

# The interleukin 28B gene polymorphism, rs8099917, in patients with chronic hepatitis C and response to the treatment with pegylated interferon and ribavirin

Hamid Kalantari<sup>1</sup>, Bahram Bagherpour<sup>2</sup>, Tahmine Tavakoli<sup>1</sup>, Mahsa Khodadoostan<sup>1</sup>, Seyed Mehdi Hejazi<sup>3</sup>, Alireza Saadatmand<sup>1</sup>

<sup>1</sup>Department of Gastroenterology, Isfahan Liver Disease Research Center, <sup>2</sup>Acquired Immunodeficiency Research Center, <sup>3</sup>Health Information Technology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

**Background:** The present study aimed to determine the frequency of the IL28B polymorphism rs8099917 in patients with genotype 1 hepatitis C virus (HCV) infection treated with pegylated-interferon- $\alpha$ 2b (PEG-IFN- $\alpha$ 2b) and ribavirin (RBV) and its treatment outcome. **Materials and Methods:** The IL28B rs8099917 genotypes were determined among 100 HCV-infected patients and the viral load was also estimated. PEG-IFN- $\alpha$ 2b and RBV combination were administrated to the patients for 48 weeks and the treatment outcome was defined. **Results:** Sixty-seven (67%), 27 (27%), and 6 (6%) of 100 patients were determined as TT, GT, and GG genotype, respectively. The response rate to treatment was significantly higher in patients with TT genotype. **Conclusion:** According to the results of the present study, patients with IL28B rs8099917 TT genotype achieve higher sustained virological response than the GT and GG genotypes. Thus, when there are no alternatives, treatment with PEG-IFN- $\alpha$ 2b and RBV combination can be suggested in patients with IL28B TT genotype.

**Key words:** Chronic hepatitis C, interleukin 28B, pegylated interferon, ribavirin

**How to cite this article:** Kalantari H, Bagherpour B, Tavakoli T, Khodadoostan M, Hejazi SM, Saadatmand A. The interleukin 28B gene polymorphism, rs8099917, in patients with chronic hepatitis C and response to the treatment with pegylated interferon and ribavirin. *J Res Med Sci* 2019;24:12.

## INTRODUCTION

Combination therapy for chronic hepatitis C (CHC) currently has drastically improved the sustained virological response (SVR) rates, more pronounced in difficult-to-treat patients.<sup>[1]</sup> From the late 1990s, the therapy of hepatitis C was interferon or pegylated-interferon (PEG-IFN- $\alpha$ 2), first without and later with ribavirin (RBV) which resulted in overall constant SVR rates of about 33%–50% from 2005 to 2015.<sup>[2,3]</sup> Recently, oral direct-acting antiviral agents (DAAs) introduced for the treatment of hepatitis C which markedly improved SVR rates among the patients and it became rapidly widespread.<sup>[4]</sup> However,

the long-term effect of treatment with DAAs has not been determined yet.<sup>[5]</sup> Thus, DDAs still need to be evaluated, especially about drug resistance and if in the future resistance or other unwanted event happens, we may come back and use the traditional interferon therapy. A significant association between genetic variants in the IFN $\lambda$  (also called IFN lambda 3 and interleukin 28B) locus and the rate of spontaneous clearance of hepatitis C virus (HCV) is documented. Patients with the ancestral IFN $\lambda$ 4 allele are capable of producing a fully active IFN $\lambda$ 4, yet are not able to eliminate HCV in the acute phase and as a result, develop CHC with >90% of probability.<sup>[6]</sup> The present study was performed to determine the frequency of the IL28B rs8099917 genotypes in treatment-naive patients

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**Address for correspondence:** Dr. Alireza Saadatmand, Department of Gastroenterology, Isfahan Liver Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: alireza.saadatmand45@yahoo.com

**Received:** 06-08-2018; **Revised:** 26-09-2018; **Accepted:** 04-12-2018

infected with genotype 1 HCV treated with PEG-IFN- $\alpha$ 2b and RBV. The results could be useful for the treatment of CHC patients when for any reason such as possible future drug resistance, there is no alternative treatment such as DDAs available for the therapy.

## MATERIALS AND METHODS

In this study, 100 treatment-naive patients with CHC infected by HCV genotype 1 referred to Omid Hepatitis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, during 2014–2016 were enrolled in the study. Patients were previously diagnosed with the genotype 1 HCV infection having HCV RNA in serum. Genomic DNA was extracted from EDTA peripheral blood using the QIAamp DNA Blood Mini Kit. The extracted DNA kept frozen for further application. Viral load was quantified by TaqMan real-time polymerase chain reaction (PCR) using Artus<sup>®</sup> HCV RG RT-PCR Kit. Genotypes of the studied HCV were determined by TaqMan real-time PCR using HCV-FRT 1,2/3 kit. IL28B rs8099917 genotypes of the patients were determined using PCR-restriction fragment length polymorphism using the following primers; forward, 5'CCCACTTCTGGAACAAATCGTCCC3' and reverse, 5'TCTCCTCCCCAAGTCAGGCAACC3'. The amplicon was subjected to restriction enzymatic digestion using BseMI restriction endonuclease and studied by gel electrophoresis. The IL28B rs8099917 TT genotype produced a 552 bp fragment, the genotype GT produced three 552, 322 and 230 bp fragments and the genotype GG produced two 322 and 230 bp fragments.<sup>[7]</sup> Patients were treated for 48 weeks with the standard dosage of PEG-IFN $\alpha$ -2b (PEG-INTRON, Behestan Darou, Iran) and a weight-based dose of RBV (Rebetol), 1000 mg/day for <75 kg and 1200 mg/day for  $\geq$ 75 kg.<sup>[8]</sup> HCV RNA viral load was determined at the end of therapy and 6 months after the therapy. The treatment outcome was defined as null virological response (NVR), SVR, and relapse.<sup>[8]</sup> This study is approved under the project number of 396014 and ethical approval number of IR. MUI.REC.1396.30014.

## RESULTS

Of the 100 patients, 74% were male and 22% were female. Treatment outcome among patients with different IL28B rs8099917 genotypes is available in Table 1. No significant difference was observed for the treatment outcome among males and females and also the genotypes' frequency was not different significantly among sexes. There was a significant relationship between the three studied genotypes and the treatment outcome ( $P < 0.001$ ), showing a higher frequency of TT genotype among SVR treatment outcome [Table 1].

**Table 1: Treatment outcome among patients with different IL28B rs8099917 genotypes**

Response	Genotype, n (%)			Total	P
	TT	GT	GG		
SVR	51 (85)	9 (15)	0 (0)	60	<0.001
Relapse	8 (53.3)	7 (46.7)	0 (0)	15	
NVR	8 (32)	11 (44)	6 (24)	25	
Total	67 (67)	27 (27)	6 (6)	100	

SVR=Sustained virological response; NVR=Null virological response

## DISCUSSION

The results showed that the IL28B rs8099917 TT genotype is predominant among the studied patients followed by GT and the least prevalent was the GG genotype. More than half of the patients were determined as SVR, and a quarter was refractory to the treatment. Higher frequency of SVR rate was observed among IL28B rs8099917 TT genotype, which is representative of well treatment response in patients' with the TT genotype.

Traditional therapy for CHC is PEG-IFN-alpha plus RBV, which sometimes does not result in a sustained SVR in all patients,<sup>[9]</sup> yet a significant association between genetic variants in the IFN $\lambda$  (interleukin 28B, IL28B, also called IFN $\lambda$ 3) locus and the rate of spontaneous clearance of HCV is documented.<sup>[6]</sup> Patients with the IL28B rs8099917 TT genotype are reported to be associated with a higher probability of spontaneous and treatment-induced HCV clearance than IL28B rs8099917 G allele carriers.<sup>[7]</sup>

In 2009, Tanaka *et al.* reported a genome-wide association study of NVR in the therapy of patients with HCV genotype 1 in the Japanese population. They reported two single nucleotide polymorphisms (SNPs) close to the IL28B gene (rs12980275 and rs8099917) on the chromosome 19 to be notably associated with NVR. They added that these SNPs are also in association with SVR (rs12980275 and rs8099917).<sup>[9]</sup> According to the results of the present study, patients with IL28B rs8099917 TT genotype achieve higher SVR than the GT and GG genotypes. In another study, conducted by Kalantari *et al.*, IL28B rs12979860 CC genotype was reported to be more important than IL-28B-CT/TT in predicting positive treatment response.<sup>[10]</sup>

Sakhaee *et al.*, studied the impact of genetic variation in IL28B, IFNL4 and HLA genes on responses to treatment (PEG-IFN- $\alpha$ , RBV) among 520 Iranian patients with CHC. They reported that in patients with achieved SVR, IL28B rs12980275, and rapid virologic response in all HCV genotypes and IFNL4 ss469415590, IL28B rs12979860, and HLA rs4273729 in HCV subtypes 1a, 1b, and 3a were the very convenient predictor factors for treatment

outcome.<sup>[11]</sup> In the present study, a similar result regarding the SVR rate was observed in IL28B rs8099917 TT genotype, which seems to be a very good positive predictive factor for SVR.

### Limitations

There are some factors that can alter the response to medication, such as level of fibrosis that may affect the outcomes among patients.

### CONCLUSION

According to the results of the present study patients with IL28B rs8099917 TT genotype achieve higher SVR rate than the GT and GG genotypes. Thus, when there are no alternatives such as DDAs resulted from any reason such as drug resistance or availability, treatment with PEG-IFN- $\alpha$ 2b and RBV combination can be suggested in patients with IL28B TT genotype to be more effective.

### Acknowledgments

The authors would like to thank Vice-chancellor of Research and Technology, Isfahan University of Medical Sciences, Isfahan, Iran for approval and financial support of this study.

### Financial support and sponsorship

Vice-chancellor of Research and Technology, Isfahan University of Medical Sciences, Isfahan, Iran.

### Conflicts of interest

There are no conflicts of interest.

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