

Genetic variation in Interleukin-28B predicts SVR in hepatitis C genotype 1 Argentine patients treated with PEG IFN and ribavirin

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ABSTRACT

Background and aims. Genetic variations in the interleukin 28B (IL28B) gene have been associated with viral response to PEG-interferon- α /ribavirin (PR) therapy in hepatitis C virus (HCV) genotype 1 infected patients from North America, Europe and Asia. The importance of these IL28B variants for Argentine patients remains unknown. **Material and methods.** IL28B host genotypes (rs8099917 and rs12979860) were determined in a population of Argentine patients with European ancestry. Results were analyzed looking for their association with sustained virologic response (SVR) to PR therapy and compared with other baseline hosts' biochemical, histological and virological predictors of response. **Results.** We studied 102 patients, 60% were men, and 40% of them were rs8099917 TT and 18% rs12979860 CC. Mean baseline serum HCV RNA was 1.673.092 IU/mL and mean F score was: 2.10 ± 1.18 (21% cirrhotic). SVR rate was higher in rs8099917 TT genotypes (55%) when compared to GT/GG (25%) ($p = 0.002$) and in rs1512979860 CC (64%) than in CT/TT (30%) ($p = 0.004$). The univariate analysis showed that rs8099917 TT (OR 3.7; 95 %CI 1.5-8.7; $p = 0.002$), rs12979860 CC (OR 4.6; 95%CI 1.5-13.7; $p = 0.006$), low viral load (OR 4.6; 95% CI 1.7-12.6; $p = 0.002$) and F0-2 (OR 8.5; 95% CI 2.3-30.6; $p = 0.001$) were significantly associated with SVR. In the multivariate analysis, rs12979860 CC, rs8099917 TT, viral load < 400.000 IU/mL and F0-2 were associated with SVR rates ($p = 0.029$, $p = 0.012$, $p = 0.013$ and $p = 0.004$, respectively). **Conclusion.** IL28B host genotypes should be added to baseline predictors of response to PR therapy in Latin American patients with European ancestry.

Key words. Hepatitis C. Sustained virological response. IL28B. Single-nucleotide polymorphisms. European ancestry. Latin American patients.

INTRODUCTION

Hepatitis C virus infection (HCV) is a global health problem, it is estimated that there are between 120 and 130 million infected people worldwide.¹ Chronic HCV infection can lead to a progressive liver disease, development of cirrhosis and its complications, requiring liver transplantation in most of

these cases.^{2,3} PEG-interferon- α /ribavirin (PR) combination for 24 or 48 weeks, according to patient's HCV genotype, is the current standard of care treatment. It is an expensive therapy, frequently associated with a wide spectrum of adverse events. Overall sustained virologic response (SVR) rates are around 50%,⁴⁻⁶ but lack of tolerance in some patients, may induce poor adherence and loss of response. For these reasons, the decision to initiate treatment in an individual patient should be based on reliable viral and host predictor factors, which lead to a cost effective approach to HCV therapy.

Recently, three genome-wide association studies (GWAS) described two single nucleotide polymorphisms (SNPs) in the interferon lambda (λ) gene region in chromosome 19, rs12979860 and

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rs8099917.⁷⁻⁹ They are presumably responsible for interferon $\lambda 1$ (*IL29*), $\lambda 2$ (*IL28A*), and $\lambda 3$ (*IL28B*) induction, and both have been associated to PR response in HCV infected patients in recently published studies.⁷⁻⁹ Genotype rs12979860 an independent predictor of PR SVR,^{7,10,11} has also been identified as an independent predictor of spontaneous clearance of HCV infection.¹² In the other hand, genotype rs8099917 has been recognized as an independent predictor of non response to PR.^{8,9,13}

Given these results in genotype 1, similar studies were performed in genotype 2 and 3 infected patients. Mangia, *et al.* showed that HCV genotype 3 infected patients with CC rs12979860 polymorphism, even those with no rapid virologic response (RVR), had higher chances of achieving a SVR.¹⁴ Larger studies are needed to prove the ability of these polymorphisms to predict SVR in non-1 genotypes.

We are currently getting close to the era of the new antiviral oral drugs. Two protease inhibitors in combination with PR (telaprevir and boceprevir), will soon be approved for HCV treatment.¹⁵⁻¹⁹ The positive predictive value of IL 28B polymorphisms in this new paradigm will probably remain there, but probably, with a weaker association than the observed with PR. Akuta, *et al.* evaluated their influence in patients treated with telaprevir + PR. In their study, rs8099917 polymorphism (genotype TT) was also associated with SVR.²⁰ Therefore, it seems that IL28-B SNPs will remain an important tool to predict SVR in genotype 1 infected patients treated with protease inhibitors.

The frequency and association of IL28 B with SVR in South-America are unknown. The main objective of this study was to evaluate their distribution and association with SVR rates in an Argentine HCV G1 population, treated with PR.

OBJECTIVE

To evaluate the influence of IL28B polymorphisms on SVR in Argentine HCV G1 infected patients treated with PR, and to compare it with other known baseline predictors of response such as gender, age, basal viral load and fibrosis stage.

MATERIALS AND METHODS

We retrospectively contacted a group of HCV genotype 1 treated patients from 4 different Argentine liver units. A hundred and two, from all patients treated, agreed to participate in the study. Five ml of fresh blood was drawn from all of them after the

consent form was signed. The protocol was approved by the Ethics and Research Committee of the *Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno* (CEMIC). As previously described, patient's confidentiality was protected and ensured. This protocol adhered to good clinical practice and ethical principles included in Helsinki Disclosure 2008.

We included naïve patients > 18 years with chronic HCV genotype 1 infection who were previously treated with standard doses of PEG-IFN $\alpha 2a$ or $\alpha 2b$ /RBV and had well documented treatment response data record. Responses were defined as sustained virological response (SVR), response and relapse (RR) and non response (NR), according to previously established response criteria.²¹ Baseline, weeks 12, 24, 48, and 72 serum viral load results had to be clearly documented in clinical records. Patients were excluded if they presented HIV and/or HBV co-infection, if they were previously transplanted, on hemodialysis, had early treatment discontinuation, or denied to sign the informed consent form. Clinical and laboratory data was obtained from their medical records by treating physicians. Data was anonymously included in an excel spreadsheet.

The study respectfully followed the National Law of Habeas Data. At the time of inclusion, subject samples were assigned with a protocol number to ensure maximal confidentiality. Their correlation with individual data was only known by the principal investigator.

Samples from included patients were genotyped for the IL28B related SNPs at CEMIC, Genotyping laboratory. DNA was obtained from peripheral white blood cells, with Magna-Pure automatic extraction of DNA and with MagNA-Pure Compact Nucleic Acid Isolation Kit I to purify high-quality under graded genomic DNA from mammalian white blood cells.

Patients were genotyped as CC, CT, or TT at the polymorphic site, rs12979860 and as GG, GT, or TT at the polymorphic site, rs8099917. Specific primers were designed for both SNPs: rs8099917 and rs12979860, to ensure a specific PCR product and a clean sequence reaction. A set of these primers was used in the PCR reaction in two alternative sequences to ensure the detection of both alleles. Primers were always designed avoiding eventual polymorphic sequences depicted in the genome flanking the SNPs. In the same line of optimization, a different primer was used for the sequence reaction in order to achieve the best specificity of the assay.

Automatic analysis was performed for sequence read with forward and reverse primers. Result of the sequences analysis in both directions was registered for further analysis.

Statistical analysis

Microsoft Excel 2007® software (Microsoft, Seattle, WA, USA) was used for the database. STATA® statistical software was used for the analysis (version 7.0 Stata Corporation, Tx., USA). The chi-square test was employed to compare categorical variables, and continuous variables were compared using the t-test. Logistic regression test was used, for univariate and multivariate analysis, to explore base-line factors predicting a virologic response. P value < 0.05 was considered statistically significant.

RESULTS

A hundred and two patients with chronic hepatitis C genotype 1 infection treated with PR were included. Sixty percent were males, with a mean age of 50 years old, 84% > 40, 77% with basal HCV RNA viral load > 400.000 IU/mL, 30% with Metavir F3-4 scores and 21% with cirrhosis. All demographic characteristics are presented in table 1. In the studied populations, 40% were rs8099917 TT genotype and 18% were rs12979860 CC genotype (Table 1, Figure 1).

Thirty six percent of the study population (37 patients) achieved a SVR, while 64% did not. Thirty five patients were relapsers and 30 were non responders; in the latter group, 12 patients were null res-

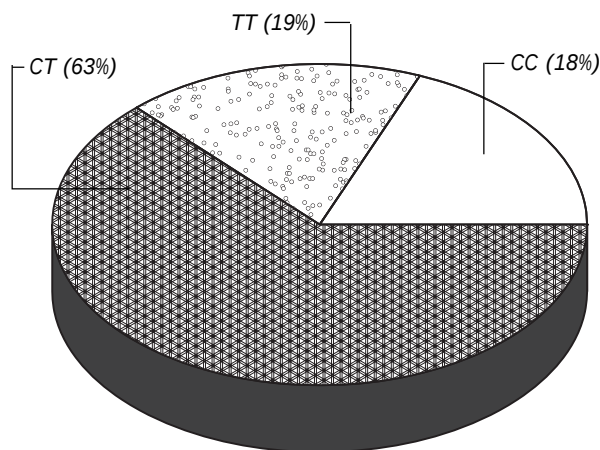
ponders. When evaluating predictors of response we found that the rs8099917 TT genotype (OR 3.7; 95%CI 1.5-8.7; p = 0.002), rs12979860 CC genotype (OR 4.6; 95%CI 1.5-13.7; p = 0.006), low viral load (OR 4.6; 95%CI 1.7-12.6; p = 0.002) and fibrosis stage F0-2 (OR 8.5; 95%CI 2.3-30.6; p = 0.001) were significantly associated with SVR in HCV genotype 1 infected patients. Gender, age, weight and ALT values (more than two times upper limit of normal, normal value < 35 IU/mL) did not influence SVR (Table 2). In the multivariate analysis, rs12979860 CC genotype, rs8099917 TT genotype, viral load < 400.000 IU/mL and fibrosis stage F0-2 were associated with SVR rates (p = 0.029, p = 0.012, p = 0.013 and p = 0.004, respectively) (Table 3).

In the group of patients with SVR, 55% had the rs8099917 TT genotype vs. 25% who had the GT/GG genotype (p= 0.002), and 64% had the rs12979860

Table 1. Demographic characteristics.

Mean age	50 ± 10 years
Age < 40 years	16%
Gender	60% men/40% women
Weight	74 ± 12 kg
rs8099917 TT genotype	40%
rs12979860 CC genotype	18%
Mean HCV RNA	1.673.092 ± 2.563.661 IU/mL
Low viral load < 400.000 IU/mL	21%
Mean fibrosis score	Metavir F 2, 10 ± 1.18
Metavir F3-4 score	30%
Pts with cirrhosis	21%
Elevated ALT	95%

A. rs12979860 genotype.



B. rs8099917 genotype.

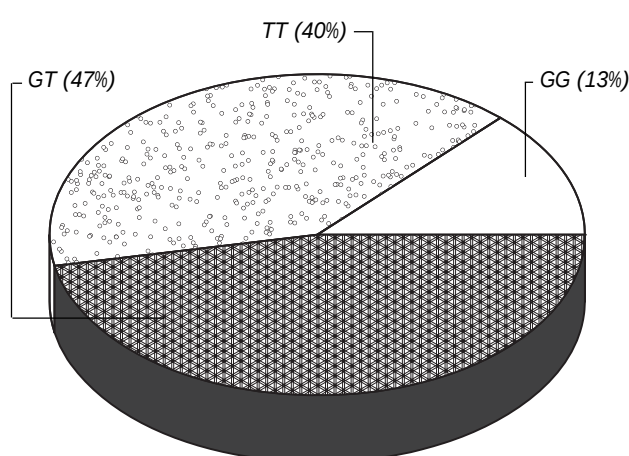


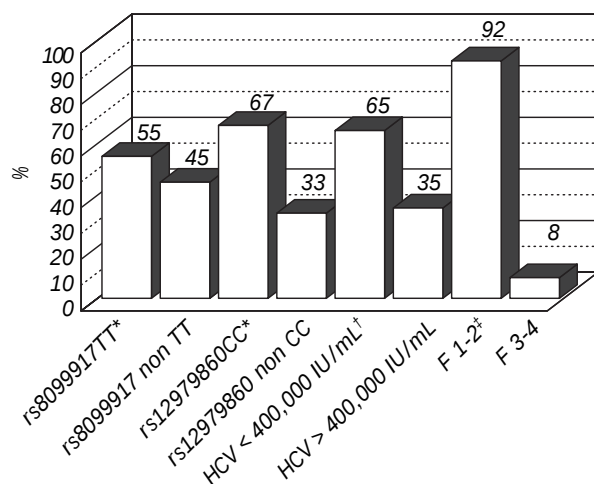
Figure 1. Percentage of patients according to IL28B genotype.

Table 2. Predictors of SVR, univariate analysis.

	Odds ratio	95% confidence interval	p value
Sex (men vs.women)	0.88	0.38-3.04	0.783
Weight	0.98	0.95-1.01	0.409
Age < 40 years	1.06	0.35-3.20	0.918
ALT value	0.27	0.02-3.17	0.303
rs8099917 TT	3.74	1.59-8.79	0.002
rs12979860 CC	4.64	1.56-13.65	0.006
Low viral load	4.68	1.74-12.61	0.002
Fibrosis stage F0-2	8.5	2.35-30.61	0.001

Table 3. Predictors of SVR, multivariate analysis.

	Odds ratio	95% confidence interval	p value
rs8099917 TT vs. non TT	3.41	1.31-8.86	0.012
rs12979860 CC vs. non CC	3.83	1.15-12.77	0.029
HCV RNA (< vs. $\geq 400,000$ IU/mL)	4	1.33-12	0.013
Fibrosis stage (Metavir F0-2 vs. F3-4)	7.39	1.88-28.96	0.004

**Figure 2.** Percentage of patients with SVR according to each parameter (* $p < 0.005$. † $p = 0.039$. ‡ $p < 0.001$).

CC genotype vs. 30% who had CT/TT genotype ($p = 0.004$). Also, 65% had HCV RNA < 400,000 IU/mL ($p = 0.039$) and 92% had Metavir stages F0-2 ($p < 0.001$) (Figure 2).

Patients with rs12979860 CC genotype had a higher basal viral load than non-CC genotype: 6.49 log IU/mL 95% CI 5.8-6.74 vs. 6.14 log IU/mL 95% CI 5.99-6.25, $p = 0.014$. There was no difference between TT and non-TT rs8099917 genotypes. Patients with rs8099917 TT genotype had a lower percentage of cirrhosis than non-TT genotype: 10% vs. 28%, $p = 0.035$. There was no difference between

CC and non-CC rs12979860 genotypes. There was no difference between CC and non-CC rs12979860 genotypes, and between TT and non-TT rs8099917 genotypes regarding Metavir F stages.

DISCUSSION

Chronic HCV infection involves a complex interaction between the virus and the host innate and adaptive immunity. Almost 80% of acute HCV infection evolves into a chronic phase of the disease. Host genetics, as previously mentioned, play an important role in treatment induced clearance as well as in spontaneous clearance.^{12,13,22} Accumulating evidence supports a critical role of host's genetics in interferon and ribavirin induced immune responses during treatment.^{23,24} Consistent with previous reports, this study established a predictive role of IL28B polymorphisms in the treatment of chronic HCV infection with PR combination in Argentine patients of European ancestry.

There are many predictors of response to HCV treatment such as viral load, fibrosis stage, age, and others. Ethnicity appears to be an important one, and Hispanics/Latino patients have been considered as a difficult to treat population. Sustained virological response rates in genotype 1 patients varied between 14 and 34% in this ethnic group.²⁵⁻²⁷ We have reported the results in our population of Hispanic patients treated in routine clinical practice: 7.6% of patients discontinued therapy due to adverse events, and 1.2% of patients dropped-out treatment; the

SVR was 51.8% in genotype 1 patients.²⁸ These results are similar to those reported by European and North-American studies in daily clinical practice²⁹⁻³² and to those reported in registration randomized clinical trials,⁴⁻⁶ and higher than in other Hispanic populations.²⁵⁻²⁷ These results show wide differences in the Hispanic population, and host genetics are likely to determine SVR rates.

Our study shows that IL28B polymorphisms predicted SVR rates in our population. SVR rate was 64% in rs12979860 CC genotype and 55% in rs8099917 TT genotype. Similar results had been previously reported. Ge, *et al.* analyzed 1137 HCV genotype 1 infected patients in USA and found in rs12979860 CC patients SVR rates of 77% in Caucasians and 53% in African Americans.⁷ In the study of Thompson, *et al.*, the rate of SVR observed in Caucasians with the CC *IL-28B* type was 69% and in Hispanics was 56%, higher than in either African Americans (48%).¹¹ Our SVR rates are slightly higher than those reported by Thompson, these might be related to different ethnic origin of these Hispanic patients.¹¹ These studies have demonstrated the predictive value of rs12979860 CC genotype for obtaining a SVR: OR, 5.79; 95%CI, 2.67-12.57; in the study of McCarthy, *et al.*,¹⁰ and OR, 5.2; 95% CI, 4.1-6.7, in the study of Thompson, *et al.*¹¹

Tanaka, *et al.* identified 2 SNPs (rs12980275 and rs8099917) in chromosome 19 near the *IL-28B* gene in 154 HCV Japanese patients. They showed a strong association between the minor allele ($P = 1.93 \times 10^{-13}$ and 3.11×10^{-15} ; odds ratio [OR] = 20.3, 95% CI = 8.3-49.9 y OR = 30.0, 95% CI = 11.2-80.5, respectively) and null response (NR) to PR treatment.⁸ These SNPs are stronger predictors of non-response (OR = 17.7 and 27.1), and has a less statistical power to predict SVR (OR = 8.8 y 12.1, respectively).⁸ A GWAS study of SVR to PEG-IFN/RBV treatment in 293 HCV genotype 1 Australians patients (North-European ancestry) confirmed the association of this SNP (rs8099917), and it was validated in a cohort of 555 Europeans patients ($P = 9.25 \times 10^{-9}$, OR = 1.98, CI95% = 1.57-2.52).⁹ Rauch, *et al.* showed that the minor allele rs8099917 is associated with non-response to treatment (OR, 5.19; 95% CI, 2.90-9.30; $P = 3.11 \times 10^{-8}$), with a stronger prediction in genotype 1 and 4 infected patients.¹³ Our results showed that rs8099917 TT genotype, can also predict SVR as the rs12979860 CC genotype, in our population. We didn't find a prediction of non response for the rs8099917 GG genotype: OR 2.09, 95% CI 0.53-8.17, $p = 0.285$.

Prevalence of IL28B polymorphisms varies among different ethnic groups. Approximately 23-55% of African-Americans patients had the C allele of rs12979860, comparing with 53-85% of European-Americans and 90% of Chinese and Japanese patients.⁷ We don't have information about prevalence in our population. In our study, only 20-30% of the patients who had completed treatment agreed to participate. Presumably, in Hispanic patients of European ancestry (most of our patients ancestors are from Spain and Italy), it has to be similar to that reported from Caucasian patients in previous studies.

Given the high percentage of non response to PR treatment, there is a clear need to develop new antiviral drugs to increase SVR rates. Two protease inhibitors, telaprevir and boceprevir, are about to be approved for HCV treatment in combination with PR. The applicability of these findings in predicting SVR rates with direct antiviral agents has to be demonstrated in future studies.³³⁻³⁵

Our results showed that IL28B host genotypes can be added to predictors of treatment response to PR in Latin American patients with European ancestry.

CONFLICT OF INTEREST

None.

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