

Association of *ITPA* polymorphism with outcomes of peginterferon- α plus ribavirin combination therapy

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Abstract

AIM: To analyze the association between inosine triphosphatase (*ITPA*) (rs1127354) genotypes and sustained virological response (SVR) rates in peginterferon (Peg-IFN) α + ribavirin (RBV) treatment.

METHODS: Patients who underwent Peg-IFN α + RBV combination therapy were enrolled ($n = 120$) and they had no history of other IFN-based treatments. Variation in hemoglobin levels during therapy, cumulative reduction of RBV dose, frequency of treatment withdrawal, and SVR rates were investigated in each *ITPA* genotype.

RESULTS: In patients with *ITPA* CC genotype, hemoglobin decline was significantly greater and the percentage of patients in whom total RBV dose was < 60% of standard and/or treatment was withdrawn was significantly higher compared with CA/AA genotype. However, SVR rates were equivalent between CC and CA/AA genotypes, and within a subset of patients with Interleukin 28B (*IL28B*) (rs8099917) TT genotype, SVR rates tended to be higher in patients with *ITPA* CC genotype, although the difference was not significant.

CONCLUSION: *ITPA* CC genotype was a disadvantageous factor for Peg-IFN α + RBV treatment in relation to completion rates and RBV dose. However, CC genotype was not inferior to CA/AA genotype for SVR rates. When full-length treatment is accomplished, it is plausible that more SVR is achieved in patients with *ITPA* CC variant, especially in a background of *IL28B* TT genotype.

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Key words: Chronic hepatitis C; Interleukin 28B; Inosine triphosphatase; Peginterferon; Ribavirin

Core tip: Inosine triphosphatase (*ITPA*) polymorphism at rs1127354 is significantly associated with hemoglobin decline and reduction of ribavirin (RBV) during peginterferon- α + RBV therapy. However, the effect of the *ITPA* gene single-nucleotide polymorphism on treatment outcome is still unclear. In this study, *ITPA*

CC genotype (rs1127354) was not inferior to CA/AA genotype for sustained virological response rates although CC genotype was a disadvantageous factor for the treatment in relation to completion rates and RBV dose. When full-length treatment is accomplished, the SVR rate tended to be higher in patients with the CC genotype, especially in a subset of patients with the favorable TT genotype (rs8099917) of Interleukin 28B.

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INTRODUCTION

Hepatitis C virus (HCV) genotype 1b accounts for around 70% of chronic hepatitis C in Japan^[1,2]. A sustained virological response (SVR) in eliminating HCV RNA by peginterferon (Peg-IFN) α + ribavirin (RBV) combination therapy is attained in 40%-50% of individuals with HCV-1b^[3-5]. Triple therapy using Peg-IFN α + RBV + telaprevir is anticipated to be effective for SVR in approximately 75% of patients with HCV-1b^[6-8]. It is known that polymorphisms located upstream of the Interleukin 28B (*IL28B*) gene, encoding for λ or type III interferon (IFN- λ), are major predictors of SVR in the Peg-IFN α -based combination therapies^[9-12]. Two single-nucleotide polymorphisms (SNPs), rs8099917 TT genotype and rs12979860 CC genotype, have been independently associated with a higher rate of SVR following Peg-IFN α -based combination therapies in individuals with HCV-1b infection. IFN- λ is believed to upregulate the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway through interaction with a cellular transmembrane receptor, resulting in antiviral activity. In Japanese individuals, strong linkage disequilibrium is recognized between the two *IL28B* SNPs, rs8099917 and rs12979860, and 99% coincidence has been reported^[13].

The most important adverse events of Peg-IFN α -based combination therapies include RBV-induced hemolytic anemia, which is severe enough to require dose reduction of RBV in 10%-20% of patients, and which may affect overall efficacy^[3]. RBV-induced ATP depletion in red blood cells is believed to be a primary mechanism for RBV-induced hemolytic anemia. A genome-wide association study has shown a strong association between SNPs of the inosine triphosphatase (*ITPA*) gene in chromosome 20 and RBV-induced anemia in patients infected with HCV-1b^[14]. Two functional SNPs, a missense variant in exon 2 (rs1127354) and a splicing altering variant in intron 2 (rs7270101), independently reduce the expression of *ITPA*, leading to inosine deficiency and protection

against RBV-induced ATP depletion^[15-18]. Accordingly, the protective genotypes, rs1127354 CA and AA as well as rs7270101 AC and CC, are associated with decreased *ITPA* activity, which confers protection against RBV-related ATP depletion and hemolytic anemia. The Japanese have the AA genotype exclusively at rs7270101, therefore the CC genotype at rs1127354 is a major predictor of RBV-induced anemia during antiviral combination therapy in Japanese patients infected with HCV-1b^[18,19].

However, it is controversial whether *ITPA* (rs1127354) CC genotype, which induces heavier hemoglobin decline, affects therapeutic outcomes. From the standpoint of health economics, it is important to examine the significance of factors predicting viral response to antiviral treatments and therapeutic outcomes. In this study, Japanese patients infected with HCV-1b, who had experienced Peg-IFN α + RBV combination therapy, were retrospectively analyzed. Patients were divided into groups according to genotyping of *ITPA* rs1127354 and *IL28B* rs8099917. Our primary analysis was focused on the quantitative change from baseline in hemoglobin levels and platelet counts, cumulative reduction of RBV dose, frequency of treatment withdrawal, and estimation of treatment outcome.

MATERIALS AND METHODS

Study patients

This retrospective cohort study was performed in 120 patients with chronic HCV-1b infection who were treated with Peg-IFN α + RBV combination therapy at Kyushu Medical Center Hospital between January 2007 and December 2009. The patients met the following inclusion and exclusion criteria. Inclusion criteria were: (1) baseline serum HCV RNA levels > 5.0 log IU/mL; and (2) Japanese patients aged 20-65 years at study entry. Exclusion criteria were: (1) decompensated liver cirrhosis; (2) serum hepatitis B surface antigen; (3) hepatocellular carcinoma or its history; (4) autoimmune hepatitis, alcoholic liver disease, hemochromatosis, or chronic liver disease other than chronic hepatitis C; (5) chronic renal disease or creatinine clearance < 50 mL/min at baseline; (6) hemoglobin < 12 g/dL, neutrophil < 1500/ μ L or platelets < 100000/ μ L at baseline; and (7) history of receiving IFN-based treatment. All patients gave consent for analysis of SNPs in *ITPA* and *IL28B* genes. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Kyushu Medical Center. Written informed consent was obtained from each patient.

Antiviral treatment

Peg-IFN α 2b (1.5 μ g/kg) or Peg-IFN α 2a (180 μ g) was injected subcutaneously once weekly. RBV (600-1000 mg/d) 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 1000 mg for > 80 kg. As a standard combination therapy, Peg-IFN α and RBV were continued for 48 wk. Treatment duration was extended up to

Table 1 Baseline characteristics of patients

Baseline characteristics	<i>ITPA</i> polymorphism (rs1127354)		<i>P</i> value
	CA/AA (<i>n</i> = 37)	CC (<i>n</i> = 83)	
Age (yr)	61 ± 8	59 ± 11	NS
Gender: male/female	18/19	37/46	NS
HCV RNA (log IU/mL)	6.2 ± 0.6	5.9 ± 0.5	NS
Hemoglobin (g/dL)	13.4 ± 1.5	13.8 ± 1.7	NS
WBC (× 10 ³ /μL)	4.7 ± 1.2	5.0 ± 1.5	NS
Platelet (× 10 ⁴ /μL)	18.0 ± 6.0	18.0 ± 7.0	NS
AST (IU/L)	56.8 ± 34.9	58.2 ± 42.3	NS
ALT (IU/L)	65.5 ± 40.0	68.4 ± 56.8	NS
GGT (IU/L)	56.1 ± 52.3	55.3 ± 49.4	NS
AFP (ng/mL)	5.3 ± 4.0	24.2 ± 61.8	NS
Staging: F _{1,2} /F _{3,4}	19/16	49/27	NS
<i>IL28B</i> : TT/TG + GG	29/8	53/30	NS

ITPA: Inosine triphosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ -glutamyl transpeptidase; AFP: α -fetoprotein; NS: Not significant; HCV: Hepatitis C virus; *IL28B*: Interleukin 28B.

72 wk in some patients in whom HCV RNA first became undetectable after week 12 but before week 48. SVR was defined as undetectable serum HCV RNA for 24 wk after treatment completion. Rapid virological response (RVR) and early virological response (EVR) were defined as undetectable serum HCV RNA at 4 wk and 12 wk of Peg-IFN α + RBV treatment, respectively. The RBV dose was reduced by 200 mg in patients receiving 600 or 800 mg (by 400 mg in those receiving 1000 mg) when hemoglobin decreased to < 12 g/dL, and by another 200 mg when it was < 10 g/dL. RBV was withdrawn or stopped temporarily when hemoglobin levels decreased to < 8.5 g/dL. Dose of Peg-IFN α 2b (or Peg-IFN α 2a) was reduced by 50% when the leukocyte count decreased to < 1500/ μ L, neutrophil count to < 750/ μ L, or platelet count to < 80000/ μ L; Peg-IFN α 2b or Peg-IFN α 2a was withdrawn when the above measures were decreased to < 1000/ μ L, < 500/ μ L or < 50000/ μ L, respectively.

Laboratory data

Hematological, biochemical, and virological parameters were determined by the clinical laboratory at Kyushu Medical Center. Serum HCV RNA concentrations were determined by the COBAS TaqMan polymerase chain reaction (PCR) HCV test (Roche Diagnostics, Tokyo, Japan). Genotyping for the *IL28B* (rs8099917) and *ITPA* (rs1127354) polymorphisms was performed by TaqMan SNP Genotyping Assays (Applied Biosystems, Branchburg, NJ, United States) that apply a PCR-based restriction fragment length polymorphism assay.

Statistical analysis

Statistical analysis was performed using JMP software (SAS Institute Inc., Cary, NC, United States). Differences between categorical variables were analyzed using Fisher's exact test or χ^2 test. Mann-Whitney *U* test was used for continuous variables. Multivariate analysis was used to identify factors independently associated with the achievement of SVR.

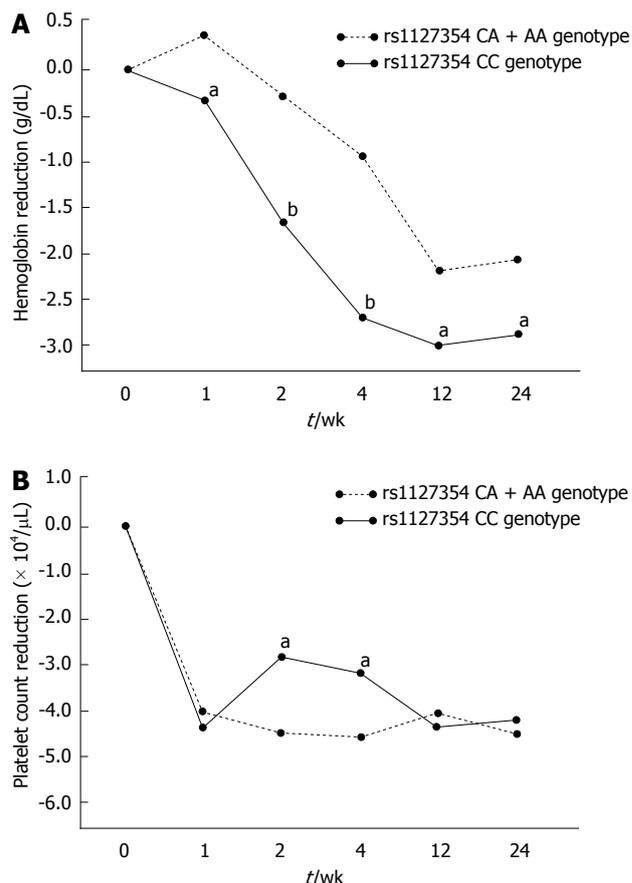


Figure 1 Chronological variation of hemoglobin levels (A) and platelet counts (B) in each inosine triphosphatase genotype at rs1127354. ^a*P* < 0.05, ^b*P* < 0.01 compared with CA/AA groups.

The OR and 95%CI were also calculated. *P* < 0.05 was considered to be statistically significant.

RESULTS

Association between *ITPA* deficiency and hemoglobin decline

Baseline characteristics of 120 enrolled patients are shown in Table 1. The study population included 83 patients with major (CC) genotype and 37 patients with minor (CA/AA) genotype of *ITPA* at rs1127354. Within listed items, no significant difference was seen between *ITPA* CC and CA/AA groups. Chronological variation of hemoglobin levels and platelet count during Peg-IFN α + RBV therapy is shown in Figure 1. As reported previously, hemoglobin decline was obvious in patients with *ITPA* CC genotype (rs1127354) and a significant difference was seen at week 1, 2, 4, 12 and 24 (Figure 1A), meaning that *ITPA* deficiency due to CA/CC genotype was associated with slower hemoglobin decline early in treatment. The greatest difference in mean hemoglobin reduction was found at week 4, while platelet reduction was temporally heavier in patients with *ITPA* CA/AA genotype at week 2 and 4 (Figure 1B). Leukocyte and neutrophil counts were equivalent between *ITPA* genotype CC and CA/AA

Table 2 Sustained virological response rates according to total ribavirin dose in each inosine triphosphatase genotype

<i>ITPA</i> genotype (rs1127354)	Patients with > 60% total RBV dose	Patients with < 60% total RBV dose	Total
CA + AA	48.3% (14/29)	12.5% (1/8)	40.5% (15/37)
CC	58.5% (31/53)	20.0% (6/30)	44.6% (37/83)

Each group includes patients in whom treatment was withdrawn. RBV: Ribavirin; *ITPA*: Inosine triphosphatase.

Table 3 Virological response according to classification by inosine triphosphatase and interleukin 28B single-nucleotide polymorphisms *n* (%)

Virological response	<i>IL28B</i> : TT		<i>IL28B</i> : TG + GG	
	CA + AA (<i>n</i> = 29) ¹	CC (<i>n</i> = 53) ¹	CA + AA (<i>n</i> = 8) ¹	CC (<i>n</i> = 30) ¹
RVR	3 (10.3)	10 (18.9)	0 (0.0)	4 (13.3)
RVR + EVR	18 (62.1)	35 (66.0)	1 (12.5)	8 (26.6)
SVR	13 (44.8)	29 (54.7)	2 (25.0)	8 (26.6)

¹Inosine triphosphatase (*ITPA*). SVR: Sustained virological response; RVR: Rapid virological response; EVR: Early virological response; *IL28B*: Interleukin 28B.

groups during treatment (data not shown).

Treatment outcome in each genotype of *ITPA*

As a result of hepatocellular carcinoma, therapeutic inefficiency, or adverse events, such as depression, appetite loss, easy fatigability, retinal hemorrhage, and hemolytic anemia, Peg-IFN α + RBV therapy was discontinued in 18 patients with *ITPA* CC genotype (21.7%) and 6 patients with CA/AA genotype (16.2%). Moreover, serious reduction of RBV administration (< 60% of scheduled total dose) was compelled in significantly more patients with CC genotype compared with the CA/AA genotype. The percentage of patients receiving < 60% total RBV dose, including patients with treatment interruption/withdrawal, was significantly higher for the CC genotype (37.3% *vs* 21.6%, *P* < 0.05). To investigate the influence of dose reduction of Peg-IFN on treatment outcome, we also analyzed the dose of Peg-IFN administered for each rs1127354 genotype, and > 70% of the expected total dose was administered to all patients with treatment completion (data not shown). SVR rates were analyzed according to the total RBV dose and *ITPA* genotype (Table 2). In the whole population, SVR rates were higher in *ITPA* genotype CC than CA/AA genotype (44.6% *vs* 40.5%), although the difference was not significant. SVR rates tended to be higher for the CC genotype than the CA/AA genotype in patients with > 60% total RBV dose (58.5% *vs* 48.3%) or < 60% total RBV dose (20.0% *vs* 12.5%), but there were no significant differences between the *ITPA* genotypes.

SVR, RVR and EVR rates were determined for *IL28B* (rs8099917) and *ITPA* (rs1127354) genotypes (Table 3). In a subset of patients with *IL28B* TT genotype, RVR, RVR + EVR and SVR showed higher rates in patients

Table 4 Comparison of profile between sustained virological response and non-sustained virological response patients

Factors	SVR (<i>n</i> = 54)	non-SVR (<i>n</i> = 66)	<i>P</i> value
Age (yr)	57 \pm 12	61 \pm 9	< 0.05
Gender: male/female	21/33	33/33	NS
Body mass index (kg/m ²)	23.5 \pm 4.1	22.6 \pm 3.3	NS
HCV RNA (log IU/mL)	5.9 \pm 0.6	6.1 \pm 0.6	< 0.05
Hemoglobin (g/dL)	13.7 \pm 1.3	13.8 \pm 1.8	NS
WBC ($\times 10^3$ /mL)	4.7 \pm 1.3	5.1 \pm 1.5	NS
Platelet ($\times 10^4$ /mL)	20 \pm 7	17 \pm 6	< 0.05
AST (IU/L)	46.2 \pm 25.8	66.7 \pm 47.1	NS
ALT (IU/L)	56.1 \pm 33.3	75.1 \pm 61.1	NS
GGT (IU/L)	39.8 \pm 24.1	67.4 \pm 61.2	NS
AFP (ng/mL)	8.3 \pm 19.8	10.1 \pm 24.2	NS
Staging: F _{1,2} /F _{3,4}	12/40	28/30	< 0.01
72 wk treatment: +/-	10/44	14/52	NS
Ribavirin dose (%) ¹	90 \pm 35	76 \pm 41	NS
<i>ITPA</i> : CC/CA + AA	38/16	45/21	NS
<i>IL28B</i> : TT/TG + GG	44/10	38/28	< 0.01

¹Percentage of ribavirin administration to the scheduled total dose of full-length treatment (48 or 72 wk). SVR: Sustained virological response; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ -glutamyl transpeptidase; AFP: α -fetoprotein; *ITPA*: inosine triphosphatase; NS: Not significant; HCV: Hepatitis C virus; *IL28B*: Interleukin 28B.

Table 5 Multivariate analysis for predictive factors associated with SVR

Factors	Category	95%CI	<i>P</i> value
HCV RNA (log IU/mL)	\geq 6.0: 1.0	1.42-10.95	0.008
	< 6.0: 3.94		
<i>IL28B</i> (rs8099917)	TG + GG: 1.0	1.18-10.10	0.023
	TT: 3.46		
	TT: 3.46		

HCV: Hepatitis C virus; *IL28B*: Interleukin 28B; SVR: Sustained virological response.

with *ITPA* CC genotype compared with CA/AA genotype, although the difference was not significant. In a subset of patients with *IL28B* TG/GG genotype, SVR rates were equivalent between CC and CA/AA genotypes.

When background of SVR and non-SVR patients was compared, there was a significant difference in age, HCV RNA concentrations, platelet counts, staging, and *IL28B* SNPs, but not in *ITPA* SNPs (Table 4). Table 5 shows the result of multivariate analysis for predictive factors associated with SVR. The multivariate analysis proved that viral load (HCV RNA < 6.0 log IU/mL) and *IL28B* TT (rs8099917) were independent factors for SVR.

DISCUSSION

It has been shown that the SNP (rs8099917) in the *IL28B* gene is strongly associated with response to IFN-based therapy for chronic HCV-1b infection, and the SNP (rs1127354) in the *ITPA* gene predicts RBV-induced anemia in the Japanese population^{19,23}. In this study, patients with *ITPA* (rs1127354) genotype CC showed a higher degree of hemoglobin reduction in response to Peg-IFN α + RBV treatment at week 1, 2, 4, 12 and 24 compared

with those with the CA/AA genotype (Figure 1A). The greatest difference in mean hemoglobin reduction was found at week 4. These findings confirmed the reported evidence that *ITPA* deficiency (rs1127354 CA/AA variants) renders protection against the development of RBV-induced hemoglobin decline in Japanese patients infected with HCV-1b^[20,23]. The exact mechanism by which *ITPA* deficiency protects against RBV-induced hemolysis has yet to be resolved. One postulated mechanism for the development of anemia is the accumulation of triphosphorylated RBV in erythrocytes, causing eventual oxidative damage to erythrocyte membranes, and *ITPA* deficiency may confer protection against RBV-induced ATP reduction by substituting for erythrocyte GTP, which is depleted by RBV in the biosynthesis of ATP^[24,26].

Thrombocytopenia, which leads to poor treatment efficacy because of the initial or early dose reduction of Peg-IFN α , is one of the critical adverse events caused by IFN-based antiviral therapy. A previous study has reported that the *ITPA* (rs1127354) CA/AA genotype is independently associated with a greater reduction in platelet count as well as protection against the reduction in hemoglobin, whereas patients with the CC genotype have significantly less reduction in mean platelet count^[27]. We also evaluated whether genetic variants in the *ITPA* gene were associated with IFN-induced thrombocytopenia. In this study, CC genotype showed lesser trend of reduction at week 2 and 4 compared with CA/AA genotype (Figure 1B). The result may support the association of *ITPA* gene SNP (rs1127354) with platelet decline in response to Peg-IFN α + RBV treatment.

Hemoglobin reduction often necessitates dose reduction of RBV and premature withdrawal from therapy, therefore the *ITPA* (rs1127354) genotype CC may be considered as a disadvantageous factor for Peg-IFN α + RBV treatment. However, although *ITPA* polymorphisms are significantly associated with RBV-induced anemia, their effect on therapeutic outcome is unclear. Some studies have shown no association^[14,28-31], and others have reported a possible association with treatment outcomes in chronic hepatitis C patients^[21,22]. In the present study, although there was no significant association between *ITPA* polymorphisms and treatment outcome, there was a trend towards higher SVR rates in patients with *ITPA* CC genotype, which seemed to contradict previous studies^[21,22,28-31]. The different outcome among the institutes may be due to the difference of inclusion and/or exclusion criteria. In this study, the relationship between *IL28B* and *ITPA* variants were additionally analyzed on treatment outcome. When analyzed in the patients available for treatment outcome, all patients were administered > 70% of the scheduled total Peg-IFN α dose, but the incidence of RBV dose reduction (< 60% of the scheduled dose) and withdrawal was significantly higher in patients with the rs1127354 genotype CC. However, the rate of SVR tended to be higher in patients with the CC genotype, especially in a subset of patients with the favorable TT genotype at rs8099917 of *IL28B*, although the difference was not significant between the CC and CA/AA

genotypes (Tables 2 and 3). Independent favorable predictors for SVR identified in multivariate analysis were low viral load (HCV RNA < 6.0 log IU/mL) and TT genotype at rs8099917 of *IL28B*, but not CC genotype at rs1127354 of *ITPA* (Table 5).

There were several limitations to this study. (1) Because of the small sample size which may have contributed to the loss of significance observed or some statistical errors, this study may be ranked at preliminary status; (2) Because of the retrospective nature of the study, enrolled patients may not represent the standard Japanese population infected with HCV; (3) Several other significant SNPs, which have been detected in *ITPA* as well as *IL28B*, may have influenced and distorted the results; and (4) Mutations in other genes and non-genetic factors that may affect response to antiviral therapy against chronic hepatitis C were not determined.

In conclusion, the SVR rates tended to be higher in patients with the CC genotype than the CA/AA genotype, especially in a subset of patients with *IL28B* (rs8099917) TT genotype, despite a higher rate of RBV dose reduction and treatment withdrawal. Multivariate analysis identified *IL28B* SNP (rs8099917) and HCV RNA as independent predictors of SVR. It is plausible that, in a background of *IL28B* (rs8099917) TT genotype, more SVR is achieved in patients with *ITPA* CC variant when full-length (duration of 48 or 72 wk) treatment is accomplished. These findings indicate that *ITPA* (rs1127354) CC genotype is by no means inferior to the CA/AA genotype for viral response to Peg-IFN + RBV combination therapy.

COMMENTS

Background

A single-nucleotide polymorphism (SNP) at rs1127354 of the inosine triphosphatase (*ITPA*) gene is associated with hemoglobin decline during peginterferon (Peg-IFN) + ribavirin (RBV) combination therapy in patients with hepatitis C virus infection. However, the effect of the *ITPA* gene SNP on treatment outcome has not been fully elucidated. Authors analyzed the association between *ITPA* (rs1127354) genotypes and sustained virological response (SVR) rates in Peg-IFN α + RBV treatment.

Research frontiers

ITPA CC genotype was a disadvantageous factor for Peg-IFN α + RBV treatment in relation to completion rates and RBV dose. However, CC genotype was not inferior to CA/AA genotype for SVR rates. When full-length treatment is accomplished, it is plausible that more SVR is achieved in patients with *ITPA* CC variant, especially in a background of Interleukin 28B (*IL28B*) TT genotype.

Innovations and breakthroughs

In patients with *ITPA* CC genotype, hemoglobin decline was significantly greater and the percentage of patients in whom total RBV dose was < 60% of standard and/or treatment was withdrawn was significantly higher compared with CA/AA genotype. However, SVR rates were equivalent between CC and CA/AA genotypes, and within a subset of patients with *IL28B* (rs8099917) TT genotype, SVR rates tended to be higher in patients with *ITPA* CC genotype, although the difference was not significant.

Peer review

The topic is interesting and relevant. The manuscript is well written and concise.

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