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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Inhibition of hepatocellular carcinoma by PegIFNα-2a in patients with chronic hepatitis C: a nationwide multicenter cooperative study

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Abstract
Background We investigated whether the administration of maintenance doses of interferon prevented hepatocellular carcinoma (HCC) in patients with chronic hepatitis C.
Methods Study 1: A multicenter, retrospective, cooperative study was carried out to determine whether long-term administration of low-dose peginterferon alpha-2a (PegIFNα-2a) prevented HCC development in patients with chronic hepatitis C. In total, 594 chronic hepatitis C patients without a history of HCC were enrolled and treated with 90 μg PegIFNα-2a administered weekly or bi-weekly for at least 1 year. Study 2: HCC developed in 16 of 99 additional patients without PegIFNα-2a treatment during 3.8 years of observation. A propensity-matched control study was then carried out to compare the incidence of

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HCC between the 59 patients who received low-dose PegIFNα-2a (PegIFNα-2a group) and 59 patients who did not receive PegIFNα-2a treatment (control group), matched for sex, age, platelet count, and total bilirubin levels.

Results Study 1: HCC developed in 49 patients. The risk of HCC was lower in patients with undetectable hepatitis C virus RNA, ≤40 IU/L alanine aminotransferase (ALT), or ≤10 ng/L alpha-fetoprotein (AFP) 24 weeks after the start of therapy. Study 2: The incidence of HCC was significantly lower in the PegIFNα-2a group than in the control group.

Conclusions Low-dose and long-term maintenance administration of PegIFNα-2a decreased the incidence of HCC in patients with normalized ALT and AFP levels at 24 weeks compared with patients without normal ALT and AFP levels.

Keywords Chronic hepatitis C · Hepatocellular carcinoma · Peginterferon

Introduction

Hepatocellular carcinoma (HCC), the sixth most common cancer worldwide, often develops because of long-term hepatitis B or C virus infection [1, 2]. In particular, chronic hepatitis C and hepatic cirrhosis increase the risk of HCC; the annual incidence of tumor development in such patients may be as high as 2–4 % [3–5]. The incidence of HCC decreases in patients who achieve a sustained virological response (SVR) to interferon (IFN) treatment, although the incidence remains high in non-SVR patients [6–9]. A detailed analysis of HCC development revealed that chronic hepatitis C patients aged 65 years or more, especially those with advanced fibrosis of the liver, were at an increased risk of developing HCC [10]. For patients 65 years or older with advanced liver fibrosis, the dose of ribavirin is often reduced or the agent is discontinued, resulting in lower SVR rates in those with discontinuation of ribavirin. Establishing an effective treatment strategy for preventing the development of HCC is important for these high-risk patients.

Factors related to the development of HCC have been analyzed in patients who did not achieve an SVR even after IFN treatment; advanced fibrosis of the liver and high levels of serum alanine aminotransferase (ALT), and alpha-fetoprotein (AFP) are risk factors for HCC development [11, 12]. A randomized controlled trial was conducted in Western countries to determine whether combined peginterferon and ribavirin treatment with weekly administration of 90 μg peginterferon alpha-2a (PegIFNα-2a) could prevent HCC in non-responders. A 3.5-year follow up showed that administration of a maintenance dose of PegIFNα-2a did not reduce tumor incidence in these patients [13]. However, after 8.5 years of observation, the incidence of HCC was decreased among those in the PegIFNα-2a group with cirrhosis [14]. Meanwhile, Bruix et al. [15] reported that maintenance therapy with PegIFNα-2b did not prevent HCC in chronic hepatitis C patients with cirrhosis. In Japan, long-term low-dose administration of natural IFN has been reported to decrease the incidence of HCC [16]. In light of these conflicting results, investigations should be carried out in a large number of patients with chronic hepatitis C to resolve the question of whether IFN treatment prevents the development of HCC.

We carried out a multicenter retrospective cooperative study of patients with chronic hepatitis C to determine whether those treated with 90 μg PegIFNα-2a without ribavirin had a reduced incidence of HCC compared with those not treated with IFN.

Patients and methods

Study 1: analysis of risk factors for HCC in patients treated with long-term low-dose-PegIFNα-2a

In total, at 21 hepatitis centers throughout Japan, 743 patients with hepatitis C who had received 90 μg of PegIFNα-2a therapy weekly or bi-weekly for 1 year or more without having received the full dose (180 μg) since December 2003 were examined retrospectively for the development of HCC. The end of enrollment in this study was the end of December 2008 and the end of follow up was the end of December 2010. Patients with a history of HCC before the start of therapy and those with a therapy period of less than 48 weeks were excluded, leaving 594 patients who had undergone long-term administration of PegIFNα-2a for analysis. At the 21 centers involved in this

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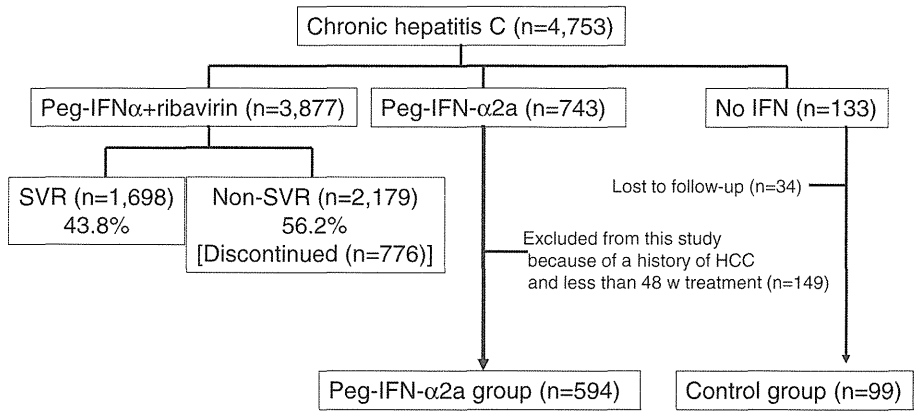

Fig. 1 Flow diagram of the patients' enrollment in the study. *Peg-IFNα* pegylated interferon α, *SVR* sustained viral response, *HCC* hepatocellular carcinoma, *w* week

study, 4,753 patients with chronic hepatitis C had been treated; Peg-IFN and ribavirin combination treatment had been administered to 3,877 patients, 743 patients had received Peg-IFN alone, and 133 patients had not agreed to receive IFN (a flow diagram of the enrollment of patients in this study is shown in Fig. 1). In the patients with Peg-IFN and ribavirin combination treatment, the SVR rate was 43.8 %; SVR was not achieved in 2,179 patients, and in 776 of these patients, the combination therapy was discontinued owing to adverse events or the patient's choice. Patients who failed to achieve an SVR were not included in this study, because the incidence of HCC is known to be reduced even in non-responders to IFN [17].

The backgrounds of the 594 patients studied are shown in Table 1. Findings from the liver biopsies of the patients were classified according to international standards [18]. Long-term PegIFNα-2a treatment is approved by the Japanese Medical Insurance system. Written informed consent was obtained from all patients prior to participation in this study. The study design was approved by the regional ethics committees of the 21 centers involved in this study, including the Musashino Red Cross Hospital, in accordance with the Helsinki Declaration. The 743 patients treated with PegIFNα-2a alone were not indicated for Peg-IFNα and ribavirin combination therapy because of anemia or heart disease. The 133 patients who did not agree to receive IFN served as the control group (see Fig. 1). A large proportion of the 594 study patients had advanced fibrosis of the liver and active inflammation. A dose of 90 μg PegIFNα-2a was administered to 512 and 82 patients weekly and biweekly, respectively, according to the patients' wishes. There were no significant differences between the weekly and biweekly groups in the patients' background data (data not shown).

The median duration of follow up in the PegIFNα-2a group was 1,273 days (range 228–2,768 days) and HCC was observed in 49 of the 594 patients (Table 1). Pretreatment and on-treatment factors associated with the development of HCC were analyzed by Student's *t*-test, the Mann–Whitney *U*-test, and the χ^2 test (Table 2). Independent factors for the development of HCC were assessed by multivariate analysis using logistic regression. The

Table 1 Background data of patients treated with PegIFNα-2a ($n = 594$)

	$n = 594$
Age (years)	61.7 ± 11.7
Sex (male/female)	258/336
BMI	23.2 ± 3.3
Genotype (1/2)	443/151
Diagnosis (ASC/CH/LC)	4/460/130
History of excess alcohol consumption (≥60 g/day; yes/no)	118/376
Fibrosis (F0, 1, 2/F3, 4)	443/151
Inflammatory activity (A0, 1/A2, 3)	469/125
Diabetes mellitus (no/yes)	499/95
LDL cholesterol (mg/dL)	94.2 ± 31.1
Fasting blood sugar (mg/dL)	106.3 ± 28.5
White blood cell count (/mm^3)	4,360 ± 1,470
Red blood cell count (×10^6/μL)	423.8 ± 56.4
Hemoglobin (g/dL)	13.3 ± 1.8
Platelet count (×10^3/μL)	137 ± 56
Albumin (g/dL)	4.0 ± 0.5
Total bilirubin (mg/dL)	0.8 ± 0.6
AST (IU/L)	65.8 ± 47.8
ALT (IU/L)	72.1 ± 68.0
Gamma-GTP (IU/L)	55.2 ± 51.3
Esophageal varices (no/yes)	344/31
Alpha fetoprotein (ng/L)	6.9 (4.2–13.8)
Once weekly or biweekly PegIFNα-2a	512:82
Baseline HCV RNA (KIU/mL)	1,024 (73–2,130)
Development of HCC (no/yes)	545/49

PegIFN pegylated interferon, *BMI* body mass index, *ASC* asymtomatic carrier, *CH* chronic hepatitis, *LC* liver cirrhosis, *LDL* low-density lipoprotein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *GTP* guanosine triphosphate, *HCV* hepatitis C virus, *HCC* hepatocellular carcinoma

Values are means ± SD, with ranges in parentheses

incidence of HCC was analyzed according to the ALT, AFP, and hepatitis C virus (HCV) RNA levels 24 weeks after the start of PegIFNα-2a administration by using the Kaplan–Meier method. The risk of HCC was analyzed, using the Kaplan–Meier method, only in the non-responders with detectable HCV RNA during PegIFNα-2a administration by dividing them according to the ALT and AFP levels 24 weeks after the start of therapy. The incidence of HCC was compared between the patients with ALT levels of <41 IU/L and those with levels of ≥41 IU/L, and between patients with serum AFP levels of <10 ng/L and those with levels of ≥10 ng/mL at 24 weeks after starting treatment, because at most of the centers participating in the this study, the upper normal range of serum ALT is set at 40 IU/L, and the most significant difference in the incidence of HCC was observed between the PegIFNα-2a and control group with the cut-off serum ALT set at 41 IU/L and cutoff serum AFP set at 10 ng/mL, 24 weeks after starting treatment. The HCV RNA level was measured using the Amplicor Monitor method with a lower detection limit of 50 IU/L (Roche Diagnostics, Tokyo, Japan). A history of excess alcohol consumption was determined as >60 g alcohol per day in order to exclude alcoholic liver disease.

An asymptomatic carrier was defined as a patient with a serum ALT level within the normal range and minimal inflammation or fibrosis in the biopsied tissues of the liver. Chronic hepatitis was defined as mild-to-severe fibrosis of the liver according to liver biopsy [18]. The diagnosis of liver cirrhosis was based on the results of histological examination of the biopsied liver tissues.

Study 2: incidence of HCC in the PegIFNα-2a therapy and non-administration (control) groups in comparison with propensity-matched controls

Ninety-nine of the 133 chronic hepatitis C patients who had not received IFN were examined as controls; patients in this group received liver-protective agents such as glycyrrhizin or were untreated, and the group was observed for more than 1 year. None of the individuals in the control groups had received IFN alone or PegIFNα and ribavirin combination treatment. They were treated for a median of 1,395 days (range 75–6,556 days). Fifty-nine of these patients underwent liver biopsy before the treatment and were considered the control group for the propensity-matched study. For the propensity-matched study, 59 patients were selected from the PegIFNα-2a group according to their age, sex, platelet count, and total bilirubin levels, which had been identified as independent pretreatment risk factors for the development of HCC in Study 1. The rates of HCC were analyzed using the Kaplan–Meier method, and the risk of HCC was analyzed particularly in patients with advanced fibrosis of the liver (F3 and F4).

Table 2 Comparison of HCC and non-HCC patients with long-term PegIFNα-2a administration ($n = 594$)

	Patients with or without development of HCC		p value
	With HCC ($n = 49$)	Without HCC ($n = 545$)	
Pretreatment parameters			
Age (years)	63.8 ± 1.7	61.3 ± 0.5	<0.05
Sex (male/female)	32/17	226/319	<0.01
BMI	24.0 ± 0.5	23.1 ± 0.2	n.s.
Genotype (1/2)	47/6	397/148	n.s.
History of excess alcohol consumption (≥60 g/day; yes/no)	11/38	107/338	n.s.
Fibrosis (F0, 1, 2/F3, 4)	25/24	418/127	<0.001
Inflammatory activity (A0, 1/A2, 3)	7/42	462/83	<0.001
Diabetes mellitus (no/yes)	38/11	461/84	n.s.
LDL cholesterol (mg/dL)	88.2 ± 9.0	94.7 ± 2.6	n.s.
White blood cell count (/mm^3)	4,355 ± 210	4,360 ± 64	n.s.
Red blood cell count (×10^6/μL)	420.8 ± 8.1	424.1 ± 2.6	n.s.
Hemoglobin (g/dL)	13.6 ± 0.3	13.3 ± 0.1	n.s.
Platelet count (×10^3/μL)	106 ± 8	140 ± 2	<0.001
Albumin (g/dL)	3.8 ± 0.1	4.0 ± 0.1	<0.001
Total bilirubin (mg/dL)	1.2 ± 0.1	0.8 ± 0.1	<0.001
AST (IU/L)	78.1 ± 6.8	64.6 ± 2.1	n.s.
ALT (IU/L)	72.8 ± 9.7	72.0 ± 2.9	n.s.
Gamma-GTP (IU/L)	68.7 ± 7.5	53.9 ± 2.3	n.s.
Alpha fetoprotein (ng/L)	17.1 (4.4–36.8)	16.7 (4.1–23.1)	n.s.
Esophageal varices	29.0 % (9/31)	6.4 % (22/344)	<0.01
On-treatment parameters			
ALT (IU/L)	59.4 ± 5.7	44.6 ± 1.8	<0.05
Alpha fetoprotein (ng/L)	9.8 (4.6–17.4)	5.5 (3.7–11.1)	<0.01
HCV RNA level (KIU/mL)	236 (<0.5–2,210)	21 (<0.5–1,780)	<0.05

n.s. not significant

Statistical analysis

Categorical data were compared using the χ^2 test or Fisher's exact test. The distributions of continuous variables were analyzed using Student's t-test and the Mann–Whitney U-test for two groups. Multivariate analysis was

conducted using logistic regression. The cumulative incidence curve was determined using the Kaplan–Meier method and differences between groups were assessed by the log-rank test. For all methods, the level of significance was set at $p < 0.05$. Multivariate analysis of the risk of HCC was carried out using the Cox proportional hazard model. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 11.0 (SPSS, Chicago, IL, USA). In Study 1, age, sex, platelet count, and total bilirubin levels were identified as independent factors for the development of HCC; therefore, these factors were selected for the propensity-matched control study (Study 2) in which 59 patients from the PegIFNα-2a group were included.

Results

Study 1

We analyzed the factors involved in the development of HCC in patients who received 90 μg PegIFNα-2a weekly or biweekly for more than a year. The incidence of HCC did not differ significantly between the groups treated with PegIFNα-2a weekly and biweekly (34 of 512 vs. 15 of 82, respectively). As shown in Table 2, univariate analysis revealed statistically significant differences in the pretreatment parameters including age, sex, fibrosis of the liver, platelet count, albumin level, and total bilirubin, between patients who developed HCC and those who did not. Endoscopy was carried out in 375 patients, and esophageal varices were noted in 31 of them. The incidence of HCC was higher in patients with esophageal varices than in those without varices [29.0 % (9 of 31) vs. 6.4 % (22 of 344)]. Assessment of on-treatment factors by univariate analysis revealed statistically significant differences in serum ALT, AFP, and HCV RNA levels 24 weeks after the start of PegIFNα-2a maintenance treatment (Table 2).

Multivariate analysis including pretreatment parameters revealed that age, sex, fibrosis of the liver, platelet count, and total bilirubin were independent risk factors for HCC development (Table 3). Multivariate analysis including on-treatment parameters identified ALT levels of ≥41 IU/L and AFP levels of ≥10 ng/L 24 weeks after the start of the PegIFNα-2a therapy as independent risk factors for HCC development (Table 3).

The incidence of HCC was significantly lower in patients with ALT levels of ≤40 IU/L than in those with ALT levels of ≥41 IU/L 24 weeks after the start of observation (Fig. 2). The incidence of HCC was also significantly lower in patients with AFP concentrations of <10 ng/mL at 24 weeks after the start of observation than in those with AFP concentrations of ≥10 ng/mL (Fig. 3). The dose of PegIFNα-2a was reduced to 45 μg in 16 patients because of neutropenia and thrombocytopenia. In addition, PegIFNα-2a was discontinued in 18 patients because of adverse events, including depression (7 patients), interstitial pneumonitis (3 patients), thrombocytopenia (3 patients), neutropenia (1 patient), itching (1 patient), and ascites (3 patients). No statistically significant differences were found between the patients with reduced dosage or treatment interruption and those without treatment modifications with respect to overall survival, HCC incidence, ascites formation, variceal bleeding, hepatic encephalopathy, and 2-point increases in the Child-Pugh score. No patients underwent liver transplantation.

Table 3 Independent risk factors for HCC development in patients treated with 90 μg PegIFNα-2a weekly or bi-weekly, evaluated by multivariate analysis (logistic regression analysis)

	Multivariate analysis		
	Odds ratio	95 % Confidence interval (CI)	*p*
Age (years) (every 5 years)	2.24	1.76–9.33	<0.005
Sex (male/female)	3.16	1.56–10.7	<0.005
Fibrosis (F3, 4/F0, 1, 2)	1.69	1.18–5.2	<0.01
Platelet count (<120 × 10^3/μL vs. ≥120 × 10^3/μL)	3.24	1.44–27.6	<0.01
Total bilirubin (mg/dL)	1.59	1.09–2.58	<0.05
ALT (at 24 weeks) (≥41 vs. <40 IU/L)	2.49	1.51–8.28	<0.05
AFP (at 24 weeks) (≥10 vs. <10 ng/L)	3.78	1.92–11.8	<0.01

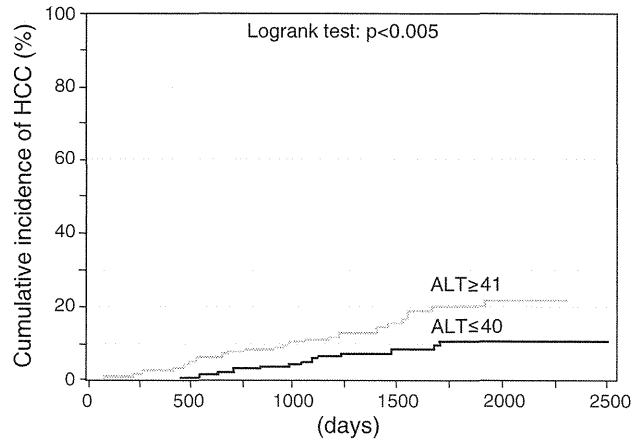

Fig. 2 Comparison of HCC rates in patients administered with PegIFNα-2a ($n = 594$) with respect to alanine aminotransferase (*ALT*) levels 24 weeks after the start of therapy. *Black line* patients with ALT ≥41 IU/L in the first 24 weeks, *gray line* patients with ALT ≤40 IU/L in the first 24 weeks

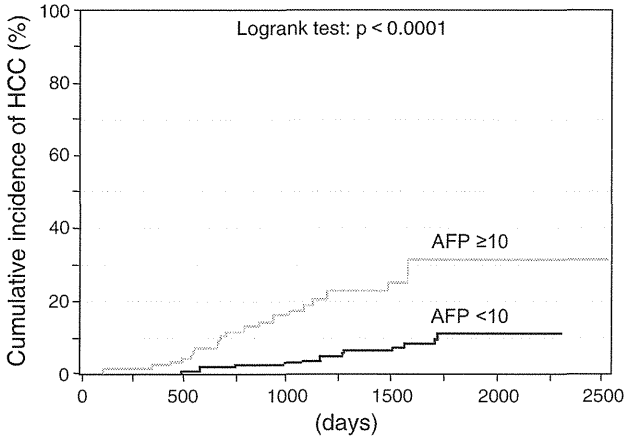

Fig. 3 Comparison of HCC rates in patients administered PegIFNα-2a ($n = 594$) with respect to alpha-fetoprotein (*AFP*) levels in the first 24 weeks after the start of therapy. *Black line* patients with AFP ≥10 ng/mL at 24 weeks, *gray line* patients with AFP <10 ng/mL at 24 weeks

Study 2

We compared the incidence of HCC between 59 patients in the control group and the same number of patients in the PegIFNα-2a group using the matched-pair test. The backgrounds of the patients are shown in Table 4. The PegIFNα-2a group had higher rates of advanced fibrosis (F3 and F4) and active inflammation (A2 and A3). No other differences were found between the two groups, except for the white blood cell count (Table 4).

Development of HCC was observed in 2 patients in the PegIFNα-2a group and 8 in the control group. The incidence of HCC was compared between the two groups, using the Kaplan–Meier method. The incidence of HCC in the PegIFNα-2a group was significantly lower than that in the control group (log-rank test, $p = 0.0187$; Fig. 4). Among the patients with advanced fibrosis of the liver (F3 and F4), those in the PegIFNα-2a group had a lower incidence of HCC than those in the control group. The independent risk factors for the development of HCC were analyzed using the stepwise Cox proportional hazard model. Only PegIFNα-2a administration and age were identified as independent risk factors for the development of HCC (Table 5).

Discussion

The number of HCC cases resulting from HCV infection continues to increase worldwide [19]. To date, IFN therapy is the most effective preventive measure against HCC in patients with chronic hepatitis C; furthermore, the incidence of HCC is reduced in patients who achieve an SVR to IFN [6–9] Therefore, achieving an SVR is the most effective approach for reducing the risk of developing HCC. In Japan, the incidence of HCC is elevated in older patients with hepatitis C. Corroborating this finding, the results of a Japanese study show a higher risk of HCC in patients aged 65 years and more [10]. Therefore, prevention of HCC in aged patients is an important challenge.

In the present multicenter, cooperative, retrospective study conducted in Japan, the incidence of HCC was reduced in patients who received 90 μg PegIFNα-2a weekly or biweekly and had AFP values of <10 ng/mL and ALT values of ≤40 IU/L 24 weeks after the start of the treatment. The results of the matched case–control study of the PegIFNα-2a group and the non-IFN control group show that the incidence of HCC was significantly lower in the PegIFNα-2a group than in the control group, especially in patients with advanced fibrosis of the liver (F3 and F4). However, there could have been a selection bias between

Table 4 Backgrounds of the patients in the propensity-matched control study (PegIFNα-2a group, $n = 59$; control group, $n = 59$)

	PegIFNα-2a group ($n = 59$)	Control group ($n = 59$)	p value
Age (years)	60.5 ± 13.0	63.3 ± 10.5	n.s.
Gender (male/female)	24/35	25/34	n.s.
BMI	22.9 ± 3.6	22.9 ± 3.4	n.s.
Genotype (1/2)	49/10	46/13	n.s.
History of excess alcohol consumption (60 g/day; yes/no)	10/49	4/55	n.s.
Fibrosis (F0, 1, 2/F3, 4)	37/22	43/16	<0.05
Development of HCC (F0–2/F3, 4)	1/1	1/7	n.s.
Inflammatory activity (A0,1/A2, 3)	19/40	30/29	<0.05
Diabetes mellitus (no/yes)	57/2	56/3	n.s.
LDL cholesterol (mg/dL)	95.3 ± 23.8	117.0 ± 4.2	n.s.
White blood cell count (/mm^3)	4,260 ± 1,239	5,193 ± 2,078	<0.05
Red blood cell count ($\times 10^{-4}$/μL)	430 ± 57.8	441 ± 44.9	n.s.
Hemoglobin (g/dL)	13.6 ± 1.5	13.6 ± 1.9	n.s.
Platelet count ($\times 10^{-3}$/μL)	14.5 ± 5.7	15.8 ± 5.7	n.s.
Albumin (g/dL)	4.1 ± 0.5	4.1 ± 0.4	n.s.
Total bilirubin (mg/dL)	0.7 ± 0.5	0.9 ± 0.7	n.s.
AST (IU/L)	58.3 ± 47.7	49.7 ± 26.6	n.s.
ALT (IU/L)	63.6 ± 68.7	58.0 ± 39.2	n.s.
Gamma-GTP (IU/L)	78.3 ± 81.3	55.3 ± 75.1	n.s.
Baseline alpha-fetoprotein (AFP) (ng/L)	7.2 (4.3–14.2)	7.7 (3.9–13.8)	n.s.
Baseline HCV RNA level (KIU/mL)	1,230 (24–3,870)	1,024 (38–3,110)	n.s.

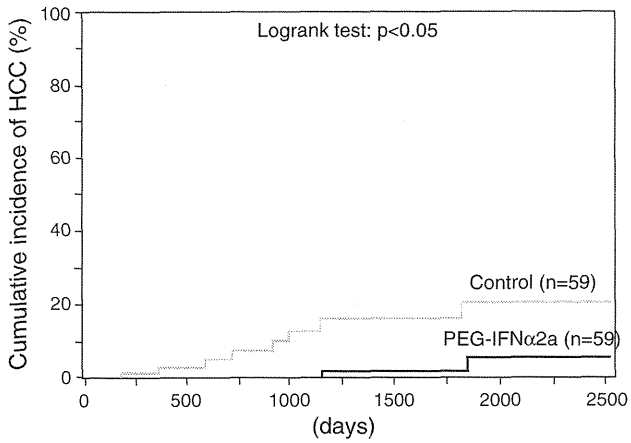

Fig. 4 Comparison of HCC rates between the long-term PegIFNα-2a administration group ($n = 59$) and non-administration group ($n = 59$) in the propensity-matched control study (Kaplan–Meier log-rank test, $p = 0.019$)

Table 5 Risk factors for HCC in the propensity-matched control study (Cox proportional hazard model)

Variables	Risk ratio	95 % CI	p value
PegIFN versus control	0.17	0.03–0.75	<0.05
Age (every 1 year)	1.12	1.02–1.25	<0.05
Fibrosis (F3, 4 vs. F0, 1, 2)	1.70	0.75–4.16	n.s.
Platelet count (every 10 × 10^3/μL)	0.89	0.73–1.09	n.s.
Albumin (every 1.0 g/dL)	0.80	0.10–6.68	n.s.
On-treatment AFP (<10 vs. ≥10 ng/L)	4.07	0.59–40.12	n.s.

the PegIFNα-2a group and the control group (patients who did not agree to receive IFN treatment), because this was a retrospective and non-randomized study. However, concordant with the findings of the HALT-C study [14], the present results show that PegIFNα-2a inhibits the development of HCC in patients with advanced fibrosis of the liver.

Recent studies show that polymorphisms in the host *IL28B* gene are important factors in the response to PegIFNα and ribavirin combination therapy [20, 21]. However, the mechanism of IL28B involvement in the response to PegIFNα and ribavirin has not been elucidated completely. A recent report has shown that IL28B is a significant factor in the development of HCC as well as in the response to IFN therapy [22]. Further studies are warranted to analyze the relationship between IL28B and inhibition of the development of HCC by PegIFNα in chronic hepatitis C.

Risk factors for the development of HCC have been discussed previously. Increased intrahepatic fat is involved in the development of HCC in chronic hepatitis C patients [23, 24]. In addition, diabetes-associated fat disorder [25, 26], hepatic iron overload [27], advanced fibrosis, older age, and fatty deposits in the liver are risk factors for HCC development [4]. Therefore, it is important to establish strategies to mitigate these risk factors to prevent the development of HCC and thus improve the outcomes of hepatitis C patients.

IFN therapy after HCC treatment is reported to inhibit the recurrence of tumors [28, 29], and a meta-analysis has revealed a trend toward inhibition of the recurrence of HCC [30, 31]. The prevention of HCC is an important issue that needs to be addressed to improve the survival of chronic hepatitis C patients. The findings of the present study and the HALT-C trial [14] indicate the effectiveness of long-term administration of maintenance IFN for preventing the development of HCC in chronic hepatitis C patients without an SVR. Improvement in ALT levels is also known to be an important predictor for the prevention of HCC [32]. A low AFP value during IFN administration is also recognized as a significant indicator of a lower risk of HCC [33, 34]. Recently, Osaki et al. [35] reported that a decrease of serum AFP during treatment with IFN was associated with a reduced incidence of HCC. Taking these findings and our own together, we conclude that maintenance administration of low-dose PegIFNα-2a weekly or biweekly to non-SVR patients with chronic hepatitis C decreases the incidence of HCC, especially in patients whose serum ALT and AFP levels are within the normal range 24 weeks after the start of treatment. The preventive effects of IFN against the development of HCC without elimination of the virus may be associated with its anticarcinogenic effects [16, 35]; however, the precise mechanism should be investigated.

The limitations of the present study are that it is retrospective and multicentric; therefore, potentially there may have been a selection bias. However, the reduction of the rate of development of HCC by maintenance administration of PegIFNα-2a in the patients in whom serum ALT and AFP levels were within the normal ranges 24 weeks after the start of treatment may be attributable to the anticarcinogenic effects of IFN without elimination of the virus.

Conclusion

The incidence of HCC was lower in non-SVR patients with chronic hepatitis C who were administered with maintenance low-dose PegIFNα-2a; especially in those whose serum ALT and AFP levels were within the normal ranges 24 weeks after the start of treatment.

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＜原　著＞

1型高ウイルス量C型慢性肝炎に対するPEG-IFNα-2a＋Ribavirin療法の治療成績—九州多施設共同研究—

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要旨：九州内肝臓専門医療機関の多施設研究により，1型，高ウイルスC型慢性肝炎（CHC）に対するペグインターフェロン（PEG-IFN）α-2a＋リバビリン（RBV）療法の有効性，安全性について検討を行なった．総数は320例，抗ウイルス効果判定症例は288例，安全性評価症例は310例．持続ウイルス陰性化（SVR）率はIntention-to-treatで53.1%，Per Protocol Set（44週間以上投与）で59.6%であった．13～36週目のRNA陰性化例では，延長投与が有効であった．SVRに寄与する因子は，治療前では年齢，BMI，総コレステロール，ウイルス量であったが，治療開始後では12週目までのウイルス陰性化のみであった．有害事象による治療中止例は14例（4.5%）であり，難治性CHCに対するPEG-IFNα-2a＋RBV療法は安全性が高く，50%以上のSVR率が期待できる．

索引用語：　難治性C型慢性肝炎　ペグインターフェロンα-2a＋リバビリン療法
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はじめに

C型慢性肝炎に対するインターフェロン（IFN）療法は，2004年12月にPEG-IFNα-2bとリバビリン（RBV）の併用療法，2007年3月にPEG-IFNα-2aとRBVの併用療法が認可され，本邦においても世界の標準治療を行うことが可能となった[1)2)]．

PEG-IFNα-2aとRBVの併用療法の国内第III相臨床試験において，genotype 1b，高ウイルス量（100 KIU/mL以上）のC型慢性肝炎に対して，48週間投与にて初回治療例は59.4%，前治療無効・再燃例に対する再治療においては54.0%のウイルス学的著効（sustained virological response：SVR）が得られている[3)]．

近年，ウイルス陰性化時期別に投与期間を調整するresponse-guided therapyの有効性が示され，genotype 1の初回症例に対するPEG-IFNα-2a＋RBV療法において，投与開始4週時HCV-RNA陰性例（rapid virological response：RVR）は24週間投与で48週間投与と同等のSVR率であり，12週時陽性かつ24週時陰性例（late virological response）では48週間より72週間投与の方がより高いSVRが得られた，と報告されている[4)5)]．

しかし，これらの成績のほとんどは治験や海外での研究によるもので，またHCV-RNAの測定は以前のア

ンプリコア法で行われたものである．2007年12月により感度の高いHCV-RNA測定法であるTaqMan PCR法が本邦で認可されたが[6]，PEG-IFNα-2a＋RBV療法における治療中のTaqMan PCR法によるウイルス動態や，市販後のいわゆる「real world」におけるウイルス陰性化時期別の治療効果，および延長投与の有効性に関しては，未だ多数例で解析した報告が少ない．

さらに，PEG-IFN＋RBV療法においては，高齢者，女性などの背景因子の違いによる有効性の低下が問題となっており[7]，これらについても多数例での検討で明らかにする必要がある．

以上の背景により，九州内の肝疾患専門医療機関で構成される九州肝疾患治療戦略研究会では，セログループ1，高ウイルス量のC型慢性肝炎に対するPEG-IFNα-2a＋RBV療法の有効性・安全性の検証，およびTaqMan PCR法によるウイルス動態と有効性の関係を明らかにするため多施設共同研究を行った．

C型肝炎の治療においてはDirect Acting Antiviral（DAA）製剤を使用したさらに強力な抗ウイルス治療の時代に入りつつあるが，これまで長い間標準治療法としての位置を占めてきたPEG-IFN＋RBV療法の我が国における治療成績をまとめておくことは，今後の治療法を考える上で重要であると考え，報告する．

対象と方法

1）対象患者

セログループ1（またはgenotype 1a/1b）かつ高ウイルス量（血中HCV-RNA≧5.0 Log IU/mL）のC型慢性肝炎患者で，以下の選択基準を満たし，かつ除外基準に抵触しない患者を対象とした．過去のIFN治療歴は問わないこととした．

2）選択基準

上記対象のうち，①年齢が20歳以上の患者，②投与開始前の臨床検査値で白血球数3,000/μL以上，好中球数1,500/μL以上，血小板数90,000/μL以上，ヘモグロビン量12 g/dL以上の基準を満たした患者，③試験の参加にあたり十分な説明を受けた後，十分な理解の上，文書による患者本人の自由意思による同意が得られた患者，を選択した．

3）除外基準

選択基準を満たす患者のうち，以下の除外基準のひとつでも当てはまる患者は除外した．①妊婦，妊娠している可能性のある婦人又は授乳中の婦人，②PEG-IFNα-2aまたは他のIFN製剤に対し過敏症の既往歴のある患者，③リバビリン又は他のヌクレオシドアナログに対し，過敏症の既往歴のある患者，④コントロール困難な心疾患（心筋梗塞，心不全，不整脈等）のある患者，⑤異常ヘモグロビン症（サラセミア，鎌状赤血球性貧血等）の患者，⑥慢性腎不全又はクレアチニンクリアランスが50 mL/分以下の腎機能障害のある患者，⑦重度のうつ病，自殺念慮又は自殺企図等の重度の精神病状態にある患者又はその既往歴のある患者，⑧重度の肝機能障害のある患者，⑨自己免疫性肝炎の患者，⑩ワクチン等生物学的製剤に対し過敏症の既往歴のある患者，⑪小柴胡湯を投与中の患者，⑫担当医師が本研究の対象者として不適当であると認めた患者．

4）PEG-IFNα-2a（Pegasys®）およびRBV（Copegus®）の投与方法

PEG-IFNα-2aは1回180μgを週1回皮下投与し，RBVは体重60 kg未満であれば600 mg/日，60 kg以上80 kg未満であれば800 mg/日，80 kg以上であれば1,000 mg/日内服を原則とした．なお，PEG-IFNα-2a，RBVとも主治医の判断により，減量しての投与開始も可能とした．

投与期間は原則48週間とし，主治医の判断により投与開始12週後のHCV-RNAが陽性の場合は，72週までの延長投与も可能とした．以下，44—55週間投与を標準投与，56週間以上の投与を延長投与と呼ぶこととする．

5）減量・中止基準

好中球数，血小板数，ヘモグロビン量の減少が発現した場合には，添付文書の基準を参考に用量調整することとした．その他副作用など，患者の状態により医師の判断で減量してもよいものとした．以下に該当する場合，その後の試験を中止し適切な処置を行うこととした．①添付文書の中止基準に該当する臨床検査値異常が発現した場合，②病勢の明らかな進行が認められた場合，③有害事象のため投与の継続が困難な場合，④被験者が投与の中止を希望した場合，⑤何らかの理由により来院しなくなった場合，⑥その他，試験責任（分担）医師の医学的判断により中止の必要性を認めた場合．

6）検査項目

開始前，治療中は4週間毎および治療終了時，治療終了後24週時にHCV-RNA（ロシュCOBAS TaqMan HCV），白血球数，好中球数，赤血球数，ヘモグロビン，ヘマトクリット，血小板数，総蛋白，アルブミン，AST，ALT，LDH，アルカリフォスファターゼ，γGTPを測定した．

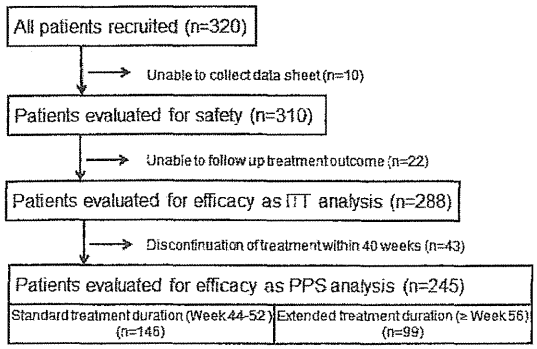

Fig. 1　Flow diagram of the patient's enrollment.

7）主要評価項目

主要評価項目は，治療終了後24週時のHCV-RNA陰性化（SVR）とし，Intention-to-treat（ITT，1回以上治療薬の投与を受け，1回以上有効性の観察がある集団）解析およびPer Protocol Set（PPS，44週間以上治療継続できた集団）解析をおこなった．本来ITT解析は登録された症例を全て対象とすべきであるが，調査票回収不能や有効性評価欠落などのプロトコール違反を除外するため上記のような定義で解析した．

8）副次的評価項目

投与開始4週，8週，12週，16週，20週，24週，48週，治療終了時のHCV-RNA陰性化率，HCV-RNA陰性化時期とSVR率との関係，背景因子別（年齢，性，IFN治療歴，前治療効果，BMI，臨床検査値，HCV-RNA量，組織学的所見（A因子，F因子），PEG-IFNα-2aおよびRBVのadherence）のSVR率とした．なおadherenceは，プロトコールに規定された48週間の予定総投与量に対する実際の総投与量のパーセンテージとした．

9）安全性判定

有害事象，臨床検査値（好中球数・血小板数・ヘモグロビン量の推移）および投与継続率，減量率，中止率について検討した．

また血球減少については，治療期間中の最小値を以下の基準に基づきgrade分類を行なった．好中球数grade 1：1,500/μL以上，grade 2：1,000/μL以上1,500/μL未満，grade 3：500/μL以上1,000/μL未満，grade 4：500/μL未満，血小板数grade 1：7.5万/μL以上，grade 2：5万/μL以上7.5万/μL未満，grade 3：2.5万/μL以上5万/μL未満，grade 4：2.5万/μL未満，ヘモグロビンgrade 1：10 g/dL以上，grade 2：8 g/dL以上10 g/dL未満，grade 3：6.5 g/dL以上8 g/dL未満，grade 4：6.5 g/dL未満．

10）統計学的解析

背景因子別のSVR率の有意差検定にはχ^2検定を行なった．SVRとnon-SVRの背景因子の比較には，χ^2検定およびunpaired t-testを行い，有意な因子についてロジスティック回帰による多変量解析を行なった．なお，有意水準を5%未満とした．

なお本研究は鹿児島大学医学部・歯学部附属病院臨床研究倫理委員会の承認を受けている．

結　果

1．登録状況（Fig. 1）

2008年1月～12月で73施設から320例が登録された．そのうち2011年2月28日の時点で調査項目記入用紙の回収が可能であった310例を解析対象とした．安全性評価は310例全例で，効果判定は判定不能の22例を除く288例で解析を行った．

2．患者背景

全例（310例）および効果判定可能例（288例）の患者背景をTable 1に示す．効果判定可能例のうち44週以上投与された完遂例（PPS）は245例（85.1%）で，そのうち標準投与は146例，延長投与は99例であった．プロトコールでは投与開始後12週目にHCV-RNAが陽性であれば延長投与可能としていたが，実際には延長投与例の中に12週目までにHCV-RNAが陰性化（early virological response：EVR）しているにもかかわらず延長投与が行われた症例が30例含まれていた．EVRにおいて延長投与が行われた例は標準投与例と比較して，高齢，再治療例が多い，BMIが高い，血小板が少ない，陰性化時期が遅いなどの背景の特徴があった（Table 2）．

3．ウイルス学的効果

①効果判定可能例（288例）におけるSVR率

ITT解析ではSVR率53.1%（153/288）であり，44週間以上投与できた治療完遂例のPPS解析では59.6%（146/245）であった．

②PPS（245例）における4週毎のウイルス陰性化率（Fig. 2）

治療期間中にTaqMan PCRで「検出せず」を示したのは，4週目（RVR）17.2%，12週目（EVR）58.0%，48週目88.3%，終了時84.1%であった．

③標準投与例，延長投与例におけるウイルス陰性化時期別SVR率（Fig. 3）

12週間以内のHCV-RNA陰性化例においては，標準

Table 1 Baseline characteristics of the patients.

	Patients for safety assessment (n＝310)	Patients for efficacy assessment (n＝288)
Age (years)	58.8±9.3	58.9±9.1
Gender (male/female)	133/177	119/169
History of IFN treatment (no/yes)	181/129	169/119
Response of prior treatment (relapse/non-response)	41/52	41/44
BMI (kg/m^2)	23.3±3.4	23.3±3.3
White blood cell count (/μL)	4999±1554	4979±1503
Neutrophil count (/μL)	2609±1084	2599±1073
Hemoglobin (g/dL)	13.7±1.5	13.7±1.5
Platelet count (×10^4/μL)	16.2±4.9	16.1±4.7
ALT (IU/L)	68.5±75.5	68.6±75.7
γ-GTP (IU/L)	61.0±71.3	60.4±71.2
Total cholesterol (mg/dL)	172.2±32.9	172.4±32.9
LDL cholesterol (mg/dL)	99.5±25.9	100.9±25.1
Triglyceride (mg/dL)	106.1±51.2	105.9±51.2
AFP (ng/mL)	9.3±13.9	9.3±13.9
HCV-RNA (Log IU/mL)	6.4±0.8	6.3±0.8
Histological grading (A0/A1/A2/A3)	3/84/95/19	3/79/90/19
Histological staging (F0/F1/F2/F3/F4)	7/85/62/40/11	7/80/61/37/10

投与，延長投与ともに70％以上のSVR率が得られ，両者に差は認められない．一方，13週目以降にHCV-RNA陰性化が得られた例においては，延長投与の方が標準投与よりも高いSVR率が得られ，特に25週以降の陰性化例においては，標準投与では1例のSVRも得られなかった．しかし，37週目以降に陰性化した例では，延長投与してもSVRとなった例は1例もなかった．

④標準投与例における年齢別，性別SVR率（Fig. 4）

男女別ではSVR率に有意な差はなかったが，60歳以上では60歳未満よりも有意にSVR率が低かった（45.9％ vs. 63.7％）．年齢と性で区分すると，60歳以上の女性のSVR率が42.6％と最も低値であった．

⑤標準投与例におけるSVR例とnon-SVR例の比較（単変量解析）（Table 3）

治療前の因子では，年齢，BMI，血小板数，総コレステロールおよび治療前HCV-RNA量に有意な相違が見られ，治療開始後の因子においては，HCV-RNA陰性化時期，治療期間とPEG-IFNα-2aおよびRBVのadherenceに有意な差を認めた．

⑥標準投与例においてSVRに寄与する因子の解析（多変量解析）（Table 4）

単変量解析にて有意であった項目について多変量解析を行った結果，治療前の因子においては，年齢が若いこと，BMIが低いこと，総コレステロールが高いこと，HCV-RNA量が少ないこと，が独立してSVRに寄与していた．これらに治療開始後の因子を加えると，EVRであることが唯一のSVRに関連する因子となった．

4．有害事象発現率および治療中止率

①有害事象（血球減少以外）の発現率（Table 5）

有害事象は213例（68.7％）に認め，総発現件数は658件であった．有害事象の中では皮膚および皮下組織障害が29.7％と最も多かった．

②血球減少発現率（grade分類）（Table 6）

ほぼ全例で血球成分すべてにgrade 1以上の減少が見られ，grade 3以上の血球減少は，好中球で58.7％，血小板で5.5％，ヘモグロビンで5.1％であった．

③中止率とその原因

44週未満での中止例は43例（13.9％）であったが，そのうち有害事象による中止は14例（4.5％）であった．それ以外の中止理由は，無効中止15例，偶発的合併症3例，経過観察不能（通院せず，など）11例であった．

考　察

九州地区は本邦の中ではHCVキャリア率および肝癌

Table 2 Comparison of patient characteristics between standard and extended treatment duration in cases with early virological response.

	Standard treatment duration (n＝111)	Extended treatment duration (n＝30)	P-value
Age (years)	57.0±9.5	61.7±7.2	0.0139*
＜60/≧60	59/52	9/21	0.0243**
Gender male/female	52/59	11/19	0.3197**
History of IFN treatment initial treatment/retreatment	71/40	11/19	0.0072**
Response of prior treatment relapse/non-response	21/6	10/4	0.0502**
BMI (kg/m^2)	22.4±2.7	24.3±3.7	0.0028*
Neutrophil count (/μL)	2739.9±1087.4	2602.6±1275.2	0.5764*
Hemoglobin (g/dL)	13.9±1.4	13.7±1.4	0.5269*
Platelet count (×10^4/μL)	17.2±4.7	14.6±4.2	0.0058*
ALT (IU/L)	71.7±105.6	50.4±36.6	0.2800*
γ-GTP (IU/L)	53.3±69.5	54.0±99.6	0.9669*
Total cholesterol (mg/dL)	177.7±28.4	176.2±34.2	0.8309*
LDL cholesterol (mg/dL)	122.1±144.8	93.7±30.9	0.5623*
Triglyceride (mg/dL)	97.6±50.4	119.6±72.0	0.0890*
HCV-RNA (Log IU/mL)	6.3±0.7	6.1±1.3	0.4188*
5.0-5.9/6.0-6.9≧/7.0	29/62/16	5/18/3	0.2645**
Histological grading A0-A1/A2-A3	31/45	9/9	0.7267**
Histological staging F0-2/F3-4	64/12	14/5	0.5188**
Timing of HCV-RNA undetectable ≦Week 4/Week 5-8/Week 9-12	36/40/35	4/8/18	0.0127**

Mean±SD *t-test, **Chi-square test

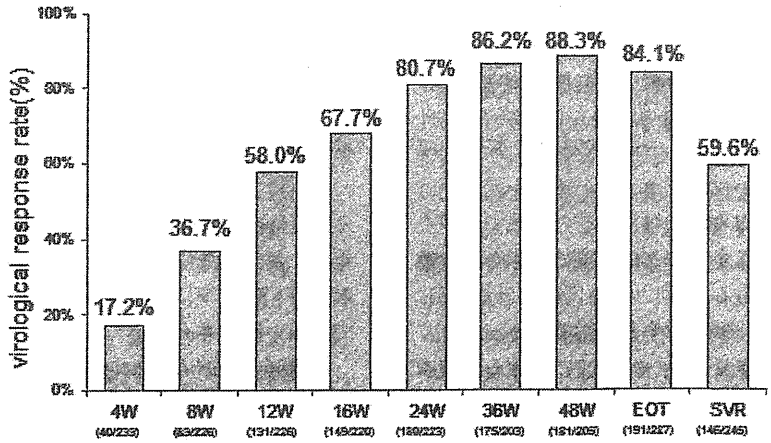

Fig. 2 Virological response rates at each point during PEG-IFNα-2a+RBV treatment in per protocol set population.

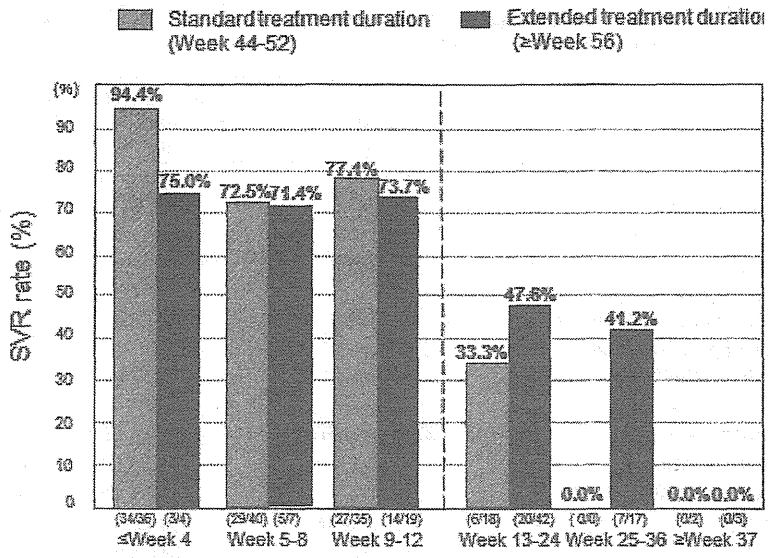

Fig. 3 Sustained virological response rates in patients with standard and extended treatment duration stratified by the time at which serum HCV-RNA became undetectable.

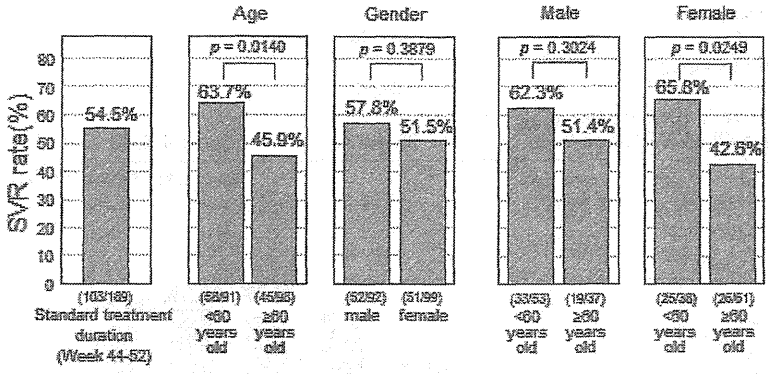

Fig. 4 Sustained virological response rates according to age and gender.

死亡率が高いことが知られており，その地域での肝炎治療の実態を明らかにすることは今後の肝癌予防対策を講じる上で重要である．今回九州地区における1型，高ウイルスのC型慢性肝炎に対するPEG-IFNα-2a＋RBV療法の市販後のいわゆる「real world」における治療成績を明らかにするため，九州全域の主な専門医療機関における多数例での前向き多施設共同研究を行った．

まずSVR率に関しては，治療完遂例で59.6%，ITT解析でも53.1%と海外および国内で行われた治験の成績[1)~3)]とほぼ同等の成績が得られた．この成績は，2009年から72週間までの長期投与が可能となった影響もあるが，「real world」での対象は治験の対象とは異なり，年齢や併発疾患など様々な条件が悪いことを考慮すると，このSVR率はかなり良好な成績であると言えるのではないかと考える．

本研究の目的のひとつは，それまでアンプリコア法により行われていたIFN治療中の効果予測を，2007年12月に臨床で使用可能となった高感度のHCV-RNA測定系であるTaqMan PCRを用いて検討することであった．結果として12週目までにHCV-RNAが「検出せず」まで減少した例においては標準投与と延長投与との間に差が見られず，13週から36週までに陰性化した例に

Table 3 Comparison of patients characteristics between SVR and Non-SVR groups.

	Non-SVR (n=86)	SVR (n=103)	P-value
Age (years)	60.0±10.0	56.8±9.4	0.0254*
<60/≥60	33/53	58/45	0.0140**
Gender male/female	38/48	52/51	0.3879**
History of IFN treatment initial treatment/retreatment	50/25	67/23	0.3301**
Response of prior treatment relapse/non-response	10/15	15/8	0.0806**
BMI (kg/m^2)	23.4±3.7	22.4±2.8	0.0297*
<25/≥25	61/23	84/19	0.1453**
White blood cell count (/μL)	4920±161	5093±147	0.4283*
Neutrophil count (/μL)	2492±990	2696±1104	0.2062*
Hemoglobin (g/dL)	13.7±1.5	14.0±1.5	0.1391*
Platelet count (×10^4/μL)	15.2±4.6	17.1±4.7	0.0066*
ALT (IU/L)	68.1±54.3	75.8±109.7	0.5505*
γ-GTP (IU/L)	67.3±71.2	58.0±70.9	0.3920*
Total cholesterol (mg/dL)	168.5±34.5	178.8±28.8	0.0469*
LDL cholesterol (mg/dL)	99.7±24.9	104.8±24.6	0.3108*
Triglyceride (mg/dL)	111.0±53.3	98.2±46.7	0.1277*
HCV-RNA (Log IU/mL)	6.5±0.6	6.2±0.8	0.0209*
5.0-5.9/6.0-6.9/≥7.0	13/53/18	30/53/16	0.0854**
Histological grading A0-A1/A2-A3	24/35	28/42	0.9377**
Histological staging F0-2/F3-4	44/16	59/11	0.1249**
Timing of HCV-RNA undetectable ≤Week 4/Week 8-12/≥Week 13	16/11/23	69/27/7	<0.0001**
Treatment duration (weeks) <Week 44/≥Week 44-52	36/50	7/96	<0.0001**
PEG-IFNα-2a Adherence <60%/60-80%/≥80%	30/16/33	12/9/82	<0.0001**
Ribavirin Adherence <60%/60-80%/≥80%	27/24/27	17/18/66	<0.0001**

Mean±SD *t-test, **Chi-square test

おいて延長投与の優位性があり，従来のアンプリコア法で得られていた結果と同様であった．よって現在の厚生労働省がガイドラインで示されている延長投与の基準は，TaqMan PCR 法を用いた場合においても妥当なものであることが検証された．

次に治療効果に影響する因子に関しては，これまでにウイルス側因子として HCV-RNA 量，コア領域の 70 番，91 番アミノ酸変異[8]，NS5A 領域の ISDR 変異[9]，IRRDR 変異[10]，宿主側因子として年齢，性，IL28B 領域の遺伝子多型[11][12]，線維化，インスリン抵抗性[13]，治療因子として PEG-IFN または RBV の adherence，延長投与などが報告されている[14]．本研究では延長投与を行う基準を規定していなかったため，標準投与例のみで治療効果に寄与する因子を解析してみると，治療前の因子としては年齢，BMI，総コレステロール，HCV-RNA 量が有意な因子であった．IL28B やウイルス変異の検査は現時点では保険適応となっていないため，一般臨床においては 48 週間の標準治療の効果予測としてこれらの因子が指標になるものと考えられる．BMI やコレステロールなど治療前に介入可能な因子に関しては，今後介入法の検討が必要であろう．また本研究でも明らかになったように，高齢女性における治療効果不良の問題も残されている．我が国の高齢女性にはウイルス変異やメタボリック因子などの IFN 抵抗性要

Table 4 Multivariate analysis for the factors associated with sustained virological response (in cases with standard treatment duration).

Factors		Before start of therapy			All		
		Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age	every 10 years of age	0.600	0.386-0.896	0.0168	0.580	0.270-1.178	0.1473
BMI	every 5 kg/m^2	0.487	0.252-0.915	0.0280	0.637	0.213-1.848	0.4069
Total cholesterol	every 20 mg/dL	1.279	1.011-1.635	0.0435	1.349	0.940-1.987	0.1123
Platelet count	every 20000/μL	1.105	0.949-1.296	0.2038	0.918	0.716-1.178	0.4946
HCV-RNA	every 1 log IU/mL	0.535	0.305-0.887	0.0205	0.555	0.236-1.195	0.1521
EVR		—	—	—	24.651	6.709-125.889	<0.0001
Treatment duration	every 4 weeks	—	—	—	1.189	0.819-1.772	0.3738
PEG-IFNα-2a Adherence	every 20%	—	—	—	1.803	0.817-4.047	0.1433
Ribavirin Adherence	every 20%	—	—	—	0.991	0.524-1.851	0.9762

EVR: early virological response

Table 5 Adverse events (except for cytopenia)

System Organ Class†	n (%)
General disorders and administration site conditions	50 (16.1%)
Skin and subcutaneous tissue disorders	92 (29.7%)
Psychiatric disorders	27 (8.7%)
Gastrointestinal disorders	30 (9.7%)
Musculoskeletal and connective tissue disorders	9 (2.9%)
Respiratory, thoracic and mediastinal disorders	8 (2.6%)
Metabolism and nutrition disorders	14 (4.5%)
Eye disorders	6 (1.9%)
Renal and urinary disorders	6 (1.9%)
Vascular disorders	2 (0.6%)
Hepatobiliary disorders	8 (2.6%)

Number of patients for safety assessment: 310
Number of patients with at least one adverse event: 213
Number of adverse events: 658
†It is reference about MedDRA.

因が集積しているとの報告があり[15]，これらの症例に対してテラプレビルなどの新規抗ウイルス薬をどのように使用していくかも今後の重要な課題である．

治療開始後の因子を加えて解析すると，SVRに寄与する因子として治療前因子はすべて有意ではなくなり，EVRのみに集約されることから，治療前にPEG-IFNα-2a＋RBV療法の効果予測をあまり綿密に行うより，現実的には治療のresponseをみてから方針を判断するresponse-guided therapyがよいのではないかと考える．

しかし，すでに現在の「real world」ではEVRが得られなかったり，EVRであっても8週目HCV-RNAが陽性の高齢女性や線維化進展例においては72週間の延長投与が一般的に行われるようになっており，本研究で抽出された治療効果規定因子はあくまで48週間治療に限定した因子と捉えなければならない．さらに，EVRでありながら延長投与された例の中に高齢者や線維化進展例が多く含まれており（Table 2），本研究の標準治療における解析にはこれらの症例を除外していることから，結果的に条件の比較的良い群が解析対象となったバイアスが存在することも念頭に置く必要がある．

有害事象に関しては，開発治験時のものと発生率に大差なく，副作用による中止率も低く，本治療は一般

Table 6 Incidence of cytopenia: grade classification

Factor	Grade classification	Number of events (%)
Neutropenia	Grade 1	29 (9.4%)
	Grade 2	87 (28.1%)
	Grade 3	161 (51.9%)
	Grade 4	21 (6.8%)
	Total	298 (96.1%)
Thrombocytopenia	Grade 1	203 (65.5%)
	Grade 2	88 (28.4%)
	Grade 3	17 (5.5%)
	Grade 4	0 (0.0%)
	Total	308 (99.4%)
Anemia	Grade 1	131 (42.3%)
	Grade 2	162 (52.3%)
	Grade 3	15 (4.8%)
	Grade 4	1 (0.3%)
	Total	309 (99.7%)

Number of patients for safety assessment: 310

臨床においても専門医の下できちんと管理して行えば，安全に行える治療であることが証明できた．

近年，C型肝炎の治療は直接ウイルスに作用するDAA製剤の開発が進み，今後DAAによる治療が中心となると予想されている．すでに本邦でもプロテアーゼ阻害薬であるテラプレビル[16][17]が使用可能となり，1型，高ウイルスの難治性C型慢性肝炎に対しては，PEG-IFN＋RBVにテラプレビルを併用する3剤療法が第一選択とされている[18]．しかし我が国のC型肝炎患者は高齢化している実態があり，現在のDAAでは使用できない，または次世代のDAA製剤が使用できるまで待てない，という患者が現実的にはたくさん存在する．このような背景を考慮すると，難治性C型慢性肝炎であってもPEG-IFNα-2a＋RBV療法で安全に50％以上のSVR率が得られることを「real world」の多数例で証明できた今回の試験の意義は大きいと考えられる．

研究参加施設

佐賀大学医学部附属病院，霧島市立医師会医療センター，製鉄記念八幡病院，国立病院機構熊本医療センター，長崎大学大学院医歯薬学総合研究科　展開医療科学講座・消化器病態制御学，福岡赤十字病院，国家公務員共済組合連合会千早病院，医療法人創起会くまもと森都総合病院，けやき会東病院，北九州市立医療センター，熊本大学医学部附属病院，藤元早鈴病院，国立病院機構九州医療センター，社会医療法人財団白十字会佐世保中央病院，宮崎医療センター病院，しみずクリニック，大牟田市立総合病院，天ヶ瀬クリニック，済生会唐津病院，国立病院機構大分医療センター，ハートライフ病院，医療法人清和会　長田病院，国立病院機構小倉医療センター，佐賀社会保険病院，日本赤十字社長崎原爆病院，熊本地域医療センター，なかそね和内科，福岡大学医学部消化器内科，久留米大学病院，朝倉医師会病院，佐世保市立総合病院，日本赤十字社長崎原爆諫早病院，長崎労災病院，熊本労災病院，大分循環器病院，宮崎県済生会日向病院，国民健康保険中部病院，鹿児島厚生連病院，串間市民病院，豊見城中央病院，高邦会高木病院，佐賀県立病院好生館，平井内科，熊本セントラル病院，玉名地域保健医療センター，八代総合病院，国立病院機構熊本南病院，大分大学医学部附属病院，大分県立病院，有田胃腸病院，森内科医院，宮崎大学医学部附属病院，鹿児島大学病院，鹿児島市立病院，済生会福岡総合病院，宗像医師会病院，久留米大学医療センター，岩本内科医院，祐愛会織田病院，いのうえ内科クリニック，日本海員掖済会長崎病院，虹が丘病院，医療法人光晴会病院，奈良尾医療センター，雄博会千住病院，上五島病院，みどりクリニック，済生会熊本病院，山崎内科，天草地域医療センター，伸和会共立病院，ひろの内科クリニック，済生会川内病院

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Efficacy and safety of pegylated interferonα-2a plus ribavirin treatment in refractory chronic hepatitis C patients —a multi-center study in Kyushu—

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We examined the efficacy and safety of peginterferon (PEG-IFN) alfa-2a plus ribavirin (RBV) therapy for chronic hepatitis C (CHC) patients with genotype 1 and high viral load by multi-center (73 institutions) study in Kyushu and totally 320 patients were enrolled. The sustained virological response (SVR) rates were 53.1% and 59.6% in intention-to-treat and per protocol set analysis, respectively. Treatment prolongation over 48 weeks was more effective in cases which serum HCV-RNA became negative between 13 and 36 weeks after start of therapy. Multivariate analysis for baseline characteristics revealed that age, BMI, total cholesterol and viral load were significantly associated with SVR. However, when added on-treatment factors, early virological response was the only factor associated with SVR. Discontinuation of treatment due to adverse events was no more than 4.5%. In conclusion, PEG-IFN alfa-2a plus RBV treatment to refractory CHC patients is a well tolerated and can achieve over 50% of SVR.

Key words: refractory chronic hepatitis C　pegylated interferon α-2a plus ribavirin treatment　anti-viral effect　multi-center study　Kyushu region

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