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Figure Legends

Figure 1: ALT levels – individual patients

Serum ALT levels are shown for the nine patients who completed 24 weeks of treatment; the patient who discontinued at week 2 is not presented. Shaded area indicates the treatment period; arrows indicate the points at which the dose of BMS-650032 was reduced from 600 mg twice daily to 200 mg twice daily. Arrow and line colors are the same for each patient. ALT=alanine aminotransferase.

Figure 2: HCV RNA levels – individual patients

Individual patient plasma HCV RNA levels during 24 weeks of treatment and through 24 weeks post-treatment (week 48) are shown. Lower limit of quantitation (LLOQ)=15 IU/mL. HCV=hepatitis C virus.

Figure 3: HCV RNA endpoints

Categorical HCV RNA endpoints are indicated for the 10 study patients. One patient discontinued at week 2 and was counted as a treatment failure at the time points shown. However, HCV RNA was undetectable in this patient at 2, 3, 13, and 24 weeks post-treatment. HCV=hepatitis C virus. LOQ=limit of quantitation. RVR=rapid virologic response. cEVR=complete extended virologic response. EOTR=end of treatment response. SVR_{12} and SVR_{24} =sustained virologic response 12 and 24 weeks post-treatment, respectively.

Table 1: Baseline demographic and disease characteristics

Parameter	Value
N	10
Age, median years (range)	62 (52–70)
Male sex, n (%)	4 (40)
Japanese race, n (%)	10 (100)
Host *IL28B* genotype,[a] n (%)	
CC	2 (20)
CT	8 (80)
HCV genotype 1b, n (%)	10 (100)
HCV RNA, mean $\log_{10}$ IU/mL (SD)	6.8 (0.61)
ALT, mean U/L (SD)	60.6 (32.9)
Platelets x 10^9 cells/mL, median (min, max)	150.5 (84.0, 166.0)
Total bilirubin, median mg/dL (min, max)	0.8 (0.6, 1.2)
Albumin, median g/dL (min, max)	3.9 (3.1, 4.2)
INR, median (min, max)	1.0 (1.0, 1.1)

[a] SNP rs12979860

INR=international normalized ratio

Table 2: On-treatment adverse events occurring in ≥2 patients

Event	Patients, n (%)
Diarrhea	7 (70)
Headache	4 (40)
ALT increased	3 (30)
AST increased	3 (30)
Lymphopenia	2 (20)
Abdominal discomfort	2 (20)
Malaise	2 (20)
Pyrexia	2 (20)
Nasopharyngitis	2 (20)
Lipase increased	2 (20)
Back pain	2 (20)

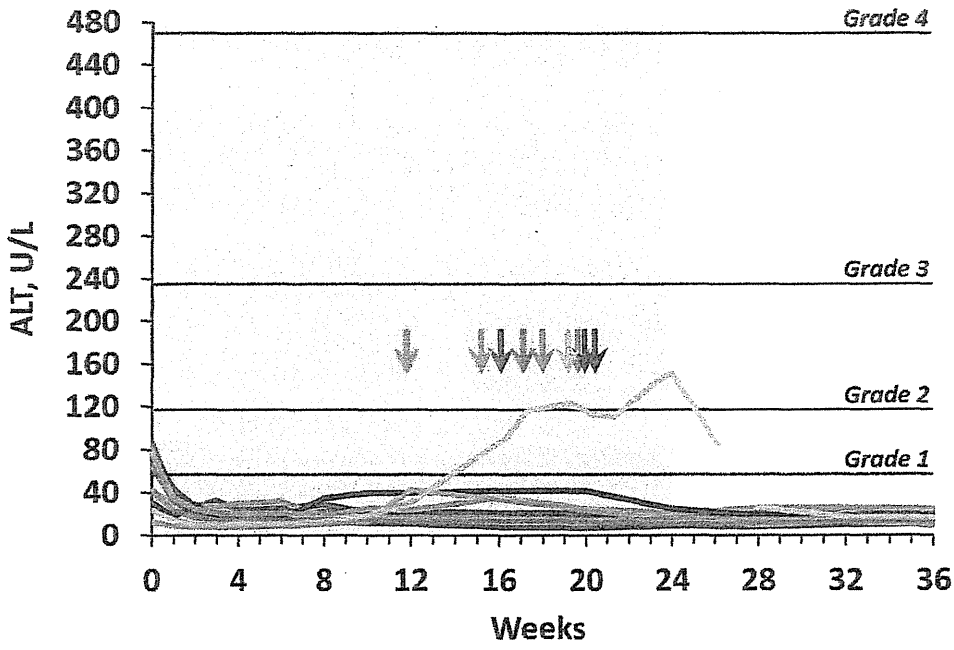

Figure 1
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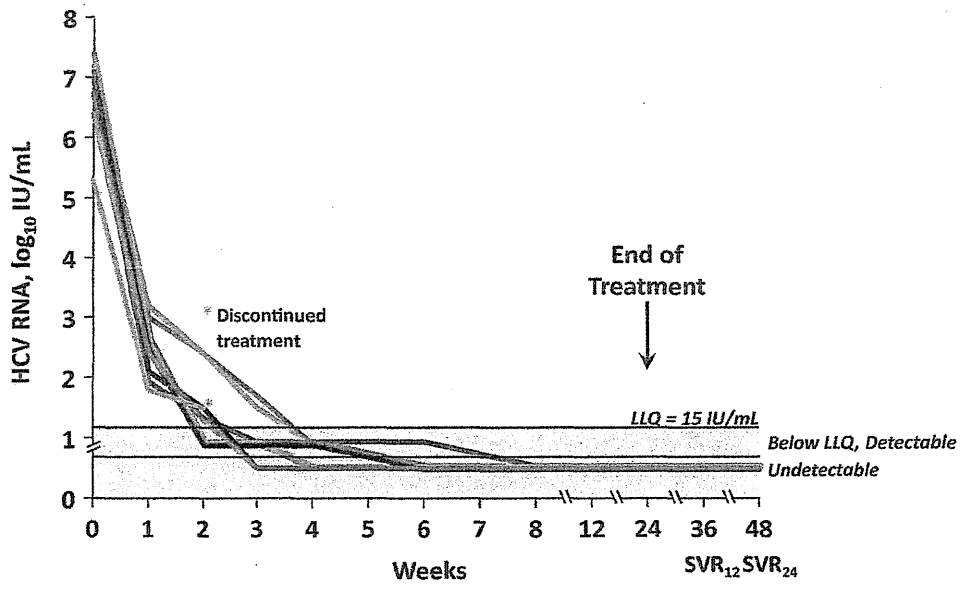

Figure 2
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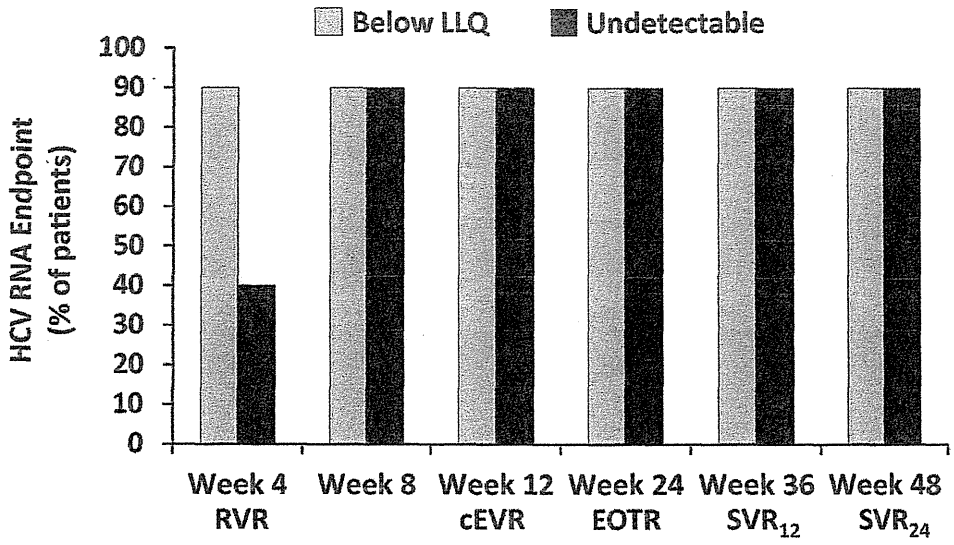

Figure 3
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Original Article

Hepatic steatosis in chronic hepatitis C patients infected with genotype 2 is associated with insulin resistance, hepatic fibrosis and affects cumulative positivity of serum hepatitis C virus RNA in peginterferon and ribavirin combination therapy

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Aim: Hepatic steatosis is one of the factors limiting the virological response to interferon-based antiviral therapy for chronic hepatitis C (CH-C) patients infected with genotype 1, while contradictory results have been reported for genotype 2. We aimed to clarify the effect of hepatic steatosis on therapeutic outcome and cumulative positivity of serum HCV RNA in CH-C patients infected with genotype 2 treated by peginterferon (PEG-IFN)α2b and ribavirin (RBV) combination therapy.

Methods: A total of 74 treatment-naïve non-cirrhotic CH-C patients infected with genotype 2 who received PEG-IFNα2b and RBV according to the standard regimen were divided into hepatic steatosis 0–10% and >10% groups. The clinical backgrounds, sustained virological response (SVR) rates and cumulative positivity of serum HCV RNA were compared between the two groups.

Results: Among the 74 patients, 61 (82.4%) had hepatic steatosis 0–10% and 13 (17.6%) had hepatic steatosis >10%. Scores of homeostasis model assessment-insulin resistance and hepatic fibrosis were higher in patients with hepatic steatosis >10% than hepatic steatosis 0–10% ($P = 0.040$ and 0.042, respectively). Non-SVR was more frequent in patients with hepatic steatosis >10% than hepatic steatosis 0–10% ($P = 0.003$). Cumulative positivity of serum HCV RNA was significantly higher in patients with hepatic steatosis >10% than hepatic steatosis 0–10% ($P = 0.004$).

Conclusions: In CH-C patients infected with genotype 2 treated by PEG-IFNα2b and RBV combination therapy, hepatic steatosis >10% was associated with increased insulin resistance, advanced hepatic fibrosis and higher cumulative positivity of serum HCV RNA, which lead to a higher risk of non-SVR.

Key words: chronic hepatitis C, genotype 2, hepatic fibrosis, hepatic steatosis, homeostasis model assessment-insulin resistance

INTRODUCTION

WITH ADVANCES IN the practice of clinical hepatology, around 50% of chronic hepatitis C (CH-C) patients infected with genotype 1, and more than 80% of genotype 2, can be cured by peginterferon (PEG-IFN) and ribavirin (RBV) combination therapy.[1,2] However, although PEG-IFN and RBV combination therapy is a powerful tool for the treatment of CH-C patients infected with genotype 2 worldwide, a significant number remain viremic.

Because of the high rate of sustained virological response (SVR) to PEG-IFN and RBV combination therapy in CH-C patients infected with genotype 2, the clinical backgrounds associated with resistance to therapy have not been evaluated in detail. Previously, CH-C patients infected with genotype 2 who had

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hepatic steatosis were reported to be resistant to interferon (IFN) monotherapy[3,4] and PEG-IFN and RBV combination therapy,[5] but several recent publications have contradicted these earlier reports.[6,7]

A recent trend in PEG-IFN and RBV combination therapy for CH-C is response-guided therapy. Several trials have evaluated short courses of treatment for CH-C patients infected with genotype 2 or genotype 3 with a rapid virological response (RVR) but controversial results also have been reported.[8–13] Recent papers on genotype 2/3 patients reported that low platelet counts and a body mass index (BMI) of 30 or higher are associated with relapse of RVR after a short regimen of 12 weeks,[14] and a body weight greater than 75 kg also affected the probability of relapse,[15] whereas the impact of hepatic steatosis on the anti-viral effect was not fully studied. In the present study, we investigated the effects of hepatic steatosis on clinical backgrounds of CH-C patients infected with genotype 2. Specifically, we investigated the impact of hepatic steatosis on cumulative positivity of serum HCV RNA during PEG-IFN and RBV combination therapy and therapeutic outcome.

METHODS

Patients

THIS STUDY WAS conducted at the university hospital of Kyoto Prefectural University of Medicine, Kyoto, Japan and related hospitals in Kinki Area (Kyoto, Osaka, Nara, Shiga Prefecture). The study protocol was approved by the ethical committee of each institution in 2005. Written informed consent was obtained from all patients before treatment. Enrollment of the patients began in January 2006 and ended in December 2008 and the follow up study was completed in August 2009. Patients with liver cirrhosis, co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, and Wilson's disease were excluded. Patients with uncontrollable hypertension or diabetes mellitus, BMI ≥30 kg/m^2, and those with a history of alcohol abuse also were excluded. The criteria for enrollment were platelet count (PLT) greater than 10×10^4/mm^3, neutrophil count greater than 1100/mm^3, and hemoglobin concentration greater than 11.0 g/dL.

Among the 136 patients enrolled, 10 dropped out because of severe adverse effects and eight were lost to follow up. Forty-four patients without liver biopsy also were excluded. Finally, 74 eligible and previously untreated Japanese CH-C patients infected with genotype 2, aged 27 to 73 years and who had high viral loads (≥100 KIU/mL by the Amplicor HCV RNA kit, version 2.0, Roche Diagnostics, Tokyo, Japan), were studied.

All 74 patients had provided a liver biopsy within a year prior to treatment. Liver biopsy was performed using a Sure-cut needle guided by ultrasound. Liver biopsy specimens were fixed in 10% formalin and stained with hematoxylin and eosin and Masson's trichrome. Histopathological diagnosis was based on the scoring of New Inuyama classification.[16] The fibrosis scores were F0: no fibrosis, F1: portal fibrous widening, F2: portal fibrous widening with bridging fibrosis, F3: bridging fibrosis plus lobular distortion. The inflammation scores were A0: none to minimal, A1: mild, A2: moderate, A3: severe. Evaluation of the percentage of hepatic steatosis was carried out by two expert hepatologists who were blinded to the treatment outcome of each patient and classified as ≥0% and ≤1%, >1% and ≤5%, >5% and ≤10%, >10% and ≤15%, >15% and ≤20%, >20% and ≤25%, >25% and ≤30%.

Study design

All patients received weekly injections of PEG-IFNα2b (PEG-INTRON; Shering-Plough, Kenilworth, NJ, USA) of 1.5 μg/kg·bw and oral administration of RBV (Rebetol; Shering-Plough) of 600 to 1000 mg/day according to the 24 week standard regimen. The amount of RBV was adjusted based on body weight (bw): 600 mg for <60 kg.bw, 800 mg for ≥60 kg.bw and <80 kg.bw, 1000 mg for ≥80 kg.bw. The dose of PEG-IFNα2b was decreased by 50% when the PLT count fell below 8×10^4/mm^3 or the neutrophil count fell below 750/mm^3. The dose of RBV was lowered by 200 mg/day when the hemoglobin concentration fell below 10 g/dL. The full dose was reinstated when the adverse events improved.

Hepatitis C virus RNA negativity at treatment week 4, based on a qualitative polymerase chain reaction (PCR) assay, was defined as RVR. HCV RNA negativity at 24 weeks after the cessation of combination therapy was defined as SVR. Those who failed to attain SVR were defined as non-SVR patients. All patients were examined serially (at 2, 4, 8, 12, 24 weeks) by qualitative HCV RNA assays and again 24 weeks after termination of the therapy.

Statistical analysis

All data analyses were carried out using the SPSS statistical software (version 17.0, SPSS Inc., Chicago, IL, USA). Individual characteristics were compared between the groups using the Mann-Whitney *U*-test or Fisher's exact test. For some variables, receiver operating characteristic analysis was performed followed by proper cat-

egorization of the data. Cumulative positivity of serum HCV RNA was calculated by the Kaplan–Meier method and analyzed by the log-rank test. A *P*-value of <0.05 was considered to be statistically significant.

RESULTS

Evaluation of hepatic steatosis in chronic hepatitis C patients infected with genotype 2

RECEIVER OPERATING CHARACTERISTIC curve analysis was performed to examine the relationship between hepatic steatosis and SVR (Fig. 1). Because the sum of sensitivity and specificity was maximum when the hepatic steatosis was 11.50% (data not shown), we classified the patients into hepatic steatosis 0–10% and hepatic steatosis >10% groups. Based on these results, the degree of hepatic steatosis was classified into seven categories from ≥0% and ≤1% to >25% and ≤30% (Fig. 2) and presented separately for the SVR and non-SVR groups (Table 1).

Correlation between hepatic steatosis and clinical and other histological features

The baseline characteristics of the 74 patients (31 male and 43 female) with chronic hepatitis C infected with genotype 2 are shown in Table 2. There were no significant differences between the patients with hepatic steatosis 0–10% and hepatic steatosis >10% in clinical backgrounds such as gender, age, baseline HCV RNA load and other laboratory data, except that homeostasis model assessment-insulin resistance (HOMA-IR) was significantly ($P = 0.040$) higher in patients with hepatic steatosis >10%. BMI and γ-glutamyl transferase (γ-GTP) also tended to be higher in patients with hepatic steatosis >10%; however, statistical significances were not demonstrated ($P = 0.052$ and $P = 0.050$, respectively). The scores of hepatic fibrosis, but not of hepatic inflammation, were significantly ($P = 0.042$) higher in patients with hepatic steatosis >10% (Table 3). Although we investigated the factors associated with hepatic steatosis >10% by multivariate regression analysis, neither HOMA-IR nor hepatic fibrosis were independently associated with it.

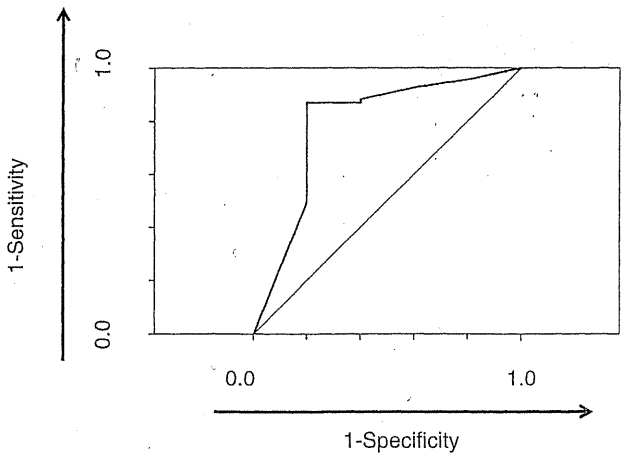

Figure 1 Receiver operating characteristic curve analysis of hepatic steatosis and sustained virological response (SVR). Receiver operating characteristic curve analysis was performed to examine the relationship between hepatic steatosis and SVR in all patients. Because the sum of sensitivity and specificity was maximum when the hepatic steatosis was 11.50% (data not shown), we classified the patients into hepatic steatosis 0–10% and hepatic steatosis >10% groups.

Table 1 Hepatic steatosis in chronic hepatitis C patients infected with genotype 2

Hepatic steatosis (%)	No. patients		
	SVR	non-SVR	Total
–1%	34	1	35
–5%	17	0	17
–10%	9	0	9
–15%	1	1	2
–20%	3	1	4
–25%	2	1	3
–30%	3	1	4
	69	5	74
IL28B major homo/ hetero (total)	10/0 (10)	3/2 (5)	

The degree of hepatic steatosis was classified as ≥0% and ≤1%, >1% and ≤5%, >5% and ≤10%, >10% and ≤15%, >15% and ≤20%, >20% and ≤25%, >25% and ≤30% and presented for the SVR and non-SVR groups.
SVR, sustained virological response.

Impact of hepatic steatosis on therapeutic response

The relationship between hepatic steatosis and SVR or RVR ratio is shown in Table 3. The SVR ratio of patients with hepatic steatosis 0–10% was significantly ($P = 0.003$) higher than that of patients with hepatic steatosis >10% and the RVR ratio of patients with hepatic steatosis 0–10% also tended to be higher; however, statistical significance was not demonstrated ($P = 0.055$). This result tempted us to investigate the impact of hepatic steatosis on the cumulative positivity of serum HCV RNA in the early phase of PEG-IFNα2b and RBV combination therapy.

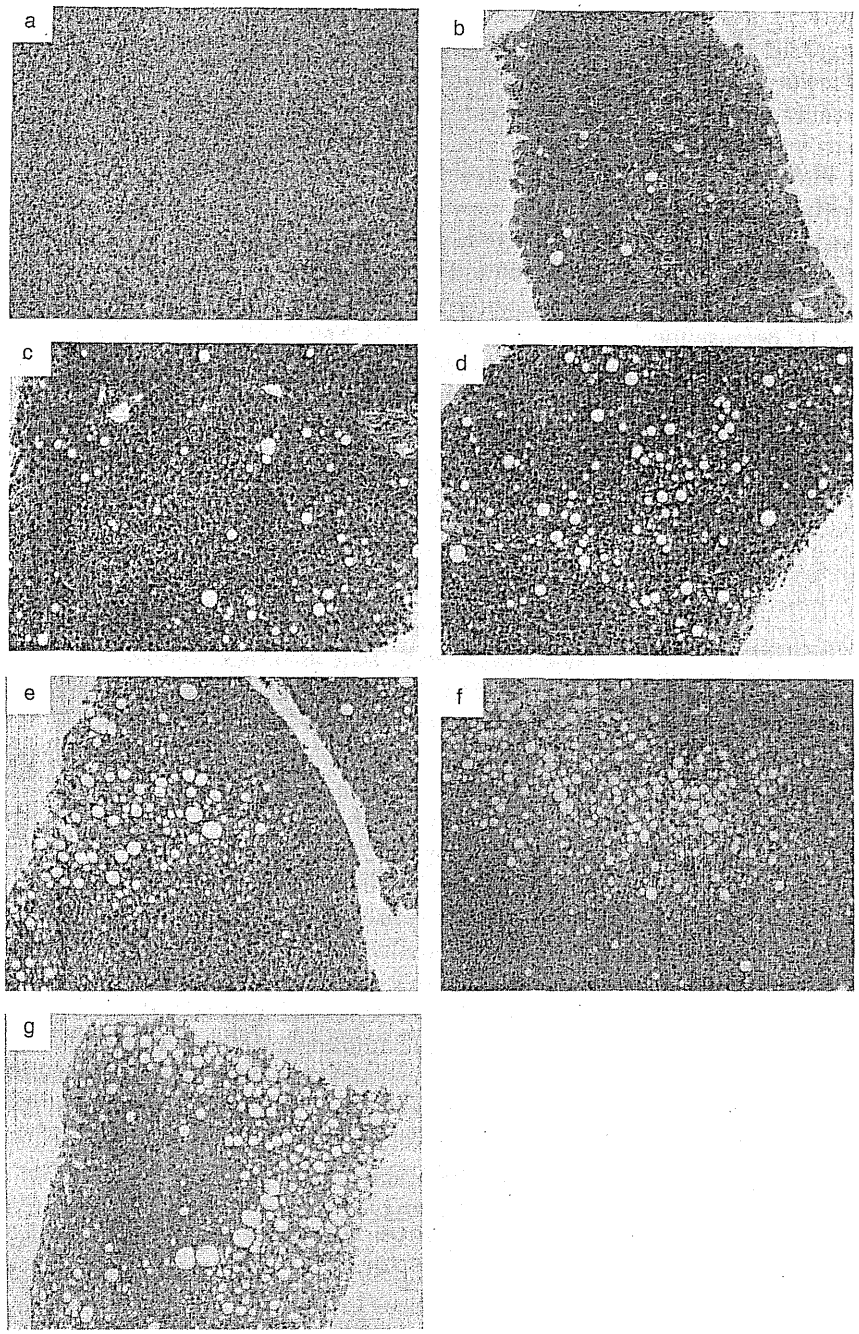

Figure 2 Histological classification of hepatic steatosis. Typical histological classification was presented. The degree of hepatic steatosis was classified as ≥0% and ≤1% (a), >1% and ≤5% (b), >5% and ≤10% (c), >10% and ≤15% (d), >15% and ≤20% (e), >20% and ≤25% (f), >25% and ≤30% (g) by two hepatologists who were blinded to the treatment outcome of each patient.

Impact of hepatic steatosis on cumulative positivity of serum HCV RNA

Here, we divided the patients based on receiver operating characteristic curve analysis and demonstrated that hepatic steatosis >10% was associated with resistance to PEG-IFNα2b and RBV combination therapy for CH-C patients infected with genotype 2. To support this finding, we compared the cumulative positivity of serum HCV RNA between the patients with hepatic steatosis 0–10% and those with hepatic steatosis >10% in the early phase of PEG-IFNα2b and RBV combination therapy using the Kaplan–Meier method.

The patients with hepatic steatosis >10% had a significantly ($P = 0.004$) higher cumulative positivity of HCV RNA than the patients with hepatic steatosis

Table 2 Relationship between hepatic steatosis (0–10% or >10%) and the clinical backgrounds of the patients

Hepatic steatosis	>10% (13) Median [range]	0–10% (61) Median [range]	*P*-value
Genotype 2a/2b/N.D.	5/6/2	28/13/10	0.148
Gender (M/F)	5/8	26/35	0.782
Age (years)	56 [33.0–70.0]	54 [27.0–73.0]	0.430
BMI (kg/m^2)	23.9 [19.9–28.8]	22.0 [17.5–29.6]*	0.052
HCVRNA (KIU/mL)	1850 [120–5000]†	1300 [130–5000]†	0.439
Hb (g/dL)	14.5 [11.8–15.1]	13.9 [11.3–17.4]	0.691
Plt (×10^4/mm^3)	19.2 [10.6–24.0]	18.9 [10.4–37.9]	0.551
WBC (×10^3/mm^3)	5.20 [3.33–7.40]	4.90 [2.30–9.40]	0.612
ALT (IU/L)	78 [16.0–248]	47 [15.0–377]	0.125
rGTP (IU/L)	56 [19–285]	23 [8–158]*	0.050
T-chol (mg/dL)	187 [130–250]	178 [108–274]	0.227
Feritin (ng/dL)	150 [22–1107]	103 [20–664]‡	0.330
HOMA-IR	4.6 [1.5–6.5]	2.0 [0.3–11.3]*	0.040
Creatinine (mg/dL)	0.6 [0.5–0.9]	0.7 [0.3–1.1]	0.172

The clinical backgrounds of the 74 patients were compared by Mann–Whitney *U*-test or Fisher's exact test. Continuous variables are presented as medians (ranges). Individual characteristics between the groups were evaluated using the Mann–Whitney *U*-test. All patients with >10% hepatic steatosis were evaluated for each parameter. In patients with 0–10% hepatic steatosis *60 patients were evaluated for body mass index (BMI), 56 patients for γ-glutamyl transferase (γ-GTP) and homeostasis model assessment-insulin resistance (HOMA-IR). †The upper limit of measurement is 5000 KIU/mL. ‡The lower limit of measurement is 20 ng/dL.
ALT, alanine aminotransferase; F, female; Hb, hemoglobin; HCV, hepatitis C virus; M, male; N.D., not determined; PLT platelet count; T-chol, total cholesterol; WBC, white blood cell count.

0–10% (Fig. 3). To exclude the possibility that adherence to PEG-IFNα2b or RBV influenced the changes in serum HCV RNA in this study, we examined the cumulative positivity of serum HCV RNA in patients who achieved ≥80% adherence (as a percentage of the expected total dose) to both PEG-IFNα2b and RBV. Patients with hepatic steatosis >10% also had significantly ($P = 0.045$) higher cumulative positivity of serum HCV RNA than those with hepatic steatosis 0–10% (data not shown). The SVR ratio of patients with ≥80% adherence to both PEG-IFNα2b and RBV did not differ significantly from those without (data not shown).

DISCUSSION

PREVIOUS PAPERS[3–5] REPORTED that hepatic steatosis affected the efficacy of IFN-based therapy for CH-C patients infected with genotype 2, whereas recent papers by Poustchi *et al.*[6] and Rodriguez-Torres *et al.*[7] denied it. Because steatosis was roughly graded (for example, less than 5%, 5–33%, 34–66%, and more than 67%) in these studies, we considered that tight grading of hepatic steatosis may lead to a different result. As we have expected, in the present study, tight grading of hepatic steatosis revealed a close relation between

Table 3 Relationship between hepatic steatosis (0–10% or >10%) and other histological features and therapeutic response

Hepatic steatosis	>10%	0–10%	*P*-value
Hepatic inflammation (0,1/2,3)	5/8	37/24	0.143
Hepatic fibrosis (0,1/2,3)	5/8	42/19	0.042
Hepatic iron deposit Yes/No/N.D.	3/5/5	16/39/6	0.455
Rapid virological response Yes/No	6/7	45/16	0.055
Sustained virological response Yes/No	9/4	60/1	0.003

The histological findings of the 74 patients were evaluated according to the scoring system of New Inuyama classification.[16] Histological features such as inflammation, fibrosis and iron deposition, were compared between the hepatic steatosis 0–10% and >10% groups by Fisher's exact test. The ratio of rapid virological response and sustained virological response were compared between the hepatic steatosis 0–10% and >10% groups by Fisher's exact test.
N.D., not determined.

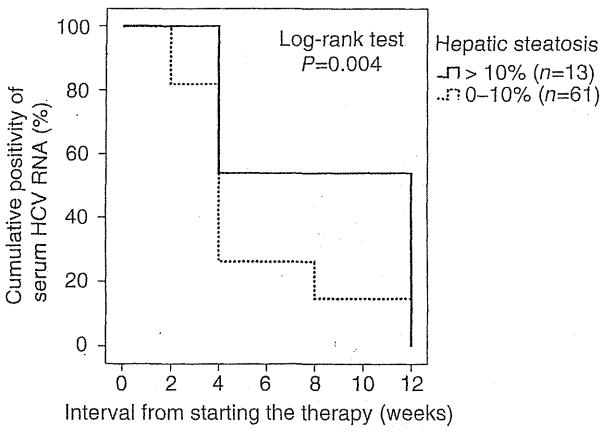

Figure 3 Cumulative positivity of serum hepatitis C virus (HCV) RNA during the early phase of pegylated interferon (PEG-IFN)α2b and ribavirin (RBV) combination therapy. Cumulative positivity of serum HCV RNA as determined by qualitative HCV RNA assay was compared between the hepatic steatosis >10% and hepatic steatosis 0–10% groups using the Kaplan–Meier method, and then analyzed by log-rank test. A *P*-value of <0.05 was considered to be statistically significant. (⌐¬): >10% ($n = 13$); (···): 0–10% ($n = 61$).

hepatic steatosis and HOMA-IR, hepatic fibrosis, and especially, cumulative positivity of serum HCV RNA during the PEG-IFN/RBV combination therapy, which was not studied as far as we investigated.

In response-guided therapy for hepatitis C, early disappearance of HCV RNA from the serum is the best predictor of SVR.[17] Therefore, our finding that >10% hepatic steatosis affected the cumulative positivity of serum HCV RNA during the PEG-IFN/RBV combination therapy for genotype 2 infected patients is useful to establish more accurate prediction of therapeutic outcome. So, we think that evaluation of hepatic steatosis before PEG-IFN/RBV combination therapy is very important.

The percentage of patients with hepatic steatosis >10% varies according to the papers; however, our result that patients with hepatic steatosis >10% was 17.6% (13/74) do not seem to be extraordinary considering a report by Rodriguez-Torres *et al.*[7] or a recent paper by Kurosaki *et al.*[18] Our results showing that hepatic steatosis >10% was associated with higher HOMA-IR and advanced hepatic fibrosis (Tables 2,3) are reasonable, judging from previous reports.[19,20] While the number of non-SVR patients was small, hepatic steatosis >10% was associated with resistance to PEG-IFN and RBV combination therapy (Table 3). To support this finding, we compared the cumulative positivity of serum HCV RNA between the patients with hepatic steatosis >10% and ≤10% and found that it was significantly ($P = 0.004$) higher in patients with hepatic steatosis >10%, compared to those without.

Patton *et al.*[20] demonstrated first that hepatic steatosis reduced the likelihood of achieving SVR in CH-C patients infected with genotype 1. This finding was confirmed by Lok *et al.*[21] in non-diabetic patients. Our result that hepatic steatosis >10% was associated with resistance to combination therapy in CH-C patients infected with genotype 2 is supported by the report by Poynard *et al.*[5] showing that absence of hepatic steatosis was associated with a higher SVR ratio to PEG-IFN and RBV combination therapy, except for genotype 3. In our study, in addition, increased cumulative positivity of HCV RNA was demonstrated in patients with hepatic steatosis >10% (Fig. 3). We speculate that there is a close relationship between hepatic steatosis >10% and impaired IFN-mediated anti-HCV activity in CH-C patients infected with genotype 2.

It is well known that metabolic diseases such as diabetes mellitus can trigger hepatic steatosis and HCV infection also causes hepatic steatosis by way of increased expression of genes including sterol regulatory element-binding protein 1c.[22] Recently, Vanni *et al.*[23] demonstrated that HCV infected patients with more hepatic steatosis revealed higher intra-hepatic lipid oxidation, which in turn stimulated gluconeogenesis and induced higher suppressor of cytokine signaling-3 (SOCS-3) expression resulting in increased insulin resistance. Because IFN unresponsiveness is, in part, linked to upregulated hepatic expression of SOCS-3 and insulin resistance as shown by increased HOMA-IR,[24] we hypothesize that enhanced hepatic staetosis in CH-C patients infected with genotype 2 may be associated with increased insulin resistance and increased hepatic expression of SOCS-3, which might have interfered with IFN signal transduction pathway.[25] It should be clarified whether or not hepatic steatosis in CH-C patients infected with genotype 2 really links to IFN unresponsiveness through this molecular pathway in the next study.

To exclude the possibility that adherence to PEG-IFNα2b or RBV may have influenced the response to the therapy, we compared the cumulative positivity of serum HCV RNA among the patients with ≥80% adherence to both drugs and demonstrated that patients with hepatic steatosis >10% showed a higher cumulative positive serum HCV RNA (data not shown).

Recently, an interleukin 28B (IL28B) gene polymorphism has been reported to be strongly associated with

the response to PEG-IFN and RBV combination therapy for CH-C.[26–28] In Japanese patients, in particular, a single nucleotide polymorphism (SNP rs8099917) near the IL28B gene on chromosome 19 was shown to be strongly associated with non-virological response in genotypes 1.[27] However, in genotype 2, this association was weak especially in genotype 2a.[29,30] A recent paper from Japan reported that CH-C patients infected with genotype 1b who showed hepatic steatosis >10% were likely to harbor IL28B minor allele (TG or GG genotype).[18] In our preliminary retrospective data, two out of five (40%) non-SVR patients had the TG genotype and ten out of ten (100%) of SVR patients had the TT genotype (Table 1). The relationship between hepatic steatosis and IL28B polymorphism may be an interesting subject for further investigation.

In conclusion, CH-C patients infected with genotype 2 with hepatic steatosis >10% showed resistance to PEG-IFNα2b and RBV combination therapy. Considering cost minimization, a variable-duration regimen is recommended.[31] We advocate that CH-C patients infected with genotype 2 should be evaluated for hepatic steatosis by biopsied liver specimens before starting PEG-IFN and RBV combination therapy. In combination with other factors such as mutations in HCV and IL28B gene polymorphism,[30] evaluation of hepatic steatosis will enable us to more accurately predict the outcome of CH-C patients infected with genotype 2 in PEG-IFN and RBV combination therapy.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Antiviral effects of peginterferon alpha-2b and ribavirin following 24-week monotherapy of telaprevir in Japanese hepatitis C patients

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Abstract
Background/aims Anemia is commonly observed as a side effect in a treatment with protease inhibitors combined with peginterferon alpha and ribavirin for hepatitis C virus infection. This study assessed the safety, tolerability, viral kinetics, and selection of variants in telaprevir monotherapy for 24 weeks, and outcomes of the off-study treatment with peginterferon alpha-2b and ribavirin among Japanese female patients at a median age of 54 years who were difficult to treat with the standard therapy (peginterferon alpha-2b and ribavirin) alone in Japan.
Methods Four treatment-naïve patients with chronic hepatitis C virus subtype 1b infection received telaprevir (750 mg every 8 h) alone for 24 weeks. All patients then started the off-study treatment with peginterferon alpha-2b and ribavirin. Safety, tolerability, hepatitis C virus RNA levels, and emergence of telaprevir-resistant variants were monitored.
Results During the 24 weeks of telaprevir monotherapy, there was no discontinuation due to adverse events, but 2 patients stopped the intake at weeks 6 and 15 because of viral breakthrough. Emergence of telaprevir-resistant variants was observed in 3 patients who showed viral breakthrough. These variants were eliminated by the off-study treatment, and sustained virological response was achieved in all patients.
Conclusions Anemia was manageable by carefully adjusting the ribavirin dosage in the standard therapy that followed telaprevir monotherapy. This sequential regimen seems to be safer and more tolerable than the triple combination of telaprevir, peginterferon alpha, and ribavirin, especially among elderly females with low baseline hemoglobin.

Keywords Hepatitis C therapy · Telaprevir · Ribavirin · Anemia

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Introduction

Hepatitis C virus (HCV) is a major cause for concern worldwide. More than 3% of the world's population is chronically infected with HCV, and 3–4 million people are newly infected each year [1]. Chronic HCV infection is relatively mild and progresses slowly; however, about 20% of chronic hepatitis C (CHC) carriers progress to potentially serious end-stage liver disease [2–4]. The current standard treatment for HCV infection is administration of pegylated alpha interferon (PEG-IFN) in combination with ribavirin (RBV) for 48 weeks. The overall sustained virological response (SVR) rates with this intervention are