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Original Article

Efficacy and safety of interferon treatment in elderly patients with chronic hepatitis C in Japan: A retrospective study using the Japanese Interferon Database

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Aim: Although interferon (IFN) treatment in elderly patients with chronic hepatitis C virus (HCV) infection has increased with the aging Japanese population, few studies have examined the efficacy and safety of IFN treatment in this population. We investigated the efficacy and safety of IFN treatment in elderly patients with chronic HCV infection using the Japanese Interferon Database.

Methods: Records of IFN treatment in 36 prefectures in Japan from December 2009 to April 2013 were examined. Patients with HCV infection who received IFN treatment were selected. We compared the sustained virological response (SVR) rate and the withdrawal from treatment proportion among elderly patients (≥75 years) with those among younger patients (<65 years, 65–74 years).

Results: We identified 15 267 patients with chronic HCV infection as the study cohort from the database. Of these, 310 patients were elderly with a mean age of 76.7 ± 1.95 years (2.03%; men, 155; women, 155), and the majority (87%) were treated with pegylated IFN. Lower SVR rates (aged <64 years, 65.3%; aged 65–74 years, 49.6%; aged ≥75 years, 46.5%; $P < 0.001$) and higher withdrawal from treatment proportions (aged <64 years, 15.0%; aged 65–74 years, 21.5%; aged ≥75 years, 32.4%; $P < 0.001$) were observed with aging.

Conclusion: We conclude that elderly patients with chronic HCV infection taking IFN therapy achieved lower SVR rates and a higher withdrawal from treatment proportion than younger patients.

Key words: chronic hepatitis C virus infection, database, elderly, interferon

INTRODUCTION

OVER 170 MILLION patients are infected with hepatitis C virus (HCV) worldwide.[1] HCV infection is the leading cause of liver disease, including hepatic failure and hepatocellular carcinoma (HCC).[2,3] In the past decade, the recommended treatment for chronic HCV infection has been interferon (IFN) therapy, and it consisted of pegylated IFN-α-2a or -α-2b (PEG IFN-α-2a or -α-2b) combined with ribavirin.[4] A number of clinical trials have compared the efficacy and safety of PEG IFN-α-2a and -α-2b treatment for chronic HCV infection; however, in most study cohorts, the mean age of the patients was between 40 and 55 years,[5] and only a few studies were conducted on IFN treatment in elderly patients with chronic HCV infection.[6–8] Arase *et al.*[6] conducted a study to compare the efficacy of normal-dose IFN treatment (group A) with that of low-dose IFN treatment (group B) in patients aged 65 years and older with chronic HCV genotype 1 infection.[7] A similar rate of sustained virological response (SVR) was observed in both groups and a higher withdrawal from treatment proportion due to adverse effects was found in group A. A subsequent study of HCV genotype 2 showed similar SVR rates in both groups, and although 30% of patients required a reduction of the IFN dose, it

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did not affect withdrawal from treatment.[7] Nishikawa *et al.*[8] similarly assessed the SVR and safety of PEG IFN-α-2a by comparing the medical records of 319 young patients (<65 years) and 108 elderly patients (≥65 years) diagnosed with chronic HCV infection. In this study, similar SVR rates and withdrawal from treatment proportions were observed in both groups.

As the population in Japan ages, an increase in the use of IFN treatment for elderly patients with chronic HCV infection is predicted. Data in the Japanese Interferon Database, comprising IFN treatment data collected from across Japan, indicates that the mean age of patients with chronic HCV is 60 years, which is approximately 10 years higher than was previously demonstrated by comparisons of the SVR rate following PEG IFN treatment.[9] Little is known about the efficacy and safety of IFN treatment in elderly patients, particularly those aged 75 years and older. We therefore evaluated the efficacy and safety of IFN treatment in this age group of patients with HCV infection using data from the Japanese Interferon Database.

METHODS

Japanese Interferon Database

THE DATA ANALYZED in this study were obtained from the Japanese Interferon Database, which collected treatment data of patients with hepatitis B virus (HBV) or HCV infection from 36 prefectures in Japan between December 2009 and April 2013. The clinical data were recorded using a standardized report form that was filled out by medical practitioners. The form included information on demographic characteristics (region, sex, birth date), IFN treatment (type, date, experience), IFN with or without ribavirin, diagnosis (chronic hepatitis or cirrhosis), results of laboratory tests (dates of tests, viral load, type of HCV genotype, aspartate aminotransferase level, alanine aminotransferase [ALT] level, platelet count), adverse drug reactions and outcomes (SVR, completion or withdrawal from treatment).

This study was approved by the institutional review board of the National Center for Global Health and Medicine, Tokyo, Japan.

Study population

Data from patients with chronic HCV infection who were treated between December 2009 and April 2013 were extracted from the database. Patients were excluded if they had missing data in their medical records (sex, age, diagnosis, comorbid conditions [liver diseases]), comorbid hepatitis B or cirrhosis, or if they were aged less than 16 years. The patients were divided into three age groups: less than 65 years (group 1); 65–74 years (group 2); and 75 years or more (group 3).

Statistical analysis

Descriptive statistics were calculated as absolute numbers, percentages and means ± standard deviation (SD) for each group. The χ^2-test was used to compare the baseline characteristics of subjects (categorical variables), the efficacy and the safety outcomes (SVR or withdrawal from treatment due to any reason or due to adverse events) in the three study groups. We also compared SVR in the study groups according to HCV genotype using the χ^2-test. To explore the association of SVR or withdrawal from treatment with the component characteristics of elderly patients with chronic HCV infection, multivariate logistic regression was used to calculated the adjusted odds ratio (OR) and its 95% confidence intervals (CI). Covariates were included to adjust for age, sex, treatment experience, genotype, viral load, ALT level, platelet count and IFN type (with or without ribavirin). Fisher's exact test was also used to explore the association between viral load level and treatment duration in group 3. For all analyses, SAS software version 9.3 was used (SAS Institute, Cary, NC, USA).

RESULTS

Study patients

A TOTAL OF 16 349 patients were recorded in the Japanese Interferon Database between December 2009 and April 2013. After excluding some patients, 15 267 patients were included in this study (Fig. 1). The majority of patients in all groups (group 1, 95.6%; group 2, 95.3%; group 3, 87.1%) were treated with PEG IFN-α-2a or -α-2b. The analyzed patient characteristics of all groups in the study are shown in Table 1. Group 1 consisted of 10 729 patients (men, 5663; women, 5066) with a mean age of 53.1 ± 9.35 years. The majority of these patients were categorized as HCV genotype 1 (62.8%), genotype 2 (37.0%) or genotype 3 (0.2%). Group 2 consisted of 4228 patients (men, 1875; women, 2353) with a mean age of 68.4 ± 2.67 years. The majority of these patients were categorized as HCV genotype 1 (70.0%) or genotype 2 (30.0%). Group 3 consisted of 310 patients (2.0% of the total: men, 155; women, 155) with a mean age of 76.7 ± 1.95 years. All

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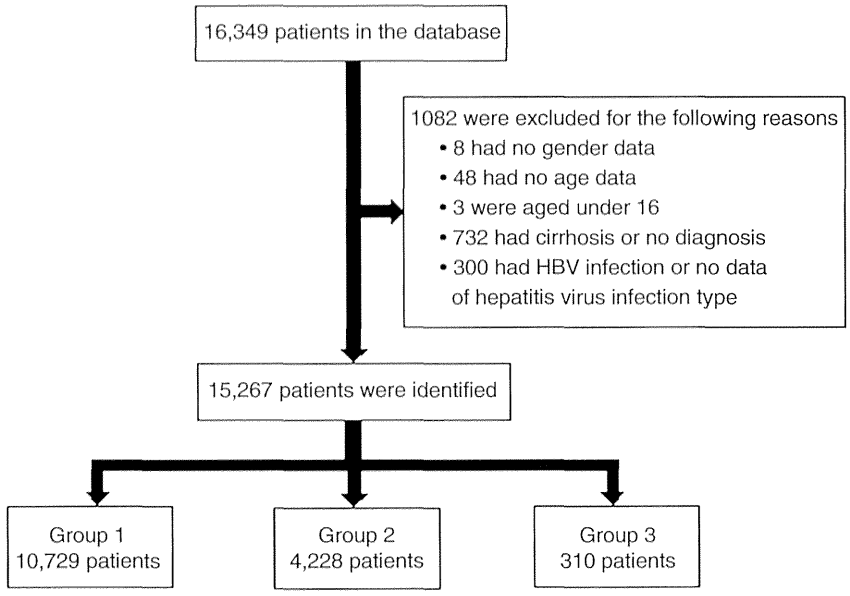

Figure 1 Identification of study patients from the database. A total of 16 349 patients were extracted from the Japanese Interferon Database between December 2009 and April 2013. Of these, 1082 patients were excluded for the following reasons: missing data in their medical records (sex, age, diagnosis, hepatitis virus infection type); aged under 16 years; and comorbid hepatitis B or cirrhosis. Some of the patients had more than one reason for being excluded. After excluding the patients, 15 267 patients were divided into three age groups: <65 years (group 1); 65–74 years (group 2); and ≥75 years (group 3). HBV, hepatitis B virus.

elderly patients were infected with either HCV genotype 1 (65.4%) or genotype 2 (34.6%). The proportions of elderly patients categorized by prefecture were 0% in five areas, 0–2% in 15 areas, 2–4% in 12 areas and more than 4% in four areas (Fig. 2).

Efficacy

A lower SVR rate was observed with aging ($P < 0.001$); namely, 65.3% in group 1, 49.6% in group 2 and 46.5% in group 3 (Table 2). Relapse occurred in 18.4%, 26.2% and 21.2% of the patients in groups 1, 2 and 3 respectively (Table 2). Among the patients with HCV genotype 1, the rate of SVR was 54.8%, 40.3% and 36.5% in groups 1, 2 and 3, respectively (Table 3).

In group 3, SVR was associated with genotype (OR, 0.34; 95% CI, 0.20–0.59; $P < 0.001$), viral load (OR, 0.22; 95% CI, 0.11–0.43; $P < 0.001$), platelet count (OR, 1.71; 95% CI, 1.02–2.88; $P = 0.041$) and treatment experience (OR, 0.56; 95% CI, 0.31–1.00; $P = 0.049$) (Table 4).

Safety

It was observed that the proportions of withdrawal from treatment for various reasons were increasing with aging: 15.0% in group 1, 21.5% in group 2 and 32.4% in group 3 ($P < 0.001$; Table 2). Increasing proportions of withdrawal from treatment due to adverse events were observed with aging: 3.1% in group 1, 14.1% in group 2 and 22.9% in group 2 ($P < 0.001$; Table 2). Withdrawal from treatment due to adverse events in group 3 was associated with viral load (OR, 2.83; 95% CI, 1.31–6.79; $P = 0.013$) as shown in Table 5. There was not a significant relationship with viral load or duration of treatment among withdrawn patients (Table 6).

DISCUSSION

BECAUSE FEW STUDIES have investigated the efficacy and safety of IFN treatment in elderly patients with chronic HCV infection,[6–8] we aimed to address this by analyzing the IFN treatment records kept in the Japanese Interferon Database, which contains data on patients infected with HBV or HCV collected from 36 prefectures in Japan. We compared the SVR rate in elderly and younger patients infected with chronic HCV, and observed lower SVR rates and higher proportions of withdrawal from treatment among elderly patients.

The data were recorded retrospectively by practitioners based on the actual treatment of each patient. We found that IFN therapy is widely utilized for the treatment of elderly patients with chronic HCV infection, based on elderly treatment data from 31 of the 36 prefectures, representing 66% of Japan's 47 prefectures.

In Japan, the number of deaths and the incidence of HCC have been increasing yearly among those aged 75 years and above.[10] To reduce the risk of developing HCC, it is common to use IFN treatment for patients

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Table 1 Characteristics of the study patients according to age group

Characteristic		Group 1, ≤64 years (n = 10 729)		Group 2, 65–74 years (n = 4228)		Group 3, ≥75 years (n = 310)		P
Age, years (mean ± SD)		53.1 ± 9.35		68.4 ± 2.67		76.7 ± 1.95		
Sex, n (%)								
	Male	5663	(52.8)	1875	(44.4)	155	(50.0)	<0.0001
	Female	5066	(47.2)	2353	(55.7)	155	(50.0)	
Genotype (n = 14 940), n (%)								
	1	6595	(62.8)	2897	(70.0)	197	(65.4)	<0.0001
	2	3886	(37.0)	1242	(30.0)	104	(34.6)	
	3	18	(0.2)	1	(0.0)	0	(0.0)	
Platelet counts ($\times 10^4/\mu L$) (n = 14 939), n (%)								
	≥15	6693	(63.7)	2025	(49.1)	129	(42.3)	<0.0001
	<15	3815	(36.3)	2101	(50.9)	176	(57.7)	
ALT (IU/L) (n = 15 137), n (%)								
	>30	8257	(77.7)	3114	(74.3)	225	(72.8)	<0.0001
	≤30	2377	(22.4)	1080	(25.8)	84	(27.2)	
Viral load† (n = 15 154), n (%)								
	High	9353	(77.7)	3649	(74.3)	255	(72.8)	0.011
	Low	1292	(12.1)	552	(13.1)	53	(17.2)	
Experience of treatment (n = 15 002), n (%)								
	Initial	8094	(76.7)	2935	(70.8)	223	(72.6)	<0.0001
	Retreatment	2455	(23.3)	1211	(29.2)	84	(27.4)	
PEG IFN use, n (%)		10256	(95.6)	4028	(95.3)	270	(87.1)	<0.0001
Ribavirin use, n (%)		9480	(88.4)	3643	(86.2)	227	(73.2)	<0.0001

†High viral load, reverse transcription polymerase chain reaction [RT–PCR] of ≥5.0 log IU/mL or amplicor of ≥100 KIU/mL; low viral load, RT–PCR of <5.0 log IU/mL or amplicor of <100 KIU/mL.
PEG IFN, pegylated interferon; SD, standard deviation.

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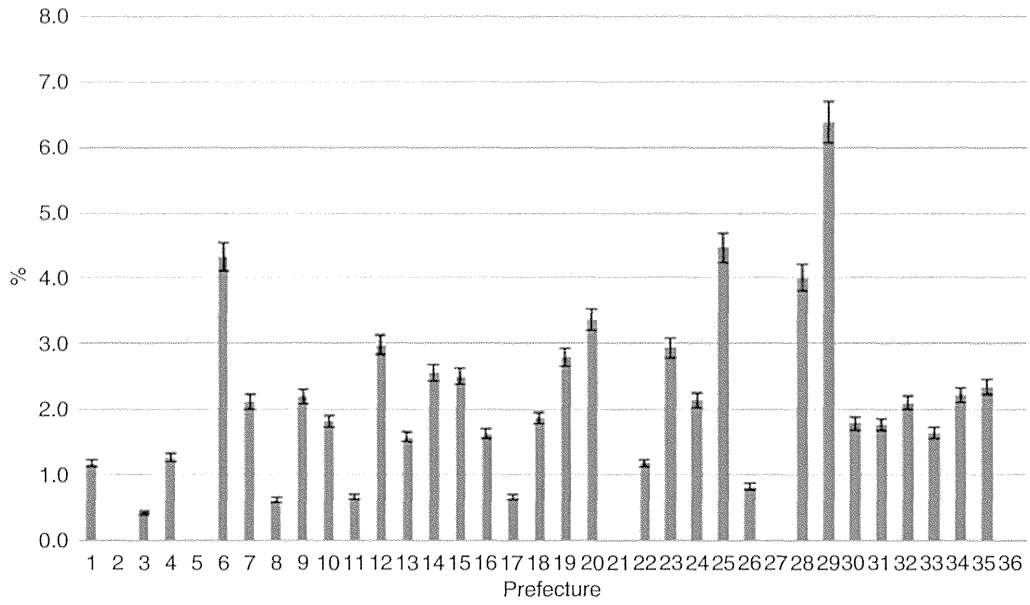

Figure 2 Proportion of elderly patients in each prefecture collaborating with this study. The 36 prefectures collaborating with this study were numbered randomly from 1 to 36 (horizontal axis), and corresponding proportions of elderly (≥75 years) are shown as bar charts with 95% confidence intervals. In five prefectures (no. 2, 5, 21, 27, 36), no elderly patients with chronic hepatitis C treated by interferon were registered.

with chronic hepatitis C.[11] Generally, the choice of treatment for elderly patients is complex in terms including comorbidity, cost and quality of life. It is natural that each practitioner needs to consider the risk and benefit of the elderly patients. Yet, there are few studies of IFN treatment in elderly patients. We also could not find any studies of untreated elderly patients with chronic HCV infection. The increased number of deaths due to HCC in the elderly population may be due to untreated patients with chronic HCV infection. Although further studies are needed to investigate these elderly patients, treatment of these patients may be needed to reduce HCC-related deaths.

The difference in SVR rate between the three groups is considered to be attributable to patient age. In previous studies, the SVR rate and the proportion of withdrawal from treatment among patients with HCV infection were similar in young (<65 years) and elderly patients (≥65 years).[8] However, previous studies were limited by a small sample size.

Table 2 Sustained virological response and withdrawal from treatment, according to age group

	Group 1 ≤64 years		Group 2 65–74 years		Group 3 ≥75 years		*P*
Virological response, *n* (%)							
SVR	6713	(65.3)	2028	(49.6)	134	(46.5)	<0.001
Relapse	1893	(18.4)	1071	(26.2)	61	(21.2)	
No response	1671	(16.3)	987	(24.2)	93	(32.3)	
Withdrawal from treatment, *n* (%)							
For any reason	1598	(15.0)	903	(21.5)	99	(32.4)	<0.001
For adverse event	866	(3.1)	597	(14.1)	71	(22.9)	<0.001

Patients with missing data were excluded. SVR, sustained virological response.

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Table 3 Sustained virological response among age groups according to the hepatitis C virus genotype

	Group 1 ≤64 years		Group 2 65–74 years		Group 3 ≥75 years		*P*
Genotype 1							
Virological response, *n* (%)							
SVR	3339	(54.8)	1083	(40.3)	58	(36.5)	<0.0001
Relapse	1387	(22.8)	795	(29.6)	34	(21.4)	
No response	1363	(22.4)	809	(30.1)	67	(42.1)	
Genotype 2 or 3							
Virological response, *n* (%)							
SVR	3014	(85.1)	827	(73.3)	55	(66.3)	<0.0001
Relapse	406	(11.5)	223	(19.8)	20	(24.1)	
No response	120	(3.4)	79	(7.0)	8	(9.6)	

Patients with missing data were excluded.
SVR, sustained virological response.

We found that a high viral load was associated with a low SVR rate in patients aged 75 years and more. As for the contributing factors for withdrawal from treatment due to severe adverse events, only the viral load was selected by multivariate logistic regression analysis (Table 5). Although a previous study showed that a long duration of treatment and high dose of PEG IFN were associated with an increased incidence of severe adverse events,[12] our study showed that there was no significant relationship with viral load and duration of treatment until withdrawal due to severe adverse events (Table 6).

Table 4 Logistic regression analysis using sustained virological response as a dependent variable in group 3

Variables	Odds ratio (95% CI)		*P*
Age, per 1-year increase	1.03	(0.90–1.19)	0.631
Sex (male vs female)	1.11	(0.67–1.86)	0.685
Platelet counts (≥15 × 10^4/μL vs <15 × 10^4/μL)	1.71	(1.02–2.88)	0.041
ALT (≥30 IU/L vs <30 IU/L)	1.20	(0.67–2.15)	0.531
Viral load (high vs low)†	0.22	(0.11–0.43)	<0.0001
Genotype (1 vs 2/3)	0.34	(0.20–0.59)	<0.0001
Experience of treatment (retreatment vs initial treatment)	0.56	(0.31–1.00)	0.049
Ribavirin use (yes vs no)	1.73	(0.91–3.28)	0.092
PEG IFN use (yes vs no)	1.12	(0.49–2.53)	0.792

Model performance: Hosmer–Lemeshow *P*-value = 0.70, receiver-operator curve/area under the curve = 0.71 (95% CI, 0.65–0.77).
†High viral load, reverse transcription polymerase chain reaction [RT-PCR] of ≥5.0 log IU/mL or amplicor of ≥100 KIU/mL; low viral load, RT-PCR of <5.0 log IU/mL or amplicor of <100 KIU/mL.
ALT, alanine aminotransferase; CI, confidence interval; PEG IFN, pegylated interferon.

Table 5 Logistic regression analysis using withdrawal from treatment due to an adverse event as a dependent variable in group 3

Variables	Odds ratio (95% CI)		*P*
Age, per 1-year increase	1.06	(0.92–1.22)	0.434
Sex (male vs female)	1.05	(0.60–1.83)	0.879
Platelet counts (≥15 × 10^4/μL vs <15 × 10^4/μL)	1.03	(0.58–1.81)	0.920
ALT (≥30 IU/L vs <30 IU/L)	0.73	(0.39–1.36)	0.309
Viral load (high vs low)†	2.83	(1.31–6.79)	0.013
Genotype (1 vs 2/3)	1.59	(0.87–3.02)	0.142
Experience of treatment (retreatment vs initial treatment)	0.90	(0.47–1.67)	0.740
Ribavirin use (yes vs no)	0.57	(0.29–1.12)	0.098
PEG IFN use (yes vs no)	1.11	(0.46–2.88)	0.827

Model performance: Hosmer–Lemeshow *P*-value = 0.45, receiver-operator curve/area under the curve = 0.65 (95% CI, 0.57–0.72).
†High viral load, reverse transcription polymerase chain reaction [RT-PCR] of ≥5.0 log IU/mL or amplicor of ≥100 KIU/mL; low viral load, RT-PCR of <5.0 log IU/mL or amplicor of <100 KIU/mL.
ALT, alanine aminotransferase; CI, confidence interval; PEG IFN, pegylated interferon.

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Table 6 Duration of treatment according to the viral load level in withdrawn patients in group 3

		Treatment (weeks)												*P*
		≤12		13–24		25–36		37–48		49–72		≥72		
All withdrawn patients	Total (*n*)	*n* (%)												
High viral load	85	31	(36.5)	16	(18.8)	16	(18.8)	16	(18.8)	4	(4.7)	2	(2.4)	0.105
Low viral load	10	4	(40.0)	5	(50.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	
Patients withdrawn due to an adverse event														
High viral load	62	23	(37.1)	14	(22.6)	13	(21.0)	8	(12.9)	3	(4.8)	1	(1.6)	0.676
Low viral load	6	4	(66.7)	2	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	

Patients with missing data were excluded.

Another explanation based on the difference in the dose of PEG IFN or ribavirin, depending on the viral load, would be possible. It may be speculated that the practitioners had occasionally administrated a higher dose of PEG IFN or ribavirin to patients with a high viral load than to those with a low viral load, although there were no actual data on the dose of the used drugs in our database.

Additionally, factors considered predictive for SVR in the current management guidelines for HCV,[10] such as platelet count and treatment experience, were also associated with SVR rate in our study. These factors could assist clinicians in selecting the appropriate treatment for elderly patients with chronic HCV infection, especially in the era of recently introduced IFN-free treatment with oral-only directly acting antivirals.[13–15]

The present study has several limitations. The database we used has no data on comorbidities and concurrent treatment, except for ribavirin. These confounding factors should certainly be considered when evaluating the efficacy and safety of IFN treatment, because most elderly patients generally have comorbid conditions.[16,17] The database also lacks any data regarding untreated elderly patients with HCV or HBV infection, and further studies are therefore needed to investigate untreated elderly patients with HCV.

We conclude that elderly patients with chronic HCV infection taking IFN therapy achieved lower SVR rates and higher withdrawal from treatment proportions than younger patients.

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ORIGINAL RESEARCH

Comparison of peginterferon alfa-2a and alfa-2b for treatment of patients with chronic hepatitis C: a retrospective study using the Japanese Interferon Database

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Purpose: We aimed to compare the rates of sustained virologic response (SVR) achieved with peginterferon (PEG-IFN) alfa-2a and alfa-2b in combination with ribavinin (RBV) for chronic hepatitis C, using a large database of hepatitis cases to improve the generalizability of these results.

Methods: We identified patients with chronic hepatitis C who were treated with PEG-IFN alfa-2a or alfa-2b and RBV, from the Japanese Interferon Database, between December 2009 and April 2013. This database contains the medical records of IFN treatment collected from 36 prefectures in Japan. Multivariable logistic regression analysis was used to compare SVR rates obtained with PEG-IFN alfa-2a and alfa-2b, in combination with RBV.

Results: A total of 16,349 patients were recorded in the Japanese Interferon Database. After application of the exclusion criteria, 12,706 patients (3,578 [1,710 males, 1,868 females] on PEG-IFN alfa-2a; and 9,128 [4,652 males, 4,476 females] on PEG-IFN alfa-2b) were included in this analysis. The SVR rate in the PEG-IFN alfa-2b group was 62.0%, as compared with a rate of 55.1% in the PEG-IFN alfa-2a group (crude odds ratio =1.31; 95% confidence interval [CI]: 1.23 to 1.44). There was no significant difference in the adjusted SVR rates between the two groups (adjusted odds ratio =0.96; 95% CI: 0.88 to 1.05). Similar proportions of adverse events were observed in the two groups, with the exception of thrombocytopenia, retinopathy, and anemia.

Conclusion: There was no significant difference in the SVR rates and safety profile between chronic hepatitis C patients treated with the PEG-IFN alfa-2a and alfa-2b.

Keywords: sustained virologic response, HCV genotype, sustained virologic response, adverse events

Introduction

More than 170 million persons worldwide are infected with the hepatitis C virus (HCV), and the number of deaths caused by HCV-related liver diseases is more than 35 thousand per year.[1] In addition, HCV infection is associated with an increased incidence of hepatocellular carcinoma.[2] To reduce the risk of developing hepatocellular carcinoma and HCV-related liver diseases, a treatment based on interferon (IFN) is commonly used for patients with chronic hepatitis C.[3] Two types of pegylated interferon (PEG-IFNs) (alfa-2a and alfa-2b) are used, which are pegylated to improve their pharmacokinetic effects and pharmacodynamic actions, and which have a higher rate of sustained virologic response (SVR) and lower frequency of incidence of adverse reactions than IFN.[4] Thus far, the general recommendation for the treatment of patients with chronic

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hepatitis C involves combination therapy with PEG-IFN (alfa-2a or alfa-2b) and ribavirin (RBV).[3] However, previous studies that have compared the effectiveness and safety of treatment with PEG-IFN alfa-2a and alfa-2b for patients with chronic hepatitis C have yielded conflicting results.[5–8]

The largest randomized controlled trial (RCT) to date was a comparison in 2009 of SVR and safety in the treatment of 3,070 patients with chronic HCV genotype 1 among three groups (low-dose PEG-IFN alfa-2b plus RBV; standard-dose PEG-IFN alfa-2b plus RBV; and PEG-IFN alfa-2a plus RBV).[9] That study excluded patients with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) infection, as well as other liver diseases, and found that the rates of SVR and adverse event profiles among the three groups were similar. On the other hand, some meta-analyses of RCTs comparing PEG-IFN alfa-2a and alfa-2b suggested a higher SVR rate in the alfa-2a group than in the alfa-2b group.[5,6] However, several limitations involving the study quality were pointed out, including a small sample size as well as inadequate blinding and randomization.[5] A large retrospective cohort study was conducted to compare the SVR rate obtained with PEG-IFN alfa-2a and alfa-2b for the treatment of patients with chronic hepatitis C in Germany.[10] A total of 3,414 patients were identified as a study cohort from the database. This study allowed the inclusion of patients who had a comorbid HBV or HIV infection and any HCV genotype, and used matched pair analysis, using the baseline patient characteristics to compare the rates of SVR with PEG-IFN alfa-2a and alfa-2b. Although a higher SVR rate was found for alfa-2a than for alfa-2b, the possibility of residual uncontrolled confounding was acknowledged, such as details of the therapeutic profiles, for eg, the duration of therapy in the two groups were different, even after subject matching.[10] Thus far, a definitive conclusion has yet to be reached regarding the superiority of one PEG-IFN over the other.

In this study, we aimed to compare the rates of SVR with PEG-IFN alfa-2a and alfa-2b in combination with RBV for chronic hepatitis C, using a large database of hepatitis cases to improve the generalizability of these results.

Methods

The Japanese Interferon Database

Because hepatitis is becoming one of the most prevalent major infectious diseases, the Basic Act on Measures against Hepatitis in Japan was established to conquer hepatitis, by providing high quality medical care for patients with a hepatitis viral infection.[11] As part of this measure, the Japanese Interferon Database, which is comprised of more than 16,000 patient records regarding IFN treatment for chronic hepatitis and/or cirrhosis, collected retrospectively from throughout Japan, was developed. This database contains diagnosis, IFN treatment data (type of IFN, with or without RBV), results of laboratory tests (date of test, HCV RNA, type of HCV genotype, aspartate aminotransferase, alanine aminotransferase [ALT], and platelet count), adverse drug reactions, and outcomes (SVR, and completed or discontinued treatment), which have been recorded in a standardized report form by practitioners. Serum HCV RNA levels were quantitated by Cobas® Amplicor HCV Monitor v2.0 (Roche Molecular Systems, Pleasanton, CA, USA) or Cobas® TaqMan HCV Test (Roche Molecular Systems).

This study was approved by the Institutional Review Board of the National Center for Global Health and Medicine.

Study population

We identified all of the patients with chronic hepatitis C from the Japanese Interferon Database who had received a combination treatment of PEG-IFN (alfa-2a or alfa-2b) and RBV between December 2009 and April 2013.

Patients meeting any of the following criteria were excluded from this study: comorbid cirrhosis or HBV infection; without RBV use; dual therapy with PEG-IFN alfa-2a and alfa-2b; any missing data items (sex, age, diagnosis, and/or comorbid condition, ie, liver diseases); and age under 16 years.

Statistical analysis

Descriptive statistics were calculated as absolute numbers, percentages, and means (± standard deviation [SD]) for each group. Patient baseline characteristics were compared between PEG-IFN alfa-2a and alfa-2b, using a *t*-test for age, the Wilcoxon rank-sum test for duration of therapy, the Mantel–Haenszel chi-square statistic for genotype, and the chi-square test for the other categorical variables. We also compared adverse events in the patients withdrawn from study, according to HCV genotype, using the Fisher's exact test. To explore the association of patient SVR with chronic hepatitis C, we used multivariate logistic regression to calculate the adjusted odds ratio (OR) and the associated 95% confidence intervals (CIs). We included covariates to adjust for age, sex, platelet counts, ALT level, HCV viral load, genotype, and frequency of treatment. Interaction analyses were performed with the logistic regression model, to test for interactions between PEG-IFN and level of treatment experience or HCV genotype. The results indicated that there were no significant interactions (between type of PEG-IFN and

treatment experience [P=0.229] or between type of PEG-IFN and HCV genotype [P=0.069]). The fit of the logistic model was assessed using Hosmer–Lemeshow tests. Subgroup analyses were performed according to treatment experience and genotype. The SAS software, version 9.3 (SAS Institute, Inc., Cary, NC, USA) was used for all analyses.

Results

Study population

Between December 2009 and April 2013, a total of 16,349 patients were recorded in the Japanese Interferon Database. Of these, 3,643 subjects were excluded for the following reasons: comorbid condition of cirrhosis in 569 subjects and HBV infection in 300 subjects; without RBV use in 2,414 subjects; dual therapy of PEG-IFN alfa-2a and alfa-2b in 225 subjects; missing data (any of sex, age, diagnose, and/or comorbid condition [liver diseases]) in 261 subjects; and under 16 years of age in three subjects (Figure 1). The remaining 12,706 patients were included in this study. Of these, 3,578 subjects (1,710 [48%] males; 1,868 [52%] females) were taking PEG-IFN alfa-2a, with a mean age (SD) of 59.1 (10.0) years; and 9,128 subjects (4,652 [51%] males; 4,476 [49%] females) were taking PEG-IFN alfa-2b, with a mean age (± standard deviation) of 57.2 (±10.9) years (Table 1). Several differences were found between the two groups, as follows: the mean age was higher in the alfa-2a group than in the alfa-2b group; the proportion of male patients was higher in the alfa-2b group; the proportion of patients with an HCV genotype1 infection in the PEG-IFN alfa-2a group (2,874 [83%]) was higher than in alfa-2b group (5,564 [62%]); and, a higher proportion of initial treatment patients was obtained in the alfa-2b group (2,181 [62%]) than in the alfa-2a (7,086 [79%]).

Outcomes

The SVR rate in patients receiving PEG-IFN alfa-2b was higher than that in patients receiving alfa-2a (crude OR=1.31; 95% CI: 1.23 to 1.44). After adjustment for potential

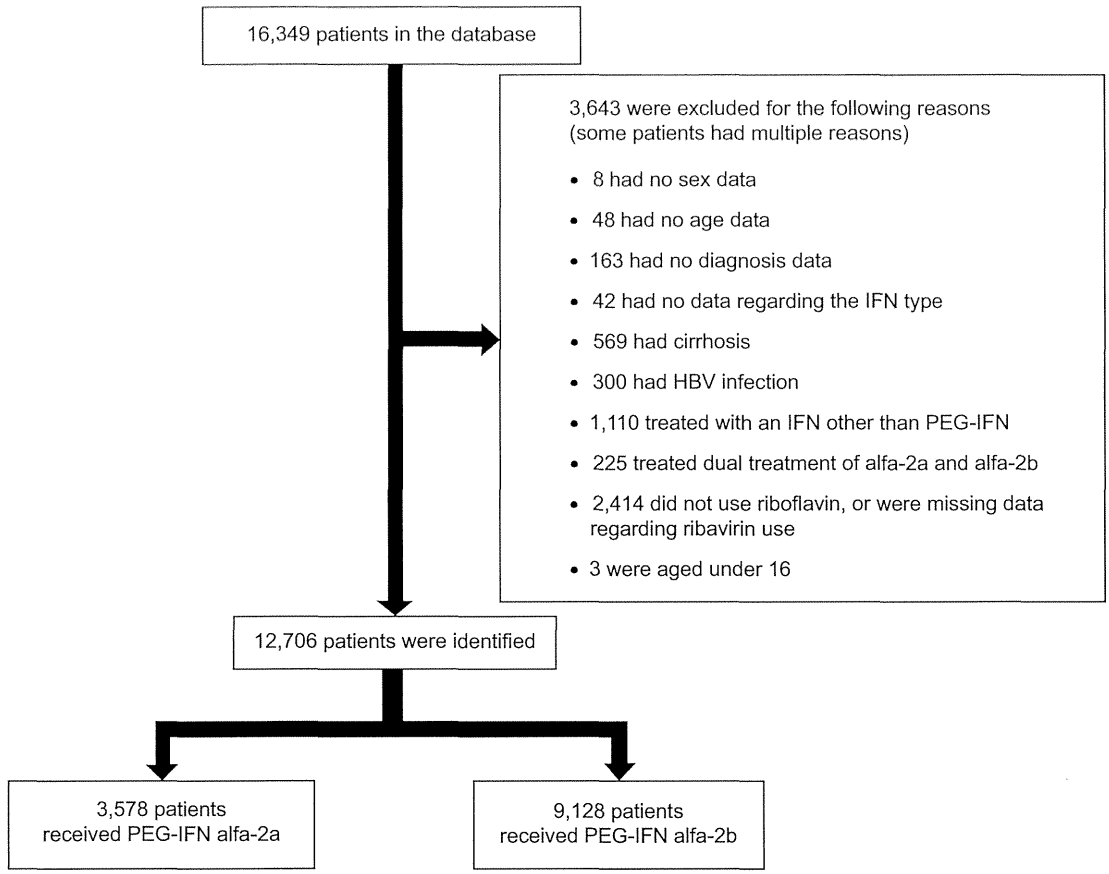

Figure 1 Identification of study patients from the database.
Notes: Patients were divided into two groups after excluding some patients according to the prespecified criteria for our study cohort. Some patients had more than one reason for being excluded.
Abbreviations: HBV, hepatitis B virus; IFN, interferon; PEG-IFN, pegylated interferon.

Table 1 Characteristics of the study subjects according to treatment group

Characteristics	PEG-IFN alfa-2a (n=3,578)	PEG-IFN alfa-2b (n=9,128)	*P*-value
Age, years (mean ± SD)	59.05±10.02	57.17±10.90	<0.001
Sex, n (%)			
Male	1,710 (47.8)	4,652 (51.0)	0.001
Female	1,868 (52.2)	4,476 (49.0)	
Genotype (n=12,453), n (%)			
1	2,874 (82.5)	5,564 (62.0)	<0.001
2	607 (17.4)	3,392 (37.8)	
3	3 (0.1)	13 (0.1)	
Platelet count ($\times10^4/\mu L$) (n=12,461), n (%)			
≤15	2,048 (58.5)	5,433 (60.6)	0.034
>15	1,450 (41.5)	3,530 (39.4)	
ALT (IU/L) (n=12,610), n (%)			
>30	2,696 (76.1)	6,953 (76.7)	0.480
≤30	847 (23.9)	2,114 (23.3)	
HCV viral load* (n=12,628), n (%)			
High	2,854 (91.8)	7,414 (93.2)	0.010
Low	255 (8.2)	539 (6.8)	
Treatment experience (n=12,494), n (%)			
Initial	2,181 (61.9)	7,086 (79.0)	<0.001
Retreatment	1,345 (38.1)	1,882 (21.0)	

Notes: *High HCV viral load: ≥5.0 LogIU/mL (RT-PCR, Cobas® TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, USA) or ≥100 KIU/mL (Cobas® Amplicor HCV Monitor v2.0; Roche Molecular Systems). Low HCV viral load: <5.0 LogIU/mL (RT-PCR, Cobas TaqMan HCV Test; Roche Molecular Systems) or <100 KIU/mL (Cobas Amplicor HCV Monitor v2.0; Roche Molecular Systems).
Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; RT-PCR, reverse-transcription polymerase chain reaction; SD, standard deviation.

confounders (including age, sex, platelet count, alanine aminotransferase [ALT] level, HCV viral load, genotype, and treatment experience), no significant difference was found in SVR rates between the PEG-IFN alfa-2a group and the PEG-IFN alfa-2b group (adjusted OR=0.96; 95% CI: 0.88 to 1.05) (Table 2).

We also performed subgroup analyses, according to treatment experience and genotype. No significant differences were found between the PEG-IFN alfa-2b and alfa-2a groups, in terms of adjusted SVR rate, in patients receiving their initial treatment (crude OR=1.27; 95% CI: 1.14 to 1.40; adjusted OR=0.90; 95% CI: 0.80 to 1.01), patients receiving retreatment (crude OR=1.15; 95% CI: 1.00 to 1.33; adjusted OR=1.09; 95% CI: 0.93 to 1.27), and patients with HCV genotype 1 infections (crude OR=1.00; 95% CI: 0.91 to 1.09; adjusted OR=0.95; 95% CI: 0.86 to 1.05). The adjusted SVR rate for PEG-IFN alfa-2b in patients with HCV genotype 2 or 3 was superior to that of PEG-IFN alfa-2a (crude OR=1.36; 95% CI: 1.10 to 1.69; adjusted OR=1.35; 95% CI, 1.08 to 1.69) (Figure 2).

Adverse events

During the study, significant differences between the two treatments were observed in patients with HCV genotype 1.

Table 2 Logistic regression analysis with SVR as dependent variable

Variables	Odds ratio (95% CI)	*P*-value
Age, per 1-year increase	0.96 (0.96–0.97)	<0.001
Sex (male vs female)	1.37 (1.26–1.49)	<0.001
PEG-IFN (alfa-2b vs alfa-2a)	0.96 (0.88–1.05)	0.396
Platelet count (≥$15\times10^4/\mu L$ vs <$15\times10^4/\mu L$)	1.51 (1.39–1.64)	<0.001
ALT (≥30 IU/L vs <30 IU/L)	1.21 (1.09–1.33)	<0.001
HCV viral load (high vs low)	0.32 (0.26–0.40)	<0.001
Genotype (genotype 1 vs genotype 2 or 3)	0.25 (0.23–0.28)	<0.001
Treatment experience (retreatment vs initial treatment)	0.69 (0.63–0.76)	<0.001

Notes: High HCV viral load: ≥5.0 LogIU/mL (RT-PCR, Cobas® TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, USA) or ≥100 KIU/mL (Cobas® Amplicor HCV Monitor v2.0; Roche Molecular Systems). Low HCV viral load: <5.0 LogIU/mL (RT-PCR, Cobas TaqMan HCV Test; Roche Molecular Systems) or <100 KIU/mL (Cobas Amplicor HCV Monitor v2.0; Roche Molecular Systems).
Abbreviations: ALT, alanine aminotransferase; CI, confidence interval; PEG-IFN, pegylated interferon; RT-PCR, reverse-transcription polymerase chain reaction; SVR, sustained virologic response.

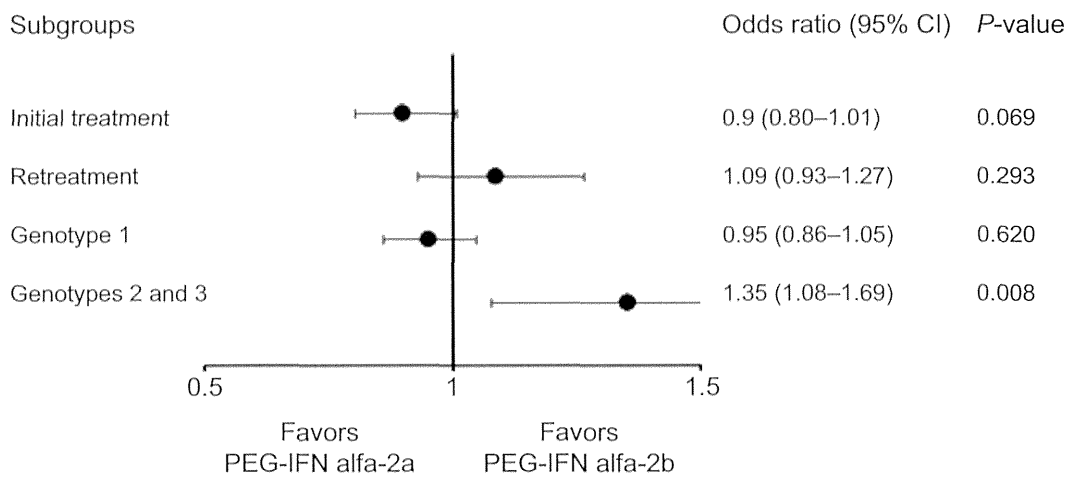

Figure 2 Results of the subgroup analysis for treatment experience and genotype.
Notes: The figure shows the forest plots of the adjusted SVR rate (odds ratio and the associated 95% confidential intervals) in the prespecified subgroup analyses (initial treatment group; retreatment group; genotype 1 group; and genotype 2 or 3).
Abbreviations: CI, confidence interval; PEG-IFN, pegylated interferon; SVR, sustained virologic response.

Ninety-six patients withdrew from treatment due to thrombocytopenia (46 [1.6%] in the PEG-IFN alfa-2a group and 50 [0.9%] in the alfa-2b group [P=0.005]), and 57 patients withdrew due to retinopathy (13 [0.5%] in the alfa-2a group and 44 [0.8%] in alfa-2b group [P=0.091]) (Table 3). In contrast were the patients with genotype 2 or 3, who displayed anemia (ten [1.6%] in the alfa-2a group and 25 [0.7%] in the alfa-2b group [P=0.034]), thrombocytopenia (eight [1.3%] in the alfa-2a group and 14 [0.4%] in alfa-2b group [P=0.012]), and retinopathy (five [0.8%] in the alfa-2a group and five [0.1%] in the alfa-2b group [P=0.010]) (Table 4). No other significant differences were observed between the study groups.

Discussion

We conducted a retrospective cohort study to compare the SVR rate in patients with chronic hepatitis C treated with PEG-IFN alfa-2a and alfa-2b in combination with RBV, using data from the large Japanese Interferon Database to improve the generalizability of the results. We employed multivariate logistic regression analysis to adjust for potential confounders, as the demographic characteristics at baseline differed between the two groups. We found similar SVR rates in patients with chronic hepatitis C who received either PEG-IFN alfa-2a or alfa-2b in combination with RBV.

Our findings were consistent with previous results from the largest reported RCT, which involved 3,070 patients.[9,12,13] On the other hand, some other previous studies,[10,14] including the largest retrospective cohort study, which involved 3,414 subjects, presented results that conflicted with our findings. As mentioned above, several limitations of these previous studies have been pointed out (eg, small sample size, inadequate blinding or randomization, difference in treatment regimen, and different study populations).[5,15] To enhance generalizability, we conducted a study with a larger sample size (12,706 subjects) than used in previous studies.[5–7,9,10]

Table 3 Adverse events of withdrawal patients according to treatment groups (genotype 1)

Adverse events	PEG-IFN alfa-2a n=2,874	PEG-IFN alfa-2b n=5,564	P-value
	N (%)		
Fatigue	144 (5.0)	294 (5.3)	0.605
Interstitial pneumonia	21 (0.7)	32 (0.6)	0.387
Stroke	2 (0.1)	6 (0.1)	0.724
Anemia	50 (1.7)	119 (2.1)	0.251
Decreased appetite	90 (3.1)	179 (3.2)	0.896
Thrombocytopenia	46 (1.6)	50 (0.9)	0.005
Psychiatric disorders	63 (2.2)	137 (2.5)	0.497
Retinopathy	13 (0.5)	44 (0.8)	0.091
Other	145 (5.0)	274 (4.9)	0.833

Abbreviation: PEG-IFN, pegylated interferon.

Table 4 Adverse events of withdrawal patients according to treatment groups (genotype 2, 3)

Adverse events	PEG-IFN alfa-2a n=610	PEG-IFN alfa-2b n=3,405	*P*-value
	N (%)		
Fatigue	19 (3.1)	90 (2.6)	0.499
Interstitial pneumonia	1 (0.2)	6 (0.2)	1.000
Stroke	1 (0.2)	1 (0.0)	0.281
Anemia	10 (1.6)	25 (0.7)	0.034
Decreased appetite	11 (1.8)	60 (1.8)	0.869
Thrombocytopenia	8 (1.3)	14 (0.4)	0.012
Psychiatric disorders	11 (1.8)	35 (1.0)	0.100
Retinopathy	5 (0.8)	5 (0.1)	0.010
Other	15 (2.5)	86 (2.5)	1.000

Abbreviation: PEG-IFN, pegylated interferon.

We found no difference in the adjusted SVR rate between the two treatment groups, even though the sample size was large enough to detect such a difference. In addition, our results were obtained from a realistic medical setting, using data recorded according to the actual treatments applied to patients with hepatitis, by practitioners. Previously, few studies had been performed that reflected a realistic medical setting for treatment of patients with chronic hepatitis C because most of the previous studies were RCTs.[5–7] We also performed two subgroup analyses, according to treatment experience and genotype, because the largest reported RCT9 had included only patients receiving their initial treatment and patients with HCV genotype 1. Similar to our other results, we also found no difference in the adjusted SVR rate between treatment with PEG-IFN alfa-2a and alfa-2b from the subgroup analyses, except for the subgroup of genotypes 2 and 3. In this subgroup, alfa-2b had higher a SVR rate, although the interaction was not significant.

While the present study suggests that PEG-IFN alfa-2b may be the preferable treatment for patients with HCV genotypes 2 and 3, the results of several RCTs[9,16,17] showed no difference between treatment with PEG-IFN alfa-2a or alfa-2b in patients with genotype 1 or with genotypes 1–4.

In a study comparing the pharmacokinetics and pharmacodynamics of the two drugs,[18] PEG-IFN alfa-2b displayed a greater effect of biological activity by reducing HCV-RNA and upregulating IFN-related response genes. However, the duration of this effect may be affected by the time period between dosing because the volume of distribution of PEG-IFN alfa-2b is large, and it is metabolized faster than PEG-IFN alfa-2a.[8] Due to its higher molecular weight and branched pegylation, the extravascular volume of distribution of PEG-IFN alfa-2a is smaller. Thus, its duration in the body is longer than that of PEG-IFN alfa-2b. In general, the amount of a drug in the body tends to decrease as body weight increases; however, in this study, the amount of PEG-IFN alfa-2b in the body was constant regardless of body weight because the dosage was adjusted for body weight.[18] In the present study, PEG-IFN alfa-2b was more effective than PEG-IFN alfa-2a for the treatment of patients with genotypes 2 and 3. This may be because the patients treated with PEG-IFN alfa-2b received a dosage based on body weight, whereas patients treated with PEG-IFN alfa-2a were treated with a fixed dosing regimen, without accounting for weight. However, information regarding the patients' body weight and dosage of PEG-IFN was not included in this database.

We found that proportions of adverse events, such as thrombocytopenia, retinopathy, and anemia, were higher in patients treated with PEG-IFN alfa-2a. In a previous study comparing pharmacokinetics and pharmacodynamics,[18] both leukocytes and neutrophils were significantly decreased in patients receiving PEG-IFN alfa-2a versus those receiving PEG-IFN alfa-2b. Additionally, the incidences of hematological abnormalities tend to be higher in PEG-IFN alfa-2a–treated patients.[18] In contrast, RCTs comparing PEG-IFN alfa-2a and alfa-2b, including a Japanese study[19] and the largest study ever conducted,[9] showed no difference in hematological abnormalities following termination of treatment. In the RCTs, the subjects may have been selected from patients in good condition or from those who were expected to adhere to the study treatment. Our data suggests that hematological abnormalities, such as thrombocytopenia, may develop in actual medical care situations, because we used data obtained from the database of medical records from patients receiving IFN treatment. Further, our results are consistent with the previous study[18] evaluating pharmacokinetics and pharmacodynamics.

The strengths of our study include the large sample size, the use of data collected from actual medical settings, and the

inclusion of patients with all types of HCV genotype infections and patients with or without previous treatment experience.

Our study also has several limitations. First, there were residual confounders, which could persist due to unmeasured or imprecisely measured potential confounding factors. To adjust for potential confounders, we used multivariable logistic regression. Secondly, there was a reporting bias because the data were recorded by practitioners using a standardized report form. Additional studies are needed to validate the data, using an alternative existing database source (eg, electronic medical records database or claims database). Thirdly, the viral load levels might have been misclassified because the measurement methods for HCV RNA in this database differed depending on the time of therapy. Finally, further studies are required to assess the rate of SVR between the two medications in combination with simeprevir, a new agent for the treatment of chronic hepatitis C, because the current standard therapy for chronic hepatitis C is triple therapy with PEG-IFN (alfa-2a or alfa-2b), RBV, and simeprevir.[20,21]

Conclusion

There was no significant difference in the SVR rates and safety profile between chronic hepatitis C patients treated with the PEG-IFN alfa-2a and alfa-2b.

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Disclosure

The authors report no conflicts of interest in this work.

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XV 特　　論

C型肝炎・肝硬変患者，キャリアのフォローアップ戦略とエビデンス

Strategy and evidence for the follow-up for the patients with HCV-related liver diseases

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Key words：C型肝炎ウイルス，C型慢性肝炎，C型肝硬変，肝癌，

はじめに

C型慢性肝疾患患者のフォローアップの目的は主に2点と考えられる．1点目は，患者個々の年齢や肝線維化を考慮した発癌リスク，合併症，社会的背景，年々進歩する抗ウイルス薬の承認状況などを総合的に判断して適切な時期に適切な抗ウイルス療法を導入することである．2点目は，C型慢性肝疾患患者は肝癌の高リスク群であり，肝癌の早期発見を念頭に置いたサーベイランスである．また今後，C型慢性肝疾患に対する複数の経口抗ウイルス薬の登場によりウイルス排除率は90％以上となることが予測され，ウイルス排除後のフォローアップの方法も議論されるべきである．

本稿では，抗ウイルス療法導入を念頭に置いたC型慢性肝疾患患者のフォローアップ，肝発癌を念頭に置いたフォローアップ，また石川県で行っているC型慢性肝疾患患者のフォローアップシステム，およびウイルス排除後のフォローアップに関する戦略とエビデンスを概説する．

1 抗ウイルス療法導入を念頭に置いたC型慢性肝疾患患者のフォローアップ

1）抗ウイルス療法導入時期の再検討

近年，C型慢性肝炎の治療は大きく変化しつつある．従来の標準的治療法であったペグインターフェロンとリバビリン併用療法における我が国での蔓延型である遺伝子型1型のC型肝炎ウイルス(HCV)のウイルス排除率(SVR)は約50％にとどまっていた．しかしながら，HCVの複製に必須なウイルスタンパクの機能を直接抑制するdirect-acting antiviral agents(DAAs)の登場によりSVRは劇的に改善しつつある．テラプレビルやシメプレビルなどのプロテアーゼ阻害薬を従来のペグインターフェロンとリバビリン療法に加えた3剤併用療法により，約70-80％のSVRが得られるようになった．さらに今後早期に経口DAAs製剤のみによる，インターフェロン製剤を利用しない複数の治療レジメが我が国においても保険承認が得られる予定であり，SVRは90％以上にまで改善することが予想される．

従来の標準治療であったインターフェロン製剤をベースとした治療法は，超高齢者，うつ病

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などの重度の精神神経疾患，間質性肺炎の合併を認めた症例には禁忌であった．またインターフェロン製剤による治療を以前に施行されたが，SVRを得られず，肝庇護療法および肝発癌サーベイランスを目的に定期通院している症例も多く存在する．さらにインターフェロン製剤に対する副作用を危惧するため，あるいは職場や家庭環境からインターフェロン製剤投与のための定期通院が困難なため，インターフェロン治療を受けられない症例も散見される．今後，C型慢性肝炎治療に対する標準治療となりうるインターフェロン製剤を利用しないDAAs製剤による経口の抗ウイルス療法は，このような多くのインターフェロン治療困難例や無効例に対する良い適応と考えられる．

2013年のC型肝炎治療ガイドライン第2版(日本肝臓学会)でも，遺伝子型1型のC型慢性肝炎患者の治療に関して，高齢者や線維化進行例に対してはプロテアーゼ阻害薬を併用したペグインターフェロンとリバビリンによる3剤併用療法を推奨しているが，非高齢者で線維化軽度例では，待機可能としている．そのため現在通院中のC型慢性肝疾患患者に関して，血小板数，各種線維化マーカー，フィブロスキャン，可能であれば肝生検を行い，現時点における肝線維化の程度を正確に評価して，個々の患者における抗ウイルス療法導入の時期を検討すべきと考えられる．

2）ALT正常例への対応

まずC型，B型慢性肝疾患患者におけるALTの基準値に関して留意する必要がある．ALTの基準値上限を40IU/Lとしている施設が散見されるが，ウイルス性肝疾患患者におけるALTの基準値上限は30IU/Lであり，31-40IU/Lは異常値であることを認識すべきである．実際ALT値が比較的低く，血小板数が正常でも肝生検をしてみると比較的進行した症例も存在する．当科での検討であるが，肝生検時ALT 50IU/L以下，血小板17万以上であった44症例の肝生検では，40％以上がF2以上の慢性肝炎であった[1]．したがって，ALTが基準値症例の中にも線維化進行例が存在することを念頭に置くべきで，'問題ない'や'通院の必要なし'との説明は不適切と考えられる．2013年のC型肝炎治療ガイドライン第2版では，血小板数を肝線維化の指標とし，ALT値と血小板数により治療適応を決定することを提案している．すなわちALT 30IU/L以内の症例でも，血小板数15万/μL未満であれば抗ウイルス療法の対象とすることを推奨し，一方，ALT 30IU/L以内かつ血小板数15万/μL以上の症例については，すぐに抗ウイルス療法を施行せずに経過観察することを推奨している．しかしながらC型慢性肝炎においては，経過中にALTが上昇する可能性もあるため，2-4カ月に1回の頻度で定期的に採血を行い，ALTが異常値を呈した時点で抗ウイルス療法を考慮すべきと考えられる．

3）抗ウイルス療法が困難なALT高値例への対応

様々な理由で抗ウイルス療法が不可能な症例に関しては，肝炎を沈静化し肝組織の線維化進展を抑えることを目的とした肝庇護療法が必要である．肝庇護療法の実際として，ウルソデオキシコール酸，強力ネオミノファーゲンシー，瀉血療法，さらにこれらの治療の組み合わせが挙げられる．肝庇護療法中の患者に関しても2-4カ月に1回の頻度で定期的に採血を行い肝機能のチェックを行うべきと考えられる．

2 肝発癌を念頭に置いたC型慢性肝疾患患者のフォローアップ

HCVの持続感染は，B型肝炎ウイルス(HBV)感染と並んで最も重要な肝発癌リスクの一つである．C型肝炎を背景とした肝発癌の特徴は，そのほとんどが肝硬変を背景に発癌を認める点であり，F4すなわち肝硬変からの年間肝発癌率は8％とされている．しかしながら非肝硬変からも発癌することが知られており，F1でも0.5％，F2で1.5％，F3で5％と報告されている．さらにHCV，HBV持続感染に加えて肝発癌の危険因子として，男性，高齢，アルコール摂取，喫煙，肥満，糖尿病なども挙げられており，これらの因子を含めて患者個々における肝

発癌リスクを総合的に判断して，肝癌サーベイランスの頻度を決定すべきと考えられる．

2013年度肝癌診療ガイドラインでは，B型慢性肝炎，C型慢性肝炎患者を高危険群，B型肝硬変，C型肝硬変患者を超高危険群に分類し，それぞれの群に対するサーベイランスアルゴリズムを提唱している[2]．すなわち，高危険群に対しては6カ月ごとの超音波検査，および腫瘍マーカー(AFP，PIVKA-II，AFP-L3)の測定を，また超高危険群に対しては，3-4カ月ごとの超音波検査，腫瘍マーカー(AFP，PIVKA-II，AFP-L3)の測定，オプションとして6-12カ月ごとのCT・MRI検査を推奨している．

3 HCV排除後の肝発癌を念頭に置いたフォローアップ

今後経口DAAs製剤の導入によりSVRは90％を超えることが予想され，従来以上にHCV排除後の患者が存在するようになる．これまでの多くの検討からHCV排除により肝発癌のリスクが低下することは明らかにされているが，HCV排除後も少数例ながら肝発癌症例が存在することが報告されている．HCV排除後の発癌症例の特徴として，HCV排除時に既に肝線維化が高度であること，血小板数が低値であること，AFPが高値であること，などが報告されている[3-5]．しかしながら，HCV排除後のフォローアップの期間，方法などに関する検討はなされていないため，現時点ではHCV排除後においても，肝発癌を念頭に置いた定期的なフォローアップは必須と考えられる．同時に，今後増加するHCV排除後の症例を蓄積して，肝発癌を念頭に置いたHCV排除後症例のフォローアップに関するエビデンスを蓄積する必要があると考えられる．

4 肝炎診療における専門医との連携

上述してきたように，HCV感染が判明した患者は，2-4カ月に1回の肝機能検査のための採血，さらに肝線維化の程度に応じた肝画像検査，および腫瘍マーカー測定のための採血が必要である．さらにC型慢性肝炎治療の劇的な進歩を受けて，日本肝臓学会および厚生労働省研究班から発表されるC型慢性肝炎に対するガイドラインは近年頻繁に改訂されている．消化器病学会専門医や，肝臓病学会専門医が最新のガイドラインを熟知することは当然と思われるが，専門外のかかりつけ医がこれらのガイドラインを熟知することは困難と考えられる．平成19年厚生労働省は‘都道府県における肝炎検査後肝疾患診療体制に関するガイドライン：http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/03.html’を発表し，肝炎ウイルス検査陽性者の診療におけるかかりつけ医と専門医療機関との連携の必要性を述べている．

石川県では，行政および医師会の協力のもと，肝炎ウイルス検診陽性者が，年1回石川県が選定した専門医療機関を受診し，肝臓専門医の診察，肝画像検査を受けることを目的とした‘石川県肝炎診療連携’を平成22年度より開始した．石川県肝炎診療連携の概要は，平成14年から行政が肝炎ウイルス検診陽性者に対して行っていた毎年の受診勧奨，受診状況調査などのフォローアップを，肝疾患診療連携拠点病院(石川県の場合，金沢大学附属病院)が中心となって行い，肝炎ウイルス検診陽性者に対して直接，フォローアップを行っていくシステムある(図1)．個人情報保護のため市町の有する氏名，住所などの個人情報を拠点病院に移管できないことが問題となったが，この連携に参加し個人情報を拠点病院に移管することに関する同意書を，市町を介してすべての肝炎ウイルス検診陽性者に発送した．その結果，同意を得られた個人に関しては，拠点病院も個人情報を有するため拠点病院が直接肝炎ウイルス検診陽性者にアクセスすることが可能となった．

さらに連携参加同意者には，年1回石川県が選定した石川県肝疾患専門医療機関の受診を勧めるリーフレットと，専門医療機関での診察内容を記載する調査票を送付している．調査票には，専門医療機関で施行した画像検査の結果と，今後の望ましい検査方針・治療方針を記載する

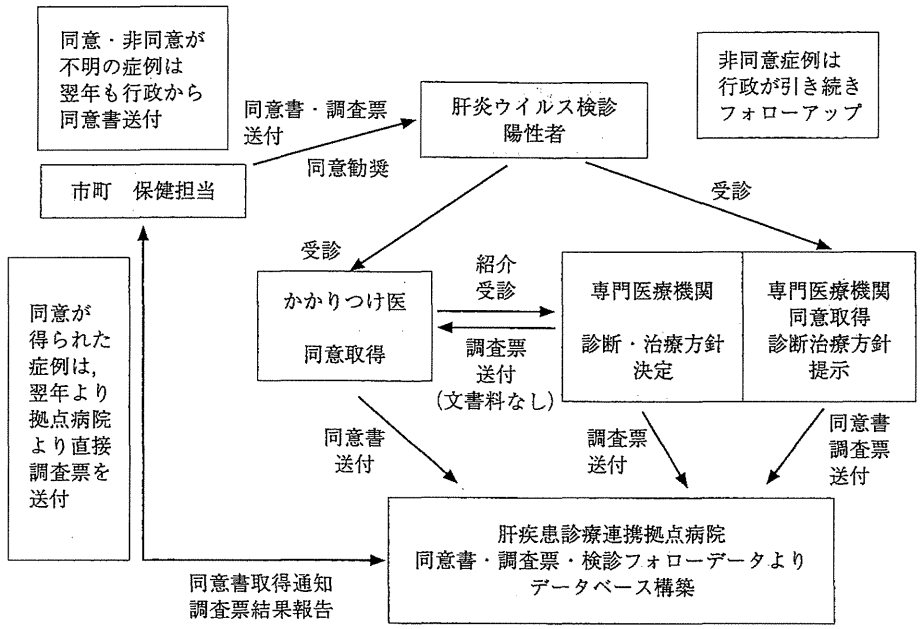

図1　石川県肝炎診療連携

こととなっている(図2). そのため連携参加者は, 年に1回の画像検査を受けることができると同時に, その時点で適切な治療方針を聞くことができる. もし同意者がかかりつけ医を受診した場合は, 調査票を紹介状の代わりとして, 専門医療機関を受診することとした. 専門医療機関における診察結果は, 複写式の調査票に記載され, かかりつけ医と拠点病院に送付される. かかりつけ医には専門医療機関での診察結果が調査票を介してフィードバックされ, 拠点病院では調査票を用いて受診状況や治療内容などをデータベース化している. また連携参加に同意を得られなかったり, 意思表示のなかったりした陽性者に関しては, 従来どおり行政側でフォローアップを続けている. 平成25年度末時点で2,840人の肝炎ウイルス検診陽性者のうち, 参加同意者は1,166人(41%), 残りの1,674人のうち, 参加非同意者が368人(13%), 意思表示のない参加未同意者が1,306人(46%)である. この意思表示のない1,306人に対しては, 連携参加を呼びかけるリーフレットとともに同意書を送付し続けている. 肝炎ウイルス検査陽性にもかかわらず自己判断で通院を中止したが, この連携に入ったことでかかりつけ医を介して専門医療機関を受診し, 肝臓癌を発見できた事例や, この連携に入ったことで専門医療機関を受診し, 専門医の指導によりインターフェロン治療まで結びついた事例も多く存在する. この連携への参加により, 肝炎ウイルス検診陽性者は, 受診忘れなどによるフォローアップからの脱落を予防できるだけでなく, 年に1回専門医療機関の受診を介して, 肝画像検査を受け, 専門医から最新の治療情報を得られるため, 極めて有用なシステムと考えられる.

おわりに

C型慢性肝疾患患者においては, 肝線維化の程度を正しく評価し, 高度線維化例においては早期の抗ウイルス療法の導入を図ることが重要であり, 逆にALTが正常値で軽度線維化例に関しては, 経過観察も可能と考えられる. 同時に, 個々の症例において肝発癌リスクを総合的に判断して, 画像検査および腫瘍マーカー測定による肝癌サーベイランスの頻度を決定すべきである. 今後, 経口DAAs製剤の登場によりSVRは90%以上となることが予測されるが, SVR後