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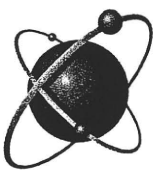

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□ ORIGINAL ARTICLE □

The Efficacy of Short-term Interferon-beta Therapy for Chronic Hepatitis C Patients with Low Virus Load

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Abstract

Objective The aim of this study was to elucidate the efficacy of short-term interferon (IFN) therapy for chronic hepatitis C patients with low virus load.

Methods The present study was a retrospective cohort study. Inclusion criteria were biopsy-proven chronic hepatitis, the serum hepatitis C virus (HCV) RNA level of less than 100 KIU/ml, IFN period of 8weeks or less. One hundred and eleven consecutive patients satisfied above criteria were treated with IFN-beta (dose: 6 MU, daily for 4, 6, or 8 weeks).

Results Background of clinical profiles were as follows: median (range) age=56 (20-73) years, male/female=64/47, genotype 1b/2a/2b=40/68/3, and median (range) HCV-RNA= 34 (4.5-81) KIU/ml. Out of 111, 64 patients (57.7%) had sustained viral response (SVR). Based on the difference of HCV genotype, the SVR rate was 47.5% (19/40) in genotype 1 and 63.3% (45/71) in genotype 2. In genotype 1, the SVR rate in patients treated with the 8-week-regimen was significantly higher than that in patients treated with the 4- or 6-week regimen. In contrast, in genotype 2, the SVR in patients treated with the 8-week regimen was not significantly different from that in patients treated with the 6-week regimen. None of the patients had severe IFN-related side effects.

Conclusions The 6 or 8-week regiment of IFN-beta therapy is one selection of therapy for chronic hepatitis C patients who have tended to have a SVR and who show IFN-related adverse events.

Key words: chronic hepatitis C, low virus load, interferon, sustained viral response

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Introduction

Current interferon (IFN) therapy for patients with chronic hepatitis C viral infection has been directed at viral clearance. Recent studies reported improvement of therapeutic efficacy when IFN is combined with ribavirin (1-5). Moreover, novel long-acting formulations of IFN known as pegylated IFN induced higher eradication rate of hepatitis C virus (HCV) (6-8). However, IFN is expensive and has a number of serious side effects. Therefore, if the treatment period becomes shorter, it could be preferable.

Several predictive factors of sustained viral response (SVR) to IFN have been identified, and these include a short duration of disease, young age, absence of liver cirrhosis, low HCV-RNA levels, HCV genotype 2a and mutant type of nonstructural 5A region (9-15). Low dose IFN tends to eradicate HCV RNA in patients who had a low serum level of HCV-RNA. However, there is also controversy over how long the IFN therapy should be continued to eradicate HCV RNA in patients. Thus, in this study we evaluated the duration of IFN therapy in order to eradicate HCV RNA in patients who had low serum levels of HCV-RNA.

Abbreviations: HCV: hepatitis C virus, IFN: interferon, SVR: sustained viral response

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Table 1. Clinical Characteristics before Interferon Therapy in Chronic Hepatitis C Patients*

Characteristics	(n=111)
Age (years old) †	56(20-73)
Male/female ‡	64/47
Liver histology (fibrosis, 1/2/3) ‡	60/25/26
HCV genotype(1b/2a/2b) ‡	40/68/3
HCV load (KIU/ml) †	34 (4.5-81)
AST (IU/L) †	56 (14-226)
ALT (IU/L) †	76 (15-434)

***ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; and HCV, hepatitis C virus.**

† Data are expressed as median(range).

‡ Data are number of patients.

Materials and Methods

Patients

A total of 111 consecutive chronic hepatitis C patients treated with IFN-beta for HCV RNA clearance at Toranomon Hospital in Tokyo, Japan between 1997 and 2006 were enrolled in this study. This study was a retrospective cohort study. Enrollment criteria were: repeated alanine aminotransferase (ALT) elevation greater than the upper normal limits (ALT normal range: 12-50 IU/L) for more than six months; histological evidence of chronic hepatitis within one year of entry into the trial; positive serum HCVRNA; serum HCV RNA level of less than 100 KIU/ml or 1 Meq/ml; genotype 1b, 2a and 2b. We excluded from the study all of the patients: 1) with concurrent hepatitis B virus (HBV); 2) with a history of IFN therapy; 3) Leukocytes <3,000/mm^3, platelets <80,000/mm^3 and bilirubin >1.5 mg/ml before IFN therapy.

One hundred eleven patients received IFN at a dose of 6 million units (MU) of natural IFN-beta (Toray Industries or Daiichi Pharmaceutical Co., Tokyo, Japan) daily for 4, 6 or 8 weeks. In general, patients were treated with IFN for 8 weeks. Eleven patients treated for 4 weeks and thirty patients treated for 6 weeks were assigned by randomized controlled trial. We regarded sustained viral response (SVR) to therapy as clearance of HCV RNA by RT-nested PCR (16) or amplicor method (17) for more than 6 months after cessation of therapy. Our study was approved by the institutional ethics review board of our hospital. The physician in charge explained the purpose and method of this clinical trial as well as the potential adverse reactions to each patient, who later gave his/her informed consent for participation.

Blood testing

Blood samples were obtained just before IFN therapy and stored at -80℃. Using these blood samples, HCV-RNA levels before IFN therapy were analyzed by quantitative PCR assay (Amplicor GT-HCV Monitor Version 2.0, Roche Molecular Systems) (18).

On the other hand, serum HCV-RNA at 6 months after the termination of IFN therapy was analyzed by the qualitative PCR assay or RT-nested PCR. The lower detection limit of the qualitative assay is 100 copies/ ml. HCV genotype was examined by the PCR assay, using a mixture of primers for the six subtypes known to exist in Japan, as reported previously (19).

Liver histology

Liver biopsy specimens were obtained percutaneously or by peritoneoscopy using a modified Vim Silverman needle

Table 2. Predictive Factors for SVR in Patients with HCV Genotype 1*

Factor	Category	Odds ratio	95% CI†	p value
Period of IFN therapy (week)	4 or 6/ 8	1/8.93	2.14-37.03	0.003
AST (IU/L)	<76/≥76	1/2.17	0.85-5.55	0.102
Sex	Man / Woman	1/0.56	0.16-2.00	0.367
ALT (IU/L)	<100/≥100	1/1.67	0.47-5.93	0.430
Liver histology (fibrosis)	1 /2,3,4	1/0.79	0.39-1.60	0.507
Age (years)	<50/ ≥50	1/0.80	0.23-2.79	0.726

***ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; IFN, interferon and CI; confidence interval.**

with an internal diameter of 2 mm (Tohoku University style, Kakinuma Factory, Tokyo, Japan), fixed in 10% formalin, and stained with hematoxylin-eosin, Masson's trichrome, silver impregnation, and periodic acid-Schiff after diastase digestion. The size of specimens for examination included more than six portal areas. Histopathological interpretations of these 3-to 4-μm thick sections were made independently by experienced liver pathologists (YA and HK) who had no clinical information or knowledge of chronological order of the biopsies in each pair. The biopsy specimens were scored according to the system of Desmet et al (20).

Statistical analysis

Independent factors that might have influenced SVR were studied using the logistic regression analysis, and the following variables were evaluated as prognostic factors: sex, age, liver histology, biochemical factors (aspartate aminotransferase (AST), ALT before IFN therapy, and period of IFN therapy. Significance of trends in SVR based on periods of IFN therapy was determined Cochran-Armitage trend test. The SPSS software package (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis. A p value of <0.05 was considered to indicate a significant difference.

Abbreviations: ALT: alanine aminotransferase, AST: aspartate aminotransferase

Results

Patients' characteristics

Table 1 shows the characteristics of the 111 patients who received IFN therapy. A total of 40 patients showed HCV genotype 1 and the remaining 71 patients showed HCV genotype 2.

Efficacy of treatment

Out of 111, 64 patients (57.7%) had SVR. Based on the difference of HCV genotype, the SVR rate was 47.5% (19/40) in genotype 1 and 63.3% (45/71) in genotype 2. We then investigated the factors associated with SVR after termination of IFN. Univariate analysis in patients with genotype 1 identified the following one factor that influenced SVR when the period of IFN treatment was 8weeks (Table 2). As one factor was associated with SVR, we did not evaluate the multivariate analysis.

On the other hand, univariate analysis in patients with genotype 2 did not identify the factor that influenced SVR (Table 3). In genotype 2, the SVR in patients treated with

Table 3. Predictive Factors for SVR in Patients with HCV Genotype 2 *

Factor	Category	Odds ratio	95% CI†	p value
AST (IU/L)	<76 /≥76	1/2.21	0.80-6.14	0.126
Sex	Man / Woman	1/0.61	0.22-1.64	0.324
Period of IFN therapy (week)	4 or 6/ 8	1/1.63	0.57-4.69	0.361
ALT (IU/L)	<100/≥100	1/1.22	0.41-3.57	0.721
Age (years)	<50/ ≥50	1/0.80	0.23-2.79	0.726
Liver histology (fibrosis)	1 /2,3	1/0.88	0.54-1.70	0.876

***ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; HCV, hepatitis C virus; and IFN, interferon and CI; confidence interval.**

Table 4. SVR Based on HCV Genotype and Administration Period of Interferon

HCV genotype	Administration period (week)		
	4W	6W	8W
Genotype 1 †	0% (0/6)	33.3% (5/15)	73.7% (14/19)
Genotype 2 † ‡	40% (2/5)	60% (9/15)	66.7% (34/51)

***HCV indicates hepatitis C virus; and SVR, sustained virological response.**
† p <0.001 in genotype 1, p =0.32 in genotype 2 by Cochran-Armitage method
‡ Three patients had HCV genotype 2b. These three patients were treated for 8 weeks and all the patients showed SVR. Remaining patients had genotype 2a.

the 8-week regimen was similar statistically to that in patients treated with the 4- or 6-week regimen.

Table 4 shows the SVR based on the HCV genotype and period of IFN therapy. According to Cochran-Armitage method, the 8-week IFN therapy regimen was the best in order to eradicate HCV RNA in genotype 1. On the other hand, in genotype 2, the 6-week regimen was almost the same as the 8-week regimen.

Adverse events

Within one week after the initiation of treatment, flu-like symptoms appeared in all the patients. Pain in the joints or muscle occurred in 50 cases. However, none of the patients withdrew from this treatment due to IFN-related side effects.

Discussion

We have described the efficacy of short-term IFN-beta therapy for chronic hepatitis C patients with low virus load. The present study was limited by a retrospective cohort trial. However, several findings from the present study have direct implications for the short-term IFN treatment of CH patients with low virus load. First, HCV RNA was cleared in more than 50% patients. Second, no patients withdrew from the treatment due to IFN-related side effects. Okanoue et al reported that side effects occurred when the daily IFN dose was increased (21). However, in the 8-week study period, there were no serious side effects. Third, the 8-week regimen of IFN therapy was preferable to eradicate HCV RNA compared to the 4 or 6-week regimen in genotype 1. On the other hand, in genotype 2, SVR by the 6-week regimen of IFN therapy was not significantly different from SVR by the 8-week regimen. These results indicate that 1) in patients with genotype 1 and low virus load, the 8-week regimen of IFN was recommended as the first treatment, 2) in patients with genotype 2 and low virus load, the 6-week regimen of IFN was recommended as the first treatment. This result is likely in agreement with several previous clinical trials (22-26).

In patients with genotype 1b and a high load of HCV-RNA, the clearance rate of HCV-RNA is less than 10% by the usual 6-month course of IFN monotherapy. In these IFN-resistant patients, the eradication rate of HCV-RNA level is at most 20-50% by the latest prolonged IFN therapy, combination therapy of IFN/ribavirin or pegylated IFN administration.

At present, combined IFN and ribavirin therapy is the standard therapy for chronic hepatitis C patients with genotype 1b and a high load of HCV-RNA. Next, in our hospital SVR of the 24-week IFN regimen in patients with a low load of HCV-RNA was 50.9% (220/432) in genotype 1b, 79.9% (279/349) in genotype 2a, and 71.4% (45/63) in genotype 2b. These results indicate that SVR of the 24-week regimen was higher than that of the short term regimen in genotype 2. However, prolonged IFN therapy is often associated with various side effects. A lower total dose and shorter administration period of IFN would be preferable in terms of both cost and safety.

Fortunately, patients with low HCV-RNA levels tend to eradicate HCV RNA with a low dose of IFN. The present study indicates that short-term IFN-beta therapy has no severe side effects. Thus, short-term IFN therapy is recommended for the patients who tend to have a SVR and have IFN- induced adverse events.

Conclusion

We think that the 6 or 8-week regimen of IFN-beta therapy is one therapy selection for chronic hepatitis C patients who tend to have a SVR and have IFN-induced adverse events.

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Hepatocarcinogenesis Following HCV RNA Eradication by Interferon in Chronic Hepatitis Patients

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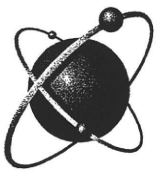

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□ ORIGINAL ARTICLE □

Hepatocarcinogenesis Following HCV RNA Eradication by Interferon in Chronic Hepatitis Patients

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Abstract

Objective Interferon (IFN) therapy reduces the incidence of hepatocarcinogenesis in patients with hepatitis C viral (HCV) infection who achieve a sustained virological response (SVR). The aim of the present study was to determine the rate of hepatocarcinogenesis and the risk factor in sustained virological responders.

Patients and Method The study subjects were 1,193 patients with HCV-related chronic liver disease and IFN- or IFN plus ribavirin-induced SVR. The age, male/female ratio, and liver fibrosis stage [(F0-F3)/LC] were 15-83 years, 808/385, and 1106/41, respectively. Patients were followed-up for 8.3 years (range, 0 to 19.0 years) and the incidence of hepatocellular carcinoma was recorded.

Results Hepatocellular carcinogenesis was detected in 23 patients during the follow-up. The crude rates of hepatocarcinogenesis at 5, 10, and 15 years were 1.5%, 2.4% and 4.1%, respectively. Multivariate analysis identified cirrhosis, male sex and age older than 50 years as determinants of hepatocarcinogenesis with hazard ratios of 12.9 ($p<0.001$), 6.45 ($p=0.012$), and 20.2 ($p=0.004$), respectively.

Conclusion Long-term follow-up of patients with chronic HCV infection is necessary even in those who show SVR, especially in male elderly patients with cirrhosis.

Key words: hepatitis C virus, hepatocellular carcinoma, chronic hepatitis, sustained virological response, cox proportional hazard model

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Introduction

Interferon (IFN) is effective in eliminating HCV and reducing serum alanine aminotransferase (ALT) in some patients with chronic hepatitis C viral (HCV) infection (1-3). A reduction in the incidence of hepatocellular carcinoma (HCC) in patients with HCV-associated hepatitis and cirrhosis treated with IFN has been reported by many investigators (4-14). The previous study (14) suggested that fluctuations and persistently high levels of ALT in patients with chronic HCV infection enhances the carcinogenic process. From the viewpoint of liver carcinogenesis, IFN plays a suppressive action on the development of HCC through reduction or complete remission of inflammatory activity. Multivariate analysis has indicated that IFN lowers the carcinogenesis rate in those patients who show IFN-induced reduction in ALT levels (15). In patients with IFN-induced normalization of ALT levels, the groups at high risk for carcinogenesis were older, male, and a more advanced histologic stage (16). Patients who show elimination of HCV RNA are considered to exhibit normalization of ALT levels. Therefore, the incidence of carcinogenesis is assumed to be lower in patients with sustained virological response (SVR) than in those who show biochemical response (BR) and no response (NR) to IFN therapy. SVR was defined as persistent disappearance of HCV RNA after therapy, BR as normal ALT values without elimination of HCV RNA for at least 6 months after therapy, and NR as persistently abnormal or only transient normalization of ALT for less than 6 months. However, he-

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patocarcinogenesis still occurs in patients with SVR (17-31). In the studies of Toyoda et al (17) and Ikeda et al (18), the risk factors for carcinogenesis were not discussed due to few sustained virological responders with carcinogenesis. Tokita et al (19) and Kobayashi et al (20) indicated that the risk factors of hepatocarcinogenesis after elimination of HCV RNA are severe fibrosis, male sex, and regular consumption of moderate amounts of alcohol, and old age at the start of IFN treatment. Their hazard ratios could not be estimated because of the relatively small number of patients with SVR. Ikeda et al (21) indicated the hazard ratios of risk factors; older age, increased aspartate aminotransferase (AST), and decreased platelet count. However, the study population was restricted to patients who received IFN monotherapy and it did not include patients who received either pegylated interferon (PEG IFN) or combination therapy of IFN and ribavirin.

The aims of this study were to estimate the rate of hepatocellular carcinogenesis in patients with chronic HCV infection who show SVR to IFN monotherapy or combination therapy of IFN and ribavirin and to determine the risk factors that affect carcinogenesis rate in such patients using multivariate analysis.

Patients and Methods

Study population

In this retrospective cohort study, all patients with chronic HCV infection who started IFN therapy between February 1987 and July 2006 in the Department of Hepatology, Toranomon Hospital were analyzed in the database. Prior to IFN therapy, they were positive for anti-HCV (second- or third generation anti-HCV, enzyme-linked immunosorbent assay, Dainabot, Osaka, Japan) and HCV RNA. Anti-HCV was assayed using stored frozen sera at -80°C. HCV RNA was determined by the Amplicor method (Cobas Amplicor HCV Monitor Test, v2.0, Roche Molecular Systems, Inc., Belleville, NJ) or the branched DNA probe assay (b DNA probe assay; version 2.0; Chiron, Dai-ichi Kagaku, Tokyo, Japan). The medical records of 1,193 patients with HCV infection, who had achieved HCV RNA elimination after IFN therapy or the combination therapy of IFN and ribavirin were obtained. The sera of all patients were negative for hepatitis B surface antigen (HBsAg; radioimmunoassay, Austria, Abbott Laboratories, Detroit, MI). The study protocol was approved by the Human Ethics Review Committee of Toranomon hospital.

Clinical background and laboratory data

The background of 1,193 patients who achieved SVR is shown in Table 1. They included 809 men and 384 women, who were 15 to 83 years old with a median age of 50 years at the commencement of therapy. HCV genotype was analyzed by the immunoserological typing method using a commercial kit (Kokusai Diagnostic Corporation, Kobe, Japan).

Table 1. Patients' Profiles, Virological, Histological Characteristics of the Patients Prior to Their Interferon (IFN) Therapy and Protocol of IFN Therapy

Number of patients	1193
Sex (M / F)	809 / 384
Age (years) *	50 (15-83)
Observation period (year) *	8.3 (0.0-19.0)
HCV genotype	
Genotype 1a, 1b	494 (41.4%)
Genotype 2a, 2b	670 (56.2%)
Genotype 1+2	5 (0.4%)
Genotype 3	1 (0.1%)
Undetermined	23 (1.9%)
Histological stage of hepatitis	
F0 (no fibrosis)	7 (0.6%)
F1 (slight fibrosis)	738 (61.9%)
F2 (moderate fibrosis)	289(24.2%)
F3 (severe fibrosis)	72 (6.0%)
F4 (cirrhosis)	41 (3.4%)
Not examined	46 (3.9%)
IFN therapy	
Monotherapy	1032 (86.5%)
Combination therapy with ribavirin	161 (13.5%)
Type of IFN	
IFN-α	850 (71.2%)
PEG IFN-α	46 (3.9%)
IFN-β	251 (21.0%)
IFN-α/PEG IFN-α+IFN-β	47 (3.9%)

IFN: interferon, PEG IFN: pegylated interferon

*Data are median (minimum, maximum) values.

The HCV genotype was 1 (genotype 1a and 1b) in 494 patients, 2 (genotype 2a and 2b) in 670 patients, 1 plus 2 in 5 patients, 3 in 1 patient. Before treatment, 1,131 patients underwent liver biopsy with or without peritoneoscopy to assess the staging of liver fibrosis and the grade of inflammatory activity based on the classification of Desmet (32). Staging of liver fibrosis was defined as F0 (no fibrosis), F1 (fibrosis portal expansion), F2 (bridging fibrosis), F3 (bridging fibrosis with architectural distortion) and F4 (cirrhosis). Additionally, 16 patients were diagnosed as cirrhosis by peritoneoscopy without biopsy, laboratory values or clinical features: 1147 patients were diagnosed with chronic hepatitis (n=1,106) and cirrhosis (n=41) (F0/F1/F2/F3/F4=7/738/289/72/41).

Treatment protocol

IFN was performed once in 973 patients and more times of therapy in 220 patients (twice/three times/four times/five times/six times=166/38/13/2/1). IFN and ribavirin combination therapy was used to eliminate HCV RNA for 161 patients, while IFN monotherapy eliminated HCV RNA for the other 1,032 patients. The type of IFN was IFN-α (natural or recombinant)/PEG IFN-α in 896 patients (75.1%); IFN-α in 850 patients (71.2%), PEG IFN-α in 46 patients (3.9%), IFN-β (natural) in 251 patients (21.0%) and IFN-α or PEG IFN-α and IFN-β in 47 patients (3.9%).

A total of 613 patients (51.4%) received 3 to 9 million units of IFN everyday for 8 weeks followed by twice or three times a week for 1 to 305 weeks (for 16 to 22 weeks in 75% of patients), 304 patients (25.5%) received 3 to 9 million units of IFN everyday for 1-5 weeks followed by three times a week, 5 patients (0.4%) for 12 weeks and one patient (0.1%) for 24 weeks followed by intermittent administration. A total of 124 patients (10.4%) underwent short therapy with IFN everyday for 4-8 weeks, 2 patients (0.2%) for 10-12 weeks, 18 patients (1.5%) for 18-24 weeks. 2 patients (0.2%) had a prolonged administration of IFN for 11 and 13 months. And 63 patients (5.3%) underwent intermittent administration of three times a week for 4weeks to 70 months. This protocol is one of the low-dose intermittent IFN therapies. A total of 48 patients (4.0%) underwent 50-180 μg of PEG IFN once a week: 8 patients for 24 weeks and 40 patients for 48 weeks.

Follow-up and diagnosis of hepatocellular carcinoma

Almost all patients were followed-up every week or biweekly during IFN monotherapy. This included hematological, biochemical, and virological tests. Patients treated with pegylated IFN were also checked every week or biweekly. After the completion of treatment, monthly follow-up was continued until the virological response could be determined. When SVR was confirmed, imaging studies were conducted once or twice per year in the majority of patients; these included computed tomography (CT) or ultrasonography (US), except those patients who were lost to follow-up. Angiography was performed only when HCC was highly suspected on CT or US. The presence of a characteristic hypervascular nodule on angiography was considered a specific finding for HCC, and histological confirmation was usually not required in the majority of such cases. The clinical trends of tumor markers were also taken into account. When angiography could not be performed, the hepatic mass was considered HCC when CT showed a hypervascular mass and the tumor marker level was elevated. No fine needle biopsy or histopathological examination was performed before treatment.

The date of the last follow-up in this study was March 1, 2007. The median observation period of the entire group was 8.3 years with a range of 0.0 to 19.0 years. As for patients of the combination therapy, the median follow-up period was 3.2 years with a range of 0.0 to 7.5 years.

Statistical analysis

Non-parametric procedures were employed for the analysis of background clinicopathological parameters, including Mann-Whitney U-test. The rate of hepatocarcinogenesis was calculated for the period between the end of IFN therapy and appearance of HCC, using Kaplan-Meier technique (33). Differences in carcinogenesis curves were tested using the log-rank test. Independent factors associated with the appearance of HCC were studied using stepwise Cox regression analysis (34). The following seven variables were analyzed for potential covariates for liver carcinogenesis; age, sex, fibrotic stage of hepatitis at the initiation of the IFN therapy, HCV genotype, use of ribavirin (monotherapy or combination therapy), type of IFN (α or β, and number of treatments. Factors found significant were entered into a multivariate Cox proportional hazard model. A P-value less than 0.05 was considered significant. Data were analyzed using the SPSS software ver. 11.0.1J (SPSS Inc., Chicago, IL).

Crude rates of hepatocarcinogenesis

During a median observation period of 8.3 years with a range of 0.0 to 19.0 years, HCC was diagnosed in 23 (1.9%) of the 1,193 patients. The median interval between the end of therapy and detection of HCC was 3.1 years (range, 0-12.9 years).

The characteristics of HCC patients are shown in Table 2. Patients who developed HCC before the initiation of IFN therapy were excluded. Four patients (Nos. 2, 5, 15 and 22) developed HCC before the diagnosis of SVR but after the elimination of HCV RNA. The surgically resected liver tissue was also examined by the PCR method in 4 cases (Nos. 1, 6, 13 and 14), which showed no HCV RNA.

HCC patients included 21 men and 2 women; the median age at the start of IFN therapy and at diagnosis of HCC was 58 (range, 50-70) and 62 (51-76), respectively. The HCV genotype was 1 in 9 patients and 2 in 14 patients. Chronic hepatitis was diagnosed in 14 patients (F1/F2/F3=2/12/0) and cirrhosis in 9, at the time of initiation of IFN therapy. The type of therapy for hepatitis was IFN monotherapy in 22 patients and the combination therapy in 1. The number of HCC tumors was one in 18 patients, two in 3 patients and more than two in 2 patients. A typical hypervascular mass on angiography or perfusion defect on CT during arterial portography (CT-AP) was noted in 20 patients. Angiography could not be performed in the other three patients; they had a hypo-enhanced, iso enhanced, and hyper-enhanced tumor on CT, respectively. Treatment was radical in 21 patients; including hepatectomy in 17 and percutaneous locoregional therapy in 4 patients. At the time of surgical resection, the fibrosis staging was histopathologically examined in 16 patients. Twelve patients was diagnosed as hepatitis (F1/F1-2/F2/F3=2/1/6/3) and 4 as cirrhosis. In

Table 2. Carcinogenesis after HCV RNA Elimination

No	Gender	Age at the start of IFN	Age at the carcinogenesis	Genotype	Type of IFN	Fibrosis staging before IFN Tx	Interval between the end of IFN Tx and carcinogenesis, yr	Number of Tumor	Tumor size, mm	Treatment for HCC	Fibrosis staging at the time of carcinogenesis	Differentiation of HCC
1	M	50	51	1b	α	F2	1.0	1	15	Hepatectomy	F3	Moderate
2	M	52	54	2a	α	F1	0.6	1	18	Hepatectomy	F2	Well
3	F	54	59	2a	α	F2	3.5	1	17	Hepatectomy	F1-2	Moderate
4	M	55	60	1b	α	F2	3.7	1	16	Hepatectomy	F2	Moderate
5	M	55	56	1b	Peg α+Rib	F2	0.0	1	21	RFA	-	-
6	M	55	57	2a	α2a	F4	1.9	1	19	Hepatectomy	F4	Moderate
7	M	57	67	2	α	F2	8.9	1	47	Hepatectomy	F1	Moderate
8	M	55	59	2a	α2a	F4	3.1	1	18	Hepatectomy	F4	Moderate
9	M	55	62	1b	β	F4	6.5	1	16	Hepatectomy	F4	Poor
10	M	57	58	1b	α	F2	0.9	1	16	Hepatectomy	F2	Moderate
11	M	57	59	1b	α	F2	1.2	1	20	Hepatectomy	F2	Moderate
12	M	58	66	2a	α2b	F1	8.7	1	26	Hepatectomy	F1	Well
13	M	58	62	1b	β	F2	3.9	1	30	Hepatectomy	F2	poor>moderate
14	M	59	69	2b	α	F2	9.1	1	21	Hepatectomy	F2	Moderate
15	M	59	61	1b	α	F4	0.1	1	30	Hepatectomy	F3	poor>moderate
16	M	61	63	2	α	F2	1.8	4+LN meta	23	Hepatectomy+MCT	F3	moderate>well
17	M	62	65	2a	β	F4	2.4	2	20,20	RFA	-	-
18	M	62	75	2a	α2a	F4	12.9	1	23	Hepatectomy	F4	Moderate
19	M	63	66	2a	β	F2	3.6	Uncountable	Diffuse	No treatment	-	
20	M	65	71	2a	α	F2	5.0	2	12, 8	Hepatectomy	-	Necrosis
21	F	66	68	2a	α	F4	0.9	1	13	RFA	-	-
22	M	69	72	1b	β	F4	0.4	2	13, 13	Hepatectomy	-	moderate, poor
23	M	70	76	2a	β	F4	5.4	1	10	RFA+PMCT	-	-

IFN: interferon, Tx: therapy, Peg: pegylated interferon, Rib: ribavirin, LN meta: lymph node metastasis,
RFA: radiofrequency ablation, MCT: microwave coagulation therapy, PMCT: percutaneous microwave coagulation therapy.

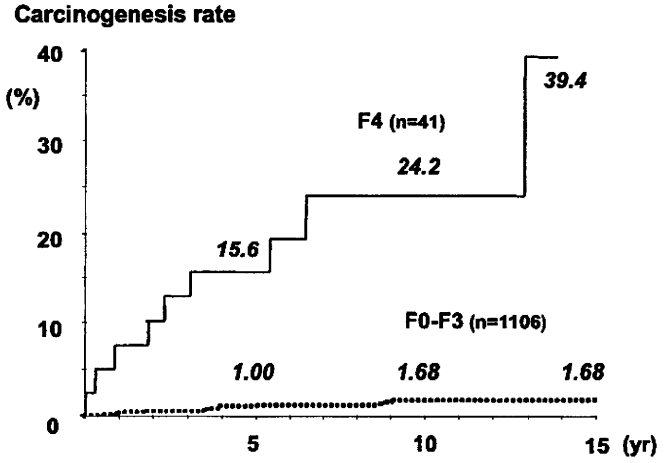

Figure 1. Rates of hepatocarcinogenesis in 41 patients with cirrhosis (F4) and 1,106 patients with liver fibrosis stage F0-F3.

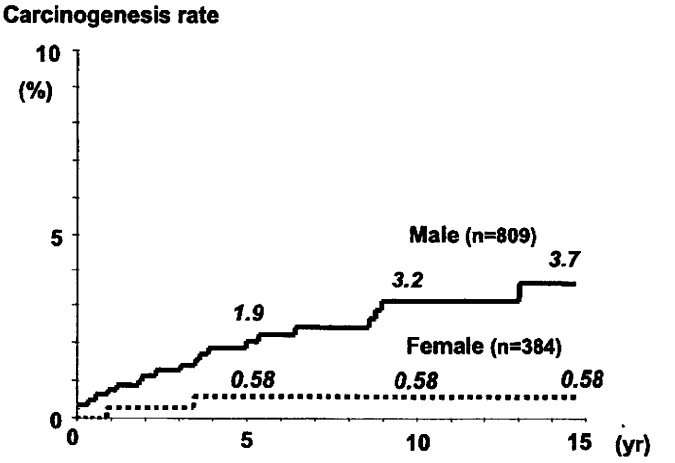

Figure 2. Rates of hepatocarcinogenesis in 809 male patients and 384 female patients.

comparison with the staging at the initiation of IFN therapy, 3 cases showed improvement in the fibrosis, 10 showed no change, and 3 showed progression.

The crude rates of hepatocarcinogenesis in the SVR patients were 1.5%, 2.4% and 2.7% at the end of the 5th year, 10th year and 15th year, respectively.

Determinants of hepatocarcinogenesis

The rate of carcinogenesis was significantly higher in 41 patients with cirrhosis (F4) than in 1,106 patients with liver fibrosis of F0-F3 ($p<0.0001$, Fig. 1). The respective cumulative HCC development rates in patients with cirrhosis at 5, 10, and 15 years after SVR were 15.6%, 24.2% and 39.4%. On the other hand, the respective rates for patients with F0-F3 were 1.00%, 1.68% and 1.68% at 5, 10, and 15 years after SVR. When patients were divided into two groups with F2-4 and with F0-1, rates of the former group were 4.16%, 6.52% and 7.58%, while those of latter group were 0.13%, 0.40% and 0.40%. The incidence rates of HCC increases with the fibrotic stage; those with F1, F2 and F4 were 0.14%, 3.43% and 15.6% at 5 years, 0.40%, 5.22% and 24.2% at 10 years, and 0.40%, 5.22% and 39.4% at 15 years, respectively.

The rate of hepatocarcinogenesis among 809 male patients was significantly higher than among 384 female patients ($p=0.018$, Fig. 2); the respective rates at 5, 10 and 15 years were 1.87%, 3.18% and 3.67% for males and 0.58%, 0.58% and 0.58% for females.

The rate of hepatocarcinogenesis among 570 patients aged >50 years was greater than among 623 patients aged <51 years at the start of IFN therapy ($p<0.0001$, Fig. 3); the respective rates at 5, 10 and 15 years for the former group were 2.92%, 4.93% and 5.81%, compared with 0.16%, 0.16% and 0.16% for the later.

Multivariate analysis identified three factors to be associated with the rate of development of HCC: sex, age at start IFN treatment, and fibrotic stage in the liver tissue. Multi-

variate analysis was performed using non-time dependent proportional hazard analysis. Fibrotic stage, sex, and age were identified as significant independent factors that influenced the rate of future hepatocarcinogenesis (Table 3). Cirrhosis (F4) was associated with a higher risk of hepatocarcinogenesis with a hazard ratio of 12.9 (95% confidence interval, 5.5-30.6, p<0.001) compared with F1-3 stage. Similarly, male sex (6.45, p=0.012) and older age than 50 years (20.2, p=0.004) were associated with a higher risk. Serological grouping of HCV, type of therapy (monotherapy or combination therapy), type of IFN of the final therapy, and number of therapies did not significantly influence the rate of hepatocarcinogenesis. When the patients were divided into two groups with F0-1 and with F2-4, hazard ratios of F2-4, male and older age were 13.4 (3.1-57.8, p<0.0001), 7.00 (1.63-29.99, p=0.0009) and 17.6 (2.3-131.6, p=0.005). When the patients were divided into two groups with F0-2 and F3-4, hazard ratios of F3-4, male and older age were 5.8 (2.5-13.8, p<0.0001), 6.78 (1.58-29.07, p=0.01) and 22.9 (3.0-172.2, p=0.002).

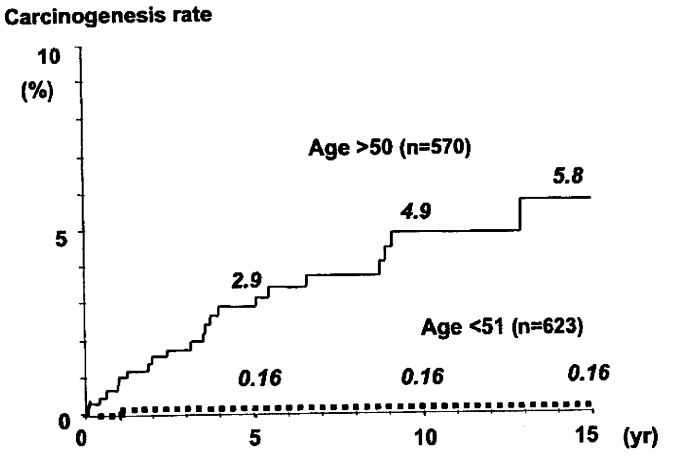

Figure 3. Rates of hepatocarcinogenesis in 570 patients older than 50 and 623 patients younger than 51 years.

Discussion

Epidemiological data on the rate of development of HCC in patients with chronic hepatitis (35) and those with cirrhosis (36) indicate that the life expectancy of patients with HCV-related chronic liver disease is significantly influenced by the development of HCC. Up to 75% of patients with HCV infection and cirrhosis eventually develop HCC (15). IFN can be considered to have anti-carcinogenic properties through its anti-inflammatory action, since several studies have already described that the cancer suppressive activity of IFN in those patients who show HCV RNA eradication was similar to that of patients with ALT normalization without HCV RNA elimination (BR) (15, 37-40). After excluding patients with cirrhosis, the previous report (40) showed that the rate of carcinogenesis was lower in patients with SVR than in those with BR because HCV-elimination does not result in re-elevation and exacerbation of ALT. As a follow-up to the above studies, the rate of hepatocarcinogenesis in SVR patients with either chronic hepatitis or cirrhosis was estimated in the present study.

In spite of the anti-carcinogenic effect of SVR, 23 cases developed HCC following elimination of HCV RNA among 1,193 patients. The median interval between the end of IFN therapy and carcinogenesis is 3.1 years with a range of 0.0 to 12.9 years. Among 23 cases, 22 patients had regular examinations of at least once a year, and 21 of them received radical treatment such as hepatectomy or radiofrequency ablation. The high rate of radical treatment was probably due to the preserved liver function after HCV RNA elimination.

HCCs in six cases that were detected in the year after the end of the interferon therapy could have been already present before elimination of HCV RNA. Even when we exclude these cases, multivariate analysis identified the same factors such as higher histological stage, male sex and age older age as determinants of hepatocarcinogenesis. The haz-

Table 3. Factors Associated with Hepatocarcinogenesis in Sustained Virological Responders with Chronic HCV Infection

Factors	Category	Hazard ratio	95% confidence interval	p
Fibrotic stage	1: F0-3	1		
	2:F4	12.9	(5.5-30.6)	<0.001
Gender	1: women	1		
	2: men	6.45	(1.51-27.64)	0.012
Age (years)	1: <51	1		
	2: >50	20.2	(2.7-152.9)	0.004

ard ratios of cirrhosis, male sex and age older than 50 years were 10.9 (4.0-29.8, p<0.001), 10.4 (1.4-78.2, p=0.024) and 17.0 (2.2-130.7, p=0.006), respectively.

The rates of hepatocarcinogenesis in patients with histological stage F0-F3 were 1.00%, 1.68%, 1.68% at 5, 10, and 15 years after SVR, respectively. These rates were about 20% less than the rates reported previously for patients with chronic hepatitis; 4.8%, 13.6%, and 26.0%, respectively (35). The rates of hepatocarcinogenesis in patients with cirrhosis were 15.6%, 24.2%, and 39.4% at 5, 10, and 15 years, respectively, which were about 65% less than the rates reported previously for patients with cirrhosis; 21.5%, 53.2% and 75.2%, respectively (36). These results indicate that IFN has a more marked effect in reducing the rate of hepatocarcinogenesis in patients with F0-F3 than in those with cirrhosis. Furthermore, the difference in the rate of hepatocarcinogenesis in patients who show SVR and those with chronic HCV-infected patients increases with time, since the likelihood of development of HCC before elimination of HCV RNA decreases as time passes after IFN therapy.

Although some studies have reported that elderly male patients with severe fibrotic stage could be at a high risk for hepatocarcinogenesis even when they show SVR, the hazard ratios in such patients have not been reported probably because of shorter follow-up period and the relatively small number of patients. In this study, the follow-up period was longer than that of previous studies, allowing meaningful multivariate analysis (e.g., Cox hazards model). The results of such analysis showed that the risk of carcinogenesis increases with the histologic stage of the liver, age and male sex. This finding was similar to that reported in a study of untreated patients (41, 42) or IFN-treated hepatitis patients with the histological stage of F0-F3 (15).

Treatment of patients with chronic HCV infection using PEG IFN-α and ribavirin resulted in persistently negative tests for serum HCV RNA in 40-50% of patients with HCV genotype 1 and 75-80% with HCV genotype 2 or 3. The present study also showed that neither type of IFN (α or β) nor the use of ribavirin altered the rate of carcinogenesis. Further studies are needed with a longer follow-up period since the follow-up period of patients treated with the combination therapy ranged from only 0 to 7.5 years (median 3.2years) and was shorter than that of patients who received IFN monotherapy.

In conclusion, the results emphasize the importance of long-term follow-up of patients with chronic HCV infection, even those who show SVR to IFN therapy, especially male elderly patients with severe fibrosis of the liver.

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INTERNAL MEDICINE

□ ORIGINAL ARTICLE □

Combination Therapy of Peginterferon and Ribavirin for Chronic Hepatitis C Patients with Genotype 1b and Low-virus Load

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Abstract

Objective The aim of this study was to evaluate the efficacy of combination therapy of peginterferon and ribavirin in patients infected with hepatitis C virus (HCV) genotype 1b and low virus load.

Methods Inclusion criteria were HCV-genotype 1b, serum HCV RNA level of <100 KIU/mL at the initiation time of treatment. A total of 60 were enrolled in this retrospective cohort study. The treatment period of combination therapy was 39.8±16.1 weeks.

Results Of the 60 study patients, 47 had sustained virological response (SVR) by the intention to treat analysis. SVR occurred when serum HCV RNA was negative 8 weeks after the initiation of the treatment (p=0.004) and continuance of negative HCV RNA during treatment was ≥30 week (p=0.016). In rapid virological response, all of seven patients with continuance of negative HCV RNA 20 to 29 weeks during treatment had SVR. In early virological response nine of 10 patients with continuance of negative HCV RNA of 30 to 39 week during treatment had SVR.

Conclusion The duration of combination therapy for chronic hepatitis C should be determined based on the time of attainment of negative HCV RNA in patients with genotype 1b and low-virus load.

Key words: chronic hepatitis C, peginterferon, ribavirin, HCV genotype 1b, low virus load, duration of treatment

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Introduction

Current evidence indicates that combination therapy of peginterferon and ribavirin for hepatitis C virus (HCV) is associated with a higher rate of sustained virological response (SVR) compared with interferon (IFN) alone (1-7). Hence, combination therapy of peginterferon and ribavirin has been recommended as a first choice for chronic hepatitis C patients with high virus-load. Now, the selection of duration of treatment and optimum doses of combination therapy is an area of active investigation (8-16).

However, the dropout rates in patients treated with combination therapy was higher than those treated with IFN monotherapy (17, 18). On the other hand, some authors have reported that in half of the patients with a low virus load HCV RNA is eradicated by IFN monotherapy. Thus, for patients with a low virus load IFN monotherapy has been recommended as a first choice in Japan. However, there is also controversy over which patients should be treated with what agent and what regimen as a first choice for good prolonged prognosis in chronic hepatitis C patients with a low virus load. There is an ongoing need to refine treatment strategies in patients with a low virus load.

Thus, in the present study, we performed a retrospective study to examine the efficacy of combination therapy in pa-

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