trial of non-peg-IFN alpha in combination with RBV, in contrast to patients with genotype 1 who had < 30% SVR.[13,14] SVR is also achieved consistently more often by patients with a low HCV-RNA level.[4–14] Moreover, host factors affect the chance of SVR, albeit less so than the genotype.[10] These factors include age, race, sex, obesity, and the degree of hepatic fibrosis and steatosis.[15] In a racial analysis, African Americans were shown to have response rates only one-half to one-third those of Caucasians.[15] In addition, Asian patients were more likely to achieve an SVR by treatment with peg-IFN alpha-2a and RBV than Caucasian patients.[16] The reasons for the racial differences in response rates to peg-IFN alpha plus RBV treatment are not well known.

Peg-IFN was a substantive breakthrough in therapy because of the longer effect; the lasting, steady therapeutic blood level is a major pharmacokinetic advance.[4,5] The most frequent adverse effects during peg-IFN plus RBV treatment are depression and hematological disorders such leukopenia, anemia, and thrombocytopenia. Therefore, the peg-IFN alpha-2b plus RBV treatment often results in discontinuation or the need for a reduction of the dosage due to the adverse effects.

To investigate the efficacy and safety of antiviral treatments for Japanese chronic hepatitis B and C patients, a multicenter study, the Kyushu University Liver Disease Study (KULDS), was launched in 2003. Our group has previously reported several clinical studies.[17–21] The present report is a prospective, multicenter study carried out to analyze the association between the treatment length and the cumulative dose and effectiveness of peg-IFN alpha-2b plus RBV treatment for a large number of Japanese patients with chronic hepatitis C.

## Methods

### Patients

Treatment of chronic hepatitis C with a combination of peg-IFN alpha-2b and RBV was accepted by the Japanese Ministry of Health in October, 2004. A prospective study of 715 Japanese patients aged 18 years or older (586 and 129 patients with genotypes 1b and 2, respectively) treated with peg-IFN alpha-2b plus RBV between December 2004 and February 2007 who were all positive for antibody to HCV and HCV-RNA for over 6 months was carried out. The respective distribution rates were 82.0% and 18.0% for genotypes 1b and 2, similar to the reported epidemiological distribution.[22]

Criteria for exclusion were: (i) clinical or biochemical evidence of hepatic decompensation, advanced cirrhosis identified by large esophageal varices (F2 or F3), history of gastrointestinal bleeding, ascites, encephalopathy, or hepatocellular carcinoma; (ii) hemoglobin level < 115 g/L, white blood cell count < $3 \times 10^9$/L, and platelet count < $50 \times 10^9$/L; (iii) concomitant liver disease other than hepatitis C (hepatitis B surface antigen positive or HIV positive); (iv) excessive active alcohol consumption > 60 g/day or drug abuse; (v) severe psychiatric disease; and (vi) antiviral or corticosteroid therapy within 12 months prior to the enrollment. Patients who fulfilled the above criteria were recruited at Kyushu University Hospital and 32 affiliated hospitals in the northern Kyushu area of Japan.

Within the 3 months before the start of the treatment and every 3 months during the treatment period, each patient was tested for alpha-fetoprotein (AFP) and had abdominal ultrasonographic examination. If an abnormal AFP level of ≥ 40 ng/mL and/or an appearance of focal lesions at ultrasonographic examination was found at any testing, further testing for hepatocellular carcinoma (HCC) was done, which included dynamic computed tomography (CT), angiography, and/or tumor biopsy. Patients so confirmed to have HCC within 3 months after the start of the treatment were excluded from this study.

Table 1 shows the baseline characteristics of the enrolled patients. The median age was 58.0 years. Of the 715 patients, 198 (27.6%) were aged 65 years or over. In Japan, many older patients with chronic hepatitis C are candidates for antiviral treatment, different from many other countries. The rates of prior non-peg-IFN monotherapy significantly differed among the genotype-classified patients (genotype 1, 41.7% and genotype 2, 28.7%).

**Table 1** Characteristics of 715 chronic hepatitis C patients treated with a combination of pegylated IFN alpha-2b and ribavirin, classified by HCV genotype

| Characteristics | Total $n = 715$ | Genotype 1 $n = 586$ | Genotype 2 $n = 129$ | *P*-value |
|---|---|---|---|---|
| Male *n* (%) | 388 (54.3) | 321 (54.8) | 67 (51.9) | 0.6250 |
| Age (years) | 56.8 ± 11.7 | 57.8 ± 10.3 | 52.6 ± 14.1 | 0.0004 |
| Body mass index (kg/m$^2$) | 23.4 ± 3.2 | 23.5 ± 3.1 | 23.5 ± 3.3 | 0.4999 |
| Prior IFN monotherapy *n* (%) | 276 (38.6) | 239 (40.8) | 37 (28.7) | 0.0140 |
| Prior combined IFN plus RBV treatment *n* (%) | 69 (9.7) | 60 (10.9) | 5 (3.9) | 0.0221 |
| Alanine aminotransferase (IU/L) | 77.1 ± 55.4 | 77.5 ± 52.8 | 70.9 ± 55.3 | 0.0594 |
| γ-Glutamyltranspeptidase (IU/L) | 60.6 ± 60.3 | 61.8 ± 58.6 | 50.8 ± 45.2 | 0.0241 |
| Albumin (g/dL) | 4.1 ± 0.4 | 4.1 ± 0.3 | 4.1 ± 0.3 | 0.1305 |
| White blood cell (/mm$^3$) | 5030.8 ± 1439.2 | 4993.0 ± 140.8 | 5260.6 ± 1658.2 | 0.3005 |
| Hemoglobin (g/dL) | 13.9 ± 1.4 | 13.9 ± 1.4 | 13.9 ± 1.5 | 0.7092 |
| Platelet count ($10^9$/L) | 165 ± 56 | 161 ± 52 | 185 ± 69 | 0.0013 |
| Creatinine (mg/dL) | 0.70 ± 0.16 | 0.70 ± 0.17 | 0.71 ± 0.16 | 0.1230 |
| Creatinine clearance (mL/min) | 97.9 ± 29.9 | 97.1 ± 29.8 | 101.3 ± 31.3 | 0.3621 |

Data are shown as the mean ± standard deviation.
HCV, hepatitis C virus; IFN, interferon; RBV, rivabirin.

Also, the rates of prior non-peg-IFN alpha plus RBV treatment significantly differed (genotype 1, 10.9% and genotype 2, 3.9%). These differences are explained by the necessity of re-treatment of patients with genotype 1 who had lower SVR by the standard IFN monotherapy than did non-genotype 1 patients, and because the RBV combination treatment with peg-IFN alpha-2b was approved in stages, first for patients with genotype 1 in October 2004, then for those with non-genotype 1 in January 2006. The means for age, platelet count, γ-glutamyltranspeptidase (γ-GTP), and total cholesterol in genotype 1 patients were significantly different than those of genotype 2 patients.

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

### Treatment regimen

All patients were treated with a weight-based, 1.5 μg/kg weekly dose of subcutaneous peg-IFN alpha-2b (PegIntron A; Schering-Plough, Osaka, Japan). In combination with peg-IFN alpha-2b, RBV (Rebetol; Schering-Plough) was given orally at a daily dose of 600–1000 mg based on bodyweight (600 mg for patients weighing < 60 kg, 800 mg for those weighing 60–80 kg, and 1000 mg for those weighing ≥ 80 kg). The lengths of treatment were 48 weeks and 24 weeks for HCV genotypes 1b and 2 patients, respectively. The above durations and dosages 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 < 100 g/L. In such cases, a reduction in the dose of RBV was required. Some patients also had peg-IFN alpha-2b-induced psychological adverse effects or a decrease of white blood cell and platelet count. In such cases, a reduction in the dosage of peg-IFN alpha-2b was required. Both peg-IFN alpha-2b and RBV were discontinued if the hemoglobin level, white blood cell count, or platelet count fell below 85 g/L, $1 \times 10^9$/L, and $2.5 \times 10^9$/L, respectively. The treatment was discontinued if severe general fatigue, hyperthyroidism, interstitial pneumonia, or severe hemolytic problems developed, continuation of treatment was judged not to be possible by the attending physician, or the patient desired discontinuation of treatment.

### Clinical and laboratory assessment

Body mass index (BMI) was calculated as weight in kilograms/height in square meters. Blood samples were taken on enrollment, in the morning after 12 h overnight fasting. Serum levels of alanine aminotransferase (ALT), γ-GTP, cholesterol, triglycerides, and high-density lipoprotein (HDL)-cholesterol, plasma glucose (PG), white blood cell count, hemoglobin, and platelet count were measured by standard laboratory techniques at a commercial laboratory.

### 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 v2.0 using the 10-fold dilution method; Roche Diagnostics, Tokyo, Japan), which has a lower limit of quantitation of 5000 IU (1350 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 a type-specific primer from the core region of the HCV genome. The protocol for genotyping was carried out as previously described.[23]

### Efficacy of treatment

Sustained virological response was defined as serum HCV-RNA undetectable at 24 weeks after the end of treatment. Patients who had undetectable HCV-RNA within the initial 12 weeks of treatment were considered to have had an early virological response (EVR). These efficacy variables, SVR and EVR, were defined as non-detectable HCV-RNA as measured by the COBAS Amplicor HCV Monitor Test v2.0, and the results were labeled as positive or negative. The lower limit of detection was 50 IU/mL (0.5 kIU/mL). The analysis of SVR and EVR was done on an intention-to-treat basis.

### Statistical analysis

Continuous data were expressed as mean values, the values ± standard deviation (SD), or the values ± standard error (SE) of the mean. The following statistics were done using a commercially available software package (BMDP Statistical Software Inc., Los Angeles, CA, USA) for the IBM 3090 system computer. The chi-squared or Fisher's exact test was used to examine the association between baseline characteristics and SVR. The Mann–Whitney *U*-test was also used to compare responders and non-responders with regard to various characteristics, when appropriate. The Cochran-Mantel-Haenszel test was used to test for statistical significance among the subgroups. A *P*-value of less than 0.05 was considered significant.

## Results

### Discontinuation of peg-IFN alpha-2b plus RBV treatment and adverse effects

Of the 715 patients, 152 (21.2%) did not complete peg-IFN alpha-2b plus RBV treatment due to adverse effects or for other reasons (Table 2). Although anemia, as a cause of discontinuation, was followed by general fatigue and depression, most patients discontinued the treatment because of general fatigue and depression together with anemia (hemoglobin 85–100 g/L).

The discontinuation rate was higher for patients with genotype 1 (138 of 586, 23.5%) than those with genotype 2 (14 of 129, 10.8%). The genotype 1 patients included 55 who stopped receiving treatment without virological effect (positive for serum HCV-RNA or no more than 2-$\log_{10}$ reduction from the pretreatment viral level) at 24 or more weeks after the start ($n = 22$), economic problems related to the high cost of treatment ($n = 6$), and other reasons (drop out, moving, nursing ill family members, and being arrested for a crime) ($n = 27$). Thus, the discontinuation rates for patients with adverse effects were only 14.1% (83 of 586) and 7.7% (10 of 129) for genotypes 1b and 2, respectively, with no significant difference. The majority were patients aged 65 years or

**Table 2** Reasons for discontinuation of pegylated IFN plus ribavirin treatment, classified by HCV genotype

| | Genotype 1 | Genotype 2 | Total |
|---|---|---|---|
| Adverse effects | | | |
| General fatigue | 29 | 0 | 29 |
| Depression | 10 | 1 | 11 |
| Encephalopathy | 2 | 0 | 2 |
| Anemia | 11 | 0 | 11 |
| Thrombocytopenia | 1 | 1 | 2 |
| Hyperthyroidism | 5 | 1 | 6 |
| Rash | 6 | 3 | 9 |
| Retinopathy | 2 | 0 | 2 |
| Interstitial pneumonia | 1 | 1 | 2 |
| Articular rheumatism | 1 | 0 | 1 |
| Brain infarction | 0 | 1 | 1 |
| Proteinuria | 1 | 0 | 1 |
| Hepatocellular carcinoma | 11 | 2 | 13 |
| Malignancy (extra-liver)† | 2 | 0 | 2 |
| Pulmonary tuberculosis | 1 | 0 | 1 |
| Other reasons | | | |
| No effect of treatment | 22 | 2 | 24 |
| Economic problems | 6 | 0 | 6 |
| Others‡ | 27 | 2 | 29 |
| Total | 138 | 14 | 152 |

†Includes one patient with gastric cancer and one patient with lung cancer.
‡Includes drop out ($n = 16$), patients who moved ($n = 6$), who nursed ill family members ($n = 3$), or who were arrested for criminal activity ($n = 2$).

over: 68 (73.1%) of the 93 discontinued due to adverse effects. The discontinuation rate due to adverse effects was significantly higher for patients aged 65 years or over (68 of 198, 34.3%) than for those aged under 65 years (25 of 517, 4.8%) ($P < 0.0001$). The mean times to discontinuation (± SD) were 23.0 ± 13.1 weeks and 20.2 ± 15.4 weeks for patients with genotypes 1b and 2, respectively.

## SVR by intention-to-treat analysis

Of the 715 patients, 345 (48.2%) achieved SVR in the intention-to-treat analysis. SVR was significantly higher in genotype 2 (96 of 129, 74.4%) than in genotype 1 (249 of 586, 42.4%) ($P < 0.0001$). No significant differences in SVR were found between patients with and without prior non-peg-IFN monotherapy or non-peg-IFN plus RBV treatment between the genotype-classified patients.

An analysis of the association between SVR and the length of treatment showed that patients who completed the combination treatment had a significantly higher rate of SVR than did those with a shortened period of treatment (Fig. 1). Completing the 48-week combination treatment resulted in a significantly higher rate of SVR than either 1–11-week and 12–23-week treatments (both $P < 0.0001$), but there was no significant difference between 24 and 47 weeks and the complete 48 weeks of treatment ($P = 0.1260$). The SVR of patients with genotype 1 was significantly associated with a ≥ 24-week treatment period when compared with treatment < 24 weeks (244 of 481, 50.7% *vs* 5 of 105, 4.7%, $P < 0.0001$). In genotype 2 patients, SVR significantly increased with the treatment period: 28.6%, 57.1%, and 78.3% by 1–11-week, 12–23-week, and 24-week periods, respectively ($P = 0.0018$ by the Cochran-Mantel-Haenszel test).

The combination treatment was done for 443 (75.5%) and 110 (85.3%) of genotype 1 and 2 patients, respectively (Fig. 2). The rates of SVR for genotype 1 and 2 patients were significantly higher in those who continued the combination treatment than in those who discontinued RBV treatment: 230 of 443 (51.9%) versus 19 of 143 (13.2%) genotype 1 ($P < 0.0001$) and 89 of 110 (80.9%) versus seven of 19 (36.8%) genotype 2 ($P = 0.0002$). In genotype 1, 286 patients who required a reduced dosage during treatment (Groups B, C, and D) were able to complete the full 48 weeks of combination treatment. There were no significant differences in SVR among Groups A to D patients with genotypes 1 and 2. Of the patients who discontinued RBV treatment (143 with genotype 1 and 19 with genotype 2), most patients (138 (96.5%) with genotype 1 and 14 (73.7%) with genotype 2) did not complete combination treatment because there was no viral effect, because of adverse effects, or because they dropped out. The remaining patients discontinued the RBV treatment but completed the combination treatment without a reduction of the peg-IFN alpha-2b target dosage (three with genotype one and five with genotype 2), or discontinued the RBV treatment and completed their peg-IFN alpha-2b treatment with a reduction of the target dosage (two with genotype 1 and none with genotype 2).

An analysis of the association between SVR and the total dosage of peg-IFN alpha-2b and RBV during the treatment showed that patients with a higher total dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage only for genotype 1 patients, although no significant difference was found in genotype 2 (Fig. 3). In genotype 1, reducing the total dosage of peg-IFN alpha-2b during the treatment significantly reduced the rate of SVR: 52.9% (187 of 353) for patients with ≥ 80% of the peg-IFN alpha-2b dosage, 36.5% (30 of 82) for those ≥ 60% but < 80% of the peg-IFN alpha dosage, and 21.1% (32 of 151) for those < 60% of the peg-IFN alpha dosage (both $P < 0.0001$). In genotype 1, the SVR rate of patients < 60% of the RBV dosage (91 of 307, 29.6%) was significantly lower than that of patients ≥ 80% of the RBV dosage (112 of 189, 59.2%) and those ≥ 60% but < 80% of the RBV dosage (46 of 90, 51.1%) (both $P < 0.0001$), although no significant difference was found between those ≥ 80% of the RBV dosage and those ≥ 60% but < 80% of the dosage. In genotype 2, neither a dosage reduction of peg-IFN nor RBV significantly influenced SVR.

An analysis of the association between SVR and the total combined dosage of peg-IFN alpha-2b plus RBV showed that patients with a higher total combined dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage for genotype 1 patients only, although no significant difference was found in genotype 2 (Fig. 4). In genotype 1, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 80% of RBV was significantly higher (78 of 122, 63.9%) than those without these combined dosages (171 of 464, 36.9%) ($P < 0.0001$). Moreover, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 60% of RBV was significantly higher (116 of 187, 62.0%) than those without these dosages (133 of 399, 33.3%) ($P < 0.0001$). However, in genotype 2, neither a dosage reduction of peg-IFN nor RBV significantly influenced SVR.

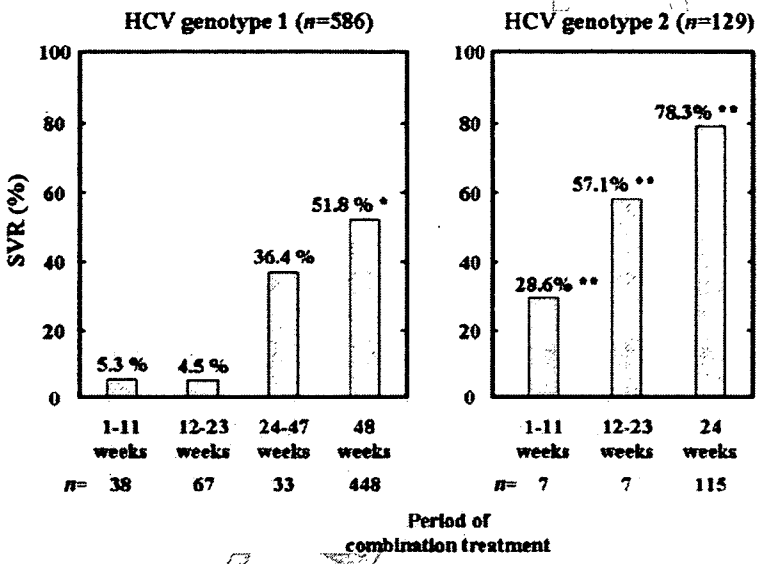


**Figure 1** Sustained virological response (SVR) rates classified by length of pegylated interferon-alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) combination treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis.

### Analysis of EVR and the first 12-week adherence

An EVR was significantly higher in patients with genotype 2 (119 of 129, 92.2%) than in those with genotype 1 (307 of 586, 52.3%) ($P < 0.0001$). An analysis of the association between SVR and EVR showed that patients with EVR had a significantly higher rate of SVR than did patients without EVR for both genotypes 1b and 2: 220 of 309 (71.1%) versus 29 of 277 (10.4%) in genotype 1, and 96 of 119 (80.6%) versus none of 10 (0%) in genotype 2 (all $P < 0.0001$).

An analysis of the association between EVR and the first 12-week combined dosage of peg-IFN alpha-2b plus RBV showed that patients with a higher total combined dosage of the combination treatment had a significantly higher rate of SVR than those with a lower dosage for genotype 1 patients only, although no significant difference was found in genotype 2 (Fig. 5). In genotype 1, the EVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 80% of RBV was significantly higher (217 of 357, 60.8%) than those without these dosages (92 of 229, 40.2%) ($P < 0.0001$). Moreover, the SVR rate of patients ≥ 80% of peg-IFN alpha-2b and ≥ 60% of RBV was significantly higher (262 of 445, 58.9%) than those without these dosages (47 of 141, 33.3%) ($P < 0.0001$). However, in genotype 2, neither a dosage reduction of peg-IFN nor RBV influenced EVR.

## Discussion

To the best of our knowledge, no reports have been written on the efficacy and safety of peg-IFN alpha-2b plus RBV treatment for a large number of Japanese HCV patients. The present study by intention-to-treat analysis included over 700 Japanese patients with chronic hepatitis C, a sufficient number to provide a meaningful statistical analysis and to be of interest to clinical physicians. Our findings show that in peg-IFN alpha-2b plus RBV treatment for chronic hepatitis C it is important to complete the target treatment duration and to use the full dosage to achieve virological efficacy.

A recent study showed Asian patients with chronic hepatitis C were more likely to achieve an SVR by treatment with peg-IFN alpha-2a and RBV than were Caucasian patients, suggesting a genetic influence on the antiviral response.[16] A significant difference between Asian and Caucasian patients with genotype 1 infections (65% and 36%) was also reported. However, the study included only 52 Asian patients and had no analysis concerning dosage of peg-IFN and RBV. Because our study included a large number of Japanese patients and an analysis of the complete combination treatment and the dosage of peg-IFN and RBV, the present study provides for meaningful statistical analysis.

Our analysis showed that the discontinuation of RBV was significantly associated with a marked decline in SVR. We also showed that a < 60% reduction of the total dosage was associated with a poor outcome. Several adverse reactions are strongly associated with RBV. One of the most significant problems is hemolytic, especially anemia.[14] Most patients with anemia have general fatigue. Careful administration is necessary for patients > 60 years old, female patients, and patients receiving an RBV dosage by bodyweight of ≥ 12 mg/kg.[24] In fact, most of our patients who required a reduction in the total dosage or who discontinued RBV had anemia or fatigue. Also, discontinuation in this study was frequently found in patients aged ≥ 65 years. In Japan, many older patients with chronic hepatitis C are candidates for antiviral treatment, different from other countries. It is important to reduce the dosage of RBV at an early a stage as possible to allow the safe continuation of the combination treatment, as shown by data that a reduction of up to 60% of the total dosage of RBV does not appear to adversely influence SVR in Japanese patients.

The duration and dose of antiviral treatment are the most important factors influencing treatment outcome, especially in

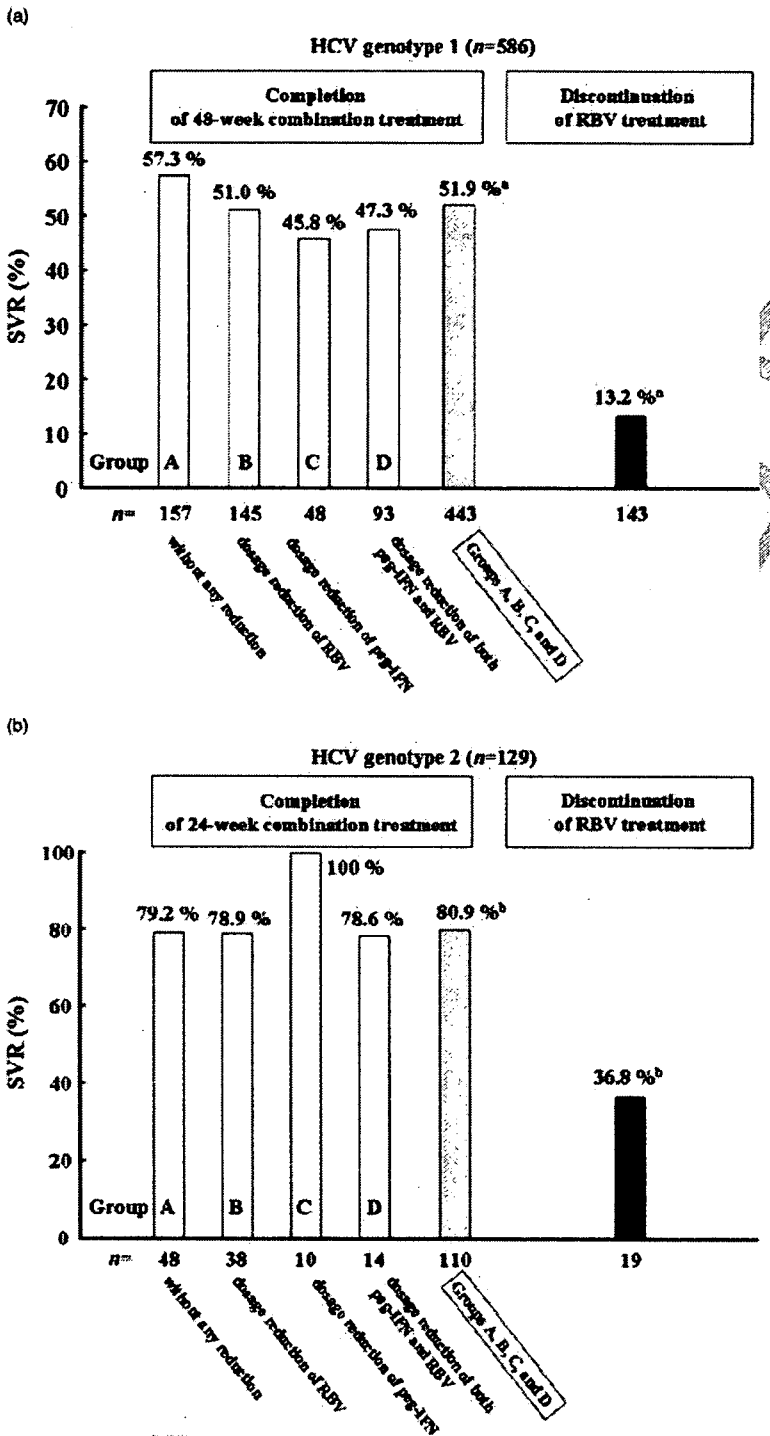


**Figure 2** Sustained virological response (SVR) rates classified by continuation, reduction of the dosage, discontinuation of pegylated interferon-alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment, and hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 2a for genotype 1 and Fig. 2b for genotype 2). The following groups A, B, C, and D consisted of patients who completed their scheduled combination treatment (48 weeks for genotype 1 patients [$n = 443$] and 24 weeks for genotype 2 patients [$n = 110$]) and patients who discontinued RBV treatment (genotype 1 patients [$n = 143$] and genotype 2 patients [$n = 19$]). Group A patients well tolerated the combination treatment with peg-IFN alpha-2b and RBV without any reduction in the target dosage of either drug; Group B patients completed the combination treatment and had no reduction of peg-IFN alpha-2b dose, but needed a reduction of the RBV target dosage; Group C patients completed the combination treatment and had no reduction of RBV dosage, but needed a reduction of the target dosage of peg-IFN alpha-2b; Group D patients completed the combination treatment, but needed a reduction of the target dosage of both peg-IFN alpha-2b and RBV. 'a' and 'b' indicate significant differences between completion of the full combination treatment and discontinuation of RBV treatment ($P < 0.0001$ and $P = 0.0002$, respectively).

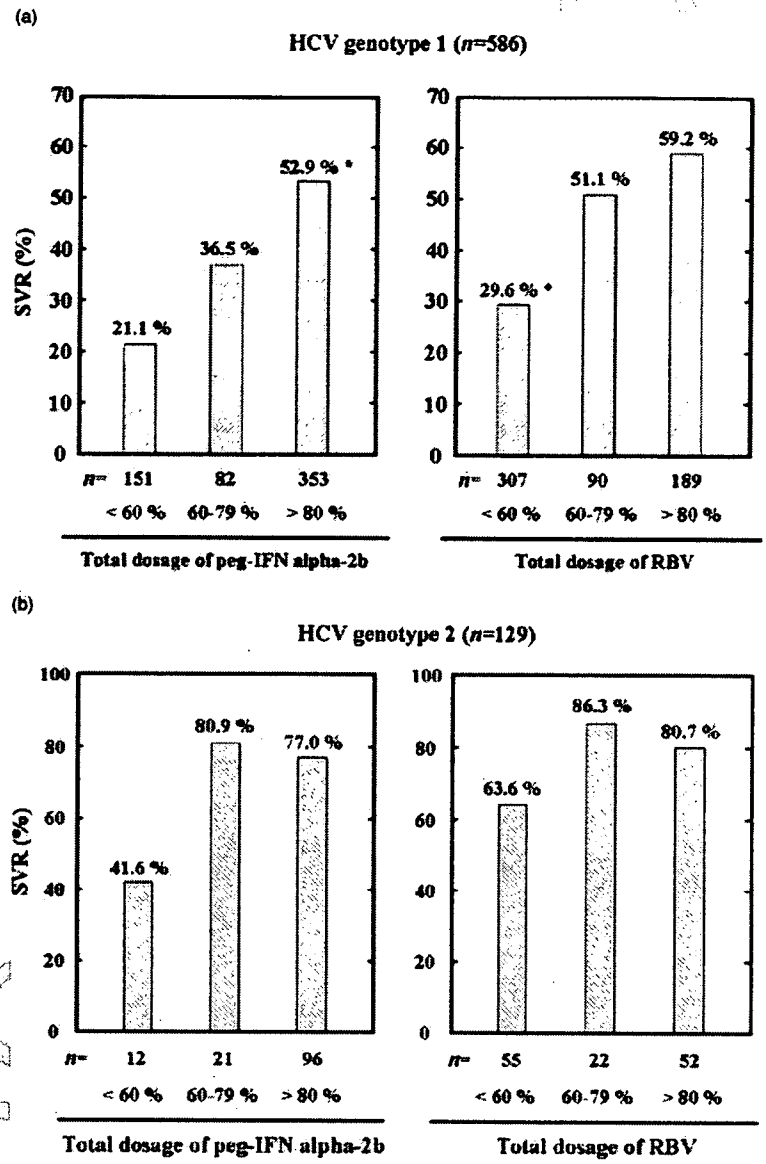


**Figure 3** Sustained virological response (SVR) rates classified by percentage of total dosage of pegylated interferon-alpha2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment and by hepatitis C virus (HCV) genotype. An intention-to-treat analysis (Fig. 3a for genotype 1 and Fig. 3b for genotype 2). * indicates a significant difference between the groups.

HCV genotype 1-infected patients.[25,26] Shiffman and colleagues reported that reducing the total dose of peg-IFN alpha-2a to < 80% within the first 20 weeks of therapy significantly reduced SVR, but reducing the dose of RBV appeared to have little impact on SVR.[25] For our patients with genotype 1, the treatment period and total dosage were important to gaining SVR with peg-IFN alpha-2b plus RBV treatment. The 48-week combination treatment is the minimum requirement for SVR by these patients. Moreover, it is necessary to give ≥ 80% of the target dosage of peg-IFN alpha-2b (suitable for the weekly ≥ 0.9–1.2 μg/kg) and ≥ 60% of the target RBV (suitable for the daily 6–8 mg/kg) throughout the treatment.

Our previous report showed that a 24-week non-peg-IFN alpha plus RBV treatment regimen produced a high rate of SVR in Japanese genotype 2-infected patients.[19] The 24-week peg-IFN alpha-2b plus RBV treatment regimen used in the present study also demonstrated a remarkable rate of SVR (74.4%) for genotype 2 patients, as expected. This can be explained by the fact that genotype 2 patients have an extremely high rate of EVR, over 80%, with this combination treatment. Another important

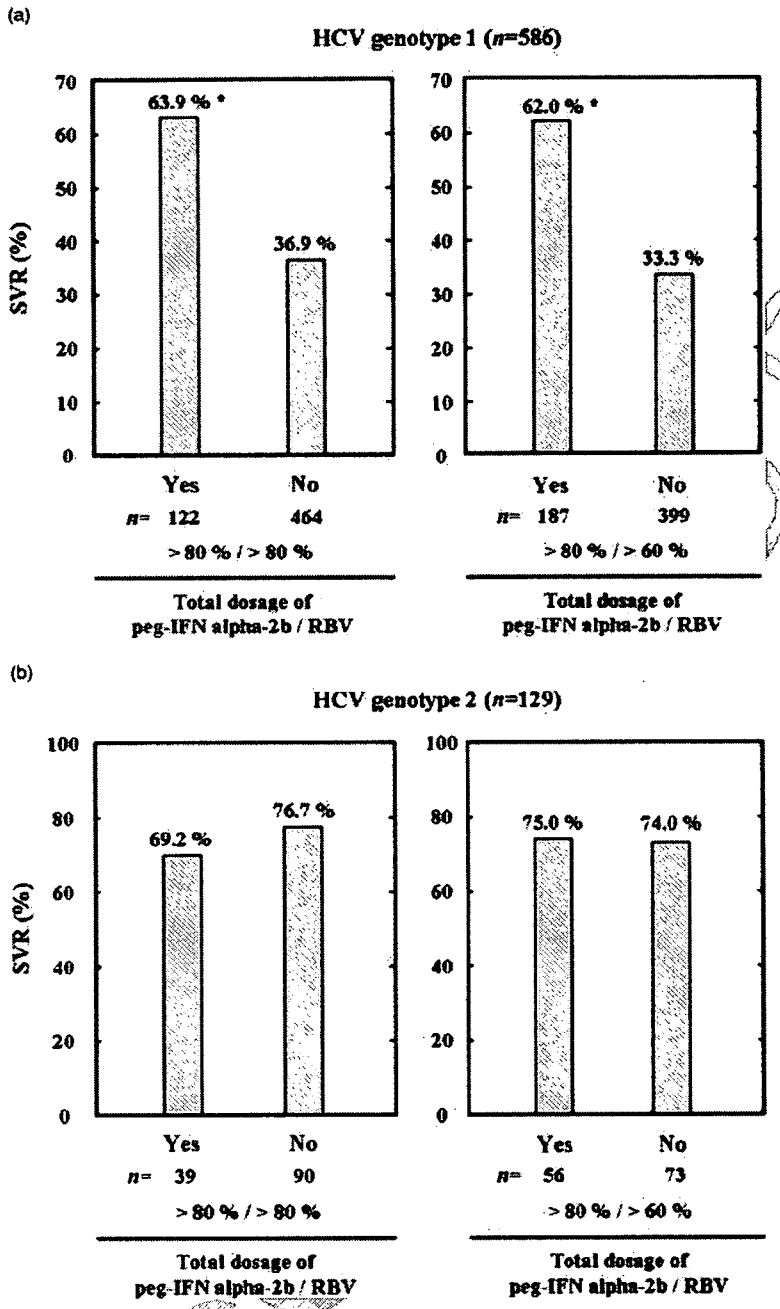


**Figure 4** Sustained virological response (SVR) rates classified by percentage of total combined dosage of pegylated interferon alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 4a for genotype 1 and Fig. 4b for genotype 2). *indicates a significant difference between the groups.

finding was that the total dosages of peg-IFN alpha-2b and RBV during the treatment for genotype 2 patients did not significantly influence SVR, although a dosage < 60% of the target resulted in a lower rate of SVR than a dosage ≥ 60%, without significant difference. These findings suggest that the target dosage can be reduced for genotype 2 patients to avoid the adverse effects such as general fatigue, depression, and anemia and that the 24-week combination treatment can still be successfully completed.

An EVR, a virological clearance by antiviral treatment in the

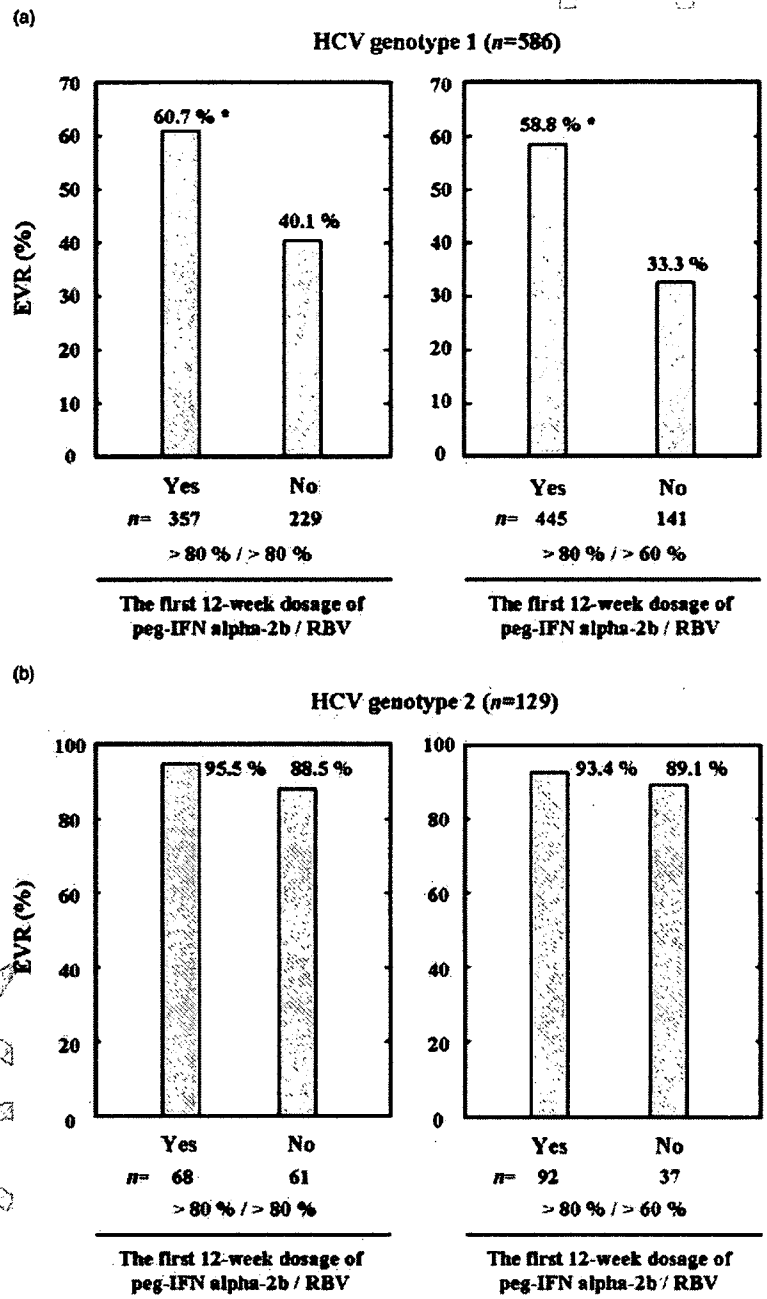


**Figure 5** Early virological response (EVR) rates classified by percentage of the first 12-week combined dosage of pegylated interferon alpha-2b (peg-IFN alpha-2b) plus ribavirin (RBV) treatment and by hepatitis C virus (HCV) genotype: An intention-to-treat analysis (Fig. 5a for genotype 1 and Fig. 5b for genotype 2). *indicates a significant difference between the groups.

initial 12 weeks, is significantly related with sustained response.[27] The present study also showed that the first 12-week combined dosage was significantly related with EVR in both genotype 1 and 2 patients, leading to the attainment of an SVR. Because of the impact of medical adherence during the first 12-week dosage on EVR, it is important to continue the dosage from the early stage to the target period in peg-IFN alpha-2b plus RBV treatment.

Since the introduction of peg-IFN alpha plus RBV combination regimen, the treatment of chronic hepatitis C has dramatically

improved over the past decade and can cure a significant proportion of the patients.[5,6] However, the combination treatment has its limitations, especially for HCV genotype 1 patients. Although the limited efficacy and adverse effects necessitate the development of new therapeutics approaches, we must acknowledge the current situation in which many older Japanese patients with chronic hepatitis C are candidates for antiviral treatment. Therefore, a key to solving the problem is managing antiviral treatment for these older patients. Recent analysis suggests that using erythropoietic agents (epoetin and dartbepoetin) for the reduction of anemia may not be cost-effective for the majority of patients.[28] A new RBV analog, viramidine, is reported to be associated with a lower incidence of anemia than RBV (4% *vs* 27%),[29] and, if proven effective, may eventually be substituted for RBV in combination with peg-IFN alpha for patients with chronic hepatitis C.

In conclusion, in peg-IFN alpha-2b plus RBV treatment for chronic hepatitis C, it is important to complete the target duration and reach the target dosage to achieve virological efficacy, especially for genotype 1 patients.

## Acknowledgments

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## Appendix I

In addition to the authors, the following investigators of the KULDS Group were involved in the present study: M Tatsukawa and M Murata, Haradoi Hospital, Fukuoka; K Toyoda, Yokota Hospital, Hirokawa, Fukuoka; E Ogawa, Yagi Hospital, Fukuoka; T Koga, H Takeoka, T Kuga and A Mitsutake, Mitsutake Hospital, Iki, Nagasaki; R Sugimoto, Harasanshin Hospital, Fukuoka; H Amagase, S Tominaga, Mihagino Hospital, Kitakyushu; K Yanagita, Saiseikai Karatsu Hospital, Karatsu; K Ogiwara, Kyusyu Rosai Hospital, Kitakyushu; M Tokumatsu, Saiseikai Fukuoka Hospital, Fukuoka; S Tabata, Hayashi Hospital, Fukuoka; M Yokota, National Kyushu Cancer Center, Fukuoka; H Tanaka, Chihaya Hospital, Fukuoka; S Nagase, Fukuoka Teishin Hospital, Fukuoka; S Tsuruta, Nakabaru Hospital, Fukuoka; S Tada, Moji Rosai Hospital, Kitakyushu; M Nagano, Kyushu Koseinenkin Hospital, Kitakyushu; M Honda, Nishi-Fukuoka Hospital, Fukuoka; T Umeno, Sawara Hospital, Fukuoka; T Sugimura, National Hospital Organization Fukuoka Higashi Hospital, Fukuoka; S Ueno, Kitakyushu Municipal Wakamatsu Hospital, Kitakyushu; K Miki, Kitakyushu Municipal Moji Hospital, Kitakyushu; H Okubo, Shineikai Hospital, Kitakyushu; H Fujimoto, Mitsubishikagaku Hospital, Kitakyushu; N Higuchi, Shin-Nakama Hospital, Kitakyushu; S Shigematsu, Kouseikan Hospital, Saga; N Higashi, National Hospital Organization Beppu Hospital, Beppu, Japan.

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ウイルス遺伝子型の違いによる治療法の実際—トライアルの結果をもとに—

# 難治性C型慢性肝炎に対するウイルスの早期陰性化率

## —九州大学関連肝疾患研究会（KULDS）の中間成績から—

林　　純*

索引用語：C型慢性肝炎，genotype 1b，高ウイルス量，ウイルス早期陰性化率


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## I．はじめに

1989年にC型肝炎ウイルス(HCV)に対する抗体が測定可能となり，1992年にはこの抗体測定系が改良され，第二世代HCV抗体として，一般医療機関でも測定されるようになった．その結果，わが国は世界的にみてもHCVの感染の高浸淫国であることが判明した[1]．HCVの感染経路としては母子感染[2]，性行為感染[3]，薬物乱用のための注射器の共用，あるいは刺青などもあるが，わが国では輸血やデイスポーザブルではなかった注射器による医療行為も重要であり，HCVの感染を拡大したものと考えられた[4]．さらに，HCVに感染すると60～80％が持続感染に移行し，慢性肝炎，肝硬変をへて，肝癌を高率に発症することから[5]，このウイルスの感染はB型肝炎ウイルスにも増して重要な肝炎ウイルスと考えられる．衛生教育・環境の整ってきている現在では，新たなHCV感染はほとんどなくなっているが，すでに感染しているものが癌年齢になり，肝癌による年間死亡者数は1970年頃の約10,000人から，この30年間に3倍に増加し，現在では34,000人に達し，悪性新生物の中では胃癌，肺癌とほぼ肩を並べている．

以上のことから，現在，肝癌発症抑制を目

*Jun HAYASHI*: Early viral response to peginterferon plus ribavirin combination therapy for chronic hepatitis with genotype 1b and high level of HCVRNA

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表1　リバビリン投与量別背景の比較

| ベースライン | 調整投与群 | 通常投与群 | p値* |
|---|---|---|---|
| 年齢 | 60.4 ± 9.1 | 56.1 ± 10.3 | ＜0.0001 |
| 性別(男：女) | 116：134 | 251：182 | 0.0041 |
| RNA量 | 1992.3 ± 1522.4 | 1949.1 ± 1983.6 | 0.2432 |
| ALT値 | 72.4 ± 50.2 | 79.1 ± 56.4 | 0.0735 |
| アルブミン値 | 4.2 ± 0.4 | 4.1 ± 0.4 | 0.0486 |
| WBC値 | 4933.1 ± 1363.1 | 5035.8 ± 1491.0 | 0.5940 |
| PLT値 | 15.9 ± 5.1 | 16.0 ± 5.3 | 0.7156 |
| Hb値 | 13.7 ± 1.4 | 14.1 ± 1.4 | ＜0.0001 |
| CCr値 | 92.9 ± 29.4 | 101.5 ± 30.9 | 0.0009 |

*性別はFisher's exact test以外はMann Whitney U test

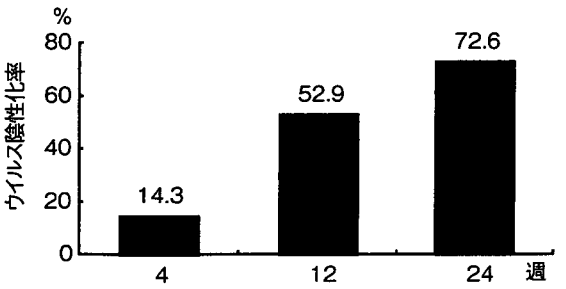

図1　経時的ウイルス陰性化率(全体)

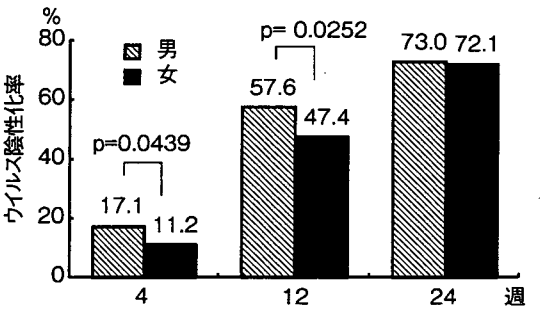

図2　経時的ウイルス陰性化率(性別)

的として，C型慢性肝炎に対するインターフェロン(IFN)療法が推進されているところである．IFN療法は1992年から始まっており，当初はIFN単独療法でα型は24週，β型は6～8週投与であった．治療終了後もウイルスが持続して血中から消失し，肝機能が正常となる著効率は全体の約25%であった．しかし，genotype 1b型で，高ウイルス量の例における著効率は5%と低率で[6]，そのため，これらの例は難治性C型慢性肝炎と呼ばれるようになった．2002年からはリバビリンとIFN α-2bの併用投与が行われ，これら難治性C型慢性肝炎の著効率は，筆者ら九州大学関連肝疾患研究会(Kyushu University Liver Disease Study; KULDS)の成績では413例中95例，23.0%と上昇した[7]．2004年末からは週1回の投与で効果が得られるPEG-IFN α-2bとリバビリン併用療法(1年間)が保険適応となった．海外の報告では難治性C型慢性肝炎に対する著効率が50～60%と高く[8]，現在，最も行われている有効なIFN療法と考えられる．

KULDSではgenotype 1b型で，高ウイルス量例，すなわち難治性C型慢性肝炎に対するPEG-IFN＋リバビリン併用療法の効果について，治療開始後24週までの成績をまとめ，検討したので報告する．

## Ⅱ．対象と方法

KULDSのグループで登録されたC型慢性肝炎900例のうちgenotype 1b型かつ高ウイルス量で，解析可能であった683例(男性

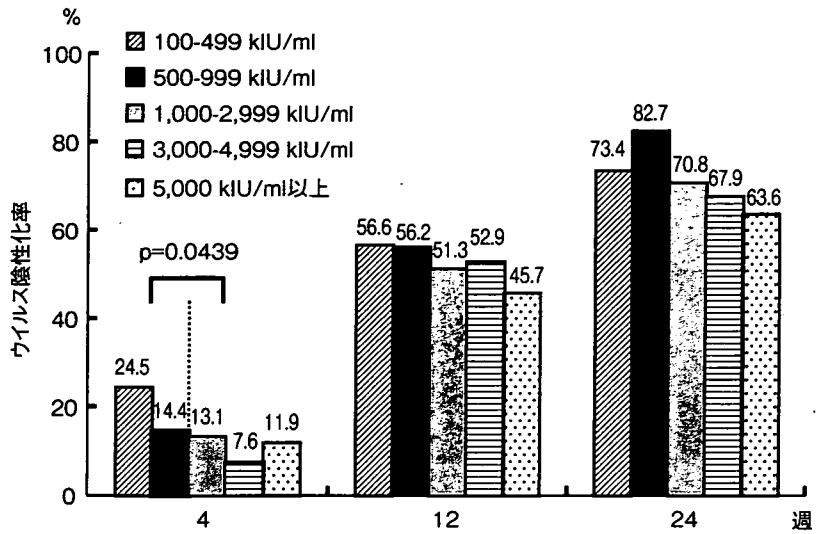


図3　経時的ウイルス陰性化率(ウイルス量別)

367，女性316例)を対象とした．年齢分布は40歳以下が38例，5.6％，40歳代が89例，13.0％，50歳代が233例，34.1％，60歳代が254例，37.2％，70歳以上が69例，10.1％であった．ウイルス量別では100～499 kIU/m*l*が96例，16.2％，500～999 kIU/m*l*が97例，16.8　％，1,000～2,999 kIU/m*l*が267例，46.1　％，3,000～4,999 kIU/m*l*が79例，13.6％，5,000 kIU/m*l*以上が42例，7.3％であった．

治療はPEG-IFN＋リバビリン併用療法で，PEG-IFN α-2bは1.5 μg/Kg/週で，通常投与群(434例)ではリバビリンは体重に応じて600 mg～1,000 mg/日で投与された．KULDSでは治療完遂率の向上を目指し有効率の向上をはかることでそれぞれ主治医の判断により，リバビリンの投与量を減量投与する調整投与群(249例)を設けた．投与前のHb値，年齢，性などを主治医が考慮し，リバビリンを200～600 mg/日に調整し投与された．その結果，調整投与群は通常投与群に比較して，有意に年齢が高く，女性が多くなり，また，Hbが低く，腎機能が低下していた(表1)．411例については肝生検が施行され，Staging別に効果の検討が可能であった．過去にIFNの治療歴がなかったのが352例，あったのが224例で，治療歴不明が107例であった．

## Ⅲ．成　績

ウイルスの陰性化率を全体でみると，治療開始後4週では579例中14.3％，12週では503例中52.9％，24週では434例中72.6％であった(図1)．男女別に検討すると，4週では男性が310例中17.1％と女性の269例中11.2％に比較し，有意に高率で($p = 0.0439$)，12週でも男性が269例中57.6％と女性の234例中47.4％に比較し有意に高率であった($p = 0.0252$)．24週では男性が237例中73.0％で，女性の197例中72.1％と差はみられなかった(図2)．

ウイルス量別(100～499　kIU/m*l*，500～999 kIU/m*l*，1,000～2,999 kIU/m*l*，3,000～4,999 kIU/m*l*，5,000 kIU/m*l*以上)に検討すると，それぞれ，4週では24.5％，14.4％，13.1％，7.6％，11.9％で，999 kIU/m*l*以下

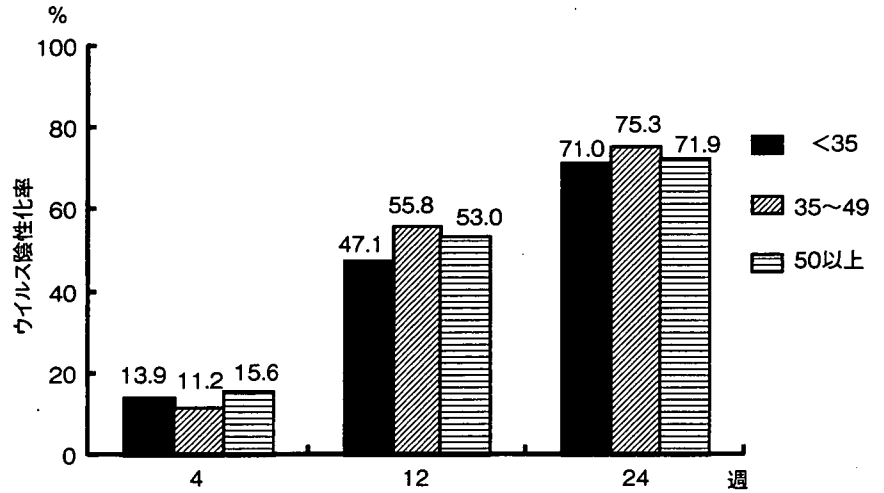


図4　経時的ウイルス陰性化率(ALT値別)

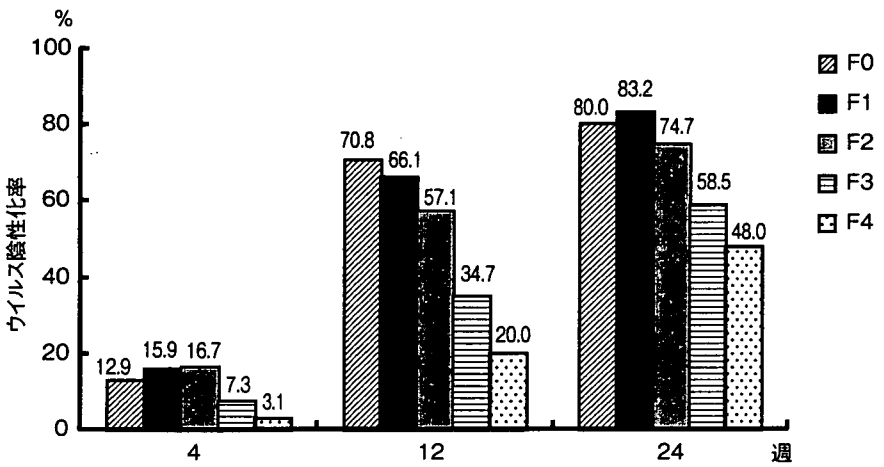


図5　経時的ウイルス陰性化率(Staging別)

の群は1,000 kIU/m*l*以上の群に比較して有意に高率であった(p = 0.0439). 12週では55.6%, 56.2%, 51.3%, 52.9%, 45.7%で, 24週では73.4%, 82.7%, 70.8%, 67.9%, 63.6%で各群間に差はみられなかった(図3).

治療開始時のalanine aminotransferase (ALT)値別(35IU/L未満, 35～49 IU/L, 50 IU/L以上)に検討すると, それぞれ, 4週では13.9 %, 11.2 %, 15.6 %, 12週では47.1%, 55.8%, 53.0%, 24週では71.0%, 75.3%, 71.9%で, 各群間に差はみられなかった(図4).

Staging別(F0, F1, F2, F3, F4)に検討すると, それぞれ, 4週では12.9%, 15.9%, 16.7 %, 7.3 %, 3.1 %, 12週では70.8 %, 66.1 %, 57.1 %, 34.7 %, 20.0 %, 24週では80.0%, 83.2%, 74.7%, 58.5%, 48.0%で, 線維化の程度の進行に伴い, ウイルス陰性化率が低下し, 12週と24週では統計学的に有意な傾向であった(p < 0.001) (図5).

IFNの治療歴が無かった群と有った群とで比較検討したが, それぞれ, 4週では352例

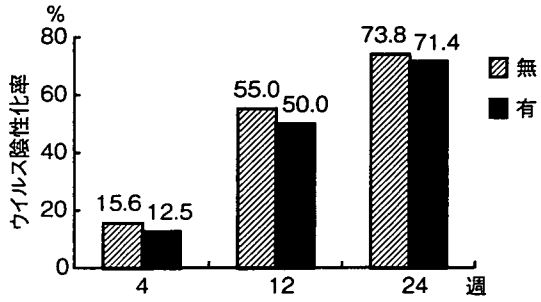


図6　経時的ウイルス陰性化率(治療歴別)

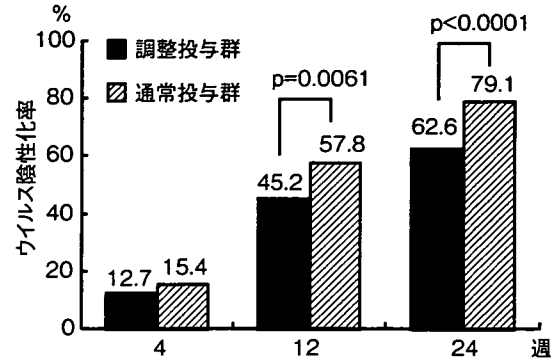


図7　経時的ウイルス陰性化率(投与群別)

表2　投与群別副作用によるリバビリン中止率

| 調整投与群 | | | | 通常投与群 | | | |
|---|---|---|---|---|---|---|---|
| 年齢 | 症例数 | 副作用による中止 例数 | % | 年齢 | 症例数 | 副作用による中止 例数 | % |
| ＜40 | 6 | 0 | 0 | ＜40 | 32 | 2 | 6.3 |
| 40～49 | 18 | 3 | 16.7 | 40～49 | 71 | 4 | 5.6 |
| 50～59 | 77 | 2 | 2.6 | 50～59 | 156 | 8 | 5.1 |
| 60～69 | 108 | 6 | 5.6 | 60～69 | 146 | 20 | 13.7 |
| 70以上 | 40 | 3 | 7.5 | 70以上 | 29 | 7 | 24.1 |
| 合計 | 249 | 14 | 5.6 | | 431 | 41 | 9.5 |

減量・中止の不明の3例を除く

中15.6％，224例中12.5％，12週では298例中55.0％，204例中50.0％，24週では248例中73.8％，185例中71.4％と両群での差はみられなかった(図6)．

調整投与群と通常投与群とで比較検討すると，それぞれ，4週では12.7％，15.4％で差はみられなかった．しかし，12週では45.2％，57.8％，24週では62.6％，79.1％といずれも通常投与群が有意に高率であった(それぞれ，$p = 0.0061$，$p < 0.0001$)（図7)．表2に調整投与群と通常投与群における治療中止率を比較した．全体でみると調整投与群では5.6％で，通常投与群は9.5％と差はなかった．しかし，60歳以上でみると調整投与群では148例中9例，6.1％で，通常投与群の175例中27例，15.9％に比較して有意に低率であった($p < 0.05$)．

ウイルスの消失に寄与する因子を，経時的に多変量解析を用いて検討した(表3)．4週では負の因子としては女性およびウイルス量で，正の因子としてはアルブミン値および血小板数であった．12週では負の因子として高齢者および女性で，正の因子としてALT値および血小板数であった．24週では負の因子として調整投与，正の因子として血小板数および腎機能であった．

## Ⅳ．考　察

以前より，IFN療法ではウイルスが早期に血中より消失する例は著効例が多いことは報

表3　経時的ウイルス消失に寄与する因子(多変量解析)

| 因子 | 投与開始4週 | 投与開始12週 | 投与開始24週 |
|---|---|---|---|
| 年齢(10歳区分) | | 0.664<br>0.0001 | |
| 女性 | 0.442<br>0.0043 | 0.508<br>0.0019 | |
| ALT値(62以上) | | 1.555<br>0.00474 | |
| Alb値(4.2以上) | 2.638<br>0.0010 | | |
| 血小板数(5万区分) | 2.000<br>＜0.0001 | 1.366<br>0.0056 | 1.484<br>0.0096 |
| CL/F (5区分) | | | 1.474<br>0.0052 |
| HCV量(＜100/＜1000/≧1000) | 0.503<br>0.0138 | | |
| 調整投与 | | | 0.521<br>0.0156 |

数値上段はOdds比，下段はp値

告されており，IFN α単独療法では治療開始後2週間以内にウイルスが陰性化した34例中17例，50%が著効例となった[9]．すなわち，治療開始後早期の結果を知ることは，治療効果を予測する上で重要と考えられる．48週間で完了するPEG-IFN＋リバビリン併用療法の治験の成績をみると4週でウイルスが陰性化した23例中100%，12週で陰性化した144例中75.7%，24週で陰性化した177例中68.4%が，治療終了後24週でもウイルスが陰性である著効例であった[10]．以上のことから，本稿では治療途中の結果ではあるが，この時期のウイルス陰性化率およびそれに関与する因子について検討した．

治験での4週，12週，24週のウイルス陰性化率は，それぞれ249例中9.2%，238例中60.5%，227例中74.9%であった[10]．筆者らの成績は対象者に高齢者が多いこと，また，100%の著効率が期待される4週でのウイルス陰性化率が，有意差はなかったが14.3%と高率であったことを考えると，治験に比較しても引けをとらないものと考えられた．

女性では男性に比較してウイルスの早期消失率が低く，著効率が低いことが予測された．リバビリンによる貧血などの副作用によるものも考えられるが，40歳以上の女性はIFN単独療法でも著効率が低いことから[11]，女性ホルモンとの関連が考えられた[12]．過去のIFN単独療法ではウイルス量は著効を予測する上で最重要の因子の一つであったが，PEG-IFN＋リバビリン併用療法ではウイルス量はその効果と関連が無いとの報告がなされている[13]．しかし，詳細に検討すると，100%の著効率が期待される4週でのウイルス陰性化率は低ウイルス量例に高率であったことから，genotype 1bで確実な効果が得ら

れるのは999 kIU/ml以下のウイルス量と考えられた.

肝硬変はIFN単独療法での著効に対して,負の因子として寄与するとの報告がなされている[14]. 今回の解析でも線維化の軽度な例にウイルス消失率が高く,また,多変量解析では肝臓の病態と強く関連する血小板数が高値である例は,いずれの時期においても独立した正の因子であった. すなわち,PEG-IFN+リバビリン併用療法でも肝臓の病態が軽度の例では,治療開始後早期にウイルスが陰性化することから,著効が期待されるものと考えられる.

本研究の特徴であるリバビリン調整投与については,単変量解析では通常投与に比較してウイルス陰性化率は低いが,多変量解析でも24週には負の因子として抽出された. しかし,調整投与群では治療中止例が少ないことを考えると,リバビリンの減量投与は,高齢で貧血傾向がみられ,腎機能が低下しているC型慢性肝炎患者の治療には意義あることと考えられた.

なお,ウイルス陰性化率はIFN治療歴に無関係であったことから,過去のIFN療法で無効であった例でも,新たなPEG-IFN+リバビリン併用療法は試みるべき治療法と考えられた.

## V. まとめ

60歳以上の例が47.3%, F3以上が23%, ウイルス量が3,000 kIU/ml以上の例が20.9%の母集団において,治療中のウイルス陰性化率は,それぞれ4週で14.3%, 12週で52.9%, 24週で72.6%とほぼ開発試験と同様の成績であった. 経時的なウイルス陰性化に影響する因子として,4週では男性,アルブミン高値,血小板数高値,低ウイルス量, 12週では男性,若年者,血小板数高値, ALT高値, 24週では血小板数高値,腎機能正常,リバビリンの非減量が抽出された.

実際の臨床での対象患者は開発治験よりも多様な症例が多かったが, PEG-IFN+リバビリン併用療法では治療開始後早期のウイルス陰性化率は高く,高い著効率が期待される. しかし,ウイルスの陰性化が得られていない症例,あるいは陰性化の遅い症例もみられ,このような症例に対する対策が必要と考えられた.

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特別講演

# C型肝炎ウイルス感染症
## ——肝癌発症と生活習慣病——

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### はじめに

1989年にC型肝炎ウイルス(HCV)の抗体が測定可能になり，1992年にはこの抗体系が改良され，第二世代HCV抗体として，一般医療機関でも測定されるようになった。その結果，わが国は世界的にみてもHCVの感染率が高いことが判明した。さらに，一般医療機関で実際に診療する慢性肝疾患のうち60%はHCV感染によるもので，内訳としては，慢性肝炎の50%，肝硬変の70%，肝癌の80%はHCV感染によるものであった[1]。衛生教育・環境の整ってきている現在では，新たなHCV感染は殆どなくなってきているが，既に感染している者が癌年齢になることから，わが国では肝癌の著明な増加が予想されていた。実際，1970年頃，肝癌による年間死亡者数は約10,000人であったが，この30年間に3倍に増加し，現在では34,000人に達しており，悪性新生物の中では胃癌，肺癌とほぼ肩を並べている。

一方，C型慢性肝炎に対するインターフェロン(IFN)療法は唯一の原因療法であることから注目され，リバビリン併用療法へ，さらには週1回の投与で血中濃度が保てるPegIFN，そして肝癌発症抑制効果がみられることから，短期・中期投与から長期投与へと保健適応が変遷してきた。

本稿では，HCVの感染経路，肝癌との関連，IFN療法さらには最近注目されてきたインスリン抵抗性との関連についても述べる。

### 1. 感染経路

HCVの家族内感染については，多くの研究がなされている。母児間の感染率は約5%とされ，その際HCV RNA量の高い母親から感染するとされている。また，夫婦間感染は結婚期間に比例して，HCVの感染率が増加しており，その重要性を指摘する報告もあるが，HCVの遺伝子解析から約3%とされている。一方，感染機会の多い特殊浴場女性従業者では6.2%で，従業期間が長いほど陽性率は高くなっており，性行為によるHCVの感染が考えられた[2]。

以上のことを踏まえて，本邦におけるHCVの主な感染経路を知るために，HCV抗体陽性率が高い福岡県H村(19.7%)[3]および長崎県I市(14.1%)[4]において疫学的検討を行った。福岡県H村では，HCV RNA陽性母親の子供のHCV抗体陽性率は17.8%と高率であったが，彼らの平均年齢は43.8±3.3歳であり，住民の40歳代の15.4%と比較して差はみられなかった。さらに，両地区とも，19歳以下の住民にはHCV抗体陽性例は1例も存在しておらず，母児間感染が主流とは考えられなかった。

夫婦間感染についてみると，福岡県H村ではHCV RNA陽性女性の夫のHCV抗体陽性率は34.8%で，HCV RNA陽性男性の妻のHCV抗体陽性率は22.2%であった。その平均年齢は，それぞれ62.7±1.6歳，61.4±1.1歳であり，住民の60歳代男性の36.2%および女性の26.6%と比較して差は見られなかった。

HCVのgenotype 1b型と2b型が混在している長崎県I市で，夫婦ともHCV RNA陽性の11組についてgenotypeを検討した。このうち6組は夫婦が同じgenotypeであったが，5組は異なっており，また，例えgenotypeが同一でも，必