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ORIGINAL ARTICLE

Observational Study

Interferon-λ-related genes and therapeutic response in Chinese hepatitis C patients

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Abstract

AIM: To determine the association between rapid viral response and *IL28B*, *IL28RA*, *IL10RB* and *MxA* polymorphisms in the Chinese Han population.

METHODS: The study cohort consisted of 238 chronic hepatitis C patients treated with interferon (IFN)-α-2b and ribavirin. Six single nucleotide polymorphisms were genotyped using the ABI TaqMan allelic discrimination assay. Biochemical indices were measured at baseline. Serum hepatitis C virus (HCV) RNA was detected at weeks 0, 4, 12 and 24 of therapy.

RESULTS: Only *IL28B* rs12980275 was associated with treatment response in the Chinese Han population. Patients carrying AG/GG genotypes had a reduced rapid viral response compared with patients carrying the AA genotype (additive model: adjusted OR = 0.43, 95%CI: 0.24-0.75). It took less time for patients with the AA genotype to achieve a viral load < 500 copies/mL (log-rank test, P = 0.004). In addition, the protective effect of genotype AA was independent of baseline viral load. HCV genotype, and baseline white blood cell count, α-fetoprotein and viral load might also help predict treatment response. The area under the receiver-operating characteristic curve was 0.726.

CONCLUSION: *IL28B* rs12980275 AA genotype is a strong predictor of positive response to IFN therapy in Chinese Han patients with hepatitis C.

Key words: Hepatitis C virus; Interferon; Rapid viral response; *IL28B*; Chinese population

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Core tip: The association between *IL28B* rs12980275 and viral response to pegylated-interferon (IFN) plus ribavirin treatment has been observed in Japanese patients, but rarely in Chinese patients. Because pegylated-IFN is more expensive, non-pegylated instead of pegylated IFN-α is more commonly used for chronic hepatitis C treatment in Chinese primary hospitals. Therefore, the role of IFN-λ-related genes in the response to non-pegylated IFN-α treatment should be established to help guide clinical decisions and improve cost-effectiveness.

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INTRODUCTION

Hepatitis C virus (HCV) poses a serious global health problem due to its adverse clinical outcomes, such as cirrhosis and hepatocellular carcinoma. The estimated prevalence of HCV is 1%-1.9% in the general population of Mainland China, with 75%-80% of those chronically infected[1,2]. The treatment for chronic hepatitis C (CHC) consists of interferon (IFN) plus ribavirin (RBV) and protease inhibitors such as telaprevir and boceprevir. Sustained virological response (SVR), which refers to a negative HCV-RNA test 6 mo after cessation of therapy, is defined as a positive treatment response. Rapid viral response (RVR; negative HCV-RNA test 4 wk after treatment) is thought to be a powerful on-treatment predictor of SVR[3,4]. Patients who achieve RVR are more likely to achieve SVR. The treatment response likely depends on a complex host-virus interaction. Many studies have suggested a range of factors that are associated with RVR and SVR, including HCV genotype, viral load, liver function, and host immune status.

The influence of host gene polymorphisms has drawn attention in recent years. Genome-wide association studies (GWASs) have demonstrated that polymorphisms near the *IL28B* gene, which codes for IFN-λ3, affect the response of CHC to pegylated (PEG)-IFN-α/RBV therapy[5-7]. IFN-λ acts through binding to *IL28RA* and *IL10RB* genes, which subsequently activates the Janus kinase-signal transducer and activator of transcription pathway to up- or down-regulate hundreds of genes, such as *MxA*, *OAS1* and *PKR*, and it is then involved in the immune response pathways[8]. *IL10RB* and *IL28RA* gene polymorphisms can predict the natural outcomes of HCV infection in the Chinese population[9]. According to our previous meta-analysis, *MxA* gene polymorphisms may also be associated with virological response to IFN in the Chinese population[10].

Given that the cost of PEG-IFN treatment is higher than non-PEG-IFN treatment, many patients in Chinese primary hospitals cannot afford PEG-IFN treatment. As a result, non-PEG IFN-α is more commonly used in the treatment of chronic hepatitis C. The previous GWASs were based on observations in Australian, European, African-American and Japanese, but not Chinese populations. Therefore, we aimed to establish pre-treatment predictors for response to non-PEG IFN-α/RBV in Chinese patients to help guide clinical decisions and improve cost-effectiveness. We investigated HCV kinetics during non-PEG IFN-α/RBV therapy, clarified the association of *IL28B*, *IL10RB*, *IL28RA* and *MxA* gene polymorphisms with RVR to non-PEG IFN-α-2b/RBV therapy, and determined the predictors of RVR in CHC.

MATERIALS AND METHODS

Patient cohort

Two hundred and fifty-six patients with CHC from Jurong Peoples' Hospital, China were enrolled in this study, fulfilling the following criteria: (1) treatment naïve; (2) positive for HCV antibody (anti-HCV) and HCV RNA for > 6 mo; and (3) without hepatitis B virus (HBV) or HIV co-infection, or other liver diseases.

All patients were treated for 48 wk with non-PEG IFN-α-2b/RBV and treatment was discontinued according to standard guidelines[11]. Blood samples for biochemical analysis, SNP determination, and HCV genotyping were collected prior to antiviral therapy. HCV-RNA viral load was determined at weeks 0, 4, 12 and 24 of therapy.

Ethical approval was obtained from the participating hospital and the study was carried out in accordance with the guidelines of the International Conference on Harmonization for Good Clinical Practice[12]. All patients gave signed informed consent for DNA genotyping before enrollment.

Viral testing

Serum hepatitis B surface antigen and anti-HCV were measured using an ELISA (Beijing Wantai Biological Pharmacy Engineering Co. Ltd., Beijing, China). Serum HCV RNA and HCV genotype were determined by reverse-transcriptase polymerase chain reaction (TaKaRa Biotechnology, Dalian, China)[13,14].

SNP genotyping

IL28B rs12980275, *IL28RA* rs10903035 and rs11249006, *MxA* rs2071430 and rs17000900, and *IL10RB* rs2834167

Table 1 Primer and probe of SNPs

SNPs		Primer and probe (5'-3')
rs10903035	Forward primer	TTGCCACCCTTGACCTCAG
	Reverse primer	GAGGTTTTGTTTAGAGGGATCCAC
	Probe-FAM	TAGCAAACCACTCCTT
	Probe-HEX	TTAGCAAATCACTCCTT
rs11249006	Forward primer	AACTGGAAGGGAGAATGGGACT
	Reverse primer	GTAACATGGCAGGAATCGGACT
	Probe-FAM	CCACAACAGTCAACCA
	Probe-HEX	CACAACGGTCAACCA
rs2834167	Forward primer	TACCACCTCCCGAAAATGTCA
	Reverse primer	GGTGCGTTCCTGCCAATAGT
	Probe-FAM	TTCCCTTTGGCAAAAG
	Probe-HEX	TTCCCTTCGGCAAAA
rs2071430	Forward primer	CCGAGAACCTGCGTCTCC
	Reverse primer	CGCGAAGAAATGAAACTCACAGAC
	Probe-FAM	CGTTTCTGCGCCCG
	Probe-HEX	CGTTTCTGCTCCCG
rs17000900	Forward primer	CCGAGAACCTGCGTCTCC
	Reverse primer	CGCGAAGAAATGAAACTCACAGAC
	Probe-FAM	CAAGTGCTGCAGGTG
	Probe-HEX	CAAGTGCTGAAGGTG
rs12980275	Forward primer	TGAGGTGCTGAGAGAAGTCAAATT
	Reverse primer	CGCTACCCCGGCAAATATT
	Probe-FAM	CTAGAAACGGACGTGTC
	Probe-HEX	CTAGAAACAGACGTGTCT

were chosen for genotyping. These SNPs are possibly associated with treatment or natural clearance of HCV[5-7,9,10]. Genomic DNA was isolated from peripheral blood mononuclear cells using protease K digestion and phenol-chloroform purification according to a standard protocol[15]. Genotyping was performed using the ABI TaqMan allelic discrimination assay on the ABI 7900HT sequence Detection System (Applied Biosystems, San Diego, CA, United States)[16]. The primers used for genotyping are listed in Table 1.

Statistical analysis

The statistical methods were reviewed by Zhao Yang, Department of Epidemiology and Biostatistics, School of Public Health, Nanjing Medical University. The distribution of patient characteristics and clinical features at baseline between the RVR and non-RVR groups were analyzed by χ^2 test. The association of genotypes with RVR were estimated by odds ratio (OR) and 95%CI using univariate and multivariate logistic regression analysis, with adjustment for sex, HCV genotype, HCV-RNA viral load at baseline, alanine aminotransferase (ALT), white blood cell (WBC) count, and α-fetoprotein (AFP). Receiver-operating characteristic (ROC) curves and areas under the curve (AUC) were calculated for the predictive model. Statistical significance between the genotypes and the time of first virus inhibition rates were analyzed using Kaplan-Meier curves and the log-rank test[17]. All statistical analyses were carried out using Stata version 10.0, and $P < 0.05$ in a two-sided test was considered statistically significant.

Table 2 Baseline characteristics of participants *n* (%)

Variables	RVR (*n* = 133)	NRVR (*n* = 105)	*P* value
Age (yr)			
≤ 50	51 (38.35)	40 (38.10)	
> 50	82 (61.65)	65 (61.90)	0.968
Sex			
Male	41 (30.83)	21 (20.00)	
Female	92 (69.17)	84 (80.00)	0.059
HCV genotype			
1a/1b	93 (69.92)	70 (66.67)	
3	14 (10.53)	5 (4.76)	
Mixed	26 (19.55)	30 (28.57)	0.102
ALT (U/L)			
≤ 40	64 (48.12)	28 (26.67)	
(40-80]	38 (28.57)	42 (40.00)	
> 80	30 (22.56)	35 (33.33)	0.003
ALB (g/L)			
[40-55]	99 (74.44)	82 (78.10)	
< 40	33 (24.81)	23 (21.90)	0.577
WBC ($\times 10^9$/L)			
[4-10]	75 (56.39)	73 (69.52)	
< 4	57 (42.86)	31 (29.52)	0.035
> 10	1 (0.75)	1 (0.95)	0.985
PLT ($\times 10^9$/L)			
[100-300]	90 (67.67)	68 (64.76)	
< 100	41 (30.83)	37 (35.24)	0.522
AFP (ng/mL)			
≤ 7	95 (71.43)	68 (64.76)	
> 7	19 (14.29)	30 (28.57)	0.016
HGB (g/L)			
[110-150]	99 (74.44)	89 (84.76)	
< 110	13 (9.77)	8 (7.62)	
> 150	21 (15.79)	8 (7.62)	0.116
Baseline RNA (lg, IU/mL)	6.02 ± 0.97	6.19 ± 0.74	0.138

ALB: Albumin; HGB: Hemoglobin; PLT: Platelet; RVR: Rapid viral response; HCV: Hepatitis C virus; ALT: Alanine aminotransferase; WBC: White blood cell; AFP: α-fetoprotein.

RESULTS

The baseline characteristics of the 256 enrolled patients are described in Table 2. Four patients withdrew because of intolerable side effects and 14 were lost to follow-up. A total of 238 patients were screened for analysis. After 4 wk of treatment, 133 patients achieved RVR (55.88%). Treatment response was not related to patient age, sex, or HCV genotype ($P > 0.05$). Among the tested biochemical indices, levels of ALT, WBCs and AFP differed between the RVR and non-RVR groups. Patients with high ALT/AFP and low WBC levels at baseline were more likely to achieve a worse treatment response.

Association of polymorphisms of IFN-λ-related genes with RVR

To examine the effects of *IL28B* rs12980275, *IL28RA* rs10903035 and rs11249006, *MxA* rs2071430 and rs17000900, and *IL10RB* rs2834167 on RVR, each SNP was analyzed in four genetic models (co-dominant, dominant, recessive, and additive). The results for

Table 3 Interferon-λ-related genes polymorphisms and rapid viral response *n* (%)

Genotype	RVR	NRVR	Crude OR (95%CI)	Adjusted OR (95%CI)
rs11249006	*n* = 133	*n* = 105		
AA	51 (38.35)	49 (46.67)	1	1
AG	62 (46.62)	49 (46.67)	1.22 (0.71-2.09)	0.86 (0.45-1.63)
GG	20 (15.04)	7 (6.67)	2.75 (1.07-7.07)	2.33 (0.84-6.48)
Dominant			1.41 (0.84-2.36)	1.06 (0.58-1.94)
Recessive			2.48 (1.01-6.11)	2.52 (0.96-6.64)
Additive			1.47 (0.99-2.19)	1.27 (0.82-1.98)
rs12980275	*n* = 133	*n* = 105		
AA	118 (88.72)	70 (66.67)	1	1
AG	8 (6.02)	28 (26.67)	0.17 (0.07-0.39)	0.11 (0.04-0.30)
GG	7 (5.26)	7 (6.67)	0.59 (0.20-1.76)	0.54 (0.17-1.74)
Dominant			0.25 (0.13-0.50)	0.19 (0.09-0.43)
Recessive			0.78 (0.26-2.29)	0.82 (0.26-2.56)
Additive			0.46 (0.28-0.76)	0.43 (0.24-0.75)
rs2834167	*n* = 133	*n* = 105		
AA	37 (27.82)	28 (26.67)	1	1
AG	79 (59.40)	62 (59.05)	0.96 (0.53-1.74)	0.90 (0.45-1.78)
GG	17 (12.78)	15 (14.29)	0.86 (0.37-2.01)	0.66 (0.23-1.88)
Dominant			0.94 (0.53-1.68)	0.85 (0.44-1.66)
Recessive			0.88 (0.42-1.86)	0.71 (0.28-1.83)
Additive			0.93 (0.62-1.41)	0.83 (0.51-1.36)
rs10903035	*n* = 133	*n* = 105		
AA	43 (32.33)	27 (25.71)	1	1
AG	56 (42.11)	48 (45.71)	0.73 (0.40-1.36)	0.68 (0.34-1.37)
GG	34 (32.28)	30 (28.57)	0.71 (0.36-1.42)	0.91 (0.41-2.02)
Dominant			0.72 (0.41-1.28)	0.76 (0.40-1.44)
Recessive			0.86 (0.48-1.53)	1.14 (0.58-2.25)
Additive			0.84 (0.60-1.19)	0.94 (0.63-1.40)
rs2071430	*n* = 127	*n* = 96		
GG	63 (49.61)	49 (51.04)	1	1
GT	49 (38.58)	40 (41.67)	0.95 (0.54-1.67)	0.94 (0.50-1.80)
TT	15 (11.81)	7 (7.29)	1.67 (0.63-4.40)	2.13 (0.66-6.85)
Dominant			1.14 (0.68-1.91)	1.26 (0.70-2.28)
Recessive			1.78 (0.70-4.54)	2.28 (0.73-7.08)
Additive			1.15 (0.77-1.72)	1.21 (0.76-1.94)
rs17000900	*n* = 130	*n* = 99		
AA	97 (74.62)	69 (69.70)	1	1
AG	29 (22.31)	27 (27.27)	0.76 (0.42-1.40)	0.79 (0.39-1.61)
GG	4 (3.08)	3 (3.03)	0.95 (0.21-4.38)	0.68 (0.13-3.70)
Dominant			0.83 (0.46-1.47)	0.83 (0.43-1.62)
Recessive			1.05 (0.23-4.82)	0.77 (0.14-4.16)
Additive			0.84 (0.51-1.38)	0.80 (0.45-1.42)

Logistic regression analyses adjusted for sex, ALT, WBC, AFP, HCV genotype and baseline viral load. RVR: Rapid viral response.

all six SNPs are shown in Table 3. *P* values of all the adjusted factors were < 0.2 in the univariate analysis. Statistical significance in any model was considered to show a potential relationship with treatment response. As shown in Table 4, the distribution of two SNPs appeared to be associated with different treatment responses. In the co-dominant genetic model, mutant G allele of *IL-28RA* rs11249006 increased RVR (crude OR = 2.75, 95% CI: 1.07-7.07). However, there was no significant difference after adjusting for multiple variables (adjusted OR = 2.33, 95%CI: 0.84-6.48). Mutant G allele of *IL28B* rs12980275 was associated with decreased RVR in the co-dominant, dominant, and additive models. The adjusted OR was 0.11 (95%CI: 0.04-0.30), 0.19 (95%CI: 0.09-0.43), and 0.43 (95%CI: 0.24-0.75), respectively. The association of *IL28B* rs12980275 with RVR to IFN-α-2b/RBV therapy was still significant after Bonferroni correction. The results of genetic analyses suggested that *IL28B* rs12980275 is an indicator of response to IFN therapy.

Predictive factors for RVR

Stepwise regression analysis showed that *IL28B* rs12980275, WBC count, AFP level, HCV genotype, and HCV-RNA viral load at baseline were independent predictors of RVR (Table 5). In addition, the ROC of these variables covered an AUC of 0.726 (Figure 1). The probability of RVR can be predicted using the following formula: log odds (RVR) = 4.13 + 0.67 × WBC (abnormal *vs* normal) - 0.98 × AFP (abnormal *vs* normal) -0.39 × HCV-genotype1-0.46 × log (base viral load) - 1.05 × rs12980275AG/GG.

The predictive value of *IL28B* rs12980275 was further analyzed in stratified analyses. The treatment response in patients with HCV genotype AA was not

Table 4 Polymorphisms of *IL28RA/IL28B* and rapid viral response *n* (%)

Genotype	RVR (*n* = 133)	NRVR (*n* = 105)	Crude OR (95%CI)	*P* value	Adjusted OR (95%CI)	*P* value
rs11249006						
AA	51 (38.35)	49 (46.67)	1		1	
AG	62 (46.62)	49 (46.67)	1.22 (0.71-2.09)	0.048	0.86 (0.45-1.63)	0.637
GG	20 (15.04)	7 (6.67)	2.75 (1.07-7.07)	0.036	2.33 (0.84-6.48)	0.104
Dominant			1.41 (0.84-2.36)	0.197	1.06 (0.58-1.94)	0.852
Recessive			2.48 (1.01-6.11)	0.049	2.52 (0.96-6.64)	0.061
Additive			1.47 (0.99-2.19)	0.055	1.27 (0.82-1.98)	0.282
rs12980275						
AA	118 (88.72)	70 (66.67)	1		1	
AG	8 (6.02)	28 (26.67)	0.17 (0.07-0.39)	< 0.001	0.11 (0.04-0.30)	< 0.001
GG	7 (5.26)	7 (6.67)	0.59 (0.20-1.76)	0.347	0.54 (0.17-1.74)	0.301
Dominant			0.25 (0.13-0.50)	< 0.001	0.19 (0.09-0.43)	< 0.001
Recessive			0.78 (0.26-2.29)	0.648	0.82 (0.26-2.56)	0.736
Additive			0.46 (0.28-0.76)	0.002	0.43 (0.24-0.75)	0.003

Logistic regression analyses adjusted for sex, HCV genotype, baseline levels of ALT, WBC, AFP, and viral loads. RVR: Rapid viral response.

Table 5 Results of multivariate stepwise regression analysis on rapid viral response

Variable	Coef	OR (95%CI)	*P* value
rs12980275	-1.05	0.35 (0.20-0.62)	< 0.001
WBC-group	0.67	1.94 (1.08-3.50)	0.027
AFP-group	-0.98	0.38 (0.19-0.76)	0.006
HCV genotype	-0.39	0.67 (0.48-0.96)	0.014
Baseline RNA(lg)	-0.46	0.63 (0.44-0.91)	0.027

Coef: Coefficient of variation. WBC-group: WBC was divided into three groups. 1: 4 × 10^9-10^{10}/L; 2: < 4 × 109/L; 3: > 10^{10}/L. AFP-group: AFP was divided into two groups. 1: ⩽ 7 ng/mL; 2: > 7 ng/mL. RVR: Rapid viral response; HCV: Hepatitis C virus.

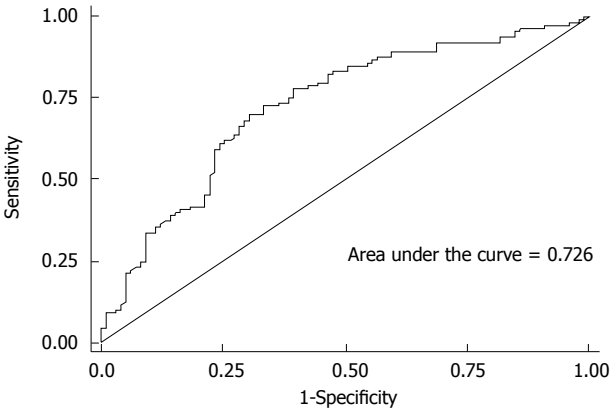

Figure 1 Prediction of rapid viral response. Receiver-operating characteristic (ROC) curve for prediction of RVR using all significant variables. areas under the curve (AUC) was 0.726. RVR: Rapid viral response.

affected by baseline HCV-RNA viral load. The mean HCV-RNA viral load (log value ± SD) in the non-RVR and RVR groups was 6.28 ± 0.75 lg(copies/mL) and 6.10 ± 0.95 lg(copies/mL), respectively (Figure 2A; *P* = 0.143). For patients carrying mutant G allele, lower baseline viral load was favored for RVR. The mean viral load in the non-RVR and RVR groups was 5.97 ± 0.67 lg(copies/mL) and 5.37 ± 1.01 lg(copies/mL), respectively (Figure 2B; *P* = 0.018).

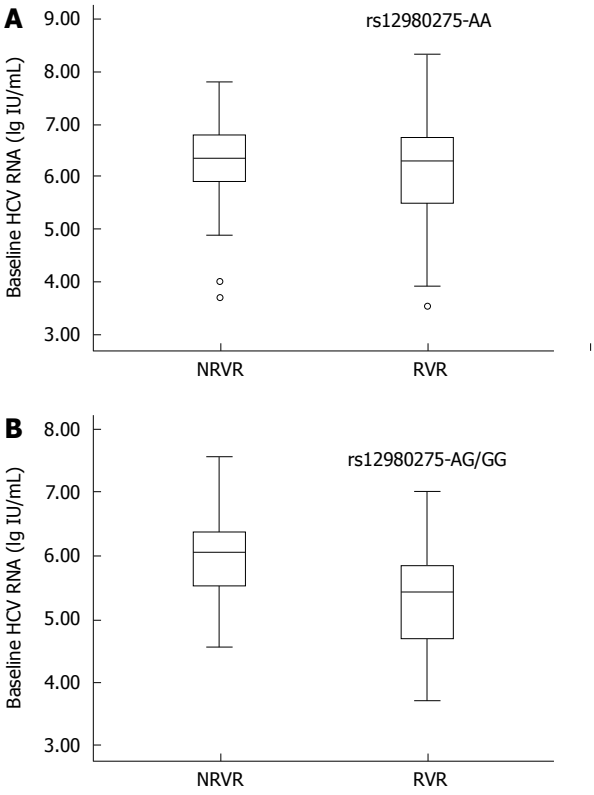

Figure 2 Stratified analysis of baseline hepatitis C virus-RNA viral load and rapid viral response. A: Box plots of baseline hepatitis C virus (HCV)-RNA levels on RVR for rs12980275 AA group. Mean log HCV-RNA viral load was 6.28 ± 0.75 lg(copies/mL) and 6.10 ± 0.95 lg(copies/mL) for the non-RVR and RVR groups, respectively (t = 1.47, P = 0.143); B: Box plots for rs12980275 AG/GG group. Mean log HCV-RNA viral load was 5.97 ± 0.67 lg(copies/mL) and 5.37 ± 1.01 lg(copies/mL), respectively (t = 2.44, P = 0.018). The error bars indicate standard deviations. RVR: Rapid viral response.

Effect of IL28B rs12980275 on time of initial virus inhibition

The Kaplan-Meier method and log-rank test were conducted to examine the association of *IL28B* rs12980275 (dominant model) with the time of initial virus inhibition (time of reaching HCV-RNA viral load < 500 copies/mL after therapy) in CHC patients.

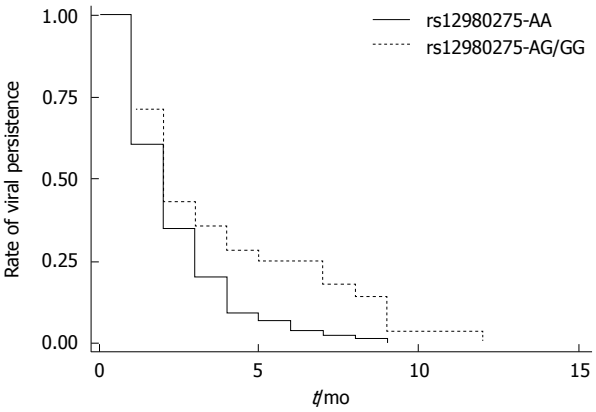

Figure 3 Kaplan-Meier plots of viral persistence rate by *IL28B* rs12980275 (log-rank *P* = 0.0041).

Figure 3 shows that the median time of initial inhibition response was 2 mo (95%CI: 1.72-2.28) for the rs12980275 AA group and 2 mo (95%CI: 1.36-2.64) for the AG/GG group. Although similar, the difference was significant (log-rank test, $P = 0.004$). Also the viral inhibition trends indicated that the inhibition rates were achieved faster in the AA group than in the AG/GG group.

Viral kinetics during therapy

Patients carrying the *IL28B* rs12980275 AA genotype achieved a greater reduction in HCV-RNA viral load at 1 mo (B-1), 3 mo (B-3) and 6 mo (B-6) than those carrying the AG/GG genotype (B-1: 6.18 ± 0.87 *vs* 5.77 ± 0.82 log IU/mL, $P = 0.003$; B-3: 6.18 ± 0.90 *vs* 5.79 ± 0.80 log IU/mL, $P = 0.01$; B-6: 6.27 ± 0.86 *vs* 5.89 ± 0.79 log IU/mL, $P = 0.021$), respectively (Figure 4A). Considering the confounding effect of baseline HCV-RNA levels, patients were further divided into four groups (baseline HCV RNA < 10^5 IU/mL, 10^5-10^6 IU/mL, 10^6-10^7 IU/mL, and ⩾ 10^7 IU/mL). *IL28B* rs12980275 AA carriers dropped to a similar viral load at 1 mo regardless of the baseline HCV-RNA levels ($F = 2.11$, $P = 0.1$) (Figure 4B). Meanwhile, the viral kinetics in the non-AA group were associated with baseline HCV-RNA levels ($F = 17.64$, $P < 0.001$). Viral load declined faster in patients with lower baseline level of virus (Figure 4C). The results of viral kinetics were consistent with the stratified analyses (Figure 2).

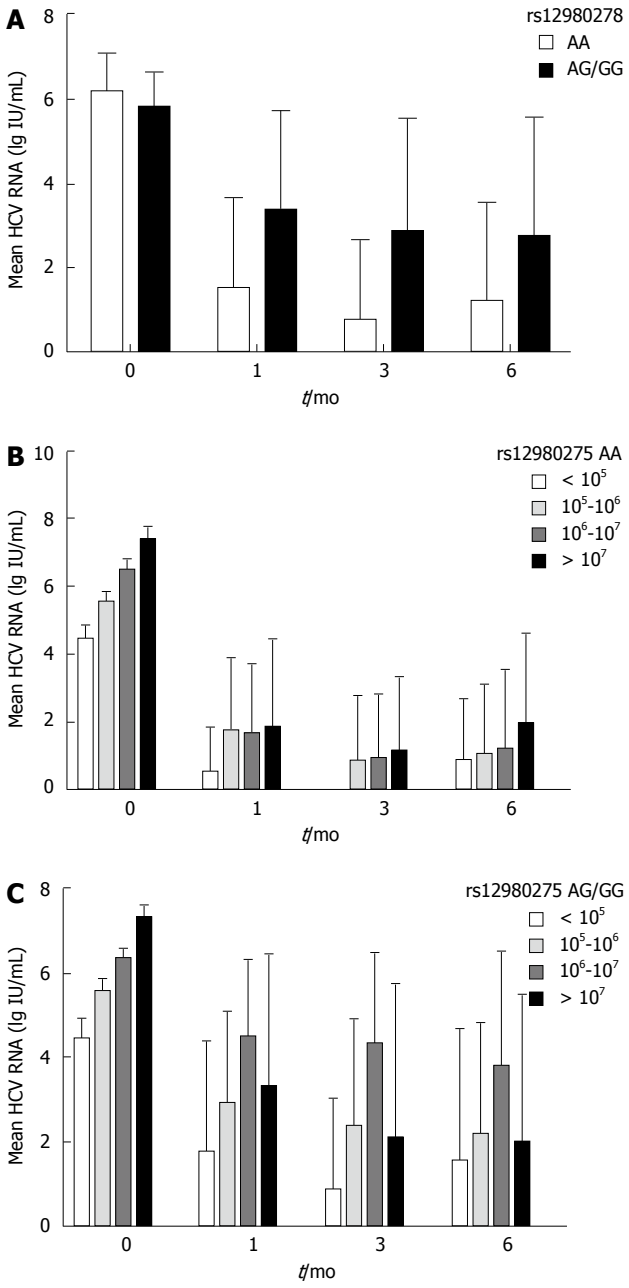

Figure 4 Viral kinetics during therapy. Mean log hepatitis C virus (HCV)-RNA levels at baseline, 1 mo, 3 mo and 6 mo. A: Stratified by *IL28B* rs12980275 (AA *vs* AG/GG); B: Stratified by baseline HCV-RNA levels (< 10^5 IU/mL, 10^5-10^6 IU/mL, 10^6-10^7 IU/mL, ⩾ 10^7 IU/mL) in rs12980275 AA group; C: Stratified by baseline HCV-RNA levels in rs12980275 AG/GG group.

DISCUSSION

GWAS studies have identified *IL28B* rs12980275 as a strong SNP associated with HCV treatment in various populations[5-7,18]. Consistent with those studies, we also found that rs12980275 AA was a strong positive response predictor of non-PEG IFN-α/RBV treatment in the Chinese Han population. In addition, patients carrying the AA genotype were likely to achieve faster virological suppression compared with those carrying non-AA loci. The earliest difference among *IL28B* rs12979860 genotypes can occur at week 2[19]. The change in viral load seemed to vary in different rs12980275 genotypes (Figure 4). Unlike AG/GG genotypes, the protective effect of the AA genotype was not affected by baseline viral load. These results suggest that the AA genotype is a strong predictor of HCV treatment. The biological reason might be interpreted by another study of HBV infection. Serum *IL28B* level is higher in patients with the AA genotype and may reduce HBV viral load and liver inflammation[20]. However, the current study did not reveal a significant association between treatment response and polymorphisms in the selected downstream genes of *IL28B*.

Our results suggest that *IL28B* rs12980275 is the most important single predictor of RVR by the Random Forest Model (data not shown). In addition, including other viral and host factors, such as baseline viral load, HCV genotype, WBC count and AFP level, improved the accuracy of the predictive model (Figure 1). The predictive model in our study was similar to that in another Japanese study[21].

After 1 mo of treatment, 55.88% of the patients achieved RVR. Since 256 patients (92.02%) were infected with HCV genotype 1, this low rate of efficacy was understandable. The response rates to IFN therapy are usually higher among patients with HCV genotype 2/3, ranging from 75% to 94%, while patients with HCV genotype 1/4 have poorer response rates of about 50%[22,23]. The fact that HCV genotype 1 was the major strain in Jurong was consistent with a previous study[24].

In conclusion, our findings imply that the genetic variants of *IL28B* rs12980275 may play an important role in determining the response to non-PEG IFN-α-2b/RBV in the Chinese Han population.

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COMMENTS

Background

Hepatitis C virus (HCV) poses a serious global health problem due to its adverse clinical outcomes, such as cirrhosis and hepatocellular carcinoma. Treatment for chronic hepatitis C consists of interferon (IFN) plus ribavirin (RBV) and protease inhibitors such as telaprevir and boceprevir. The treatment response likely depends on a complex host-virus interaction. The influence of host gene polymorphisms has attracted attention in recent years. Therefore, establishing calculable pre-treatment predictors for response to IFN-α/RBV in the Chinese population should guide clinical decisions and improve cost-effectiveness.

Research frontiers

Many studies have suggested a range of factors associated with treatment response, including HCV genotype, viral load, liver function, and host immune status. Previous genome wide association studies (GWASs) have demonstrated that polymorphisms near the *IL28B* gene, which codes for IFN-λ3, affect the response to pegylated (PEG)-IFN-α/RBV in CHC.

Innovations and breakthroughs

Previous GWASs were based on observations in Australian, European, African-American, and Japanese, but not Chinese populations. In addition, because PEG-IFN is more expensive, non-PEG-IFN-α is more commonly used for chronic hepatitis C (CHC) in Chinese primary hospitals. The authors in their previous studies showed that *IL10RB* and *IL28RA* gene polymorphisms could predict the natural outcomes of HCV infection in the Chinese population. The present study aimed to clarify the association of IFN-λ-related genes with Rapid viral response to non-IFN-α-2b/RBV therapy in the Chinese Han population.

Applications

The results suggest that IL28B rs12980275 AA genotype is a strong predictor of positive response to IFN therapy in the Chinese Han population with CHC, and HCV genotype, baseline levels of white blood cells, α-fetoprotein, and viral load may help predict treatment response.

Peer-review

It is important to know new predictive factors in the treatment of this disease. The study is innovative in nature. The original study conducted on large groups of patients is very valuable.

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