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***Original Article***

# Prolonged treatment with pegylated interferon α 2b plus ribavirin improves sustained virological response in chronic hepatitis C genotype 1 patients with late response in a clinical real-life setting in Japan

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*Aim:* This study was conducted to clarify the factors related to sustained virological response (SVR) to pegylated interferon α 2b (PEG-IFN) plus ribavirin (RBV) combination therapy administered for 48 weeks in patients with chronic hepatitis C virus (CHCV) and to evaluate the usefulness of prolonged treatment in patients with late virological response (LVR).

*Methods:* Of 2257 patients registered at 68 institutions, those with genotype 1 and high viral load were selected to participate in two studies. Study 1 (standard 48-week group, $n = 1480$) investigated SVR-determining factors in patients who received the treatment for ≤52 weeks, whereas study 2 compared SVR rates between patients with LVR who received treatment for either 36–52 weeks (48-week group, $n = 223$) or 60–76 weeks (72-week group, $n = 73$).

*Results:* In study 1, SVR rate was 44.9%; that in male subjects (50.4%) was significantly ($P < 0.0001$) higher than in female subjects (36.4%). SVR rate significantly ($P < 0.0001$) decreased with 10-year age increments in both sexes. Multivariate logistic regression analysis revealed that age, F score, platelet count, and HCV load were SVR-related factors. In study 2, SVR rate in the 72-week group (67.1%) was significantly ($P = 0.0020$) higher than in the 48-week group (46.2%).

*Conclusions:* Patients with CHCV genotype 1 infection should be treated with PEG-IFN plus ribavirin combination therapy as early as possible, and 72 weeks' treatment is recommended in patients with LVR regardless of age.

**Key words:** chronic hepatitis C virus, elderly patients, pegylated interferon, prolonged treatment, ribavirin

## INTRODUCTION

THE TOTAL NUMBER of patients infected with the hepatitis C virus (HCV) is estimated at 170 million worldwide, of whom 1.5–1.7 million are Japanese. Treatment of HCV infection began with interferon (IFN) monotherapy before the discovery of HCV in 1989. At that time, responders to treatment were mostly limited to patients with HCV genotypes 2 or 3 infection, which is highly sensitive to IFN. The sustained virological response (SVR: HCV-RNA negative at 24 weeks after end of treatment) to IFN monotherapy in genotype 1 patients known from that time to be difficult to treat was only about 5%. SVR rate has since increased thanks to concomitant administration of the antiviral drug ribavirin (RBV), and with the development of the long-acting

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IFN product pegylated interferon (PEG-IFN) it has increased to 50%.[1-4] Today, PEG-IFN plus ribavirin regimen is internationally recognized as a standard therapy for chronic hepatitis C virus (CHCV) infection.[5,6] Early clinical trials of this regimen focused on specific patient populations. Subsequently, several multinational studies such as WIN-R,[7] HALT-C,[8] EPIC3,[9] and REPEAT Study[10] have been conducted in the general clinical setting. The results of the IDEAL Study[11] directly comparing PEG-IFN α 2a versus PEG-IFN α 2b have also been published. From these studies, variables predictive of SVR have been identified, including ethnicity, sex, age, and weight as demographic parameters, staging and hepatic steatosis as histological parameters, viral load, genotype, NS5A, and core mutation as virologic parameters, alanine aminotransferase (ALT) and γ-glutamyl transpeptidase (GGT) as biochemical parameters, and even the timing of viral negativity as a treatment variable.[12-15] More recently, the SVR rate was reported to increase in association with decrease in the relapse rate with 72-week treatment in patients with delayed HCV-RNA negativity.[15,16] However, the majority of patients participating in previous studies in western countries were aged in their 40s on average, and the influence of aging of the patient population has not been studied adequately.

We therefore examined SVR-determining factors with 48-week PEG-IFN α 2b plus RBV combination therapy in the prevailing Japanese clinical setting characterized by increasing numbers of elderly patients. We also compared SVR rate between 48-week and 72-week treatment in patients with late virological response (LVR) defined as achieving HCV-RNA negativity in the period from weeks 13 to 24 after the start of treatment so as to examine the significance of prolonged treatment.

## METHODS

### Patients

A MULTICENTER STUDY was conducted at 68 institutions in Tokyo and Yamanashi prefectures (PERFECT Study Group; see Appendix I) to survey the actual state of combination therapy with PEG-IFN α 2b (PegIntron; Schering Plough, Kenilworth, NJ) and RBV (Rebetol, Schering Plough) in 2008. A total of 2257 chronic hepatitis C virus (CHCV) patients seen from December 2004 who completed combination treatment by September 2007 were registered regardless of genotype, history of IFN treatment, and ALT levels. The presence of HCV in serum had to be confirmed by Cobas Amplicor HCV Monitor, version 2.0 (Roche Diagnostic, Tokyo) for registration.

Excluded from this study were pregnant or possibly pregnant and lactating women, and patients with severe heart disease, chronic kidney failure or creatinine clearance of ≤50 mL/min, current or history of severe psychiatric disorder, and autoimmune hepatitis.

Demographic characteristics examined included age, sex, height and weight, the presence or absence of diabetes mellitus, hypertension, heavy drinking, and history of IFN therapy and hepatic cancer. Hepatic histological data recorded were stage (F0–F4) and grade (A0–A3). Laboratory tests recorded were ALT, platelet count, albumin, and α-fetoprotein (AFP) before the start of PEG-IFN α 2b plus RBV combination therapy.

As indicated in Figure 1, of the total 2257 patients registered, patients with genotype 1 and high viral load (>100 KIU/mL: Amplicor PCR quantitation) who satisfied the following conditions were included in this study: patients who received treatment for ≤52 weeks (standard 48-week treatment group, $n = 1480$) in study 1, and patients with LVR who received treatment for either 36–52 weeks (48-week treatment group, $n = 223$) or 60–76 weeks (72-week treatment group, $n = 73$) in study 2.

This multicenter study was approved by IRB at each participating institution. The study protocol was carried out according to the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained from each patient.

### Treatment

PEG-IFN α 2b was administered subcutaneously once weekly at a dose of 1.5 μg/kg. Dose reduction and treatment discontinuation followed the instructions given in the package insert, i.e., the dose was reduced by half if WBC decreased to <1500/mm$^3$, neutrophils to <750/mm$^3$ or platelet count to <80000/mm$^3$, and treatment was discontinued if WBC decreased to <1000/mm$^3$, neutrophils to <500/mm$^3$ or platelet count to <50000/mm$^3$. RBV was administered in two divided doses of 600, 800, or 1000 mg/day in patients weighing <60, 60–<80, and ≥80 kg, respectively. Dose reduction and treatment discontinuation followed the package insert, i.e., dose was reduced from 600 mg/day to 400 mg/day, from 800 mg/day to 600 mg/day, or from 1000 mg/day to 600 mg/day if hemoglobin (Hb) concentration decreased to <10 g/dL, and administration was discontinued if Hb decreased to 8.5 g/dL. Duration of treatment was 48 weeks as a rule. In LVR patients who did

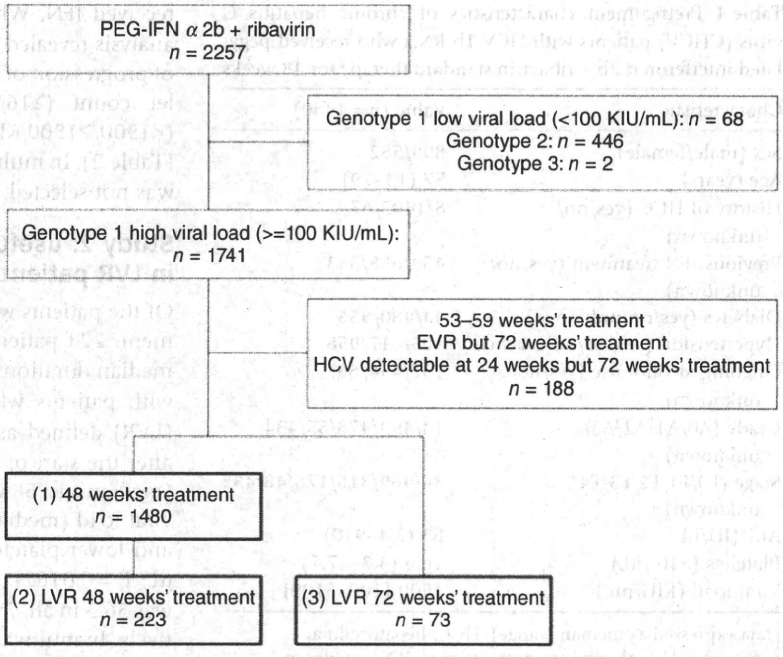


**Figure 1** Flow-chart of study subjects. (1) 48 weeks' treatment (48-week standard therapy group): patients with genotype 1 and high viral load who received pegylated interferon α 2b (PEG-IFN α 2b) + ribavirin (RBV) for 52 weeks. Multiple logistic regression analysis was used to evaluate the response to PEG-IFN α 2b + RBV in this group (2) Late virological response (LVR) 48 weeks' treatment: patients with genotype 1 and high viral load who received PEG-IFN α 2b + RBV for 36–52 weeks (3) LVR 72 weeks' treatment: patients with genotype 1 and high viral load who received PEG-IFN α 2b + RBV for 60–76 weeks. SVR rate was compared between LVR 48 weeks' treatment group (2) and LVR 72 weeks' treatment group (3). EVR, early virologic response; HCV, hepatitis C virus.

not achieve HCV-RNA negativity by week 12, treatment could be extended for 48 weeks or longer based on individual patients' desire and investigators' judgment.

### Evaluation of response to treatment

Determination of genotype and measurement of HCV-RNA levels were performed at each center. Pre-treatment HCV-RNA levels were determined by Amplicor PCR quantitation. Viral negativity was defined as HCV below detection limit (<50 IU/mL) by Amplicor qualitative analysis (Roche Molecular Systems, NJ).

SVR was defined as HCV below detection limit at 24 weeks after the end of PEG-IFN α 2b plus RBV combination therapy by Amplicor HCV qualitative analysis.

### Statistical analysis

All statistical analyses were performed using SAS, version 9.13 (SAS Institute, Cary, NC). Intergroup comparison of SVR rate was performed by Fisher's exact test; that of background variables by Fisher's exact test and Mann–Whitney *U*-test. Trend of SVR rate by age was assessed by Cochran–Armitage test, and intergroup comparison after adjustment of stratification factors was conducted by Mantel–Haenstzel method. Determination of factors associated with SVR was conducted by a stepwise procedure using the results of logistic univariate analysis ($P < 0.2$) into logistic multivariate analysis. All tests were two-sided, with significance level set at $P < 0.05$.

## RESULTS

### Study 1: SVR-related factors in patients receiving standard 48-week treatment

AS INDICATED IN Table 1 and Figure 1, 1480 subjects (male, $n = 898$ [60.7%]; median age, 57 [range, 13–79] years) were eligible for analysis. SVR rate based on ITT was 44.9%. SVR rate in subjects who completed and who discontinued treatment was 56.5% ($n = 1110$) and 10.3% ($n = 370$), respectively, a statistically significant difference ($P < 0.0001$). SVR rate in male subjects (50.4%; 453/898) was significantly ($P < 0.0001$) higher than in female subjects (36.4%; 212/582). SVR rate significantly ($P < 0.0001$) decreased as age increased by 10 years in both male and female subjects (Fig. 2); the odds ratio for SVR decreasing with 10-year increase in age was 0.688 (95% CI, 0.604–0.784; $P < 0.0001$) in male subjects and 0.546 (0.449–0.663; <0.0001) in female subjects, indicating that the influence of aging was greater in female than in male subjects. There was no bias of older versus younger age among patients who had and had not previously

**Table 1** Pretreatment characteristics of chronic hepatitis C virus (CHCV) patients with HCV-1b RNA who received pegylated interferon α 2b + ribavirin standard therapy for 48 weeks

| Characteristic | Value ($n = 1480$) |
|---|---|
| Sex (male/female) | 898/582 |
| Age (years) | 57 (13–79) |
| History of HCC (yes/no/unknown) | 8/1405/67 |
| Previous IFN treatment (yes/no/unknown) | 459/688/333 |
| Diabetes (yes/no/unknown) | 44/480/956 |
| Hypertension (yes/no/unknown) | 105/417/958 |
| Ongoing alcohol use (yes/no/unknown) | 157/456/867 |
| Grade (A0/A1/A2/A3/unknown) | 14/499/478/55/434 |
| Stage (F0/F1/F2/F3/F4/unknown) | 36/469/316/176/48/435 |
| ALT (IU/L) | 63 (8.4–910) |
| Platelets ($\times 10^4/\mu L$) | 16.6 (4.3–47.7) |
| Viral load (KIU/mL) | 1900 (100–5100) |

Data expressed as median (range). HCC, hepatocellular carcinoma; ALT, alanine aminotransferase; IFN, interferon.

received IFN. Whereas, multivariate logistic regression analysis revealed that older age (<55/≥55 years), degree of progression of hepatic fibrosis (F0–1/2–4), low platelet count (≥16/<16×10⁴/μL), and high viral load (<1900/≥1900 KIU/mL) are resistance factors to SVR (Table 2). In multivariate logistic regression analysis, sex was not selected.

## Study 2: usefulness of prolonged treatment in LVR patients

Of the patients who completed standard 48-week treatment, 223 patients (20.0%) showed LVR (Fig. 1), and median duration of treatment was 48 weeks. Compared with patients who exhibited early virologic response (EVR) defined as HCV-RNA negative within 12 weeks after the start of treatment, those with LVR were older (median age, 58 vs 55 years; $P = 0.0043$) and had higher viral load (median, 2700 vs 1620 KIU/mL; $P < 0.0001$) and lower platelet count (median, 16.5 vs $17.3 \times 10^4/\mu L$; $P = 0.0162$). SVR rate based on treatment analysis was 56.5 in all, 79.2% in EVR and 46.2% in LVR, respectively. In multivariate logistic regression analysis of SVR-related factors in LVR patients who completed standard 48-week treatment, age (10-year groups) was selected as a significant factor.

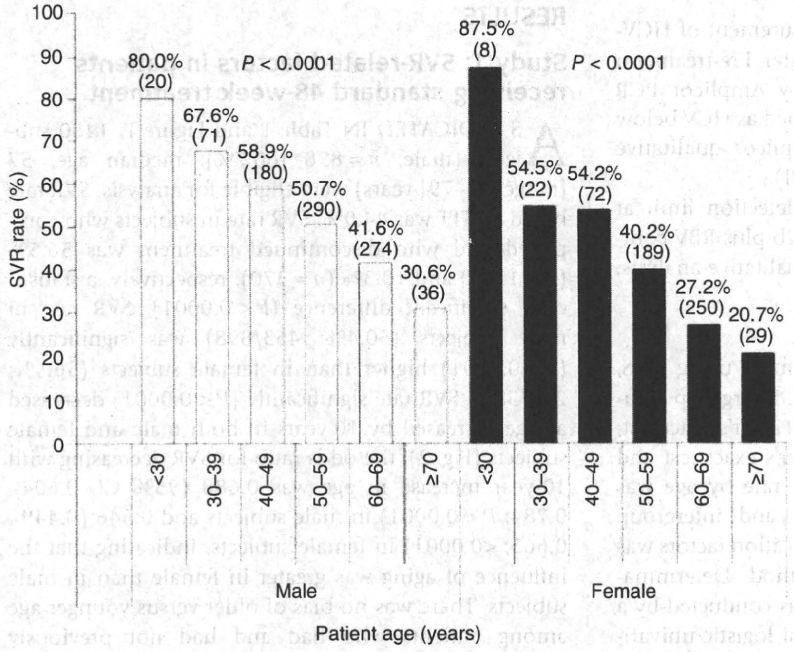


**Figure 2** Sustained virological response (SVR) rate to 48 weeks' standard treatment with pegylated interferon α 2b (PEG-IFN α 2b) + ribavirin in male and female patients stratified by age. Cochran–Armitage test was used to study the underlying trend.

**Table 2** Independent factors associated with sustained virological response in genotype 1 chronic hepatitis C virus patients who received pegylated interferon α 2b + ribavirin standard therapy for 48 weeks

| | Odds ratio | 95% confidence interval | *P*-value† |
|---|---|---|---|
| Age <55/≥55 years | 0.414 | 0.293–0.585 | <0.0001 |
| Stage 0–1/2–4 | 0.633 | 0.442–0.906 | 0.0124 |
| Platelets <16/≥16 × $10^4$/μL | 1.876 | 1.305–2.696 | 0.0007 |
| Viral load </≥1900 KIU/mL | 0.663 | 0.471–0.935 | 0.0192 |

†Multiple logistic regression analysis.

Prolonged treatment was conducted in 73 LVR patients (Fig. 1), with mean duration of 72 weeks. As shown in Table 3, whereas among LVR patients there were significantly ($P = 0.0061$) more female subjects in 72-week group than 48-week group, no intergroup difference of other factors was observed. Overall, SVR rate based on treatment analysis was significantly ($P = 0.0020$) higher in 72-week treatment group than in 48-week treatment group (67.1% [49/73] vs 46.2% [103/223]; Fig. 3A).

When stratified by sex, SVR rate with 48-week and 72-week treatment was 51.4% and 68.6% ($P = 0.0809$) in male subjects and 37.3% and 65.9% ($P = 0.0039$) in female subjects, with SVR in 72-week treatment being significantly higher in female subjects and indicating that, in LVR patients, efficacy comparable to male subjects is achieved in female subjects with 72-week treatment.

In patients aged <55 years SVR rate in the 48- and 72-week treatment groups was 57.6% and 78.9% ($P = 0.1100$) in male subjects and 40.0% and 76.9% ($P = 0.0724$) in female subjects, respectively, with higher SVR rates for the 72-week treatment group (Fig. 3B). In patients aged ≥55 years this parameter was 44.6% and 53.8% ($P = 0.5619$) in male subjects and 37.1% and 60.7% ($P = 0.0425$) in female subjects, respectively, with higher SVR rates for the 72-week treatment group than for the 48-week treatment group as in the case of the younger age group (Fig. 3C).

## DISCUSSION

### Study 1: SVR-related factors in patients receiving standard 48-week treatment

SVR RATE WITH standard 48-week treatment in this study was 44.9%, roughly equal to the 45% reported in previous clinical trials in Japan.[4,17–19] The present results are also similar to those of clinical trials conducted in patients aged in their mid-40s in western countries and in the general clinical setting.[1–4] Age was

**Table 3** Comparison of clinical and virological characteristics between groups receiving pegylated interferon α 2b + ribavirin therapy for 48 and 72 weeks among patients showing late virological response

| | 48 weeks' group ($n = 223$) | 72 weeks' group ($n = 73$) |
|---|---|---|
| Sex (male/female) | 140/83* | 32/41* |
| Age (years) | 58 (21–75) | 56 (22–71) |
| History of HCC (yes/no/unknown) | 1/221/11 | 0/73/0 |
| Previous IFN treatment (yes/no/unknown) | 68/113/42 | 29/32/12 |
| Diabetes (yes/no/unknown) | 11/71/141 | 1/34/38 |
| Hypertension (yes/no/unknown) | 18/62/143 | 6/29/38 |
| Ongoing alcohol use (yes/no/unknown) | 17/75/131 | 6/27/40 |
| Grade (A0/A1/A2/A3/unknown) | 2/66/82/6/67 | 0/21/26/4/22 |
| Stage (F0/F1/F2/F3/F4/unknown) | 7/68/45/32/5/66 | 2/16/20/12/2/21 |
| ALT (IU/L) | 61.5 (14–550) | 52 (17–254) |
| Platelets (×$10^4$/μL) | 16.5 (8.5–43.2) | 16.6 (4.3–40.2) |
| Viral load (KIU/mL) | 2700 (160–5100) | 2100 (130–5000) |

Data expressed as median (range). *$P = 0.006$. ALT, alanine aminotransferase; HCC, hepatocellular carcinoma; IFN, interferon.

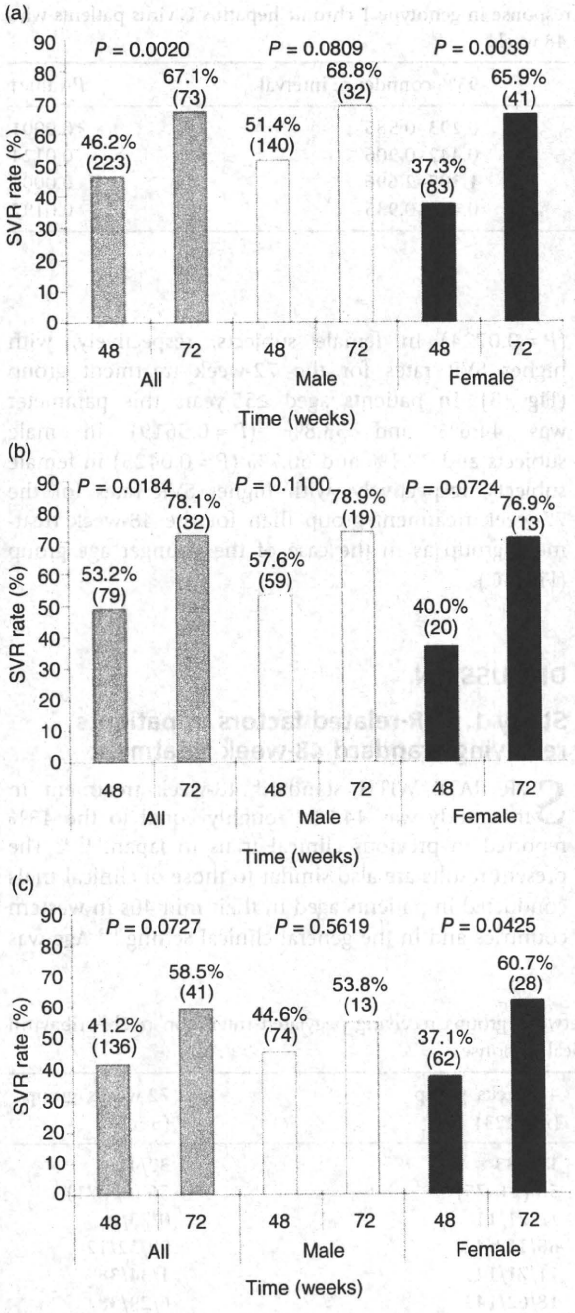


**Figure 3** Sustained virological response (SVR) rate based on treatment analysis between groups receiving pegylated interferon α 2b (PEG-IFN α 2b) + ribavirin therapy for 48 and 72 weeks who exhibited late virological response (LVR). (A) Overall; (b) patients aged <55 years; (c) patients aged ≥55 years. Data on age not available for 7 male patients and 1 female patient.

selected among factors for SVR with PEG-IFN plus RBV combination therapy in an aging patient population, the examination of which was the objective of this study, and SVR rate decreased stepwise with 10-year age increase. Of particular note was the greater impact of aging observed in female than male subjects.

Lower efficacy in elderly female patients infected with HCV genotype 1 has already been reported in Japan.[20] A low SVR rate was also observed in elderly female subjects in this study. Although female sex was considered a favorable prognostic factor in some Western studies, there is no established opinion on sex difference. Change associated with aging of the patient population in Japan is considered to account for this phenomenon observed in the present study. This may be due to decrease in compliance among elderly women; on the other hand, however, there was no difference between male and female subjects aged ≥55 years in the rate of completion of treatment. Although the rate of dose reduction of RBV tended to be slightly higher in female subjects (data not shown), the difference was not significant. These findings suggest the influence of factors other than adherence to treatment for the low SVR rate among elderly women. One possible factor for reduced SVR rate among these individuals may be the effect of menopause. In women, insulin resistance begins to worsen after the age of 50 years,[21,22] and this is reported more closely associated with the effect of menopause than age itself.[23]

The presence of insulin resistance has been reported to lower efficacy of PEG-IFN and RBV combination therapy.[24–27] Insulin resistance is also a cause of advanced fibrosis and fatty change of the liver.[28–31] It is possible that such changes combined with other factors associated with metabolic syndrome interact in a complex way to reduce the efficacy of this therapy.[32–35] In fact, the incidence of non-alcoholic fatty liver disease (NAFLD) among elderly Asians was reported higher in women as compared with that in men.[36–38] However, while older age, advanced fibrosis, low platelet count and high HCV load were selected as factors for reduction of SVR rate in our multivariate logistic regression analysis, sex was not selected. It is therefore necessary to examine further the confounding of these selected factors with sex. It also should be taken into consideration that, due to limitations imposed by the retrospective nature of this study, data on factors affecting the efficacy of PEG-IFN plus RBV therapy such as insulin resistance, steatosis, and core mutation are lacking. A large-scale prospective study is

required to examine the lower efficacy observed in elderly women.

### Study 2: usefulness of prolonged treatment in LVR patients

EVR (viral load reduced by 2 log or undetected in week 12) has been used for determining continuation or discontinuation of treatment in western countries. Recently, however, EVR was divided into complete EVR (HCV RNA <50 IU/mL at week 12) and partial EVR (>2 log drop in HCV RNA but still detectable [>50 IU/mL]). Fried *et al.*[15] and Berg *et al.*[16] reported that the SVR rate was a high 68–84% in patients showing complete EVR but only 17–29% in those with partial EVR with treatment for 48 weeks. They also reported that treatment for 72 weeks was effective in patients with partial EVR. In the clinical study for health registration in Japan, the SVR rate by timing of HCV-RNA negativity at 4, 12, and 24 weeks was 100%, 71.1%, and 36.4%, respectively, and no patient with HCV-RNA negativity after 25 weeks achieved SVR.[4] With these studies as reference, patients with LVR were defined as those who were positive (>50 IU/mL) at week 12 and became negative (<50 IU/mL) by week 24. To minimize the influence of treatment discontinuation, only patients who completed the standard duration of treatment were selected as subjects in this study. In the comparison of patient background, there was no significant intergroup difference except for a significantly greater number of female subjects in the 72-week treatment group. This finding might be related to the observation that it was already widely believed that efficacy in elderly women in Japan is low and that duration of treatment was at the discretion of individual physicians. Nevertheless, it is noteworthy that the SVR rate was significantly higher in the 72-week treatment group than in the 48-week treatment group and that a high 60% SVR rate was achieved with 72-week treatment in elderly female patients, a population in whom a relatively low SVR was observed with standard 48-week treatment.

This retrospective study had the limitation that duration of treatment was at the sole discretion of each participating physician. A prospective study is necessary to demonstrate whether 72-week treatment in elderly women with LVR is more efficaous than 48-week treatment in male patients. Although the number of younger subjects examined was rather low, it is noteworthy that an SVR rate of >75% was observed with 72-week treatment in both male and female patients. This also should be confirmed by prospective study.

## CONCLUSIONS

PATIENTS WITH CHCV genotype 1 infection should be treated with PEG-IFN and ribavirin combination therapy as early as possible. Seventy-two weeks' treatment is recommended in patients with LVR, regardless of age.

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## APPENDIX I

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

# Thrombocytopenia is more severe in patients with advanced chronic hepatitis C than B with the same grade of liver stiffness and splenomegaly

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**Abstract**
*Background and aim* The mechanism responsible for thrombocytopenia in chronic liver diseases (CLD) is not yet fully understood. The prevalence of thrombocytopenia has been reported to be higher in patients with hepatitis C virus-related hepatocellular carcinoma (CLD-C) than in those with hepatitis B virus-related hepatocellular carcinoma (CDC-B). We have examined the potential difference in thrombocytopenia between patients with CLD-B and those with CLD-C in terms of liver fibrosis adjustment and splenomegaly.
*Methods* The study cohort consisted of 102 patients with CLD-B and 143 patients with CLD-C were enrolled. Liver stiffness, which is reported to be well correlated with the degree of liver fibrosis, was measured by transient elastography.
*Results* The analysis of covariance with liver stiffness as a covariate revealed that the platelet count was lower in CLD-C patients than in CLD-B patients. Following stratification for liver stiffness, thrombocytopenia was found to be more severe in CLD-C patients than CLD-B patients with advanced liver stiffness, whereas the degree of splenomegaly was not significantly different. The plasma thrombopoietin level was not different between CLD-B and CLD-C patients with advanced liver stiffness, and the immature platelet number was lower in CLD-C patients despite thrombocytopenia being more severe in these patients.
*Conclusions* CLD-C patients with advanced liver stiffness presented with more severe levels of thrombocytopenia than CLD-B patients even with the same grade of splenomegaly. Impaired platelet production rather than enhanced platelet destruction may underlie the mechanism responsible for thrombocytopenia in patients with CLD.

**Keywords** Liver stiffness · Splenomegaly · Thrombocytopenia · Thrombopoietin · Transient elastography

**Abbreviations**

| | |
|---|---|
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| CLD | Chronic liver disease |
| HBeAg | Hepatitis B envelope antigen |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| IPF | Immature platelet fraction |
| IQR | Interquartile ranges |

## Introduction

Advanced chronic liver disease (CLD) has long been known to be accompanied by thrombocytopenia.

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