

Regular Article

Comparison of the Safety Profiles of Pegylated Interferon α -2a and α -2b Administered in Combination with Ribavirin for Chronic Hepatitis C Infection: A Real-World Retrospective Cohort Study

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This study compares the safety profiles of pegylated interferon (PEG-IFN) α -2a and α -2b administered in combination with ribavirin, based on the variable of time to withdrawal from treatment due to adverse events. We conducted a real-world retrospective cohort study using the Japanese interferon database. Based on eligibility criteria, individuals with chronic hepatitis C virus (HCV) infection were identified in the database covering the period December 2009 to August 2015. The primary outcome measure was defined as difference in time to withdrawal from treatment due to adverse events between patients receiving PEG-IFN α -2a combined with ribavirin and those receiving PEG-IFN α -2b combined with ribavirin. The difference was analyzed using the multivariate Cox proportional hazards regression model. A frailty model was also applied to consider regional (prefectural) variation. After eligibility evaluation, 11058 individuals were included in the analysis. 3774 were treated with PEG-IFN α -2a, and 6764 with PEG-IFN α -2b, with 11.84 and 12.30% respectively withdrawing from treatment due to adverse events. The Cox model showed no significant difference between the two groups (hazard ratio (HR), 95%CI; 0.918, 0.817 to 1.031; $p=0.1475$). The results were consistent even when regional variation and other confounding variables were adjusted in the frailty model. In conclusion, there may be no difference in time to withdrawal from treatment due to adverse events between PEG-IFN α -2a and PEG-IFN α -2b combined with ribavirin. Applying the method used here to future studies using novel treatment regimens may also provide important information for the treatment of chronic HCV infection in clinical practice.

Key words hepatitis C virus (HCV); interferon; ribavirin; regional difference; nationwide database

The WHO has reported that over 130 million individuals suffer from chronic hepatitis C virus (HCV) infection worldwide.¹⁾ Moreover, every year 500000 individuals die from hepatitis C related liver disease.¹⁾ In recent years, the development of direct-acting antiviral agents has resulted in an improvement in the sustained virologic response rate, a common treatment outcome based on viral RNA levels, to more than 90% in phase II and III trials.^{2–4)} While this approach is very useful for the treatment of HCV infection, it is extremely expensive at present.⁵⁾ Therefore, the well-established approach of combining pegylated interferon (PEG-IFN) and ribavirin to treat chronic HCV infection is still used in particular situations.

When PEG-IFN and ribavirin are used in combination to treat chronic HCV infection, a crucial problem is the occurrence of adverse events and related withdrawal from treatment.^{6–8)} In clinical trials, over 60% of participants suffer from adverse events, including fatigue, anemia, and neutropenia.^{6,7)} Not only are adverse events frequent, they are also the second most common cause of withdrawal from treatment.^{6,7)} Severe adverse events are especially common with HCV genotype 1 infection, because the sustained virologic response rate is relatively low.^{9–11)}

Studies investigating differences in adverse events between PEG-IFN α -2a combined with ribavirin and PEG-IFN α -2b combined with ribavirin, including the safety outcomes of randomized clinical trials in Japan and other countries, as well as the pooled analysis of these studies, have suggested that there are no or few differences between the two treatments.^{6,7,12,13)} However, these studies were conducted in clinical trial settings, and until now there have been no studies carried out in Japan using a nationwide database compiled from real world settings.¹⁴⁾ In addition, most of the previous studies did not consider confounding variables and time to withdrawal from treatment due to adverse events in their analyses.^{6,7,12,13)} To assess the safety profile of the two types of PEG-IFN accurately, it is crucial to include adjustments for these variables. Furthermore, the results may be affected not only by patient characteristics, but also by regional differences in treatment outcomes, a concern that has been identified by several previous studies as being worthy of future investigation.^{14–16)} Investigations comparing the safety profile of the two types of PEG-IFN using real-world data based on the variable of time and adjusted for confounding variables give us useful information to aid the selection of the PEG-IFN type to use in clinical practice.

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With these concerns in mind, we conducted a nationwide retrospective cohort study using the Japanese interferon database to compare the safety of PEG-IFN α -2a combined with ribavirin and PEG-IFN α -2b combined with ribavirin, based on the variable of time before withdrawal from treatment due to adverse events. The study focuses on individuals with HCV genotype 1 infection, with our statistical models taking into consideration time before adverse events and variations among Japan's regions (specifically, prefectures, which are roughly equivalent to U.S. states), along with other confounding variables.

METHODS

Study Design A real-world retrospective cohort study was conducted using the Japanese interferon database.¹⁴ The database was authorized by the government of Japan in the Basic Act on Hepatitis Measures (Act No. 97; December 4, 2009), and cases have been registered since December 2009. All of Japan's 47 prefectures are invited to contribute to the database, and physicians in contributing prefectures send their data to the Hepatitis Information Center (Chiba, Japan). Physicians reporting data use a standard case report form, which includes the following information: sex, date of birth, age, clinical and/or histologic diagnosis, treatment experience, type(s) of treatment, treatment period (start and end of treatment), laboratory test results (serum HCV RNA level, HCV serotype and/or genotype, aspartate aminotransferase level, alanine aminotransferase (ALT) level, and platelet count), adverse events, date of completion of treatment, and treatment outcome. The treatment outcome is defined as sustained virological response (SVR), and is evaluated 24 weeks after cessation of treatment. If serum HCV RNA level is reduced to less than detectable levels, the case is judged to have SVR.

In the present study, the data registered in the Japanese interferon database was used to evaluate the safety profiles of PEG-IFN α -2a combined with ribavirin and PEG-IFN α -2b combined with ribavirin for the treatment of chronic hepatitis C infection. Written informed consent was obtained from participants before enrollment, and the study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine of Japan (No. 738; October 1, 2009). The study was conducted in accordance with the Declaration of Helsinki. The STROBE checklist was used to confirm the content and quality of this report (see **Checklist 1**, Supplementary materials).

Study Population The study focused on withdrawal from treatment due to adverse events by patients receiving PEG-IFN α -2a or PEG-IFN α -2b combined with ribavirin for chronic HCV genotype 1 infection. Individuals with chronic HCV infection registered in the database between December 2009 to August 2015 were identified, and those who met the following criteria were excluded: not genotype 1, hepatitis B virus (HBV) infection, cirrhosis, not treated with PEG-IFN and ribavirin, age <16 years, and clinical data missing. The age criterion was included as disease prognosis is different in children and adults.¹⁷

Study Outcome The primary outcome measure was defined as difference in time to withdrawal from treatment due to adverse events between patients receiving PEG-IFN α -2a combined with ribavirin and those receiving PEG-IFN α -2b

combined with ribavirin. The variables used to evaluate the outcome were treatment performance (completion or withdrawal), reasons for withdrawal, and treatment period. The secondary outcome measures were 1) difference in time to withdrawal from treatment due to adverse events taking into consideration the different regions (prefectures) of Japan, and 2) number of each type of adverse event. Adverse events were categorized and summarized as follows: malaise, interstitial pneumonia, cerebral hemorrhage, anemia, anorexia, thrombocytopenia, psychoneurosis, retinopathy, and any other reason.

Statistical Analysis Continuous variables were expressed as the mean \pm standard deviation (S.D.), and categorical variables were expressed as number and percentage (%). The difference between the two groups in time to withdrawal from treatment due to adverse events was analyzed using the multivariate Cox proportional hazards regression model.¹⁸ In the analysis, the following variables were considered to be confounding, based on the medical implications of previous reports^{11,15,16,19}: age, sex, platelet count, ALT level, HCV viral load, and treatment experience. The analysis taking into consideration regional variation was performed using the Cox proportional hazards regression with a shared frailty model (frailty model).²⁰ In the frailty model, hazard functions were defined as:

$$\lambda(t_{ij}|Z_i) = Z_i \lambda_0(t_{ij}) \exp(\beta^t X_{ij})$$

in which the hazard function is of the j th individual in prefecture i , given by the frailty group of $i(Z_i)$, where $\lambda_0(t_{ij})$ is the arbitrary baseline hazard rate, β is the regression parameter, and X_{ij} is the corresponding confounding vector. The distribution of frailty Z in this study was assumed to have a log-normal distribution. In the analysis using the multivariate Cox proportional hazards regression and frailty model, hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. Statistical significance was set to $p < 0.05$. All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, U.S.A.).

RESULTS

Clinical Characteristics of Registered Individuals The flow diagram for the study is shown in Fig. 1, and the clinical characteristics of individuals are presented in Table 1. Thirty eight prefectures agreed to participate in the study, and 25989 individuals were registered from December 2009 to August 2015. Among these, 14931 cases were excluded for the reasons indicated in Fig. 1. Several individuals had two or more reasons for exclusion. In total, 11058 individuals were included in the analysis. The number of individuals treated with PEG-IFN α -2a combined with ribavirin (PEG-IFN α -2a group) was 3774 (age, the mean \pm S.D.; 59.5 \pm 9.7) and PEG-IFN α -2b combined with ribavirin (PEG-IFN α -2b group) was 6764 (age, the mean \pm S.D.; 58.6 \pm 9.8). For the PEG-IFN α -2a group, the duration of treatment ranged from 1 to 1338 d (median, 339 d), and for the PEG-IFN α -2b group, from 1 to 1415 d (median, 337 d).

Withdrawal from Treatment Due to Adverse Events The results of the descriptive analysis of adverse events are shown in Table 2. Withdrawal from treatment due to adverse events occurred in 447 individuals (11.84%) in the PEG-IFN α -2a group, and 832 individuals (12.30%) in the PEG-IFN

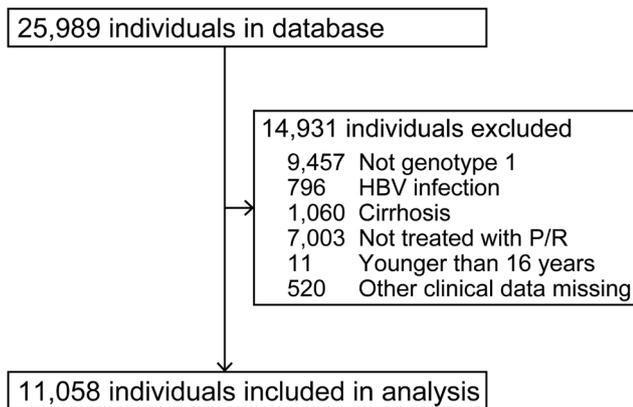


Fig. 1. Flow Diagram of Study

Table 1. Clinical Characteristics

Characteristics	PEG-IFN α -2a		PEG-IFN α -2b	
	(n=3774)		(n=6764)	
Age—yrs, mean (\pm S.D.)	59.5 (\pm 9.7)		58.6 (\pm 9.8)	
Period of treatment—days, mean (\pm S.D.)	364.7 (\pm 138.6)		353.5 (\pm 138.2)	
Minimum—days	1		1	
Max—days	1338		1415	
Median—days	339		337	
Gender—no. (%)				
Male	1798	(47.64)	3432	(50.74)
Female	1976	(52.36)	3322	(49.26)
Platelet count ($\times 10^4/\mu$ L)—no. (%)				
≥ 15	2102	(55.70)	3775	(55.81)
< 15	1672	(44.30)	2989	(44.19)
ALT (IU/L)—no. (%)				
> 30	2953	(78.25)	5337	(78.90)
≤ 30	821	(21.75)	1427	(21.10)
HCV viral load*—no. (%)				
High	3550	(94.06)	6444	(95.27)
Low	224	(5.94)	320	(4.73)
Treatment experience—no. (%)				
Initial treatment	2479	(65.69)	5218	(77.14)
Retreatment	1295	(34.31)	1546	(22.86)
Unknown	0	(0.0)	0	(0.0)

*High viral load: ≥ 5.0 Log IU/mL (RT-PCR, Cobas[®] TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, U.S.A.), or ≥ 100 KIU/mL (Cobas[®] Amplicor HCV Monitor v2.0; Roche Molecular Systems, Pleasanton, CA, U.S.A.); Low viral load: < 5.0 Log IU/mL (RT-PCR, Cobas[®] TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, U.S.A.), or < 100 KIU/mL (Cobas[®] Amplicor HCV Monitor v2.0; Roche Molecular Systems, Pleasanton, CA, U.S.A.). ALT, alanine aminotransferase; HCV, hepatitis C virus; PEG-IFN, pegylated interferon; S.D., standard deviation; yrs, years.

α -2b group. In both groups, malaise was the most frequent adverse event leading to treatment withdrawal (175 in the PEG-IFN α -2a group, 320 in the PEG-IFN α -2b group), excluding the category of “any other reason.” Other major adverse events included anorexia, psychoneurosis, and anemia.

Multivariate Cox Proportional Hazards Regression and Frailty Model Analysis The results of the multivariate Cox proportional hazards regression analysis are shown in Table 3. There was no significant difference in time to withdrawal from treatment due to adverse events between the two groups (HR, 95%CI; 0.918, 0.817 to 1.031; $p=0.1475$). Among the confounding factors, age (HR, 95%CI; 1.041, 1.034 to 1.048;

Table 2. Adverse Events That Caused Withdrawal

	PEG-IFN α -2a		PEG-IFN α -2b	
	n	%	n	%
Withdrawal from treatment	447	11.84	832	12.30
Malaise	175	—	320	—
Interstitial pneumonia	28	—	31	—
Cerebral hemorrhage	3	—	8	—
Anemia	54	—	115	—
Anorexia	102	—	188	—
Thrombocytopenia	46	—	50	—
Psychoneurosis	75	—	169	—
Retinopathy	20	—	52	—
Any other reason	182	—	335	—

PEG-IFN, pegylated interferon.

$p<0.0001$) and treatment experience (HR, 95%CI; 0.850, 0.747 to 0.966; $p=0.0127$) significantly affected withdrawal from treatment.

The results of the frailty model analysis are shown in Table 4. Among the different regions, there were no significant differences in time to withdrawal from treatment due to adverse events between the two groups (HR, 95%CI; 0.902, 0.801 to 1.016; $p=0.0883$). In this model, age (HR, 95%CI; 1.041, 1.034 to 1.049; $p<0.0001$) and treatment experience (HR, 95%CI; 0.847, 0.745 to 0.964; $p=0.0118$) significantly influenced withdrawal from treatment. The regression parameters which reflect the influence of region in the analysis are shown in Fig. 2. The point estimates of these values ranged from 0.682 to 1.675.

DISCUSSION

This study was conducted using a nationwide database to compare the safety profiles of PEG-IFN α -2a combined with ribavirin and PEG-IFN α -2b combined with ribavirin based on time to withdrawal from treatment due to adverse events. Our results suggest that there may be no difference in safety profile between the two PEG-IFN treatments. These results remain consistent even when different regions and confounding variables are taken into consideration in a frailty model.

Withdrawal from treatment due to adverse events occurred at a rate of 11.84% in the PEG-IFN α -2a group and 12.30% in the PEG-IFN α -2b group. The difference was $< 1\%$, suggesting that there may be no difference in time to treatment withdrawal due to adverse events between the two groups. With respect to the rate of treatment withdrawal, Miyase *et al.* previously reported in a randomized controlled study conducted in Japan that discontinuation of treatment due to adverse events caused by PEG-IFN α -2a combined with ribavirin and PEG-IFN α -2b combined with ribavirin were 8.9 and 9.0%, respectively.⁷ These values were approximately 3% lower than the results of the present study, which may be due to the settings of the two studies. Our study was a real-world study involving individuals who were not selectively enrolled, as participants in clinical trials are, and this may have influenced the difference.

The results of our multivariate Cox proportional hazards regression analysis also support the findings of previous studies that there may be no difference in treatment withdrawal due

Table 3. HR for Withdrawal from PEG-IFN Treatment

Variables	HR	95% CI	<i>p</i> -Value
PEG-IFN (α -2a vs. α -2b)	0.918	(0.817–1.031)	0.1475
Age (per 1 yr—increase)	1.041	(1.034–1.048)	<.0001
Sex (male vs. female)	0.947	(0.847–1.060)	0.3463
Platelet count ($\geq 15 \times 10^4 \mu\text{L}$ vs. $< 15 \times 10^4 \mu\text{L}$)	0.886	(0.792–0.991)	0.0349
ALT ($\geq 30 \text{ IU/L}$ vs. $< 30 \text{ IU/L}$)	1.031	(0.898–1.183)	0.6652
HCV viral load (high vs. low)*	0.968	(0.740–1.265)	0.8101
Treatment experience (initial- vs. re-treatment)	0.850	(0.747–0.966)	0.0127

*High viral load: $\geq 5.0 \text{ Log IU/mL}$ (RT-PCR, Cobas[®] TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, U.S.A.), or $\geq 100 \text{ KIU/mL}$ (Cobas[®] Amplicor HCV Monitor v2.0; Roche Molecular Systems, Pleasanton, CA, U.S.A.); Low viral load: $< 5.0 \text{ Log IU/mL}$ (RT-PCR, Cobas[®] TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, U.S.A.), or $< 100 \text{ KIU/mL}$ (Cobas[®] Amplicor HCV Monitor v2.0; Roche Molecular Systems, Pleasanton, CA, U.S.A.). ALT, alanine aminotransferase; HCV, hepatitis C virus PEG-IFN, pegylated interferon; yr, year.

Table 4. HR in Frailty Model Analysis

Variables	HR	(95% CI)	<i>p</i> -Value
PEG-IFN (α -2a vs. α -2b)	0.902	(0.801–1.016)	0.0883
Age (per 1 yr—increase)	1.041	(1.034–1.049)	<.0001
Sex (male vs. female)	0.946	(0.846–1.059)	0.3359
Platelet count ($\geq 15 \times 10^4$ vs. $< 15 \times 10^4 \mu\text{L}$)	0.878	(0.784–0.982)	0.0230
ALT ($\geq 30 \text{ IU/L}$ vs. $< 30 \text{ IU/L}$)	1.011	(0.881–1.160)	0.8789
HCV viral load (high vs. low)*	0.971	(0.743–1.270)	0.8312
Treatment experience (initial- vs. re-treatment)	0.847	(0.745–0.964)	0.0118

*High viral load: $\geq 5.0 \text{ Log IU/mL}$ (RT-PCR, Cobas[®] TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, U.S.A.), or $\geq 100 \text{ KIU/mL}$ (Cobas[®] Amplicor HCV Monitor v2.0; Roche Molecular Systems, Pleasanton, CA, U.S.A.); Low viral load: $< 5.0 \text{ Log IU/mL}$ (RT-PCR, Cobas[®] TaqMan HCV Test; Roche Molecular Systems, Pleasanton, CA, U.S.A.), or $< 100 \text{ KIU/mL}$ (Cobas[®] Amplicor HCV Monitor v2.0; Roche Molecular Systems, Pleasanton, CA, U.S.A.). ALT, alanine aminotransferase; HCV, hepatitis C virus PEG-IFN, pegylated interferon; yr, year.

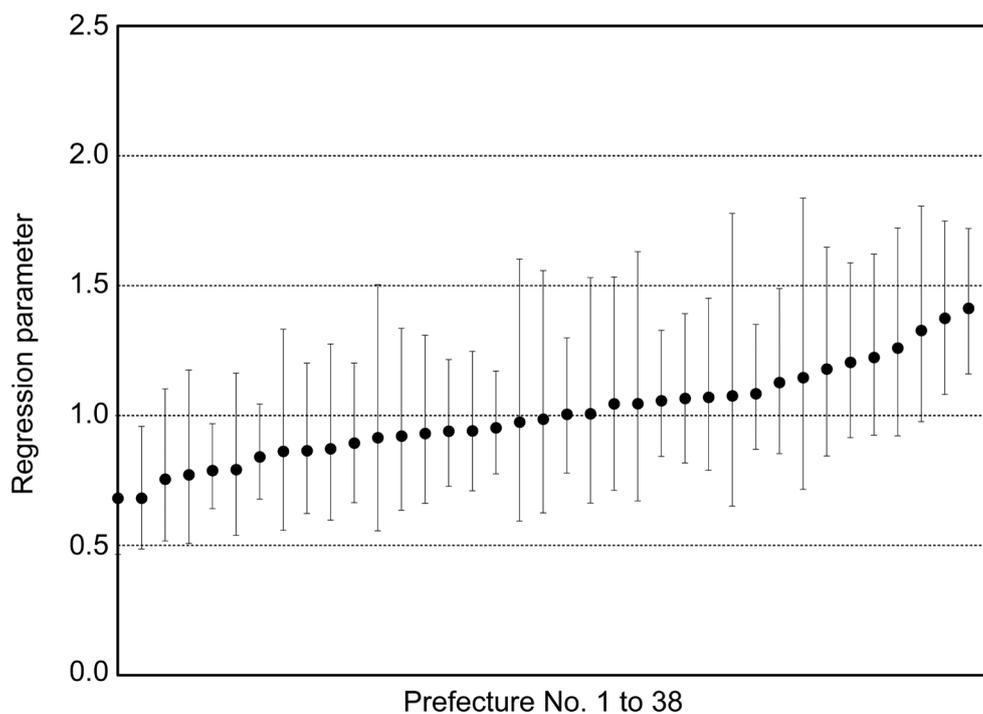


Fig. 2. Regression Parameters in Frailty Model

to adverse events between the two groups. In this analysis, confounding variables which had medical implications were included in the statistical models and adjusted. The results showed that the *p* value was > 0.05 , that the hazard ratio point estimate of 0.918 was close to 1, and that the confidence interval of 0.817 to 1.031 was very narrow. These results indicate

that the estimation was performed well, and therefore that there may be no difference between the two PEG-IFN treatments.

In the frailty model analysis, the range of the point estimates of the regression parameter was 0.682 to 1.675, which indicates that the regions should be considered in the analysis.

Several previous studies have also demonstrated that there may be regional differences (in prefectural and/or larger groupings) in treatment outcomes.^{14–16} Therefore, we included regions in our analysis, on the assumption that consistency of results between analyses would be meaningful. The results of the frailty model analysis also indicated that there may be no differences between the two PEG-IFN groups. The results of descriptive and several multivariate analyses that included confounding factors were consistent. Taken together, the above evidence strongly suggests that there may be no difference in time to withdrawal from treatment due to adverse events between PEG-IFN α -2a combined with ribavirin and PEG-IFN α -2b combined with ribavirin, even in real world clinical settings. In contrast to prior clinical studies, this investigation reflected the treatment period and the patient age range present in real-world settings, and we included previously treated patients.^{6,7,12,13} Ours is the first study focusing on the safety profiles of PEG-IFNs in a patient population with the variety of characteristics seen in actual clinical practice. As we have demonstrated that there is no significant difference in the safety profile of the two types of PEG-IFN when used in clinical practice, physicians can select the treatment regimen based on the predicted efficacy for each patient.

However, several limitations of this study should be pointed out. The major limitation is the coverage in the database of individuals who were treated for chronic HCV infection. Based on statistics regarding the governmental subsidy of chronic HCV infection treatment, the number of individuals included in the analysis covered only *ca.* 20% of infected individuals in Japan.¹⁴ In studies of this kind, wide coverage of individuals is important for the analysis of real-world data, but the present study included only a little over 10000 individuals, and the confidence intervals of the results were very narrow. However, the fact that these confidence intervals are very narrow strongly suggests that the results of this study may still be sufficiently generalizable. Another possible limitation of this study is that it did not include new treatments, such as three-agent combinations. Future studies that include these new treatment regimens should provide further important information for clinical practice. The methods used in the present study should also be useful in such studies. Additionally, as the treatment for chronic HCV infection has changed dramatically in recent years, the historical trends in treatment tolerability and threshold of withdrawal from treatment are also important.^{2–4} Future studies with a larger sample size are needed to provide this information.

In summary, this study has found that there may be no difference in the safety profiles of PEG-IFN α -2a combined with ribavirin and PEG-IFN α -2b combined with ribavirin, based on the variable of time to withdrawal from treatment due to adverse events. Consistency in results among analyses was observed, which indicates the robustness and accuracy of the findings. The method used in the present study can also be applied to future studies on new treatment regimens to provide important information for the treatment of chronic HCV infection in clinical practice.

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

REFERENCES

- 1) World Health Organization. "Hepatitis C. Fact sheet No. 164." <<http://www.who.int/mediacentre/factsheets/fs164/en/>>, cited 28 July, 2016.
- 2) Gane EJ, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N. Engl. J. Med.*, **368**, 34–44 (2013).
- 3) Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet*, **383**, 515–523 (2014).
- 4) Mizokami M, Yokosuka O, Takehara T, Sakamoto N, Korenaga M, Mochizuki H, Nakane K, Enomoto H, Ikeda F, Yanase M, Toyoda H, Genda T, Umemura T, Yatsushashi H, Ide T, Toda N, Nirei K, Ueno Y, Nishigaki Y, Betular J, Gao B, Ishizaki A, Omote M, Mo HM, Garrison K, Pang PS, Knox SJ, Symonds WT, McHutchison JG, Izumi N, Omata M. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naïve and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. *Lancet Infect. Dis.*, **15**, 645–653 (2015).
- 5) Pawlotsky JM. New hepatitis C therapies: the toolbox, strategies, and challenges. *Gastroenterology*, **146**, 1176–1192 (2014).
- 6) McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS, IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N. Engl. J. Med.*, **361**, 580–593 (2009).
- 7) Miyase S, Haraoka K, Ouchida Y, Morishita Y, Fujiyama S. Randomized trial of peginterferon alpha-2a plus ribavirin versus peginterferon alpha-2b plus ribavirin for chronic hepatitis C in Japanese patients. *J. Gastroenterol.*, **47**, 1014–1021 (2012).
- 8) Calvaruso V, Mazza M, Almasio PL. Pegylated-interferon-alpha(2a) in clinical practice: how to manage patients suffering from side effects. *Expert Opin. Drug Saf.*, **10**, 429–435 (2011).
- 9) Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M-H, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*, **358**, 958–965 (2001).
- 10) Poynard T, Marcellin P, Lee SS, Niederau C, Minuk GS, Ideo G, Bain V, Heathcote J, Zeuzem S, Trepo C, Albrecht J, International Hepatitis Interventional Therapy Group (IHIT). Randomised trial of interferon α 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon α 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet*, **352**, 1426–1432 (1998).
- 11) Minami T, Kishikawa T, Sato M, Tateishi R, Yoshida H, Koike K. Meta-analysis: mortality and serious adverse events of peginterferon

- on plus ribavirin therapy for chronic hepatitis C. *J. Gastroenterol.*, **48**, 254–268 (2013).
- 12) Zhao S, Liu E, Chen P, Cheng D, Lu S, Yu Q, Wang Y, Wei K, Yang P. A comparison of peginterferon alpha-2a and alpha-2b for treatment-naive patients with chronic hepatitis C virus: A meta-analysis of randomized trials. *Clin. Ther.*, **32**, 1565–1577 (2010).
 - 13) Singal AK, Jampana SC, Anand BS. Peginterferon alfa-2a is superior to peginterferon alfa-2b in the treatment of naive patients with hepatitis C virus infection: meta-analysis of randomized controlled trials. *Dig. Dis. Sci.*, **56**, 2221–2226 (2011).
 - 14) Masaki N, Yamagiwa Y, Shimbo T, Murata K, Korenaga M, Kanto T, Mizokami M, prefectural members contributing to the Japanese Interferon Database. Regional disparities in interferon therapy for chronic hepatitis C in Japan: a nationwide retrospective cohort study. *BMC Public Health*, **15**, 566 (2015).
 - 15) Ide K, Kawasaki Y, Yamada H, Masaki N. Regional differences in hepatitis C treatment with peginterferon and ribavirin in Japan: a retrospective cohort study. *Drug Des. Devel. Ther.*, **10**, 1217–1223 (2016).
 - 16) Ide K, Kawasaki Y, Akutagawa M, Yamada H, Masaki N. Regional differences in hepatitis C treatment with peginterferon and ribavirin in Japan in both genotype 1 and genotype 2: A retrospective cohort study. *Biol. Pharm. Bull.*, **39**, 1538–1543 (2016).
 - 17) González-Peralta RP, Kelly DA, Haber B, Molleston J, Murray KF, Jonas MM, Shelton M, Mieli-Vergani G, Lurie Y, Martin S, Lang T, Baczkowski A, Geffner M, Gupta S, Laughlin M, International Pediatric Hepatitis C Therapy Group. Interferon alfa-2b in combination with ribavirin for the treatment of chronic hepatitis C in children: efficacy, safety, and pharmacokinetics. *Hepatology*, **42**, 1010–1018 (2005).
 - 18) Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*, **81**, 515–526 (1994).
 - 19) Sato I, Shimbo T, Kawasaki Y, Masaki N. Comparison of peginterferon alfa-2a and alfa-2b for treatment of patients with chronic hepatitis C: a retrospective study using the Japanese Interferon Database. *Drug Des. Devel. Ther.*, **9**, 283–290 (2014).
 - 20) Wintrebert CMA, Putter H, Zwiderman AH, van Houwelingen JC. Centre-effect on survival after bone marrow transplantation: Application of time-dependent frailty models. *Biom. J.*, **46**, 512–525 (2004).