Journal of Liver
ISSN: 2167-0889

Ikezaki et al., J Liver 2014, 3:3
DOI; 10.4172/2167-0889.1000155

Research Article Open Access

Efficacy and Tolerance of Interferon β Plus Ribavirin Treatment for Chronic Hepatitis C Patients with Depression or Thrombocytopenia Comparison with Pegylated Interferon α Plus Ribavirin Treatment

Hiroaki Ikezaki, Norihiro Furusyo*, Eiichi Ogawa, Motohiro Shimizu, Satoshi Hiramine, Kazuya Ura, Fujiko Mitsumoto, Kouji Takayama, Kazuhiro Toyoda, Masayuki Murata and Jun Hayashi

Department of General Internal Medicine, Kyushu University Hospital, Fukuoka, Japan

Abstract

Objective: Limited data has been reported comparing natural human interferon β (nIFNβ) and pegylated IFN-α (PEG-IFNα) when Ribavirin (RBV) is combined. This case-control study was done to compare the efficacy and adverse effects of a combination treatment of nIFNβ or PEG-IFNα plus RBV for chronic hepatitis C patients.

Methods: Sixty patients with chronic hepatitis C, 42 infected with hepatitis C virus (HCV) genotype 1 and 18 infected with genotype 2, were treated with nIFNβ plus RBV. Of them, 23 (38.3%) suffered pre-treatment severe depression. Their data was compared with 60 undepressed patients treated with a combination of PEG-IFNα plus RBV. nIFNβ was given intravenously and PEG-IFNα was injected subcutaneously.

Results: Sustained virological response (undetectable HCV RNA at 24 weeks after the end of treatment) did not significantly differ between the nIFNβ and PEG-IFNα treated patients (genotype 1, 21.4% vs. 33.3%, P=0.328; genotype 2, 72.2% vs. 88.9%, respectively, P=0.402). None of the nIFNβ treated patients showed exacerbation of depression, while 7 (11.7%) of 60 PEG-IFNα treated patients developed severe depression or malaise. The platelet count of nIFNβ treated patients increased to higher than baseline after week 8, but the platelet count of PEG-IFNα treated patients decreased throughout the treatment. There were significant differences of the changes of platelet counts between the both groups throughout the treatment (all $P<0.001$).

Conclusion: nIFNβ plus RBV treatment was well tolerated by chronic hepatitis C patients with depression or thrombpcytopenia.

Keywords: Interferon β; Ribavirin; Chronic hepatitis C; Depression; Thrombocytopenia

Introduction

Hepatitis C virus (HCV) infection is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC) and thus represents a significant public health problem [1,2]. The primary objective of treatment for chronic hepatitis C is to eradicate HCV, achieve Sustained Virological Response (SVR), and to prevent progression to cirrhosis or HCC [3]. We previously reported that the eradication of HCV infection decreases the occurrence of hepatocellular carcinoma [4].

Pegylated interferon α (PEG-IFNα) plus Ribavirin (RBV) combination treatment has improved the SVR rate for patients with chronic hepatitis C [5]. Previous studies reported that 25-40% of such patients discontinued the combination treatment due to adverse effects, such as psychological problems or cytopenia [5-8]. Patients with depression are not considered suitable for this combination treatment. In Japan, natural human interferon β (nIFNβ) and RBV combination treatment has been approved and recommended for depressed patients with chronic hepatitis C, and some studies have shown that nIFNβ plus RBV treatment has equivalent efficacy and mild adverse effects [9-11].

This case-control study was done to compare the efficacy and safety of nIFNβ plus RBV combination treatment for Japanese chronic hepatitis C patients with that of PEG-IFNα plus RBV combination treatment.

Patients and Methods

Patients

A total of 60 Japanese patients with chronic hepatitis C treated with nIFNβ plus RBV between 2009 and 2012 at Kyusyu University Hospital were enrolled in this study. Of the 60 patients, 42 infected with HCV genotype 1b were placed in group B1 and 18 with genotype 2 in group B2. To compare the clinical efficacy and safety of the treatment, we retrospectively selected 60 patients treated with PEG-IFNα2b and RBV treatment, matched with the group B for genotype, sex, age, and body weight before treatment (Group A1: HCV genotype 1b, n=42 and A2: HCV genotype 2, n=18). Patients who had severe depression with suicidal ideation and / or attempt were excluded.

This study was carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000 and was approved by the Kyushu University Hospital Ethics Committee. Informed consent was obtained from all patients before treatment.

Treatment protocol, dose reduction, and discontinuation of treatment

Treatment periods were 24 for genotype 2 and 48 weeks for

***Corresponding author:** Norihiro Furusyo, Department of General Internal Medicine, Kyushu University Hospital, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan, Tel: +81-92-642-5909; Fax: +81-92-642-5916; E-mail: furusyo@gim.med.kyushu-u.ac.jp

Received April 03, 2014; **Accepted** April 22, 2014; **Published** May 05, 2014

Citation: Ikezaki H, Furusyo N, Ogawa E, Shimizu M, Hiramine S, et al. (2014) Efficacy and Tolerance of Interferon β Plus Ribavirin Treatment for Chronic Hepatitis C Patients with Depression or Thrombocytopenia Comparison with Pegylated Interferon α Plus Ribavirin Treatment. J Liver 3: 155. doi:10.4172/2167-0889.1000155

genotype 1 patients, respectively, with a subsequent 24-week follow-up period. Two types of interferon were prescribed, as below.

Groups B1 and B2: nIFNβ (Feron®; Toray Industries Inc., Tokyo, Japan) was given intravenously at a dose of 6 million units daily for first 4 weeks of treatment, followed by three times a week for the remaining 20-44 weeks.

Groups A1 and A2: PEG-IFNα2b (Peg-Intron®; MSD Co., Tokyo, Japan) was injected subcutaneously at a dose of 1.5 μg/kg once a week for 24-48 weeks.

RBV (Rebetol®; MSD Co., Tokyo, Japan) was given orally twice a day at a total dose of 600-1,000 mg for 24-48 weeks. The initial dose was adjusted according to body weight (600 mg for patients weighing ≤ 60 kg, 800 mg for those between 60 and 80 kg, and 1,000 mg for those ≥ 80 kg). Both nIFNβ or PEG-IFNα2b and RBV were concurrently initiated. The above durations and dosages are those approved by the Japanese Ministry of Health, Labor, and Welfare [12].

The dose of nIFNβ or PEG-IFNα2b was reduced if a patient had an adverse psychological effect, the white blood cell count fell below 1500×10^6 /L, or the platelet count fell below 50×10^9 /L. Likewise, the dose of RBV was reduced if the hemoglobin level decreased to under 100 g/L. Treatment was discontinued if the hemoglobin level, white blood cell count, or platelet count fell below 85 g/L, 1000×10^6 /L, or 25×10^9 /L, respectively.

HCV RNA detection and clinical evaluation

Blood samples were collected from the patients just before treatment, at weeks 4, 8, 12, 24, and 48 of the treatment, at the end of treatment (EOT), and at 24 weeks after EOT. The serum HCV RNA level at each point was determined by quantitative real time Polymerase Chain Reaction (PCR) assay (COBAS TaqMan HCV assay; Roche Diagnostics) with a linear dynamic range of 1.2 to 7.8 $\log_{10}$ IU/mL [13]. Biochemical and hematological tests were performed once each month during treatment. All were measured by standard laboratory techniques in our hospital laboratory. Liver biopsy was performed for 103 (85.8%) of the 120 patients by experienced hepatologists and the stage of fibrosis (F0-4) and the grade of activity (A0-3) were established according to the METAVIR score [14].

Interleukin 28B and inosine triphosphate pyrophosphatase

Human genomic DNA was extracted from peripheral blood. Genotyping by the Single-Nucleotide Polymorphism (SNP) of the interleukin 28B (*IL28B*) (rs8099917) and inosine triphosphate pyrophosphatase (*ITPA*) (rs1127354) genes was done using the TaqMan Allelic Discrimination Demonstration Kit (7500 Real-Time PCR System; Applied Biosystems, Foster City, CA). Patients were genotyped as *IL28B* TT, TG, or GG and as *ITPA* CC, CA, or AA at the polymorphic site [15].

Virological response

SVR was defined as undetectable HCV RNA at 24 weeks after the end of treatment. Early virological response during treatment was categorized as follows: Rapid Virological Response (RVR), undetectable HCV RNA at week 4. Complete early viological response (cEVR), detectable HCV RNA at week 4 but undetectable at week 12. Relapse was defined as undetectable HCV RNA at the end of treatment, but non-SVR. Non-response was defined as detectable HCV RNA through treatment. Non-SVR was defined as not achieving SVR, including relapse and non-response.

Assessment of depression

A questionnaire survey was conducted when physicians perceived the necessity or patients complained depressive symptom, using the Beck Depression Inventory II (BDI-II) and the Pittsburgh Sleep Quality Index (PSQI) [16,17]. Patients with a BDI-II score of 14 or more were considered to have the onset of depression symptoms. Patients with a PSQI score of 11 or more were identified as having sleep disorder.

Statistical analysis

All statistical analyses were performed using JMP® ver. 9 (SAS Institute Inc., Cary, NC). Data are reported as mean ± standard error (SE), median [first quartile, third quartile], or percentage for each category. Spearman correlation coefficient analysis was used to analyze patient characteristics. The student's *t* test and the Mann-Whitney *U* test were used to compare between-group differences. A *P* value of <0.05 was considered statistically significant.

Results

Clinical characteristics

Table 1 shows the pretreatment clinical characteristics of the patients of groups B and A. No significant differences in baseline serum HCV RNA levels, histology of fibrosis, or distribution of *IL28B* or *ITPA* genotype were found between the B1 and A1 or B2 and A2 groups. Group B1 had a significantly higher rate of history of IFN therapy, higher levels of aspartate aminotransferase and α-fetoprotein, and a significantly lower platelet count than group A1. Group B2 had a significantly higher rate of depression and a lower rate of *IL28B* TT genotype than group A2. The discontinuation rates of group B1 and B2 during prior IFN treatment were higher than those of group A1 and A2, but there was no significant difference.

Efficacy of treatment

Tables 2 and 3 show the virological response to both treatments. There was no significant difference in the SVR rates of groups B1 and A1 (21.4% vs. 33.3%, P=0.328) or groups B2 and A2 (72.2% vs. 88.9%, P=0.402). Patients with RVR achieved SVR significantly more often than patients without RVR in group B1 and B2 (P = 0.001 and 0.029, respectively), but no significance was found for groupA1 and A2 (P=0.106 and 0.065, respectively). Patients with cEVR achieved SVR significantly more often than patients without cEVR in group B1, B2 and A1 (P<0.001 and P=0.008 and 0.020, respectively), but no significance was found for group A2 (P=0.111). In B1, *IL28B* TT patients showed significantly higher SVR rates than *IL28B* non-TT patients (33.3%, 8 of 24 patients and 0.0%, 0 of 14, respectively, P=0.017). In group B2 and A1, *IL28B* TT patients showed higher SVR rates than *IL28B* non-TT patients (B2; 75.0%, 9 of 12 vs. 60.0%, 3 of 5, and A1; 34.6%, 9 of 26 vs. 25.0%, 2 of 8, respectively) but the difference was not significant (P=0.600 and P>0.999, respectively). In group A2, all patients determined *IL28B* genotype had *IL28B* TT genotype.

Safety and tolerance of nIFNβ plus RBV treatment

There was no significant difference in the discontinuation rates between group B1 and A1 (P=0.164) or group B2 and A2 (P=0.486). Of the 42 group B1 patients, 11 (26.2%) discontinued the treatment because of malaise (3 patients at weeks 14, 20, 24), hyperthyroidism (1 patient at week 9), poor response (4 patients at weeks 15, 16, 19, 38), new occurrence of HCC (2 patients at weeks 3, 25), and for personal reasons (1 patient at week 24). Of the 42 group A1 patients, 5 (11.9%) discontinued treatment, two because of malaise at week 38

Citation: Ikezaki H, Furusyo N, Ogawa E, Shimizu M, Hiramine S, et al. (2014) Efficacy and Tolerance of Interferon β Plus Ribavirin Treatment for Chronic Hepatitis C Patients with Depression or Thrombocytopenia Comparison with Pegylated Interferon α Plus Ribavirin Treatment. J Liver 3: 155. doi:10.4172/2167-0889.1000155

Groups	Group B1	Group A1		Group B2	Group A2	
Treatment	nIFNβ + RBV	PEG-IFNα2b + RBV	*P* value	nIFNβ + RBV	PEG-IFNα2b + RBV	*P* value
Studied n	42	42	matched	18	18	matched
Depression, n (%)	12 (28.6)	5 (11.9)	0.102	11 (61.1)	1 (0.6)	< 0.001
HCV genotype	1b			2		
Men, n (%)	16 (38.1)	16 (38.1)	matched	7 (38.9)	7 (38.9)	matched
Prior IFN treatment history, n (%)	34 (81.0)	14 (33.3)	< 0.001	10 (55.6)	7 (38.9)	0.505
Prior treatment outcome (Relapse / Non response / Discontinuation)	5 / 22 / 7	4 / 8 / 2	0.518	3 / 3 / 4	2 / 5 / 0	0.116
Prior treatment discontinuation, n (%)	7 (20.6)	2 (14.3)	0.611	4 (40.0)	0 (0.0)	0.056
Age (years)	66 [60, 71]	65 [59, 71]	0.648	60 [50, 69]	57 [48, 65]	0.537
Body weight (kg)	59.2 [50.8, 69.3]	57.2 [51.4, 68.1]	0.858	54.1 [46.9, 67.8]	56.4 [49.2, 67.0]	0.764
Body mass index (kg/m^2)	23.1 [21.4, 26.4]	23.4 [21.3, 25.6]	0.906	22.9 [19.7, 25.6]	23.3 [20.9, 26.4]	0.448
Histology						
Activity (A0/A1/A2/A3)	1 / 17 / 16 / 1	0 / 13 / 20 / 3	0.549	0 / 6 / 8 / 1	0 / 4 / 11 / 2	0.531
Fibrosis (F0/F1/F2/F3/F4)	1 / 16 / 8 / 8 / 2	2 / 18 / 7 / 4 / 5	0.667	2 / 5 / 5 / 0 / 3	5 / 7 / 1 / 0 / 4	0.246
Not determined histology study	7	6		3	1	
IL28B (TT / TG·GG)	24 / 14	26 / 8	0.218	12 / 5	15 / 0	0.042
ITPA (CC / CA·AA)	22 / 16	21 / 13	0.626	14 / 3	11 / 4	0.472
Not determined *IL28B* or *ITPA* phenotype	4	8		1	1	
Serum HCV RNA level (log IU/mL)	6.25 [5.68, 6.83]	6.05 [5.54, 6.50]	0.175	5.99 [4.85, 6.76]	6.23 [5.20, 6.60]	0.812
Serum albumin (g/L)	39 [37, 41]	40 [37, 44]	0.063	42 [39, 45]	43 [39, 44]	0.691
Aspartate aminotransferase (IU/L)	67 [48, 100]	49 [38, 78]	0.022	41 [27, 91]	56 [36, 71]	0.874
Alanine aminotransferase (IU/L)	66 [38, 94]	54 [35, 94]	0.607	40 [23, 129]	52 [31, 100]	0.788
γ-glutamyl transpeptidase (IU/L)	55 [34, 98]	41 [26, 67]	0.171	40 [21, 69]	35 [18, 84]	0.937
eGFR (mL/min/1.73m^2)	78.7 [69.0, 88.5]	72.0 [61.5, 87.5]	0.168	81.7 [69.5, 91.7]	83.2 [75.8, 91.4]	0.420
White blood cell (×10^6/L)	4325 [3798, 5300]	4610 [3838, 5850]	0.431	4870 [3500, 6020]	5000 [3750, 6800]	0.448
Hemoglobin (g/L)	135 ± 2	134 ± 2	0.872	135 ± 4	131 ± 4	0.438
Platelet (×10^9/L)	110 [84, 161]	169 [143, 214]	< 0.001	166 [111, 202]	167 [128, 196]	0.681
α-fetoprotein (ng/mL)	10.5 [5.1, 29.1]	6.5 [3.6, 13.3]	0.069	4.8 [3.0, 26.6]	4.9 [2.5, 12.7]	0.764
Initiation dose of RBV / body weight (mg/kg)	12.1 ± 0.2	11.2 ± 0.2	0.069	12.2 ± 0.3	11.4 ± 0.3	0.730

IFN, interferon; nIFNβ, natural interferon β; PEG-IFNα2b, pegylated interferon α2b; RBV, ribavirin; HCV, hepatitis C virus; *IL28B*, interleukin 28B; *ITPA*, inosine triphosphate pyrophosphatase; eGFR, estimated glomerular filtration rate
Liver activity histology was classified as : A1, mild ; A2, moderate ; A3 severe.
Liver fibrosis histology was classified as : F1, periportal expansion ; F2, portoportal septa ; F3, portocentral linkage or bridging fibrosis ; F4, cirrhosis.
Data are shown as median [first-quartile, third-quartile], mean ± standard error, and number.
P values were calculated between Group B1 and A1 or between Group B2 and A2.

Table 1: Comparison of baseline clinical characteristics of patients with nIFNβ plus RBV and PEG-IFNα2b plus RBV.

	Group B1 (nIFNβ + RBV) (n = 42)			Group A1 (PEG-IFNα2b + RBV) (n = 42)		
	SVR (n = 9)	non-SVR (n = 33)	*P* value	SVR (n = 14)	non-SVR (n = 28)	*P* value
Pretreatment depression, n (%)	2 (22.2)	10 (30.3)	> 0.999	1 (7.1)	4 (14.3)	> 0.999
Exacerbation or new developed depression, n (%)	0 (0.0)	0 (0.0)	> 0.999	1 (7.1)	6 (21.4)	0.242
Men, n (%)	2 (22.2)	14 (42.4)	0.442	6 (42.9)	10 (35.7)	0.742
Age (years)	64 [57, 71]	68 [60, 72]	0.539	63 [58, 67]	67 [60, 71]	0.186
Age over 65, n (%)	4 (44.4)	22 (66.7)	0.265	5 (35.7)	17 (60.7)	0.192
Body mass index (kg/m^2)	26.4 [22.7, 28.1]	22.9 [20.9, 25.4]	0.138	23.1 [21.1, 24.8]	23.4 [21.4, 27.2]	0.386
RVR / cEVR, n	5 / 3	1 / 2	< 0.001	2 / 9	0 / 10	0.011
IL28B (TT / TG·GG)	8 / 0	16 / 14	0.017	9 / 2	17 / 6	> 0.999
ITPA (CC / CA·AA)	5 / 3	17 / 13	> 0.999	7 / 4	14 / 9	> 0.999
Histology Fibrosis (F0 / F1 / F2 / F3 / F4)	0 / 3 / 2 / 2 / 0	1 / 13 / 6 / 6 / 2	0.907	1 / 7 / 2 / 2 / 1	1 / 11 / 5 / 2 / 4	0.862
Prior interferon history, n (%)	5 (55.6)	29 (87.9)	0.050	2 (14.3)	12 (42.9)	0.089
Prior treatment outcome (Relapse / Non response)	3 / 2	2 / 27	0.015	2 / 0	2 / 10	0.066
Serum HCV RNA level (log IU/mL)	5.12 ± 0.47	6.42 ± 0.10	0.006	6.02 ± 0.21	6.10 ± 0.11	0.521
Serum albumin (g/L)	40 ± 2	38 ± 1	0.324	41 ± 1	40 ± 1	0.698
Aspartate aminotransferase (IU/L)	58 [27, 76]	76 [54, 102]	0.064	47 [38, 76]	49 [37, 79]	0.968
Alanine aminotransferase (IU/L)	42 [25, 83]	69 [42, 118]	0.086	52 [34, 98]	54 [36, 92]	0.894
γ-glutamyl transpeptidase (IU/L)	48 [15, 80]	56 [36, 110]	0.191	30 [23, 63]	48 [26, 88]	0.173

eGFR (mL/min/1.73m^2)	77.8 [68.6, 82.5]	78.7 [69.0, 89.7]	0.709	77.4 [66.3, 87.7]	68.8 [60.8, 90.7]	0.584
White blood cell (/μL)	4100 [3690, 5180]	4360 [3830, 5300]	0.510	4610 [3840, 5510]	4620 [3830, 5950]	0.979
Hemoglobin (g/L)	132 ± 5	136 ± 3	0.480	137 ± 3	132 ± 3	0.603
Platelet (×10^4/μL)	14.4 [8.5, 18.2]	10.7 [8.4, 15.2]	0.416	20.0 [16.6, 21.5]	15.0 [13.4, 17.8]	0.023
α-fetoprotein (ng/mL)	5.7 [3.2, 8.7]	12.9 [6.3, 42.5]	0.011	5.6 [3.1, 7.4]	6.9 [3.7, 15.4]	0.225
Adherence rates of IFN (%)	100	100	> 0.999	98.7 ± 2.7	87.8 ± 3.2	0.034
Initiation dose of RBV / body weight (mg/kg)	12.1 ± 0.4	12.1 ± 0.3	0.915	11.9 ± 0.5	10.9 ± 0.2	0.093
Adherence rates of RBV (%)	100 [73.7, 103.4]	100 [94.2, 100]	0.919	64.7 [49.4, 100]	41.6 [26.7, 77.8]	0.049

Data are shown as median [first-quartile, third-quartile], mean ± standard error, and number.
IFN, interferon; HCV, hepatitis C virus; SVR, sustained virological response; RVR, rapid virological response; cEVR, complete early virological response; *IL28B*, interleukin 28B; *ITPA*, inosine triphosphate pyrophosphatase; nIFNβ, natural interferon β; PEG-IFNα2b, pegylated interferon α2b; RBV, ribavirin; eGFR, estimated glomerular filtration rate
Liver fibrosis histology was classified as F1, periportal expansion ; F2, portoportal septa ; F3, portocentral linkage or bridging fibrosis ; F4, cirrhosis.
P values were calculated between SVR and non-SVR patients of each groups.

Table 2: Results of patients infected HCV genotype 1 treated with nIFNβ plus RBV and PEG-IFNα2b plus RBV.

	Group B2 (nIFNβ + RBV) (n = 18)			Group A2 (PEG-IFNα2b + RBV) (n = 18)		
	SVR (n = 13)	non-SVR (n = 5)	P value	SVR (n = 16)	non-SVR (n = 2)	P value
Pretreatment depression, n (%)	8 (61.5)	3 (60.0)	> 0.999	1 (6.3)	0 (0.0)	> 0.999
Exacerbation or newly developed depression, n (%)	0 (0.0)	0 (0.0)	> 0.999	0 (0.0)	0 (0.0)	> 0.999
Men, n (%)	5 (38.5)	2 (6.1)	> 0.999	7 (43.8)	0 (0.0)	0.497
Age (years)	56.0 ± 4.2	60.8 ± 4.6	0.882	54.4 ± 3.1	61.0 ± 6.0	0.439
Age over 65, n (%)	4 (30.8)	2 (40.0)	> 0.999	4 (25.0)	1 (50.0)	0.490
Body mass index (kg/m2)	22.6 ± 1.1	24.4 ± 1.7	0.430	23.8 ± 0.7	22.9 ± 2.7	0.527
RVR / cEVR, n	9 / 3	0 / 1	0.006	13 / 3	0 / 1	0.006
IL28B (TT / TG·GG)	9 / 3	3 / 2	0.600	13 / 0	2 / 0	
ITPA (CC / CA·AA)	11 / 1	3 / 2	0.191	9 / 4	2 / 0	> 0.999
Histology fibrosis (F0 / F1 / F2 / F3 / F4)	1 / 5 / 4 / 0 / 2 / 1	1 / 0 / 1 / 0 / 1 / 2	0.439	5 / 7 / 1 / 0 / 2 / 0	0 / 0 / 0 / 0 / 2 / 0	0.061
Prior IFN treatment history, n (%)	7 (53.8)	3 (60.0)	> 0.999	7 (43.8)	0 (0.0)	0.497
Prior treatment outrcome (Relapse / Non response)	2 / 5	1 / 2	> 0.999	2 / 5	0 / 0	> 0.999
Serum HCV RNA level (log IU/mL)	5.08 ± 0.50	6.43 ± 0.26	0.126	5.86 ± 0.27	5.84 ± 0.66	0.622
Serum albumin (g/L)	42 [41, 46]	42 [34, 48]	0.843	43 [40, 45]	32 [29, 34]	0.032
Aspartate aminotransferase (IU/L)	40 [26, 84]	72 [29, 113]	0.622	51 [33, 67]	75 [62, 87]	0.206
Alanine aminotransferase (IU/L)	41 [30, 135]	32 [18, 119]	0.554	52 [27, 101]	52 [33, 70]	0.725
γ-glutamyl transpeptidase (IU/L)	35 [18, 49]	74 [44, 185]	0.038	46 [22, 95]	15 [13, 17]	0.079
eGFR (mL/min/1.73m2)	82.7 ± 3.8	80.3 ± 7.7	0.657	87.0 ± 4.5	78.7 ± 3.7	0.440
White blood cell (/μL)	5072 ± 467	3968 ± 428	0.168	5197 ± 436	4895 ± 1905	0.888
Hemoglobin (g/L)	135 ± 4	135 ± 7	0.921	133 ± 4	114 ± 4	0.079
Platelets (×104/μL)	17.2 ± 1.6	12.6 ± 2.2	0.168	17.8 ± 1.4	10.9 ± 0.2	0.106
α-fetoprotein (ng/mL)	3.5 [2.5, 15.7]	7.4 [4.0, 34.3]	0.168	4.0 [2.4, 7.4]	13.9 [13.6, 14.1]	0.058
Adherence rates of IFN (%)	100	100	> 0.999	96.7 ± 3.5	96.1 ± 0.3	> 0.999
Initiation dose of RBV / body weight (mg/kg)	12.4 ± 0.3	11.6 ± 0.5	0.182	11.5 ± 0.4	10.8 ± 0.0	0.527
Adherence rates of RBV (%)	100 [93.8, 100]	100 [88.0, 100]	> 0.999	75.7 [57.8, 99.0]	31.8 [13.6, 50.0]	0.078

HCV, hepatitis C virus ; SVR, sustained virological response ; RVR, rapid virological response ; cEVR, complete early virological response ; IL28B, interleukin 28B ; ITPA, inosine triphosphate pyrophosphatase ; IFN, interferon ; nIFNβ, natural interferon β ; PEG-IFN, pegylated interferon α2b ; RBV, ribavirin ; eGFR, estimated glomerular filtration rate
Liver fibrosis histology was classified as : F1, periportal expansion ; F2, portoportal septa ; F3, portocentral linkage or bridging fibrosis ; F4, cirrhosis.
Data are shown as median [first-quartile, third-quartile], mean ± standard error, and number.
P values were calculated between SVR and non-SVR patients of each groups.

Table 3: Results of patients infected HCV genotype 2 treated with nIFNβ plus RBV and PEG-IFNα2b plus RBV.

and three because of poor response at weeks 16, 18, and 24. Of the 18 group B2 patients, 2 (11.1%) discontinued treatment, one because of poor response at week 28 and the other because of the recurrence of maxillary cancer at week 29 week. Of the 18 group A2 patients, none discontinued treatment. Although the total rate of discontinuation of the 60 group B patients (21.6%) was significantly higher than that of the 60 group A patients (8.3%) (P=0.041), there was no significant difference in the rates of discontinuation because of treatment-related side effect (malaise and hypothyroidism) between groups B (n=4, 6.7%) and A (n=2, 3.3%) (P=0.402).

Of the 60 group B patients, none had exacerbated or newly developed depression during treatment, but 7 (11.7%) of the 60 group A patients developed depression during treatment (P=0.002) and all of 7 required to reduce the dose of PEG-IFNα2b.

Of the 60 group B, none required a reduction of the dose of nIFNβ.

However, in the 42 group A1 patients, the adherence rate to PEG-IFNα2b was 85.2 [72.2, 96.9]% (median [first quartile, third quartile]), and in the 18 group A2 patients, the rate was 96.0 [87.8, 108.5]%. There was a significant difference in the adherence rates to IFN between groups B1 and A1 (P=0.005), but not between groups B2 and A2 (P=0.230). In 60 group A patients, 14 required a reduction of the dose of PEG-IFNα2b, 7 required because they developed depression, and other 7 required because their platelet counts fell below 50 × 10^9/L. The SVR rate of these 14 group A, PEG-IFNα2b reduction patients was significantly lower (2 patients, 14.3%) than that of 46 group A patients who did not required a reduction (28 patients, 60.9%) (P=0.002). None required discontinuation the therapy because of adverse effect.

There was a significant difference in the adherence rates to RBV between groups B1 and A1 (100 [86.8, 100]% and 31.9 [21.2, 50.3]%, respectively (P<0.001)) and between groups B2 and A2 (100 [96.9, 100]% and 50.0 [27.7, 55.2]%, respectively (P=0.002)).

Influence of nIFNβ to blood count

The platelet count of group B increased to higher than baseline after week 8, but the platelet count of group A decreased throughout the treatment. Significant differences were found between groups B and A throughout the treatment (all P<0.001). Figure 1 shows the differences in the on-treatment changes of platelet count by *ITPA* genotype. The platelet counts of *ITPA* non-CC patients were lower than those of *ITPA* CC patients (significantly at weeks 4, 12 and 24, P = 0.013, 0.102, 0.039 and 0.008 at weeks 4, 8, 12 and 24, respectively) for group B (Figure 1a). The *ITPA* non-CC patients had a significantly higher decrease than the *ITPA* CC patients at week 4 (P=0.001), but there were no significant differences after week 8 (P = 0.141, 0.329 and 0.281 at weeks 8, 12 and 24, respectively) for group A (Figure 1b).

There was no significant difference in the decrease of hemoglobin level at weeks 4, 8 or 12 between groups B and A. At week 24, the decrease of the hemoglobin level of group A became significantly higher than that of group B (P=0.048), even though the adherence rate to RBV of group A was significantly lower than group B. Figure 2 shows on-treatment differences in the decrease of hemoglobin levels, by *ITPA* genotype. The hemoglobin levels of *ITPA* CC patients decreased significantly more than those of *ITPA* non-CC patients (P<0.001 at week 4 and P=0.002, 0.005, and 0.022 at weeks 8, 12 and 24, respectively) in group B (Figure 2a). The hemoglobin of *ITPA* CC patients decreased significantly more than those of *ITPA* non-CC patients at week 4 (P<0.001), but there was no significant difference between the genotypes after week 8 (P=0.252, 0.621 and 0.787 at weeks 8, 12 and 24, respectively) in group A (Figure 2b).

Discussion

The four major findings of the present study are as follows. First, the efficacy of the nIFNβ plus RBV treatment was equivalent to that of PEG-IFNα2b plus RBV treatment. Second, none of the patients treated with nIFNβ plus RBV had exacerbated or newly developed depression. Third, the platelet count of patients treated with nIFNβ plus RBV increased to higher than baseline after week 8 whereas they fell with PEG-IFN2b plus RBV. Finally, significantly fewer *ITPA* non-CC patients than *ITPA* CC patients treated with nIFNβ plus RBV had a decrease in the hemoglobin level.

Although the overall discontinuation rates for nIFNβ plus RBV treatment were slightly higher than for PEG-IFNα2b and RBV treatment, the number of patients discontinued because of interferon-induced side effects, such as malaise or thyroid disease, was equivalent. And the platelet count of patients taking nIFNβ increased to higher than baseline. The SVR rates for nIFNβ plus RBV treatment and PEG-IFNα2b plus RBV treatment were equivalent for chronic hepatitis C patients, however, because the mean age of the patients with HCV genotype 1 was over 65 years, the SVR rate of these patients was low as the previous studies [8,18]. These results indicate that nIFNβ plus RBV combination treatment is effective and safe for patients with chronic hepatitis C, in particular for those with depression or thrombocytopenia.

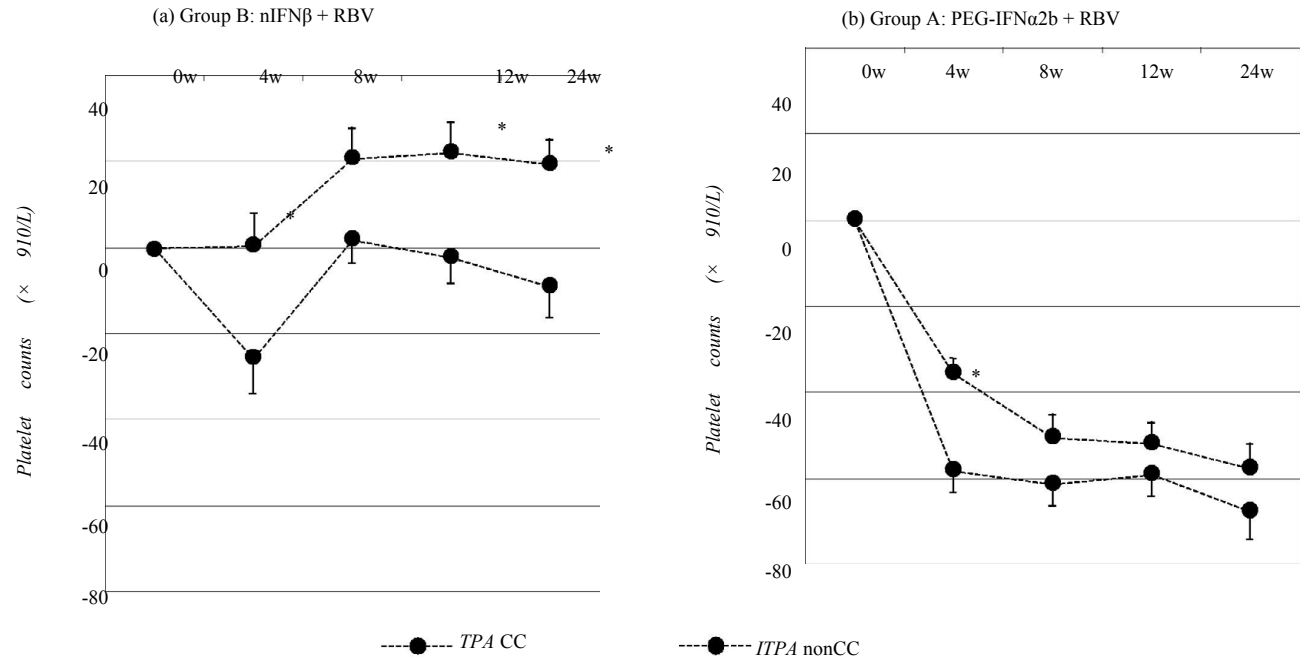

Figure 1: Change in platelet count by *ITPA* genotype.

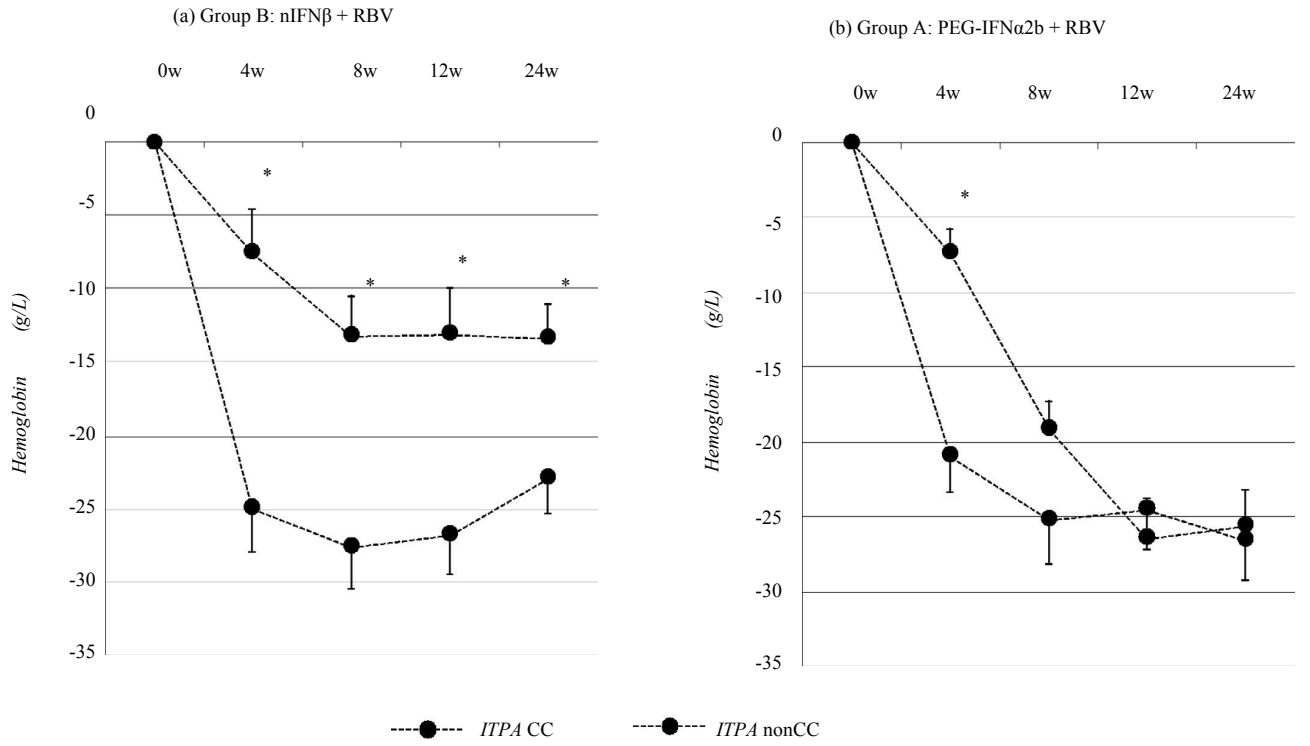

Figure 2: Decreases of the hemoglobin level by ITPA genotype.

PEG-IFNα is known to often cause and exacerbate psychological problems (the range was reported to be from 30 to 80%) [19,20]. The incidence of nIFNβ-induced psychological problems has been reported to be from 0 to 10% [9-11,21]. In this study, 38.3 % (23 0f 60) of the patients who received nIFNβ plus RBV treatment suffered depression before treatment, but all of them completed treatment without increasing antidepressants or reduction of nIFNβ. Of the patients who received PEG-IFNα2b and RBV treatment, 11.6% (7 of 60) developed depression during treatment. The difference in the frequency of nIFNβ-induced and PEG-IFNα-induced psychological problems may be related to the higher elevation of serum level of interleukin-1 receptor antagonist (IL-1Ra) with anti-inflammatory effects by nIFNβ than by PEG-IFNα. The ratio of interleukin-1β to IL-1Ra is maintained within normal range because IL-1Ra does not decrease when nIFNβ is used [22,23].

PEG-IFNα often causes cytopenia. This side effects often lead to decrease the treatment dosage. In this study, patients who underwent nIFNβ plus RBV treatment had an increased platelet count after week 8 of treatment. Moreover, the platelet count of patients with *ITPA* CC was higher than at baseline after week 4 of treatment. In contrast, the platelet count of patients who underwent treatment with PEG-IFNα2b and RBV decreased throughout treatment, regardless of *ITPA* genotype. Fewer patients who underwent nIFNβ plus RBV treatment had a decrease in hemoglobin level than did patients who underwent PEG-IFNα2b and RBV, even though the adherence rate to RBV was significantly higher for the patients treated with nIFNβ plus RBV than for those treated with PEG-IFNα2b and RBV. Although the mechanism of the platelet count increase of the patients who receive nIFNβ plus RBV treatment remains to be clarified, the physiological linkage of hematopoietic factors may explain this phenomenon. Thrombosis has been reported in patients with iron deficiency anemia and Bilic and Bilic reported that the amino acid sequence homology of thrombopoietin and erythropoietin might explain it [24-26]. From our results, the *ITPA* CC might be associated with the increase of platelet count during nIFNβ plus RBV treatment. Further studies will be necessary to clarify the relation between nIFNβ plus RBV treatment and changes of platelet count.

The histories of prior IFN treatment of patients of both groups were different. However, patients of groups B were considered to be less tolerant to IFN treatment than those of groups A, because the discontinuation rates of prior IFN treatment among groups B were higher than those among groups A. Thus, we did not consider that that difference might weaken our result that nIFNβ plus ribavirin treatment had enough tolerance.

Because patients must go to a hospital for treatment three times a week, nIFNβ is somewhat more inconvenient than PEG-IFNα. However, this inconvenience is offset by the milder and fewer nIFNβ-related side effects and the increased platelet count during treatment.

This study has some limitations. One is the small number of patients. Although the SVR rates were not statistically different between groups B and A, there is a probability of difference when the number of patients were more. Further study with more patients will be necessary. Another is that the *IL28B* genotype was not determined for some patients, so careful interpretation must be made of the evaluation of the influence of *IL28B* on the efficacy of both treatments. Further study to determine the *IL28B* of all patients is desirable. The final limitation is that the study was not of a randomized design. Unfortunately, for ethical reasons it is very difficult to conduct a randomized study in Japan.

In conclusion, nIFNβ plus RBV combination treatment is an optional treatment for chronic hepatitis C, especially for patients with depression or thrombopenia.

References

1. Hayashi J, Furusyo N, Ariyama I, Sawayama Y, Etoh Y, et al. (2000) A relationship between the evolution of hepatitis C virus variants, liver damage, and hepatocellular carcinoma in patients with hepatitis C viremia. J Infect Dis 181: 1523-1527.
2. Kanwal F, Hoang T, Kramer JR, Asch SM, Goetz MB, et al. (2011) Increasing prevalence of HCC and cirrhosis in patients with chronic hepatitis C virus infection. Gastroenterology 140: 1182-1188.
3. Mazzella G, Accogli E, Sottili S, Festi D, Orsini M, et al. (1996) Alpha interferon treatment may prevent hepatocellular carcinoma in HCV-related liver cirrhosis. J Hepatol 24: 141-147.
4. Ogawa E, Furusyo N, Kajiwara E, Takahashi K, Nomura H, et al. (2013) Efficacy of pegylated interferon alpha-2b and ribavirin treatment on the risk of hepatocellular carcinoma in patients with chronic hepatitis C: A prospective, multicenter study. J Hepatol 58: 495-501.
5. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, et al. (2002) Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N Engl J Med 347: 975-982.
6. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, et al. (2001) 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.
7. Schaefer M, Schmidt F, Folwaczny C, Lorenz R, Martin G, et al. (2003) Adherence and mental side effects during hepatitis C treatment with interferon alfa and ribavirin in psychiatric risk groups. Hepatology 37: 443-451.
8. Kainuma M, Furusyo N, Kajiwara E, Takahashi K, Nomura H, et al. (2010) Pegylated interferon a-2b plus ribavirin for older patients with chronic hepatitis C. World J Gastroenterol 16: 4400-4409.
9. Arase Y, Suzuki F, Akuta N, Sezaki H, Suzuki Y, et al. (2010) Efficacy and safety of combination therapy of natural human interferon beta and ribavirin in chronic hepatitis C patients with genotype 1b and high virus load. Inter Med 49: 957-963.
10. Arase Y, Suzuki F, Akuta N, Sezaki H, Suzuki Y, et al. (2010) Efficacy and safety of combination therapy of natural human interferon ß and ribavirin in chronic hepatitis C patients with genotype 2 and high virus load. Inter Med 49: 965-970.
11. Nomura H, Miyagi Y, Tanimoto H, Yamashita N, Oohashi S, et al. (2012) Occurrence of clinical depression during combination therapy with pegylated interferon alpha or natural human interferon beta plus ribavirin. Hepatol Res 42: 241-247.
12. Kumada H, Okanoue T, Onji M, Moriwaki H, Izumi N, et al. (2010) Guidelines for the treatment of chronic hepatitis and cirrhosis due to hepatitis C virus infection for the fiscal year 2008 in Japan. Hepatol Res 40: 8-13.
13. Ogawa E, Furusyo N, Toyoda K, Taniai H, Otaguro S, et al. (2010) Excellent superiority and specificity of COBAS TaqMan HCV assay in an early viral kinetic change during pegylated interferon alpha-2b plus ribavirin treatment. BMC Gastroenterol 10: 38.
14. [No authors listed] (1994) Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 20: 15-20.
15. Ahmed WH, Furusyo N, Zaky S, Eldin AS, Aboalam H, et al. (2013) Pre-treatment role of inosine triphosphate pyrophosphatase polymorphism for predicting anemia in Egyptian hepatitis C virus patients. World J Gastroenterol 19: 1387-1395.
16. Beck AT, Steer RA, Ball R, Ranieri W (1996) Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess 67: 588-597.
17. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28: 193-213.
18. Honda T, Katano Y, Shimizu J, Ishizu Y, Doizaki M, et al. (2010) Efficacy of peginterferon-alpha-2b plus ribavirin in patients aged 65 years and older with chronic hepatitis C. Liver Int 30: 527-537.
19. Evon DM, Ramcharran D, Belle SH, Terrault NA, Fontana RJ, et al. (2009) Prospective analysis of depression during peginterferon and ribavirin therapy of chronic hepatitis C: results of the Virahep-C study. Am J Gastroenterol 104: 2949-2958.
20. Lang JP, Melin P, Ouzan D, Rotily M, Fontanges T, et al. (2010) Pegylated interferon-alpha2b plus ribavirin therapy in patients with hepatitis C and psychiatric disorders: results of a cohort study. Antivir Ther 15: 599-606.
21. Furusyo N, Hayashi J, Ohmiya M, Sawayama Y, Kawakami Y, et al. (1999) Differences between interferon-alpha and -beta treatment for patients with chronic hepatitis C virus infection. Dig Dis Sci 44: 608-617.
22. Nicoletti F, Patti F, DiMarco R, Zaccone P, Nicoletti A, et al. (1996) Circulating serum levels of IL-1Ra in patients with relapsing remitting multiple sclerosis are normal during remission phases but significantly increased either during exacerbations or in response to IFN-beta treatments. Cytokine 8: 395-400.
23. Loftis JM, Huckans M, Ruimy S, Hinrichs DJ, Hauser P (2008) Depressive symptoms in patients with chronic hepatitis C are correlated with elevated plasma levels of interleukin-1beta and tumor necrosis factor-alpha. Neurosci Lett 430: 264-268.
24. Schloesser LL, Kipp MA, Wenzel FJ (1965) Thrombocytosis in iron-deficiency anemia. J Lab Clin Med 66: 107-114.
25. Akan H, Güven N, Aydogdu I, Arat M, Beksaç M, et al. (2000) Thrombopoietic cytokines in patients with iron deficiency anemia with or without thrombocytosis. Acta Haematol 103: 152-156.
26. Bilic E, Bilic E (2003) Amino acid sequence homology of thrombopoietin and erythropoietin may explain thrombocytosis in children with iron deficiency anemia. J Pediatr Hematol Oncol 25: 675-676.