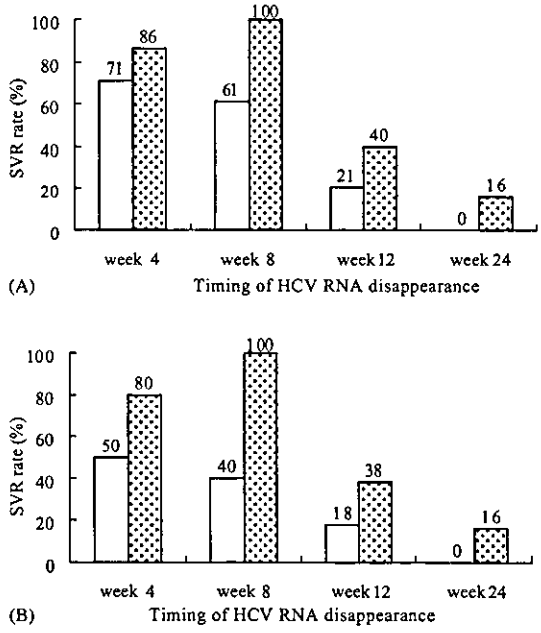

Fig. 3. Timing of HCV RNA disappearance and SVR rate (A) all patients, (B) patients with genotype 1 and high viral loads. (▭) Combination therapy of interferon and ribavirin (24-week treatment); (▨) combination therapy followed by interferon monotherapy (48-week treatment).

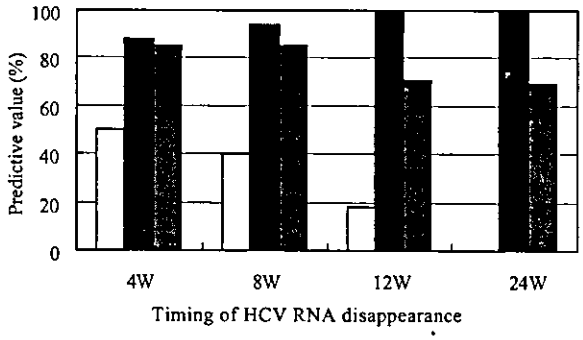

Fig. 4. Timing of HCV RNA disappearance and prediction value in patients with genotype 1 and high viral loads who received the combination therapy of interferon and ribavirin for 24 weeks. (□) Positive prediction value; (■) negative prediction value; (■) predictive accuracy.

of the patients who were positive for HCV RNA at week 12 attained SVR.

4. Discussion

In Japan, randomized control studies were performed on the combination therapy of interferon and ribavirin for 24 weeks in patients with chronic hepatitis C, and the combination therapy was approved in November 2001. However, the duration of the combination therapy is limited to 24 weeks in the medical insurance because of the lack of clinical mega-trial evidence for the combination therapy for 48 weeks in Japan. From the results of international trials, the SVR rate in 1H patients treated by the combination therapy for 48 weeks has been shown to be higher than that of those treated for 24 weeks [10]. Moreover, for interferon monotherapy, prolonged interferon treatment was reported to suppress relapse after cessation of therapy and to lead to a higher SVR rate in patients with chronic hepatitis C [15]. Our strategy, the interferon and ribavirin combination therapy with an additional 24 weeks of interferon monotherapy, was conducted against this background.

Poynard et al. [22,23] evaluated the HCV RNA relapse rates after cessation of the combination therapy in naïve patients with chronic hepatitis C. Among patients with genotype 1, the relapse rates were 62% in those treated by interferon and ribavirin combination therapy for 24 weeks and 26% in those treated for 48 weeks: among patients with genotype 2/3, 21% in those for 24 weeks and 15% in those for 48 weeks. Among patients with genotype 1, the SVR rate increased due to suppression of the relapse rate by the combination therapy for 48 weeks. On the other hand, the patients with genotype 2/3 require only 24 weeks of therapy. In our study, patients with genotype 1 and high viral load (1H group) were evaluated, distinguishing them from others (non-1H group) since the efficacy of anti-viral therapy for the 1H patients has been known to be remarkably low. Among the 1H patients, the HCV relapse rate was significantly higher in those receiving 24-week combination treatment than in those receiving 48-week treatment, 24-week combination treatment followed by interferon monotherapy for 24 weeks (78% versus 42%, $P = 0.003$). Among the non-1H patients, no significant difference was found between those receiving 24-week treatment and those receiving 48-week treatment (14% versus 20%). These results indicate that our strategy of 48-week treatment is useful for the 1H group; the non-1H group seems to require only 24 weeks of therapy, similar to the patients with genotype 2/3 in the above-mentioned.

In the 1H patients receiving 48-week treatment, HCV RNA reappeared during interferon monotherapy in 11 out of 37 patients (30%) who were negative for HCV RNA at the end of 24-week combination therapy. The break through phenomenon should be taken into account when the efficacy of this treatment is evaluated. The SVR ratio in 1H patients receiving 48-week treatment can be calculated from the prevalence of undetectable HCV RNA at 24 weeks after the beginning of combination therapy of interferon and ribavirin (75%, 82/109), of break though (30%, 11/37) and of HCV relapse rate (42%, 11/26); the expected SVR is 30% ($(82/109) \times (1 - (11/37)) \times (1 - (11/26)) \fallingdotseq 0.30$). In the same manner, the SVR ratio in 1H patients receiving 24-week treatment is expected to be 17% $(82/109) \times (1 - (35/45)) \fallingdotseq 0.17$. In 1H patients, 48-week treatment, 24-week combination treatment followed by interferon monotherapy for 24 weeks, may be the useful treatment which can be actually performed in Japan.

The relationship between the timing of HCV RNA disappearance and the SVR rate according to the duration of treatment was evaluated. SVR rates decreased with a delay in the timing of HCV RNA disappearance in patients receiving 24-week treatment; the negative prediction value at week 12 was 100%, that is, none of the patients who were positive for HCV RNA at week 12 had SVR. In spite of the small rate (16%), SVR was attained for patients who became negative for HCV RNA by week 24 (beyond week 12) only in those receiving 48-week treatment. Accordingly, treatment withdrawal should be offered to patients who remain HCV RNA-positive after 12 weeks of therapy if the patient cannot continue treatment for 48 weeks for reasons including side effects and social issues. The patients who were positive for HCV RNA at week 24 should stop treatment because additional interferon monotherapy for 24 weeks could not clear HCV RNA in all five patients who were positive for HCV RNA at week 24.

Pol et al. [24] have reported the synergistic effect of ribavirin and interferon in 343 patients with the genotype 1b. In the study, ribavirin was administered for 4, 6, 12 months in combination with interferon-α for 12 months. A 12-month course of ribavirin achieved significantly greater virological efficacy than 6 or 4 months at the end of the 12-month course of interferon-α (59, 49, and 29%), the same trend seen at the end of follow-up duration (43, 36, and 21%). These results indicate that the maximum efficacy can be obtained

when ribavirin is administered for 12 months in combination with interferon. In our study, the break through ratio was expected to decrease with the administration of ribavirin for 48 weeks. In fact, a patient to whom ribavirin was given again after the break through, achieved marked decrease of HCV RNA (data not shown). Thus, in some patients who were negative for HCV RNA during the combination treatment, the additional ribavirin can be essential for eradicating HCV RNA. Longer duration of combination therapy with interferon and ribavirin is also most effective for suppressing HCV RNA relapse after 24 weeks of therapy [22,23]. Therefore, we would like to emphasize that combination therapy of ribavirin and interferon for 48 weeks should be permitted even in Japan. At present, 24-week combination therapy followed by 24-week interferon monotherapy is thought to be the most useful therapy that the medical insurance can be applied in Japan for suppressing the relapse rate of HCV RNA, leading to SVR.

Acknowledgements

In addition to the study authors, the following institutions and physicians were participants in the Osaka Liver Disease Study Group (Digestive Disease Study Group of Osaka Renaissance): Osaka National Hospital, R. Sakamori; Osaka Rousai Hospital, N. Kurashige, O. Nishiyama, and S. Shinzaki; Osaka Kouseinenkin Hospital, M. Kurokawa and A. Uemura; National Osaka South Hospital, T. Oze and N. Tsuda; Kansai Rousai Hospital, T. Yoshio; Osaka Police Hospital, K. Koga; Osaka Prefectural Hospital, A. Arimitsu; and Osaka University Graduate School of Medicine, S. Yamaguchi, M. Miyazaki, H. Miyatake, I. Itose, S. Egawa, and T. Nishida.

This work was supported by a Grant-in-Aid for Research on Hepatitis and BSE from the Ministry of Health Labour and Welfare of Japan, and Scientific Research from the Ministry of Education, Science, and Culture of Japan.

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肝臓　45巻11号　581-588（2004）

＜原　著＞

HBVマーカーと発癌リスクよりみたHBVキャリアのステージ分類
—適切な抗ウイルス治療の選択に向けて—

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分島　一　里見絵理子　道田　知樹*　林　紀夫**

要　旨：HBVキャリアには様々な病態が存在するが，明瞭なステージ分類が存在せず，客観的な病態把握が困難である．そこでHBVマーカー，ALT値，年齢および発癌リスクによるHBVキャリアのステージ分類を考案し，それに基づく治療方針について検討した．ステージ0：HBe(e)抗原陽性，ALT正常値持続の無症候性キャリア．ステージI：e抗原陽性，ALT異常値でHBV-DNA(DNA)量が$10^{7.6}$ copies/ml以上(若年例：ステージIa，高年例：ステージIb)．ステージII：e抗原陽性，ALT異常値でDNAが$10^{7.6}$ copies/ml未満(若年例：ステージIIa，高年例：ステージIIb)．ステージIII：e抗原陰性，DNA 10^5 copies/ml以上．ステージIV：e抗原陰性，DNA 10^5 copies/ml未満．ステージV：HBs抗原が消失した状態．今回考案したステージ分類はHBVキャリアの病期の把握と治療選択に有用と考える．

索引用語：HBVキャリア　B型慢性肝炎　ステージ分類　発癌リスク　抗ウイルス治療

はじめに

HBVキャリアは，HBe抗原陽性無症候性キャリアから慢性肝炎，肝硬変，肝細胞癌，あるいは臨床的治癒とされているHBe抗体陽性無症候性キャリアまで様々な病態が存在する．そして，その経過も様々であるが，大別すると肝硬変，肝細胞癌に進行する群と，臨床的治癒の状態に落ち着く群に二分される．約80%は後者になると考えられるが，B型肝癌も全肝細胞癌中10～15%を占め，現在死亡者数は横ばいで年間約5000名を数えており，肝癌発癌抑止がC型のみならずB型肝炎においても最大の課題である．HBVキャリアのそれぞれが現在どの病期にいるのか，発癌リスクはどの程度であるのか，積極的な治療の必要性はあるのか，そしてあるならどのような治療を選択すべきかという問いに明確に対処できるステージ分類が現在存在せず，客観的な病態把握が困難である．そこで，今回B型肝癌発癌抑止を目的とした適切な抗ウイルス治療の選択に向けての，HBVマーカーと発癌リスクよりみたHBVキャリアのステージ分類を試みたので報告する．

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＜受付日2004年2月3日＞

対象と方法

対象は1995年11月以降に当院を初診したHBVキャリア207例である．対象の性別は男性138例，女性69例で，平均年齢はそれぞれ44.3±13.4歳，42.8±15.6歳であった．ステージ分類の根拠はHBs抗原の有無，HBe抗原の有無，HBV-DNA量，年齢，ALT値，組織学的診断および発癌リスクとした．また，統計学的解析はχ^2検定およびt検定を用いた．

成　績

HBVキャリアのclinical stage(HBステージ)を8ステージに分類した(Table 1)．

HBステージ0：HBs抗原陽性，HBe抗原陽性，ALT正常値持続のいわゆる無症候性キャリアの状態．対象(Table 2)中のステージ0群は9例(4.3%)で，発癌数は0であった．発癌リスクはほとんどなく，抗ウイルス治療の適応なし．

HBステージI：HBs抗原陽性，HBe抗原陽性，ALT異常値(持続正常以外)で，HBV-DNA量が$10^{7.6}$ copies/ml以上の高ウイルス群．若年例(男性：30歳未満，女性：35歳未満)をステージIa，高年例(男性：30歳以上，女性：35歳以上)をステージIbとする．ステージIa群は23例(11.1%)で，発癌数は0

Table 1　Clinical stages(HB stage)of HBV carriers

HB stage	0	I	II	III	IV	V
HBs Ag	+	+	+	+	+	*−
HBe Ag	+	+	+	−	−	N/A
HBV-DNA (copies/m*l*)	N/A	$10^{7.6}$≦	$10^{7.6}$>	10^{5}≦	10^{5}>	N/A
ALT	Persistently normal	Abnormal	Abnormal	N/A	N/A	N/A
Age	N/A	**Younger/ Older (Ia/ Ib)	**Younger/ Older (IIa/IIb)	N/A	N/A	N/A
Risk of carcinogenesis	Very low	Low/High	Low/Very high	Very high	Very low	Very low

N/A：Not applicable
*Confirmed HBs Ag (+) period must be needed
**Younger：Males under 30 years old and females under 35 years old
Older：Males aged 30 years old or over and females aged 35 years old or over

Table 2　Characteristics of each clinical stage

HB stage	0	I a	I b	IIa	IIb	III	IV
	HBe Ag(+) asymptomatic carrier	HBe Ag(+) HCV-RNA $10^{7.6}$≦ Younger*	HBe Ag(+) HCV-RNA $10^{7.6}$≦ Older*	HBe Ag(+) HCV-RNA $10^{7.6}$> Younger*	HBe Ag(+) HCV-RNA $10^{7.6}$> Older*	HBe Ag(−) HCV-RNA 10^{5}≦	HBeAg(−) HCV-RNA 10^{5}>
number of cases(%)	9(4.3)	23(11.1)	44(21.3)	10(4.8)	31(15)	49(23.7)	41(19.8)
gender(M/F)	3/6	16/7	32/12	4/6	24/7	38/11**	21/20**
age(y.o.)	34.4±9.1	25.5±3.4	44.8±11.0	24.0±2.5	48.5±9.8	53.1±9.7***	45.6±15.7***
ALT(I.U)	17.7±4.4	129.0±101.4	193.6±204.2	105.6±80.3	130.5±194.2	117.2±112.3****	41.0±39.7****
platelet(×10^{4})	20.4±4.2	20.1±3.6	16.5±6.2	18.1±4.3	15.4±7.9	14.4±5.9*****	19.3±7.5*****
HCC negative/ positive cases at the first visit	9/0	23/0	44/0	9/1	24/6	39/10	35/6
carcinogenesis within follow up periods	0	0	3	0	4	9	1
carcinogenetic rate(%)	0	0	6.8	0	16.7	23.1*****	2.9******

* Younger：Males under 30 years old and females under 35 years old　　(1995. 11〜 n=207)
,* $p<0.01$
****,***** $p<0.001$
****** $p<0.05$
Older：Males aged 30 years old or over and females aged 35 years old or over

であった．ステージ Ia 群も発癌リスクは極めてまれで，通常は抗ウイルス治療の必要はないが，組織学的に線維化ステージが進行している例は抗ウイルス治療の適応となる．一方，ステージ Ib 群は 44 例(21.3%)で，このうちの発癌数は 3 例(6.8%)と発癌リスクを有し，抗ウイルス治療の必要を認める．

HB ステージ II：HBs 抗原陽性，HBe 抗原陽性，ALT 異常値（持続正常以外）で，HBV-DNA 量が $10^{7.6}$ copies/m*l* 未満の低ウイルス群．若年例をステージ IIa，高年例をステージ IIb とする．ステージ IIa 群は

Table 3 Histological findings of each clinical stage

HB stage	0	Ia	Ib	IIa	IIb	III	IV	total
cases of liver biopsy	0	10	23	5	10	12	0	60
F0, 1	0	8	11	3	0	3	0	25
F2, 3, (4)	0	2	10(2)	2	8(2)	9	0	31(4)
				Ib vs IIb,	Ia+Ib vs IIa+IIb,	Ia+IIa vs Ib+IIb		$p<0.05$
A1, 2	0	7	15	5	5	10	0	42
A3, 4	0	3	8	0	5	2	0	18
								N.S

10例(4.8%)で，ステージ I からステージ IV まででは初診患者に占める割合は最も少ない．発癌リスクも少ないが対象中の1例(25歳男性)のような若年発癌例が存在し，また transaminase 高値が持続する例も多く，抗ウイルス治療の適応になる．ステージ IIb 群は31例(15.0%)で，発癌例は10例，初診時以降の発癌率は12.5%(3/24)と発癌リスクが極めて大で，抗ウイルス治療の絶対適応である．

HB ステージ III：HBs 抗原陽性，HBe 抗原陰性，HBV-DNA 10^5 copies/ml 以上の precore(pre-C) mutant 株の replication が持続している群である．対象に占める割合は23.7%(49例)と全ステージ中最大である．発癌リスクは極めて大(発癌例は20例，初診時以降の発癌率は21.6%(8/37))で，ALT 値異常の，とくに男性はステージ IIb とともに抗ウイルス治療の絶対適応である．

HB ステージ IV：HBs 抗原陽性，HBe 抗原陰性，HBV-DNA 10^5 copies/ml 未満のいわゆる臨床的治癒の状態である．41例(19.8%)と多数を占め，初診時以降の発癌例を1例認めたが，発癌リスクとしては極めてまれで原則的には抗ウイルス治療の必要はないと考える．

HB ステージ V：HB キャリア(HBs 抗原陽性の時期が確認されている例)で，HBs 抗原が消失した状態である．HB ステージ IV と同様，発癌リスクは極めてまれで抗ウイルス治療の必要はない．

各ステージの性別，平均年齢，ALT 値は Table 2 に示すが，HB ステージ III と HB ステージ IV の平均年齢はそれぞれ，53.1±9.7歳，45.6±15.7歳と HB ステージ IV が有意($p<0.01$)に若年齢であり，性別も HB ステージ III は男性38例，女性11例であったが，HB ステージ IV では男性21例，女性20例と，女性は有意($p<0.01$)にステージ III 例が少なかった．また，ALT 値も HB ステージ III 117.2±112.3 IU/l，HB ステージ IV 41.0±39.7 IU/l と，ステージ IV が有意($p<0.001$)に低値であった．

肝生検を行った60例の組織学的診断と HB ステージとの関係を Table 3 に示す．ステージ Ia は線維化ステージ(F)0，1例が F2 以上例より多数を占めたが，ステージ Ib とステージ IIa では F0，1例と F2 以上例がほぼ同数で，ステージ IIb とステージ III では F2 以上例が多数を占めた．Ib vs IIb，Ia+Ib vs IIa+IIb，Ia+IIa vs Ib+IIb でそれぞれ有意差($p<0.05$)を認めた．grading と HB ステージには有意な関係を認めなかった．尚，ステージ 0，ステージ IV およびステージ V の症例は肝生検の必要性を認めず，施行していない．

発癌例(初診時有発癌例を含む)における性別および発癌確認時の年齢，ALT 値について検討した(Table 4)．発癌率の性差は，男性24.6%(138例中34例)，女性10.1%(69例中7例)で，男性が有意に発癌率が高率($p<0.02$)であった．発癌例の年齢分布は50歳代が55.0%と最も多く，60歳代，40歳代がそれぞれ17.5%，15.0%で，40歳未満は25歳と35歳の2例のみであった．また，発癌確認時の ALT 値は30 IU/l 未満が6例(15.0%)，40 IU/l 未満12例(30.0%)および50 IU/l 未満19例(47.5%)と ALT 低値例が約半数を占めた．

考　察

B 型慢性肝炎に対する治療法として IFN 長期投与[1~3]，ラミブジン治療[4~6]が保険適応となり，アデフォビル[7, 8]，エンテカビル[9, 10]の治験が進行中である．

Table 4 Relationship between hepatocelluler carcinoma development and clinical characteristics (age, ALT value and gender) of patients

Age(y.o.)	～30	31～40	41～50	51～60	61～70	71～	total
number of HCC(%)	1(2.5)	1(2.5)	6(15.0)	22(55.0)	7(17.5)	3(7.5)	40

ALT(IU/l)	～30	(～40)	(～50)	31～50	51～100	100～	total
number of HCC(%)	6(15.0)	12(30.0)	19(47.5)	13(32.5)	12(30.0)	9(22.5)	40

Gender	male	female	total
total cases	138	69	207
number of HCC(%)	33(23.9)*	7(10.1)*	40(19.3)

* $p<0.02$

また，HBワクチンによる治療成績[11]も報告されている．このような状況下において，それらの抗ウイルス剤による治療の適応をHBキャリアの経過における発癌リスクから考慮することが，B型肝癌発癌抑止の観点からみて極めて重要であると考えられる．そのためにはHBキャリアの経過を客観的に表すことが必要であり，今回，HBVマーカー，血清トランスアミナーゼ値，および発癌リスクを基準としたHBステージ分類を発案した．組織学的診断については対象中の肝生検施行例60例の検討より，stagingはその進展とHBステージで有意な関係があり，HBステージよりstagingをある程度類推することが可能と考えられる．すなわち，発癌リスクの高いステージIIbやステージIIIではF2以上の症例が大半を占め，発癌リスクの低いステージIaではF0，1が多数を占める．ステージIIa，IIb，IIIは全例抗ウイルス治療の対象と考えられるが，ステージIa，Ibでstagingが進行していない症例では，経過観察のみで自然経過によるHBe Ag，Ab seroconversionを待つという選択肢も存在する．その判断には組織学的診断が重要であるので，生検を行った症例にはHBステージと新犬山分類を，Ib (A1F1) のように併記することが適切ではないかと考える．

HBVマーカーと肝発癌との関係について，我々[12]はインターフェロン治療を施行した症例（平均年齢35歳）の検討より，HBe抗原持続陽性例はHBe抗原消失例に比し有意にB型肝癌発癌率が高く，できるだけ若年齢の間にHBe抗原を消失させる必要性について報告した．池田ら[13]もB型肝硬変例の検討より，肝硬変診断時にHBe抗原陽性例は陰性例に比べ発癌率が高い傾向を示し，HBe抗原陰性例での発癌はHBV-DNA陽性（間歇的陽性も含めて）例にのみ認められ，持続陰性例には1例も認められなかったと報告している．今回の検討は対象の平均年齢が約45歳と比較的高齢のためHBe抗原消失例が多数を占め，HBe抗原陰性，HBV-DNA陽性例であるステージIIIが最も高い発癌率を示した．B型慢性肝疾患においてはHBe抗原持続陽性例が最も発癌リスクが高く，HBe抗原陰性にseroconversionしてもpre C mutantの増殖が続くHBV-DNA陽性例も高い発癌リスクを有し，HBV-DNA持続陰性になってはじめて発癌リスクから回避されると考えられる．

Chu ら[14]はHBe抗原陰性B型慢性肝炎の治療について，HBV-DNA 10^5 copies/ml 以上は抗ウイルス治療の必要があるが，10^5 copies/ml 未満ではその必要がないと報告している．抗ウイルス治療対象の境界をHBV-DNA量 10^4 copies/ml，10^5 copies/ml のいずれにするかは発癌リスクを考慮するうえで極めて重要なポイントと考えられるため，このHBステージ分類を作成するにあたっても詳細に検討した．10^4 copies/ml 以上を治療対象にした場合，発癌防止をさらに押し進めることは期待できるが，過度に治療対象を増やしてしまうマイナス面が大きく，また，10^5 copies/ml を境界とした場合の方が性別，年齢，ALT値，血小板数および発癌率の各因子の有意差が 10^4 copies/ml を境界

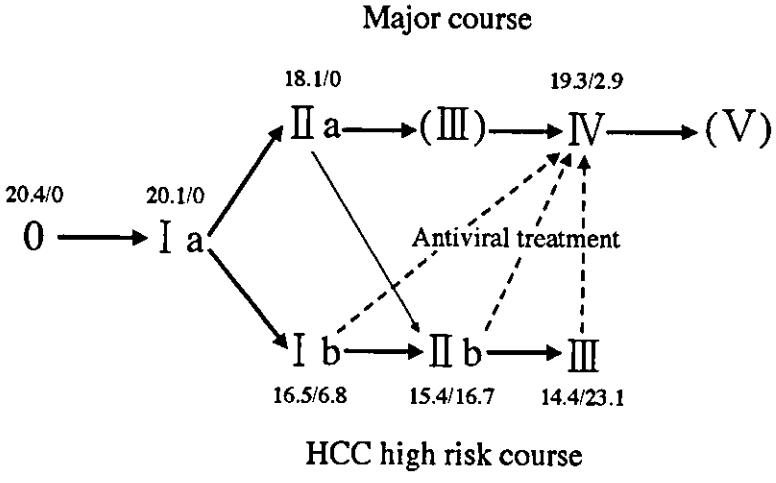

Fig. 1　Clinical courses of HBV carriers

とした場合よりもおしなべて強くでるため 10^5 copies/m*l* が妥当と考えた．すなわち，HBe 抗原陰性で HBV-DNA 10^5 copies/m*l* 以上のステージ III は，10^5 copies/m*l* 未満のステージ IV に比し男性に多く($p<0.01$)，ALT は高値($p<0.001$)，血小板数は低値($p<0.001$)で，発癌率は高率($p<0.05$)であった．特筆すべきは，平均年齢がステージ III 例がステージ IV 例に比し有意に高齢($p<0.01$)であることで，ステージ III とステージ IV は，ステージ III からステージ IV へと移行するという時間的経過の差ではなくて，病態の異なる集団と考えられる．

HBV キャリアの大多数が歩む臨床的治癒の状態へのコースは，ステージ Ia からステージ IIa となり，その後短期間ステージ III を経由した後，速やかにステージ IV に移行するものと考えられる．そしてステージ IV が長期間続いた後 HBs 抗原が消失し，ステージ V となる．一方，B 型肝癌発癌ハイリスク群はステージ Ia からステージ Ib，ステージ IIb と進行し，HBe 抗原が陰性化してステージ III までは到達するが HBV の増殖は持続し，ステージ IV に至ることはない(Fig. 1)．臨床的治癒コースの各ステージにおける初診時の血小板数と発癌リスクは，ステージ 0，Ia，IIa および IV で，それぞれ 20.4 万 0%，20.1 万 0%，18.1 万 0%および 19.3 万 2.9%とほとんど変化を認めないが，B 型肝癌発癌ハイリスクコースにあたるステージ Ib，IIb および III では，それぞれ 16.5 万 6.8%，15.4 万 16.7%および 14.4 万 23.1%と，ステージの移行に従って血小板数の低下と発癌率の増加が認められ，ステージ Ib，IIb および III のキャリアに対する抗ウイルス治療の必要性が強く示唆される．

各ステージにおける抗ウイルス治療薬剤に関しては，今後使用可能となる新しい薬剤も含めて考察する．ステージ Ia は，ステージ 0 の無症候性キャリアが肝炎期に移行した状態のすべての HB キャリアが通過する高ウイルスのステージであり，発癌リスクが極めてまれで，通常は抗ウイルス治療の必要はない．しかし，組織学的に線維化ステージが F2 以上に進行している例は早期に肝硬変に進展する可能性があり，抗ウイルス治療の適応と考えられる．ALT 値が高値を持続する例は，通常 HBV-DNA 量が減少しステージ IIa となるが，ステージ IIa からは若年発症の B 型肝癌例があり，ALT 値持続高値例は抗ウイルス治療の適応となる．Ia，IIa とも薬剤としては若年で免疫応答が良好であるので IFN が第一選択となると考える．IFN について我々は，少量間歇投与が若年例に有効であることを報告した[15]が，特に 30 歳未満例には IFN 治療は長期投与でなくても有効性は高いと考える．一方，高年例に対しては現在行われている 6 カ月投与が基本になると考えられるが，海外ではペグ IFN の有効性についても報告[16]され，本邦でも早期の使用が望まれるところである．ステージ Ib は若年齢を過ぎても HBV-DNA 量の高値が持続する群で，発癌リスクはステージ IIb よりは低頻度であるが，リスク大で抗ウイルス治療の必要がある．Suzuki ら[17]は多変量解析によって，高ウイ

ルス群(HBV-DNA≧100 Meq/ml)であることがYMDD変異株出現に最も寄与する因子であることを報告しており，HBV-DNA量が極めて高値のこの群はラミブジン単独での治療効果の持続は困難で，エンテカビル等の抗ウイルス効果の強い薬剤あるいは併用治療が適応になると考えられる．ステージIIbは発癌リスクが極めて大で抗ウイルス治療の絶対適応である．薬剤はラミブジン等の核酸アナログ単独あるいはIFN，HBワクチンとの併用の選択が考えられる．Ib，IIbはともにHBe抗原陽性期であるが，我々はこの時期においても大半の例はpre-C mutantの出現が確認され，また，IFNはpre-C wild，pre-C mutantのいずれの株にも同等に有効であることを報告[18]した．ラミブジンはpre-C mutant株に対してより強い抗ウイルス効果が得られる[19]こと，また，ラミブジンのYMDD変異株はIFN前投与あるいは併用群において出現率が低率であること(自験例，未発表)を考慮すると，ステージIb，IIb群にはラミブジン単独よりもIFNとの併用がより有効ではないかと考えられる．Schalmら[20]，Barbaroら[21]もIFN，ラミブジン併用治療の有効性について報告している．ステージIII，ステージIVについては前述のとおりであるが，ステージIIIの発癌数は全ステージ中最大で，ALT値の正異に関係なく発癌例がみられる．受診キャリア中の頻度も最大で，全例に対して治療が必要かどうかは今後の検討課題と考えられるが，少なくともALT値異常のとくに男性例は絶対適応であろう．薬剤は高年例が大半を占め，ラミブジンの治療効果が良好で，YMDD変異株の出現も低率であるため，現在のところラミブジンが第一選択であり，YMDD変異株出現例にはアデフォビル等の他の核酸アナログの併用あるいは切り替えで対応できると考えられる．ステージIVはいわゆる臨床的治癒といわれる病態で，抗ウイルス治療の最終目標である．女性の比率が有意に高率であり，このことが女性の発癌率が低い原因と考えられる．まれに発癌例を認めるが，治療の対象にはならない．ステージVに関する我々の15例の長期経過についての検討[22]では，最終観察ポイントにおいて14例が血清HBV-DNA 10^4 copies/ml未満であった(1例は 3.6×10^4 copies/ml)．非B非C肝癌におけるオカルトB型肝癌の問題も残るが，抗ウイルス治療の対象にはならないと考えられる．

B型肝癌発癌抑止のためには，HBVキャリアがどの病期にいるかを診断することが肝要である．我々が提唱したこのHBステージ分類はその診断に極めて有用で，治療適応例には早期に適切な抗ウイルス治療を開始し，発癌例を1名でも減少させたいと考えている．

おわりに

HBVキャリアを，HBe抗原陽性無症候性キャリアからHBs抗原消失までの8ステージに分類した．各ステージにおける発癌リスクと抗ウイルス治療の適応，さらに治療方法はそれぞれ異なり，的確なステージ分類と適切な治療方針の選択が，B型肝炎治療の標準化およびB型肝癌発癌抑止に繋がると考える．最後に，肝硬変例は現在，IFN治療もラミブジン治療も保険適応外である．HBV-DNA陽性の肝硬変例は慢性肝炎例に比し発癌リスクは極めて高く，同病態に対する保険診療での治療が一刻も早く行えることを熱望する．

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Staging of hepatitis B virus carriers based on HBV markers and cancer risk—A system to assist in the selection of appropriate antiviral treatment—

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The clinical manifestations of hepatitis B virus (HBV) carrier state vary and are difficult to be objectively determined due to the lack of a clear staging system (criteria). We therefore devised an HBV carrier staging system based on HBV markers, ALT level, age, and cancer risk and also examined clinical treatments based on this staging system. We determined each stage as follows, stage 0 is HBe antigen-positive asymptomatic carriers with persistently normal ALT values, stage I is HBe antigen-positive carriers with abnormal ALT values and $10^{7.6}$ copies/m*l* and moreof HBV-DNA (younger patients：stage Ia；older patients：stage Ib), stage II is HBe antigen-positive carriers with abnormal ALT values and less than $10^{7.6}$ copies/m*l* of HBV-DNA (younger patients：stage IIa；older patients：stage IIb), stage III is HBe antigen-negative carriers with 10^5 copies/m*l* and more of HBV-DNA, stage IV is HBe antigen-negative carriers with less than 10^5 copies/m*l* of HBV-DNA, and stage V is carriers who no longer have HBs antigens. We believe that this staging system is useful for understanding HBV carrier stage that is related to the proper selection of clinical treatment.

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Jpn. J. Pharm. Health Care Sci.
ノ ー ト 30(1) 53 — 58 (2004)

C型慢性肝炎に対するインターフェロンα-2bとリバビリン併用療法におけるヘモグロビン減少に関する検討

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Study on Decreased Hemoglobin Levels in Combination Therapy with Interferon α-2b and Ribavirin for Chronic Hepatitis C

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Received July 3, 2003
Accepted October 24, 2003

The approval of ribavirin for reimbursement under the health insurance scheme in Japan in 2001 started a new era in interferon (IFN) therapy against chronic hepatitis C, enabling a change from IFN mono therapy to combination therapy with IFN and ribavirin. As the major safety problems of ribavirin, teratogenicity, hemolytic anemia and skin symptoms may be given. Also, there is known to be a greater incidence of decreased hemoglobin (Hb) in combination therapy with IFNα-2b and ribavirin than in the case of IFN mono therapy. Despite this, however, it has been considered that combination therapy may be accomplished if the criteria for reducing the dosage of ribavirin are strictly followed.

In this study, patients receiving combination therapy with IFNα-2b and ribavirin in Osaka National Hospital were followed up to evaluate the decrease in Hb in cases in which the ribavirin was reduced in dosage or discontinued (reduced/discontinued group). Hb levels in this group decreased by 3.0±1.6 g/dL on average after 4 weeks, significantly lower than pretreatment levels. In these subjects, it seemed that the decreased Hb levels after 4 weeks of the combination therapy aggravated anemia symptoms and subjective symptoms such as general fatigue, with the result that combination therapy could not be accomplished.

Key words —— chronic hepatitis C, interferon therapy, ribavirin, decreased hemoglobin level

緒　　言

C型慢性肝炎に対するインターフェロン(IFN)療法が，1992年に導入されてから10年以上が経過した．日本人の場合，C型肝炎ウイルス(HCV)の遺伝子型がgenotype1bでHCV-RNA量が分岐鎖DNAプローブ法で1 Meq/mL以上，またはアンプリコア定量法で100KIU/mL以上あるIFN難治性症例が多く，これまで林ら[1]や加藤ら[2]，奥新らなど[3,4]によりIFN療法における投与方法の工夫が行われてきた．1998年にMcHutchisonら[5]やPoynardらなど[6,7]が，C型慢性肝炎患者に対してリバビリンとIFNα-2bの併用療法とIFNα-2b単独療法での臨床比較試験を行い，併用療法の高い治療効果と安全性について報告した．現在，欧州肝臓学会(EASL)やアジア太平洋肝臓学会(APASL)などにおいて併用療法を標準的治療法としている．わが国でも1998年から2000年にかけて行われた臨床比較試験の結果[8,9]，2001年にリバビリンが保険適応になり，C型慢性肝炎に対するIFN療法は，IFN単独療法からIFNとリバビリンの併用療法という新しい時代になった．リバビリンの安全性上の問題点として，催奇形性と溶血性貧血，皮膚症状などが挙げられる．

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療センター)で行われた併用療法施行症例において追跡調査を行い，リバビリンの減量，または併用療法中止症例(減量・中止群)における要因を明らかにすることを目的に，ヘモグロビン(Hb)値の推移と減少量などについての検討を行ったので報告する．

対　　象

平成14年2月より平成15年3月までに大阪医療センター消化器科において，C型慢性肝炎患者で高ウイルス量(HCV-RNA量が分岐鎖DNAプローブ法で1 Meq/mL以上)のIFN初回治療症例，またはIFN治療後再燃症例に対してリバビリンとIFN α-2bの併用療法を行った全症例を対象とした．投与方法は，IFN α-2b 6～10MIU/dayを2週間連日投与後，週3回22週間歇投与に，リバビリン600mg(体重60kg未満)～800mg(体重60kg以上)/dayを連日併用投与とした．

方　　法

併用療法施行患者を6カ月間の継続終了群と減量・中止群の2群に分類した．両群において，投与開始2週後，4週後のHb値の推移について投与前値との比較を行った．両群間では投与開始4週後のHb値，およびHb減少量について比較検討を行った．投与前Hb値による(投与前Hb値<12g/dL，12g/dL≦Hb値<14g/dL，14g/dL≦Hb値の3群に分類)リバビリンの減量，併用療法中止の割合，投与開始4週後のHb減少量による(Hb減少量≧3.0g/dL，Hb減少量<3.0g/dLの2群に分類)リバビリンの減量，併用療法中止の割合について調査した．合併症および既往歴については，診断記録より調査した．リバビリンの減量および投与中止基準として，Hb値10g/dL未満で200mg減量とし，8.5g/dL未満でIFNとともに投与中止とした．Hb減少以外の有害事象が発現し，投与量の減量または併用療法中止を行う必要がある場合は，主治医の判断でそれを行うこととした．Hb値の推移における投与前値との比較および群間比較には分散分析を使用し，Hb減少量の群間比較には対応のないt検定を使用した．有意差の判定基準は$p<0.05$を有意差とした．

結　　果

併用療法施行症例は44例であった．うち1例は，抗ウイルス効果が認められないため，主治医の判断により併用療法が中止となったため除外した．解析対象症例43例のうち，IFN初回治療症例が6例，再燃症例が37例であり，継続終了群は23例，減量・中止群は20例(リバビリンの減量症例は7例，併用療法の中止症例は13例)であった．減量・中止群における平均年齢は，62.1±8.4歳と継続終了群よりも有意に高く，併用療法開始前の血小板数(PLt)は，平均11.6±3.2×10⁴/μLと有意に低値であった．患者背景を**Table 1**に示す．リバビリンの減量理由の内訳は，Hb値が減量基準に達した症例が6例，併用療法による全身倦怠感症状のため主治医が判断した症例が1例であった．併用療法中止理由の内訳は，Hb値が

Table 1. 患者背景

背景因子	継続終了群		減量・中止群		検定
症例(M/F)	23(18／5)		20(11／9)		
年齢(歳)	56.3±10.9		62.1±8.4		$p<0.05$
セロタイプ(1／2)	19／2 不明 2		16／4		
IFN投与量(6MIU／10MIU)	16／7		11／9		
Rib投与量／day(600mg／800mg)	12／11		11／9		
体重当たりのRib投与量(mg／kg／day)	11.3±2.4	(n=21)	11.8±1.1	(n=14)	N. S
AST(IU／L)	79.6±39.8		75.0±26.5		N. S
ALT(IU／L)	102.2±77.2		95.0±37.7		N. S
T-bil値(mg／dL)	0.9±0.3		0.8±0.3		N. S
RBC($\times10^4$／μL)	4.4±0.5		4.3±0.6		N. S
WBC($\times10^3$／μL)	4.9±1.6		4.3±1.1		N. S
PLt($\times10^4$／μL)	15.7±6.4		11.6±3.2		$p<0.05$
Hb値(g／dL)	13.9±1.8		13.7±1.5		N. S
Scr(mg／dL)	0.8±0.2		0.7±0.1		$p<0.05$
BUN(mg／dL)	15.5±4.5		15.6±2.7	(n=19)	N. S

mean±S. D
対応のないt検定
P<0.05　N. S.　:not significant