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

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
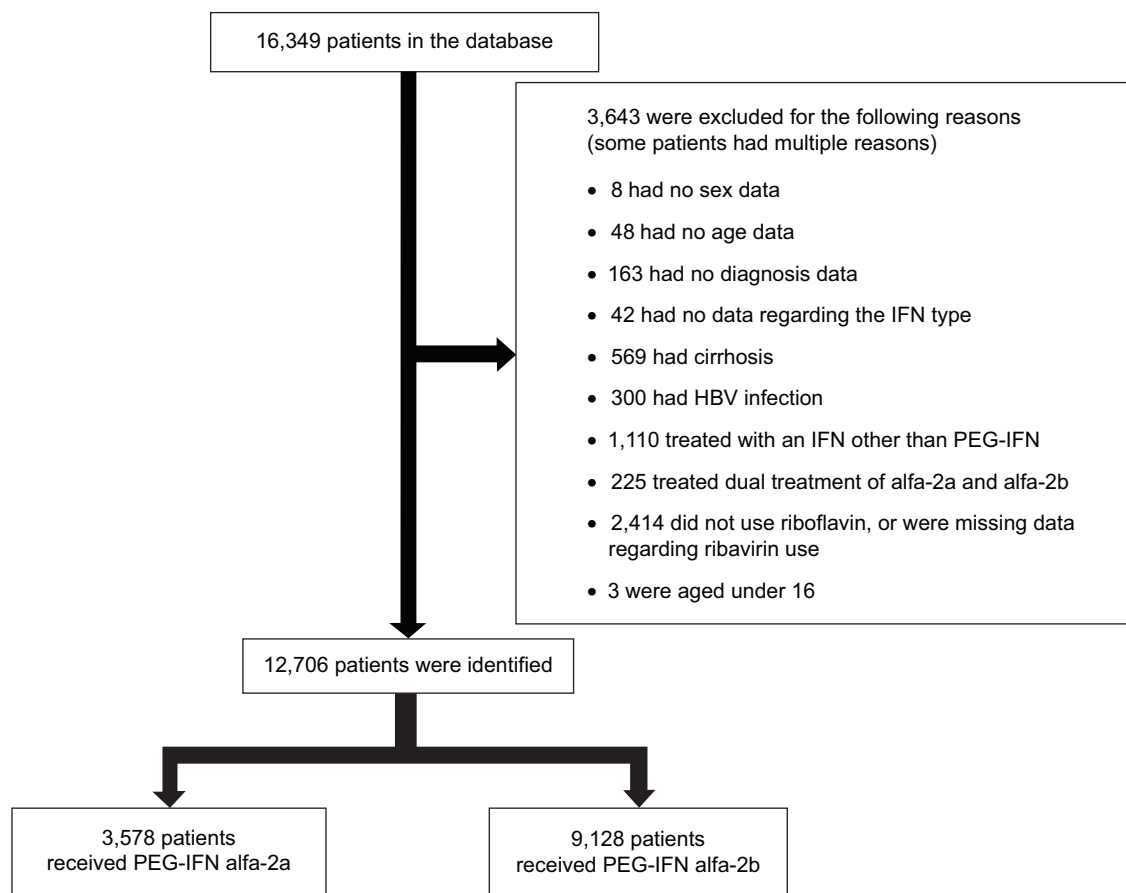

Figure 1 Identification of study patients from the database.
Notes: Patients were divided into two groups after excluding some patients according to the prespecified criteria for our study cohort. Some patients had more than one reason for being excluded.
Abbreviations: HBV, hepatitis B virus; IFN, interferon; 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 (×10⁴/μL) (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 (≥15×10⁴/μL vs <15×10⁴/μL)	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.
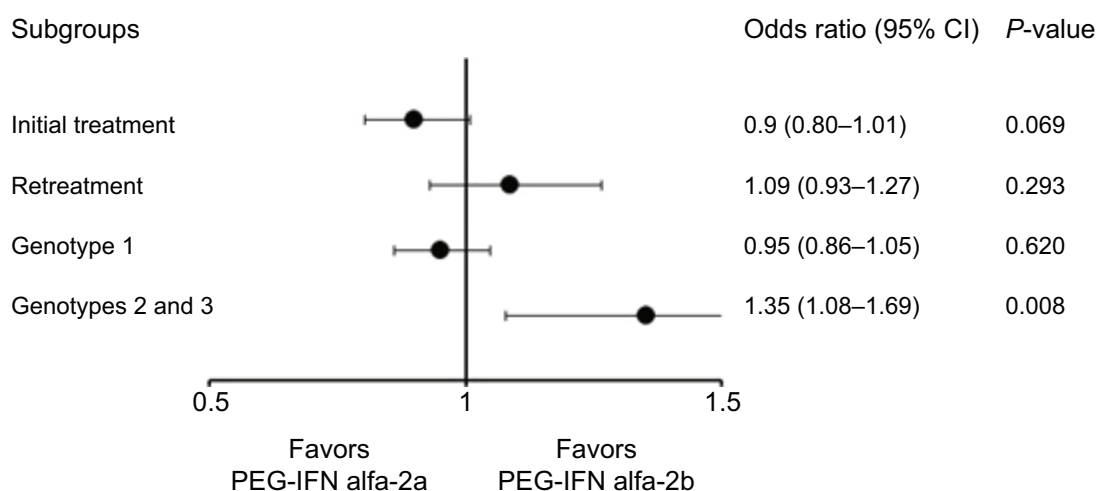
Figure 2 Results of the subgroup analysis for treatment experience and genotype.
Notes: The figure shows the forest plots of the adjusted SVR rate (odds ratio and the associated 95% confidential intervals) in the prespecified subgroup analyses (initial treatment group; retreatment group; genotype 1 group; 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.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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