Research Article

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Treatment Response to Oral Antivirals in Chronic Hepatitis B Patients: Assessment of Polymorphism in the IL-28B Gene (rs809991)

Kronik Hepatit B Hastalarında Oral Antivirallere Tedavi Yanıtı: *IL-28B* Gen Polimorfizminin (rs809991) Değerlendirilmesi

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ABSTRACT

Objectives: Chronic hepatitis C treatment response is strongly associated with interleukin 28B (IL-28B) single nucleotide gene polymorphism (SNP). In this study, we aimed to investigate the association of the IL-28B rs8099917 SNP with the first-year virological response in chronic hepatitis B (CHB) patients receiving antiviral treatment.

Materials and Methods: We enrolled 100 CHB patients over the age of 18 years who had been on oral antiviral treatment for at least a year. IL-28B rs8099917 SNP was analyzed from the blood samples by polymerase chain reaction. The first-year virological response was investigated retrospectively.

Results: No statistically significant association was found between the IL-28B rs8099917 SNP and first-year virological response (p=1.000). The mean age of patients who did not obtain a first-year virological response was significantly lower than that of those who did (p=0.022), and the median values of alanine aminotransferase (xULN) and hepatitis B virus (HBV)-DNA $\log_{10}$ IU/mL were higher (p<0.001 and p<0.001, respectively). The first-year virologic response rate was significantly lower in hepatitis B e antigen-positive patients than in negative patients (p<0.001). In the multivariate model, it was found that having a high HBV-DNA level was strongly linked to not having a first-year virological

ÖZ

Amaç: Kronik hepatit C tedavisine yanıt, interlökin-28B (IL-28B) tek nükleotid polimorfizmi (SNP) ile güçlü bir şekilde ilişkilendirilmiştir. Bu araştırmada antiviral tedavi alan kronik hepatit B (KHB) hastalarında IL-28B rs8099917 SNP'nin birinci yıl virolojik yanıt ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Araştırmaya, en az bir yıldır oral antiviral tedavi gören 18 yaş üstü 100 KHB hastasını dahil ettik. IL-28B rs8099917 SNP, kan örneklerinden polimeraz zincir reaksiyonu ile analiz edildi. İlk yıldaki virolojik yanıt geriye dönük olarak araştırıldı.

Bulgular: IL-28B rs8099917 SNP ile birinci yıl virolojik yanıt arasında istatistiksel olarak anlamlı bir ilişki bulunamadı (p=1,000). Birinci yılda virolojik yanıt sağlanamayan hastaların ortalama yaşı, sağlanabilenlere göre istatistiksel açıdan anlamlı olarak daha düşük (p=0,022), alanin aminotransferaz (xULN) ve hepatit B virüs (HBV)-DNA $\log_{10}$ IU/mL ortanca değerleri daha yüksekti (sırasıyla; p<0,001 ve p<0,001). Birinci yıldaki virolojik yanıt oranı, hepatit B e antijen pozitif hastalarda negatif hastalara göre istatistiksel açıdan anlamlı derecede düşüktü (p<0,001). Çok değişkenli modelde, yüksek düzeyde HBV-DNA'ya sahip olmanın, ilk yılda virolojik yanıtın olmamasıyla güçlü bir şekilde bağlantılı olduğu bulundu (risk oranı: 1,995, %95 güven aralığı: 1,311-3,036, p=0,001).

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response (risk ratio: 1.995, 95% confidence interval 1.311-3.036, p=0.001).

Conclusion: An association between IL-28B SNP and first-year virological response was not found in patients with CHB. Studies assessing different IL-28B SNPs are warranted to understand the factors affecting treatment response.

Keywords: Chronic hepatitis B, single nucleotide polymorphism, treatment response, interleukin-28B

Sonuç: KHB hastalarında IL-28B SNP ile birinci yıl virolojik yanıtı arasında bir ilişki bulunamamıştır. Tedavi yanıtını etkileyen faktörleri anlamak için farklı IL-28B SNP'lerini değerlendiren çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kronik hepatit B, tek nükleotid polimorfizmi, tedavi yanıtı, interlökin-28B

Introduction

Chronic hepatitis B (CHB) is one of the main causes of cirrhosis and hepatocellular carcinoma, making it a serious health concern. Interferon-alpha (IFN-α) is an antiviral protein used for treating CHB. IFN-λ induces a signaling pathway similar to IFN-α and thus shows antiviral activity. IFN-λ3, also known as interleukin-28B (IL-28B), exerts an antiviral effect via IFN-stimulated gene (ISG) up-regulation (1). Chronic hepatitis C (CHC) treatment response was strongly associated with IL-28B single nucleotide gene polymorphism (SNP) (2,3,4,5). However, studies with peg-IFN treatment and IL-28B SNP in patients with CHB have had conflicting results (6,7,8,9,10), and there are few studies on the response to oral antiviral treatments. The aim of this study was to evaluate the influence of IL-28B rs8099917 SNP and other factors on the first-year virologic response to oral antiviral treatment in patients with CHB.

Materials and Methods

Study Design, Selection of Cases, and Collection of Data

This research is a retrospective descriptive study. We included 100 CHB patients who had received oral antiviral agents for at least one year, aged 18 years and older, and who came to the Ankara Training and Research Hospital, Infectious Diseases and Clinical Microbiology Department from December 1, 2016, to January 1, 2017, in the study. Patients who were not compliant with treatment, were under 18 years of age, had a malignancy, metabolic or immunological disease, CHC or HIV infection, became pregnant during treatment, or received immunosuppressive therapy, systemic corticosteroids, or chemotherapy were excluded. Demographics, laboratory, and treatment information were retrospectively collected from patient records. The patients underwent liver biopsy before treatment. Biopsy results were analyzed as defined by Ishak et al. (11), and modified histological activity index (HAI) scores and fibrosis stages were recorded. Alanine aminotransferase (ALT) values, hepatitis B serology, and HBV-DNA levels measured during therapy were recorded. Hepatitis B surface antigen, anti-HBs, hepatitis B e antigen (HBeAg), and anti-HBe were examined with the (ELISA) method using the Roche Diagnostics/Cobas 6000 e601 analyzer. The HBV-DNA test was performed using a Qiagen polymerase chain reaction (PCR) kit (Artus Qiagen GmbH, Hilden, Germany).

The upper limit of normal (ULN) for ALT was 40 U/L, as determined by laboratory reference ranges. The ALT (xULN) value was calculated using the formula (ALT/ULN) to evaluate how many times the ALT value was the ULN.

The first-year virological response was defined as having an HBV-DNA level below the detectable limit at the end of the first year in patients with CHB treated with oral antivirals.

IL-28B Gene Polymorphism Analysis

Under the supervision of the investigator, 5 mm of the patients' blood was drawn into EDTA tubes. and stored at -80 °C in the laboratory of Ankara Numune Training and Research Hospital until examination. The extraction of genomic DNA from the blood samples was performed using theGeneMATRIX Quick Blood DNA Purification Kit, as per the manufacturer's recommendations. For PCR analysis, PCR buffer, MgCl2, dNTP mix, forward and reverse primers, Taq DNA polymerase, and DNA template components were prepared. The SNP of rs8099917 near IL-28B was investigated. PCR conditions were applied to the prepared samples. The target region of the *IL-28B* gene was amplified in a Kyratec thermocycler using the primer pair TCCATGTGTTTTATTTGTGC and GGAGAATGCAAATGAGAGA. The obtained PCR products were carried out by electrophoresis at 100 volts for 70 min on a 1.5% agarose gel prepared with 1x TAE buffer. The image was taken under UV light with ethidium bromide dye. After purification, PCR products were sent for DNA sequencing, which was performed unidirectionally in Macrogen with an ABI 3730XL automated sequencer device (Applied Biosystems, Foster City, CA) and BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems). BLAST analysis was performed using the obtained sequence analysis results and gene bank data for each sample and its type was determined. SNP genotyping analysis was performed by aligning with the sequence analysis results using the online Multalin program.

Statement of Ethics

Research ethics committee approval was obtained from the Ankara Numune Training and Research Hospital Ethics Committee (approval number: 990/2016, date: 29.06.2016). Informed consent was obtained from the patients.

Statistical Analysis

The study statistics were made using the IBM Statistical Package for the Social Sciences (SPSS) Version 22.0 (Armonk, NY: IBM Corp) program. The conformity of the variables to the normal distribution was examined using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Chi-square, Fisher's exact test, independent samples t-test, and Mann-Whitney U tests were used for statistical evaluation. Whether the possible factors identified in the previous analyses to predict treatment outcome

were independent predictors was examined by logistic regression analysis in multivariate analysis. The Hosmer-Lemeshow test was used for model fit. A p-value 0.05 was considered statistically significant. Power analysis was conducted with a power of 80% and a margin of error of 0.05 using the G*Power 3.1.9.2 program. The analysis revealed that a minimum sample size of 64 participants was required to achieve adequate statistical power. The statistical significance level was set at 0.05.

Results

In this study, we enrolled 100 CHB patients who had been on oral antiviral treatment for at least a year. Because one patient was excluded because genotyping could not be performed, 99 patients were included in the study. The mean age of the patients was 44±11.7 years, and 54 (54.5%) were female. The median initial ALT was 30 U/L (minimum-maximum: 6-282 U/L), ALT (xULN) was 0.75 (minimum-maximum: 0.15-7.05) and HBV-DNA value was 4.36 log10 IU/mL (minimum-maximum: 3-10 log10 IU/mL). HBeAg positivity was detected at the beginning of treatment in 20 (20.2%) patients. 22 (22.2%) of the patients were receiving treatment with lamivudine, 20 (20.2%) with telbivudine, 24 (24.2%) with entecavir, and 33 (33.3%) with tenofovir disoproxil fumarate (TDF).

A liver biopsy could not be performed in the two patients before treatment. For patients who underwent biopsy, the median HAI score was 4 (minimum-maximum: 0-14) and the fibrosis stage was 2 (minimum-maximum: 0-5). Genotyping of rs8099917 near IL-28B revealed that 63 (63.7%) patients had the TT genotype and 36 (36.3%) had the non-TT genotype [34 (34.3%) with GT and 2 (2%) with GG]. There was no difference between the TT and non-TT genotype groups in gender, HBeAg positivity rate, mean age, HAI score, fibrosis stage, ALT (xULN), and HBV-DNA log10 IU/mL levels (p>0.05 for each) (Table 1).

Virological Response

The virological response was observed in 77 (77.7%) patients during the first year. No difference in the first-year virological response rate was found between the IL-28B rs8099917 TT and non-TT genotype groups (p=1.000) (Table 1).

The mean age of patients who did not obtain a first-year virological response was found to be significantly lower than that of those who did (p=0.022). The median values of ALT (xULN) and HBV-DNA $\log_{10}$ IU/mL were significantly higher in patients who did not achieve a first-year virological response than those who did (p<0.001 and p<0.001, respectively). HBeAg-positive patients had a significantly lower first-year virological response rate than HBeAg-negative patients (p<0.001) (Table 1). The multivariate model was performed using the variables of age, ALT (xULN), HBV-DNA $\log_{10}$, HBeAg positivity, and IL-28-B rs8099917 TT genotype. Having a high initial HBV-DNA $\log_{10}$ IU/mL level was statistically significant for lack of first-year virological response (risk ratio: 1.995, 95% CI: 1.311-3.036, p=0.001) (Table 2).

Discussion

There were 63.7% TT genotypes and 36.3% non-TT (34.3% GT, 2% GG) genotypes for IL-28B rs8099917 in our study. As stated in other studies, the dominant genotype was found to be TT (8,12,13).

Table 1. Distribution of patients' IL-28B rs8099917 genotypes and first-year virological responses

		IL28-B rs8099917 genotype		p-value	The first-year virological response		p-value
		TT*, (n=63)	Non-TT*, (n=36)		No†, (n=22)	Yes†, (n=77)	
Gender; (n %)	Female	35 (55.6)	19 (52.8)	0.789**	14 (25.9)	40 (74.1)	0.332**
	Male	28 (44.4)	17 (37.8)		8 (17.8)	37 (82.2)	
Age (years)‡; (mean ± SD)		44.2±11.1	43.6±12.8	0.801††	38.9±12.1	45.4±11.2	0.022††
ALT (×ULN)‡; [median (min.-max.)]		0.83 (0.15-7.05)	0.68 (0.35-7.03)	0.948‡‡	1.8 (0.45-4.48)	0.65 (0.15-7.05)	<0.001‡‡
HBV-DNA ($\log_{10}$ IU/mL)‡; [median (min.-max.)]		4.5 (3.3-9)	4.1 (3.3-9.8)	0.779‡‡	7.5 (4-10)	4 (3-9)	<0.001‡‡
HBeAg; (n, %)*‡	Negative	47 (74.6)	32 (88.9)	0.089**	10 (12.7)	69 (87.3)	<0.001§§
	Positive	16 (25.4)	4 (11.1)		12 (60)	8 (40)	
HAI§; [median (min.-max.)]		4 (0-14)	4 (2-11)	0.620‡‡	5 (0-12)	2 (0-5)	0.153‡‡
FS§; [median (min.-max.)]		2 (0-5)	2 (0-4)	0.814‡‡	4 (1-14)	2 (1-5)	0.772‡‡
Antiviral treatment (n %)	Lamivudine	14 (22.2)	8 (22.2)	0.372**	6 (27.3)	16 (72.7)	0.212**
	Telbivudine	16 (25.4)	4 (11.1)		1 (5)	19 (95)	
	Entecavir	14 (22.2)	10 (27.8)		7 (29.2)	17 (70.8)	
	Tenofovir disoproxil fumarate	19 (30.2)	14 (38.9)		8 (24.2)	25 (75.8)	
IL28-B rs8099917 genotype; (n %)	TT		-		14 (22.2)	49 (77.8)	1.000**
	Non-TT				8 (22.2)	28 (77.8)	

*Column percentage, †Row percentage, ‡At the beginning of treatment, §Since liver biopsy did not performed in two patients, the data of 97 patients were used, **Chi-square test was used, ††Independent samples t-test was used, ‡‡Mann-Whitney U test was used, §§Fisher's exact test was used. ALT: Alanine aminotransferase, ULN: Upper limit of normal (accepted as 40 U/L), HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen, HAI: Histology activity index, FS: Fibrosis score

Table 2. Risk factors for failure to achieve a first-year virological response

Risk factor	RR (95% CI)	p-value
Age	0.953 (0.902-1.007)	0.085
ALT (xULN)*	0.929 (0.553-1.563)	0.783
HBV-DNA (log_{10} IU/mL)*	1.995 (1.311-3.036)	0.001
HBeAg positivity*	3.324 (0.756-14.614)	0.112
IL-28-B rs8099917 TT genotype	1.175 (0.275-5.024)	0.112

*At the beginning of treatment. ALT: Alanine aminotransferase, ULN: Upper limit of normal (accepted as 40 U/L), HBV: Hepatitis B virus, HBeAg: Hepatitis B e antigen, RR: Risk ratio, CI: Confidence interval

It is known that there is a relationship between the CHC treatment response and IL-28B SNPs. The IL-28B rs8099917 TT genotype was associated with a higher virological response to peg-IFN and ribavirin (5), and the GG genotype was associated with a higher early virological response rate to direct-acting antiviral therapy (14). Patients with the rs8099917 TG and GG genotypes had an increased risk of null virological response in dual CHB and CHC infection (15). IL-28B rs12979860 and rs8099917 SNPs were related to the peg-IFN response in patients with chronic hepatitis D (16). However, few studies have investigated the association of IL-28B SNP with oral antiviral treatment response in patients with CHB. No relationship was observed between the IL-28B rs12979860 SNP and virological response to oral antiviral therapy or peg-IFN therapy in patients with CHB (17). Yu et al. (18) found that CHB patients with the rs8099917 GT genotype were associated with better treatment response to lamivudine, whereas Cakal et al. (19) reported that there was no relationship between rs8099917 genotypes and virological response to entecavir, TDF, and tenofovir alafenamide fumarate treatments. In our study, no relationship was found between the IL-28B rs8099917 genotype groups and first-year virological response to oral antiviral treatment in CHB patients (p=1.000). IFN-λ shows antiviral activity by inducing a signaling pathway similar to IFN-α. It is thought that the IL-28B pathway contributes more to the response to hepatitis C virus infection than to hepatitis B virus infection (20). In addition to activating ISG expression, IFN-λ may also induce other antiviral signaling pathways that may be important in the hepatitis C virus (21). This may help explain why we failed to link the IL-28B SNP to the virological response in patients with CHB.

The virological response rates were lower in HBeAg-positive patients treated with entecavir (22) and telbivudine (23) than in HBeAg-negative patients. However, Lim et al. (24) reported that baseline HBeAg status does not affect the virological response of patients with CHB receiving adefovir treatment. HBeAg-positive patients in our study exhibited a lower virological response rate than HBeAg-negative patients, although multivariate analysis did not statistically confirm this link.

Studies have shown a relationship between age and virological response. It has been reported that the rate of virological response to adefovir treatment is higher in older patients (24). A study by Ono et al. (25) evaluated treatment response in patients receiving entecavir. In univariate analysis, being over 40 years of age was found to be a factor associated with the first-year virological response, but no significant relationship was found when multivariate analysis was performed. Similarly, we found that patients with first-year virological response had a higher mean age than those without (p=0.022), but age was not evaluated as a risk factor in multivariate analysis.

Zeuzem et al. (26) reported that HBeAg-positive patients with HBV-DNA values below 9 log_{10} copies/mL and HBeAg-negative patients whose HBV-DNA values were below 7 log_{10} copies/mL before treatment had a higher virological response rate with telbivudine treatment than those with the above. CHB patients receiving entecavir therapy with HBV-DNA levels above 7.3 log_{10} copies/mL were found to have a lower first-year virological response rate (70.4%) than those with lower HBV-DNA levels (88.7%) (27). Ono et al. (25) reported that an HBV-DNA value below 7.6 log_{10} copies/mL was associated with a first-year virological response to entecavir treatment. Consistent with the literature, we found that the median HBV-DNA log_{10} value of patients who did not obtain a first-year virological response was higher than that of those who did (p<0.001) and this relationship was statistically significant in multivariate analyses.

Patients with ALT above 2xULN were found to have a higher virological response rate to telbivudine in the second year of treatment (26). Tsai et al. (28) found that patients with initial ALT values higher than 2xULN showed a better first-year virological response rate. However, Lim et al. (24) reported no significant relationship between ALT levels and the rate of virological response to adefovir therapy. In contrast to other studies in the literature, we found that patients who did not obtain a first-year virological response had a significantly higher median ALT (xULN) value compared with those who did (p<0.001) but this association could not be demonstrated in the multivariate model.

Study Limitations

The first limitation of this study is that it is retrospective. Therefore, examining the factors affecting response to treatment was not comprehensive. As a limitation of the study, it is stated that treatment groups (such as lamivudine, entecavir, etc.) of CHB patients were not shown homogenous distribution according to the retrospective study design. The other limitation is that we only tested one SNP near IL-28B. Hence, evaluation of other IL-28B SNPs could not be performed.

Conclusion

No association between IL-28B rs8099917 SNP and first-year virological response to oral antiviral therapy in patients with CHB was found in our study. There are very few studies in the literature investigating the link between IL-28B SNP and oral antiviral treatment response in patients with CHB. We believe that studies examining not only different IL-28B SNPs but also other cytokine polymorphisms are warranted. Thanks to these studies, it will be possible to identify markers that will help predict treatment response in patients with CHB.

Ethics

Ethics Committee Approval: Research ethics committee approval was obtained from the Ankara Numune Training and Research Hospital Ethics Committee (approval number: 990/2016, date: 29.06.2016).

Informed Consent: Informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.İ., Concept: T.İ., Ç.A.H., C.B., S.K., Design: T.İ., Ç.A.H., C.B., S.K., Data Collection or Processing: T.İ., Ş.A.D., S.K., Analysis or Interpretation: T.İ., C.B., Ş.A.D., Literature Search: T.İ., Ş.A.D., Writing: T.İ., Ç.A.H.

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