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Original Article

Individualized treatment strategies and predictors of virological response for chronic hepatitis C: a multicenter prospective study from China

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Abstract: Combination therapy comprising pegylated interferon-alpha (PegIFNα) and ribavirin (RBV) has been the standard of care for the chronic hepatitis C patients for more than a decade. Recently, direct antiviral agents show better efficacy, tolerance, and shorter treatment duration. However, the prohibitive costs of the regimens limit their use in developing countries where most of the HCV infection exists. Optimizing the treatment and understanding the host- and virus-factors associated with viral clearance were necessary for individualizing therapy to maximize sustained virologic response. To explore individualized antiviral strategies with PegIFNα-2a/IFNα-2b plus ribavirin for CHC patients, and to clarify predictive factors for virological response. A cohort of 314 patients were included in this open-label, prospective clinical trial, which received individualized doses of PegIFNα-2a or IFNα-2b combined with RBV according to body weight, disease status and complications, with the duration of 44 weeks after HCV RNA undetectable. All the IL-28B (rs8099917), IL-17A (rs8193036), IL-17B (rs2275913) and PD-1.1 SNPs were genotyped using the TaqMan system. The sustained virological response (SVR) in PegIFNα-2a group was significantly higher than that in IFNα-2b (85.8% vs 75.0%, $P = 0.034$), especially in HCV genotype 1 (84.0% vs 64.3%, $P = 0.022$). However, no significant differences were found in rapid virological response (RVR), complete early virological response (cEVR) and SVR between PegIFNα-2a and IFNα-2b according to different doses, respectively. The genotype frequency of IL-28B TT in patients with cEVR, SVR was higher than that in non-responsed patients (93.8% vs 78.1%, $\chi^2 = 7.827$, $P = 0.005$; 95.9% vs 80.4%, $\chi^2 = 9.394$, $P = 0.002$). No significant correlation between the genotype distribution of IL-17A, IL-17B and PD-1.1 with virological response. Individualized regimens of PegIFNα-2a/RBV and IFNα-2b/RBV could achieve satisfied virological response in Chinese HCV patients. The IL-28B (rs8099917) TT genotype is a clinical usefully marker for cEVR and SVR.

Keywords: Chronic hepatitis C, interferon, pegylated interferon, ribavirin, virological response, single nucleotide polymorphisms

Introduction

Chronic Hepatitis C virus (HCV) infection is a global health problem that affects more than 180 million people worldwide [1, 2]. The severity of the disease varies from asymptomatic chronic infection to cirrhosis and hepatocellular carcinoma (HCC). The risk of cirrhosis is 5% to 30% within 20 years of infection and the risk of HCC in patients with cirrhosis is 2% to 4% annually [3, 4]. Effective antiviral treatment can delay or even prevent disease progression and end-stage liver disease, which contributed to the improvement in long-term prognosis [5-7]. In Asia including China, the standard of care (SOC) with combination of pegylated interferon (Peg-IFN) α-2a or α-2b plus ribavirin (RBV) achieved high virological eradication in 41%-

59% in HCV-1 patients and 78%-95% in HCV non-1 patients [8, 9]. However, some patients (e.g. those with compensated cirrhosis, leukocytopenia) showed poor virological response or could not endure the SOC because of adverse events or high costs.

Although various direct-acting antiviral drugs (DAAs) have shown better efficacy, tolerance, and shorter treatment duration for those refractory HCV patients or who cannot endure the SOC [10, 11]. The non-listed drugs, high cost of treatment and uncovered by health insurance or national health policies were the greatest obstacles for widely to be used in China. Therefore, although there are some guidelines, considering the lower body weight of Chinese patients, there continues to be debate regarding personalized optimization of the dose and duration of IFN/Peg-IFN combined RBV in patients with HCV infection.

It is important to predict more accurately the response to treatment. In addition to allowing the customization of therapy, predicting response may help reduce the significant adverse events and high cost associated with this therapy. Different virus- and host-related baseline parameters are known to predict the probability of sustained virological response (SVR) including HCV genotype, HCV viral load, age, sex, presence of rapid virological response (RVR) or complete early virological response (cEVR), and genetic polymorphisms such as interleukin (IL)-28B [12, 13]. To explore the new predictors of virological response is helpful to guide clinical treatment decisions.

PD-1 is a receptor of the CD28 family and is well characterized as a negative regulator of T cells through delivering inhibitory signals. Accumulative evidence suggests that PD-1 is a negative regulator of the immune response during chronic HCV infection [14-16]. The SNP might have a direct or indirect functional impact on PD-1, associated with a variety of diseases, including type 1 diabetes [17], ankylosing spondylitis [18], systemic lupus erythematosus [19], and rheumatoid arthritis [20].

Th17 cells have recently been identified as a third subset of effector T helper cells distinct from Th1 and Th2 cells. IL-17, the founding cytokine secreted by Th17 cells, could amplify Th17 responses [21], The proportion of Th17 cells in the peripheral blood and serum IL-17 levels are increased in HCV-infected patients [22] suggesting that Th17 cells and IL-17 play important roles in the pathogenesis of HCV infection by regulating innate and adaptive immunity [23]. Several SNPs in the IL-17 gene (rs8193036 and rs2275913) are associated with autoimmune and inflammatory diseases, such as asthma, rheumatoid arthritis [24, 25] and intestinal Behcet's disease [26]. Whether the PD-1.1 and IL-17 SNPs influence the outcome of IFNα and RBV treatment is unknown.

The present study aimed to optimize HCV therapy with IFN/RBV with regard to dose and duration, based disease severity, early viral kinetics, genetic and immunological factors, economic conditions, and treatment tolerance, accompanied by proper management of adverse events, to achieve the greatest likelihood of a long-term response. Second, we aimed to investigate the above mentioned factors which predict virological response in patients with chronic HCV infection in China.

Patients and methods

Ethics statement

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1. The study protocol conformed to the guidelines of the 1975 Declaration of Helsinki and was approved on October 13th, 2010 by the ethics committees of Third Hospital of Hebei Medical University, Shijiazhuang, China, and all patients provided written informed consent. We confirm that all ongoing and related trials for this drug/intervention are registered at the Chinese Clinical Trial Registry. The name of the registration is "A study on optimizing Pegasys or recombinant human interferon α-2b plus ribavirin in treatment of naïve patients with chronic hepatitis C". The registration number is ChiCTR-TNRC-10001090. Full details of the trial protocol can be found in the Supplementary Appendix, available with the full text of this article at www.chictr.org/cn/.

Patients and therapy

A cohort of 314 consecutive unrelated Chinese patients diagnosed with CHC or compensated cirrhosis between November 2010 and October

Table 1. The IL-28B, IL-17 and PD-1 sequences of primers and TaqMan probes

TaqMan probes	Sequences of primers
IL-28B rs8099917	VIC-TTTGTTTTCCTTTCTGTGAGCAAT[G]TCACCCAAATTGGAACCATGCTGTA-MGBNFQ
	FAM-TTTTGTTTTCCTTTCTGTGAGCAAT[T]TCACCCAAATTGGAACCATGCTGTA-MGBNFQ
IL-17 rs8193036	VIC-CCCCCTGCCCCCCTTTTCTCCATCT[C]CATCACCTTTGTCCAGTCTCTATCC-MGBNFQ
	FAM-CCCCCTGCCCCCCTTTTCTCCATCT[T]CATCACCTTTGTCCAGTCTCTATCC-MGBNFQ
IL-17 rs2275913	VIC-TGCCCTTCCCATTTTCCTTCAGAAG[A]AGAGATTCTTCTATGACCTCATTGG-MGBNFQ
	FAM-TGCCCTTCCCATTTTCCTTCAGAAG[G]AGAGATTCTTCTATGACCTCATTGG-MGBNFQ
PD-1.1	VIC-GGCAGGTGCCTGGCCTCTGCCTTCC[C]GGCCCATCCCCCTTCGCTGGGGCAC-MGBNFQ
	FAM-GGCAGGTGCCTGGCCTCTGCCTTCC[T]GGCCCATCCCCCTTCGCTGGGGCAC-MGBNFQ

2012 was included. The patients were diagnosed and treated at seven hospitals, including the Third Hospital of Hebei Medical University, the Fifth Hospital of Shijiazhuang City, Bethune International Peace Hospital of the Chinese People's Liberation Army, People's Hospital of Xingtai City, Infectious Diseases Hospital of Handan City, Infectious Diseases Hospital of Cangzhou City, and the First Hospital of Hebei Medical University. Each patient was defined by positive serum anti-HCV antibody, presence of serum HCV RNA, and persistent elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) for at least 6 months, and imaging suggested chronic hepatitis or cirrhosis. Eligible patients were 18-65 years old, with platelet count $\geq 50\times10^9$/L, neutrophil count $\geq 1.0\times10^9$/L, and hemoglobin ≥100 g/L. Exclusion criteria were: presence of decompensated liver cirrhosis; HCC; human immunodeficiency virus (HIV) co-infection; hepatitis A, B or D virus co-infection; autoimmune or genetic liver disease (e.g. Wilson disease or hemochromatosis); serious cardiac, autoimmune or hematological disease; neuropsychiatric disorders; or current pregnancy or lactation. Other issues that investigators consider unsuitable are for this trial.

According to disease status and body weight, all patients were divided into two groups. One was the routine-dose group (body weight ≥60 kg, age >18-60 years), with doses of IFNα-2b (Beijing Kawin Technology Share-holding Co. Ltd. China) of 500 MIU on alternate days and PegIFNα-2a (F. Hoffmann-La Roche Ltd, Basel, Switzerland) at 180 μg/week. The other was the low-dose group (compensated cirrhosis, leukocytopenia, body weight <60 kg, age 60-65 years), with doses of IFNα-2b of 100-300 MIU on alternate days and PegIFNα-2a at 67.5-135 μg/week. The dose of RBV was adjusted according to body weight, because the mean body weight is lower for Chinese than western patients (<65 kg, 900 mg/day; 65-85 kg, 1000 mg/day; >85 kg, 1200 mg/day). The treatment duration was according to the virological response of the patients. Patients with undetectable HCV RNA continued under therapy for an additional 44 weeks. Patients were monitored for at least 24 weeks post-treatment. Treatment response and adverse events were retrospectively compared between the two groups by an independent investigator unaware of the study or treatment details. Standard definitions of responses were used. Rapid virological response (RVR) was defined as an undetectable serum HCV RNA levels at 4 weeks after treatment. Complete early virological response (cEVR) was defined as undetectable serum HCV RNA level 12 weeks after starting therapy. End-of-treatment (EOT) was defined as undetectable serum HCV RNA level at the end of treatment. Sustained virological response (SVR) was defined as undetectable serum HCV RNA level at 24 weeks after stopping therapy. The treatment was halted in patients whose HCV RNA was detectable after 24 weeks of therapy, these patients and those HCV RNA level decreased less than 2 log10 IU/ml from baseline at 12 weeks of therapy were classified as non-responders (NRs). Patients with serum HCV RNA positive during follow-up were defined as relapsers. Treatment was discontinued if adverse events were intolerable or if laboratory findings such as severe neutropenia (<500/mm^3) or anemia (hemoglobin <6 g/dL) were abnormal in two consecutive samples.

Biochemical analyses

Serum ALT and AST levels were measured by the enzymatic method using an automatic biochemical analyzer (Olympus UA5400, Tokyo,

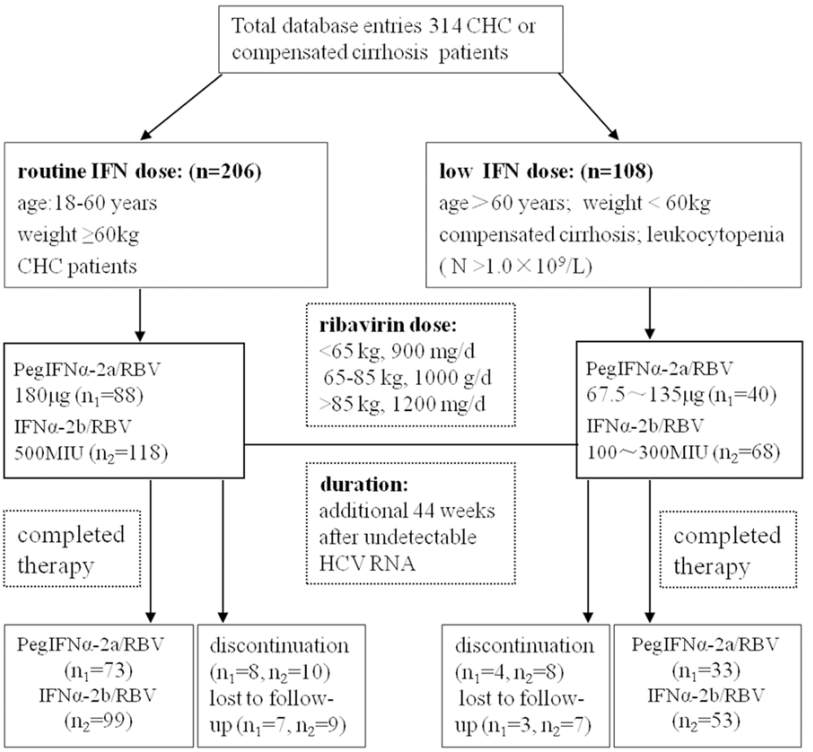

Figure 1. The flow diagram of the progress through the phases of the trial.

Japan) according to the manufacturer's instructions. The plasma level of IL-17 was determined by ELISA (RapidBio Lab, West Hills, CA, USA).

Detection of antibody, viral load and genotypes of HCV

The plasma antibodies of HCV were detected by enzyme linked immunosorbent assay (ELISA) with a commercial detection kit (Livzon diagnostics INC, Zhuhai, China). HCV RNA was determined by RT-PCR using Cobas Taqman HCV Test (Roche Molecular Diagnostics, Branchburg, NJ, USA), and the lower limit of quantitation was 15 IU/mL. Genotyping of HCV was performed by oligochip (Tianjin Third Central Hospital, China) [27].

DNA extraction and SNP

Genomic DNA from peripheral blood mononuclear cells was isolated using the QIAamp DNA mini kit (Qiagen, Sample & Assay Technologies, Germany) and quantitated on the NanoDrop 2000C spectrophotometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). All SNPs were genotyped using the TaqMan system (Applied Biosystems, Foster City, CA, USA). The samples were amplified in a 10-μL reaction mixture (10 ng DNA, 5 μL TaqMan Universal Master Mix (2×) (Applied Biosystems), 0.25 μM 40× working stock of SNP Genotyping Assay (Applied Biosystems). Real-time PCR was performed in an ABI 7500 sequence detection system (Applied Biosystems), as follows: 10 min at 95°C for AmpliTaq Gold preactivation, with amplification for 50 cycles (15 s at 92°C and 1 min at 60°C). The IL-28B, IL-17A, IL-17B and PD-1.1 sequences of primers and TaqMan probes were shown in **Table 1**.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as frequencies (%). The differences in the continuous variables between the groups were determined by *t* test. The associations between categorical variables were evaluated using χ^2 test. $P<0.05$ was considered significant.

Results

Patients' characteristics

A total of 314 consecutive CHC patients were enrolled in this study. The flow diagram of the progress through the phases of the trial is shown in **Figure 1**. The clinical and demographic characteristics of all the patients are shown in **Table 2**. There were no significant differences between the IFNα-2b and PegIFNα-2a groups for age, sex, body mass index (BMI), HCV RNA load, HCV genotype, ALT and AST levels at baseline.

There were 258 patients including 232 CHC patients and 26 cirrhosis patients completed therapy, whose data were analyzed. Overall analysis, 160 (160/258, 62.0%) patients achieved RVR, 219 (219/258, 84.9%) achieved

Table 2. Baseline characteristics of the study population

Characteristics	IFNα-2b group (n = 152)	PegIFNα-2a group (n = 106)	χ^2/t/*P*
Age, years	46.28±11.55	46.32±13.90	T = 0.024 *P* = 0.981
Gender distribution [n (%)]			χ^2 = 0.319 *P* = 0.572
Male	72 (47.4%)	54 (50.9%)	
Female	80 (52.6%)	52 (49.1%)	
BMI, kg/m^2	23.29±2.92	23.05±2.66	T = 1.428 *P* = 0.155
HCV genotype			χ^2 = 0.395 *P* = 0.530
1 (n = 105)	56 (74.7%)	49 (70.0%)	
2 or 3 (n = 40)	19 (25.3%)	21 (30.0%)	
HCV RNA			χ^2 = 0.200 *P* = 0.655
>1×10^6 IU/mL	76 (50.0%)	50 (47.2%)	
≤1×10^6 IU/ml	76 (50.0%)	56 (52.8%)	
Biochemical Analyses			
Abnormal ALT (n%)	111 (73.0%)	75 (70.8%)	χ^2 = 0.160 *P* = 0.689
Abnormal AST (n%)	98 (64.5%)	67 (63.2%)	χ^2 = 0.043 *P* = 0.835

Abbreviations: ALT, Alanine transaminase; AST, Aspartate transaminase.

cEVR, 232 achieved EOT (232/258, 89.9%), and 205 (205/258, 79.5%) achieved SVR. The incidences of RVR and cEVR were significantly higher in the SVR group than that in non-SVR group (62.6% vs 25.8%, χ^2 = 13.741, *P* = 0.000; 96.1% vs 45.2%, χ^2 = 55.082, *P* = 0.000). Twenty-five patients were classified as NRs and 28 patients as relapsers. The most patients (26/28, 92.9%) relapsed during the first 3 months of post-treatment follow-up.

The sex distribution (male) between the SVR and non-SVR groups did not differ significantly (47.3% vs 38.7%, *P* = 0.386). BMI was 23.2±2.7 in the SVR group and 23.9±3.2 in the non-SVR group, and there was no significant difference between the two groups (*t* = 1.638, *P* = 0.103). The SVR rates in <60 years group and ≥60 years group were 79.2% and 75.7%, and there was no significant difference between the two groups (χ^2 = 0.233, *P* = 0.629). For subgroup analysis, no significant correlation between the sex distribution, age with SVR for genotype 1, 2 or 3, respectively (*P*>0.05).

The virological response in patients with different doses of IFNα-2b and PegIFNα-2a

There were 106 in the PegIFNα-2a group and 152 patients in the IFNα-2b group. Overall analysis, the RVR, cEVR and SVR rates for the different types of IFN were 64.2% vs 60.5%, 85.8 vs 84.2%, and 85.8% vs 75.0% respectively. There were no significant differences between the PegIFNα-2a and IFNα-2b groups for RVR and cEVR, whereas the SVR rate in the PegIFNα-2a group was significantly higher than that in the IFNα-2b group (*P* = 0.034) (**Figure 2A**). There were 172 patients in the routine-dose group (99 IFNα-2b and 73 PegIFNα-2a) and 86 in the low-dose group (53 IFNα-2b and 33 PegIFNα-2a). For the routine-dose group, the RVR, cEVR and SVR rates in the IFNα-2b and PegIFNα-2a groups were 64.6% vs 67.1%, 86.9% vs 87.7%, and 78.8% vs 86.3%, respectively, and there were no significant differences between the two groups (**Figure 2B**). The RVR, cEVR and SVR rates in the low-dose group for IFNα-2b and PegIFNα-2a were 52.8% vs 57.6%, 79.2% vs 81.8%, and 67.9% vs 84.8%, respectively, and there were no significant differences between the IFNα-2b and PegIFNα-2a groups (**Figure 2C**).

The SVR rates in PegIFNα-2a/RBV group with HCV genotype 1 was significant higher than that in IFNα-2b/RBV group

Genotype data for HCV were available in 145 patients. The rate of genotypes 1, 2 and 3 were 72.4% (*n* = 105), 24.8% (*n* = 36) and 2.8% (*n* = 4), respectively. The incidence of RVR was significant higher for HCV genotypes 2 and 3 than genotype 1 (80.0% vs 53.8%, *P* = 0.004), whereas there was no significant difference for cEVR and SVR rates (90.0% vs 83.0%, *P* = 0.293; 87.5% vs 73.6%, *P* = 0.073) (**Figure 3A**). For genotype 1, there were no significant differences for RVR and cEVR rates between the IFNα-2b and PegIFNα-2a groups (50.0% vs 57.1%, *P* = 0.410; 82.1% vs 84.0%, *P* = 0.799). The incidence of SVR was significantly higher in PegIFNα-2a group than that in IFNα-2b group (84.0% vs 64.3%, *P* = 0.022) (**Figure 3B**). For genotypes 2 and 3, although the incidence of RVR was higher in the PegIFNα-2a group than that in IFNα-2b group (90.5% vs 68.4%, *P* = 0.082), the difference was not significant. There were no significant differences for cEVR and SVR rates between the IFNα-2b and

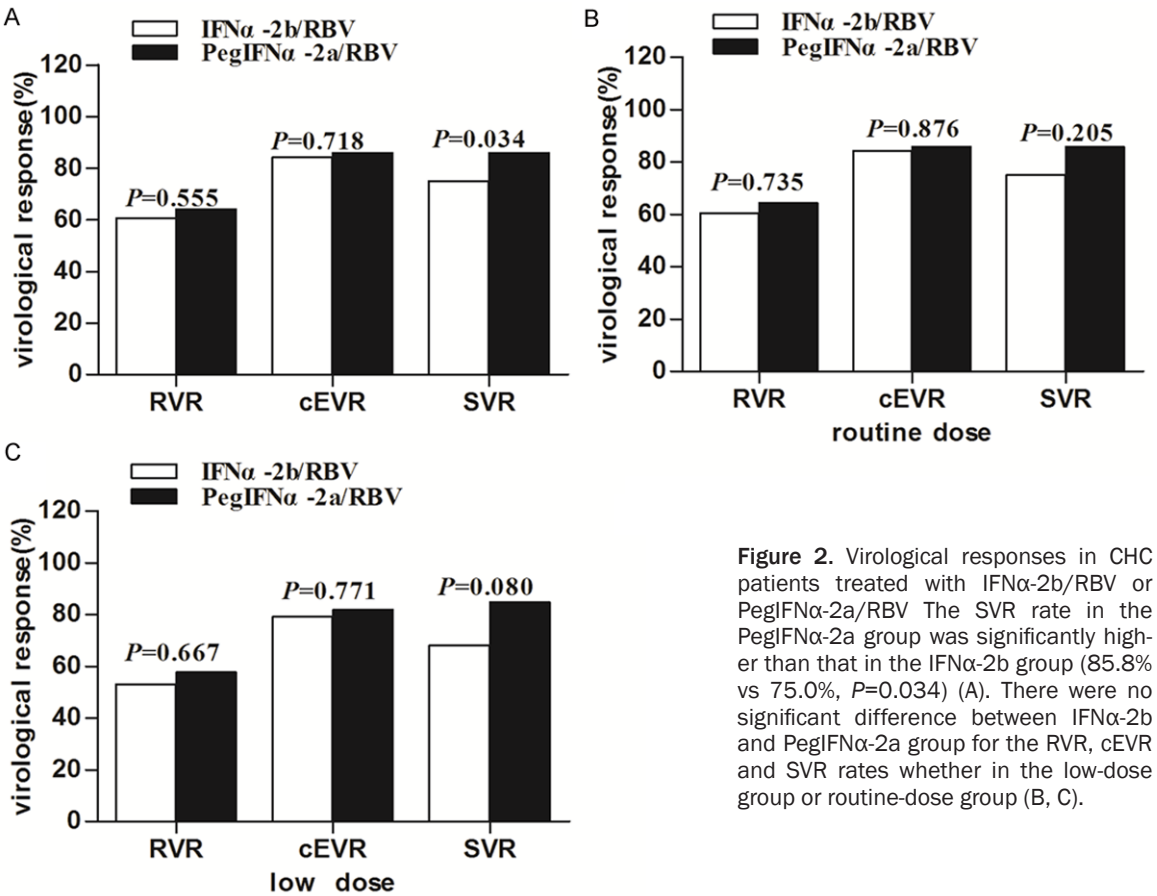

Figure 2. Virological responses in CHC patients treated with IFNα-2b/RBV or PegIFNα-2a/RBV The SVR rate in the PegIFNα-2a group was significantly higher than that in the IFNα-2b group (85.8% vs 75.0%, *P*=0.034) (A). There were no significant difference between IFNα-2b and PegIFNα-2a group for the RVR, cEVR and SVR rates whether in the low-dose group or routine-dose group (B, C).

PegIFNα-2a groups (89.5% vs 90.5%, *P* = 0.609; 90.5% vs 84.2%, *P* = 0.916) (**Figure 3C**).

The rates of RVR, cEVR and SVR in high HCV RNA load patients were significantly lower than that in low HCV RNA load patients

The rates of RVR, cEVR and SVR in high HCV RNA load (>10^6 IU/mL) patients were significantly lower than those in low HCV RNA load patients (55.6% vs 68.2%, *P* = 0.037; 80.2% vs 89.4%, *P* = 0.038; 72.2% vs 86.4%, *P* = 0.005) (**Figure 4A**). There were no significant differences for RVR, cEVR and SVR rates between the IFNα-2b and PegIFNα-2a groups at baseline HCV RNA load ≤10^6 IU/mL (64.5% vs 73.2%, *P* = 0.287; 88.2% vs 91.1%, *P* = 0.591; 84.2% vs 89.3%, *P* = 0.401) (**Figure 4B**). There were no significant differences for RVR, cEVR and SVR rates between the IFNα-2b and PegIFNα-2a groups at baseline HCV RNA load >10^6 IU/mL (56.6% vs 60.0%, *P* = 0.704; 80.3% vs 82.0%, *P* = 0.808; 67.1% vs 76.0%, *P* = 0.283) (**Figure 4C**).

The rates of RVR, cEVR and SVR in CHC patients were significantly higher than that in compansated cirrhosis patients

The rates of RVR, cEVR and SVR in CHC patients was significantly higher than that in compansated cirrhosis patients (65.9% vs 38.5%, *P* = 0.006; 87.5% vs 65.4%, *P* = 0.003; 80.6% vs 61.5%, *P* = 0.024) (**Figure 5A**). Whether CHC or compansated cirrhosis patients, there were no significant difference for RVR, cEVR and SVR rates between IFNα-2b and PegIFNα-2a group (63.7% vs 69.1%, *P* = 0.395, 35.3% vs 44.4%, *P* = 0.648; 87.4% vs 87.6%, *P* = 0.960, 58.8% vs 77.8%, *P* = 0.334; 78.5% vs 83.5%, *P* = 0.343, 52.9% vs 77.8%, *P* = 0.216) (**Figure 5B**, **5C**).

The baseline serum IL-17 level was higher in non-SVR than that in SVR patients

The baseline serum IL-17 level was significant higher in non-SVR than that in SVR patients (120.53±51.94 vs. 84.21±26.32, *P* = 0.035).

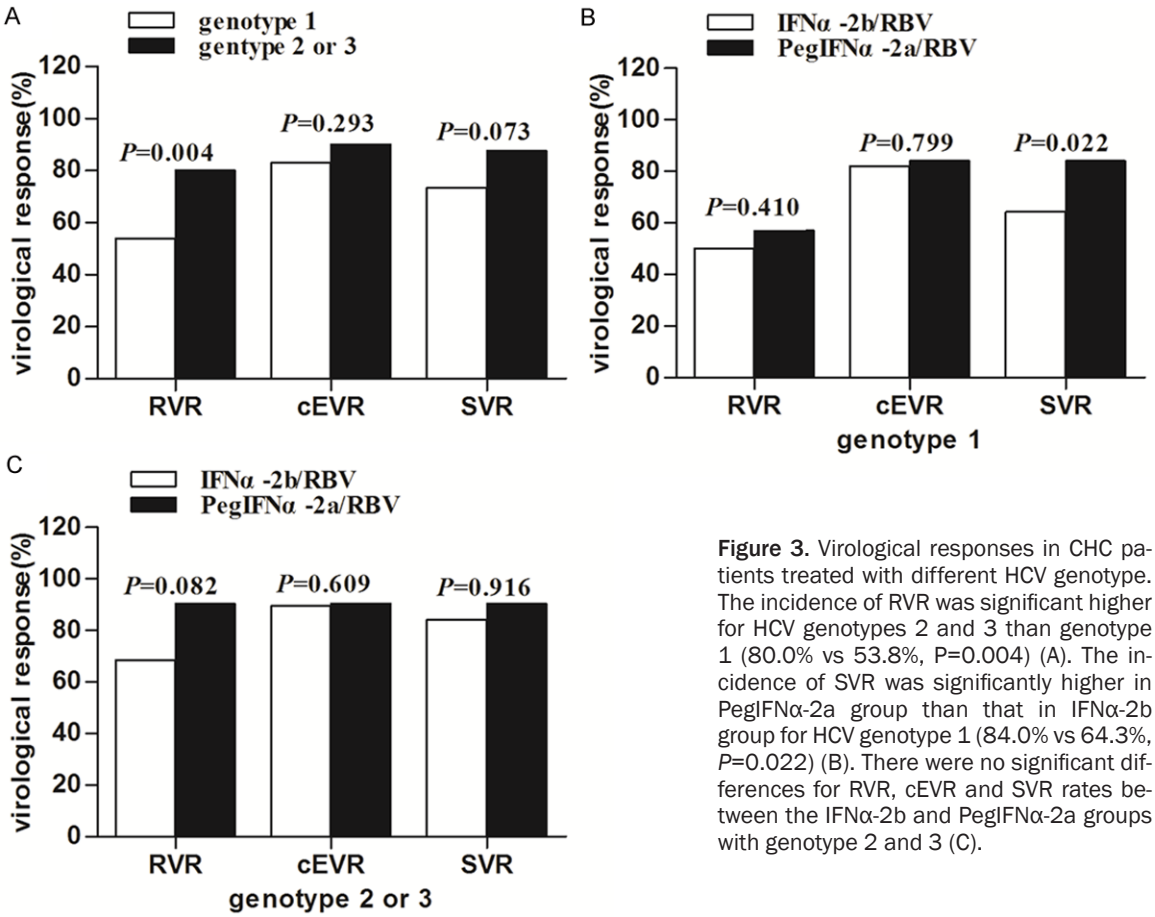

Figure 3. Virological responses in CHC patients treated with different HCV genotype. The incidence of RVR was significant higher for HCV genotypes 2 and 3 than genotype 1 (80.0% vs 53.8%, P=0.004) (A). The incidence of SVR was significantly higher in PegIFNα-2a group than that in IFNα-2b group for HCV genotype 1 (84.0% vs 64.3%, *P*=0.022) (B). There were no significant differences for RVR, cEVR and SVR rates between the IFNα-2b and PegIFNα-2a groups with genotype 2 and 3 (C).

However, there was no difference in serum IL-17 level between the EVR and non-EVR patients (85.51±27.55 vs. 110.42±49.68, *P* = 0.135).

The IL-28B (rs8099917) TT genotype frequency was significantly higher in cEVR, SVR patients than that in non-cEVR, non-SVR patients

All 178 patients IL-28B (rs8099917), IL-17A (rs8193036), IL-17B (rs2275913) and PD-1.1 SNPs were genotyped. The IL-28B (rs8099917) TT genotype frequency was significantly higher in cEVR, SVR patients than that in non-cEVR, non-SVR patients (93.8% vs 75.8%, χ^2 = 10.122, *P* = 0.001; 95.9% vs 78.9%, χ^2 = 12.842, *P* = 0.000) (**Figure 6A**, **6B**). No significant differences were observed in the genotype distribution of IL-17A, IL-17B and PD-1.1 variants between cEVR, SVR and non-cEVR, non-SVR patients (*P*>0.05) (**Figure 6C-H**).

Tolerability and adverse events

Adverse events included flu-like symptoms and transient bone marrow suppression was the most frequently reported adverse events, which were found in most of the patients in the early stage of treatment. Other adverse events including neutropenia, anemia, rash, fever, thyroid dysfunction and depression were shown in **Table 3**. There was no significant difference between low-dose group (50/86, 58.1%) and routine-dose group (118/172, 68.6%) (*P* = 0.096). There were 29 (9.2%) patients showed premature discontinuation of treatment. There was no significant difference between low-dose group (12/86, 14.0%) and routine-dose group (17/172, 9.9%) (*P* = 0.329).

Discussion

In the present study, the SVR rates for the PegIFNα-2a and IFNα-2b groups were 85.8% and 75.0%, respectively, which demonstrates higher SVR rates than the domestic and foreign reports [8, 9, 28]. The personalized doses of PegIFNα-2a/IFNα-2b and RBV and response-guided therapy could make patients well-tolerated, improve their tolerance, acceptance and curative effect. Based on comparison of the

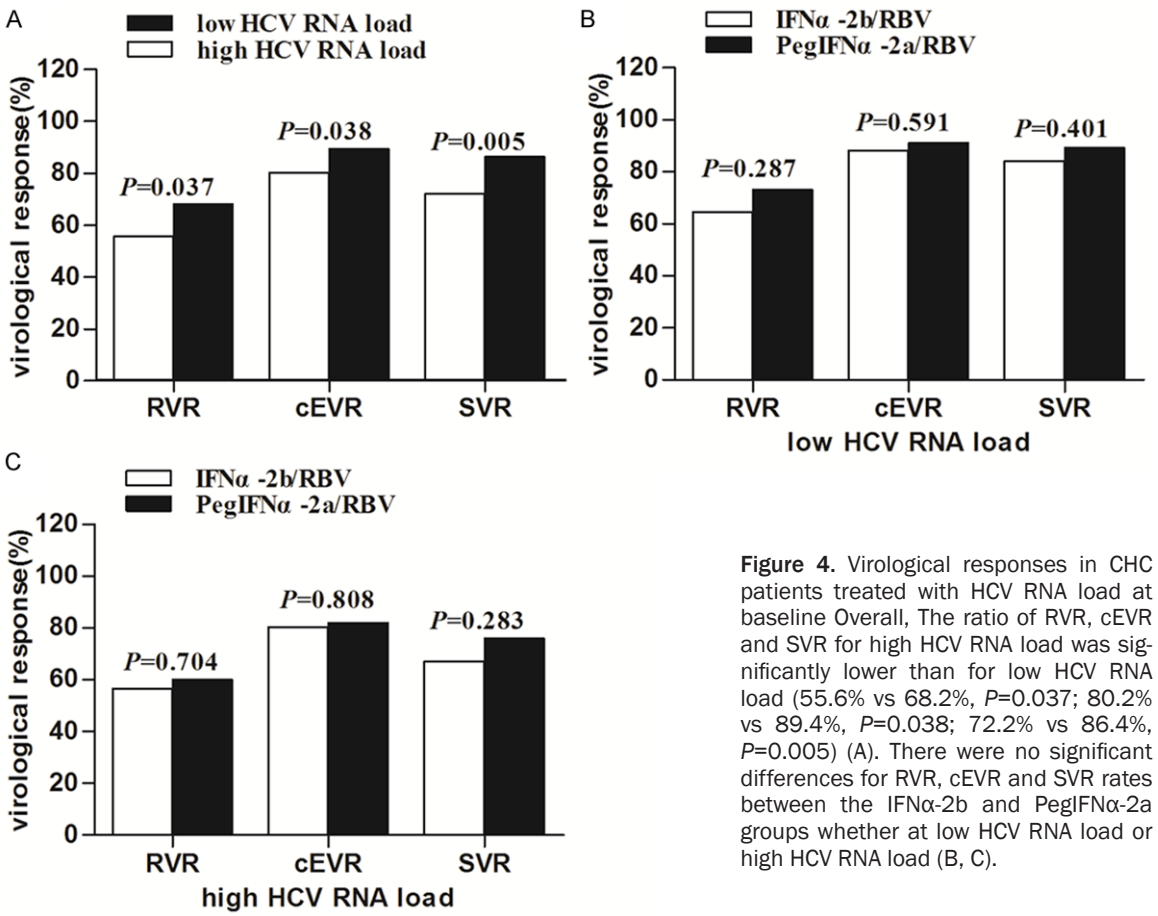

Figure 4. Virological responses in CHC patients treated with HCV RNA load at baseline Overall, The ratio of RVR, cEVR and SVR for high HCV RNA load was significantly lower than for low HCV RNA load (55.6% vs 68.2%, *P*=0.037; 80.2% vs 89.4%, *P*=0.038; 72.2% vs 86.4%, *P*=0.005) (A). There were no significant differences for RVR, cEVR and SVR rates between the IFNα-2b and PegIFNα-2a groups whether at low HCV RNA load or high HCV RNA load (B, C).

efficacy of different types and doses of IFN, we established the optimal treatment strategy for different CHC patients.

Virological responses through the RVR, cEVR and SVR rates were compared for different type of IFNs. The RVR and cEVR rates were similar between INFα-2b and PegIFNα-2a, while the SVR rate in the PegIFNα-2a group was significantly higher than that in the INFα-2b group. Our results showed that INFα-2b or PegIFNα-2a plus RBV individualized therapy can achieve a similar antiviral response, while PegIFNα-2a/RBV regimen was superior to INFα-2b/RBV. The RVR, cEVR and SVR rates were compared for IFNα-2b and PegIFNα-2a in routine- and low-dose treatment. There were no significant differences for routine and low doses between the IFNα-2b and PegIFNα-2a groups, although for low-dose treatment, the PegIFNα-2a group had higher SVR rates than the IFNα-2b group had. Based on our results, IFNα-2b/RBV therapy is advantageous for patients who cannot afford PegIFNα-2a/RBV therapy.

The efficacy for routine- and low-dose treatment between the IFNα-2b and PegIFNα-2a groups were compared. There were no significant differences in the PegIFNα-2a group between routine- and low-dose treatment for RVR, cEVR and SVR rates. Although the cEVR and SVR rates were higher in the routine-dose than the low-dose group for IFNα-2b, there was no significant difference between the two groups. The results showed that low dose of IFNα-2b or PegIFNα-2a is advantageous for patients who are not tolerant of routine-dose IFN. So, for the present, individualized dose of IFNα-2b/RBV is optimal for different CHC patients who are not available for routine dose or who cannot afford PegIFNα-2a/RBV therapy.

In this study, the host- and virus-related factors which possibale associated with virological response were explored. Firstly, the antiviral response between CHC and cirrhosis patients according to different type of IFN was compared respectively. CHC patients treated with IFNα-2b/RBV had significantly higher RVR,

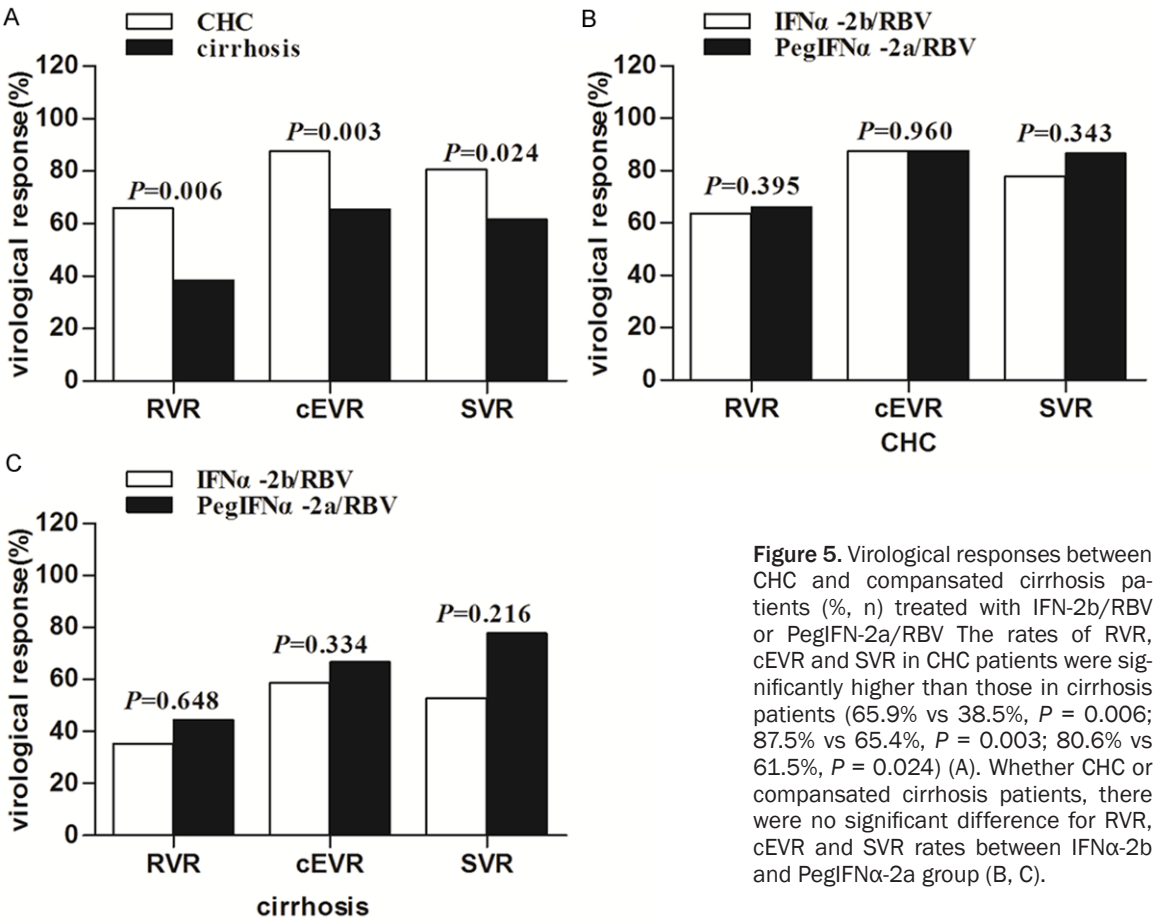

Figure 5. Virological responses between CHC and compansated cirrhosis patients (%, n) treated with IFN-2b/RBV or PegIFN-2a/RBV The rates of RVR, cEVR and SVR in CHC patients were significantly higher than those in cirrhosis patients (65.9% vs 38.5%, *P* = 0.006; 87.5% vs 65.4%, *P* = 0.003; 80.6% vs 61.5%, *P* = 0.024) (A). Whether CHC or compansated cirrhosis patients, there were no significant difference for RVR, cEVR and SVR rates between IFNα-2b and PegIFNα-2a group (B, C).

cEVR and SVR than cirrhosis patients had, while there were no significant differences between CHC and cirrhosis patients treated with PegIFNα-2a/RBV. Three randomized international phase III studies showed that SVR rates decreased progressively from 60% in genotype 1/4 patients without advanced fibrosis to 51% in those with bridging fibrosis and 33% in those with cirrhosis (*P* = 0.0028); and from 76% to 61% and 57%, respectively, in genotype 2/3 patients treated for 24 weeks (*P*<0.0001) [29]. A cohort study involving 2011 patients, including 306 with cirrhosis, showed that SVR was achieved in 28% of treatment-naive genotype 1 patients with cirrhosis compared with 68.6% in patients without fibrosis [30]. A recent review showed that the rate of SVR with SOC ranged from 10% to 44% for HCV genotypes 1 and 4 and 33% to 72% for genotypes 2 and 3 in patients with compensated cirrhosis [31]. For the present study, the reason is not consistent with the above results of the study may be relatively small number of cirrhosis cases in PegIFNα-2a group. Based on our current results, CHC patients have a high virological response whether treated with IFNα-2b/RBV or PegIFNα-2a/RBV, while for cirrhosis patients, PegIFNα-2a/RBV treatment is recommended to achieve a better curative effect. Future large sample study should focus on cirrhosis patients to verify the above results.

Secondly, the association between age and SVR was conducted. There was no significant difference between age <60 years group and age ≥60 years group, the SVR rates were comparable between the two groups in patients with genotype 1, 2 or 3, respectively. It was partially consistent with other several studies that there was no significant difference in the overall SVR rate between younger and elderly patients, while among one of the study for subgroup analysis, the elderly group had a significantly lower SVR rate than the non-elderly group (30.8% vs. 66.0%, *P* = 0.03) with HCV genotype 1 infection, the SVR rate in patients with HCV genotype 2 or 3 was comparable between the two groups (84.0% vs. 81.3%, *P* = 0.85) [32-34]. The inconsistency may be due to good adherence and hence higher SVR rate in

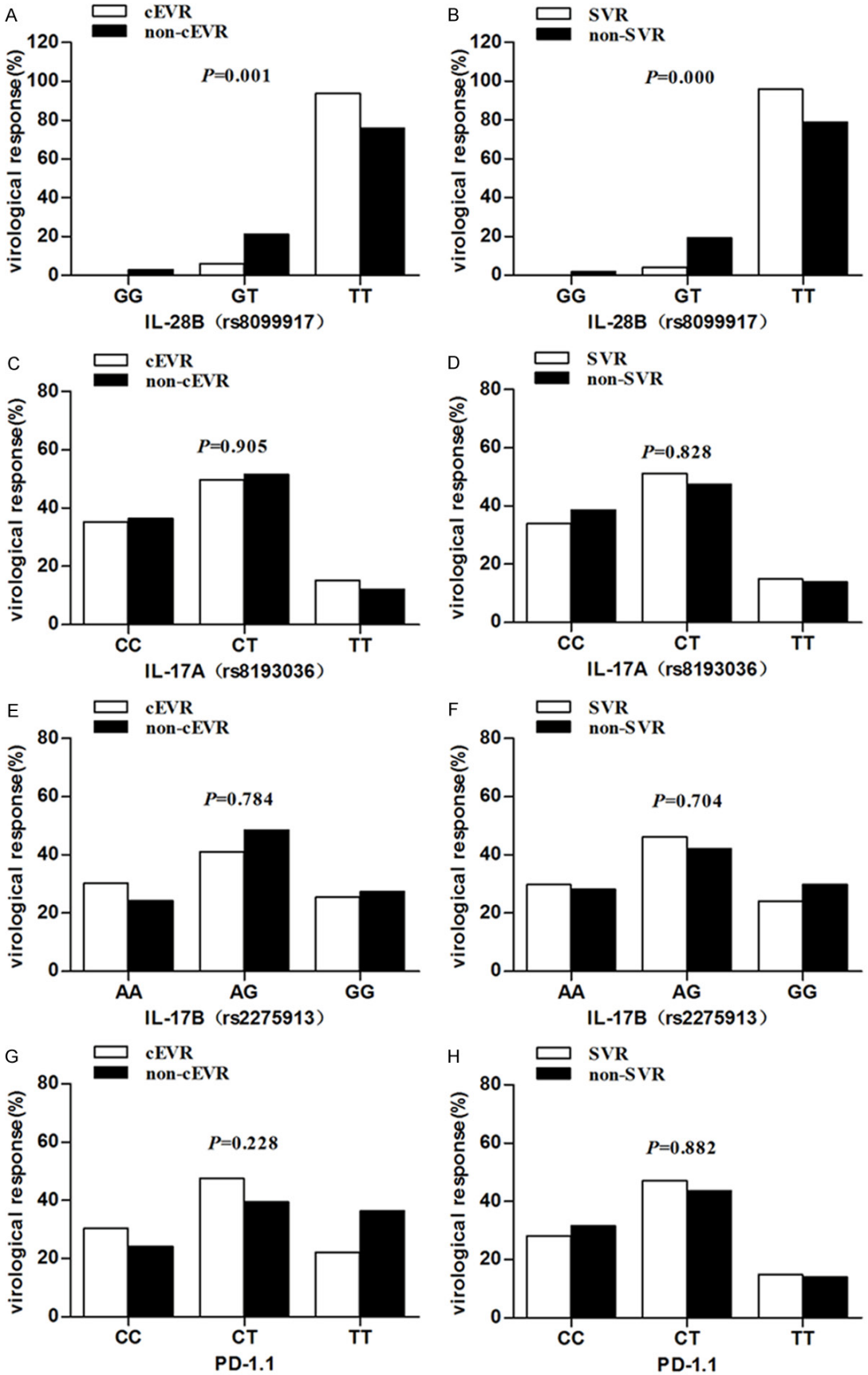
A
cEVR
non-cEVR
virological response(%)
P=0.001
GG
GT
TT
IL-28B（rs8099917）
B
SVR
non-SVR
virological response(%)
P=0.000
GG
GT
TT
IL-28B（rs8099917）
C
cEVR
non-cEVR
virological response(%)
P=0.905
CC
CT
TT
IL-17A（rs8193036）
D
SVR
non-SVR
virological response(%)
P=0.828
CC
CT
TT
IL-17A（rs8193036）
E
cEVR
non-cEVR
virological response(%)
P=0.784
AA
AG
GG
IL-17B（rs2275913）
F
SVR
non-SVR
virological response(%)
P=0.704
AA
AG
GG
IL-17B（rs2275913）
G
cEVR
non-cEVR
virological response(%)
P=0.228
CC
CT
TT
PD-1.1
H
SVR
non-SVR
virological response(%)
P=0.882
CC
CT
TT
PD-1.1

Figure 6. Association of IL-28B, IL-17 and PD-1 polymorphisms with cEVR and SVR The IL-28B rs8099917 TT genotype was significantly higher in cEVR, SVR patients than that in non-cEVR, non-SVR patients (93.8% vs 75.8%, χ^2 = 10.122, *P* = 0.001; 95.9% vs 78.9%, χ^2 = 12.842, *P* = 0.000) (A, B). No significant differences were observed in the genotype distribution of IL-17A (C, D), IL-17B (E, F) and PD-1.1 (G, H) variants between cEVR, SVR and non-cEVR, non-SVR patients.

Table 3. Adverse events in combination therapy, n (%)

Variables	IFNα-2b/RBV routine dose (n=99)	PegIFNα-2a/RBV routine dose (n=73)	IFNα-2b/RBV low dose (n=53)	PegIFNα-2a/RBV low dose (n=33)
Neutropenia	17 (17.2%)	12 (16.9%)	8 (15.1%)	5 (15.2%)
Anemia	14 (14.1%)	10 (13.7%)	7 (13.2%)	4 (12.1%)
Rash	6 (6.1%)	5 (6.8%)	4 (7.5%)	2 (6.1%)
Fever	21 (21.2%)	12 (16.4%)	6 (11.3%)	4 (12.1%)
Hyperthyroidism	4 (4.0%)	2 (3.8%)	2 (3.8%)	1 (3.0%)
Hypothyroidism	5 (5.1%)	3 (4.1%)	3 (5.7%)	1 (3.0%)
Depression	4 (4.0%)	3 (4.1%)	2 (3.8%)	1 (3.0%)
Total	71 (71.2%)	47 (63.4%)	32 (60.4%)	18 (54.5%)

≥60 years group and relatively small sample in our study. Further trial will focus on ≥65 years patients with HCV infection.

In addition to above factors which were associated with virological response, other viral factors including HCV genotype and HCV viral load are important predictive factors. The PegIFNα-2a group had a higher SVR rate than the IFNα-2b group with HCV genotype 1 patients. While, for genotype 2 or 3, there were no significant differences for RVR, cEVR and SVR rates between the PegIFNα-2a and IFNα-2b groups. It is suggested that PegIFNα-2a/RBV therapy is superior to IFNα-2b/RBV therapy, especially when the patients have infection with HCV genotype 1. In our study, the rate of RVR, cEVR and SVR for high HCV RNA load (>10^6 IU/mL) was significantly lower than for low HCV RNA load. For subgroup analysis, there was no significant difference for the rate of RVR, cEVR and SVR between the PegIFNα-2a and IFNα-2b groups, whether HCV RNA load was high or low. Based on the results that the RVR and cEVR rates were significantly higher in SVR patients than that in non-SVR patients, it is shown that the presence of RVR or cEVR is another reliable predictor of antiviral treatment response.

In order to search for new predictors of virological response, the association between host SNPs and immune related serum cytokines with virological response were analylized The frequency of IL-28B (rs8099917) TT genotype was high in this study, especially TT genotype were significant higher in cEVR and SVR patients than that in non-cEVR and non-SVR patients. It was consistent with previously reported results that genetic variants near the IL28B gene that are strongly associated with treatment response [14, 35-39] and spontaneous HCV clearance [40-42], whether HCV genotype 1 or 4 [43, 44]. It can partly explain why most HCV genotype 1 Chinese patients can obtain a satisfactory therapeutic effect. The IL-28B (rs8099917) TT genotype is a clinical usefully marker for the prediction of cEVR and SVR. Though no statistically significant differences were observed in the genotype distribution of IL-17A (rs8193036), IL-17B (rs2275913) and PD-1.1 variants between cEVR, SVR patients and non-cEVR, non-SVR patients in our study. The baseline serum IL-17 level was significantly higher in non-SVR patients than in SVR patients. It have been reported that elevated levels of Th17 cells and IL-17 may facilitate viral persistence in the host [45], and IL-17 contributes to viral replication in a model of disseminated vaccinia infection, rather than providing host defense against viral infection [46], The A allele of IL-17 rs2275913 associated with higher production of IL-17 compared with the G allele, and exhibits greater promoter activity, and has higher affinity to transcriptional factor nuclear factor activated T cells (NFAT), a critical regulator of the IL-17 promoter [47, 48].

Although no prediction of IL-17, PD-1.1 SNPs on virological response was found in this study, it cannot exclude the impact on genetic susceptibility. The following probable reasons are wor-

thy of further exploration and research. First, in samples from different sources, the genotype and allele distribution for different genes is associated with ethnic, racial, living habits and other confounding factors, which led to bias. Second, the choice of sample size, and the relatively low number was a major cause of statistical error. Third, the change in SNPs may have occurred at the replication, transcription or translation levels. In a word, the host SNPs, which are associated with host immune function or antiviral-related factors are worthy of in-depth study.

In conclusion, individualized doses of IFNα-2b/RBV therapy are optimal for different CHC patients who are not available for routine doses or who cannot afford PegIFNα-2a/RBV therapy. PegIFNα-2a/RBV therapy is superior to IFNα-2b/RBV therapy, especially in patients with HCV genotype 1 and compensated cirrhosis. The HCV genotype, HCV viral load, presence of RVR or cEVR and IL-28B (rs8099917) TT genotype are prognostic factors for cEVR and SVR.

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Disclosure of conflict of interest

None.

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