

Pegylated interferon α -2b plus ribavirin for older patients with chronic hepatitis C

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Received: February 18, 2010 Revised: April 19, 2010

Accepted: April 26, 2010

Published online: September 21, 2010

Abstract

AIM: To analyze the efficacy and safety of a combination therapy of pegylated interferon (PEG-IFN) α -2b plus ribavirin (RBV) in older Japanese patients (65 years or older) infected with hepatitis C virus (HCV).

METHODS: This multicenter study included 938 patients with HCV genotype 1 who received 1.5 μ g/kg per week PEG-IFN α -2b plus RBV 600-1000 mg/d for 48 wk and 313 HCV genotype 2 patients who received this treatment for 24 wk.

RESULTS: At 24 wk after the end of combination therapy, the overall sustained virological response (SVR) for genotypes 1 and 2 were 40.7% and 79.6%, respectively. The SVR rate decreased significantly with age in each genotype, and was markedly reduced in genotype 1 ($P < 0.001$). Moreover, the SVR was significantly higher in patients with genotype 1 who were less than 65 years (47.3% of 685) than in those 65 years or older (22.9% of 253) ($P < 0.001$) and was higher in patients with genotype 2 who were less than 65 years (82.9% of 252) than in those 65 years or older (65.6% of 61) ($P = 0.004$). When patients received a dosage at least 80% or more of the target dosage of PEG-IFN α -2b and 60% or more of the target dosage of RBV, the SVR rate significantly increased to 66.5% in patients less than 65 years and to 45.2% in those 65 years or older ($P <$

0.001). Adverse effects resulted in treatment discontinuation more often in patients with genotype 1 (14.4%) than in patients with genotype 2 (7.3%), especially by patients 65 years or older (24.1%).

CONCLUSION: PEG-IFN α -2b plus RBV treatment was effective in chronic hepatitis C patients 65 years or older who completed treatment with at least the minimum acceptable treatment dosage.

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Key words: Hepatitis C virus; Gerontology; Pegylated interferon; Ribavirin

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Kainuma M, Furusyo N, Kajiwara E, Takahashi K, Nomura H, Tanabe Y, Satoh T, Maruyama T, Nakamura M, Kotoh K, Azuma K, Shimono J, Shimoda S, Hayashi J, The Kyushu University Liver Disease Study Group. Pegylated interferon α -2b plus ribavirin for older patients with chronic hepatitis C. *World J Gastroenterol* 2010; 16(35): 4400-4409 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v16/i35/4400.htm> DOI: <http://dx.doi.org/10.3748/wjg.v16.i35.4400>

INTRODUCTION

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, affecting 170 million individuals worldwide^[1]. It is well known that patients with chronic hepatitis C eventually develop hepatocellular carcinoma (HCC)^[2]. Previous studies have made clear that interferon (IFN) treatment is effective for eliminating HCV^[3,4] and that it significantly reduces the progression of liver fibrosis and the risk of HCC^[5,6]. Antiviral treatment for chronic hepatitis C has greatly improved, and the combination treatment of pegylated (PEG)-IFN α -2b plus ribavirin (RBV) has been approved and recommended in Japan since 2004, as the first choice for chronic hepatitis C. This combination treatment attained a sustained virological response (SVR) rate of 50%-60% for genotype 1 in the United States and Europe^[7]. However, SVR was relatively low (42.4%) in Japan^[8], where chronic hepatitis C patients are older, indicating that older patients did not respond well to IFN treatment^[9]. Moreover, the combination treatment was associated with more adverse effects than IFN monotherapy^[7,10]. Older patients who have decreased cardiovascular, pulmonary and renal function have a higher incidence of adverse effects than younger patients. The rate of discontinuation due to adverse effects was reported to be significantly higher in patients aged 65 years or more than in those less than 65 years^[11]. Older patients with HCV infection are at risk for progressive liver disease. It was reported that clearance of HCV after IFN therapy significantly reduces the incidence of HCC and death in older chronic hepatitis C patients^[6,12]. Ikeda *et al*^[13] dem-

onstrated that IFN treatment is needed for 65-70-year-old patients with chronic hepatitis C to prevent the occurrence of HCC. We also consider older patients to be acceptable candidates for antiviral treatment to prevent the development of HCC, and previously reported that monotherapy with natural IFN α was not effective in older patients^[9]. Therefore, in an attempt to ameliorate these problems, we decided to treat older patients with a combination of PEG-IFN plus RBV therapy.

Little data concerning the response and safety of this combination treatment in a large number of older patients with chronic HCV infection has been published. A multicenter study of the efficacy and safety of antiviral treatments for Japanese patients with chronic liver disease, the Kyushu University Liver Disease Study (KULDS), was launched in 2003^[8,14]. The present prospective study was carried out to analyze the efficacy and safety of the combination treatment of PEG-IFN α -2b plus RBV in older patients.

MATERIALS AND METHODS

Patients

Treatment of chronic hepatitis C with a combination of PEG-IFN α -2b plus RBV was accepted by the Japanese Ministry of Health in October, 2004. We used this combination treatment from December 2004 to July 2008, and enrolled chronic hepatitis C patients with exclusion criteria which included: (1) clinical or biochemical evidence of hepatic decompensation, advanced cirrhosis identified by bleeding, high-risk esophageal varices, history of gastrointestinal bleeding, ascites, encephalopathy, or HCC; (2) hemoglobin level < 11.5 g/L, white blood cell count < 3×10^9 /L, and platelet count < 50×10^9 /L; (3) concomitant liver disease other than hepatitis C (hepatitis B surface antigen positive or HIV positive); (4) excessive active alcohol consumption > 60 g/d or drug abuse; (5) severe psychiatric disease; or (6) antiviral or corticosteroid treatment within 12 mo prior to enrollment. Patients who fulfilled the above criteria were recruited at Kyushu University Hospital and 32 affiliated hospitals in the northern Kyushu area of Japan. We have treated 2270 Japanese patients aged 18 years or older with PEG-IFN α -2b plus RBV. All patients who were positive for both antibody to HCV and HCV RNA for over 6 mo were enrolled in KULDS. Three months before the start of treatment and every 3 mo during the treatment period, each patient was tested for α -fetoprotein (AFP) and had an abdominal ultrasonographic examination. If an abnormal AFP level of 40 ng/mL and/or focal lesions on ultrasonographic examination were found at any testing, further testing for HCC was carried out, which included dynamic computed tomography, and angiography. Patients confirmed to have HCC within 3 mo after starting treatment were excluded from this study ($n = 14$). Of 2270 patients, 1021 were currently under combination treatment or we were not yet able to judge the effect of the combination treatment. This left the data of 1251 patients (938 with genotype 1 and 313 with genotype 2) available for analysis.

Table 1 Characteristics of 938 chronic hepatitis C genotype 1 patients treated with a combination of pegylated interferon plus ribavirin according to age (mean \pm SD)

	Group A (age < 65 yr) (n = 685)	Group B (age \geq 65 yr) (n = 253)	P-value
Age (yr)	53.1 \pm 8.9	68.6 \pm 3.1	< 0.001
Male/female	374/311	122/131	0.090
Body mass index (kg/m ²)	23.7 \pm 3.3	22.8 \pm 2.7	< 0.001
Prior IFN monotherapy, n (%)	163 (23.8)	76 (30.0)	0.052
Prior combined IFN plus RBV treatment, n (%)	51 (7.4)	20 (7.9)	< 0.001
Alanine aminotransferase (IU/L)	80.2 \pm 62.0	67.9 \pm 46.6	0.004
γ -glutamyltranspeptidase (IU/L)	60.2 \pm 56.6	57.1 \pm 49.2	0.708
Albumin (g/dL)	4.1 \pm 0.4	4.0 \pm 0.4	< 0.001
White blood cell count (/mm ³)	5200.0 \pm 1476.7	4756.3 \pm 1458.9	< 0.001
Hemoglobin (g/dL)	14.1 \pm 1.4	13.5 \pm 1.4	< 0.001
Platelet count (10 ⁹ /L)	16.6 \pm 5.3	15.0 \pm 5.2	< 0.001
Creatinine (mg/dL)	0.7 \pm 0.6	0.8 \pm 1.4	0.107
Creatinine clearance (mL/min)	105.5 \pm 28.7	75.8 \pm 17.5	< 0.001
Serum HCV-RNA level (kIU/mL)	1776.1 \pm 1500.0	1986.9 \pm 1604.5	0.125
Histological fibrosis			0.008
F0/F1/F2/F3/F4	36/155/121/61/30	9/46/49/31/17	

IFN: Interferon; RBV: Ribavirin; HCV: Hepatitis C virus.

Table 2 Characteristics of 313 chronic hepatitis C genotype 2 patients treated with a combination of pegylated interferon plus ribavirin according to age (mean \pm SD)

	Group C (age < 65 yr) (n = 252)	Group D (age \geq 65 yr) (n = 61)	P-value
Age (yr)	47.7 \pm 10.4	69.2 \pm 3.4	< 0.001
Male/female	124/128	28/33	0.671
Body mass index (kg/m ²)	23.1 \pm 3.5	22.8 \pm 2.9	0.577
Prior IFN monotherapy, n (%)	47 (18.7)	16 (26.2)	< 0.001
Prior combined IFN plus RBV treatment, n (%)	5 (2.0)	4 (6.6)	0.056
Alanine aminotransferase (IU/L)	79.9 \pm 78.7	68.9 \pm 52.9	0.821
γ -glutamyltranspeptidase (IU/L)	55.8 \pm 64.7	44.3 \pm 34.7	0.937
Albumin (g/dL)	4.2 \pm 0.4	3.9 \pm 0.5	< 0.001
White blood cell count (/mm ³)	5276.3 \pm 1636.3	4958.0 \pm 1495.6	0.005
Hemoglobin (g/dL)	14.1 \pm 1.4	13.4 \pm 1.3	< 0.001
Platelet count (10 ⁹ /L)	18.9 \pm 6.3	15.6 \pm 4.7	< 0.001
Creatinine (mg/dL)	0.8 \pm 1.5	0.7 \pm 0.2	0.581
Creatinine clearance (mL/min)	112.1 \pm 31.4	74.6 \pm 17.2	< 0.001
Serum HCV-RNA level (kIU/mL)	1588.3 \pm 1628.7	1195.4 \pm 1645.5	0.038
Histological fibrosis			< 0.001
F0/F1/F2/F3/F4	30/77/39/10/10	1/21/9/2/12	

IFN: Interferon; RBV: Ribavirin; HCV: Hepatitis C virus.

Informed consent was obtained from all patients before enrollment in this study. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization of guidelines for good clinical practice.

Table 1 (genotype 1) and Table 2 (genotype 2) show the baseline characteristics of the enrolled patients, who were further classified into four groups according to age and genotype status: group A, genotype 1 aged less than 65 years ($n = 685$); group B, genotype 1 aged 65 years or older ($n = 253$); group C, genotype 2 aged less than 65 years ($n = 252$); and group D, genotype 2 aged 65 or older ($n = 61$). In group B, body mass index, prior combined IFN plus RBV treatment, alanine aminotransferase, albumin, white blood cell count, hemoglobin, platelet count, and creatinine clearance calculated using the Modification of Diet in Renal Disease equation^[15] were significantly lower than in

group A ($P < 0.010$). In group D, albumin, hemoglobin, platelet count, creatinine clearance and serum HCV RNA level were significantly lower than in group C ($P < 0.010$). The percentage of patients with platelet counts below $10 \times 10^9/L$ was significantly higher in group B (36 of 253, 14.2%) than in group A (56 of 685, 8.2%) ($P = 0.006$), however, there was no significant difference between group C (16 of 252, 6.3%) and group D (7 of 61, 11.5%).

Liver histology

Liver biopsy was performed in 555 patients (59.2%) with genotype 1 and 209 patients (66.8%) with genotype 2. The other patients refused liver biopsy. Fibrosis was staged on a 0-4 scale as follows: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, F4 = cirrhosis. Liver fibrosis was more advanced in group B than in group A

and was more advanced in group D than in group C ($P = 0.008$, $P < 0.001$, respectively).

Treatment regimen

All patients were treated with a weight-based, 1.5 $\mu\text{g}/\text{kg}$ weekly dose of subcutaneous PEG-IFN α -2b (PegIntron, Schering-Plough, Osaka, Japan), in combination with RBV (Rebetol, Schering-Plough), which was given orally at a daily dose of 600-1000 mg based on body weight (600 mg for patients weighing less than 60 kg, 800 mg for those weighing 60-80 kg, and 1000 mg for those weighing 80 kg or over). The length of treatment was 48 wk for patients with HCV genotype 1 and 24 wk for patients with genotype 2. The above duration and dosage are those approved by the Japanese Ministry of Health, Labor and Welfare. Patients were considered to have RBV-induced anemia if the hemoglobin level decreased to less than 100 g/L. In such cases, a reduction in the dose of RBV was required. Patients aged 65 years or older had a significantly higher frequency of RBV dose reduction during the treatment period than those aged less than 65 years old (HCV genotype 1: group A *vs* group B, 41.2% *vs* 49.0%, $P = 0.032$, genotype 2: group C *vs* group D, 28.6% *vs* 54.1%, $P < 0.001$). Some patients also had PEG-IFN α -2b-induced psychological adverse effects or a decrease in white blood cell and platelet counts. In such cases, a reduction in the dosage of PEG-IFN α -2b was required. Both PEG-IFN α -2b and RBV were discontinued if the hemoglobin level, white blood cell count, or platelet count fell below 85 g/L, $1 \times 10^9/\text{L}$, and $25 \times 10^9/\text{L}$, respectively. The treatment was discontinued if severe general fatigue, hyperthyroidism, interstitial pneumonia, or severe hemolytic disorders developed, continuation of treatment was judged not to be possible by the attending physician, or if the patient desired discontinuation of treatment.

Determination of baseline HCV RNA level and HCV genotype

The pretreatment, baseline, serum HCV RNA level was measured by a quantitative HCV RNA polymerase chain reaction (PCR) assay (COBAS Amplicor HCV Monitor Test v 2.0 using the 10-fold dilution method; Roche Diagnostics, Tokyo, Japan), which has a lower limit of quantitation of 5000 IU (13 500 copies)/mL (5 kIU/mL) and an outer limit of quantitation of 5 100 000 IU/mL (5100 kIU/mL). The HCV genotype was determined by type-specific primers of the core region of the HCV genome. The protocol for genotyping was carried out as previously described^[3].

Efficacy of treatment

End of treatment (EOT) response and SVR were defined as serum HCV RNA undetectable at the end of treatment and at 24-wk follow-up after the end of treatment, respectively. EOT response and SVR were defined as non-detectable HCV-RNA as measured by qualitative COBAS Amplicor HCV Monitor Test v 2.0, with the results labeled as positive or negative. The lower limit of detection was 50 IU/mL (0.5 kIU/mL). The analysis of EOT and SVR was performed on an intention-to-treat basis.

Statistical analysis

Continuous data are expressed as mean \pm SD. The statistics were carried out using a commercially available software package (BMDP Statistical Software Inc., Los Angeles, CA, USA) for the IBM 3090 system computer. The χ^2 test, Fisher's exact test and Kruskal-Wallis test were used to determine the differences in baseline clinical characteristics, safety, efficacy of the combination therapy, adherence to the total dose, and the association between the adherence and SVR. Logistic regression analysis was used to identify the association between age and SVR. A $P < 0.05$ was considered significant.

RESULTS

EOT response rate by intention-to-treat analysis

Among patients with genotype 1, the EOT response rate was significantly higher in group A (497 of 685, 72.5%) than in group B (129 of 253, 45.0%) ($P < 0.001$). Among patients with genotype 2, there was no significant difference between groups C (239 of 252, 94.8%) and D (55 of 61, 90.1%).

SVR rate by intention-to-treat analysis

Of 1251 patients, 631 (50.4%) achieved SVR in the intention-to-treat analysis. The SVR rate was significantly higher for genotype 2 (249 of 313, 79.6%) than for genotype 1 patients (382 of 938, 40.7%) ($P < 0.001$). Among patients with genotype 1, the SVR rate was significantly higher in group A (324 of 685, 47.3%) than in group B (58 of 253, 22.9%) ($P < 0.001$). Among patients with genotype 2, SVR was also significantly higher in group C (209 of 252, 82.9%) than in group D (40 of 61, 65.6%) ($P = 0.004$). The rate of SVR was significantly higher for females (113 of 128, 88.3%) than for males (96 of 124, 77.4%) in group C only (Figure 1). Furthermore, we analyzed whether or not the SVR rate differed according to the age at which the combination treatment of PEG-IFN α -2b plus RBV was started. The results showed that the SVR rate decreased significantly with age for both genotype 1 and 2. SVR was achieved by 5.6%-26.3% of genotype 1 patients aged 70 years or older, and by 57.1%-100% of genotype 2 patients aged 70 years or older (Figure 2).

We previously reported a minimum acceptable dose of at least 80% or more of the target dosage of PEG-IFN α -2b and 60% or more of the target dosage of RBV for the successful treatment of Japanese patients with genotype 1^[8]. Therefore, we analyzed the SVR rates in patients with genotype 1 by the dosage they actually received during treatment (a total dose of at least 80% or more of PEG-IFN α -2b and 60% or more of RBV) (Table 3). The number who received at least this minimum acceptable dosage during treatment were 278 (40.6%) of 685 patients in group A and 62 (24.5%) of 253 in group B, significantly lower in group B than in group A ($P < 0.001$). Compared with patients who received less than the minimum acceptable dosage, in patients who received at least this minimum dosage, the SVR rates increased from 34.2% to 66.5% in group A patients and from 15.7% to 45.2%

Table 3 The comparison of the rate of sustained virological response of patients with genotype 1 receiving a dose of 80% or more of pegylated interferon α -2b plus 60% or more of ribavirin and the reduced dosage group *n* (%)

	Male		Female		Total	
	<i>n</i>	SVR	<i>n</i>	SVR	<i>n</i>	SVR
Group A						
Minimum acceptable	168	116 (69.0)	110	69 (62.7)	278	185 (66.5)
Reduced	206	73 (35.4)	201	66 (32.8)	407	139 (34.2)
Total	374	189 (50.5)	311	135 (43.4)	685	324 (47.3)
Group B						
Minimum acceptable	31	15 (48.4)	31	13 (41.9)	62	28 (45.2)
Reduced	91	18 (19.8)	100	12 (12.0)	191	30 (15.7)
Total	122	33 (27.0)	131	25 (19.1)	253	58 (22.9)

Minimum acceptable: patients who received 80% or more of the target dose of pegylated interferon (IFN) α -2b and 60% or more of ribavirin (RBV). Reduced: Patients who received less than 80% of pegylated IFN α -2b and less than 60% of RBV. SVR: Sustained virological response.

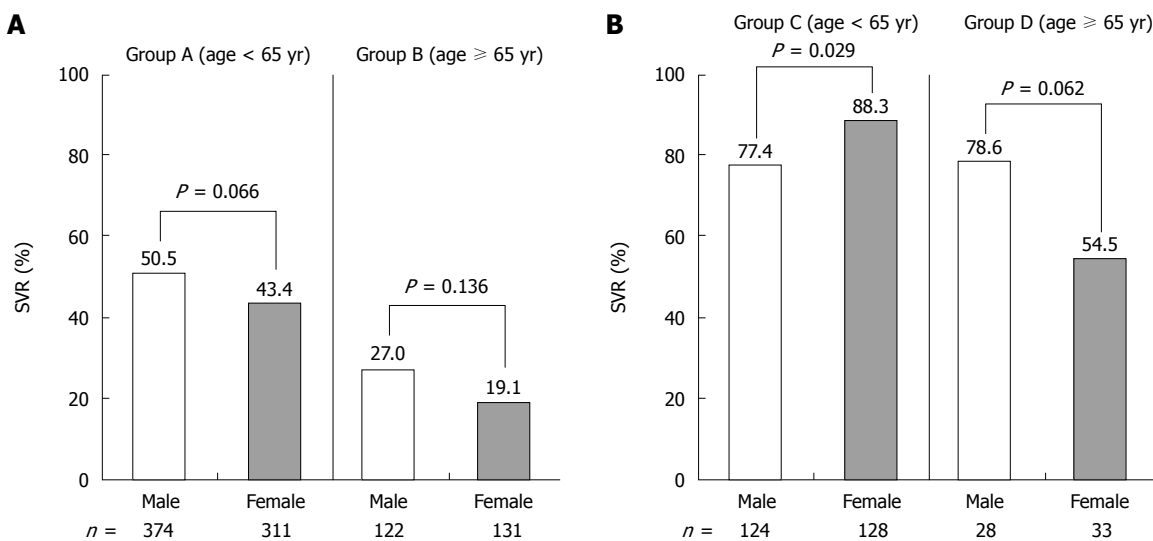


Figure 1 Virological response to the combination treatment by age and sex of patients with genotype 1 (A) and genotype 2 (B). SVR: Sustained virological response.

($P < 0.001$) in group B patients. No significant difference between groups C and D was observed. On comparing patients whose platelet count was under $10 \times 10^{10}/L$, the SVR rate for genotype 1 was significantly lower in group B (2 of 36, 5.6%) than in group A (16 of 56, 28.6%) ($P < 0.001$). Among the patients with genotype 2, SVR was not significantly different between group C (9 of 16, 56.3%) and group D (2 of 7, 28.6%).

In a comparison of the SVR rate in patients with or without one or more previous courses of IFN plus RBV, there was no significant difference between the genotypes (genotype 1: 118 of 310, 38.1% *vs* 264 of 628, 42.0%, genotype 2: 44 of 72, 61.1% *vs* 141 of 241, 58.5%). Furthermore, we compared the EOT response rate and SVR rate of cirrhosis patients whose liver fibrosis was F4, and found no significant difference between groups A (EOT: 16 of 30, 53.3%, SVR: 7 of 30, 23.3%) and B (EOT: 6 of 17, 35.3%, SVR: 2 of 17, 11.8%). In addition, no significant difference was found between groups C (EOT: 8 of 10, 80.0%, SVR: 6 of 10, 60.0%) and D (EOT: 9 of 12, 75.0%, SVR: 5 of 12, 41.7%).

Discontinuation of PEG-IFN α -2b plus RBV treatment and adverse effects

Of 1251 patients, 314 (25.1%) did not complete PEG-IFN α -2b plus RBV treatment due to adverse effects or other reasons. The discontinuation rate was significantly higher in patients with genotype 1 (273 of 938, 29.1%) than in those with genotype 2 (41 of 313, 13.1%) ($P < 0.001$) (Tables 4 and 5). Furthermore, the rate of discontinuation due to adverse effects was significantly higher in patients with genotype 1 (135 of 938, 14.4%) than in those with genotype 2 (23 of 313, 7.3%) ($P < 0.010$). The rates of discontinuation due to lack of treatment efficacy and for economic reasons (loss of job, inability to pay the medical costs) were also significantly higher in patients with genotype 1 (55 of 938, 5.9%, 15 of 938, 1.6%) than in those with genotype 2 (1 of 313, 0.3%, 0 of 938, 0%) ($P < 0.001$ and $P = 0.025$, respectively).

For genotype 1 patients, the discontinuation rate was significantly higher in group B (106 of 253, 42.9%) than in group A (167 of 685, 24.4%) ($P < 0.001$), and the rate of discontinuation due to adverse effects was also significantly

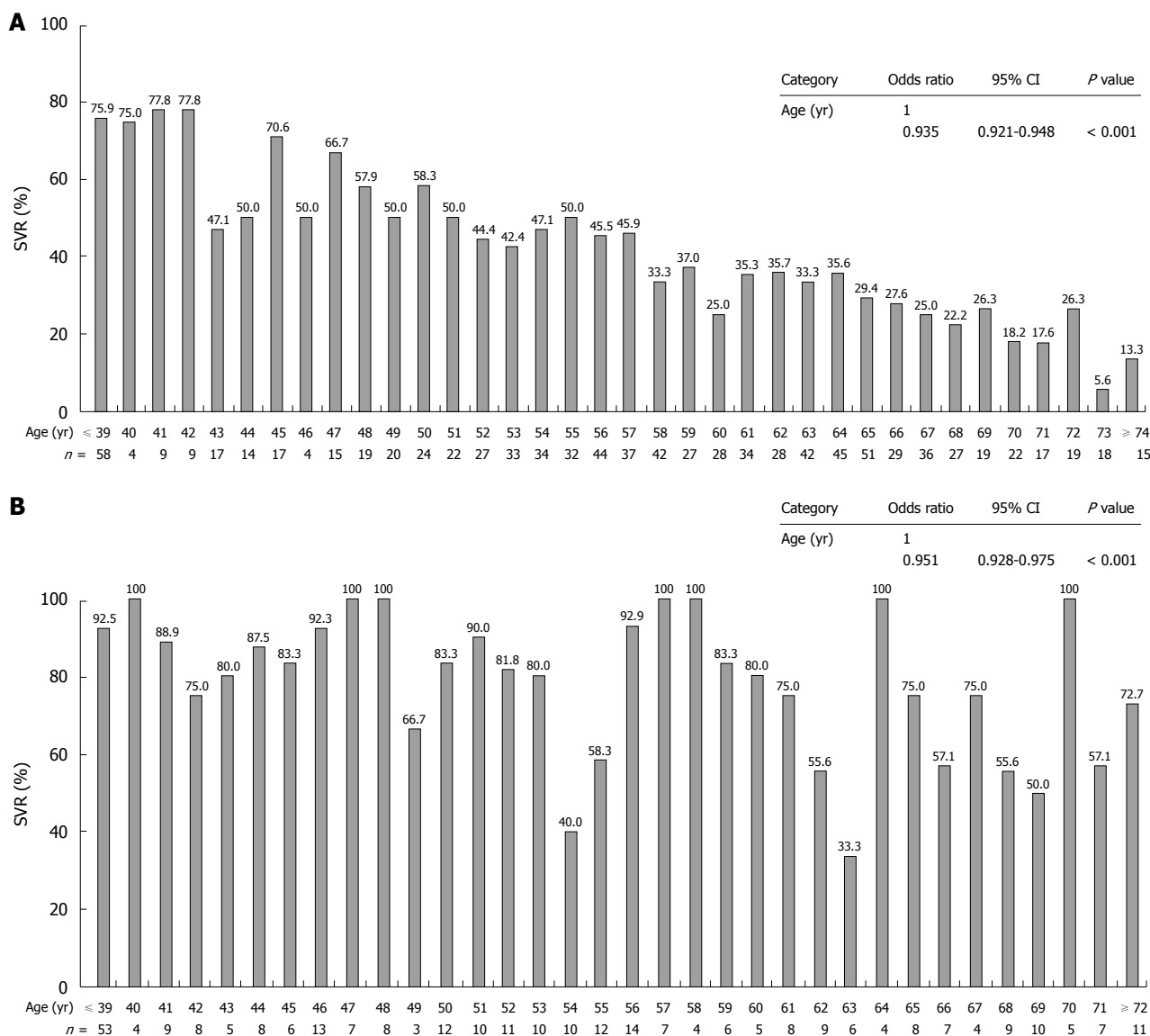


Figure 2 Virological response to the combination treatment by age of patients with genotype 1 (A) and genotype 2 (B). SVR: Sustained virological response; CI: Confidence interval.

higher in group B (61 of 253, 24.1%) than in group A (74 of 685, 10.8%) ($P < 0.001$). General fatigue was the most frequent adverse effect, and was significantly more frequent in group B than in group A ($P < 0.001$). However, in these group 1 patients, RBV was reduced due to anemia in 12.5% (3 of 24) of group A and in 30.4% (7 of 23) of group B. Furthermore, rash and thrombocytopenia were significantly more frequent in group B than in group A ($P = 0.014$ and $P = 0.007$, respectively). In group A, depression was significantly more frequent in females than in males ($P = 0.012$). In genotype 2 patients, treatment discontinuation did not differ between group C (33 of 252, 13.1%) and group D (8 of 61, 13.1%), and the rate of discontinuation due to adverse effects did not differ between these groups (17 of 252, 6.7%, 6 of 61, 9.8%, respectively).

The mean time to discontinuation in group A (21.6 ± 11.9 wk) was not significantly different from group B (21.5 ± 12.6 wk), and the mean time in group C (11.0 ± 6.8 wk) was also not significantly different from group D ($11.6 \pm$

6.0 wk). There was no significant difference between male and female patients in each group (male: 21.0 ± 12.4 vs female: 22.1 ± 11.8 in group 1, male: 11.3 ± 7.1 vs female: 10.9 ± 6.1 in group 2).

HCC was not seen in genotype 2 patients; only in patients with genotype 1 (29.5 ± 9.9 wk) and was more frequent in group B (5 of 253, 2.0%) than in group A (2 of 685, 0.3%) ($P = 0.008$).

DISCUSSION

In a large, national, multicenter Greek study involving 993 treated and 734 untreated patients with chronic hepatitis C, patients with cirrhosis, showed a protective effect of treatment even among those without SVR. For patients without cirrhosis, the beneficial effect of IFN α treatment was particularly evident in older patients; patients with the worst prognosis if left untreated. Therefore, IFN α -based treatment should be offered to older persons, as these are

Table 4 Reasons for discontinuation of pegylated interferon plus ribavirin treatment by hepatitis C virus genotype 1 patients

	Group A (age < 65 yr)		Group B (age ≥ 65 yr)		Total
	Male (n = 374)	Female (n = 311)	Male (n = 122)	Female (n = 131)	
Discontinued number	101	66	52	54	273
Adverse effects	43	31	33	28	135
General fatigue	17	7	12	11	47
Depression	3	11	4	5	23
Appetite loss	1	0	1	0	2
Rash	3	2	3	4	12
Encephalopathy	1	0	0	0	1
Neutropenia	2	0	0	0	2
Anemia	3	2	4	1	10
Thrombocytopenia	1	0	3	1	5
Elevation of ALT	1	0	0	0	1
Hyperthyroidism	3	2	0	1	6
Hypothyroidism	0	1	0	0	1
Retinopathy	1	0	1	0	2
Interstitial pneumonia	2	0	1	1	4
Pulmonary disease (others) ¹	0	1	1	1	3
Psychoneurotic disorder ²	2	0	2	0	4
Nervous disease ³	1	1	0	1	3
Autoimmune disease ⁴	0	2	0	1	3
Metabolic disease ⁵	0	2	0	0	2
Digestive disorder ⁶	2	0	1	1	4
Hepatocellular carcinoma	2	0	4	1	7
Malignancy (extra-liver)	0	1	1	0	2
No effect of treatment	22	18	7	8	55
Economic problem	9	3	0	3	15
Others ⁷	25	13	7	14	59

¹Includes pulmonary tuberculosis (n = 1), pneumonia (n = 1), tuberculous pleuritis (n = 1); ²Includes psychiatric disorder (n = 2), disquiet (n = 1), insomnia (n = 1); ³Includes nerve paralysis (n = 1), cerebral infarction (n = 1); ⁴Includes rheumatoid arthritis (n = 2), myasthenia gravis (n = 1); ⁵Includes diabetes mellitus (n = 1), hypertriglycemia (n = 1); ⁶Includes cholecystitis (n = 3), pancreatitis (n = 1); ⁷Includes 25, 13, 6 and 13 drop-outs from groups A, B, C and D, respectively: One for excessive alcohol consumption in group C and one was nursing in group D. ALT: Alanine aminotransferase.

the patients with the greatest potential benefit and may achieve SVR^[16]. In Japan, the prevalence of chronic HCV infection increases with age, however, the optimal management of older patients has not yet been accurately defined. Whether or not to treat patients older than 65 years with antiviral treatment is highly debated, especially in terms of cost/benefit ratio. In addition, the natural history of chronic hepatitis C in elderly patients is not accurately known, as the presence of comorbidity can affect illness progression and life expectancy. HCV became more prevalent in Japan decades before the United States^[17]. Japanese patients with chronic hepatitis C treated with IFN are currently 10 to 15 years older than corresponding patients in the United States and European countries, where patients treated with antiviral treatment tend to average 45 years of age^[18-20]. Therefore, our results can serve as a world-wide model for the treatment of older chronic hepatitis C patients.

It has been well documented that the combination therapy of PEG-IFN α -2b plus RBV is more effective than previous IFN monotherapy in chronic hepatitis C patients^[7,8]. There have been four studies on the efficacy of PEG-IFN plus RBV therapy in patients 65 years or older with genotype 1, which revealed low rates of SVR (31.1%-51.9%)^[21-24]. However, these studies were too small (11-93 patients) for conclusive recommendations to be made. Because the present study was a large multicenter

design, it is useful for clarifying the efficacy and safety of PEG-IFN plus RBV combination therapy in older patients. The present study confirmed the results of our previous study which showed that the SVR rate was significantly higher for genotype 2 than for genotype 1 patients^[8]. Another important result was that the ability to take at least a minimum acceptable dosage during treatment increased the SVR rate by about three times in older patients with genotype 1. This result also confirmed previous studies which indicated the importance of giving at least the minimum acceptable treatment dosage in patients infected with HCV genotype 1, especially older patients^[23,24].

Secondly, we compared discontinuation of treatment by genotype and sex. In genotype 1 patients, adverse effects were seen more often in older than in younger patients. This was the most important reason why the rate of treatment discontinuation was higher in older than in younger patients, and affected the outcome of PEG-IFN α -2b plus RBV combination therapy. General fatigue was the most common adverse effect in older patients. Because older patients often have impaired renal function, they have increased blood levels of RBV^[25,26]. They are also inclined to be anemic and to have general fatigue. However, only a small number of older patients in the present study had reduced RBV due to anemia. Therefore, general fatigue is probably a direct adverse effect of PEG-IFN α -2b. We previously reported that herbal medicine

Table 5 Reasons for discontinuation of pegylated interferon plus ribavirin treatment by hepatitis C virus genotype 2 patients

	Group C (age < 65 yr)		Group D (age ≥ 65 yr)		Total
	Male (n = 124)	Female (n = 128)	Male (n = 28)	Female (n = 33)	
Discontinued number	18	15	4	4	41
Adverse effects	6	11	3	3	23
General fatigue	1	3	1	0	5
Depression	0	2	0	0	2
Appetite loss	0	0	0	0	0
Rash	2	1	0	2	5
Encephalopathy	0	0	0	1	1
Neutropenia	0	2	0	0	2
Anemia	0	0	2	0	2
Thrombocytopenia	2	0	0	0	2
Elevation of ALT	0	0	0	0	0
Hyperthyroidism	0	1	0	0	1
Hypothyroidism	0	1	0	0	1
Retinopathy	0	0	0	0	0
Interstitial pneumonia	0	0	0	0	0
Pulmonary disease(others)	0	0	0	0	0
Psychoneurotic disorder	0	0	0	0	0
Nervous disease ¹	1	1	0	0	2
Autoimmune disease	0	0	0	0	0
Metabolic disease	0	0	0	0	0
Digestive disorder	0	0	0	0	0
Hepatocellular carcinoma	0	0	0	0	0
Malignancy (extra-liver)	1	0	0	0	1
No effect of treatment	1	0	0	0	1
Economic problem	0	0	0	0	0
Others ²	10	4	1	1	16

¹Includes nerve paralysis (n = 1), tetany (n = 1); ²All patients were drop out. ALT: Alanine aminotransferase.

relieved the adverse effects of IFN, including general fatigue^[27]. Herbal medicine may be useful for mitigating general fatigue during PEG-IFN α -2b plus RBV combination treatment, especially in older patients.

The rate of discontinuation was lower in patients with genotype 2 than in patients with genotype 1, and there was no difference between the older and the younger patients with genotype 2. These results are possibly a consequence of the shorter term of treatment in genotype 2 and the many genotype 1 patients who discontinued due to lack of efficacy.

Two of the characteristics of older patients in the present study were that both hemoglobin and platelet count were significantly lower than in younger patients. The SVR rate was significantly lower when the platelet count was less than $10 \times 10^{10}/L$. Furthermore, the older genotype 1 patients were often forced to discontinue treatment due to thrombocytopenia and the occurrence of HCC. These findings appear to result from advanced liver fibrosis in older chronic hepatitis C patients. Therefore, the possibility of HCC during long-term IFN treatment in older patients must be considered.

We previously reported that older female patients had a low response to IFN- α monotherapy^[9], and other investigators have reported that older female patients have a poor response to PEG-IFN α -2b plus RBV^[22,28]. Although our data showed that sex was not related to SVR, the reason for this finding was not fully elucidated. In any case, studies have conclusively shown that it is important to begin treatment with PEG-IFN α -2b plus RBV combi-

nation therapy as soon as possible. Our data suggest that age may be a more important factor than sex for increasing the rate of SVR. Resistance to treatment in older patients may be due to IFN-immunomodulation, advanced liver fibrosis, or reduced dosage.

To maximize adherence to the optimal treatment regimen, the treatment schedule can be modified or other therapeutic modalities added, such as hematopoietic growth factors^[29] or the new thrombopoietin-receptor agonist, eltrombopag, for the antiviral treatment of older patients with chronic hepatitis C^[30]. A further individualized treatment protocol based on viral kinetics might be more practical^[31].

In conclusion, PEG-IFN α -2b plus RBV treatment was effective in the treatment of older chronic hepatitis C patients when they received at least the minimum acceptable treatment dosage. However, there were frequent adverse effects and treatment discontinuation. It is necessary to control for adverse effects that might interrupt treatment and to begin this combination therapy as soon as possible, especially in older patients.

ACKNOWLEDGMENTS

We greatly thank Drs. Yasunori Sawayama, Masayuki Murata, Shigeru Otaguro, Hiroaki Taniai, Eiichi Ogawa, Kazuhiro Toyoda, Haru Mukae, Tsunehisa Koga, Kunimitsu Eiraku, Takeshi Ihara, Hiroaki Ikezaki and Takeo Hayashi of our department for their clinical and research assistance with the present study.

COMMENTS

Background

Whether or not to treat patients older than 65 years with antiviral treatment is highly debated, especially in terms of cost/benefit ratio. However, there is little data concerning the response and safety of combination treatment for a large number of older patients with chronic hepatitis C virus infection. Therefore, in an attempt to ameliorate these problems, the authors decided to treat older patients with pegylated interferon (PEG-IFN) α -2b plus ribavirin (RBV) combination therapy.

Research frontiers

The combination treatment of PEG-IFN α -2b plus RBV improved the sustained virological response rate in chronic hepatitis C patients. However, the current issue is whether or not to treat older patients because of low response and high dropout rate.

Innovations and breakthroughs

There have been four studies on the efficacy of PEG-IFN plus RBV therapy in patients 65 years or older with genotype 1. However, these studies were too small (11-93 patients) for conclusive recommendations to be made. This study is very useful for clarifying the efficacy and safety of PEG-IFN plus RBV combination therapy in older patients, because of its large scale, multicenter design.

Applications

The study demonstrated that PEG-IFN α -2b plus RBV treatment was effective in chronic hepatitis C patients 65 years or older who completed treatment with at least the minimum required treatment dosage. Furthermore, this study suggested that the combination treatment and beginning this therapy as soon as possible are important, especially in older patients.

Peer review

The study has been well conducted and includes a large number of patients. Results have been described in a lucid and informative manner and are of clinical relevance.

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S- Editor Tian L L- Editor Webster JR E- Editor Lin YP