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Host interleukin-28B genetic variants versus viral kinetics in determining responses to standard-of-care for Asians with hepatitis C genotype 1

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ABSTRACT

Background: Both interleukin-28B genetic variants and on-treatment virological responses are factors predictive of treatment outcome in hepatitis C virus genotype 1 (HCV-1) patients. We aimed to compare the clinical significance of the two factors.
Methods: Rs8099917 genotype and on-treatment responses were determined in 182 HCV-1 patients with 48-week peginterferon/ribavirin.
Results: Comparing to patients with rs8099917 TG/GG genotype, those with TT genotype had significantly higher rapid virological response (RVR, 46.2% vs. 19.2%, $P = 0.01$) and sustained virological response (SVR, 85.3% vs. 42.3%, $P < 0.001$) rates. Logistic regression analysis revealed that the strongest factor predictive of a RVR was the carriage of rs8099917 TT genotype (odds ratio/95% confidence intervals [OR/CI]: 4.25/1.39-13.01). The most important factor predictive of an SVR was the attainment of a RVR (OR/CI: 57.22/6.23-525.37), followed by the carriage of rs8099917 TT genotype (OR/CI: 10.06/3.12-32.44). However, while on-treatment factors were taken into account, the cEVR was the most important determinant to an SVR (OR/CI:54.98/9.07-333.38), whereas the influence of rs8099917 genotype became non-significant in non-RVR patients.
Conclusions: Rs8099917 TT genotype is significantly independently predictive of on-treatment virological responses, which were the major determinants of an SVR, in Asian HCV-1 patients.

1. Introduction

Pegylated interferon (peginterferon) and ribavirin combination therapy is now recommended for the treatment of chronic hepatitis C (CHC) infection. Based on current standard of care (SOC), 48-week regimens are recommended for patients infected with hepatitis C virus genotype 1 (HCV-1) (Ghany et al., 2009). Host factors are key elements to the outcome in the treatment of HCV infection (Dai et al., 2006a,b, 2009; Yu and Chuang, 2009). Recent studies based on genome-wide associated studies (GWAS) have demonstrated that single nucleotide polymorphisms (SNPs) at and/or near the interleukin 28B (IL-28B) gene play a crucial role in the management of HCV infection. It has been suggested that favorable host genetic variants of IL-28B would enhance the treatment outcome in HCV-1-infected patients receiving standard 48 weeks of treatment (Ge et al., 2009; McCarthy et al., 2010; Rauch et al., 2010; Tanaka et al., 2009; Thompson et al., 2010). When it comes to the viral factor, the great advance in the study of HCV viral

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; APRI, the aspartate aminotransferase-to-platelet ratio index; CHC, chronic hepatitis C; EOTVR, end-of-treatment virological response; GWAS, genome-wide associated studies; HCV, hepatitis C virus; IL-28B, interleukin 28B; NPV, negative predictive value; PPV, positive predictive value; RVR, rapid virological response; SNP, single nucleotide polymorphism; SVR, sustained virological response.

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kinetics has facilitated the response-guide therapy (RGT) for CHC. The achievement of a rapid virological response (RVR, seronegative of HCV RNA at week 4 of treatment) is by far the most powerful on-treatment factor predictive treatment efficacy (Jensen et al., 2006; Kamal et al., 2007; Mangia et al., 2005; Yu et al., 2006b, 2007, 2008). Both the viral and host factors above contribute to the final treatment outcome.

The role of IL-28B genetic predisposition on the achievement of a sustained virological response (SVR, seronegativity of HCV RNA throughout 24 weeks of post-treatment follow-up period) was particularly enhanced for patients who failed to achieve a RVR (Mangia et al., 2011; Thompson et al., 2010). Yet our previous study has demonstrated that the achievement of a complete early virological response (cEVR, HCV RNA seropositivity at week 4 but seronegativity at week 12 of treatment) was the most pivotal factor predictive of an SVR in non-RVR patients (Huang et al., 2010). Taken collectively, the individual contributory power of the host and on-treatment factor to treatment efficacy is not clear and the association of host IL-28B gene and viral kinetics to final treatment outcome has rarely been studied. The current study aimed to elucidate whether host IL-28B genetic variants or on-treatment responses, both week-4 and week-12 virological responses, were the major determinants of SVR in HCV-1 Asian patients with a 48-week standard-of-care regimen in Taiwan where HCV infection is endemic (Yang et al., 2010).

2. Methods

2.1. Study population

One hundred and eighty-two consecutive patients who had an early virological response (EVR, seronegative or at least a 2-$\log_{10}$ decrease from baseline of serum HCV RNA at 12 weeks of treatment) and maintained at least 80% of assigned 48-week treatment duration or who terminated early at treatment week 16 due to not achieving an EVR were included for analysis retrospectively. Eligible subjects were treatment-naïve and were seropositive for HCV antibodies (third-generation, enzyme immunoassay; Abbott Laboratories, North Chicago, IL) and HCV RNA by polymerase chain reaction (PCR) for more than 6 months. Patients were excluded in case of following concurrent diseases or conditions: HIV infection, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, Wilson's disease, α_1-antitrypsin deficiency, decompensated cirrhosis, overt hepatic failure, current or past history of alcohol abuse ($\geqslant$20 g daily), psychiatric condition, previous liver transplantation, or evidence of hepatocellular carcinoma. All participants received either peginterferon alfa-2a (180 μg/week) or peginterferon alfa-2b (1.5 μg/kg/week) subcutaneously plus weight-based ribavirin (1000 mg/d for weight <75 kg and 1200 mg/d for weight >75 kg). Serum HCV RNA at the baseline, treatment weeks 4 and 12, the end-of-treatment and 24 weeks after therapy were determined by qualitative PCR (Cobas Amplicor Hepatitis C Virus Test, V.2.0; Roche Diagnostics, Branchburg, NJ; detection limit: 50 IU/mL). Serum levels of HCV RNA at the baseline and week 12 were measured using the branched DNA assay (Versant HCV RNA 3.0, Bayer, Tarrytown, NJ; quantification limit: 615 IU/mL) if qualitative HCV RNA seropositivity. HCV genotypes were determined by the method described by Okamoto et al. (1993). The study was approved by the ethics committees at the participating Hospitals and carried out according to the guidelines of the International Conference on Harmonization for Good Clinical Practice. All patients gave written informed consent before enrollment.

2.2. Assessment of efficacy

The endpoint of the study was achievement of an SVR, defined as seronegativity of HCV RNA throughout 24 weeks of post-treatment follow-up period. RVR was defined as seronegativity of HCV RNA at treatment week 4. EVR was defined as seronegative or at least a 2-$\log_{10}$ decrease from baseline of serum HCV RNA at 12 weeks of treatment. cEVR was defined as HCV RNA seropositivity at week 4 but seronegativity at week 12 of treatment. End-of-treatment virological response (EOTVR) was defined as seronegativity of HCV RNA at the end of treatment. Relapse was defined as HCV RNA reappearance during the follow-up period in patients who achieved an EOTVR.

2.3. IL-28B genotyping and statistical analyses

Rs8105790, rs8099917, rs4803219 and rs10853728 were noted to be associated with antiviral treatment responses based on GWAS and replication study in Asian ethnicity (Tanaka et al., 2009). We have previously demonstrated that the former three SNPs have very strong linkage disequilibrium (LD) with one another and SNP rs10853728 had no role in the treatment of HCV-2 infection (Yu et al., 2011). Rs809917 and rs12979860 have been also noted to be in very strong LD (Ochi et al., 2011), and rs8099917 has suggested to be the most suitable SNP for predicting treatment responses in Asian patients (Ito et al., 2011). We therefore selected rs8099917 as candidate SNP in the current study. Frequency was compared between groups using the χ^2 test, with the Yates correction, or Fisher exact test. Group means, presented as mean values standard deviation, were compared using analysis of variance and the Student t test or Mann–Whitney U test. Serum HCV RNA levels were expressed after logarithmic transformation of original values. Creatinine clearance was estimated via the Cockcroft-Gault Equation, which includes sex, age, body weight and serum creatinine level as values. The aspartate aminotransferase (AST)-to-platelet ratio index (APRI) was calculated by the following equation: (AST level/upper limit of normal range)/platelet counts (10^9/L) $\times$ 100, to represent the severity of liver fibrosis (Martinez et al., 2011; Wai et al., 2003; Yu et al., 2006a). The frequencies of the rare allele (G) of rs8099917 genotype were too low and the rare homozygote (GG) and heterozygote (GT) were combined together while analyzing the SNP. To assess the relative contribution of predictors of RVR and SVR, a multivariable model was applied with age, sex, baseline HCV RNA levels, ribavirin exposure by body weight, APRI and rs8099917 genotype as co-variants. The statistical analyses were performed using the SPSS 12.0 statistical package (SPSS, Chicago, IL). All statistical analyses were based on two-sided hypothesis tests with a significance level of $P < 0.05$.

3. Results

3.1. Patient profiles and virological responses

The basic demographical, virological, and clinical features of the patients were shown in Table 1. 156 (85.7%) of the182 patients carried rs8099917 TT genotype, whilst 26 (14.3%) patients were with rs8099917 GT/GG genotype. The rates of RVR, EVR, EOTVR, SVR and relapse were 42.3%, 95.6%, 91.8%, 79.1% and 13.8%, respectively.

3.2. Factors associated with RVR and SVR

As shown in Table 2, univariate analysis revealed that the carriage of rs8099917TT genotype, lower baseline HCV RNA levels and higher ribavirin exposure by body weight during the first four week of treatment were factors significantly associated with a higher RVR rate. Stepwise logistic regression analysis revealed that the carriage of rs8099917 TT genotype was the strongest predictor of a RVR, followed by baseline HCV viral loads <400,000 IU/mL and higher ribavirin exposure by body weight during the first four

Table 1
Basic demographic, virological, and clinical features of the 182 patients.

Age (years, mean (SD))	51.0 (11.4)
Male, *n* (%)	96(52.7)
Body weight (kg, mean (SD))	64.8 (10.9)
Baseline HCV RNA (log IU/mL, mean (SD))	5.62(0.91)
Baseline HCV RNA >400,000 IU/mL, *n* (%)	105 (57.7)
APRI (mean (SD))	1.63 (1.64)
AST (IU/L, mean (SD))	92.7 (57.6)
ALT (IU/L, mean (SD))	137.9 (77.1)
Ccr (mL/min, mean (SD))	100.2 (32.0)
Fasting blood sugar (mg/dL, mean (SD))	99.8 (23.6)
Rs8099917	
TT/GT + GG, *n* (%)	156/26 (85.7/14.3)

Note: SD, standard deviation; AST, aspartate aminotransferase (normal range < 42 IU/L); ALT, alanine aminotransferase (normal range < 40 IU/L); Ccr, Creatinine clearance rate; APRI, aspartate aminotransferase-to-platelet ratio index. Fasting sugar normal range < 100 mg/dL.

week (Table 3). Patients with rs8099917 TT genotype, a younger age, male sex, higher ribavirin exposure by body weight, lower pretreatment AST levels and APRI score, and the achievement of RVR were factors predictive of an SVR in univariate analysis (Table 2). Logistic regression analysis revealed that the most important factor associated with SVR was the attainment of RVR, followed by the carriage of rs8099917 TT genotype, male sex and lower APRI score (Table 3).

3.3. Influence of SNP rs8099917 on treatment responses

Basic demographical, virological, and clinical features were similar between patients with the major homozygote (TT) and GT/GG genotype of rs8099917 (Table 4).

Comparing to G allele carriers (GT/GG), those with the homozygous TT genotype had significantly higher rates of RVR (46.2% vs. 19.2%, $P = 0.01$), cEVR (82.9% vs.28.6%, $P < 0.001$), EOTVR (94.2% vs. 76.9%, $P = 0.01$) and SVR (85.3% vs. 42.3%, $P < 0.001$) and lower relapse rate (9.5% vs. 45.0%, $P = 0.001$). Between groups analysis of the influence of the SNP on SVR by stratifying the achievement of a RVR is shown in Table 5. The SVR rate was similar between different rs8099917 genotypes in patients achieving a RVR, whatever the levels of baseline HCV viral loads. Among non-RVR patients, those with rs8099917 TT genotype had a significantly higher SVR rate than those who carried rs8099917 TG/GG genotype (72.6% vs. 33.3%, $P = 0.001$). The difference was mainly restricted to non-RVR patients with high baseline HCV viral loads (74.2% vs. 33.3%, $P = 0.02$). Moreover, The SVR rate did not differ between different rs8099917 genotypes in patients with or without cEVR. Further analysis by multivariate analysis revealed that the carriage of rs8099917 TT genotype was the most important factor predictive of SVR in non-RVR patients (OR/CI: 8.98/2.48-32.47, $P = 0.001$) if the variable of on-treatment response was not considered. However, while the factor of cEVR was taken into account, the achievement of a cEVR became the most important determinant of SVR (OR/CI:56.78/9.07-355.62, $P < 0.001$), whereas the influence of rs8099917 genotype on treatment outcome became non-significant in patients without RVR (Table 6).

Table 3
Logistic regression analysis of factors associated with RVR and SVR.

Dependent	Variables	OR	95% CI	*P* value
RVR	Rs8099917			
	GT/GG genotype	1		
	TT genotype	4.25	1.39–13.01	0.01
	Baseline HCV RNA levels			
	>400,000 IU/mL	1		
	<400,000 IU/mL	3.63	1.84–7.17	<0.001
	Ribavirin exposure during the first 4 week			
	Per 1 mg/kg/d increase	1.27	1.12–1.44	<0.001
SVR	Achievement of a RVR			
	No	1		
	Yes	57.22	6.23–525.37	<0.001
	Rs8099917			
	GT/GG genotype	1		
	TT genotype	10.06	3.12–32.44	<0.001
	Gender			
	Male = 1, female = 0	3.50	1.30–9.39	0.01
	APRI			
	Per 1 unit increase	0.64	0.46–0.89	0.008

Note: OR, Odds Ratio; CI, Confidence Intervals; RVR, rapid virologic response; SVR, sustained virologic response; APRI, aspartate aminotransferase-to-platelet ratio index.

4. Discussion

HCV-1, the most prevalent HCV genotype in Taiwan (Dai et al., 2010), patients with rs8099917 TT genotype were more likely to achieve RVR, EVR and SVR, and had lower likelihood of relapse. The IL-28B genetic variant is the most important predictor of

Table 2
Univariate analysis of factors associated with rapid virological response and sustained virological response.

	Week 4 virological response			End of follow-up virological response		
	RVR (+) (*n* = 77)	RVR (−) (*n* = 105)	*P* value	SVR (+) (*n* = 144)	SVR(−) (*n* = 38)	*P* value
Rs8099917 genotype TT/ GT + GG, n (%)	72/5 (93.5/6.5)	84/21 (80.0/20.0)	0.01	133/11 (92.4/7.6)	23/15 (60.5/39.5)	<0.001
Male sex, *n* (%)	40 (51.9)	56 (53.3)	0.85	82 (56.9)	14 (36.8)	0.03
Age (yrs, mean(SD))	49.7 (11.8)	51.9 (11.1)	0.21	49.6 (11.7)	56.2 (8.7)	<0.001
Baseline HCV RNA (log IU/mL, mean(SD))	5.21 (1.05)	5.93 (0.63)	<0.001	5.56 (0.95)	5.85 (0.68)	0.08
Baseline HCV RNA >400,000 IU/mL, *n* (%)	31 (40.3)	74 (70.5)	<0.001	81 (56.3)	24 (63.2)	0.44
APRI, mean (SD)	1.42 (1.14)	1.78 (1.92)	0.15	1.37 (1.14)	2.59 (2.62)	0.009
AST (IU/L, mean (SD))	89 (54)	95 (60)	0.63	87 (58)	113 (51)	0.001
ALT (IU/L, mean (SD))	142 (73)	135 (80)	0.30	136 (81)	146 (58)	0.09
Fasting blood sugar (mg/dL, mean (SD))	96.4 (22.1)	102.4 (24.4)	0.08	98.9 (24.6)	103.5 (18.6)	0.30
Ribavirin per body weight (mg/kg/d, mean(SD))	18.7 (2.8)*	17.0 (2.9)*	<0.001	14.8 (3.2)	13.3 (4.2)	0.02
RVR (+) (*n* (%))	–	–	–	76 (52.8)	1 (2.6)	<0.001
cEVR (+) for non-RVR patients (*n*/N, (%))**	–	–	–	64/68 (94.1)	11/37 (29.7)	<0.001

Note: SD, standard deviation; SVR, sustained virological response; RVR, rapid virological response; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase-to-platelet ratio index.

* The first 4 weeks of ribavirin exposure.

** cEVR: complete early virological response, defined as non-RVR patients with HCV RNA <50 IU/L at treatment week 12.

Table 4
Basic demographical, virological, and clinical features of the patients with different rs8099917 genotypes.

	Rs8099917, TT-genotype (n = 156)	Rs8099917, GT/GG-genotype (n = 26)	P value
Age (years, mean (SD))	51.5 (11.5)	50.7 (11.0)	0.92
Male, n (%)	83 (53.2)	13 (50.0)	0.76
Body weight (kg, mean (SD))	64.8 (10.8)	65.2 (11.6)	0.85
Baseline HCV RNA (log IU/mL, mean (SD))	5.61 (0.92)	5.68 (0.86)	0.72
Baseline HCV RNA >400,000 IU/mL, n (%)	92 (59.0)	13 (50.0)	0.39
AST (IU/L, mean (SD))	91 (59)	101 (46)	0.43
ALT (IU/L, mean (SD))	138 (80)	139 (55)	0.91
Fasting blood sugar (mg/dL, mean (SD))	99.8 (24.1)	99.8 (20.5)	0.99
APRI (mean (SD)	1.59 (1.68)	1.85 (1.33)	0.45
Ribavirin per body weight (mg/kg/d, mean(SD))	14.4 (3.4)	15.1 (3.9)	0.45

Note: HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aspartate aminotransferase; Ccr, Creatinine clearance rate; APRI, aspartate aminotransferase-to-platelet ratio index.

Table 5
SVR rates stratified by RVR status in patients with different rs8099917 genotypes.

	Rs8099917, TT genotype	Rs8099917, GT + GG genotype	P value
RVR(+), n/N (%)	72/72 (100)	4/5 (80.0)	0.07
LVL, n/N (%)	42/42 (100)	3/4 (75.0)	0.09
HVL, n/N (%)	30/30 (100)	1/1 (100)	1
RVR(−), n/N (%)	61/84 (72.6)	7/21 (33.3)	0.001
LVL, n/N (%)	15/22 (68.2)	3/9 (33.3)	0.11
HVL, n/N (%)	46/62 (74.2)	4/12 (33.3)	0.02
cEVR(+), n/N (%)	58/69 (83.8)	6/6 (100)	0.58
LVL, n/N (%)	15/20 (75.0)	2/2 (100)	1
HVL, n/N (%)	43/49 (87.8)	4/4 (100)	1
cEVR(−), n/N (%)	3/15 (20.0)	1/15 (6.7)	0.60
LVL, n/N (%)	0/2 (0)	1/7 (14.3)	1
HVL, n/N (%)	3/13 (23.1)	0/8 (0)	0.26

Note: SVR, sustained virological response; RVR, rapid virological response; cEVR, complete early virological response; LVL, low viral loads, defined as HCV RNA levels <400,000 IU/mL; HVL, high viral loads, defined as HCV RNA levels >400,000 IU/mL.

attaining a RVR. When it concerns final treatment outcome, the attainment of a RVR remains the most important factor predictive of SVR in HCV-1 patients with standard of care regimens. The effect of IL-28B genetic polymorphisms was restricted and enhanced in non-RVR patients with high viral loads. For the non-RVR HCV-1 patients, however, the most important determinant of SVR was the achievement of cEVR regardless of host genetic predispositions.

Although the role of IL-28B genetic variants in the final treatment outcome of HCV-2 infection remains an argument of debate (Mangia et al., 2011; McCarthy et al., 2010; Rauch et al., 2010; Sarrazin et al., 2011; Yu et al., 2011), its impact in HCV-1 patients have been well recognized (Ge et al., 2009; McCarthy et al. 2010; Ochi et al. 2011; Rauch et al. 2010; Stättermayer et al., 2011; Suppiah et al., 2009; Tanaka et al., 2009; Thompson et al., 2010). It is noteworthy that even that the probability of SVR achievement essentially depends on IL-28B genotype, the attainment of RVR remains the most important factor predictive of SVR in the current study, as in Caucasian patients (Stättermayer et al., 2011; Thompson et al., 2010). Accordingly, although there were dissimilar results regarding IL-28B gene and early viral kinetics in the treatment of HCV-2 infection (Mangia et al., 2010; Sarrazin et al., 2011; Yu et al., 2011), it has been suggested that variants in the locus determined the rapidity of HCV-1 viral decline after peginterferon/ribavirin therapy (Hsu et al., 2011; Stättermayer et al., 2011; Thompson et al., 2010). Our finding echoed previous studies that the carriage of rs8099917 TT genotype played a critical role in the achievement of SVR and was the most important factor independently predictive of RVR. Apart from host genetics and HCV viral loads, the only adjustable factor to enhance the RVR rate in the current study was the dosage of ribavirin exposure during early phase of therapy. Low body weight (Ferenci et al., 2008), higher ribavirin dose(Jensen et al., 2006) and higher dose of weight-based ribavirin exposure (Rodriguez-Torres et al., 2010) have been mentioned to enhance RVR. Should patients with unfavorable IL-28 genotype receive higher initial dose of ribavirin so as to enhance RVR and consequent SVR deserves further studies. The impact of sex on treatment efficacy remains debatable. Better response to antiviral treatments and slow progression of fibrosis in women than in men has been proposed in some studies (Conjeevaram et al., 2006; Poynard et al., 1997, 1998, 2000) but there exist contradictory results (Chayama et al., 2010; Oze et al., 2011; Sezaki et al., 2009). After adjusting other factors including IL-28B genetic variants, male gender had favorable treatment responses in the current study. The finding was in line with the finding by Tanaka et al. (2009) that female gender as well as the carriage of rs8099917 G allele were factors associated with null virological response in the logistic regression model.

Despite the attainment of RVR is the landmark to treatment success, only 12–44% of patients with HCV-1 infection could achieve it (Berg et al., 2006; Bronowicki et al., 2006; Fried et al., 2002; Yu et al., 2008). More attentions should be paid on the majority of patients who fail to reach the early goal. The observation of the influence of IL-28B gene on SVR in non-RVR patents resulted in different results in HCV-2 infection (Mangia et al., 2010; Sarrazin et al., 2011; Yu et al., 2011). However, Thompson et al. demonstrated that, in comparison with minor alleles carriers, HCV-1 patients who carried rs12199860

Table 6
Multivariate analysis of factors associated with SVR in non-RVR patients with or without cEVR achievement as a covariant.

	OR	95% CI	P value	OR	95% CI	P value
cEVR achievement	–	–	–	54.98	9.07–333.38	<0.001
Rs8099917 TT genotype	8.98	2.48–32.47	0.001	1.55	0.23–10.44	0.65
Male sex	2.91	1.05–8.09	0.04	5.70	1.30–25.03	0.02
Age	0.95	0.90–1.00	0.06	0.96	0.89–1.03	0.28
Ribavirin exposure	1.05	0.90–1.22	0.58	1.03	0.85–1.26	0.74
APRI	0.75	0.53–1.06	0.10	0.72	0.49–1.07	0.10
Low viral loads	0.50	0.16–1.52	0.22	0.32	0.08–1.29	0.11

Note: cEVR, complete early virological response; OR, Odds Ratio; CI, Confidence Intervals; RVR, rapid virologic response; SVR, sustained virologic response; APRI, aspartate aminotransferase-to-platelet ratio index. Odds ratio are for rs8099917 (TT vs. GT/GG); age (per year increase); sex (male vs. female); ribavirin exposure (per 1 mg/kg/day increase); APRI (per 1 unit increase); viral loads (<400,000 IU/mL vs.>400,000 IU/mL) and cEVR (yes vs. no).

CC genotype had a higher SVR rate if they could not reach RVR (Thompson et al., 2010). We have concordant findings that the discriminatory power of the SNP rs8099917 was enhanced in non-RVR patients, particularly with high baseline viral loads in the current study. These results highlight the role of IL28B genetic variants in the so-called "difficult-to-treat" patients. Further studies are warranted to clarify the potential role of the genetic variants for those patients with respect to the use of extended course of regimens or potent direct antiviral agents. Nevertheless, the effect of SNP rs8099917 in non-RVR patients was eliminated if the factor of cEVR status was taken into account. In other words, the achievement of cEVR is the most important factor to access treatment success for SOC patients who failed to clear HCV during the first 4 weeks. The result echoed Mangia and colleagues' finding (2011) that the carriage of rs12979860 CC genotype seemed to have limited potential for Caucasian patients with RGT, where the frequency of favorable genetic variants were much less common than that of Asian patients in the current study. We previously demonstrated that cEVR is the most important independent factor predictive of SVR in non-RVR patients (Huang et al., 2010). Providing and maintaining optimal dose of ribavirin within 12 weeks of treatment was pivotal for the attainment of cEVR and efforts have to be made to achieve the second goal, cEVR, if patients failed for accomplish RVR (Huang et al., 2010). Subsequent change of viral kinetics remains the key to improve the treatment success for non-RVR patients.

The limitation of the current study was its retrospective basis and case number in certain subgroups might be too small to draw a definite conclusion. Liver fibrosis is a negative predictor for treatment response (Craxi, 2011). The completed histological data were unavailable in the current study and we used APRI score to represent the severity of liver disease (Martinez et al., 2011; Wai et al., 2003; Yu et al., 2006a). Although the application of APRI has been shown to provide only moderate degree of accuracy in predicting the severity (Lin et al., 2011), it could predict the long-term outcome of CHC patients with and without antiviral therapy (Yu et al., 2006a). The current study echoed the recent finding that liver fibrosis, represented by high APRI score, was associated with poor treatment response independent of host IL-28B rs8099917 genotype (Ochi et al., 2011).

In conclusion, IL-28B genetic variants independently predict on-treatment responses and SVR in HCV-1 patients, particularly those without RVR and with baseline high viral loads. Nevertheless, the major determinant of treatment success remains the achievement of RVR. For patients who failed to reach RVR, the accomplishment of cEVR was the most critical predictor to SVR irrespective of IL-28B genetic variants for Asian patients with SOC.

Contributions of authors

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Disclosures

No conflict of interests.

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References

Berg, T., von Wagner, M., Nasser, S., Sarrazin, C., Heintges, T., Gerlach, T., Buggisch, P., Goeser, T., Rasenack, J., Pape, G.R., Schmidt, W.E., Kallinowski, B., Klinker, H., Spengler, U., Martus, P., Alshuth, U., Zeuzem, S., 2006. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. Gastroenterology 130, 1086–1097.

Bronowicki, J.P., Ouzan, D., Asselah, T., Desmorat, H., Zarski, J.P., Foucher, J., Bourlière, M., Renou, C., Tran, A., Melin, P., Hézode, C., Chevalier, M., Bouvier-Alias, M., Chevaliez, S., Montestruc, F., Lonjon-Domanec, I., Pawlotsky, J.M., 2006. Effect of ribavirin in genotype 1 patients with hepatitis C responding to pegylated interferon alfa-2a plus ribavirin. Gastroenterology 131, 1040–1048.

Chayama, K., Hayes, C.N., Yoshioka, K., Moriwaki, H., Okanoue, T., Sakisaka, S., Takehara, T., Oketani, M., Toyota, J., Izumi, N., Hiasa, Y., Matsumoto, A., Nomura, H., Seike, M., Ueno, Y., Yotsuyanagi, H., Kumada, H., 2010. Accumulation of refractory factors for pegylated interferon plus ribavirin therapy in older female patients with chronic hepatitis C. Hepatol. Res. 40, 1155–1167.

Conjeevaram, H.S., Fried, M.W., Jeffers, L.J., Terrault, N.A., Wiley-Lucas, T.E., Afdhal, N., Brown, R.S., Belle, S.H., Hoofnagle, J.H., Kleiner, D.E., Howell, C.D., 2006. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. Gastroenterology 131, 470–477.

Craxi, A., 2011. EASL clinical practice guidelines: management of hepatitis C virus infection. J. Hepatol. 55, 245–264.

Dai, C.Y., Chuang, W.L., Lee, L.P., Chen, S.C., Hou, N.J., Lin, Z.Y., Hsieh, M.Y., Hsieh, M.Y., Wang, L.Y., Chang, W.Y., Yu, M.L., 2006a. Associations of tumour necrosis factor alpha promoter polymorphisms at position −308 and −238 with clinical characteristics of chronic hepatitis C. J. Viral Hepat. 13, 770–774.

Dai, C.Y., Chuang, W.L., Chang, W.Y., Chen, S.C., Lee, L.P., Hsieh, M.Y., Hou, N.J., Lin, Z.Y., Huang, J.F., Hsieh, M.Y., Wang, L.Y., Yu, M.L., 2006b. Tumor necrosis factor-alpha promoter polymorphism at position −308 predicts response to combination therapy in hepatitis C virus infection. J. Infect. Dis. 193, 98–101.

Dai, C.Y., Huang, J.F., Hsieh, M.Y., Hou, N.J., Lin, Z.Y., Chen, S.C., Hsieh, M.Y., Wang, L.Y., Chang, W.Y., Chuang, W.L., Yu, M.L., 2009. Insulin resistance predicts response to peginterferon-alpha/ribavirin combination therapy in chronic hepatitis C patients. J. Hepatol. 50, 712–718.

Dai, C.Y., Ho, C.K., Huang, J.F., Hsieh, M.Y., Hou, N.J., Lin, Z.Y., Chen, S.C., Hsieh, M.Y., Wang, L.Y., Chang, W.Y., Yu, M.L., Chuang, W.L., 2010. Hepatitis C virus viremia and low platelet count: a study in a hepatitis B & C endemic area in Taiwan. J. Hepatol. 52, 160–166.

Ferenci, P., Laferl, H., Scherzer, T.M., Gschwantler, M., Maieron, A., Brunner, H., Stauber, R., Bischof, M., Bauer, B., Datz, C., Löschenberger, K., Formann, E., Staufer, K., Steindl-Munda, P., 2008. Peginterferon alfa-2a and ribavirin for 24 weeks in hepatitis C type 1 and 4 patients with rapid virological response. Gastroenterology 135, 451–458.

Fried, M.W., Shiffman, M.L., Reddy, K.R., Smith, C., Marinos, G., Gonçales Jr., F.L., Häussinger, D., Diago, M., Carosi, G., Dhumeaux, D., Craxi, A., Lin, A., Hoffman, J., Yu, J., 2002. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. N. Engl. J. Med. 347, 975–982.

Ge, D., Fellay, J., Thompson, A.J., Simon, J.S., Shianna, K.V., Urban, T.J., Heinzen, E.L., Qiu, P., Bertelsen, A.H., Muir, A.J., Sulkowski, M., McHutchison, J.G., Goldstein, D.B., 2009. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature 461, 399–401.

Ghany, M.G., Strader, D.B., Thomas, D.L., Seeff, L.B., 2009. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 49, 1335–1374.

Hsu, C.S., Hsu, S.J., Chen, H.C., Tseng, T.C., Liu, C.H., Niu, W.F., Jeng, J., Liu, C.J., Lai, M.Y., Chen, P.J., Kao, J.H., Chen, D.S., 2011. Association of IL28B gene variations with mathematical modeling of viral kinetics in chronic hepatitis C patients with IFN plus ribavirin therapy. Proc. Natl. Acad. Sci. USA 108, 3719–3724.

Huang, C.F., Yang, J.F., Huang, J.F., Dai, C.Y., Chiu, C.F., Hou, N.J., Hsieh, M.Y., Lin, Z.Y., Chen, S.C., Hsieh, M.Y., Wang, L.Y., Chang, W.Y., Chuang, W.L., Yu, M.L., 2010. Early identification of achieving a sustained virological response in chronic hepatitis C patients without a rapid virological response. J. Gastroenterol. Hepatol. 25, 758–765.

Ito, K., Higami, K., Masaki, N., Sugiyama, M., Mukaide, M., Saito, H., Aoki, Y., Sato, Y., Imamura, M., Murata, K., Nomura, H., Hige, S., Adachi, H., Hino, K., Yatsuhashi, H., Orito, E., Kani, S., Tanaka, Y., Mizokami, M., 2011. The rs8099917 polymorphism, when determined by a suitable genotyping method, is a better predictor for response to pegylated alpha interferon/ribavirin therapy in Japanese patients than other single nucleotide polymorphisms associated with interleukin-28B. J. Clin. Microbiol. 49, 1853–1860.

Jensen, D.M., Morgan, T.R., Marcellin, P., Pockros, P.J., Reddy, K.R., Hadziyannis, S.J., Ferenci, P., Ackrill, A.M., Willems, B., 2006. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. Hepatology 43, 954–960.

Kamal, S.M., El Kamary, S.S., Shardell, M.D., Hashem, M., Ahmed, I.N., Muhammadi, M., Sayed, K., Moustafa, A., Hakem, S.A., Ibrahiem, A., Moniem, M., Mansour, H., Abdelaziz, M., 2007. Pegylated interferon alpha-2b plus ribavirin in patients with genotype 4 chronic hepatitis C: the role of rapid and early virologic response. Hepatology 46, 1732–1740.

Lin, Z.H., Xin, Y.N., Dong, Q.J., Wang, Q., Jiang, X.J., Zhan, S.H., Sun, Y., Xuan, S.Y., 2011. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology 53, 726–736.

Mangia, A., Santoro, R., Minerva, N., Ricci, G.L., Carretta, V., Persico, M., Vinelli, F., Scotto, G., Bacca, D., Annese, M., Romano, M., Zechini, F., Sogari, F., Spirito, F., Andriulli, A., 2005. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. N. Engl. J. Med. 352, 2609–2617.

Mangia, A., Thompson, A.J., Santoro, R., Piazzolla, V., Tillmann, H.L., Patel, K., Shianna, K.V., Mottola, L., Petruzzellis, D., Bacca, D., Carretta, V., Minerva, N., Goldstein, D.B., McHutchison, J.G., 2010. An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. Gastroenterology 139, 821–827.

Mangia, A., Thompson, A.J., Santoro, R., Piazzolla, V., Copetti, M., Minerva, N., Petruzzellis, D., Mottola, L., Bacca, D., McHutchison, J.G., 2011. Limited use of interleukin 28B in the setting of response-guided treatment with detailed on-treatment virological monitoring. Hepatology 54, 772–780.

Martinez, S.M., Fernández-Varo, G., González, P., Sampson, E., Bruguera, M., Navasa, M., Jiménez, W., Sánchez-Tapias, J.M., Forns, X., 2011. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. Aliment. Pharmacol. Ther. 33, 138–148.

McCarthy, J.J., Li, J.H., Thompson, A., Suchindran, S., Lao, X.Q., Patel, K., Tillmann, H.L., Muir, A.J., McHutchison, J.G., 2010. Replicated association between an interleukin-28B gene variant and a sustained response to pegylated interferon and ribavirin. Gastroenterology 138, 2307–2314.

Ochi, H., Maekawa, T., Abe, H., Hayashida, Y., Nakano, R., Imamura, M., Hiraga, N., Kawakami, Y., Aimitsu, S., Kao, J.H., Kubo, M., Tsunoda, T., Kumada, H., Nakamura, Y., Hayes, C.N., Chayama, K., 2011. IL-28B predicts response to chronic hepatitis C therapy – fine-mapping and replication study in Asian populations. J. Gen. Virol. 92, 1071–1081.

Okamoto, H., Tokita, H., Sakamoto, M., Horikita, M., Kojima, M., Iizuka, H., Mishiro, S., 1993. Characterization of the genomic sequence of type V (or 3a) hepatitis C virus isolates and PCR primers for specific detection. J. Gen. Virol. 74, 2385–2390.

Oze, T., Hiramatsu, N., Yakushijin, T., Mochizuki, K., Oshita, M., Hagiwara, H., Mita, E., Ito, T., Fukui, H., Inui, Y., Hijioka, T., Inada, M., Kaytayama, K., Tamura, S., Yoshihara, H., Inoue, A., Imai, Y., Kato, M., Miyagi, T., Yoshida, Y., Tatsumi, T., Kiso, S., Kanto, T., Kasahara, A., Takehara, T., Hayashi, N., 2011. Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alfa-2b plus ribavirin combination therapy. J. Hepatol. 54, 604–611.

Poynard, T., Bedossa, P., Opolon, P., 1997. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 349, 825–832.

Poynard, T., Marcellin, P., Lee, S.S., Niederau, C., Minuk, G.S., Ideo, G., Bain, V., Heathcote, J., Zeuzem, S., Trépo, C., Albrecht, J., 1998. Randomised trial of interferon alpha2b plus ribavirin for 48 weeks or for 24 weeks versus interferon alpha2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). Lancet 352, 1426–1432.

Poynard, T., McHutchison, J., Goodman, Z., Ling, M.H., Albrecht, J., 2000. Is an "a la carte" combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? The ALGOVIRC Project Group. Hepatology 31, 211–218.

Rauch, A., Kutalik, Z., Descombes, P., Cai, T., Di Iulio, J., Mueller, T., Bochud, M., Battegay, M., Bernasconi, E., Borovicka, J., Colombo, S., Cerny, A., Dufour, J.F., Furrer, H., Gunthard, H.F., Heim, M., Hirschel, B., Malinverni, R., Moradpour, D., Mullhaupt, B., Witteck, A., Beckmann, J.S., Berg, T., Bergmann, S., Negro, F., Telenti, A., Bochud, P.Y., 2010. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. Gastroenterology 138, 1338–1345.

Rodriguez-Torres, M., Sulkowski, M.S., Chung, R.T., Hamzeh, F.M., Jensen, D.M., 2010. Factors associated with rapid and early virologic response to peginterferon alfa-2a/ribavirin treatment in HCV genotype 1 patients representative of the general chronic hepatitis C population. J. Viral Hepat. 17, 139–147.

Sarrazin, C., Susser, S., Doehring, A., Lange, C.M., Müller, T., Schlecker, C., Herrmann, E., Lötsch, J., Berg, T., 2011. Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. J. Hepatol. 54, 415–421.

Sezaki, H., Suzuki, F., Kawamura, Y., Yatsuji, H., Hosaka, T., Akuta, N., Kobayashi, M., Suzuki, Y., Saitoh, S., Arase, Y., Ikeda, K., Miyakawa, Y., Kumada, H., 2009. Poor response to pegylated interferon and ribavirin in older women infected with hepatitis C virus of genotype 1b in high viral loads. Dig. Dis. Sci. 54, 1317–1324.

Stättermayer, A.F., Stauber, R., Hofer, H., Rutter, K., Beinhardt, S., Scherzer, T.M., Zinober, K., Datz, C., Maieron, A., Dulic-Lakovic, E., Kessler, H.H., Steindl-Munda, P., Strasser, M., Krall, C., Ferenci, P., 2011. Impact of IL28B genotype on the early and sustained virologic response in treatment-naive patients with chronic hepatitis C. Clin. Gastroenterol. Hepatol. 9, 344–350.

Suppiah, V., Moldovan, M., Ahlenstiel, G., Berg, T., Weltman, M., Abate, M.L., Bassendine, M., Spengler, U., Dore, G.J., Powell, E., Riordan, S., Sheridan, D., Smedile, A., Fragomeli, V., Müller, T., Bahlo, M., Stewart, G.J., Booth, D.R., George, J., 2009. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. Nat. Genet. 41, 1100–1104.

Tanaka, Y., Nishida, N., Sugiyama, M., Kurosaki, M., Matsuura, K., Sakamoto, N., Nakagawa, M., Korenaga, M., Hino, K., Hige, S., Ito, Y., Mita, E., Tanaka, E., Mochida, S., Murawaki, Y., Honda, M., Sakai, A., Hiasa, Y., Nishiguchi, S., Koike, A., Sakaida, I., Imamura, M., Ito, K., Yano, K., Masaki, N., Sugauchi, F., Izumi, N., Tokunaga, K., Mizokami, M., 2009. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat. Genet. 41, 1105–1109.

Thompson, A.J., Muir, A.J., Sulkowski, M.S., Ge, D., Fellay, J., Shianna, K.V., Urban, T., Afdhal, N.H., Jacobson, I.M., Esteban, R., Poordad, F., Lawitz, E.J., McCone, J., Shiffman, M.L., Galler, G.W., Lee, W.M., Reindollar, R., King, J.W., Kwo, P.Y., Ghalib, R.H., Freilich, B., Nyberg, L.M., Zeuzem, S., Poynard, T., Vock, D.M., Pieper, K.S., Patel, K., Tillmann, H.L., Noviello, S., Koury, K., Pedicone, L.D., Brass, C.A., Albrecht, J.K., Goldstein, D.B., McHutchison, J.G., 2010. IL28B polymorphism improves viral kinetics and is the strongest pre-treatment predictor of SVR in HCV-1 patients. Gastroenterology 139, 120–129.

Wai, C.T., Greenson, J.K., Fontana, R.J., Kalbfleisch, J.D., Marrero, J.A., Conjeevaram, H.S., Lok, A.S., 2003. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 38, 518–526.

Yang, J.F., Lin, C.I., Huang, J.F., Dai, C.Y., Lin, W.Y., Ho, C.K., Hsieh, M.Y., Lee, L.P., Ho, N.J., Lin, Z.Y., Chen, S.C., Hsieh, M.Y., Wang, L.Y., Yu, M.L., Chuang, W.L., Chang, W.Y., 2010. Viral hepatitis infections in southern Taiwan: a multicenter community-based study. Kaohsiung J. Med. Sci. 26, 461–469.

Yu, M.L., Chuang, W.L., 2009. Treatment of chronic hepatitis C in Asia: when East meets West. J. Gastroenterol. Hepatol. 24, 336–345.

Yu, M.L., Lin, S.M., Lee, C.M., Dai, C.Y., Chang, W.Y., Chen, S.C., Lee, L.P., Lin, Z.Y., Hsieh, M.Y., Wang, L.Y., Chuang, W.L., Liaw, Y.F., 2006a. A simple noninvasive index for predicting long-term outcome of chronic hepatitis C after interferon-based therapy. Hepatology 44, 1086–1097.

Yu, M.L., Chuang, W.L., Dai, C.Y., Lee, L.P., Hsieh, M.Y., Lin, Z.Y., Chen, S.C., Hsieh, M.Y., Wang, L.Y., Chang, W.Y., Tsai, S.L., Kuo, H.T., 2006b. Different viral kinetics between hepatitis C virus genotype 1 and 2 as on-treatment predictors of response to a 24-week course of high-dose interferon-alpha plus ribavirin combination therapy. Transl. Res. 148, 120–127.

Yu, M.L., Dai, C.Y., Huang, J.F., Hou, N.J., Lee, L.P., Hsieh, M.Y., Chiu, C.F., Lin, Z.Y., Chen, S.C., Hsieh, M.Y., Wang, L.Y., Chang, W.Y., Chuang, W.L., 2007. A randomised study of peginterferon and ribavirin for 16 versus 24 weeks in patients with genotype 2 chronic hepatitis C. Gut 56, 553–559.

Yu, M.L., Dai, C.Y., Huang, J.F., Chiu, C.F., Yang, Y.H., Hou, N.J., Lee, L.P., Hsieh, M.Y., Lin, Z.Y., Chen, S.C., Hsieh, M.Y., Wang, L.Y., Chang, W.Y., Chuang, W.L., 2008. Rapid virological response and treatment duration for chronic hepatitis C genotype 1 patients: a randomized trial. Hepatology 47, 1884–1893.

Yu, M.L., Huang, C.F., Huang, J.F., Chang, N.C., Yang, J.F., Lin, Z.Y., Chen, S.C., Hsieh, M.Y., Wang, L.Y., Chang, W.Y., Li, Y.N., Wu, M.S., Dai, C.Y., Hank Juo, S.H., Chuang, W.L., 2011. Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. Hepatology 53, 7–13.