Predictive value of the IFNL4 polymorphism on outcome of telaprevir, peginterferon and ribavirin therapy for older patients with genotype 1b chronic hepatitis C

Hatsue Fujino[1], Michio Imamura[1], Yuko Nagaoki[1], Yoshiiku Kawakami[1], Hiromi Abe[1], C. Nelson Hayes[1], Hiromi Kan[1], Takayuki Fukuhara[1], Tomoki Kobayashi[1], Keiichi Masaki[1], Atsushi Ono[1], Takashi Nakahara[1], Youji Honda[1], Noriaki Naeshiro[1], Ayako Urabe[1], Satoe Yokoyama[1], Daisuke Miyaki[1], Eisuke Murakami[1], Tomokazu Kawaoka[1], Nobuhiko Hiraga[1], Masataka Tsuge[1], Akira Hiramatsu[1], Hideyuki Hyogo[1], Hiroshi Aikata[1], Shoichi Takahashi[1], Daiki Miki[2], Hidenori Ochi[2], Waka Ohishi[3], Kazuaki Chayama[1,2] and Hiroshima Liver Study Group

[1]Department of Gastroenterology and Metabolism, Applied Life Science, Institute of Biomedical & Health Science, Hiroshima University, Hiroshima, Japan

[2]Laboratory for Digestive Diseases, Center for Genomic Medicine, The Institute of Physical and Chemical Research (RIKEN), Hiroshima, Japan

[3]Department of Clinical Studies, Radiation Effects Research Foundation, Hiroshima, Japan

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Corresponding author:

Prof. Kazuaki Chayama, MD, PhD

Department of Gastroenterology and Metabolism, Applied Life Sciences

Institute of Biomedical & Health Sciences, Hiroshima University

1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan

Tel: +81-82-257-5190, Fax: +81-82-255-6220

E-mail: chayama@hiroshima-u.ac.jp

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Abstract (236 out of 250 words**)**

Background: Older patients with chronic hepatitis C have a lower virological response to interferon (IFN) treatment compared to younger patients. The efficacy of telaprevir (TVR), PEG-IFN plus ribavirin (RBV) combination therapy and the predictive value of recently identified IFN lambda (IFNL) 4 polymorphisms on the outcome of therapy for older patients have not been addressed.

Methods: We assessed predictive factors for sustained virological response (SVR) to triple therapy in 226 younger (≤65 years) and 87 older (>65 years) Japanese patients with chronic genotype 1 hepatitis C. IFNL4 polymorphism ss469415590 was analyzed by Invader assay.

Result: The SVR rate for older patients was slightly lower than for younger patients (69% vs 82%, p=0.043). In the older group, the SVR rate for patients with the IFNL4 TT/TT genotype was significantly higher than patients with TT/ΔG or ΔG/ΔG genotypes (81.8% and 42.9%, p=0.003). In multivariate regression analysis, rapid virological response (OR 36.601, p=0.002) and IFNL4 TT/TT genotype (OR 19.502, p=0.009) were identified as significant independent predictors for SVR in older patients. Treatment-related decrease in hemoglobin and increase in serum creatinine were higher in older patients than younger patients. Reduction of initial TVR dose to 1,500 mg per day alleviated these adverse events without compromising SVR rate in older patiens.

Conclusions: Analysis of IFNL4 polymorphisms is a valuable predictor in older patients receiving TVR triple therapy. 1,500 mg per day is a suitable initial TVR dose for older Japanese patients.

Key words: hepatitis C virus, telaprevir, older patients, IFNL4, RVR

Introduction

Hepatitis C virus (HCV) infection affects more than 3% of the world's population [1] and often causes cirrhosis and hepatocellular carcinoma (HCC) [2, 3]. To prevent the development of HCC and advanced liver disease, interferon (IFN)-based therapies are administered to patients with chronic HCV infection. Success of chronic HCV infection treatment with pegylated IFN-alpha (PEG-IFN) and ribavirin (RBV) varies by HCV genotype, and HCV genotype 1 tends to be less responsive to PEG-IFN/RBV.

Average patient age has been increasing in Japan [4], and such older patients have a lower virological response with PEG-IFN/RBV treatment compared to younger patients [5-7]. Anemia and other adverse events also occur more frequently in older patients [8, 9].

Recently telaprevir (TVR) has been approved for clinical use in several countries. Patients with high viral load of genotype 1 are treated with a three-drug combination therapy of TVR and PEG-IFN/RBV for 24 weeks. Since TVR is a selective inhibitor of HCV NS3/4A protease activity, marked improvement in sustained virological response (SVR) rates are expected [10-14]. Furusho et al. examined the efficacy of triple therapy among older Japanese patients [15], but the effects of TVR dose reduction on treatment response and adverse events for older patients are unknown.

Recent genome-wide association studies have shown that common single nucleotide polymorphisms (SNPs) rs8099917 and rs12979860 near the *interleukin (IL)-28B* gene on chromosome 19 are strongly associated with outcome of both PEG-IFN plus RBV [16-19] dual therapy and TVR, PEG-IFN and RBV triple therapy [20, 21]. More recently, a polymorphism (ss469415590) within the gene encoding a novel interferon-lambda 4 (IFNL4) protein has been found to be more strongly associated with HCV clearance and outcome of PEG-IFN plus RBV combination treatment compared to rs12979860 [22]. IFNL4 protein can

be produced by individuals who carry the ΔG allele of the ss469415590 variant (IFNL4-ΔG) but not by individuals who are homozygous for the IFNL4-TT allele because of a frameshift in exon 1 caused by the insertion variant [22]. The rs12979860 variant is located within intron 1 of IFNL4. Linkage disequilibrium is strong between the IFNL4-ΔG allele and the unfavorable rs12979860-T allele in individuals of European or Asian ancestry, whereas this linkage disequilibrium is moderate in individuals of African ancestry. Compared to rs12979860, ss469415590 is more strongly associated with HCV clearance in individuals of African ancestry, although it provides comparable information in Europeans and Asians.

In the present study, we assessed the efficacy of the IFNL4 polymorphism and the effect of TVR dose reduction on treatment response and adverse events on TVR, PEG-IFN plus RBV triple therapy in older Japanese patients.

Methods

Patients

A total of 313 patients with chronic genotype 1 HCV infection who were treated with TVR, PEG-IFNα2b and RBV triple therapy between November 2011 and July 2013 at Hiroshima University Hospital and hospitals belonging to the Hiroshima Liver Study Group were enrolled. Inclusion criteria for the therapy included remaining positive for genotype 1 HCV RNA for 6 months and having an HCV RNA level ≥5.0 log IU/mL, as determined by the COBAS TaqMan HCV test (Roche Diagnostics KK). Patients with cirrhosis were excluded.

Patients were classified according to response to prior interferon therapy. Non-responders never became HCV RNA negative during prior therapy, whereas relapsers became HCV RNA negative before the end of treatment but reverted to being HCV RNA

positive after treatment was discontinued.

HCV RNA Levels

HCV RNA levels were measured using the TaqMan reverse transcription polymerase chain reaction (PCR) test. The linear dynamic range was 1.2-7.8 log IU/ml. Samples that exceeded the measurement range were diluted with phosphate-buffered saline and reanalyzed. Amino acid substitutions at position 70 in the HCV core protein (core70) were determined using direct sequencing of PCR products after extraction and reverse transcription of HCV RNA as in Akuta et al. [23, 24].

Single-Nucleotide Polymorphism (SNP) Genotyping

Each patient was genotyped for rs8099917 in the IL28B locus, ss469415590 in the IFNL4 locus and rs1127354, an inosine triphosphate pyrophosphate (ITPA) SNP reported to be associated with ribavirin-induced anemia [25-27]. Samples were genotyped using the Illumina HumanHap610-Quad Genotyping BeadChip or with the Invader or TaqMan assays, as described previously [28, 29].

Therapeutic protocol

In this study, 750 mg of TVR (Telavic; Mitsubishi Tanabe Pharma, Osaka, Japan) were administered 3 times a day at 8-hour intervals after meals (2,250 mg/day) in 174 patients and twice per day (1,500 mg/day) in 139 patients. The TVR dose was determined by each physician according to age, sex, body weight and hemoglobin level. PEG-IFNα2b (PEG-Intron, MSD, Tokyo, Japan) was injected subcutaneously at a median dose of 1.5 μg/kg once per week (50-150μg/week). 200-600 mg of RBV (Rebetol, MSD) was administered after breakfast and dinner. The RBV dose was adjusted by body weight (600 mg

for <60 kg; 800 mg for 60-80 kg; and 1,000 mg for >80 kg). Triple therapy with PEG-IFNα2b, RBV, and TVR was continued for 12 weeks and then switched to PEG-IFNα2b and RBV dual therapy for an additional 12 weeks. Completion of the treatment was defined as completion of both the 12 weeks of TVR and the 24 weeks of PEG-IFN/RBV treatment.

Efficacy of the treatment

Sustained virological response (SVR) was defined as undetectable serum HCV RNA at 24 weeks after the end of treatment. Rapid virological response (RVR) was defined as undetectable HCV RNA at week 4 of treatment.

Statistical analysis

Continuous variables are presented as median and range and were analyzed using the Mann-Whitney *U*-test. Categorical variables were compared using the chi-square or Fisher exact test, as appropriate. Multivariate analysis was conducted with a Cox proportional hazard model using the stepwise selection of variables or two logistic analyses. All statistical analyses were performed using the SPSS software package (version 12.0 for Windows, SPSS Inc., Chicago, IL, USA), with $p < 0.05$ denoting statistical significance.

Results

Baseline patient characteristics

Patients are grouped according to age (younger: ≤65 years, n=226; older: >65 years, n=87) in Table 1. As IFNL4 SNP ss469415590 is in strong linkage disequilibrium with IL28B SNPs rs8099917 and rs12979860 [22], only 4 out of 313 patients (1.3%) showed discrepant

haplotypes in this study. In older patients, hemoglobin levels were lower and serum creatinine levels were higher than in younger patients. More older patients received a reduced initial dose of TVR (1,500 mg) compared to younger patients. The older group included 17 treatment-naïve patients, 40 prior relapsers and 30 previous non-responders. The younger group included 96 treatment-naïve patients, 94 prior relapsers and 63 previous non-responders *(p*=0.138).

The initial average dosage based on weight of TVR was similar between older and younger patients (32.6 ± 0.97 vs. 32.0 ± 0.54 mg/kg); however, the initial PEG-IFNα2b dosage was significantly larger and the RBV dosage was significantly smaller in older patients compared to younger patients (1.49 ± 0.02 vs 1.46 ± 0.01 μg/kg, *p*=0.04 and 10.1 ± 0.3 vs 11.0 ± 0.14 mg/kg, *p*=0.012, respectively).

Sustained virological response by age

Outcome of therapy could be determined for 154 out of the 226 younger patients and 58 out of the 87 older patients. The SVR rate for older patients was slightly lower than that for younger patients (69% vs 82%, *p*=0.043) (Fig. 1). SVR was more likely to be achieved in treatment-naïve patients and prior relapsers than in prior non-responders in both younger (94% vs 57%, *p*<0.001) and older patients (84% vs 50%, *p*=0.005). Prior relapsers achieved higher SVR rates regardless of age.

Predictive factors associated with SVR in older and younger patients

In older patients, significant univariate predictors for SVR included clinical factors (platelet count, rs8099917 and ss469415590 genotype), response to prior treatment (naïve or relapse), and on-treatment factors (RVR) (Table 2). In the multivariate model, RVR (OR 36.601 for

non-RVR, p=0.002) and ss469415590 TT/TT genotype (OR 19.502 for TT/ΔG+ΔG/ΔG genotype, p=0.009) were identified as significant independent predictors for SVR for older patients. In younger patients, multiple logistic regression analysis identified three independent predictive factors for SVR: platelet count ≥12×10^4/μl (OR 24.841 for <12×10^4/μl, p=0.012), completion of the treatment (OR 47.776 for discontinuation of the treatment, p=0.013), and IL28B TT genotype (OR 71.693 for TG+GG genotypes, p=0.002) (Table 3).

Effect of IFNL4 genotype and response to previous interferon treatment in older patients

We assessed the relationship between IFNL4 genotype and SVR in older patients. Patients with ss469415590 TT/TT genotype were significantly more likely to achieve SVR compared to those with TT/ΔG or ΔG/ΔG genotypes (82% vs. 43%, *p=0.012*) (Table 2). According to the response to previous IFN treatment, the SVR rate for treatment-naïve and prior relapsers was significantly higher than for prior non-responders in ss469415590 TT/TT (92% vs. 56%, p=0.017) (Fig. 2A).

Relationship of IFNL4 to SVR and RVR in non-responders to prior treatment

RVR was achieved in 37 of 49 (76%) older patients. SVR rates were significantly higer for RVR than in non-RVR in patietnts with both ss469415590 TT/TT (96% vs 50%, *p=0.003*) and TT/ΔG or ΔG/ΔG (64% vs. 0%, *p=0.011*) genotypes (Fig. 2B). No older patient with ss469415590 TT/ΔG or ΔG/ΔG and non-RVR patient achieved SVR.

Adverse events

TVR and PEG-IFN/RBV combination treatment is associated with a high frequency of adverse events such as anemia and renal dysfunction [10-14]. Pre-treatment hemoglobin levels were significantly lower in older patients than younger patients, and serum creatinine

levels were significantly higher (Table 1). Similarly, treatment-related decrease in hemoglobin levels (Fig. 3A) and increase in serum creatinine levels (Fig. 3B) were higher in older patients compared to younger patients. These adverse events resulted in a significantly higher frequency of discontinuation of the treatment in older patients (33% vs. 16%, p=0.008) (Fig. 3C).

The total average dosages based on body weight of TVR, PEG-IFNα2b during the treatment tended to be larger in younger patients than older patients (2,286.5 ± 68.8 vs. 2,076.6 ± 99.0 mg/kg and 31.1 ± 1.1 vs. 28.0 ± 1.5 μg/kg, respectively) and that of RBV was significantly larger in younger patient than older patients (1,068.0 ± 37.9 vs. 903.6 ± 88.8 mg/kg, p=0.004). The difference of the total dosages of agents may be one of the contributing factors for the higher SVR rate in younger patients compared to older patients.

Effect of initial TVR dose on adverse events and treatment response in older patients

33 out of 87 (38%) older patients were treated with an initial TVR dose of 2,250 mg, and the remaining 54 patients (62%) were administered a reduced initial dose of 1,500 mg (Table 1). The average dosage of total TVR based on body weight was significantly larger in patients treated with an initial TVR dose of 2,250 mg than patients with an initial TVR dose of 1,500 mg (*p=0.006*) (Fig.4A). Both the decrease of hemoglobin levels (Fig. 4B) and the increase of creatinine levels (Fig. 4C) in older patients treated with the 1,500 mg TVR dose were smaller than in patients who received the 2,250 mg dose. However, initial TVR dose was not associated with the rate of SVR (Fig. 4D). The oldest patient in this study, an 80 year-old male, was treated with the reduced initial dose of TVR. The patient was able to complete the 24-week treatment and achieved SVR.

Discussion

Elimination of HCV after IFN therapy significantly reduces the risk of hepatocellular carcinoma (HCC) and death in older patients [30]; however, the best way to treat older patients with genotype 1 HCV infection is controversial because of the lower viral response rate and higher frequency of adverse events in this group [7, 31, 32]. In fact, this study also showed that adverse events such as anemia and renal dysfunction were more serious (Figs. 3A and 3B) and SVR rate was significantly lower (Fig. 1) in older patients than younger patients.

In this study, SVR rates were higher in treatment-naïve patients and prior relapsers than prior non-responders in both younger and older patients (Fig. 1). This suggests that treatment-naïve patients and prior treatment relapsers are suitable candidates for triple therapy regardless of age.

SNP ss469415590 in the IFNL4 gene is strongly associated with HCV clearance through both the innate immune reaction and by PEG-IFN plus ribavirin therapy [22]. IFNL4 genotype is also an important predictor of the probability of eradicating the virus by triple therapy. While the SVR rate of older patients with IFNL4 genotype TT/TT was 82%, the eradication rate was 56% even in older patients with non-response to prior therapy (Fig. 2A). In contrast, patients with IFNL4 TT/ΔG or ΔG/ΔG, especially among non-responders to prior therapy, had poor response. Therefore, older patients who have IFNL4 genotype TT/TT should be treated by triple therapy. Older patients with IFNL4 genotype TT/ΔG or ΔG/ΔG are expected to have poor response to the therapy.

IFNL4 SNP ss469415590 is in strong linkage disequilibrium with IL28B SNP rs8099917, especially in Asians [22]. In this study, only 4 out of 313 patients (1.3%) showed discrepant haplotypes. Further analysis with many more patients is needed to determine whether rs8099917 or ss469415590 is more important for prediction of the treatment response. However, to a large extent the polymorphisms provide equivalent information, and patients who have already been genotyped for rs8099917 would probably not benefit from genotyping for ss469415590.

It is important to predict the effect of the therapy as early as possible in older patients. In this study, the rapid change in HCV RNA levels early in treatment is an important predictor of treatment success. More than 85% of patients who achieved RVR also achieved SVR. In contrast, patients who did not achieve RVR showed poor response to the therapy, especially in patients with IFNL4 TT/ΔG or ΔG/ΔG genotypes (Fig. 2B). Accordingly, termination or prolongation of the therapy should be considered when patients with IFNL4 genotypes associated with poor response fail to show RVR in older patients.

The dose of TVR for use in triple therapy was determined based on a dose-finding study conducted in the United States and Europe, which found that the 2,250 mg regimen achieved the greatest reduction of HCV RNA [33]. However, average body weights of Japanese patients are lower than American and European patients. It was reported that the anti-HCV effect of triple therapy was similar when patients were given TVR at 1,500 mg/day compared with those given at 2,250 mg/day in the Japanese patients [34]. In the present study, dose reduction of the initial TVR dose alleviated adverse events such anemia and renal dysfunction (Fig. 4B, 4C) without affecting the virological response rate in older patients (Fig. 4D), suggesting that reduction of TVR might be possible for older patients.

In conclusion, older patients who received triple therapy with TVR and PEG-IFN/RBV showed a lower viral response than younger patients. Analysis of IFNL4 polymorphism is a valuable predictor in older patients receiving telaprevir triple therapy. TVR dose reduction could alleviate adverse events without compromising of the treatment response in older patients.

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Japan), Toshiyuki Masanaga (Masanaga Clinic, Hiroshima, Japan), Toshio Miura (Akitsu Prefectural Hospital, Hiroshima, Japan), Nami Mori (Hiroshima Red Cross Hospital, Hiroshima, Japan), Takashi Moriya (Chugoku Rousai Hospital, Hiroshima, Japan), Yutaka Nabeshima (Chuden Hospital, Hiroshima, Japan), Yuko Nagaoki (Higashihiroshima Medical Center, Hiroshima, Japan), Toshio Nakamura (Nakamura Clinic, Hiroshima, Japan), Toshio Nakanishi (Miyoshi Cyuo Hospital, Hiroshima, Japan), Ryo Nakashio (Nakashio Clinic, Hiroshima, Japan), Michihiro Nonaka (Hiroshima General Hospital, Hiroshima, Japan), Makoto Ohbayashi (Onomichi General Hospital, Hiroshima, Japan), Shintaro Takaki (Hiroshima Red Cross Hospital, Hiroshima, Japan), Eichi Takesaki (Higashihiroshima Medical Center, Hiroshima, Japan), Toru Tamura (Mazda Hospital, Hiroshima, Japan), Keiji Tsuji (Hiroshima City Asa Hospital, Hiroshima, Japan), Koji Waki (Hiroshima City Asa Hospital, Hiroshima, Japan), Masashi Watanabe (Kuchiwa Clinic, Hiroshima, Japan), Syuji Yamaguchi (Kure Kyosai Hospital, Hiroshima, Japan), Keitaro Yamashina (Hiroshima General Hospital of West Japan Railway Company, Hiroshima, Japan).

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Figure legends

Fig. 1. SVR rates for triple therapy grouped by response to prior interferon treatment and age. SVR: sustained virological response 24 weeks after the end of therapy. Patients were grouped by age (younger group, ≤65 years and older group, >65 years) and response to prior interferon treatment.

Fig. 2. Relationship between IFNL4 genotype and treatment reponse. (A)SVR rates for triple therapy grouped by ss469415590 genotype (TT/TT and TT/ΔG or ΔG/ΔG) and response to prior interferon treatment. (B) Relationship between rapid virological response (RVR) and SVR according to IFNL4 genotype. RVR: undetectable HCV RNA at week 4 of therapy.

Fig. 3. Relationship between age and adverse events. Time courses of hemoglobin (A) and serum creatinine (B) levels grouped by age. *, $P<0.05$. (C) Frequency of discontinuation of the treatment by age.

Fig.4. Relationship between TVR dose and adverse events, and treatment response in older patients. (A) Differences in the average dosage of total TVR based on body weight between initial TVR doses. Medians are shown as horizontal bars. Boxes cover the interquartile range and tails show the minimum and maximum values. Time courses of hemoglobin (B), serum creatinine (C) levels and SVR rates (D) grouped by initial TVR dose in older patients. *$P<0.05$.

Table 1. Patient characteristics by age

Variables	≤65 years (n=226)	>65 years (n=87)	P value
Sex (male/female)	128/98	43/44	0.251
Age (years)	59 (20-65)	69 (66-79)	<0.001
Body weight (kg)	63(37-100)	55(36-81)	<0.001
Body mass index (kg/m^2)	23.3(14.7-37.0)	22.3(16.1-27.3)	0.022
Aspartate aminotransferase (IU/l)	38(16-145)	36(16-111)	0.110
Alanine aminotransferase (IU/l)	40(13-286)	37(10-174)	0.001
γ-glutamyl-transpeptidase (IU/L)	32(9-442)	29(10-221)	0.190
Serum creatinine (mg/dL)	0.69(0.44-1.3)	0.71(0.44-1.8)	0.032
eGFR (mL/min/1.73m^2)	78.0(43.9-145.8)	72.6(30.6-119)	0.016
Leukocyte count (/mm^3)	4990(2400-11830)	4700(3100-7804)	0.406
Hemoglobin (g/dl)	14.1(10.0-17.4)	13.7(10.4-17.6)	0.017
Platelet count (×10^4/μl)	17.0(5.2-30.0)	14.0(6.7-22.1)	0.022
Previous treatment response			
naïve/relapser/NR	96/94/63	17/40/30	0.138
Initial TVR dose (2,250/1,500 mg/day)	141/85	33/54	<0.001
Level of viremia (log IU/ml)	6.6(5-7.8)	6.6(5-7.4)	0.182
Core70 amino acid substitutions			
wild /mutant /ND	74/51/101	34/25/28	0.840
IL28B genotype			
rs8099917 (TT / TG+GG / ND)	134/65/27	54/31/2	0.535
IFNL4 genotype			
ss469415590 (TT/TT / TT/ΔG+ΔGΔG / ND)	112/65/49	49/30/8	0.848
ITPA genotype			
rs1127354 (CC/CA+AA/ND)	147/52/27	62/23/2	0.871

Categorical data are represented as numbers of patients, and continuous data is represented as median and range.

TVR, telaprevir; NR, non-responder; HCV, hepatitis C virus; IL28B, interleukin 28B; Core70, HCV core protein amino acid 70; IFNL4, interferon lamda 4; ITPA, inosine triphosphate pyrophosphatase; ND, not determined

Table 2. Univariate and multivariate analyses of host and viral factors associated with SVR during triple therapy in older patients.

	SVR (n=40)	Non-SVR (n=18)	Univariate Analysis	Multivariate Analysis	
			p value	OR (95% CI)	P value
Sex (male/female)	22/18	8/10	0.631		
Age (years)	68(66-76)	68(66-73)	0.760		
Body weight (kg)	58.4(44-70)	58.1(44-77)	0.204		
Body mass index (kg/ m^2)	22.3 (19.2-26.1)	22.6 (19.1-27.3)	0.713		
Aspartate aminotransferase (IU/l)	27.0(19-146)	40.5(23-78)	0.158		
Alanine aminotransferase (IU/l)	26.0(10-141)	38.5(15-71)	0.444		
eGFR (mL/min/1.73 m^2)	72.6(43-119)	70.8(58-103)	0.989		
Leukocyte count (/mm^3)	4620 (3200-7450)	4200 (3100-6400)	0.453		
Hemoglobin (g/dl)	13.8 (10.4-15.4)	13.4 (11.4-15.9)	0.342		
Platelet count ($\times 10^4$/μl)	14.5 (7.6-21.9)	11.2 (6.7-24.8)	0.016		
Platelet count ($\geq 12/<12\times 10^4$/μl)	35/5	10/8	0.007		
Previous treatment response (naïve or relapse / NR)	27/13	5/13	<0.001		
Initial TVR dose (2,250 mg/1,500 mg)	19/21	7/11	0.542		
Rapid viral response (with/without/ND)	32/3/5	5/9/4	<0.001	36.601 (3.562-376.148)	0.002
Completion / discontinuation of the treatment	30/10	9/9	0.076		
Core70 amino acid substitutions (wild / mutant/ND)	17/11/12	4/6/8	0.463		
IL28B genotype rs8099917 (TT / TG+GG/ND)	30/10	6/12	0.009		
IFNL4 genotype ss469415590 (TT/TT/TT/ΔG+ΔGΔG/ND)	27/9/4	6/12/0	0.012	19.502 (2.104-180.812)	0.009
ITPA genotype rs1127354 (CC/CA+AA)	28/12	16/2	0.219		

Categorical data are represented as numbers of patients, and continuous data is represented as median and range.

SVR, sustained virological response; NR, non-responder; TVR, telaprevir; HCV, hepatitis C virus; Core70, HCV core protein amino acid 70

Table 3. Univariate and multivariate analyses of host and viral factors associated with SVR during triple therapy in younger patients.

	SVR (n=126)	Non-SVR (n=28)	Univariate Analysis	Multivariate Analysis	
			p value	OR (95% CI)	P value
Sex (male/female)	70/56	15/13	0.913		
Age (years)	58(24-65)	61(27-65)	0.203		
Body weight (kg)	60.5(37-100)	64.3(48-81)	0.471		
Body mass index (kg/ m^2)	23.3 (14.7-34.7)	22.9 (19.1-34.0)	0.230		
Aspartate aminotransferase (IU/l)	31(18-133)	46(21-145)	0.002		
Aspartate aminotransferase (≦35/>35×10^4/μl)	64/62	6/22	0.005		
Alanine aminotransferase (IU/l)	36(13-286)	41(21-137)	0.078		
eGFR (mL/min/1.73 m^2)	81(43-120)	76(51-145)	0.516		
Leukocyte count (/mm^3)	5250 (2400-11830)	4900 (2400-7660)	0.161		
Hemoglobin (g/dl)	14.2 (10.3-17.4)	13.7 (10.8-16.8)	0.029		
Hemoglobin (≥14/<14×10^4/μl)	73/53	10/18	0.033		
Platelet count (×10^4/μl)	17.2 (5.2-40.4)	12.1 (5.4-24.4)	<0.001		
Platelet count (≥12/<12×10^4/μl)	110/16	13/15	<0.001	24.841 (2.030-303.947)	0.012
Previous treatment response (naïve or relapser/NR)	103/23	7/21	<0.001		
Initial TVR dose (2,250 mg/1,500 mg)	81/45	19/9	0.682		
Rapid viral response (with/without/ND)	99/18/9	13/13/2	0.001		
Completion / discontinuation of the treatment	114/12	15/13	<0.001	47.776 (2.286-998.663)	0.013
Core70 amino acid substitutions (wild / mutant/ND)	46/23/57	2/15/11	<0.001		
IL28B genotype rs8099917 (TT / TG+GG/ND)	84/24/8	6/22/0	<0.001	71.692 (4.617-1113.33)	0.002
IFNL4 genotype ss469415590 (TT/TT/TT/ΔG+ΔGΔG/ND)	74/26/26	4/23/1	<0.001		
ITPA genotype rs1127354 (CC/CA+AA/ND)	80/28/8	20/8/0	0.860		

Categorical data are represented as numbers of patients, and continuous data is represented as median and range.

SVR, sustained virological response; NR, non-responder; TVR, telaprevir; HCV, hepatitis C virus; Core70, HCV core protein amino acid 70

Fig. 1

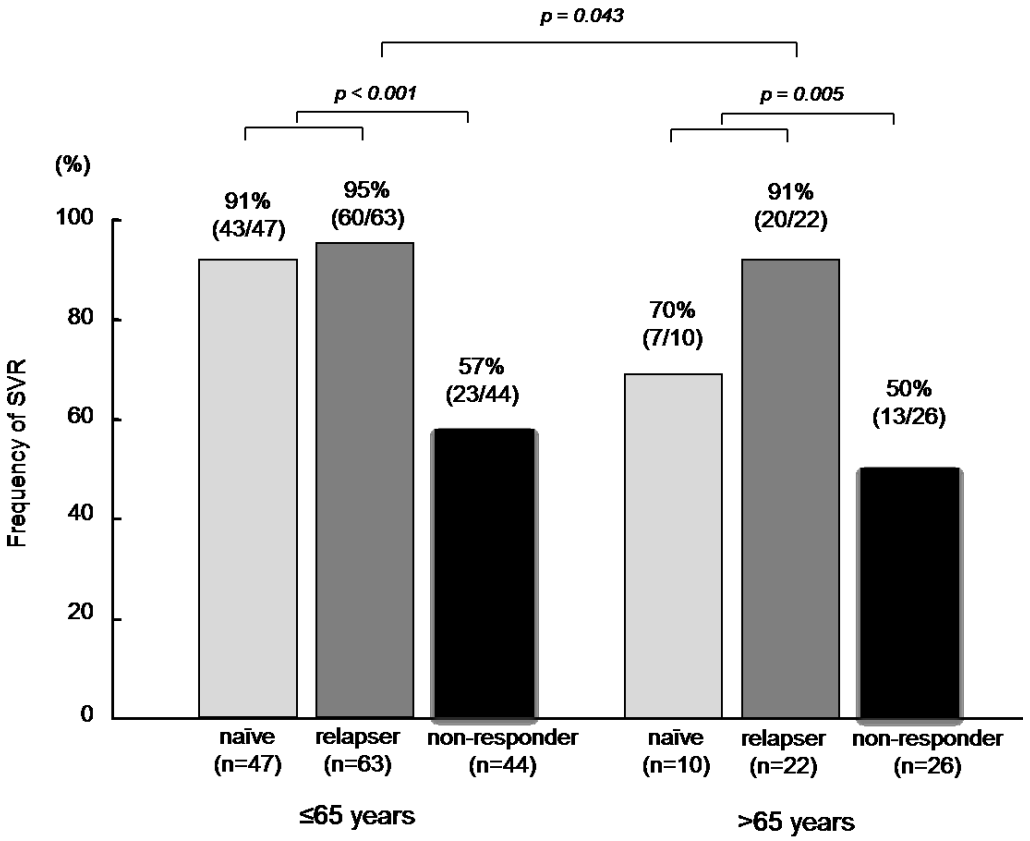

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Fig. 2A

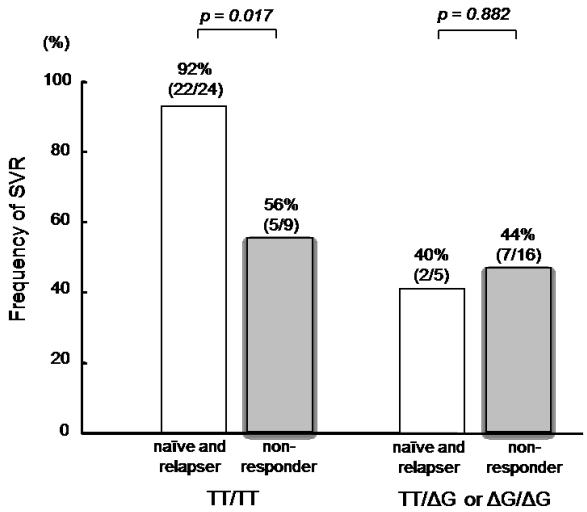


Fig. 2B

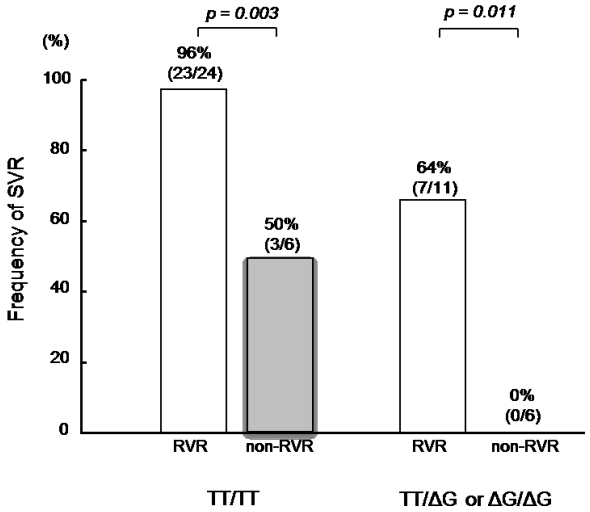


Fig. 3A

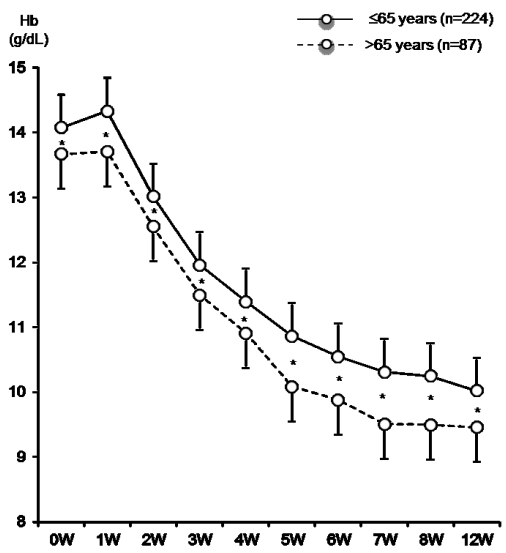


Fig. 3B

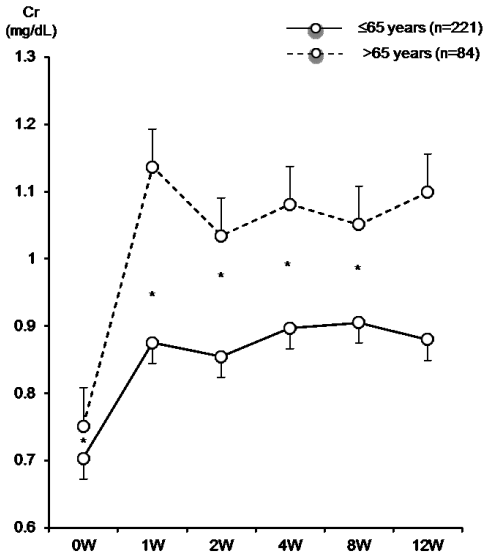
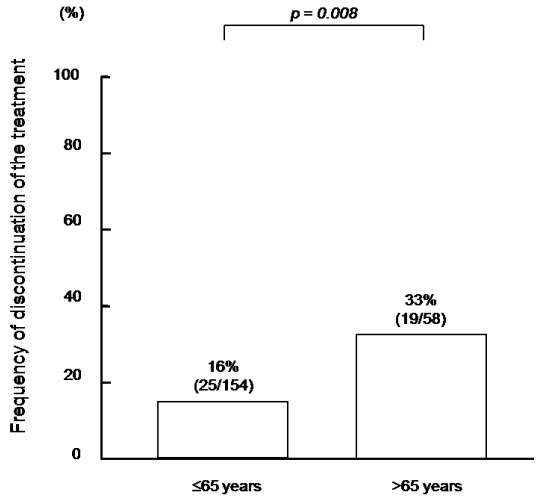


Fig. 3C



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