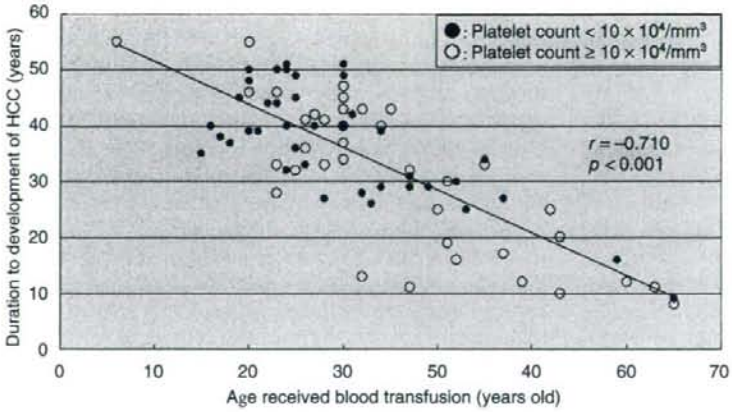

Fig. 1. Interval between age at blood transfusion and age at initial diagnosis in 79 patients with pure hepatitis C virus (HCV)-related hepatocellular carcinoma (*HCC*). *Closed circles*, patients with platelet count $<10 \times 10^4/mm^3$; *open circles*, patients with platelet count $\geq 10 \times 10^4/mm^3$. Statistical analysis by Spearman's nonparametric test

Table 6. Significant variables in association with duration to development of HCC within 25 years using univariate logistic analysis

Variables	Odds ratio	95% confidence interval	*P* value
Age received BT ≥35 years[a]	48.831	5.823–409.514	<0.001
Platelet count $\geq 10 \times 10^4/mm^3$[a]	8.462	1.733–41.306	0.008
Child-Pugh class A	5.173	1.064–25.160	0.042

BT, blood transfusion
[a] Significant variables in multivariate analysis

Discussion

In the present study, we demonstrated the clinicopathological features of elderly patients with HCV-related HCC compared with younger patients. The elderly patients were characterized as lower male/female ratio, better liver function, and less alcohol consumption than the younger patients. At first, we examined all 693 patients with anti-HCV and without HBsAg. Next, we examined 337 patients after excluding patients with factors affecting development of hepatocarcinogenesis. Results of these two examinations were almost the same, as already mentioned. Ultimately, we wanted to emphasize that elderly patients with HCV-related HCC tend to develop HCC despite their low-grade fibrosis stage, and they should be followed more closely.

Several risk factors for the development of HCV-related HCC have been identified to date, such as age, degree of liver fibrosis, male sex, alcohol consumption, positivity for HBsAg, and high AFP level.[15–20] Recently, elderly HCC patients with HCV have increased in number in Japan.[24–26] To improve the survival of elderly cirrhotic patients by increasing the percentage of cancers amenable to effective treatment, it is important to clarify the characteristics of elderly HCC patients with HCV. In the present study, we divided patients with HCV-related HCC into two groups, the younger and the elderly group, according to age at first diagnosis. In previous studies,[16,18,20] the authors divided HCC patients into two groups by age 50, 60, or 70. As we reported previously, elderly patients with HCV-related HCC have recently increased in number,[24] and in this study the median ages of patients were 66 and 69 for men and women, respectively. Because we want to clarify the characteristics of elderly patients in detail, they were divided by age less than or more than 70 years.

The incidence of HCC in HCV-related liver cirrhosis is significantly higher in patients with HBV antibody, such as anti-HBs and anti-HBc, than in those without.[27] First, we analyzed the patients who were positive for anti-HCV but negative for HBsAg. Furthermore, we also excluded anti-HBc-positive patients to reduce the influence of HBV on such analysis, and then we performed the next examination.

Several studies have shown that high AFP value is one of the risk factors of HCC.[15–20] In the present study, there was no significant difference in AFP between the elderly and the younger group.

Alcohol consumption is considered a significant risk factor for HCV-related HCC.[15,16,18] Our results showed significant differences between the elderly and the younger group, which might suggest that habitual alcohol drinkers develop HCC earlier than non-drinkers.

Silini et al.[37] reported a close association between HCV 1b and HCC, but recent studies have failed to

establish a correlation between HCV genotype and HCC.[28,38] In our study, the proportion of patients with genotype 1b was significantly greater in the younger group than the elderly group.

The Child-Pugh class correlates well with liver function. Our results showed that the elderly group tended to have better Child-Pugh class than the younger group. Platelet counts also indicated that the elderly group had better liver function and lower grade of fibrosis stage. The results of the pathological examination might support a tendency for the elderly group to have a lower grade of fibrosis stage, although this result may have a bias for selecting patients with good liver function when elderly patients underwent hepatic resection. Several studies reported that fibrosis stage and aging have major impacts on the incidence of HCC.[15–21] Yoshida et al.[21] suggested that the risk of HCC is strongly associated with the stage of liver fibrosis and that the annual incidence of HCC increased with the degree of liver fibrosis in Japan. In addition, progression of liver fibrosis is also strongly associated with aging.[22,23] As we recently reported, the time interval between blood transfusion and diagnosis of HCC was significantly shorter when patients received blood transfusions at an older age than at a younger age.[24] Therefore, we assumed that fibrosis stage could correlate strongly with aging for hepatocarcinogenesis and that elderly HCC patients should have a higher grade of fibrosis stage than younger patients. However, we found many cases with HCC and low-grade fibrosis stage among the elderly group. Furthermore, patients who received blood transfusions at an older age developed HCC within a shorter period of time than those at a younger age. It should be noted, however, that the former included more patients with a noncirrhotic liver than the latter. Elderly patients seemed to have a tendency to develop HCC earlier despite their low-grade fibrosis stage. Why is aging an independent risk factor for hepatocarcinogenesis? Chiaramonte et al.[39] suggested that increasing age is a risk factor, probably because it reflects a longer duration of cirrhosis, but in our study the majority of elderly patients developed HCC from a noncirrhotic liver. These findings suggest that the shorter duration to development of HCC was not only the result of early progression of liver fibrosis stage but caused by other reasons, e.g., aging. Surprisingly, fibrosis stage seemed to be inversely proportional to age at diagnosis. This finding could mean that the impact of aging is stronger than the degree of liver fibrosis for development of HCV-related HCC. However, the present study is a retrospective study and included only HCC patients while excluding non-HCC patients with HCV. Further studies are needed to determine the correlation between HCV patients with HCC and those without.

Benson et al.[40] suggested that the increase in cancer rates that occurs after the age of 30 is the result of activation of quiescent cells with damaged DNA, or deactivation of DNA surveillance or repair, or impaired apoptosis. We reported previously that in chronic hepatitis C patients, the rate of DNA synthesis becomes high and genomic instability may increase during alternating necrosis and regeneration, resulting in malignant transformation and progression to an aggressive state.[41] We also reported that telomere length in the liver shortened not only with progression of fibrosis staging but also with aging. Another study suggested that the reduction of telomere length in chronic liver disease increased the risk of HCC development.[42] Considered together, the foregoing results suggest that elderly patients might have sufficiently short telomeres for developing HCC even if they had a noncirrhotic liver because the telomeres have shortened in length with aging.

In conclusion, we demonstrated in the present study that elderly patients with HCV developed HCC despite low-grade fibrosis stage. Further studies will be required about the impact of aging on HCV-related hepatocarcinogenesis.

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ORIGINAL ARTICLE

Combination therapy of lamivudine and adefovir in Japanese patients with chronic hepatitis B

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Abstract
Purpose This study aimed to clarify the long-term efficacy of the lamivudine treatment in Japanese patients with chronic hepatitis B either with or without lamivudine resistance or with or without adefovir add-on treatment.
Methods We followed 110 patients who received lamivudine for more than 12 months, including 67 hepatitis B e antigen (HBeAg)-positive and 43 HBeAg-negative patients.
Results The median follow-up after the onset of lamivudine was 48 (range = 12–86) months. In all the patients with or without lamivudine resistance, the level of alanine aminotransferase (ALT) normalization decreased from 70.0% at 1 year to 36.4% at 5 years and the loss of serum HBV DNA level decreased from 72.7% at 1 year to 31.8% at 5 years. Sixty patients (54.6%) developed a lamivudine-resistant mutation, and this occurrence was more frequently observed in those who were HBeAg-positive ($P < 0.01$), those with a low level of ALT ($P < 0.05$), and those with a high level of serum HBV DNA ($P < 0.01$). Thirty-six of 60 patients received adefovir in addition to lamivudine to treat breakthrough hepatitis. A Cox proportional hazards model analysis revealed the level of baseline HBV DNA to be the best predictive factor for the virus recrudescence (risk ratio = 0.466, 95% confidence interval [CI]: 0.246–0.842, $P = 0.011$) and the breakthrough hepatitis (risk ratio = 0.444, 95% CI: 0.218–0.879, $P = 0.019$). We carefully monitored the efficacy of this treatment both in patients

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who received adefovir and in those who did not since the beginning of the lamivudine treatment. The normalization level of ALT was 61.4% at 5 years and the loss of serum HBV DNA was 61.4% at 5 years since lamivudine was started. A histologic improvement was observed in patients with ALT levels less than two times the upper limit of normal at the time of a second liver biopsy.

Conclusions Although the efficacy of lamivudine is limited because of breakthrough hepatitis, adefovir was used as a salvage treatment of patients with lamivudine-resistant chronic hepatitis B. In addition, lamivudine was used for the treatment of Japanese patients with chronic hepatitis B with or without lamivudine resistance, and was found to be useful regarding the long-term virologic and biochemical responses.

Keywords Chronic hepatitis B Lamivudine Adefovir

Introduction

The number of patients chronically infected with hepatitis B virus (HBV) is reported to be more than 350 million worldwide [1, 2]. These patients are at an increased risk to develop cirrhosis, hepatic decompensation, and hepatocellular carcinoma [3, 4]. The aims of treatment of chronic hepatitis B are to achieve a sustained suppression in HBV replication and remission in liver disease. The endpoints used to assess the treatment response include the normalization of the alanine aminotransferase (ALT) level, the loss of serum HBV DNA, the loss of hepatitis B e antigen (HBeAg) with or without the detection of antibody to HBeAg (HBeAb), and an improvement in the liver histology.

Interferon, which has been shown to have an antiproliferative effect on the virus, has been used for the treatment of chronic hepatitis B; however, its efficacy has been limited to only a small percentage of preselected patients [5, 6]. Lamivudine is the first nucleoside analog to be approved for the treatment of the patients with chronic hepatitis B. Although the short-term efficacy of lamivudine therapy has been well documented, the occurrence of lamivudine-resistant mutations has also been reported to increase with extended use [7–9]. Adefovir dipivoxil is a nucleotide analogue of adenosine monophosphate and has been shown to be effective in suppressing not only wild-type HBV but also lamivudine-resistant HBV [10, 11].

Lamivudine has been used in Japan since November 2000 for the treatment of patients with chronic hepatitis B. Since December 2004, adefovir, which decreases the incidence of lamivudine-resistant mutations, has been administered to patients demonstrating a flare-up of hepatitis. The aims of this study were to clarify (1) the long-term efficacy of the lamivudine treatment of Japanese patients with chronic hepatitis B with or without adefovir add-on treatment of breakthrough hepatitis due to lamivudine resistance, (2) the rate of both occurrence of the lamivudine-resistant mutant virus and recurrence of hepatitis related to the lamivudine-resistant virus, and (3) the long-term consequences of the lamivudine and adefovir combination therapy for chronic hepatitis B.

Patients and methods

Eligible patients were enrolled at Fukuoka University Hospital. The key inclusion criteria were seropositivity for hepatitis B surface antigen and serum HBV DNA. Both HBeAg-positive and HBeAg-negative patients were included. Lamivudine was administered orally at a dose of 100 mg daily for the treatment of the patients who had elevated ALT levels, namely, more than 1.5 times the upper limit of normal. Exclusion criteria included decompensated liver disease, a coexisting serious medical or psychiatric illness, a history of alcohol or drug abuse within 1 year before entry, and coinfection with hepatitis C virus or human immunodeficiency virus, and advanced hepatocellular carcinoma. We examined the effects of the lamivudine treatment on the normalization of the ALT levels, the loss of HBeAg, HBeAg seroconversion, and the loss of serum HBV DNA at 1, 2, 3, 4, and 5 years, respectively. To determine the factors that influenced the occurrence of lamivudine-resistant mutation in HBV, we also examined the pre-treatment clinical factors.

Among the patients who developed a lamivudine-resistant virus, the patients who showed an elevated ALT levels of more than two times the upper limit of normal and that continued for longer than 2 months received adefovir at an oral dose of 10 mg daily in addition to lamivudine. In those patients who had adefovir in addition to lamivudine for the treatment of recurrence hepatitis, we examined the effect of the adefovir treatment on the normalization of the ALT levels and the loss of serum HBV DNA since the time the adefovir treatment was started. Furthermore, we studied the efficacy of this combination therapy on the normalization of the ALT levels and the loss of serum HBV DNA at 1, 2, 3, 4, and 5 years, respectively, since the time the lamivudine treatment was started.

The histologic improvement was analyzed in 15 patients who underwent a second liver biopsy. The patients were subjected to a liver biopsy using a Menghini needle guided by ultrasonography. Formalin-fixed liver specimens were stained with hematoxylin and eosin for morphologic evaluations, with Masson's trichrome staining for the assessment of fibrosis.

HBeAg and HBeAb were detected via a chemiluminescent enzyme immunoassay (ARCHITECT HBeAg and ARCHITECT HBeAb, Abbott Japan, Tokyo, Japan). The serum HBV DNA levels in all patients before and during lamivudine treatment were measured via Transcription Mediated Amplification (DNA probe [FR]-HBV; Fujirebio Inc, Tokyo, Japan). The HBV levels were expressed as the log genome equivalent per milliliter (LGE/ml) and the upper and lower detection limits of the assay were 8.7 and 3.7 log copies/ml, respectively. The incidence of lamivudine mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) motif was measured by means of a polymerase chain reaction-enzyme linked mini-sequence assay (PCR-ELMA; SMITEST HBV-YMDD Mutation Detection Kit, Medical and Biological Laboratories, Nagano, Japan).

Statistical analysis

Fisher's exact test was used for sex and HBeAg positivity for comparisons between groups. Comparisons of the means ± standard deviations were performed using Student's *t*-test for age, the ALT level, and the serum HBV DNA level. A *P*-value of less than 0.05 was considered to be statistically significant. For multivariate analyses, the Cox proportional hazards model analysis was used. Ninety-five CIs were used throughout.

Results

Patients ($n = 327$) who were seropositive for hepatitis B surface antigen were from our hospital and all were Japanese patients. Among these cases, 141 patients received lamivudine as the therapy for chronic hepatitis B and 110 eligible patients have been followed for more than 1 year (67 patients who were HBeAg-positive and 43 patients who were HBeAg-negative) (Table 1). This study reviewed the cumulative outcome of the patients with chronic hepatitis B who were treated with lamivudine, and the patients who had been followed for more than 2, 3, 4, and 5 years numbered 94, 79, 63, and 44, respectively. The median follow-up after the start of lamivudine was 48 (range = 12–86) months. In all patients, including those who were either HBeAg-positive or HBeAg-negative, the normalization of ALT levels decreased with the duration of lamivudine treatment from 70.0% at 1 year to 56.4%, 48.3%, 49.2%, and 36.4% at 2, 3, 4, and 5 years and the loss of serum HBV DNA decreased from 72.7% at 1 year to 53.2%, 41.8%, 39.7%, and 31.8% at 2, 3, 4, and 5 years, respectively (Table 2). These results included all the patients with or without lamivudine resistance. In our intention-to-treat analysis, the patients who had an efficacy of adefovir salvage treatment of breakthrough hepatitis were excluded from the efficacy group of lamivudine treatment. In the HBeAg-positive patients, the normalization of the ALT levels decreased during the lamivudine treatment from 71.6% at 1 year to 55.7%, 42.6%, 41.9%, and 22.6% at 2, 3, 4, and 5 years, respectively (Table 2). Their loss of serum HBV DNA was 22.6% and HBeAg seroconversion was 22.6% during the 5-year period of lamivudine treatment. In the HBeAg-negative patients, the normalization of the ALT levels was 67.4% at 1 year and 57.6%, 60.0%, 65.0%, and 69.2% at 2, 3, 4, and 5 years and the loss of serum HBV DNA was 76.7% at 1 year and 69.7%, 66.0%, 53.0%, and 53.8% at 2, 3, 4, and 5 years, respectively.

The occurrence of a lamivudine-resistant mutation was seen in 60 patients. The mutation proportion increased from 27.3% at 1 year to 43.6%, 50.1%, 53.6%, and 54.6%

Table 1 Patients baseline demographics and disease characteristics ($n = 110$)

	HBeAg-positive $n = 67$	HBeAg-negative $n = 43$	All patients $n = 110$
Gender, male:female (%male)	43:24 (64.2%)	29:14 (67.4%)	72:38 (65.6%)
Age (years)			
Mean ± SD	41.0 ± 12.5	47.9 ± 9.4	43.7 ± 11.9
Median	42	47	45
Range	18–68	27–69	18–69
Alanine aminotransferase (IU/l)[a]			
Mean ± SD	208.5 ± 246.9	185.4 ± 238	199.3 ± 244.8
Median	110	89	92
Range	45–1148	45–907	45–1148
HBV DNA (LGE/ml)			
Mean ± SD	7.52 ± 1.06	6.16 ± 1.95	6.99 ± 1.62
Median	7.6	6.9	7.3
Range	4.3–8.7	3.7–8.4	3.7–8.7

HBeAg: Hepatitis B e antigen

[a] The upper limit of the normal range is 30 IU per liter

Table 2 The efficacy of lamivudine treatment in the patients with or without lamivudine-resistance ($n = 110$)

	At 1 year ($n = 110$)	At 2 years ($n = 94$)	At 3 years ($n = 79$)	At 4 years ($n = 63$)	At 5 years ($n = 44$)
All patients ($n = 110$)					
ALT normalization	77 (70.0%)	53 (56.4%)	38 (48.3%)	31 (49.2%)	16 (36.4%)
Loss of HBV DNA	80 (72.7%)	50 (53.2%)	33 (41.8%)	25 (39.7%)	14 (31.8%)
	At 1 year ($n = 67$)	At 2 years ($n = 61$)	At 3 years ($n = 54$)	At 4 years ($n = 43$)	At 5 years ($n = 31$)
HBeAg-positive patients ($n = 67$)					
ALT normalization	48 (71.6%)	34 (55.7%)	23 (42.6%)	18 (41.9%)	7 (22.6%)
Loss of HBV DNA	47 (70.1%)	27 (44.3%)	19 (35.2%)	14 (32.6%)	7 (22.6%)
Loss of HBeAg	20 (29.9%)	20 (32.8%)	19 (35.2%)	13 (30.2%)	7 (22.6%)
HBeAg seroconversion	16 (23.9%)	9 (31.1%)	18 (33.3%)	13 (30.2%)	7 (22.6%)
	At 1 year ($n = 43$)	At 2 years ($n = 33$)	At 3 years ($n = 25$)	At 4 years ($n = 20$)	At 5 years ($n = 13$)
HBeAg-negative patients ($n = 43$)					
ALT normalization	29 (67.4%)	19 (57.6%)	15 (60.0%)	13 (65.0%)	9 (69.2%)
Loss of HBV DNA	33 (76.7%)	23 (69.7%)	14 (66.0%)	11 (53.0%)	7 (53.8%)

ALT: Alanine aminotransferase

HBeAg: Hepatitis B e antigen

at 2, 3, 4, and 5 years of treatment, respectively. Table 3 shows the number of patients who developed virus recrudescence at each year. This occurrence was more frequent in those who were HBeAg-positive ($P < 0.01$), those with a low ALT level ($P < 0.05$), and those with a high level of serum HBV DNA ($P < 0.01$) at the time the lamivudine treatment was started (Table 4). Thirty-six (60.0%) of the 60 patients received adefovir for the treatment of breakthrough hepatitis due to a lamivudine-resistant mutation, whereas the other 24 patients with a slight elevation in the ALT level did not receive adefovir. The patients who received adefovir had significantly higher levels of serum HBV DNA at the time the lamivudine treatment was started than those who did not receive adefovir (Table 5). Cox proportional hazards model analysis was used to determine the factors predicting viral recrudescence and breakthrough hepatitis. The patients who had more than 7.0 LGE/ml of serum HBV DNA level at the time the lamivudine treatment was started showed a significantly frequent occurrence of a lamivudine-resistant mutation (risk ratio = 0.466, 95% CI: 0.246–0.842, $P = 0.011$; Table 6). The patients who had more than 7.7 LGE/ml of serum HBV DNA at the time the lamivudine treatment was started more frequently received adefovir add-on therapy for breakthrough hepatitis (risk ratio = 0.444, 95% CI: 0.218–0.879, $P = 0.019$; Table 6).

Table 3 The occurrence of lamivudine-resistant mutation during 5 years

	Number of patients	Baseline HBV DNA levels Mean ± SD (LGE/ml)
At 1 year	30	7.46 ± 1.15
At 2 years	18	7.56 ± 1.07
At 3 years	8	6.98 ± 2.35
At 4 years	3	7.46 ± 0.70
At 5 years	1	6.3

Table 4 Comparison between those patients who had virus recrudescence and those who did not

	Virus recrudescence ($n = 60$)	Non-virus recrudescence ($n = 50$)	P
Age (years) mean ± SD	43.5 ± 11.4	44.4 ± 12.3	NS
Gender: male:female (%male)	44:16 (73.3%)	28:22 (56.0%)	NS
HBeAg-positive patients	44 (73.3%)	23 (46.0%)	<0.01
Alanine aminotransferase (IU/l)			
Mean ± SD	157.9 ± 218.5	246.6 ± 261.6	<0.05
Serum HBV DNA (LGE/ml)			
Mean ± SD	7.40 ± 1.36	6.49 ± 1.75	<0.01

HBeAg: Hepatitis B e antigen

NS: Not significant

Table 5 Comparison between those patients who received adefovir and those who did not

	Administration of adefovir ($n = 36$)		No administration of adefovir ($n = 24$)		P
Age (years) mean ± SD	45.0 ± 10.5		41.3 ± 12.3		NS
Gender: male:female (%male)	29:7 (80.1%)		15:9 (62.5%)		NS
HBeAg-positive patients	25 (69.4%)		19 (79.2%)		NS
Alanine aminotransferase (IU/l)					
Mean ± SD	148.7 ± 202.5		170.0 ± 239.6		NS
Serum HBV DNA (LGE/ml)					
Mean ± SD	7.64 ± 1.03		6.91 ± 1.30		<0.05
YMDD mutation	YIDD	20	YIDD	13	
	YVDD	8	YVDD	4	
	YIDD + YVDD	3	YIDD + YVDD	0	

HBeAg: Hepatitis B e antigen
NS: Not significant
YMDD mutation: YMDD motif of the HBV DNA polymerase
YIDD: Methionine to isoleucine
YVDD: Methioneine to valine

Table 6 Multivariate analysis with Cox proportional hazards model

	Variable	P-value	Risk ratio	95% CI
Virus recrudescence	HBV DNA ≧ 7.0 LGE/ml	0.011	0.466	0.246–0.842
Breakthrough	HBV DNA ≧ 7.7 LGE/ml	0.019	0.444	0.218–0.879

Only variables that achieved statistical significance ($P < 0.05$) are shown
CI: Confidence interval
Breakthrough; administration of adefovir for breakthrough hepatitis due to lamivudine resistance

Table 7 The efficacy of the adefovir add-on treatment

	At 1 year ($n = 36$)	At 2 years ($n = 19$)	At 3 years ($n = 11$)
All patients ($n = 36$)			
ALT Normalization	17 (47.2%)	11 (57.9%)	9 (81.8%)
Loss of HBV DNA	17 (47.2%)	13 (68.4%)	10 (90.9%)
	At 1 year ($n = 25$)	At 2 year ($n = 13$)	At 3 years ($n = 8$)
HBeAg-positive patients ($n = 25$)			
ALT Normalization	12 (48.0%)	7 (53.8%)	7 (87.5%)
Loss of HBV DNA	9 (36.0%)	8 (61.5%)	7 (87.5%)
Loss of HBeAg	3 (12.0%)	5 (38.5%)	6 (75.0%)
HBeAg seroconversion	3 (12.0%)	5 (38.5%)	6 (75.0%)
	At 1 year ($n = 11$)	At 2 year ($n = 6$)	At 3 years ($n = 3$)
HBeAg-negative patients ($n = 11$)			
ALT Normalization	5 (45.5%)	4 (66.7%)	2 (66.7%)
Loss of HBV DNA	8 (72.7%)	5 (83.3%)	3 (100%)

ALT: Alanine aminotransferase
HBeAg: Hepatitis B e antigen

Of these 36 patients who received adefovir, the normalization of ALT levels was 47.2%, 57.9%, and 81.8% at 1, 2, and at 3 years and their loss of serum HBV DNA was 47.2%, 68.4%, and 90.9% at 1, 2, and at 3 years, respectively (Table 7). At the time of this analysis, the median total duration of adefovir treatment was 24 (range = 12–56) months and no adefovir-resistant mutation has been detected in any of these patients.

Fifty patients who did not develop lamivudine resistance showed the normalization of their ALT levels to be 84.0% at 1 year and 86.1%, 92.0%, 90.9%, and 91.9% at 2, 3, 4, and 5 years and the loss of serum HBV DNA was

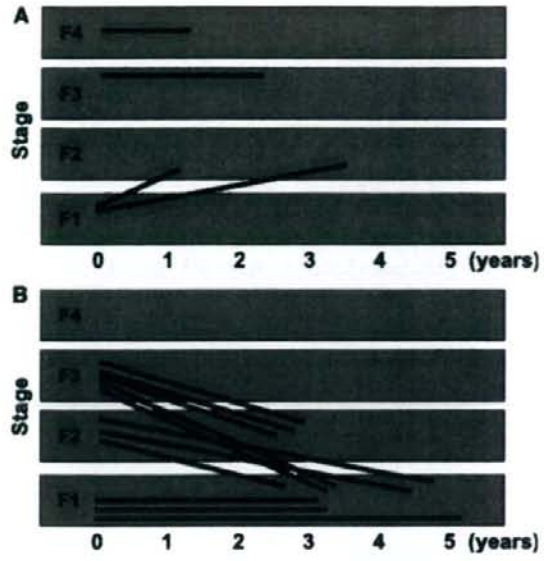

Fig. 1 A follow-up study of liver histology on the patients with chronic hepatitis B treated with lamivudine. (**a**) Four patients whose alanine aminotransferase levels were more than 2 times the upper limit of normal showed no improvement in liver fibrosis at the second liver biopsy. (**b**) Nine patients whose alanine aminotransferase levels were less than 2 times the upper limit of normal demonstrated an improvement in liver fibrosis at the second liver biopsy even if the serum HBV DNA was positive. Another 3 patients whose degree of fibrosis was diagnosed to be F1 at the first liver biopsy showed no change in liver fibrosis

92.0% at 1 year and 94.4%, 96.0%, 95.5%, and 100% at 2, 3, 4, and 5 years, respectively. The results were good for the patients who did not develop lamivudine resistance.

Fifteen patients who were treated with lamivudine underwent a repeat liver biopsy. The changes in stages of liver fibrosis are shown in Fig. 1. Figure 1a shows the group of the patients whose ALT levels were more than two times the upper limit of normal. Figure 1b shows the group of the patients whose ALT levels were less than two times the upper limit of normal. A progression in the fibrosis stage was observed in two patients and an improvement in the fibrosis stage was observed in 8 patients. Even if the serum HBV DNA level showed positive values, the degree of liver fibrosis improved on the basis of the findings of a second liver biopsy in the patients who were treated with lamivudine if the ALT level was less than two times the upper limit of normal.

To clarify the long-term efficacy of the lamivudine treatment of Japanese patients with chronic hepatitis B with or without adefovir add-on treatment of breakthrough hepatitis due to lamivudine-resistance, we investigated the efficacy of the lamivudine treatment by our new approach. Table 2 shows those patients who had an efficacy of adefovir salvage treatment of breakthrough hepatitis and were excluded from the efficacy group of the patients with lamivudine treatment. In addition, in Table 8, the patients who had the efficacy of adefovir add-on treatment were included in the efficacy group for 5-year period since lamivudine treatment was started. These results included all the patients

Table 8 The efficacy of lamivudine treatment with or without adefovir add-on ($n = 110$)

	At 1 year ($n = 110$)	At 2 years ($n = 94$)	At 3 years ($n = 79$)	At 4 years ($n = 63$)	At 5 years ($n = 44$)
All patients ($n = 110$)					
ALT normalization	77 (70.0%)	55 (58.5%)	48 (60.8%)	42 (66.7%)	27 (61.4%)
Loss of HBV DNA	80 (72.7%)	55 (58.5%)	43 (54.4%)	36 (57.1%)	27 (61.4%)
	At 1 year ($n = 67$)	At 2 years ($n = 61$)	At 3 years ($n = 54$)	At 4 years ($n = 43$)	At 5 years ($n = 31$)
HBeAg-positive patients ($n = 67$)					
ALT normalization	48 (71.6%)	34 (55.7%)	29 (53.7%)	26 (60.5%)	17 (54.8%)
Loss of HBV DNA	47 (70.1%)	27 (44.3%)	24 (44.4%)	21 (48.8%)	16 (51.6%)
Loss of HBeAg	20 (29.9%)	20 (32.8%)	20 (37.0%)	18 (41.9%)	14 (45.2%)
HBeAg seroconversion	16 (23.9%)	19 (31.1%)	19 (35.2%)	18 (41.9%)	14 (45.2%)
	At 1 year ($n = 43$)	At 2 years ($n = 33$)	At 3 years ($n = 25$)	At 4 years ($n = 20$)	At 5 years ($n = 13$)
HBeAg-negative patients ($n = 43$)					
ALT Normalization	29 (67.4%)	21 (63.6%)	19 (76.0%)	16 (80.0%)	10 (76.9%)
Loss of HBV DNA	33 (76.7%)	28 (84.8%)	19 (76.0%)	15 (75.0%)	11 (84.6%)

ALT: Alanine aminotransferase

HBeAg: Hepatitis B e antigen

with or without lamivudine-resistance and all the patients with or without adefovir add-on therapy. In all these patients, including those who were HBeAg-positive and those who were HBeAg-negative, the normalization of the ALT levels was 61.4% at 5 years since lamivudine treatment was started (Table 8). The loss of serum HBV DNA was 61.4% at 5 years since the lamivudine treatment was started. In the HBeAg-positive patients, the normalization of the ALT levels, the loss of serum HBV DNA, and HBeAg seroconversion was 54.8%, 51.6%, and 45.2% at 5 years, respectively, since the lamivudine treatment was started. In the HBeAg-negative patients, the normalization of the ALT levels and the loss of serum HBV DNA was 76.9% and 84.6% at 5 years, respectively, since the lamivudine treatment had been started.

Discussion

We herein describe the long-term efficacy of lamivudine treatment over a 5-year period. In all patients, including those who were HBeAg-positive and those who were HBeAg-negative, the normalization of ALT levels and the loss of serum HBV DNA gradually decreased to 36.4% and 31.8% at 5 years, respectively. The efficacy of lamivudine treatment was only about 30%. This result showed that lamivudine monotherapy could not improve the long-term outcomes in the patients with chronic hepatitis B. However, in the HBeAg-negative patients, the effects of lamivudine treatment were maintained for long-term. Although we assessed only a small number of patients in this study, we consider lamivudine monotherapy to be an effective treatment modality for patients with HBeAg-negative chronic hepatitis B to improve the long-term outcomes. On the other hand, because in the HBeAg-positive patients, virus recrudescence was more frequently observed than in the HBeAg-negative patients, the efficacy of the lamivudine treatment for 5 years was only about 20%. HBeAg-positive patients who demonstrated a high value of serum HBV DNA level and a low ALT level at the start of the lamivudine therapy showed a significant correlation with an increase in the occurrence of lamivudine-resistant mutations. Our Cox proportional hazards model analysis shows that to obtain serum HBV DNA levels of less than 7.7 LGE/ml before lamivudine treatment might associate with good outcomes in those patients. These patients are therefore recommended to reduce their serum HBV DNA levels before commencing lamivudine treatment and using interferon α or other therapeutic options [5, 6, 12]. Further large-scale and long-term studies are needed to confirm these observations.

In our study, although most virus recrudescence was observed within 1 year after the lamivudine treatment, 1 patient demonstrated virus recrudescence at 5 years after the lamivudine treatment was started. This is a very important finding and we must therefore carefully monitor the serum HBV DNA levels of the patients even if they show a good long-term response to the lamivudine treatment. Thirty-six of the patients with virus-recrudescence had adefovir added to the lamivudine regimen for the treatment of breakthrough hepatitis. However, the other 24 patients (40%) did not need adefovir to be added to the treatment regimen because they did not demonstrate hepatitis. In our study, even if the serum HBV DNA level was found to be positive, a histologic improvement was obtained in patients with ALT levels that were under 2 times the upper limit of normal at the time of a second liver biopsy. We thus consider that the normalization of ALT levels might therefore be more important than achieving a negative serum HBV DNA state to achieve a remission of liver disease. However, the risks of hepatocellular carcinoma and cirrhosis in the patients with chronic hepatitis B have recently been reported to be related to the serum HBV DNA levels [13, 14]. Our 24 patients who did not have adefovir added to the treatment regimen, even if they had virus recrudescence, all required a long-term follow-up to monitor whether or not they might progress to either cirrhosis or hepatocellular carcinoma.

Some reports have shown that among patients who experienced HBeAg seroconversion during the lamivudine treatment, the durability of the response after the cessation of therapy ranged from 38% to 77% [15–17]. Because lamivudine therapy still continues to be administered in Japan to avoid any posttreatment flare-ups of hepatitis [18–20], our patients continue to receive lamivudine treatment; therefore, our data are not comparable with other studies involving a cessation of treatment.

Previous studies reported that in patients receiving adefovir, the HBV DNA level decreased by 3.5 to 3.9 $\log_{10}$ from the baseline level [21, 22]. In addition, studies from Asia reported that patients with lamivudine resistance have been treated with adefovir either in monotherapy or in combination with lamivudine without any significant differences between the 2 regimens [23, 24]. On the other hand, studies from Europe reported that adding adefovir to lamivudine for the treatment of patients with lamivudine-resistant HBeAg-negative chronic hepatitis B maximizes the anti-viral efficacy because of the absence of viral resistance [25, 26]. In Japan, adefovir has been used as an additional therapy to suppress viral replication with lamivudine-resistant mutations. In all the patients investigated in our study, adefovir was added to the lamivudine regimen. However, no virologic or biochemical breakthrough was reported because no adefovir-resistance occurred in any of our patients. We thus considered that the condition of no adefovir-resistance might have occurred as all

our patients received adefovir in combination with lamivudine.

To clarify the long-term efficacy of the lamivudine treatment of Japanese patients with chronic hepatitis B, we investigated the efficacy of lamivudine treatment on the basis of our new approach. In all the patients with or without lamivudine resistance and with or without adefovir add-on treatment, the normalization of the ALT levels was 61.4% and the loss of serum HBV DNA was 61.4% after the 5-year period of treatment from the time of lamivudine-treatment. This study is the first report to clarify the long-term efficacy of lamivudine treatment either with or without adefovir from the time the lamivudine treatment was started. Our study suggests that even in patients with chronic hepatitis B who have a high HBV DNA level and/or who are HBeAg-positive, the combination therapy of lamivudine and adefovir appears to be an effective treatment modality. This is a retrospective observational study with a relatively heterogeneous patient population. Although this study has its limitation, it represents the real situation for the treatment of chronic hepatitis B in Japan. The advantages of this study, such as being a single-center study, where all tests were performed in the same laboratory using the same methods, are thus considered to outweigh these limitations. These preliminary observations need to be validated in future studies with a larger number of patients.

In conclusion, although the efficacy of lamivudine is limited because of breakthrough hepatitis, adefovir was used as a salvage treatment of lamivudine resistance in patients with chronic hepatitis B. Therefore, the use of lamivudine for the treatment of Japanese patients with chronic hepatitis B with or without lamivudine-resistance is thus considered to be a useful treatment modality for obtaining long-term virologic and biochemical responses.

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肝臓　49巻11号　524-525（2008）

＜速　報＞

肝硬変に対する瀉血療法による血清AFP値の低下

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緒言：瀉血療法はC型慢性肝炎においてALTを低下させ，さらに発癌抑制効果を持つことが報告されている[1]．AFPは肝癌の診断に有用な腫瘍マーカーであるが，肝硬変における高AFP血症は肝癌発生の危険因子と考えられている[2]．そこで我々は肝硬変に対する瀉血療法中のAFP値の変化に着目した．

対象と方法：6カ月以上の瀉血療法を行った肝硬変患者9例を対象とした．平均年齢は53.9歳（45-62歳）で全例男性であった．HCV症例7例，NASH症例2例で，ラジオ波焼灼術による肝癌の治療歴のある2例を含むが，これらは治療後の造影CTで焼灼が十分であることが確認され，その後も6カ月以上再発を認めていない．瀉血は1回400 mlで月1回のペースで行い，治療前と開始6カ月または12カ月の検査値の比較を行った．

成績：9症例の検査値（平均±SE）を治療前後で比較すると，ALTは111.4±22.9 IU/lから76.1±19.4 IU/lと低下傾向を認めた．AFPは102.0±72.0 ng/mlから35.5±19.2 ng/mlとフェリチンと同様に有意に低下した．なお，2例ではALTが瀉血後に上昇していたが，AFPはこれらの症例も含む全例で低下していた（Table 1）．

考察：肝硬変においては強力ネオミノファーゲンC投与によってALTを低下させた場合でもAFPの有意な低下はみられないとの報告がある[3]．瀉血療法によるALTの低下は，十分な除鉄後に始まるが，本9症例のAFPの低下は治療早期よりみられ，ALTよりもむしろフェリチンと平行しており，抗炎症ではなく除鉄による直接的な効果が推測される．一方，インターフェロンα（IFNα）はALTの低下だけでなくAFPを低下させるが，IFNαは直接的な発癌抑制作用を持つため，このAFPの低下は発癌抑制につながると考えられている[3]．瀉血療法も著明にAFPを低下させたことから，IFNαと同様に抗炎症以外の発癌抑制効果を持つ可能性がある．現在，メカニズムの解明と長期観察を行っている．

Table 1　Changes of serum ALT, ferritin and AFP levels during phlebotomy therapy

age	gender	etiology	follow up period/ total volume of phlebotomy	ALT (IU/L)		ferritin (μg/dL)		AFP (ng/mL)	
				before	after	before	after*	before	after*
61	M	HCV**	6 months/2400 L	87	143	323	21	670.9	110.3
60	M	HCV	12 months/4800 L	73	34	2382	22	109.9	12.3
44	M	HCV**	12 months/4800 L	43	59	665	29	56.1	16.3
51	M	HCV	12 months/4800 L	160	76	871	28	40.4	6.0
56	M	NASH	6 months/2400 L	61	55	272	8	11.2	6.8
45	M	HCV	12 months/4800 L	131	96	842	19	11.1	7.2
59	M	HCV	6 months/2400 L	156	19	2100	31	7.8	2.0
47	M	NASH	12 months/4800 L	249	212	1359	36	6.3	5.3
62	M	HCV	12 months/4800 L	43	30	418	10	4.4	3.6

*$p < 0.01$ compared to the data before therapy

**have a history of curative therapy for hepatocellular carcinoma

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英文要旨

Reduction of serum alpha-fetoprotein levels by phlebotomy in patients with cirrhosis

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Phlebotomy is a possible therapy for cirrhosis. We have performed phlebotomy in 9 cirrhotic patients consisting of 7 with HCV infection and 2 with non-alcoholic steatohepatitis. Two of these patients have a history of curative therapy for hepatocellular carcinoma. All patients who received phlebotomy had a marked reduction of serum alpha-fetoprotein levels as well as transaminase levels. Although suppression of hepatocellular damage and liver regeneration cause a reduction in AFP, other mechanisms may also be behind such a reduction. However an elevated serum AFP level is thought to be an important predictor of hepatocarcinogenesis, suggesting that phlebotomy may have a strong potential in the suppression of hepatocellular carcinoma.

Key words: phlebotomy, alpha-fetoprotein, liver cirrhosis

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C型慢性肝炎に対するペグインターフェロンα-2a単独療法の治療効果と治療効果予測因子の検討

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＜原　著＞

C型慢性肝炎に対するペグインターフェロンα-2a単独療法の治療効果と治療効果予測因子の検討

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要旨：C型慢性肝炎の抗ウイルス療法は，ペグインターフェロンとリバビリン併用療法が主流であるが，リバビリンの副作用のため併用療法困難な症例ではペグインターフェロンα-2a（PEG-IFN）単独療法も考慮される．今回我々は，PEG-IFN単独療法の治療効果とSustained virological response（SVR）予測因子について検討を行った．PEG-IFN単独療法を行った84例のうち，SVRは56例（ITT解析，66.7%）であった．治療前のSVR予測因子は，若年例（$p=0.0464$），肝線維化が軽度の症例であり（$p=0.0002$），治療後の因子は，治療開始後4週以内のHCV RNA定性陰性化を来たすRapid virological response（RVR）（$p<0.0001$）であった．多変量解析では，RVRがSVR予測因子であった（オッズ比：17.2，$p=0.0001$）．また，セロタイプ1型では，治療前HCV RNA量が400 KIU/ml未満（$p=0.037$），セロタイプ2型では500 KIU/ml未満（$p=0.047$）であればSVRを来たす可能性が高く，PEG-IFN単独療法のよい適応であると考えられた．

索引用語：C型慢性肝炎　ペグインターフェロン単独療法
SVR（Sustained virological response）
RVR（Rapid virological response）　肝線維化

はじめに

C型慢性肝炎の世界標準治療は現在，ペグインターフェロンとリバビリン併用療法である[1)2)]．しかしながら，高齢者や腎障害，貧血を合併する患者にはリバビリンの副作用が強く発現するため，リバビリンの併用が困難な例も多い[3)]．また，挙児希望患者においてもリバビリンの催奇形性が問題となる．このようなリバビリン併用困難なC型慢性肝炎患者の抗ウイルス療法では，インターフェロン単独療法が選択されると考えられる．現在，本邦では従来のインターフェロンとペグインターフェロンα-2a（以下PEG-IFN）が保険適用を受けている．

PEG-IFNは投与初期の副作用が少なく，高齢者であっても十分耐用可能と考えられている[4)]．しかしながら，本邦におけるペグインターフェロン単独治療の治療成績に関する報告は少ない[5)~7)]．そこで，今回，当科ならびに当科関連施設におけるC型慢性肝炎患者に対するPEG-IFN単独療法の治療成績と治療効果に影響を及ぼす因子を解析し，本邦におけるPEG-IFN単独療法の治療適応を明らかにする目的で本研究を行った．

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Table 1 Baseline characteristics of the patients studied

Subjects	Overall (n = 84)	Serotype 1 (n = 20)	Serotype 2 (n = 63)
Gender			
Male : Female	42 : 42	9 : 11	33 : 30
Fibrosis stage*			
F0/F1/F2	2/36/23	0/8/5	2/27/18
F3/F4/	10/4	5/2	5/2
(No Bx**)	(10)	(1)	(9)
Age (yrs)	49.7 ± 14.4	57.8 ± 9.6	47.6 ± 14.7
ALT (IU/l)	95.4 ± 85.6	79.9 ± 61.8	96.1 ± 78.1
Platelet counts ($\times 10^4$/ul)	19.0 ± 6.97	17.8 ± 5.74	19.7 ± 7.25
BMI*** (kg/m^2)	23.1 ± 3.45	23.0 ± 3.09	23.2 ± 3.63
HCV RNA (KIU/ml)	655 ± 1060	319 ± 511	761 ± 1190

Values are means ± SD

* Fibrosis stage was evaluated by New Inuyama's classification.

** No Bx: The cases which liver biopsy was not performed before treatment.

*** BMI: Body mass index

対象と方法

当科ならびに当科関連施設において，2004年1月から2005年9月までに，C型慢性肝炎治療としてPEG-IFN単独療法を施行された84症例を対象とした．HBs抗原陽性患者，抗ミトコンドリア抗体陽性患者，アルコール性肝炎，自己免疫性肝炎合併患者は本研究の対象から除外された．PEG-IFN（PEGASYS®，Rosch, Switzerland，日本販売元：中外製薬（株），東京）は180 μgを週1回皮下投与し，48週投与を原則とした．治療開始後，好中球750/mm^{3}未満，血小板数5万/mm^{3}未満となればPEG-IFNを90 μg/週に減量し，好中球500/mm^{3}未満，血小板数2.5万/mm^{3}未満，ヘモグロビン値8.5 g/dl未満となればPEG-IFN投与は中止とした．PEG-IFN治療開始前に同意を得られた75例では，エコーガイド下の肝生検を施行し（16 G-automatic needleを使用），当院病理医により新犬山分類に基づいた肝線維化の評価を行った[8]．治療終了6カ月後の血清HCV RNA陰性が得られた症例をsustained virological response (SVR)とし，SVR率を求めた．また，SVR症例とnon-SVR症例の二群間で，年齢，性，投与開始前の血清ALT値，血小板数，Body mass index（BMI），肝線維化，HCV RNAセロタイプ，HCV RNA量（アンプリコア，ハイレンジ法）を比較した．さらに，セロタイプ1型，2型各々の症例におけるSVR例とnon-SVR例の二群間での検討を加えた．次に，投与開始後の血清HCV RNA定性陰性化時期別のSVR率を求めた．また，PEG-IFN治療中の血清ALT値の変動についても検討した．

二群間の有意差検定については，フィッシャーの直接確率法を用い，平均±SDで比較する群ではt-検定を用いた．傾向検定はCochran-Armitage検定を行った．多変量解析は多重ロジスティック回帰分析を行った．いずれもp値0.05未満を有意差ありとした．

結　果

当科ならびに関連施設においてPEG-IFN単独療法を受けた症例は84例であった．その内訳は，男性42例，女性42例，平均年齢49.7歳であった．HCVセロタイプ別では，1型20例，2型63例，分類不能1例であった（Table 1）．治療終了後24週時点での効果判定が可能であった症例は全体で81例であり，そのうちSVR例は56例（66.7%），non-SVR例は25例（29.7%）であった．治療開始後，副作用や，他疾患の加療に専念する等の理由のためPEG-IFN療法を中止され，中止後6カ月後の効果判定が不明であった例（Drop out）は3例（3.6%）であった（Fig. 1）．全体における治療結果を踏まえ，SVR群とnon-SVR群における患者背景をTable 2に示す．治療前における因子の検討について，SVR群の平均年齢はnon-SVR群に比して有意に低かった（p=0.0464）．また，SVR群では，non-SVR群に比較して，治療前の血小板数が高く，BMIは低値であり，HCV RNA量（アンプリコア法）が低い傾向を認めたが，両

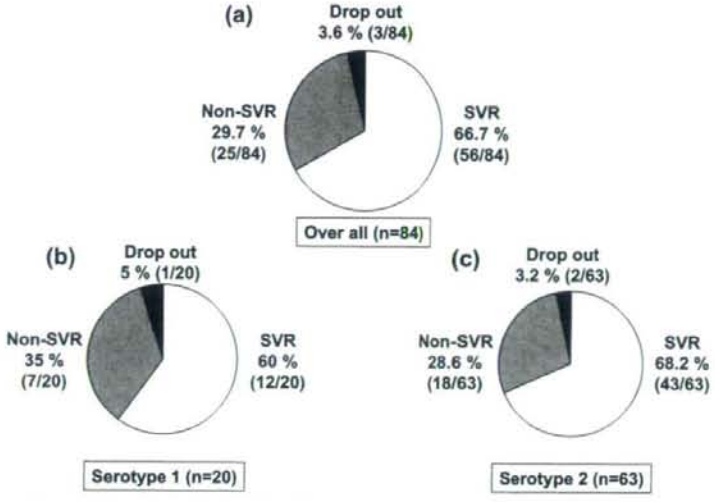

Fig. 1 The outcome of the PEG-IFN monotherapy is shown. (a) The study included a total of 84 patients. SVR * was achieved in 56 cases (66.7%), while non-SVR was observed in 25 cases (29.7%). (b) Among 20 patients with serotype 1, SVR was achieved in 12 cases (60%). (c) Among 63 patients with serotype 2, SVR was achieved in 43 cases (68.2%). (Intention to treat analysis)
* SVR; Sustained virological response

群間で有意差を認めなかった．また，HCVセロタイプにおいても両群間で有意差を認めなかった．Drop out症例を除いた肝線維化とSVR率の検討では，F0＋F1の軽度線維化群，F2＋F3の線維化進行群，F4の肝硬変群，の三群間で傾向検定を行ったところ，SVR率に有意差を認めた(Fig. 2，$p=0.0002$)．また，F4ステージ（肝硬変例）は3例あったが，1例もSVRに至らなかった．

次に，HCVセロタイプ別におけるSVR群，non-SVR群間の検討を示す．セロタイプ1型では，治療前HCV RNA量で有意差を認めたが(Table 3，$p=0.0048$)，セロタイプ2型では各項目で明らかな有意差を認めなかった(Table 4)．また，HCV RNA量からみたSVR率では，セロタイプ1型かつ低ウイルス量（100 KIU/ml以下）症例のSVR率は85.7%（7例のうち6例），セロタイプ2型かつ低ウイルス量症例では90.5%（21例のうち19例）と，いずれもHCV RNA量100 KIU/ml以下の低ウイルス症例において高いSVR率を示した(Table 5)．

治療開始後におけるHCV RNA定性陰性化時期の検討では，治療開始後4週以内にHCV RNA定性陰性化が得られたRapid virological response(RVR)群では，5週～12週の間にHCV RNA定性陰性化が得られたEarly virological response（EVR）群より，有意にSVR率が高率であった(Fig. 3，89.5% 対 61.5%，$p=0.028$)．また，治療開始後12週目以降にHCV RNA定性陰性化を認めた群では，1例もSVRに至らなかった．

これらの結果を踏まえ，多変量解析を行ったところ，SVRに寄与する因子としては，RVRが最も有意な予測因子であった（オッズ比：17.2，95%CI 4.38-84.5，$p=0.0001$)．また，RVRを来した症例がSVRである感度は82.3%，特異度は78.7%，陽性的中率(Positive predictive value：PPV)は89.6%，陰性的中率(Negative predictive value：NPV)は66.7%であった(Table 7)．

PEG-IFNの副作用としての血清ALT値上昇の頻度を明らかにするために，SVR症例の血清ALT値の変動を検討した．SVR症例56例中，治療中の血清ALT値を経時的に確認できた例は23例あったが，そのうち10例(43.5%)では，PEG-IFN投与中に血清ALT値が正常上限値(30 IU/l)よりも高値で推移した(Fig. 4)．

Table 2 Results and characteristics post PEG-IFN monotherapy

	SVR (n = 56)	non-SVR (n = 25)	*p* value
Male : Female	29 : 27	13 : 12	0.5885
Age (yrs)	50.5 ± 14.2	54.4 ± 11.9	0.0464
ALT (IU/l)	99.2 ± 88.6	92.1 ± 81.2	0.7303
Platelet counts ($\times 10^4$/ul)	19.9 ± 6.8	17.7 ± 7.0	0.1742
BMI (kg/m^2)	22.7 ± 3.2	24.1 ± 3.9	0.1202
HCV RNA (KIU/ml)	532 ± 998	947 ± 1204	0.1190
HCV Serotype			
1/2/unknown	12/43/1	7/18/0	0.5787
Fibrosis stage			
F0 + 1/F2 + 3/F4	30/20/0	7/12/3	
(No Bx*)	(6)	(3)	
RVR**	83.0% (44/53)	21.7% (5/23)	< 0.0001

* No Bx; The cases which liver biopsy was not performed before treatment.
** RVR indicates rapid virological response, which is defined as HCV RNA PCR-seronegative at week 4 of treatment.

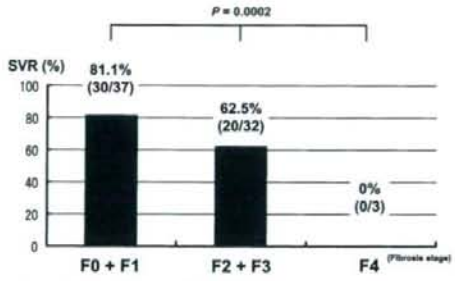

Fig. 2 The rate of SVR at different stages of liver fibrosis progression. Cochran-Armitage trend test analysis showed significant differences in the SVR coefficient among nominal to mild fibrosis (F0 + F1), moderate to severe fibrosis (F2 + F3) and cirrhosis (F4) (p = 0.0002). Drop out cases were excluded (n = 3).

考　察

C型慢性肝炎では，本邦，海外において現在ではペグインターフェロンとリバビリンの併用療法が標準的治療法である．Fried らは，C型慢性肝炎高ウイルス量の症例に対する PEG-IFNα-2a（180 μg/週）とリバビリン（1000–1200 mg/日）の48週併用療法群の SVR は，PEG-IFNα-2a（180 μg）48週単独療法群の SVR と比較して，有意に高率であると報告している（56% 対 29%）[9]．しかしながら実際の臨床の現場ではリバビリンの併用が困難である症例も散見されるため，この様な症例に対してはインターフェロン単独療法あるいは，ペグインターフェロン単独療法が選択される．PEG-IFN は副作用が軽く，週1回の投与で済むため，本邦においては第1選択になると思われる．

Zeuzem らはペグインターフェロン α-2a 単独療法における SVR に寄与する独立因子として，40歳以下，非肝硬変の状態，体表面積 2 m^2 以下，PEG-IFNα-2a による治療，治療前ウイルス量2百万コピー/ml，ALT 値が正常の3倍以上，HCV genotype1 以外を挙げ[10]，Lee らは，Zeuzem らの結果に加え，開始時の体重が 85 kg 以下，HAI score 10 点以上のものを挙げている[11]．我々の検討では，SVR 群と non SVR 群では，治療前の年齢においてのみ有意差を認めたが，HCV RNA セロタイプ，血小板数，BMI，ALT 値，HCV RNA 量においては有意差を認めなかった．ジェノタイプ1型かつ高ウイルス量の症例では PEG-IFN 単独療法における SVR が低いことが報告されているが[5]，本研究において HCV セロタイプは SVR 予測因子とならなかった．このため，セロタイプ別での検討を加えたところ，まず治療前のセロタイプ1型と2型の各因子を比較すると，セロタイプ1型の SVR 群では比較的治療前の HCV RNA 量が低かったこと（平均：121 KIU/ml）が挙げられ，セロタイプ1型の SVR 率上昇と，セロタイプ2型の SVR

Table 3 Results and characteristics between SVR and non-SVR groups in serotype 1

	SVR (n = 12)	non-SVR (n = 7)	*p* value
Male : Female	7 : 5	2 : 5	0.3498
Age (yrs)	56.5 ± 9.17	60.0 ± 11.1	0.4445
ALT (IU/l)	73.3 ± 44.6	91.1 ± 87.0	0.5396
Platelet counts (×10⁴/ul)	17.4 ± 5.86	18.4 ± 5.93	0.0821
BMI (kg/m²)	23.2 ± 3.5	22.6 ± 2.2	0.7180
HCV RNA (KIU/ml)	121 ± 113	659 ± 738	0.0048
Fibrosis stage			
F0 + 1/F2 + 3/F4	7/5/0	1/5/1	
(No Bx*)	(0)	(0)	
RVR**	81.8% (9/11)	0% (0/6)	0.0002

* No Bx: The cases which liver biopsy was not performed before treatment.
** RVR indicates rapid virological response, which is defined as HCV RNA PCR-seronegative at week 4 of treatment.

Table 4 Results and characteristics between SVR and non-SVR groups in serotype 2

	SVR (n = 43)	non-SVR (n = 18)	*p* value
Male : Female	22 : 21	11 : 7	0.5778
Age (yrs)	45.6 ± 15.4	52.2 ± 11.9	0.1038
ALT (IU/l)	97.5 ± 95.2	92.5 ± 81.4	0.8220
Platelet counts (×10⁴/ul)	20.5 ± 6.99	17.4 ± 7.63	0.1107
BMI (kg/m²)	22.7 ± 3.1	24.5 ± 4.3	0.0687
HCV RNA (KIU/ml)	636 ± 1113	1059 ± 1344	0.2178
Fibrosis stage			
F0 + 1/F2 + 3/F4	22/15/0	6/7/2	
(No Bx*)	(6)	(3)	
RVR**	83.3% (35/42)	29.4% (5/17)	0.0004

*No Bx: The cases which liver biopsy was not performed before treatment.
**RVR indicates rapid virological response, which is defined as HCV RNA PCR-seronegative at week 4 of treatment.

率低下を招いた一因と考えられた．その他にも，今回の我々の対象症例にはセロタイプ2型の症例が比較的多く，統計学的有意差が出なかったことも一因と考えられた．

また，治療前HCV RNA量に関し詳細に検討を行った．今回エントリーされた症例のHCV RNA量は，全体でも平均655 KIU/mlであり，HCV RNA量が100 KIU/ml以上の，いわゆる「高ウイルス量」症例であっても，1000 KIU/ml未満の症例が多かった．このため，HCV RNA量100から1000 KIU/ml間に100 KIU/ml毎に境界を設定し，各々の境界においてSVR率に有意差があるか検討したところ，セロタイプ1型ではHCV RNA量の境界を400 KIU/ml，セロタイプ2型では境界を500 KIU/mlまで設定したところSVR率に有意差を認めた（Table 6，セロタイプ1：$p=0.037$，セロタイプ2：$p=0.047$）．このため，セロタイプ1型かつ高ウイルス量の症例であっても，400 KIU/ml以下であればSVRを得る可能性が高いことが示唆された．しかしながら，本