IL-17 and IL-22 genetic polymorphisms in HBV vaccine non- and low-responders among healthcare workers

Zohreh Borzooy[1], Adrian Streinu-Cercel[2,], Abbass Mirshafiey[3], Azam Khamseh[4], Masoud Karkhaneh Mahmoudie[5], Shadi Sadat Navabi[6], Marjan Nosrati[7], Zahra Najafi[8], Mostafa Hosseini[9], Seyed Mohammad Jazayeri[10]*

Abstract

Background **Healthcare workers constitute a population at high risk for HBV infection. Efficient vaccination options are available; however, the individual response to HBV vaccination may vary widely between subjects, potentially due to cytokine profiles and genetic variations. In the present study, we investigated the relationship between IL-17 and IL-22 gene polymorphisms versus non- and low-responsiveness to HBV vaccination in healthcare workers.**

Methods **We selected the following IL-17 and IL-22 polymorphisms: rs4711998 (A/G) from IL-17 and rs2227501 (A/T), rs2227503 (A/G), rs1026786 (A/G) from IL-22 sequences genes. These were determined by polymerase chain reaction restriction fragment length polymorphisms.**

Results **The IL-17 rs4711998 GG genotype had a significantly lower frequency in non-responders compared to low-responders (p=0.025). However, we did not identify a relationship between IL-22 rs1026780, rs2227501 and rs2227503 genotypes and the anti-HBs response following HBV vaccination.**

Conclusion **These data suggest that genetic variation in rs4711998 polymorphisms in the IL-17 cytokine may influence vaccine-induced immune responses to HBV vaccine in healthcare workers.**

Keywords **HBV vaccine, healthcare workers, IL-17, IL-22, gene polymorphisms**

Background

Hepatitis B virus (HBV) is a global threat for public health and one of the leading reasons of chronic (long-term) liver disease. According to the World Health Organization (WHO), more than 240 million people have chronic HBV infection and more than 780,000 patients die because of the acute or chronic consequences of hepatitis B in the entire world every year. In Iran 1.3% to 8.69% and in Romania 2% to 7% of the population are chronic HBV carriers, approximately.[1,2]

Also, HBV is one of the occupational menaces for healthcare workers (HCW), the infection risk through exposure to blood and infectious body fluids being highest in this category.[3] The WHO estimates that per year 66,000 HBV infections take place in HCWs due to career exposure to percutaneous damages.[4]

One of the most effective ways to prevent

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[1]PhD student, Department of Infectious Diseases, Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; Department of Immunology and Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [2]MD, PhD, Department of Infectious Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; National Institute of Infectious Diseases, "Prof. Dr. Matei Balş", Bucharest, Romania; [3]Ms, PhD, Head of the department of Pathobiology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [4]Bs, Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [5]Bs, Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [6]Ms, Department of Immunology, Tehran University of Medical Sciences, Tehran, Iran; [7]Bs, Department of Infection Control, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran; [8]Ms, Bahrami Hospital, Tehran University of Medical Sciences, Tehran, Iran; [9]Ms, PhD, Department of Epidemiology and Biostatistics School of Public Health, Tehran University of Medical Sciences, Tehran, Iran; [10]MD, PhD, Clinical Virologist, Hepatitis B Molecular Laboratory, Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

*Corresponding author: Adrian Streinu-Cercel, MD, PhD, Department of Infectious Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, National Institute for Infectious Diseases, "Prof. Dr. Matei Balş", No. 1 Dr. Calistrat Grozovici street, Bucharest, 021105, Romania. E-mail: astreinucercel@germs.ro

HBV transmission is through vaccination, but the same vaccine regimen may register substantial inter-individual variation in immune response. Between 5% and 10% of healthy immune-competent subjects do not have hepatitis B antibody (anti-HBs) response to the surface antigen element present in these preparations (non-responder: <10 IU/L anti-HBs) or they respond poorly (low-responder: 10-100 IU/L anti-HBs).[5]

Numerous mechanisms involved in the lack of response to HBV vaccination have been proposed. However, the cellular and molecular causes have not been completely understood. Deficiency in HBsAg-specific T cells or B cells, cytokine secretion profiles, and immunologic tolerance may be some of the mechanisms that determine the rate of protection and individuals' anti-HBs titers.[6] Genetic factors may also have important roles and many studies have been performed to determine the variations of genes for cytokines and cytokine receptors.[7,8]

Cytokines are essentially chemical messengers and have key roles in mediation and regulation of immune responses. One of their functions in the response to vaccine antigens is the regulation of the Th_1/Th_2 balance. Many researches have addressed the link between HBV vaccine response and gene polymorphisms in cytokines such as interleukin (IL)-1β, tumor necrosis factor (TNF), transforming growth factor (TGF)-β1, IL-10, IL-6, interferon gamma (IFNG) single nucleotide polymorphisms (SNPs).[9-11]

In recent years, a novel T helper subset has been described, adding to the complexity of the Th1/Th2 binary system originally described 25 years ago by Mosmann et al.[12] The T helper type 17 (Th17) subset, initially discovered in a study performed on an autoimmune model,[13] is a separate lineage of T cells and the polarization of these cells relies critically upon the actions of cytokines (e.g., IL-23) secreted by antigen-presenting cells.[14] These cells produce the pro-inflammatory and effector cytokines of the IL-17 family, IL-22 and IL-21. Th17 cells play a meaningful role in infectious diseases, autoimmune conditions, adaptive immune response and mucosal immunity.[15,16]

Interleukin-17A (IL-17A) generates massive tissue inflammation and can promote the progression of autoimmune diseases through mobilizing, raising and activating neutrophils;[4] scientists have also found that IL-17 could be extensively involved in the pathogenesis of chronic liver disease and in antiviral therapy.[17,18] Some observations suggest that IL-17 may also be indirectly involved in immunoglobulin production by increasing the production by other immune cells of B-cell activators.[19,20]

Interleukin-22 (IL-22) is part of the IL-10 family and is produced by restricted cells such as Th17 cells, gamma delta T cells, natural killer (NK) T cells, and according to recent reports, innate lymphoid cells.[21] This cytokine, similar to IL-17, is a pro-inflammatory cytokine but one of its key roles is protecting hepatocytes from injury by increasing proliferative and antiapoptotic responses.[22]

The aim of this study was to determine if there are genetic differences between two categories of HBV vaccine responders, non- and low- responders, in healthcare workers.

Methods

This project utilized resources of 3 hospitals (Tehran Cardiac Center, Mirza Koochak Khan and Bahramie, Iran). Non- and low- responders to HBV vaccine were selected from the Infection Control database. The study included 120 HCWs with anti-HBs titers <10 IU/L (Group 1, 10 males and 11 females, age range 24-57 years and mean ± standard deviation (SD) 37±9.6) and low-responders to HBV vaccine 10-99 IU/L (Group 2, 34 males and 65 females, age range 22-60 years and mean±SD 38±9.1), respectively. They had received full HBV vaccination according to the standard schedule (3 vaccine doses at months 0, 1, 6 injected intramuscularly into the deltoid muscle) in the past five years. Non-responders were given an additional three dose vaccination series after an interval of one

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month. They had no evidence of co-infection with other hepatitis viruses or HIV. A questionnaire was provided for collection of demographic and laboratory information and potential risk factors for HBV transmission.

The study was approved by the ethics committee of Tehran University of Medical Sciences. DNA was extracted from blood samples according to the manufacturer's instructions (QIAamp DNA Blood Midi Kit, Qiagen Venlo, Limburg, Netherlands), and was qualified by spectrophotometer and stored at -70°C until use. Polymorphisms rs2227501 (A/T), rs2227503 (A/G), rs1026786 (A/G) from IL-22 and rs4711998 (A/G) from IL-17 were selected and determined by polymerase chain reaction-restriction fragment length polymorphisms (PCR-RFLP). PCR was performed in the volume of 10 µL comprising 1 µL of 10X buffer PCR, 1.5 mM of $MgCl_2$, 250 ng DNA, 300 µM of each dNTPs, 1 unit of Taq DNA polymerase, 0.5 pM of each primers restriction enzymes (Thermo Scientific, Waltham, MA, USA) digested the PCR products of IL-22 and IL-17 into two fragments and then the digested products were separated on 2% agarose (Sigma-Aldrich, St. Louis, MO, USA) gel then stained with ethidium bromide and finally studied on UV transilluminator. Allele and genotype frequencies were calculated for patients by direct gene counting. The statistical analyses between the two groups were performed with the χ^2 test using SPSS software version 20 (IBM, Armonk, NY, USA) and Epi Info version 7 (CDC, Atlanta, GA, USA).

Results

A total of 21 non-responders and 99 low-responders were genotyped in order to distinguish the susceptibility to HBV vaccine response associated with genetic variants of IL-17

Table 1. The frequencies of IL-22 genotypes in non- and low-responders to HBV vaccination

Genotype rs2227501	Non-responder, n (%)	Low-responder, n (%)	χ^2	P-value	OR (95% CI)
AA	1 (4.8)	3 (3)	0.16	0.542[a]	0.62 (0.06-6.32)
AT	7 (33.3)	29 (29.3)	0.13	0.714	0.83 (0.3-2.26)
TT	13 (61.9)	67 (67.7)	0.26	0.610	0.77 (0.23-2.06)
Alleles					
A	9 (21.4)	35 (17.7)	0.32	0.568	**1.27 (0.55-2.9)**
T	33 (78.6)	163 (82.3)			
Genotype rs2227503					
AA	15 (71.4)	69 (69.7)	0.20	0.875	1.08 (0.38-3.07)
AG	6 (28.6)	30 (30.3)	0.02	0.875	0.92 (0.32-2.60)
GG	0	0	-	-	-
Alleles					
A	36 (85.7)	168 (84.8)	0.02	0.887	1.07 (0.41-2.76)
G	6 (14.3)	30 (15.2)			
Genotype rs-1026786					
AA	18 (85.7)	87 (87.9)	0.07	0.785	0.82 (0.21-3.23)
AG	3 (14.3)	12 (12.1)	0.07	0.785	1.2 (0.3-4.72)
GG	0	0	-	-	-
Alleles					
A	39 (39.4)	186 (93.9)	0.69	0.792	0.84 (0.22-3.11)
G	3 (7.1)	12 (6.1)			

CI – confidence interval, **OR** – odds ratio
[a]Fisher's exact test

Table 2. The frequencies of IL-17 genotypes in non- and low-responders to HBV vaccination

Genotype rs4711998	Non-responder, n (%)	Low-responder, n (%)	χ^2	P-value	OR (95% CI)
AA	2 (9.5)	3 (3)	1.82	0.210[a]	3.36 (0.52-21.54)
AG	9 (42.9)	24 (24.2)	3	0.083	2.34 (0.88-6.23)
GG*	10 (47.6)	72 (72.7)	5.04	0.025*	0.34 (0.13-0.89)
Alleles					
A	13 (31)	30 (15.2)	5.88	0.015	2.5 (1.17-5.37)
G	29 (69)	168 (84.8)			

CI – confidence interval, **OR** – odds ratio
[a]Fisher's exact test
*statistically significant

and IL-22. There were no significant differences in the frequencies of IL-22 at each polymorphic region (p>0.05, Table 1). Homozygous GG in rs1026786 A/G and homozygous TT in rs2227501 A/T were not determined in both groups. However IL-17 rs4711998 A/G gene polymorphisms showed meaningful differences between low- and non-responders in the frequency of homozygous GG (p=0.025, odds ratio (OR)=0.34, 95% confidence interval (CI)=0.13-0.89).

The allele frequencies of IL-17 polymorphisms were also calculated. There was a valid difference between the two groups in the frequency of A and G. (p=0.015, OR=2.5, 95%CI=1.17-5.37, Table 2).

Discussion

In this study we have assessed the differences in genetic polymorphisms for two cytokines, IL-17 and IL-22, between healthcare workers who were HBV vaccine low- and non-responders. We observed a strong relationship between single nucleotide polymorphisms of the IL-17 gene and low-or non-response to HBV vaccine in healthcare workers.

Healthcare workers are considered at high risk for HBV infection all over the world and vaccination, which is an effective way of preventing infection, has been recommended for healthcare workers internationally since the early 1980s.[23] Th17 is a $CD4^+$T cell subset contending with both Th1 and Th2 cells,[24] important for remedying extracellular infection by affecting B cell isotype switching and neutrophil recruitment and intracellular infections by macrophage activation and Th1 recruitment.[25,26]

Studies have reported that there is an inverse correlation between Th17 frequency and hepatitis B virus viral load.[27] Th17 and T regulatory (Treg) cells have complementary relationships and field literature has shown that in patients with hepatitis B peripheral blood levels of Treg cells are decreased, while Th17 cell levels are increased.[28] Recent studies have also shown a direct relationship between circulating Th17 cells and B cells maturation, differentiation and isotype switching.[29]

IL-17A and IL-22 control the responses of several cells, including hepatocytes.[27] IL-17A mRNA in peripheral blood mononuclear cells is higher in HBV-infected patients compared to normal individuals.[30] Also, IL-17A protein and mRNA levels are increased in occult chronic HBV infection.[31]

Zhang et al. have studied the effect of IL-22 in a murine model and in patients with acute HBV infection, concluding that IL-22 was significantly increased in serum.[32] In acute HBV infection, IL-22 drives inflammation, potentially through increasing immune cell infiltration and clearance of the virus, but in chronic HBV infection it appears to play a protective role.[33] Many results suggest that IL-17 may play cooperative roles with IFNG in vaccine-derived protective immunity.[34] Wu et al. have proved in a transgenic murine model that IL-22 has a powerful effect on cellular immune response through Th17 after hepatitis B vaccination.[35]

Li et al. have reported that the frequency of rs8193036 allele T was higher in patients who

resolved HBV infection, and that patients with hepatocellular carcinoma (HCC) had higher frequencies of rs2275913 genotype GG and allele G, as well as more frequent haplotypes CG and TG of rs8193036 and rs2275913. Thus, their results showed that IL17A polymorphisms may influence the risk for HCC in chronic HBV infection through IL17A production.[36] Xi et al. suggested that IL-17A rs4711998, IL-17A rs2275913, and IL-17F rs763780 polymorphisms do not have roles in HBV-related HCC. Nevertheless, the IL-17 ACA haplotype might be a risk factor and the GCG haplotype a protective factor, respectively, for HBV-related HCC in a Chinese population.[37] We could not find relevant information in field literature about IL-22 gene polymorphisms and immunity against HBV, so comparing our results with other studies was not possible but there are several reports on IL-22 gene variants and other diseases. For example, two SNPs in IL-22 are correlated with treatment outcome in hepatitis C virus infection.[38] The relationship of nine SNPs of IL-22 with gender were studied in HIV-positive Han Chinese patients, and the results showed a higher prevalence of the A/G genotype and G allele in rs2227513 in women, but not in men.[39] Interestingly, IL-17 and IL-22 signals and target genes are cytokines similar to IL-1, IL-4, IL-6, IL-10, which have significant impact in the response to HBV vaccine.[9,16.]

From the results of the current investigation, it may be suggested that IL-17A may potentially interfere in the degree of response to HBV vaccine. We have found that the IL-17 rs4711998 GG genotype has a significantly lower frequency in non-responders compared to low-responders. Theoretically, IL-17A polymorphisms may affect the anti-HBs titer directly or indirectly through its signals on other cytokines genes. Our study did not identify a relationship between IL-22 rs1026786, rs2227501, rs22275503 genotypes and the anti-HBs response following HBV vaccination.

The result of the present study may shed some light on the individual genetic susceptibility associated with HBV vaccine response, a public health priority worldwide, particularly in healthcare workers.

Conclusion

In conclusion, this study indicated that in healthcare workers the IL-17 rs4711998 GG genotype had a significantly lower frequency in non-responders to HBV vaccination (<10 IU/L) compared to low-responders (10<anti-HBs<100 IU/L), while the three investigated polymorphisms (rs1026786, rs2227501, rs2227503) in the IL-22 gene were not correlated with anti-HBs levels in the study population.

Authors' contributions statement: ZB collected samples, performed experiments, collected and analyzed data, interpreted data and wrote the manuscript. ASC acted as project supervisor, discussed the results and implications of the study and commented on the manuscript at all stages. AM acted as project co-supervisor and advised on immunology. AK and MK provided technical support. SSN developed analytical tools. MN selected eligible healthcare workers at Tehran Cardiac Center Hospital and presented them the project. ZN selected eligible healthcare workers at Bahrami Hospital and presented them the project. MH advised and conducted bioinformatics analyses. SMJ acted as project supervisor, designed the project and gave technical support. All authors contributed to the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

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