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Association Between IFN-λ4 rs12979860 And rs11322783 Polymorphisms with Spontaneous Clearance In Chronic Hepatitis B

Kronik Hepatit B'de IFN-λ4 rs12979860 ve rs11322783 Polimorfizmlerinin Spontan Klirens ile İlişkisi

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Abstract: Many studies have been published on the association between IFN-λ3 and IFN-λ4 polymorphisms and treatment related or spontaneous clearance of chronic hepatitis C. To date there is little known about the impact of IFN-λ4 polymorphisms on the natural history of chronic hepatitis B(CHB). This study aimed to investigate the role of IFN-λ4 polymorphisms on the course of CHB and to influence the presence of spontaneous clearance (SC) in CHB patients. One hundred and twenty-two patients who had CHB, and 81 subjects who had spontaneous resolution of HBV were analyzed regarding IFN-λ4 rs12979860 and rs11322783 single-nucleotide polymorphisms. We couldn't found any significant difference between CHB groups and SC groups in terms of IFN-λ4 rs12979860 polymorphisms and, the CC, C/T and TT genotypes represented 49%, 45% and 5% of CHB patients and, %46, 43% and 11% of SC group respectively (p=0.65). On the other hand, in IFN-λ4 rs11322783 polymorphisms analysis, recessive G/G allele was more common in SC group compared to CHB group (5% vs 16%, p=0.04; OR: 3,55). Moreover, non-G/G genotypes had significantly higher in CHB patients compared to SC group (95% vs 84%, p=0.013; OR:3.55). Our results suggest that IFN-λ4 rs11322783 polymorphism may be a predictor of spontaneous clearance in HBV infected patients. The role of IFN-λ4 polymorphisms needs to be investigated in the natural history of HBV.
Keywords: Interferon-λ4, Hepatitis B virus, Single nucleotide polymorphism, Spontaneous clearance

Özet: IFN-λ3 ve IFN-λ4 polimorfizmleri ile kronik hepatit C'nin tedaviye bağlı veya spontan klirensi arasındaki ilişki hakkında birçok çalışma yayınlanmıştır. Bugüne kadar IFN-λ4 polimorfizmlerinin kronik hepatit B'nin (KHB) doğal seyri üzerindeki etkisi hakkında çok az şey bilinmektedir. Bu çalışma, IFN-λ4 polimorfizmlerinin KHB'nin seyri üzerindeki rolünü ve KHB hastalarında spontan klirens (SK) mevcudiyeti üzerine etkisini araştırmayı amaçlamıştır. Yüz yirmi iki KHB hastası ve spontan HBV rezolüsyonu olan 81 birey IFN-λ4 rs12979860 ve rs11322783 tek nükleotid polimorfizmleri açısından analiz edilmiştir. IFN-λ4 rs12979860 polimorfizmleri açısından KHB ve SK grupları arasında anlamlı bir fark bulunamamış olup, CC, C/T ve TT genotipleri sırasıyla KHB hastalarının %49, %45 ve %5'ini, SK grubunun ise %46, %43 ve %11'ini temsil etmiştir (p=0.65). Öte yandan, IFN-λ4 rs11322783 polimorfizm analizinde, resesif G/G alleli KHB grubuna kıyasla SK grubunda daha sıktı (%5'e karşı %16, p=0,04; OR: 3,55). Ayrıca, G/G olmayan genotipler KHB hastalarında SK grubuna kıyasla anlamlı derecede daha yüksekti (%95'e karşı %84, p=0,013; OR:3,55). Sonuçlarımız, IFN-λ4 rs11322783 polimorfizminin HBV ile enfekte hastalarda spontan klirensin bir belirleyicisi olabileceğini düşündürmektedir. IFN-λ4 polimorfizmlerinin HBV'nin doğal seyrindeki rolünün araştırılması gerekmektedir.
Anahtar Kelimeler: İnterferon-λ4, Hepatit B virüsü, Tek nükleotid polimorfizmi, Spontan klirens

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1. Introduction

Hepatitis B virus is a virus that affects more than 350 million people and causes health problems such as cirrhosis, hepatocellular carcinoma, chronic hepatitis and approximately 1 million deaths per year. It is thought that 2 billion people worldwide have encountered this virus and close to 400 million people are chronically infected with HBV (1).

Patients with infectious diseases often show heterogeneous clinical courses associated with a range of morbidities and variable mortality. This is due to a number of factors that encompass complex aspects of host-pathogen interactions. Interferons play an important role in these interactions that determine the outcome of many viral, bacterial, fungal and parasitic infections (2, 3).

Interferon-lambdas (IFN-λs) modulate immunity through a network of genes induced in infections and autoimmune diseases. IFN-λs act by binding to the heterodimeric IFN-λ receptor (IFN-λR), which activates the STAT phosphorylation-dependent signal cascade. Thus, hundreds of IFN-stimulated genes are induced and this complex modulates various immune functions via feed-forward and feedback loops.

The genetic variations in the form of a series of single-nucleotide polymorphisms (SNPs) associated with genes involved in the IFN-λ signaling cascade have been identified, and these single-nucleotide polymorphisms have been associated with the clinical course and treatment outcomes of hepatitis B and C virus infection (4). In the past decade, it was demonstrated that homozygous carriage of the C allele in rs12979860 of IFN-λ3 gene on chromosome 19 (also known as IL28B polymorphism) substantially increases the likelihood of spontaneous clearance of acute HCV infection, and also improves outcome of interferon-based HCV therapy. After the widespread use of direct acting antiviral agents (DAA) for HCV treatment, the clinical relevance of the IFN- -λ3 polymorphism decreased.

IFN-λ4 is the most divergent member of the IFN- λ family and has only 29% amino acid identity with IFN- λ3, unlike the >80% homology observed between IFN- λ1, IFN- λ2 and IFN-λ3 (5). Several studies demonstrated that several IFN-λ4 better outcomes for the clearance of chronic HCV (5-7). Beside the association of IFN-λ gene polymorphisms with the immune response, disease progression and hepatocellular carcinoma in patients with HBV infection, IFN-λ gene polymorphisms also affect the spontaneous viral clearance rate of HBV patients through interaction with other genes (8). There are insufficient data about the influence of IFN-λ4 polymorphisms on treatment related or spontaneous clearance of HBV infection (9, 10).

In the current study, we aimed to investigate the effect of IFN-λ4 rs12979860 and rs11322783 polymorphisms on the spontaneous clearance of HBV among subjects infected with HBV and subjects who had spontaneous HBV seroclearance.

2. Materials and Methods

2.1. Study Population

This study included a total of 214 subjects who applied to the Gastroenterology Clinic xxx Medicine Faculty between August 2018 and March 2019. One hundred and twenty-two of them had chronic hepatitis B (CHB) infection and 81 subjects had spontaneous clearance for HBV. All subjects in CHB group were seropositive for HBsAg for at least 6 months, and 80% of them on therapy with nucleoside/nucleotide analogues(NA). These patients had elevated serum alanine aminotransferase (ALT) levels and serum HBV DNA levels before therapy. Subjects who had seronegative results for HBsAg in combination with seropositive results for anti-HBs and/or anti-HBc IgG were recruited to spontaneous clearance group for HBV (SC). Individuals under the age of 18, pregnant women and individuals who did not want to participate in the study were excluded. Patients co-infected with hepatitis C virus and/ hepatitis D virus were also excluded.

Serum samples were tested for HBsAg, anti-HBs, anti-HBc IgG, HBeAg, Anti-HBe and anti-HCV with macro enzyme-linked immunosorbent assay (ELISA) using Abbott Architect kits in the Abbott Architect i2000 SR system (Abbott, Axsym, Ireland) according to the manufacturer's instructions. The presence of anti-HDV was analyzed using micro-ELISA (HDV Ab, Enzyme Immunoassay Test Kit, Delta Biologicals, Italy) with the Triturus system (Triturus, Grifols, Spain) according to the manufacturer's instructions. A 5 ml blood samples taken from the study participitans at the time of admission were collected into tubes with ethylenediaminetetraacetic acid (EDTA) and stored at -80 degrees, and polymorphisms were studied from these blood.

2.2.Molecular analysis

DNA isolation protocol

DNA of the patients was extracted using Invitrogen Purelink Genomic DNA extraction kit (Thermo Fischer Scientific, Wilmington, DE, USA) with the following the manufacturer's protocol. Quality control and quantity measurements of the isolated genomic DNA samples were performed by Qubit Fluorometer protocol as recommended by the manufacturers (Thermo Fischer Scientific, Wilmington, DE, USA).

SNP Genotyping

IFN-λ4 (rs12979860) and IFN-λ4 (rs11322783) genotyping was performed by TaqMan technology (Thermo Fisher Scientific) in a StepOne Plus Real Time PCR System (Applied Biosystems, Foster City, CA). SNP and allele (genotype) calling was carried out by a standard end-point analysis with the aid of commercial genotype-calling software (TaqMan™ Genotyper Software v1.0.1).

2.3. Statistical analysis

Statistical analyzes were performed using the SPSS (Statistical Program for Social Sciences) version 22 software. Results were presented as numbers (percentage) for categorical variables, mean ± standard deviation for normally distributed continuous variables, and median ± interquantil range (IQR) for non-normally distributed variables. Chi-square and Fisher's exact test were used to compare group ratios. While Student's t test was used for normally distributed variables, Mann-Whitney U and Wilcoxon sign tests were used for non-normally distributed variables to compare group means. Odd ratio (OR) and confidence interval(CI) were used to evaluate the relationship for IFN--λ4 polymorphism alleles between the CHB group and the spontaneous clearance group. Odd ratio and CI were calculated with logistic regression analysis and Hardy-Weinberg equilibrium using SNPStat program. P< 0.05 was considered statistically significant.

2.4. Figures

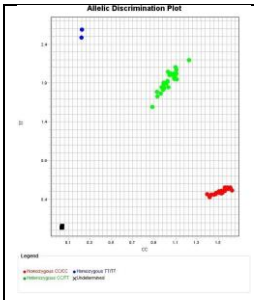

Figure 1. Allelic discrimination plot for IFN-λ4 (rs12979860) polymorphism

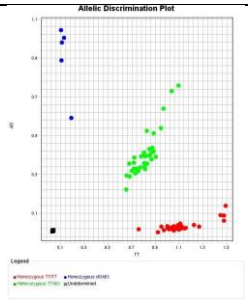

Figure 2. Allelic discrimination plot for IFN-λ4 (rs11322783) polymorphism

2.5. Tables

Table 1. Demographic, serological and laboratory parameters of CHB group and SC group

	CHB group (n=122)	**SC group (n=92)**	**P**
Age	47.1±12.6	66.2±14.2	**<0.01**
Gender, male (%)	69 (56)	51 (55)	0,87
NA tratment, n(%)	98 (80)	-	
IFN α/ PegIFN α	-	-	
Lamuvidine	6 (6)	-	
Telbivudine	5 (5)	-	
Entecavir	31 (32)	-	
Tenofovir	56 (57)	-	
HBeAg, n (%)	17 (14)	-	
Anti-HBe, n (%)	94 (77)	-	

White blood cell count	6320 ± 2530	6525 ± 2945	0.45
Hemoglobin	14.3 ± 2.7	11.9 ± 2.4	**<0.01**
Platelet count	237000 ± 75000	225000 ± 147000	0.87
ALT	21 ± 14	22.5 ± 29	0.81
AST	22 ± 12	25.5 ± 23	0.08
GGT	16 ± 19	48 ± 111	**<0.01**
ALP	73 ± 32	81.5 ± 71	**<0.01**
LDH	198 ± 42	212 ± 110	**<0.01**
Protein	7.3±0.6	6.4±1.1	**<0.01**
Albumin	4.3±0.4	3.6±0.6	**<0.01**
BUN	29 ± 10	34 ± 24	**<0.01**
Creatinin	0.76 ± 0.26	0.76 ±0.37	0.71
INR	1.0±0.1	1.1±0.2	**<0.01**
aPTT	23±7	26 ± 5	**<0.01**

Table 2. Comparison of IFN-λ4 rs12979860 polymorphism analysis of CHB and SC groups

Genotype	**CHB group (%) (N=128)**	**SC group (%) (N=81)**	**p**	**OR (95% CI)**
C/C	63 (49%)	37 (46%)		1.00
C/T	58 (45%)	35 (43%)	0.65	1.09 (0.60-1.97)
T/T	7 (5%)	9 (11%)		1.59 (0.49 -5.10)
C	184 (72%)	109 (67%)		
T	72 (28%)	53 (33%)		

Table 3. Comparison of IFN-λ4 rs11322783 polymorphism analysis of of CHB and SC groups

Genotype	**CHB group (%) (N=128)**	**SC group (%) (N=81)**	**p**	**OR (95% CI)**
T/T	63 (49%)	33 (41%)		1.00
T/D	58 (45%)	35 (43%)		1.15 (0.64 -2.09)
G/N	7 (5%)	13 (16%)	**0.04**	3.55 (1.29-9.74)
T/T - T/G	121 (95%)	68 (84%)	**0.01**	1.00
G/N	7 (5%)	13 (16%)		3.30 (1.26-8.68)
T	184 (72%)	101 (62%)		
G	72 (28%)	61 (38%)		

3. Results

A total of 214 patients, 92 in CHB group and 122 in SC group, were recruited to this study. Sixty-nine of patients (56%) in CHB group and 51 subjects (55%) in SC group were male (p>0.05). Patients in CHB group were older then in SC group (66.2±14.2 years vs 47.1±12.6 years; p<0,01). Fourteen patients (17%) in CHB group were HBeAg positive. Ninety-eight patients in CHB group were on treatment with NA. Six of them were on Lamuvidine (6%), five (5%) on Telbivudine, 31 (32%) on Entecavir, and 56 (57%) on Tenefovir disoproxil fumarate treatments. Demographic, serological and laboratory parameters of two groups were given in Table 1.

3.1. Analysis of IFN-λ4 rs12979860 and rs11322783 single-nucleotide polymorphisms

Allelic discrimination plot for IFN-λ4 rs12979860 polymorphism was given in Figure 1. No significant difference was found between the groups in the comparison of the allele and genotype frequency of IFN-λ4 rs12979860 in chronic HBV patients and HBV-experienced groups during DNA extraction for interferon lambda four rs12979860 polymorphism analysis (p=0.65) (Table 2).

Allelic discrimination plot for IFN-λ4 rs 1322783 polymorphism was given in Figure 2. Comparing the allele and genotype frequency of IFN-λ4 rs12979860 in the DNA extraction stage for interferon lambda four rs11322783 polymorphism analysis, it was found that the G/G allele was more common in SC group than in chronic HBV patients (p=0.04; OR: 3,55 (1,29-9,74) (Table 3). In the evaluation of co-dominant alleles by combining them, it was observed that the recessive allele was more frequent in the similarly SC group than in the group with chronic HBV [p=0.013; OR: 3.55 (1.29-9.74) 3.30 (1.26-8.68)] (Table 3).

4. Discussion

Interferon λs modulate immunity through a network of genes induced in infections and autoimmune diseases. STAT acts by binding to the heterodimeric IFN-λR, which activates the phosphorylation-dependent signal cascade. Thus, hundreds of IFN-stimulated genes are induced and this complex modulates various immune functions via feed-forward and feedback loops (2).

Expression of interferon λ ligands is modulated by SNPs in both transcription factor binding sites and methylation sites of the promoter region, as well as frameshift mutations. The dual role of interferon lambdas, their direct antiviral effects and longer-lasting immunomodulatory effects on T and B cell activation and modulation, may lead to possible multiple interactions with different types of infectious diseases. IFNs protect cells against viral infections. On top of that, each virus has developed specific ways to inhibit IFN signaling and its effects (11). Although these results from mouse studies are very important, a number of important differences from human results have also been noted. In a human chimeric mouse model using human hepatocytes, the response rates of human and mouse hepatocytes to IFN-λ were found to be quite different, and especially in mice, hepatocytes did not respond to IFN-λ (12). Also, the expression of IFN-λR in immune cells appears to be strikingly different. B-cells in humans were responsive to IFN-λs, whereas B-cells in mice were unresponsive to IFN-λs (13).

The clinical impact of SNPs at the IFN-λ3/4 locus was initially observed in the context of IFN-α therapy outcomes in patients with chronic HCV. Most studies have concluded that the minor alleles of the SNPs rs12979860 (CT/TT) and rs8099917 (TG/GG) are associated with reduced IFN-λ3 expression observed in serum in liver biopsies during chronic HCV infection. However, the TT allele of rs12979860 in hepatocytes has also been shown to express higher levels of IFN- λ1 and IFN-λ3(14). Although the rs12979860 SNPs have been specifically associated with IFN- λ3/λ4 expression, these SNPs may also affect the expression of other IFN-λ genes (15). In a study examining the effect of IFN-λ4 rs12979860 polymorphism on HCV-related diseases, it was found that HCV-related diseases were more common in individuals with C/T or T/T genotype (16).

Recently, several studies were also evaluated several IFN-λ4 polymorphisms on Sars-cov-2. In one study conducted by Mohlenberg et al., the effect of IFN-λ4 polymorphism on immune response was investigated in individuals infected with Sars-cov-2, and no significant difference was found between significant groups (15). Likewise, results of another study on individuals infected with Covid-19 showed that the rate of infection was higher in individuals carrying the IFN-λ4 rs12979680 polymorphism (16).

In this study, it was aimed to determine whether IFN-λ4 rs12979860 and rs11322783 polymorphisms have a role on the clearance of chronic HBV infection. In the literature, only two studies

evaluated IFN-λ4 polymorphisms in HBV infection. In a retrospective study, Limothai et al. investigated IFN-λ4 ss469415590 polymorphism in 254 CHB patients that treated with PEGIFN for 48 weeks, and showed that there was no relationship between IFN-λ4 ss469415590 polymorphism and treatment response (9). Another study investigated IFNL4rs368234815, rs12971396, rs12979860, and rs8099917 polymorphisms among patients with CHB and those had seroclearance for HBV. They found that none of these IFN polymorphisms related with clearance of virus (10). Our results were compatible with the results of mentioned study. We also couldn't detect any difference in terms of IFN-λ4 rs12979860 polymorphism between CHB group and SC group.

On the other hand, in the rs11322783 polymorphism analysis, when the allele and genotype frequencies were compared between the groups, we found that the G/G allele was more common in SC group compared to CHB group. In the evaluation of co-dominant alleles by combining them, it was seen that the recessive allele was more common in the similarly passed group than in the group with chronic HBV. To our knowledge, this is the first study evaluating IFN-λ4 rs11322783 polymorphism in HBV. While individuals carrying IFN-λ4-TT allele of the rs11322783 polymorphism show aborted expression of IFN-λ4 protein, IFN-λ4-ΔG polymorphism can synthesize the full-length functional IFN-λ4 protein (17). According to the current knowledge, IFN-λ4 is produced and secreted in response to viral infections, at relatively low levels and compared to other IFN-λs. IFN-λ4 is a more potent and locally acting IFN λ form (18). Full-length production of IFN-λ4 protein among patients carrying IFN λ4-ΔG allele may result in higher production of this more potent IFN and, thus increasing possibility of spontaneous clearance of viral infections like HBV. Today, studies on polymorphisms are ongoing.

In a study, it was shown that PEG-IFN activity was higher in patients with genetic variations in IL28B and HbeAg positive CHB patients (19). In another study, HbsAg seroclerance rate was found to be higher in young patients diagnosed with CHB infection with HLA-DP and IL28B genetic mutations (20). IFNL4 rs12979860 showed a significant increase in HBV DNA loads in patients with the CC genotype compared to patients with the CT and TT genotypes. However, no consistent relationship was found between the IFNL4 rs12979860 polymorphism and the outcome of HBV infection (21). One of the most fatal outcomes of CHB infection is the development of HCC. There are many developments on this subject in global studies. In a study, no significant difference was observed between polymorphisms in the IL28B gene and the development of HCC (22). In another study conducted on IL28B, while no activity was found regarding the immune response in patients diagnosed with CHB and HIV, it was observed that the polymorphism was effective in the response to treatment in patients diagnosed with HCV (23).

Limitations

There are several limitations in the current study, which must be addressed. Our study is a single center study which included in a small number of patients and, thus our results are not sufficient to comment on IFN-λ4 polymorphisms in the natural history of chronic HBV infection. Secondly, we were unable to verify our findings using another independent population and, our results cannot be generalized to the whole population. Moreover, the significant diversity in IFNs and multiple SNPs poses a complexity problem that is difficult to address.

5. Conclusion

In conclusion, it is increasingly recognized that IFN-λs and their modulation by SNPs are factors that play important roles in a wide range of infectious diseases. Though most of the studies in the literature about IFN-λs are mostly on HCV. In this study, the incidence of IFN-λ4 rs11322783 and rs12979860 polymorphisms in patients with CHB and those had spontaneous clearance for HBV were investigated. The IFN-λ4-ΔG allele of rs11322783 polymorphism was found to be more common in spontaneous clearance group. Using IFN-λ4 rs11322783 SNP may guide us to predict the more probable group of spontaneous clearance among CHB patients. These findings need to be confirmed in larger groups of patients with CHB.

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