

The effects of IL28B rs12979860 and rs8099917 polymorphism on hepatitis B infection

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ABSTRACT

OBJECTIVE: The purpose of this study was to evaluate the relationship of IL28B rs12979860 and rs8099917 polymorphisms with the clinical, histological, and virological outcomes of patients with chronic hepatitis B (CHB) also the treatment responses of patients who received Nucleos(t)ide analogs (NAs) therapy.

METHODS: This study included 152 CHB patients who were underwent liver parenchymal biopsy. The IL28B rs12979860 and rs8099917 polymorphism were genotyped using the TaqMan assay.

RESULTS: The IL28B rs12979860 CC and IL28B rs8099917 TT were identified as the genotypes with the highest frequency in all patients. On the other hand, IL28B rs12979860 TT and IL28B rs8099917 GG were the genotypes with the lowest frequency. The frequency of IL28B rs8099917 TG genotype was significantly different between patients with hepatitis B, who has histologically defined liver cirrhosis and no-fibrosis ($p=0.02$). In addition, a statistically significant correlation was found between the presence of IL28B rs8099917 G allele and virological unresponsiveness to NAs treatments in CHB patients ($p=0.028$).

CONCLUSION: The presence of the IL28B rs8099917 G allele in CHB patients might be associated with the risk of developing cirrhosis and virological unresponsiveness to NAs treatments.

Keywords: Chronic hepatitis B; cirrhosis; interleukin 28B; treatment response.

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Chronic liver diseases such as cirrhosis and hepatocellular carcinoma (HCC), which can be caused by hepatitis B Virus (HBV), continue to be an important public health problem. HBV is the most significant viral hepatitis factors, affecting more than 300 million people with more than 0.8 million deaths worldwide [1]. The

natural course of chronic HBV infection and the host factors of the virus-infected individuals can be determinative on the pathogenesis and the progression of the liver diseases they are associated with. The human immune system can impact the pathogenesis, clinical course, and outcomes of viral and non-viral liver diseases [2].



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Interferons lambda (IFN- λ s; IFNL1-4), classified as type III IFN, is a cytokine that plays a role in the formation of antiviral immune responses, encoded by interleukin 28B (IL28B) which mostly acts on epithelial surfaces [3]. It has been suggested that IL28B rs12979860 and rs8099917 polymorphisms may be associated with spontaneous clearance, clinical and histological outcomes of chronic viral hepatitis caused by HBV. In general, IL28B rs12979860CC and rs8099917 TT genotypes are reported as favorable genotypes, due to the reduced risk of advanced liver damage such as HBV related cirrhosis and HCC, and the positive effects on the clinical course and outcomes of the patients as well. On the other hand, the genotypes characterized by the presence of computer tomography and TT polymorphisms for rs12979860 and TG and GG minor allele polymorphisms for rs8099917 are considered unfavorable genotypes due to their negative effects on the clinical course and outcomes of patients with HBV related increased risk of cirrhosis, and HCC [4–7].

Some studies have reported that there is no relationship between IL28B rs1297986 and rs8099917 polymorphisms and the virological and clinical outcomes of patients. In addition, they found no correlation between IL28B rs1297986 and rs8099917 polymorphisms and the risk of developing HBV related cirrhosis and HCC [8]. The data on the effects of IL28B rs12979860 and rs8099917 genotypes in treatment response of patients with chronic hepatitis B (CHB) receiving nucleos(t)ide analog (NA) therapy are limited [5, 9]. In addition, most studies conducted for this purpose included patients who developed HBV related cirrhosis and HCC. The data on the association of IL28B polymorphisms with liver histology, clinical, and virological characteristics of patients with CHB are limited.

Purpose of this study was to evaluate evaluate the IL28B rs12979860 and rs8099917 gene polymorphisms among the patients with CHB who underwent liver biopsy, in terms of: (a) determination of genotype and frequency, (b) analysis of the relationship between the biochemical, virological, clinical and histological results of patients with viral hepatitis, and (c) the relationship between the treatment responses of patients with CHB who received Nucleos(t)ide analogs (Nas) therapies.

MATERIALS AND METHODS

This study was supported by the Scientific Research Projects Coordination Unit of Istanbul University with the project number TSA-2018-30611. The ethics ap-

Highlight key points

- In a total of 152 patients, the association of rs12979860 and rs8099917 polymorphisms at IL28B gene with CHB patients was evaluated.
- No significant association was found between the demographic and clinical laboratory data of CHB patients, virological data including HBV DNA levels, and IL28B rs12979860 and IL28B rs8099917 polymorphisms.
- The presence of the IL28B rs8099917 G allele in CHB patients may be associated with the risk of developing cirrhosis and virological unresponsiveness to NAs treatments.

proval of the study was provided by Istanbul University Ethics Committee at Istanbul Faculty of Medicine (no: 2018/895). All patients included in this study gave informed consent for participation. The study was carried out in accordance with the Helsinki Declaration.

Patients

In the present study, a total of 152 patients were followed up by the Gastroenterohepatology Department of Istanbul University Istanbul Faculty of Medicine, for CHB, whose liver parenchymal biopsy was performed. Anti-HCV antibodies of patients with CHB were seronegative. All patients were seronegative for human immunodeficiency virus antibodies. Furthermore, patients with such conditions such as HDV co-infection, presence of autoimmune and hereditary liver diseases (such as Wilson and hemochromatosis), and alcohol-induced liver disease were excluded from the study.

Clinical Materials

Liver biopsies were performed in the Interventional Radiology Unit of the Radiology Department and in the Gastroenterohepatology Department of Internal Medicine, in Istanbul Faculty of Medicine. One set of liver-tissue specimens was preserved in Hollande's fixative and sent to the Pathology Department for evaluation. A second tissue fragment or another biopsy sample was immediately snap-frozen in liquid nitrogen and kept at 80°C before use for genotype analysis.

DNA Extraction from Liver-biopsy Specimens

The total genomic DNA was extracted from each liver-tissue sample using a commercially available kit (QIAamp DNA Mini kit, Qiagen GmbH, Hilden, Germany). PCR products were purified by using one commercial kit

(E.Z.N.A.® Cycle Pure Kit; Omega). Measured of DNA concentrations were carried out by spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, USA).

IL28B Genotyping

Genotyping of IL28B rs12979860 rs8099917 was performed using TaqMan SNP Genotyping Assay. The Allele discrimination plots and analysis of results were performed through StepOne Software (Applied Biosystems, Foster City, CA, USA).

Liver Histopathology

Histology of liver biopsy specimens was evaluated in the Department of Pathology of Istanbul Faculty of Medicine, Istanbul University. Liver biopsy samples were fixed in a formalin solution and stained with Masson's trichrome. Inflammation and fibrosis for CHB patients were assessed by modified Ishak scoring system [10]. Patients were divided into groups in terms of inflammation: minimal/mild (0–7), moderate (8–11), and severe (12–18), and fibrosis: none/mild (0–1), moderate/severe (2–4), and cirrhosis (5–6).

Clinical Laboratory Data

Demographic and pre-biopsy patient data including HBV DNA viral load were obtained from patient files or from the hospital's electronic data management system (Table 1).

Anti-HBV Treatment and Virological Response

The study included 74 CHB patients who received NAs therapy and whose serum/plasma HBV DNA results could be obtained at least 1 year and after the treatment. 44 (57.14%) patients received tenofovir disoproxil fumarate, 21 (28.37%) received entecavir (ETV), and 9 (12.16%) received tenofovir alafenamide fumarate. The level of HBV DNA measured in the 1st year of anti-HBV therapy was below the detectable level by PCR that was evaluated as the virological response, the presence of measurable level of HBV DNA was considered as virological unresponsiveness.

Statistical Analysis

Descriptive statistics were used to describe the continuous variables (Mean, standard deviation). Comparison of two independent and normally distributed variables was performed using the Student's t-test. The comparison of

TABLE 1. Demographic, clinical, clinical laboratory and histopathological characteristics of the patients

Data	CHB (n=152)
Mean age±SD (years)	43.33±13.31
Gender (M/F)	74/78
Clinical laboratory	
ALT (U/L), mean±SD	46.66±62.14
AST (U/L), mean±SD	65.71±121.21
ALP (U/L), mean±SD	74.63±26.86
GGT (U/L), mean±SD	31.26±35.45
Total bilirubin (mg/dl), mean±SD	0.71±1.15
Direct bilirubin(mg/dl), mean±SD	0.35±0.98
Indirect bilirubin (mg/dl), mean±SD	0.35±0.25
INR, mean±SD	1.02±0.12
AFP (ng/ml), mean±SD	3.96±4.37
Albumin (g/dl), mean±SD	4.51±0.45
Platelet count (106/ml), mean±SD	233.32±58.24
Histology	
Inflammation (Grade) mean±SD	4.97±2.84
Fibrosis (Stage), mean±SD	2.05±1.32

ALT: Alanine aminotrasferase; AST: Aspartate aminotrasferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio; AFP: Serum alpha-fetoprotein; M: Male; F: Female; SD: Standard deviation.

two independent and non-normally distributed variables was made using the Kruskal–Wallis or Mann–Whitney U test. The independent variable effects on the dichotomous dependent variable were investigated by Logistic Regression Analysis. Analyses were performed using IBM SPSS Version 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp, Chicago/USA). Linkage disequilibrium, between pairwise SNPs, was calculated using Haploview software. Hardy-Weinberg equilibrium (HWE), allele frequencies, and genotype distributions were analyzed using the Chi-square test. Statistical significance level was determined as 0.05.

RESULTS

The Demographic, Clinical, and Histopathological Characteristics of Patients

Table 1 summarizes the demographic, clinical, clinical laboratory, and histopathological data of the total 152 patients, consisting of 74 (48.7%) men, 78 (51.3%) women, with a mean age of 43.33±13.31 years. Histologically, the mean inflammation grade of patients with CHB was 4.97±2.84 and mean fibrosis stages were 2.05±1.32.

TABLE 2. IL 28B genotype and frequency of patients

Patients	rs12979860			rs8099917*		
	CC (%)	CT (%)	TT (%)	TT (%)	TG (%)	GG (%)
CHB (n=152)*	49.34	39.47	11.18	71.05	22.37	6.58

Major allele: C. Minor allele: T. for rs12979860. Major allele: T. Minor allele: G. for rs8099917. *: HWE: Hardy-Weinberg Equilibrium was $p < 0.05$; CHB: Chronic hepatitis B.

The Genotype and Frequency of IL28B rs12979860 and rs8099917

The genotypes and frequencies detected for IL28B rs12979860 and rs8099917 polymorphisms in this study are shown in Table 2. No deviation from HWE for rs12979860 and rs8099917 at IL28B gene was found in both patient groups (χ^2 tests, $p \geq 0.05$) except rs8099917 for CHB patient groups (χ^2 tests, $p < 0.05$). The IL28B rs12979860 CC and IL28B rs8099917 TT were identified as the genotypes with the highest frequency in all patients. On the other hand, IL28B rs12979860 TT and IL28B rs8099917 GG were the genotypes with the lowest frequency.

IL-28B Polymorphisms in Patients with CHB

Table 3 summarizes the clinical laboratory virological and histological data of CHB patients, as well as IL28B genotypes and frequencies. Accordingly, no significant association was found between the demographic and clinical laboratory data of CHB patients, virological data including HBV DNA levels, and IL28B rs12979860 and IL28B rs8099917 polymorphisms. In this study, a statistically significant difference was found between the IL28B rs8099917 TG genotype frequencies of patients with histologically defined liver cirrhosis (fibrosis stage; F 5–6) and those defined as no-fibrosis (F0) ($p = 0.02$) (Table 3). Nevertheless, no statistically significant relationship was identified between genotypes of IL28B rs8099917 other than the TG genotype and IL28B rs12979860 polymorphisms; and histological data including necro-inflammatory activity grade and fibrosis stages of the patients.

Association between IL-28B Polymorphism and Outcome of Treatment with anti-HBV in Patients with CHB

Measurable levels of serum HBV DNA were detected in 5 (11.90%) of 42 patients with IL28B rs12979860 CC genotype and in 8 (25.0%) of 32 patients with non-CC gen-

otype (CT and TT) in the 1st year ($p > 0.05$). Measurable levels of serum HBV DNA were detected in the 1st year in 7 (12.28%) of 57 patients with the IL28B rs8099917 TT genotype, and 6 (35.29%) of 17 patients with a non-TT genotype (TG and GG) ($p = 0.028$) (Table 3).

DISCUSSION

In our study population, the frequencies of IL28B rs12979860 CC and IL28B rs8099917 TT, which are described as favorable genotypes, were determined as 75 (49.34%) and 108 (71.05%), respectively (Table 2). The association between polymorphisms near the IL28B gene and occurrence, progression, and outcomes of the viral or non-viral liver diseases is quite challenging because of the studied geography, genetic background of populations, characteristics, and extent of patient groups, and other various factors, such as viral factors and so on. There is no clear consensus on the relationship between IL28B polymorphisms and the clinical course and consequences of chronic HBV infection. In some studies, it has been suggested that the presence of IL28B rs12979860 TT genotype and rs8099917 G allele is associated with the risk of developing HBV-associated HCC. Moreover, IL28B rs12979860 polymorphism is also associated with the persistence of HBV infection [4, 6, 7, 11, 12]. Nevertheless, it is reported that IL28B polymorphisms had no association with the clinical results of HBV infection overall including HBV-related HCC susceptibility. [8,13-15]

In this study, no relationship was identified between IL28B rs12979860 and rs8099917 gene polymorphisms and the demographic, clinical laboratory, and virological data of patients with hepatitis B. In addition, no relationship was identified between IL28B rs12979860 and IL28B rs8099917 genotypes other than the TG genotype and the histopathological results of the patients, including HBV-related liver damage stages. The frequency

TABLE 3. Demographic, clinical laboratory, virological histological characteristics, and response treatment with IL28B polymorphisms of patients with CHB

Data	rs12979860			rs8099917				
	CC (%)	CT (%)	TT n (%)	P	TT (%)	TG (%)	GG (%)	P
All patients (n=152)								
Mean age±SD (years)	43.33±13.31	42.87±13.77	43.88±11.83	NS	42.78±13.25	44±14.58	45.3±10.38	NS
Gender (M/F)	74/78	31/29	7/10	NS	54/54	16/18	4/6	NS
Clinical laboratory								
ALT (U/L), Mean±SD	46.66±62.14	41.1±40.41	33.18±14.6	NS	48.82±70.29	42.18±39.12	38.5±14.82	NS
AST (U/L), Mean±SD	65.71±121.21	49.23±53.85	50.76±40.72	NS	70.4±139.08	52.29±59.91	60.7±48.96	NS
ALP (U/L), Mean±SD	74.63±26.86	72.77± 23.09	71.24±21.96	NS	73.66±27.64	78.91±26.06	70.5±20.69	NS
GGT (U/L), Mean±SD	31.26±35.45	27.32±21.51	24.59±	NS	32.8±39.76	28.32±23.31	24.7±13.81	NS
AFP (ng/ml), Mean±SD	3.96±4.37	4.44±6.4	3.82±2.01	NS	4.12±5.06	3.39±1.4	4.18±2.48	NS
Viral factors								
HBV DNA log ₁₀	2.06E+07	2.57E+07	1.83E+07	NS	2.30E+07	1.11E+07	2.63E+07	NS
IU/ml (Mean±SD)	+8.98E+07	+1.32E+08	+4.38E+07		+1.03E+08	+3.65E+07	+5.51E+07	
Histology								
Inflammation (grade) Mean±SD	4.97±2.84	4.93±3.19	4.59±1.58	NS	4.73±2.79	5.74±3.19	4.9±1.6	NS
Inflammation score								
Minimal/mild (0–7)	84.21	38.28	13.28	NS	70.31	21.88	7.81	NS
Moderate (8–11)	11.84	50.00	0.00	NS	77.78	22.22	0.00	NS
Severe (12–18)	3.94	33.33	0.00	NS	66.67	33.33	0.00	NS
Fibrosis (stage) Mean±SD	2.05±1.32	2.03±1.47	1.94±1.09	NS	1.96±1.33	2.32±1.34	2±1.15	NS
Fibrosis score								
None (F0)	15.78	45.83	12.50	NS	79.17	12.50*	8.33	NS
Mild (F1–2)	53.94	39.02	9.76	NS	71.95	23.17	4.88	NS
Moderate/severe (F3–4)	25.00	31.58	15.79	NS	68.42	21.05	10.53	NS
Cirrhosis (F5–6)	5.26	62.50	0.00	NS	50.00	50.00*	0.00	0.02*
Treatment with nas								
TDF/ETV/TAF	44/21/9	16/9/2	4/0/1	NS	33/18/6	10/3/2	1/0/1	NS
Virological response/non-response	61/13	21/6	3/2	NS	50/7	10/5	1/1	0.028**

SD: Standard deviation; TDF: Tenofovir disoproxil fumarate; ETV: Entecavir; TAF: Tenofovir alafenamide fumarate; NS: Not significant; *: Frequencies of IL 28 rs8099917 TG genotype between patients with liver cirrhosis and no-fibrosis (p=0.02); **: Between the virological responses of IL28B rs8099917 TT genotype and patients other than TT genotype (TG/GG) to NAs therapies (p=0.028).

of IL28 rs8099917 TG genotype was found higher in patients with HBV-associated liver cirrhosis than in patients with no-fibrosis (F0) (Table 3). The small number of patients makes it difficult to make a final assessment. Based on the data obtained from this study, it can be suggested that the rs8099917 TG genotype and the presence of minor alleles may be associated with an increased risk of developing HBV-related cirrhosis in patients with CHB on an individual basis.

In this study, no statistically significant correlation was found between virological responses of chronic B patients to oral NAs therapies, and IL28B rs12979860 genotypes. On the other hand, a statistically significant difference was found between the virological responses of IL28B rs8099917 TT genotype and patients other than TT genotype (TG/GG) to NAs therapies ($p=0.028$) (Table 3). Therefore, based on these data, it can be suggested that the presence of the IL28B rs8099917 G allele may be associated with virological unresponsiveness to NAs therapies in patients with chronic B hepatitis. However, larger studies are needed to confirm this approach.

The limited number of patients with CHB included in this study and the low number of patients with advanced liver damage such as HBV associated cirrhosis, and also who received NAs therapy were limiting factors for this study. Hereafter, this study included patients with histologically chronic hepatitis, as shown in Table 1, rather than advanced liver damage such as HBV associated cirrhosis and HCC.

Conclusions

In conclusion, it is suggested according to the data obtained from this study that IL28B rs12979860 and rs8099917 polymorphisms are not associated with the clinical and histopathological outcomes of viral hepatitis B. Furthermore, in patients with CHB, it is suggested that IL28B rs12979860 polymorphisms and rs8099917 TT genotype are not associated with the clinical and histopathological results of the patients and the responses to NAs treatments. However, it can be revealed that IL28B rs8099917 TG genotype may be associated with virological unresponsiveness to NAs treatments and the risk of developing cirrhosis in patients with CHB.

Ethics Committee Approval: The Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 13.06.2018, number: 2018/895).

Conflict of Interest: No conflict of interest was declared by the authors.

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