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RETROSPECTIVE STUDY

IL28B polymorphism genotyping as predictor of rapid virologic response during interferon plus ribavirin treatment in hepatitis C virus genotype 1 patients

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Abstract

AIM: To clarify the association of interleukin-28B (*IL28B*) single nucleotide polymorphisms (SNPs) with hepatitis C virus (HCV) viremia changes for assessment of interferon (IFN) response.

METHODS: A cohort of 118 Caucasian treatment-naïve HCV-G1 infected patients, treated with pegylated-IFN alpha 2a or 2b associated with ribavirin (53 responders, 65 non-responders) during the period 2010-2012, were genotyped for *IL28B* SNPs rs12979860 C>T and rs8099917 T>G. Genotyping was performed by real-time allelic discrimination assay. Serum HCV RNA levels were assayed at 2, 4, 12, 24 and 48 wk during therapy. Correlation between *IL28B* genotypes and serum HCV RNA kinetics was investigated. Multivariable logistic regression analysis was performed to identify predictors of null-response.

RESULTS: Twenty-six out of 118 patients (22%) had no HCV RNA decline ⩾ 1 log IU/mL at therapy week 4 (null-responders). *IL28B* genotype was rs8099917 (G*)/rs1297860(**) in 21/26 (80%) of null-responder patients. Using multivariate analysis, it was shown that the presence of the rs8099917 G allele was the best predictor of null-response (OR = 7.9, 95%CI: 1.99-31.18). The presence of at least one favorable genotype showed a positive predictive value of above 90% for HCV RNA reduction ⩾ log at week 4. Analysis of the HCV RNA kinetics during 12 wk of therapy in patients with *IL28B* rs12979860 CT heterozygosis (n = 73), according to their rs8099917 status, showed that the viremia reduction was significantly different in patients carrying the rs8099917 G allele compared to those with favorable homozygosis.

CONCLUSION: Our findings emphasize the association of the *IL28B* rs8099917 G allele with HCV. Genotyping for both *IL28B* SNPs is useful in clinical practice for thorough patient risk stratification based on IFN responsiveness.

Key words: Hepatitis C virus-G1; Interleukin-28B rs12979860; Interleukin-28B rs8099917; Interferon sensitivity; Triple therapy

Core tip: This work provides more insights into the advantage of interleukin-28B rs12979860 and rs8099917 genotyping for therapy management in hepatitis C virus-G1 infected patients. The relevance of this ap-

proach is cost-effective at the time of decisions regarding triple therapy. We observed that in rs12979860 heterozygous patients, carriage of the rs8099917 G allele correlated with lack of viremia decrease early during treatment, when it is critical to assess for interferon sensitivity.

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INTRODUCTION

For years, the standard of care for hepatitis C virus genotype 1 (HCV-G1) infected patients consisted of 48 wk of combination therapy with pegylated-interferon α and ribavirin (PEG-IFN/RBV)[1]. This treatment regimen underwent a major change after the introduction of direct antiviral agents (DAAs). DAAs directly inhibit specific steps in the HCV life cycle, for example, the two currently approved molecules, boceprevir and telaprevir, target NS3/4A serine protease (protease inhibitors, PIs)[2]. Triple therapy with PIs improves on-treatment kinetics and increases sustained virological response (SVR) rate with decreased duration of therapy in both naïve and treatment-experienced HCV-G1 patients[3-6], but raises concerns regarding the generation of resistant viral variants and significant side effects[7]. Furthermore, PIs are expensive and are not yet available in many countries[8].

With PEG-IFN/RBV therapy, pre-treatment patient features, such as viral genotype 1, older age, high baseline viral load and the degree of fibrosis, markedly affect the likelihood of attaining a SVR and assist physicians in patient management[9]. A major breakthrough in the study of baseline predictors of dual therapy response has been the finding of two single nucleotide polymorphisms (SNPs) rs12979860 and rs8099917, located near the interleukin-28B (*IL28B*) gene encoding for IFN-λ-3, which display a strong association with SVR, mainly in HCV-G1 infected patients[10-14]. Subjects with favorable *IL28B* genotypes (such as CC for rs12979860 or TT for rs8099917) have a twofold improvement in SVR rates compared to patients carrying the risk allele for both SNPs. These genetic variants also affect viral kinetics on-therapy and during spontaneous viral clearance[15,16]. On-therapy viremia changes are even more informative: achievement of rapid viral response (RVR), defined as undetectable serum HCV RNA at treatment week 4, is considered the strongest predictor of SVR, and the lack of early viral response, defined as undetectable serum HCV RNA at week 12, has been correlated with treatment failure[15]. Patients who fail PEG-IFN/RBV therapy (non-responders, NR) are distinguished as follows: partial-responder (par-R) if HCV RNA declines > 2 log IU/mL early on treatment but is still positive at week 12; null-responder (null-R) when HCV RNA reduction is less than 1 log at week 4 on treatment, and relapser (Rel) when HCV RNA is undetectable at end of therapy but becomes positive during follow-up period[17]. Data from randomized controlled trials for PIs in pre-treated HCV-G1 patients clearly show that the pattern of response to dual therapy strongly affects the probability of achieving SVR after triple therapy, with a progressive increase in SVR rates from NR (31%-37%) to par-R (52%-57%) and to Rel (75%-86%)[5,6,18].

Although scientific communities and governmental health care organizations recommend triple therapy in HCV-G1 patients[19-21], the use of PIs in clinical practice needs optimization, especially in distinguishing subjects who can still benefit from PEG-IFN/RBV therapy or those who need triple therapy or should wait for new, more potent drugs. In a recent multicentric study, including 1045 HCV-G1 treatment-naïve patients, it has been shown that a consistent subset of this cohort, identified by features such as *IL28B* genotype, could benefit from conventional dual therapy leading to a reduction in adverse effects and economic costs[22,23].

The aim of this study was to retrospectively investigate the association of *IL28B* SNPs with viremia changes at week 4 in a cohort of treatment-naïve HCV-G1 infected patients during combination therapy and to evaluate the advantage of typing for both SNPs for the identification of IFN-sensitive patients.

MATERIALS AND METHODS

One-hundred and eighteen patients (M/F 62/56, median age 49 years, interquartile range 16) with HCV-G1 infection undergoing antiviral therapy at the Gastroenterology and Hepatology Division of Molinette Hospital, Turin, Italy, during the period 2010-2012, were retrospectively included in this analysis. Inclusion criteria were: (1) diagnosis of chronic hepatitis C (CHC) G1; (2) serum HCV RNA positive; (3) Caucasian ethnicity; (4) no co-infection with hepatitis B virus, hepatitis delta virus and human immunodeficiency virus; and (5) naïve to HCV treatment. Patients were treated with standard doses of PEG-IFN-α-2a or -2b associated with RBV. Ribavirin dosage was based on weight: patients less than 75 kg received 800 mg and those more than 75 kg received 1000-1200 mg. Therapy duration was 48 wk or less according to specific guideline stopping rules or to patients withdrawing due to severe side effects[24,25]. The stage of liver fibrosis was described according to the METAVIR score. Significant fibrosis was defined as F3-F4. The AST-to-platelet ratio index (APRI) was calculated according to the formula proposed by Wai *et al*[26]. The research was approved by the institutional ethics committee and was performed according to the 1979 Declaration of Helsinki. All patients

Table 1 Demographic and clinical features of 118 hepatitis C virus genotype 1 infected patients *n* (%)

Variables	Patients
Age, yr	49 (16)
Male gender	52.5%
BMI, kg/m^2	23.5 (3.6)
AST, IU/mL	82 (71)
ALT, IU/mL	55 (48)
gGT, IU/mL	46 (57)
Platelets, 10^9 L	182 (90)
APRI index	0.4 (0.6)
Basal HCV RNA, log IU/mL	6 (1.1)
Fibrosis (stiffness)	6.7 (19)
Fibrosis Metavir	
F0-F1-F2	20 (25)
F3-F4	59 (75)
IL28B SNP rs8099917	
TT	59 (50)
TG	56 (47)
GG	3 (3)
IL28B SNP rs12979860	
CC	30 (25)
CT	73 (62)
TT	15 (13)
HCV RNA decline < 1 log$_{10}$ IU/mL w4	26 (22)
rs8099917_G*/rs12979860_**	21 (81)
rs8099917_TT/rs12979860_T*	3 (11)
rs8099917_TT/rs12979860_CC	2 (8)
Therapy outcome	
R	53 (55)
NR	65 (45)

Data are reported as median (interquartile range) and frequencies (%). IL: Interleukin; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; gGT: Gamma-glutamyl transpeptidase; IL28B: Interleukin-28B; SNP: Single nucleotide polymorphism; w4: Treatment week 4; R: Responder; NR: Non-responder.

signed an informed consent for genetic testing.

Serum HCV RNA levels were assayed at 2, 4, 12, 24 and 48 wk during therapy, using real-time polymerase chain reaction (PCR) assay with a limit of detection of 15 IU/mL (CAP/CTM HCV 2.0, Roche Molecular Diagnostics, Pleasanton, CA). Patients were monitored for at least 6 months after the end of treatment in order to assess therapy outcome. Genomic DNA was isolated from 350 μL of blood sample using the EZ1 DNA Blood kit (Qiagen GmbH, Hilden, Germany). Genotyping for *IL28B* SNP rs12979860 and rs8099917 was performed by real-time allelic discrimination assay (TaqMan SNP Genotyping Assay, Applied Biosystems, Foster City, CA) using TaqMan SNP Genotyping Master Mix (Applied Biosystems) on a CFX96 Real-time PCR instrument (Bio-Rad Laboratories, Hercules, CA).

Statistical analysis

Continuous variables are summarized as median ± interquartile range, and categorical variables as frequency and percentage. Comparisons between groups were performed using a Mann-Whitney *U*-test for non-normal continuous variables. For categorical data, the Fisher exact test was used. $P < 0.05$ (two-sided) was considered statistically significant. Stepwise logistic regression analysis was performed to identify predictors of null-R. For the regression model, the *IL28B* SNPs were evaluated according to the presence of the risk allele *vs* favorable homozygosis. All calculations were performed using SPSS software version 20.0 (IBM SPSS Statistics for Windows, Chicago, IL).

RESULTS

A total of 118 Caucasian HCV-G1 infected patients were included in the study. Demographics and clinical characteristics of the patient cohorts are reported in Table 1. *IL28B* typing showed that 59 of them (50%) carried genotype TG/GG at rs8099917 while 88 (75%) had genotype CT/TT at rs12979860.

Twenty-six patients out of 118 (22%) did not achieve an HCV RNA drop ⩾ 1 log at week 4 (null-R) and 21/26 (81%) carried the rs8099917 G allele. All of them were NR to therapy at week 12. Univariate analysis revealed that baseline factors which were significantly associated with null-R were higher levels of AST, ALT, gGT (P = 0.032, 0.002, 0.001 respectively), lower platelet levels (P = 0.019), higher APRI index (P = 0.033) and the carriage of the rs8099917 G allele ($P < 0.001$). After logistic regression analysis, rs8099917 G allele carriage was determined to be the best predictor of null-R (OR = 7.9, 95%CI: 1.99-31.18, Table 2).

The predictive value analysis of single and combined *IL28B* SNPs for achieving HCV RNA decline ⩾ 1 log after 4 wk of treatment shows that the presence of at least one favorable genotype yields a positive predictive value (PPV) above 90%, with the combination of both SNPs showing a mild improvement (likelihood ratio = 3.82), Table 3.

We analyzed HCV RNA kinetics during 12 wk of therapy in patients with *IL28B* rs12979860 CT heterozygosis (n = 73), according to their rs8099917 status. The reduction in viral load during treatment was significantly different in patients carrying the rs8099917 G allele compared to those with favorable homozygosis ($P < 0.01$). The decrease in serum HCV RNA levels at week 2, 4 and 12 was 2.1, 3.5 and 6.2 log$_{10}$ in patients with the rs8099917 TT compared to 0.9, 1.55 and 3.7 log$_{10}$, respectively, in those with the unfavorable TG/GG genotypes ($P < 0.001$), Figure 1.

DISCUSSION

The major implication for recommending triple rather than dual therapy for HCV-G1 patients is that higher numbers of patients may achieve a RVR and most likely respond to treatment. Considering the enthusiasm in the run to embrace new therapies, it should not be forgotten that an appreciable number (about 20%) of HCV-G1 patients (mainly those experiencing RVR) are able to eliminate the virus with conventional dual therapies[22]. The treatment risk/benefit ratio is mainly bound to the

Table 2 Univariate and multivariate analysis of baseline factors associated with hepatitis C virus RNA reduction < 1 log_{10} IU/mL at week 4 on treatment *n* (%)

Baseline factors	Univariate			Multivariate		
	HCV RNA drop < 1 log_{10}: w4 (*n* = 26)	HCV RNA drop ⩾ log_{10}: w4 (*n* = 92)	*P* value	OR	95%CI	*P* value
Age, yr	49 (14)	49 (18)	NS	-	-	NS
Male gender	15 (26)	47 (74)	NS	-	-	NS
BMI, kg/m^2	23 (2)	24 (4)	NS	-	-	-
AST, IU/mL	90 (46)	67 (74)	0.032	1.01	0.99-1.02	NS
ALT, IU/mL	73 (60)	49 (44)	0.002	0.97	0.95-0.99	0.018
gGT, IU/mL	68 (71)	39 (43)	0.001	0.99	0.98-0.99	0.009
Platelets, 10^9 L	151 (93)	196 (83)	0.019	-	-	NS
APRI index	0.6 (1.2)	0.4 (0.6)	0.033	-	-	NS
Basal HCV RNA, log IU/mL	6.1 (0.8)	6 (1.1)	NS	-	-	-
Fibrosis F3/F4	11 (58)	48 (80)	NS	-	-	NS
IL28B rs8099917_TG/GG	21 (81)	38 (41)	< 0.001	7.90	1.99-31.18	0.003
IL28B rs12979860_CT/TT	23 (88)	65 (71)	NS	-	-	NS

Data are reported as median (interquartile range) and frequencies (%). IL: Interleukin; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; gGT: Gamma-glutamyl transpeptidase; Null-R: Null-responders; NS: Not significant.

Table 3 Sensitivity, specificity, positive and negative predictive value of single and combined *IL28B* polymorphisms for achieving hepatitis C virus RNA drop ⩾ 1 log at treatment week 4

IL28B polymorphisms	Sn	Sp	PPV	NPV	LR
rs8099917_TT	59%	81%	91%	36%	3.05
rs12979860_CC	29%	88%	90%	26%	2.54
rs8099917_TT or rs12979860_CC	29%	92%	93%	27%	3.82

IL: Interleukin; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; LR: Likelihood ratio.

incidence and severity of side effects, which are significantly increased with triple therapy and occur mostly in the main candidates for treatment, *i.e.*, patients with advanced fibrosis or cirrhosis[26]. In a multicentric French trial, including about 500 cirrhotic treatment-experienced patients treated with triple therapy (CUPIC cohort), 40% showed serious adverse events, with high rates of discontinuation, and there were 1.7% and 0.5% cases of mortality in the groups treated with telaprevir and boceprevir, respectively[27]. Moreover, both PIs are metabolized through cytochromes P450 3A4 and 3A5. With regard to this, the risk of drug-drug interactions is a concern in clinical practice[28,29].

In the era of DAAs, *IL28B* testing offers the minimal additional information that could influence the clinician's decision[27]. Nevertheless, triple therapy is not recommended in all patients and the evaluation of pretreatment factors such as the *IL28B* SNPs still holds significance to establish the therapeutic schedule. Moreover, in a recent review, Matsuura *et al*[30] reported that *IL28B* polymorphisms may affect viral kinetics even in the context of IFN-free regimens. In a phase 2, randomized, open-label trial of faldaprevir (NS3/4A protease inhibitor) and deleobuvir (NS5B polymerase inhibitor), the SVR rates tended to be higher in patients with CC at rs12979860 than in those with non-CC. This suggests that innate immunity may still be important and confirms the importance of *IL28B* genotyping in the context of new and future therapy regimens[30].

Our data show that *IL28B* rs8099917 G allele carriage is the most significant baseline feature associated with lack of IFN sensitivity at week 4, in treatment-naïve HCV-G1 infected patients treated with PEG-IFN/RBV, independently of rs12979860T allele carriage. Evaluation of the PPV for the HCV RNA decrease ⩾ 1 log at treatment week 4 according to each single SNP shows no difference between them, with a mild likelihood ratio for the two SNPs together. Nevertheless, the combined *IL28B* genotype of week-4 null-R was rs8099917_G*/rs1297860_** in 21/26 (80%) patients. In our cohort, all null-R become NR at week 12 and may be considered as interferon insensitive.

The *IL28B* locus (coding for IFN-λ3) is pivotal to the pathogenesis of HCV chronic infection[9-13]. Two SNPs, rs8099917 T/G and rs12979860 C/T, located 8 and 3 kb upstream of the *IL28B* gene, respectively, showed the strongest association with SVR to dual therapy, especially in HCV-G1 infected patients. Both SNPs are in linkage disequilibrium but allele frequencies may be quite different among different ethnic groups. In addition, it has been reported that *IL28B* genetic variants affect HCV RNA decline early on therapy[15-17].

The mechanism by which the *IL28B* genetic variants influence the efficacy of dual treatment remains unknown and the need to genotype for both SNPs in the clinical setting, prior to therapy, remains questionable. In the majority of studies, only one SNP, either rs12979860 or rs8099917, was assayed according to prevailing ethnicity. In Japan, the favorable rs8099917_T allele has higher frequency in the general population compared to Caucasians, thus explaining why there is higher spontaneous or therapy-induced clearance of HCV infection, and why

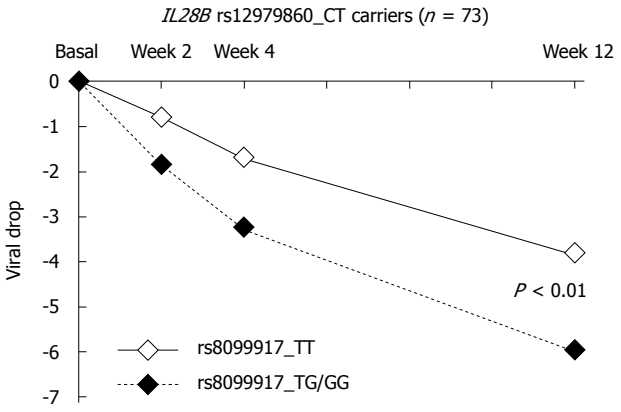

Figure 1 Hepatitis C virus RNA kinetics in *IL28B* rs12979860 heterozygous according to rs8099917 genotypes (median log$_{10}$ IU/mL).

genotyping for this SNP is informative enough. Moreover, in the European cohort of 910 G1 CHC patients analyzed by Suppiah *et al*[31], *IL28B* rs8099917 TG/GG variants were associated with lack of treatment-induced clearance. Halfon *et al*[32] reported that analysis of a single *IL28B* SNP was sufficient to predict treatment failure in patients with HCV. Furthermore, Lazarevic *et al*[33], comparing 3 *Il28B* SNPs, observed that the rs12979860 CC genotype was a better predictor of therapy success in a cohort of 106 HCV patients.

Our study confirms that *IL28B* alleles impact on viral kinetics during treatment in patients with HCV-G1 infection. In order to investigate the usefulness of typing for both SNPs, we analyzed HCV RNA kinetics during 12 wk of therapy in the sub-group of patients with rs12979860 heterozygosis with respect to rs8099917 genotypes. We observed a significant difference for HCV RNA decline in the absence of rs8099917 G allele carriage. These observations highlight the association of the *IL28B* rs8099917 G allele with the lack of HCV RNA reduction > 1 log at treatment week 4 in HCV-G1 patients treated with PEG-IFN/RBV therapy. Thus, genotyping for both *IL28B* SNPs is advantageous in clinical practice for patient risk stratification at therapy week 4, a key time-point for assessment of IFN responsiveness before the addition of PIs. In patients with favorable *IL28B* genotypes and RVR, clinicians could still afford to treat with combination therapy, with no addition of first generation PIs and without losing therapy response. With the new and future antiviral regimens entering clinical practice (2nd class PIs and IFN-free regimens), *IL28B* genotyping may guide clinicians to offer personalized therapy to difficult-to-treat patients, hopefully sparing side effects and costs.

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COMMENTS

Background

Hepatitis C virus (HCV) therapy is currently undergoing a radical transformation with the advent of the direct antiviral agents. These new molecules have higher cure rates (about 70% to 80%) than dual therapy with pegylated interferon (Peg-IFN) plus ribavirin (RBV) and may allow reduction in treatment duration. Although in the United States, triple therapy is considered the new standard of care treatment for HCV-G1 infected patients, in most European countries and in the developing countries, dual therapy remains the standard of care treatment. In this context, pre-treatment patient features, such as viral G1, older age, high baseline viral load, the degree of fibrosis and interleukin (*IL*)*28B* polymorphisms, markedly affect the likelihood of attaining a sustained virological response (SVR) and assist physicians in patient management.

Research frontiers

IL28B genotyping is advantageous in clinical practice for patient risk stratification at therapy week 4, a key time-point for assessment of interferon responsiveness before the addition of PIs. The results of this study provide a strong rationale for the use of *IL28B* single nucleotide polymorphism (SNPs) testing to personalize antiviral therapy.

Innovations and breakthroughs

This work aims at emphasizing the role of *IL28B* polymorphism genotyping in HCV genotype-1 patients for whom triple therapy is not suited. In these patients, the evaluation of pre-treatment factors such as the *IL28B* SNPs still holds significance to establish the therapeutic schedule.

Applications

In patients with favorable *IL28B* genotypes and rapid viral response (RVR), clinicians could still afford to treat with combination therapy, with no addition of first generation PIs and without losing therapy response. The relevance of this approach is cost-effective at the time of triple therapy.

Terminology

IL28B is a cytokine that plays a role in immune defense against viruses, including the induction of an "antiviral state". Two SNPs, rs8099917 T/G and rs12979860 C/T, located 8 and 3 kb upstream of the *IL28B* gene, respectively, showed the strongest association with SVR to PEG-IFN/RBV therapy, especially in HCV-G1 infected patients.

Peer review

This study has shown that *IL28B* SNP can determine the effectiveness of PEG-IFN/RBV treatment in HCV genotype 1 patients. In the study, patients carrying both *IL28B* rs12979860CT and rs8099917TT show more sensitivity to PEG-IFN/RBV than patients carrying *IL28B* rs12979860CT and other SNPs. Furthermore, the study reports that the *IL28B* rs8099917G allele possesses resistance to PEG-IFN/RBV. Accordingly, the authors propose that genotyping of both *IL28B* SNPs is useful in clinical practice for patient risk stratification based on IFN responsiveness.

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