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ITPA genetic variants influence efficacy of PEG-IFN/RBV therapy in older patients infected with HCV genotype 1 and favourable *IL28B* type

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SUMMARY. Inosine triphosphatase (*ITPA*) genetic variants are strongly associated with ribavirin (RBV)-induced anaemia during pegylated interferon (PEG-IFN) plus RBV therapy. However, the treatment efficacy of *ITPA* genetic variants has not been fully explored. We enrolled 309 individuals infected with hepatitis C virus genotype 1, who were treated with PEG-IFN plus RBV for 48 weeks. The *ITPA* SNP: rs1127354 and *IL28B* SNP: rs8099917 were genotyped. We examined the risk factors for severe anaemia up to week 12 after the start of treatment and treatment efficacy. The incidence of severe anaemia, ≥3 g/dL reduction or <10 g/dL of haemoglobin (Hb) up to week 12, was more frequent in patients with CC at rs1127354 [65% (145/224), 33% (73/224)] than in those with CA/AA [25% (21/85), 6% (8/85)] ($P < 0.0001$). *ITPA* genotype, pretreatment Hb level and age were independent predictive factors for severe anaemia: Hb < 10 g/dL. In *IL28B* favourable type, the sustained virologic response rate was higher in ≥60-year-old patients with CA/AA than in those with CC [71% (22/31) *vs* 40% (26/65), $P = 0.005$], although there was no significant difference in treatment efficacy according to *ITPA* genetic variants in the <60-year-old patients. The proportion of patients administered ≥80% of the dosage of RBV was significantly higher in the patients with CA/AA than in those with CC ($P = 0.025$), resulting in a lower relapse rate. In conclusion, *ITPA* genetic variants were associated with severe RBV-induced anaemia and could influence the efficacy of PEG-IFN plus RBV treatment among elderly patients with *IL28B* favourable type.

Keywords: anaemia, *IL28B*, interferon, *ITPA*, ribavirin.

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) presents a significant health problem worldwide with approximately 170 million people being infected [1]. More than 70% of HCV-infected individuals go on to develop chronic infection, being at significant risk of progressive liver fibrosis and subsequent liver cirrhosis (LC) and hepatocellular carcinomas (HCC). Antiviral treatment has been shown to improve liver histology and reduce the incidence of HCC in chronic hepatitis C (CHC) [2, 3]. However, <50% of patients infected with HCV genotype 1 treated with pegylated interferon (PEG-IFN) plus ribavirin (RBV) achieve a sustained viral response (SVR) [4, 5].

Abbreviations: γ-GTP, γ-glutamyl transpeptidase; ALT, Alanine aminotransferase; CHC, chronic hepatitis C; GWAS, genomewide association studies; Hb, haemoglobin; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IL28B, interleukin 28B; ITPA, inosine triphosphatase; LC, liver cirrhosis; NVR, null viral response; PCR, polymerase chain reaction; PEG-IFN, pegylated interferon; RBV, ribavirin; SNP, single nucleotide polymorphism; SVR, sustained viral response; TVR, transient viral response.

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Virus and host factors have been indicated as relevant determinants of treatment outcome. Among patients with HCV genotype 1 infection, factors associated with a lower rate of SVR include baseline high viral load, male gender, older age, African American race, insulin resistance, advanced fibrosis and hepatic steatosis [6]. In addition, the administered dose of PEG-IFN or RBV affects the outcome of treatment, as rates of viral clearance are significantly reduced in patients who cannot be maintained on at least 80% of their PEG-IFN and RBV dosage for the duration of treatment [7].

Anaemia is common with PEG-IFN plus RBV treatment due to the bone marrow suppression by PEF-IFN and haemolysis from RBV. Anaemia is the reason for discontinuation of treatment or dose reduction in drugs in 10–14% of patients treated with PEG-IFN plus RBV [4, 8, 9]. In particular, the incidence of adverse events and laboratory abnormalities is more frequent in older patients, resulting in poor adherence and lower SVR [10–12]. In Japan, HCV-infected patients are relatively old, and some have severe fibrosis [10]. Additionally, the use of erythropoietin-stimulating agents is not allowed in Japan; therefore, anaemia during PEG-IFN plus RBV treatment is an important problem that affects drug adherence and treatment efficacy.

Recent genomewide association studies (GWAS), including our study on HCV infection [13], have identified two important host genetic variants: the single nucleotide polymorphism (SNP) in the interleukin-28B (*IL28B*) gene, which is strongly associated with the response to therapy for chronic genotype 1 HCV infection [13–18], and the SNP in the inosine triphosphatase (*ITPA*) gene, which precisely predicts RBV-induced anaemia in European American [19] and Japanese populations [20]. It has been reported that variants of the *ITPA* gene affected RBV-induced anaemia and the dosage of RBV; however, the effect of the SNP on therapy outcome has not been fully explored. Some reports suggested an association of the polymorphism with SVR [21, 22], and Kurosaki *et al.* reported that the protective variant of *ITPA* was associated with less reduction in RBV and a high SVR rate in patients with the rs8099917 TT genotype [23]. On the other hand, in other reports, those variants were not associated with treatment outcome [19, 24].

In the present study, we aimed to replicate the risk factors in RBV-induced anaemia including *ITPA* genetic variants and the impact of *ITPA* and *IL28B* genetic variants on the effect of PEG-IFN plus RBV treatment in CHC patients.

PATIENTS AND METHODS

Patients and treatment protocol

From April 2007 to April 2010, samples were obtained from 309 patients with chronic HCV genotype 1 infection who were treated at 6 multicentre hospitals, Nagoya City University Hospital, Nagoya Daini Red Cross Hospital, Musasino Red Cross Hospital, Tokyo Medical and Dental University Hospital, Yamanashi University Hospital and National Nagasaki Medical Center. All patients had tested positive for HCV RNA for more than 6 months. HBsAg-positive, anti-HIV-positive patients and patients with other causes of liver disease such as autoimmune hepatitis and primary biliary cirrhosis were excluded from this study. Each patient was treated with PEG-IFN-α2b (1.5 μg/kg body weight subcutaneously once a week) or PEG-IFN-α2a (180 μg once a week) plus RBV (600–1000 mg daily according to body weight) for 48 weeks. The dose of PEG-IFN or RBV was reduced according to the recommendation on the package inserts or the clinical condition of individual patients. Erythropoietin and other growth factors were not given.

The treatment outcomes were defined as SVR; undetectable HCV RNA levels at 24 weeks after cessation of treatment; transient viral response (TVR); HCV RNA levels became undetectable during treatment, but reappeared after the end of treatment; and null viral response (NVR); HCV RNA levels were persistently detectable.

Written informed consent was obtained from each patient, and the study protocol conformed to the ethics guidelines of the Declaration of Helsinki and was approved by the institutional ethics review committees.

SNP genotyping

Genetic polymorphisms as SNPs of the *ITPA* (rs1127354) and the *IL28B* gene (rs8099917) were determined using ABI TaqMan Probes (Applied Biosystems, Carlsbad, CA) or the DigiTag2 assay [25], respectively. In Caucasian patients, two SNPs (rs1127354 and rs7270101) are associated with *ITPA* enzyme activity [19, 24]; however, there are no variants in rs7270101 in the Japanese population [20, 21, 23].

Laboratory tests

Blood samples were obtained before treatment, at weeks 1, 2, 4, 8 and 12 and every 4 weeks up to treatment completion, and they were analysed for haematologic tests, blood chemistry and HCV RNA. Follow-up measurements were obtained at weeks 4, 12 and 24 after the end of treatment. HCV RNA levels were measured throughout the course of therapy using the COBAS TaqMan HCV test (Roche Diagnostics K.K., Tokyo, Japan). The measurement range of this assay was 1.2–7.8 log IU/mL.

Association between ITPA SNP and anaemia during the early periods of treatment

We examined the association between *ITPA* genetic variants and haemoglobin (Hb) levels and the proportion of

patients suffering clinically significant anaemia, which we defined as a decline in Hb of more than 3 g/dL or <10 g/dL, which is the threshold at which RBV dose reduction is recommended according to the package insert, during the initial 12 weeks of treatment. Additionally, we examined the factors for Hb < 10 g/dL during the initial 12 weeks of treatment in logistic regression models that included gender, age, baseline weight, Hb, platelet count and *ITPA* genetic variants and so on as covariates.

Association between ITPA genetic variants and anti-HCV treatment outcomes or RBV adherence

We examined the association between *ITPA* genetic variants and anti-HCV treatment outcomes in logistic regression models that included gender, age, baseline Hb, platelet count, HCV RNA level and *IL28B* genetic variants as covariates. In addition, we analysed RBV adherence during treatment in these patients. The patients were divided into three groups by administered dosage of RBV: <60%, ≥60 to <80%, ≥80% of the planned RBV dosage.

Statistical analysis

Categorical variables were compared between groups by the chi-squared test or Fisher's exact test, and noncategorical variables, by the Student's t-test. Multivariate logistic regression analysis with stepwise forward selection was performed with $P < 0.05$ in univariate analysis as the criteria for model inclusion. $P < 0.05$ was considered significant. These statistical analyses were conducted using SPSS software package, version 18J (Chicago, IL, the USA).

RESULTS

Patient characteristics and distribution of ITPA and IL28B genetic variants

The clinical characteristics of the study population are described in Table 1. Genotyping of rs1127354 revealed that 224 patients (72%) had CC and 85 patients (28%) had CA or AA (CA/AA). *IL28B* genotype resistant to PEG-IFN and RBV, TG or GG (TG/GG) at rs8099917 was possessed by 33% (102/309) of the patients. There were no significant differences in baseline clinical characteristics between the patients with CC and CA/AA genotypes at rs1127354.

Association between ITPA genetic variants and Hb levels during PEG-IFN plus RBV treatment

Hb levels during the initial 12 weeks of therapy are shown in Fig. S1. Patients with CA/AA at rs1127354 showed a lower degree of Hb reduction at weeks 2, 4, 8 and 12 during therapy than those with CC ($P < 0.0001$ for weeks 2, 4, 8 and 12). The greatest difference in mean Hb reduction was found at week 4, −0.8 ± 0.9 g/dL in patients with CA/AA and −2.5 ± 1.2 g/dL in those with CC.

Table 1 Clinical characteristics of total 309 chronic hepatitis C patients

Characteristic	(n = 309)
Male gender	160 (52%)
Age, years	57 ± 10
Body weight, kg	60 ± 11
Haemoglobin, g/dL	14.1 ± 1.4
Platelet count, $\times 10^4/\mu$L	16.4 ± 5.6
ALT, IU/L	74 ± 65
γ-GTP, IU/L	61 ± 71
Creatinine, mg/dL	0.7 ± 0.2
HCV RNA, log IU/mL	6.2 ± 0.6
rs8099917, TT/TG+GG	207/102
rs1127354, CC/CA+AA	224/85

ALT, alanine aminotransaminase; γ-GTP, γ-glutamyl transpeptidase. rs8099917: TT is favourable to treatment efficacy, and rs1127354: CA/AA is protectable to RBV-induced anaemia in PEG-IFN plus RBV therapy.

Incidence of severe anaemia during PEG-IFN plus RBV treatment

As depicted in Fig. 1, the incidence of severe anaemia up to week 12 (≥3 g/dL reduction or <10 g/dL of Hb) was more frequent in the patients with CC at rs1127354 [65% (145/224), 33% (73/224)] than in those with CA/AA [25% (21/85), 6% (8/85)] ($P < 0.0001$). These results show that the CA/AA genotypes are significantly associated with less absolute reduction in Hb levels, especially during the early weeks of therapy, and protect against the development of severe anaemia.

Factors for the incidence of Hb < 10 g/dL up to week 12

By univariate analysis, pretreatment factors for severe anaemia, Hb < 10 g/dL up to week 12, were female gender, older age, lower body weight and baseline Hb level as well as rs1127354 CC genotype. Multivariate logistic regression analysis was then carried out using these factors as covariates. As a result, *ITPA* genotype, pretreatment Hb levels and age were independent predictive factors for severe anaemia (Hb < 10 g/dL) up to week 12 (Table 2). Therefore, we analysed the proportions of Hb < 10 g/dL up to week 12 by *ITPA* genotype, pretreatment Hb levels and age. As depicted in Fig. S2, the incidence of Hb < 10 g/dL up to week 12 was most frequent in ≥60-year-old patients with CC genotype of rs1127354 and baseline Hb < 14 g/dL [61% (39/64)], indicating that these patients were the highest risk group for severe anaemia.

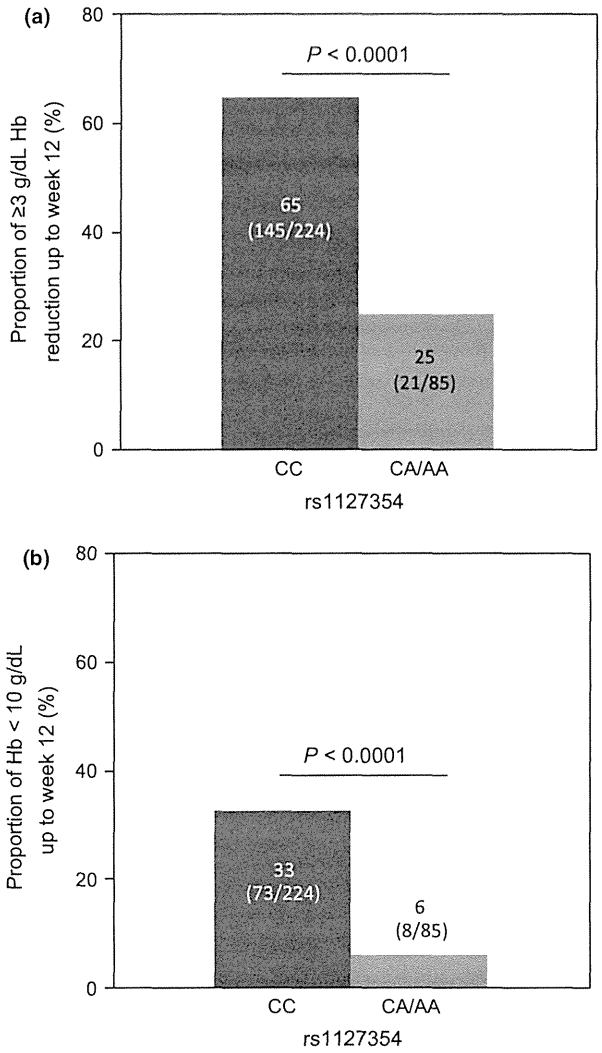

Fig. 1 Proportion of the incidence of severe anaemia up to the initial 12 weeks of treatment. The incidence of severe anaemia, (a) ≥3 g/dL reduction or (b) <10 g/dL of haemoglobin, was more frequent in the patients with CC at rs1127354 [65% (145/224), 33% (73/224)] than in those with CA/AA [25% (21/85), 6% (8/85)] ($P < 0.0001$).

Association between ITPA genetic variants and anti-HCV treatment outcomes or RBV adherence

We examined the pretreatment factors associated with SVR. By univariate analysis, gender, age, baseline Hb, platelet count, gamma-glutamyl transpeptidase, HCV RNA level and rs8099917 and rs1127354 genotypes were significantly associated with SVR. In logistic regression models that included these factors, age, platelet count, gamma-glutamyl transpeptidase, HCV RNA level and rs8099917 and rs1127354 genotypes were independent pretreatment predictive factors for SVR (Table 3). *IL28B* genetic variants were very strongly associated with SVR ($P < 0.0001$, OR = 23.9); therefore, we analysed the associations between *ITPA* genetic variants and treatment outcome in subgroups according to *IL28B* genotype. In all patients, the proportions of SVR, TVR and NVR were 44, 25 and 31%, respectively. In patients with TT at rs8099917 (*IL28B* favourable type), the SVR rate in patients with CA/AA at rs1127354 was higher than in those with CC [72% (46/64) *vs* 55% (78/143), $P = 0.019$], while no difference in the SVR rate was found in the *IL28B* unfavourable type due to poor virologic response (Fig. 2). When we examined the administered dosage of RBV during treatment in patients with TT at rs8099917, by dividing into three groups; ≥80%, ≥60 to <80% and <60% of the planned RBV dosage, the proportion of patients administered ≥80% of the dosage of RBV was significantly higher in CA/AA than in CC at 1127354 ($P = 0.025$, Fig. 3), resulting in a lower relapse rate [19% (12/64) *vs* 34% (48/143)] (Fig. 2).

It has been reported that the incidence of RBV-induced anaemia was more frequent in older patients, resulting in poor adherence to RBV; therefore, we examined the associations between *ITPA* genetic variants and treatment outcome according to age in the patients with the *IL28B* favourable type. As a result, the SVR rate was higher in ≥60-year-old patients with CA/AA at rs1127354 than in those with CC [71% (22/31) *vs* 40% (26/65), $P = 0.005$], although there was no significant difference in treatment efficacy according to *ITPA* genetic variants in the <60-year-old patients (Fig. 4a). Regardless of age, the percentage of patients receiving ≥80% of the planned RBV dosage was higher in the patients with CA/AA at rs1127354 than in those with CC; however, the differences were not significant in <60- or ≥60-year-old patients (Fig. 4b). In this study, there were 46 patients aged ≥65 years with *IL28B* favourable type. In these patients, the dosage of RBV also tended to be higher in the patients with CA/AA at rs1127354 than in those with CC, resulting in higher SVR rate that in those with CA/AA [(9/14 (64%) *vs* 11/32 (34%)].

DISCUSSION

Haemolysis is a common side effect of RBV and is the major reason for the dose reduction in RBV. Age, female gender, baseline platelet level, baseline Hb level and the plasma concentration of RBV have been reported to contribute to RBV-induced anaemia and dose reduction [26–28]. In several countries, including Japan, administration of erythropoietin-stimulating agents to CHC patients during PEG-IFN plus RBV treatment is not approved, and so RBV-induced anaemia could influence the treatment response, especially the relapse rate.

Recently, *ITPA* genetic variants have been shown to predict RBV-induced anaemia in European American [19] and Japanese populations [20]. In addition, we have identified that *ITPA* genetic variants are associated with reduction in

Table 2 Univariate and multivariate regression analysis of pretreatment factors associated with Hb < 10 g/dL up to 12 weeks

	Univariate analysis			Multivariate analysis	
	Hb < 10 g/dL (n = 78)	Hb ≥ 10 g/dL (n = 231)	P value	OR (95% CI)	P value
Male gender	24	136	<0.0001	-	-
Age, years	61 ± 8	55 ± 10	<0.0001	1.04 (1.01–1.09)	0.017
Body weight, kg	56 ± 10	61 ± 11	<0.001	-	-
Haemoglobin, g/dL	13.2 ± 1.4	14.4 ± 1.2	<0.0001	0.45 (0.41–0.73)	<0.0001
Platelet count, $\times 10^4$ /μL	15.4 ± 5.2	16.7 ± 5.7	0.079		
ALT, IU/L	62 ± 47	79 ± 69	0.056		
Creatinine, mg/dL	0.7 ± 0.2	0.7 ± 0.2	0.550		
rs1127354, CC/CA+AA	73/5	151/80	<0.0001	7.73 (2.87–20.82)	<0.0001

Data are expressed as number for categorical data or the mean ± standard deviation for continuous data. rs1127354: CA/AA is protectable to RBV-induced anaemia in PEG-IFN plus RBV therapy.

Table 3 Univariate and Multivariate regression analysis of pretreatment factors associated with sustained virologic response

	Univariate analysis			Multivariate analysis	
	SVR (n = 136)	non-SVR (n = 173)	P value	OR (95% CI)	P value
Male gender	79	81	0.049	-	-
Age, years	55 ± 10	58 ± 10	0.004	0.96 (0.93–01.00)	0.028
Body weight, kg	61 ± 11	59 ± 11	0.116		
Hb, g/dL	14.3 ± 1.2	13.9 ± 1.4	0.008	-	-
Platelet count, $\times 10^4$ /μL	17.9 ± 6.1	15.1 ± 4.9	<0.0001	1.10 (1.03–1.16)	0.004
ALT, IU/L	79 ± 69	71 ± 61	0.299		
γ-GTP, IU/L	47 ± 55	71 ± 80	0.003	0.99 (0.99–1.00)	0.012
HCV RNA, log IU/mL	6.1 ± 0.6	6.3 ± 0.5	<0.0001	0.27 (0.14–0.51)	<0.0001
rs8099917, TT/TG+GG	124/12	83/90	<0.0001	24.52 (9.94–60.48)	<0.0001
rs1127354, CC/CA+AA	87/49	137/6	0.003	2.57 (1.29–5.13)	0.008

Data are expressed as number for categorical data or the mean ± standard deviation for continuous data. rs8099917: TT is favourable to treatment efficacy, and rs1127354: CA/AA is protectable to RBV-induced anaemia in PEG-IFN plus RBV therapy.

platelet counts as well as anaemia in PEG-IFN plus RBV therapy [29]. The *ITPA* genetic variation causing an accumulation of inosine triphosphate (ITP) has been shown to protect patients against RBV-induced anaemia during PEG-IFN plus RBV treatment. It has previously been reported that the two functional variants in the *ITPA* gene, rs1127354 in exon 2 and rs7270101 in intron 2, were associated with ITPase deficiency, resulting in an accumulation of ITP in erythrocytes [30–33]. A recent report showed a biologic mechanism in which ITP confers protection against RBV-induced ATP reduction by substituting for erythrocyte GTP, which is depleted by RBV, in the biosynthesis of ATP [34].

The previous studies examined the association between *ITPA* genetic variants and RBV-induced anaemia at week 4 after the start of PEG-IFN plus RBV therapy [19–21]. However, it is important to evaluate the incidence of severe anaemia, which requires reduction in RBV dosage, which usually occurs up to week 12 after the start of therapy. In the present study, we replicated the previous study that *ITPA* genetic variants were associated with Hb reduction during PEG-IFN plus RBV treatment. Furthermore, we indicated that the incidence of severe anaemia during the initial 12 weeks of treatment was more frequent in patients with CC at rs1127354 than in those with CA/AA. In addition, *ITPA* genotype, pretreatment Hb levels and age were independent predictive factors for severe anaemia (Hb < 10 g/dL) up to week 12 by multivariate logistic regression analysis. In older patients, pretreatment Hb levels tend to be lower than in younger patients, suggesting

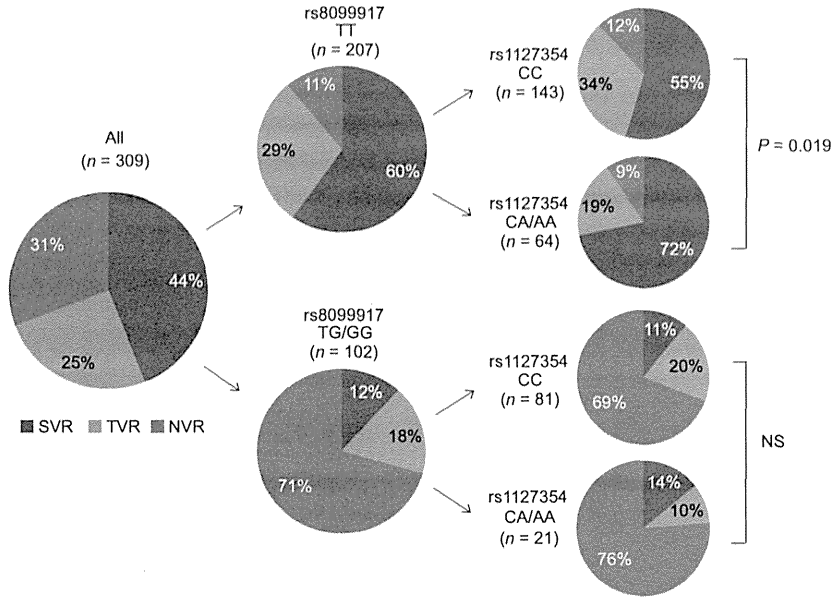

Fig. 2 Treatment outcome according to *IL28B* and *ITPA* genetic variants. In patients with *IL28B* favourable type, rs8099917: TT, the sustained viral response rate in the patients with CA/AA at rs1127354, protected against RBV-induced anaemia, was higher than in those with CC [72% (46/64) *vs* 55% (78/143), $P = 0.019$], while no difference in the sustained viral response rate was found in the *IL28B* unfavourable type (rs8099917: TG/GG) due to poor virologic response. SVR, sustained viral response; TVR, transient viral response; NVR, null viral response.

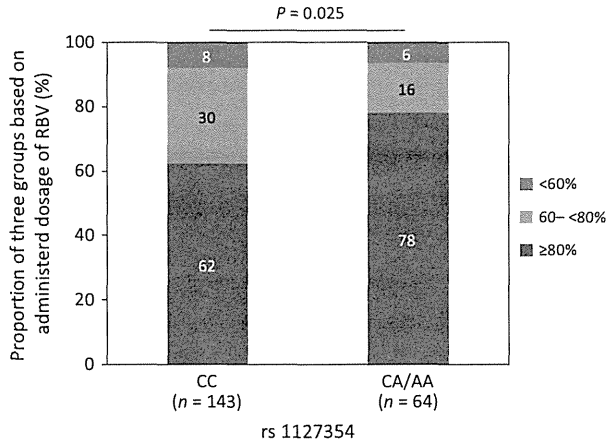

Fig. 3 Proportions of administered dosage of ribavirin in patients with *IL28B* favourable type. We examined the administered dosage of ribavirin during treatment in patients with *IL28B* favourable type, rs8099917: TT, by dividing them into three groups: ≥80%, ≥60 to <80% and <60% of the planned ribavirin dosage. The proportion of patients administered ≥80% of the dosage of ribavirin was significantly higher in the patients with CA/AA, protected against RBV-induced anaemia, than in those with CC at 1127354 ($P = 0.025$).

that not only *ITPA* genotype, but also age is an important predictive factor causing severe anaemia. In Japan, older HCV-infected patients developing liver fibrosis have been prevalent [11]; therefore, *ITPA* genotype is of significance in the Japanese population consisting of many elderly CHC patients.

With regard to the relationship between the effect of treatment and *ITPA* genetic variants, no association between the *ITPA* genetic variants and SVR was demonstrated in two previous studies of genotype 1 CHC patients [19, 24]. However, some reports from Japan suggested an association between *ITPA* genetic variants and SVR [21, 22], and Kurosaki *et al.* reported that the protective variant of *ITPA* was associated with less reduction in RBV and a high SVR rate in patients with *IL28B* favourable type [23]. In this study, the *ITPA* genetic variants were associated with treatment outcome in the overall cohort, especially in the patients with *IL28B* favourable type; the SVR rate in patients with CA/AA at rs1127354 was higher than in those with CC. The percentage of patients receiving ≥80% of the planned RBV dosage was higher in patients with CA/AA at rs1127354 than in those with CC. It has been reported that reduction in RBV to <80% results in a decreased rate of SVR [7]. Taken together, we showed that *ITPA* genetic variants were associated with the dose of RBV and the relapse rate in patients with *IL28B* favourable type.

It is well known that treatment efficacy is poorer in elderly patients, and the incidence of drug dose reduction or discontinuation could increase according to old age as well as advanced stage [10, 11]; however, we showed that the SVR rate and dosage of RBV in ≥60-year-old patients

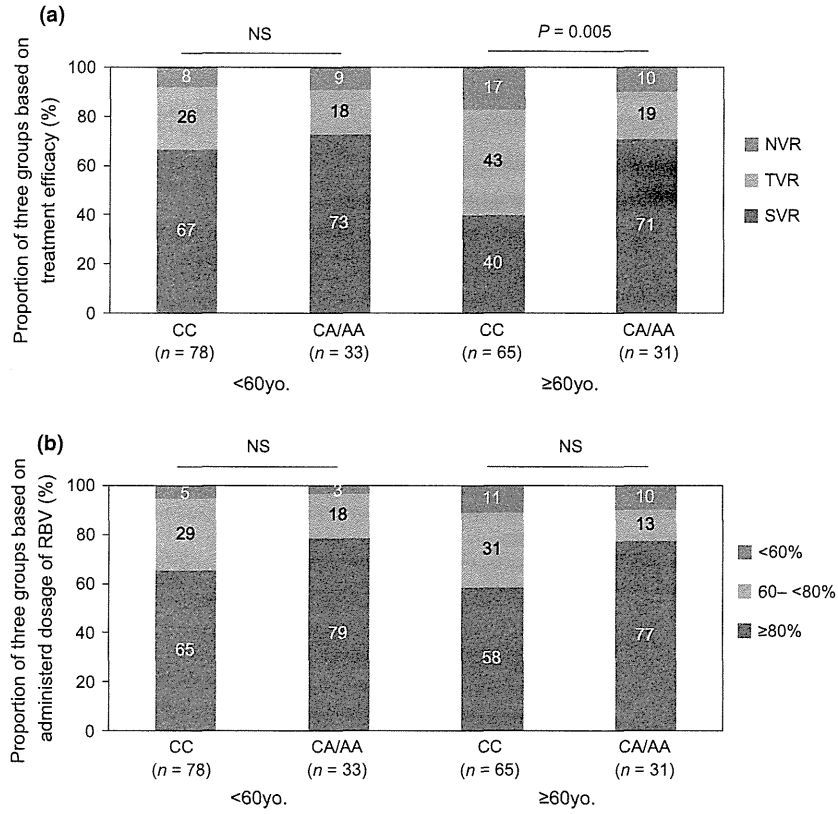

Fig. 4 Treatment outcome and administered dosage of ribavirin according to age and *ITPA* genetic variants in patients with *IL28B* favourable type. (a) The sustained viral response rate was higher in ≥60-year-old patients with CA/AA at rs1127354, protected against RBV-induced anaemia, than in those with CC [71% (22/31) *vs* 40% (26/65), $P = 0.005$], although there was no significant difference in treatment efficacy according to *ITPA* genetic variants in the <60-year-old patients. SVR, sustained viral response; TVR, transient viral response; NVR, null viral response. (b) Regardless of age, the percentage of patients receiving ≥80% of the planned RBV dosage was higher in the patients with CA/AA at rs1127354 than in those with CC; however, the differences were not significant in <60- or ≥60-year-old patients.

with CA/AA at rs1127354 were equivalent to <60-year-old patients (Fig. 4). In Japan, HCV-infected patients are relatively older than in Europe and the USA. In the present study, the risk of severe anaemia was higher, and treatment efficacy was poorer in elderly patients with CC at rs1127354. Additionally, administration of erythropoietin is not allowed in Japan; therefore, *ITPA* genetic variants could influence the treatment efficacy more strongly in the Japanese CHC population than in European and American populations. In these patients with a high risk of severe anaemia, it is necessary for erythropoietin to be used to improve treatment efficacy.

Recently, direct-acting antiviral agents (DAAs), such as telaprevir, have been shown to have a strong antiviral effect on HCV; however, treatment outcome was poorer in IFN and telaprevir without than in IFN and telaprevir with RBV regimens in clinical trials; thus, RBV is a key drug for treatment efficacy in regimens including IFN and DAAs as well as PEG-IFN/RBV therapy. In regimens including PEG-IFN, RBV and telaprevir, severe anaemia is a serious adverse effect [9, 35]. Recently, it was reported that *ITPA* genetic variants influenced haemoglobin levels during telaprevir, PEG-IFN plus RBV therapy [36]; however, the association between *ITPA* genotype and treatment efficacy did not reach significance [37]. In intractable cases with *IL28B* unfavourable type, RBV adherence could influence treatment response [38]; therefore, *ITPA* genetic variants associated with RBV adherence might be important for achieving SVR by triple combination therapy. As more recently reported, the *ITPA* SNP (rs1127354) may be a useful tool in predicting patients susceptible to RBV-induced anaemia during IFN-free treatments for HCV [39].

In conclusion, *ITPA* genetic variants, pretreatment Hb levels and age were associated with severe RBV-induced anaemia. In addition, *ITPA* genetic variants could influence the efficacy of PEG-IFN plus RBV treatment among elderly patients with *IL28B* favourable type. These findings may

have the potential to support an individualized treatment strategy.

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CONFLICT AND INTERESTS

Yasuhito Tanaka has carried out contracted research for MSD (Merck Sharp & Dohme) and Chugai Pharmaceutical Co. Ltd.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Reduction in haemoglobin levels up to the initial 12 weeks of treatment according to *ITPA* genetic variants.

Fig. S2. Proportion of haemoglobin <10 g/dL up to the initial 12 weeks of treatment according to baseline haemoglobin level, age and *ITPA* genetic variants.

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Original Article

Serum interferon-gamma-inducible protein-10 concentrations and *IL28B* genotype associated with responses to pegylated interferon plus ribavirin with and without telaprevir for chronic hepatitis C

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Aim: Several studies have shown that high pretreatment concentrations of serum interferon-γ-inducible protein-10 (IP-10) are correlated with non-response to pegylated interferon (PEG-IFN) plus ribavirin (RBV) for chronic hepatitis C (CHC). However, there are few reports on their effect on the Asian population.

Methods: We enrolled 104 Japanese genotype 1 CHC individuals treated with PEG-IFN/RBV and 45 with PEG-IFN/RBV/telaprevir, and evaluated the impact of pretreatment serum IP-10 concentrations on their virological responses.

Results: The pretreatment serum IP-10 concentrations were not correlated with *IL28B* genotype. The receiver–operator curve analysis determined the cut-off value of IP-10 for predicting a sustained virological response (SVR) as 300 pg/mL. In multivariate analysis, the *IL28B* favorable genotype and IP-10 concentration of less than 300 pg/mL were independent factors for predicting SVR. In a subgroup of patients with the *IL28B* favorable genotype, the SVR rate was higher in the patients with IP-10 of less than 300 than in those with 300 pg/mL or more, whereas no patient with the *IL28B* unfavorable genotype and IP-10 of 300 pg/mL or more achieved SVR. Among the patients treated with PEG-IFN/RBV/telaprevir, low pretreatment concentrations of serum IP-10 were associated with a very rapid virological response, defined as undetectable HCV RNA at week 2 after the start of therapy.

Conclusion: Pretreatment serum IP-10 concentrations are associated with treatment efficacy in PEG-IFN/RBV and with early viral kinetics of hepatitis C virus in PEG-IFN/RBV/telaprevir therapy.

Key words: hepatitis C, *IL28B*, interferon, interferon-γ-inducible protein-10, ribavirin, telaprevir

INTRODUCTION

CHRONIC INFECTION WITH hepatitis C virus (HCV) presents a significant health problem worldwide and approximately 170 million people are infected.[1] Over 70% of individuals acutely infected with HCV go on to develop chronic infection and are at significant risk of progressive liver fibrosis and subsequent liver cirrhosis and hepatocellular carcinoma (HCC). Antiviral treatment has been shown to improve liver histology and decrease the incidence of HCC in chronic hepatitis C (CHC).[2,3] Until 2011, the standard treatment for chronic HCV infection was weekly pegylated interferon (PEG-IFN) doses in association with daily doses of ribavirin (RBV); however, less than 50% of patients infected with HCV genotype 1 treated in this way achieve a sustained virological response (SVR).[4,5] Newly developed treatments involve

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Conflicts of interests: Y. T. has research contracts with MSD (Merck Sharp & Dohme) and Chugai Pharmaceutical.

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