ARTÍCULO ORIGINAL

THE ASSOCIATION BETWEEN HLA-B40, HLA-DQA1*01 AND HLA-DQB1*05 ALLELES AND ANTIBODY RESPONSE TO HEPATITIS B VACCINATION IN TURQUISH HEMODISLYSIS PATIENTS

*ASOCIACIÓN ENTRE LOS ALELOS HLA-B40, HLA-DQA1*01 Y HLA-DQB1*05 Y RESPUESTA DE ANTICUERPOS A LA VACUNA CONTRA LA HEPATITIS B EN PACIENTES TURCOS EN HEMODIÁLISIS*

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Rev Nefrol Dial Traspl. 2019; 39 (3): 167-74

ABSTRACT

Introduction: Hepatitis B virus (HepB) infection is a global health problem with increasing cause of morbidity and mortality. Hemodialysis patients are especially vulnerable to HepB infection due to uremia-related immune dysfunction, frequent interventions they exposed, and health-care personnel's unsafe care. The vaccination against HepB confers the primary preventive measure. However, unresponsiveness to vaccination constitutes a major problem. Several factors can influence the immune response to vaccines but human genetic variations are thought to strongly militate the variability in vaccine responsiveness. We aimed to determine the association with specific HLA alleles and response to HepB vaccination in hemodialysis patients. **Methods:** The study included in-center hemodialysis patients. We retrospectively collected data regarding demographic, clinical, and laboratory features including anti-HBs antibody, antibody to hepatitis C (anti-HCV), anti-HIV, and specific HLA class I and II alleles (HLA-A, HLB, HLA-DR) from electronical medical record system. The frequencies of HLA class I and II antigens in nonresponders and responders were analyzed. **Results:** The most commonly observed HLA alleles in patients were DQA1*01 (%73.7), DQA1*05 (%57.9), DQB1*03 (%53.8), DQB1*05 (%38.5), and DRB1*11 (%37.3), respectively. The frequency of HLA-B40 allel was significantly higher in nonresponders (p=0.02, OR=6.25, 95% CI =1.33-29.3). HLA-DQA1*01 and HLA-DQB1*05 alleles were observed significantly more in responders (p=0.019, OR =6.9, 95% CI=1.40-33.91, and p=0.028, OR =10, 95% CI=1.12-88.91, respectively). **Conclusion:** This is the first study to our knowledge demonstrating the association between antibody response to HBsAg and HLA-B40, HLA-DQA1*01, and HLA-DQB1*05 alleles in Turkish hemodialysis patients.

KEYWORDS: hemodialysis; hepatitis B vaccine; human leukocyte antigens; immune response

RESUMEN

Introducción: La infección por el virus de la hepatitis b (VHB) constituye un problema de salud mundial con una morbimortalidad cada vez mayor. Los pacientes que reciben hemodiálisis están particularmente expuestos a una infección por el virus de la hepatitis b debido a una disfunción del sistema inmunitario relacionada con la uremia, las intervenciones a las que se someten frecuentemente y prácticas poco seguras por parte del personal de salud. La vacuna contra el VHB constituye la medida preventiva principal. Sin embargo, la falta de respuesta a la vacuna supone un gran problema. Existen varios factores que pueden influir sobre la respuesta inmunitaria a la vacuna, pero se cree que las variaciones genéticas humanas tienen una gran incidencia sobre la variación en la respuesta a la vacuna. El objetivo de este trabajo fue determinar la relación entre alelos HLA específicos y la respuesta a la vacuna contra el VHB en pacientes que reciben hemodiálisis. **Material y métodos:** El estudio incluyó pacientes en hemodiálisis hospitalaria. Se recopilaron datos retrospectivamente del sistema electrónico de registros médicos sobre características demográficas, clínicas y de laboratorio, incluidos anticuerpos anti-HBs, anticuerpos contra la hepatitis C (anti-VHC), anti-VIH y alelos HLA específicos de clase I y II (HLA-A, HLA-B, HLA-DR). Se analizaron las frecuencias de los antígenos HLA clase I y II en pacientes que no respondían y en aquellos que sí lo hacían. **Resultados:** Los alelos HLA más comúnmente observados en pacientes fueron DQA1 * 01 (73,7%); DQA1 * 05 (57,9%); DQB1 * 03 (53,8%); DQB1 * 05 (38,5%), y DRB1 * 11 (37.3%), respectivamente. La frecuencia del alelo HLA-B40 fue significativamente mayor en los que no respondieron (p=0,02; OR = 6,25; IC 95% = 1,33-29,3). Se observó que los alelos HLA-DQA1*01 y HLA-DQB1*05 aparecían mayormente en los pacientes que respomdían (p=0,019; OR = 6,9; IC 95% = 1,40-33,91, y p=0,028; OR=10; IC 95% = 1,12-88,91, respectivamente). **Conclusión:** Este es el primer estudio que conocemos que demuestra la asociación entre la respuesta de anticuerpos a HBsAg y a alelos HLA-B40, HLA-DQA1*01 y HLA-DQB1*05 en pacientes turcos en hemodiálisis.

PALABRAS CLAVE: hemodiálisis; vacuna contra la hepatitis B; antígenos de leucocitos humanos; respuesta inmune

INTRODUCTION

World Health Organization (WHO) global hepatitis report in 2017 declared that 257 million persons with the global prevalence rate of 3.5% were living with chronic HepB infection in the world in 2015, and the trend in mortality due to viral hepatitis is increasing gradually.[1] Hemodialysis patients have several factors that predispose them to viral infections including acquired immune deficiency of uremic milieu, frequent exposure to parenteral interventions and blood products, and health-care professionals' inability to maintain universal precautions.[2] The prevalence of HepB infection in hemodialysis patients in western countries ranges from 0.6% to 6.6 % whereas in the Asian-Pacific region it may reach up to 14.6%.[3] The primary measure to prevent the occurrence of new infections and reduce mortality is vaccination.[1] However, there is a substantial rate of failure in developing antibody respone to hepatitis B surface antigen (HBsAg) after a standard course, ranging from 5% to 15% in healthy persons, and reaching up to 50% in hemodialysis group.[2-4] The antibody response to HepB vaccination has been mainly related to hosting factors and vaccination procedures. Host-related factors shown to decrease response to HepB vaccination include low-birth weight, male gender, advanced age, obesity, smoking, short sleep duration, and presence of immunosuppression.[5-9] Vaccination-related factors such as the type and dose of the vaccine, storage conditions, adjuvants, and injection route also play a role in immunization.[10-12]

The major immunological mechanisms playing role in unresponsiveness to HBsAg comprise impaired antigen presentation, T and/or B cell dysfunctions, defects in the cytokine production, T cell receptor (TCR) gene repertoire malfunctions, and overexpression of some HLA antigens.[13-15] The primary cause of immune deficiency in chronic kidney disease is a disturbance of relation between T lymphocytes and antigen-presenting cells. Uremia-related toxins, use of bioincompatible dialyzers, presence of co-morbidities, such as diabetes mellitus, hepatitis C, human immune deficiency virus (HIV) infections, and malnutrition further compromise host immune dysfunction and hence the immune response [3,16-17] The variability in immune response in different ethnic groups can be explained by genetic factors that are mainly determined by specific HLA class I and II genes.[5,18-19] In caucasions, for instance, HLA-DR3,-DR7,-B44,-DRB1*0701, and -DQB1*0202 genotypic alleles were reported to attenuate vaccine response.[19-20] A study from our country on healthy volunteers revealed that HLA-B13 allele was associated with impaired antibody response whereas HLA-DRB1*04X,- DRB1*0401X, -DRB1*11/13, and -DRB1*0401X0201 alleles were positively correlated with the immune response.[4,19]

In this study, we evaluated specific HLA class I and II alleles that are deemed to affect antibody response to HBsAg in Turkish hemodialysis group.

PATIENTS AND METHODS

This retrospective and the observational study included in-center, thrice-weekly scheduled 74 Hep B vaccinated Turkish hemodialysis patients of whom 51 had HLA class I (HLA-A, -B, and -C) and class II (HLA-DR,-DQ, and -DP) antigens typed while waitlisted for renal transplantation. The primary objective was to investigate the association of specific HLA alleles with the Hep B vaccine response. The study was approved by our institutional ethics committee (2018/13-1). The data regarding demographical, clinical, and laboratory variables were collected retrospectively through electronical medical record system.

The patients with the end-stage renal disease once commenced on dialysis were put on standart vaccination protocol with currently licensed hepatitis B recombinant vaccines at a dosage of 40 μg injected intramuscularly at 0,1,6 months. They were administered an additional three-dose series when failed to respond to the first one. The patients with anti-HBs antibody titers <10 IU/L one month after completion of vaccine series were classified as nonresponders and those with anti-HBs titers ≥10 IU/L as responders.

HLA tissue typing of hemodialysis patients on waitlist were tested by sequence specific oligonucleotide probe (SSOP) method with low resolution. SSOP method was performed using a low resolution commercial kit (Lifecodes HLA Typing Kit Immucor Gamma, USA) according to the manufacturer's instructions. This method consists of two steps: amplification and hybridization. A total of 20 μl reaction mix (containing 4 μl DNA sample) was prepared for the polymerized chain reaction (PCR) amplification. Probes were pre-heated at 56 ^{0}C for 7 minutes before hybridization step and added on 15 μl amplicon. The hybridization PCR protocol was performed according to the manufacturer's instructions. The samples were analyzed in a Luminex fluoroanalyzer instrument.

Statistical analysis was conducted by using IBM SPSS Statistics for Windows, version 25.0. (IBM Corp., Armonk, N.Y., USA). The Kolmogorov-Smirnov normality test was used to examine if variables are normally distributed. The unequally distributed continuous variables were compared by the Mann–Whitney test. The HLA allele frequency distributions of the responders and non-responders were compared in a Chi-square test of homogeneity, or Fisher's exact test if any value was less than five. Odds ratios (OR) given with 95% confidence

intervals reflect the likelihood of carrying a particular HLA allele in the nonresponder group compared with the responder group. The level of significance was set at two-sided p<0.05.

RESULTS

We obtained anti-HBs antibody levels in 74 hemodialysis patients (34 female, 40 male, mean age of 51.24±18.03 years), and accordingly divided them into two groups: responders (82.4%) and nonresponders (17.6%). The demographic, clinical, and laboratory characteristics of responders and non-responders to Hep B vaccination among HD patients are presented in **Table 1**. The cause of ESRD was frequently not specified in the records but coded as "CKD with unknown etiology" in the majority, therefore, we could not conduct any statistical analysis to show a causative relationship between the etiology and responsiveness to Hep B vaccination. There were no significant differences regarding gender, mean age, hemodialysis adequacy (kT/V>1.4), nutritional status (albumin>3.5 gr/dl), obesity (defined as body mass index (BMI ≥ 30kg/m^2), smoking status, and prevalence of diabetes mellitus between groups. HCV or HIV infections were not encountered in any patient. We recognized that one patient had previous renal transplantation and that patient was responsive to Hep B vaccination, he has not on any immunosuppressive medication already.

The study group with predetermined HLA antigens while wait-listed included 51 patients (39 responders, 12 nonresponders). **Table 2** and **3** show the distribution of frequencies of HLA class I and II antigens in two groups, respectively.

The most frequently observed alleles in all patients were DQA1*01 (73.7%), DQA1*05 (57.9%), DQB1*03 (53.8%), DQB1*05 (38.5%) and DRB1*11 (37.3%), respectively. With regard to HepB vaccine response, the ratio of distribution of alleles in responders in decreasing order were DQA1*01 (85.2%), DQA1*05 (55.6%), DQB1*03 (53.6%) and DQB1*05 50.0(%) whereas in nonresponders the frequencies varied as DQA1*05 (63.6%), DQB1*03 (54.5%), DQA1*01/DQB1*02 (45.5%), and A02/A24/DRB1*11 (41.7%), respectively.

HLA B40 allele was significantly more prevalent in nonresponders (p=0.02, OR=6.25, %95CI= 1.33-29.30). HLA DQA1*01 and DQB1*05 allelles were significantly more prevalent in responders (p= 0.019 and p=0.028, respectively), and absence of these alleles increased the probability of unresponsiveness (OR=6.9, 95% CI=1.40-33.91 and OR=10, 95% CI=1.12-88.91, respectively).

Table 1. Demographic and clinical findings of study groups

	Responders (n=61)	**Nonresponders (n=13)**	**p value**
Age (mean±SD, years)	49.5±17.8	59.1±17.6	0.127
Gender (F/M)	26/35	8/5	0.214
Diabetes mellitus (n)	9	5	0.062
Albumin (mean±SD, gr/dl)	4.04±0.46	4.06±0.37	0.949
Hemodialysis adequacy (Kt/V)	1.57±0.21	1.65±0.24	0.051
Obesity (BMI≥30kg/m^2, n)	6	2	0.624
Smoking (n)	20	4	1
Previous transplantation (n)	1	0	-

Table 2. The frequencies of HLA class I alleles in HepB vaccine responders and no responders

HLA class I alleles	**Responders (39) N, (%)**	**Nonresponders (12)N, (%)**	**Total (51)N, (%)**	**p**
HLA-A1	12 (30.8)	3 (25)	15 (29.4)	1
HLA-A2	10 (20.5)	5 (41.7)	15 (29.4)	0.302
HLA-A3	6 (15.4)	1 (8.3)	7 (13.7)	1
HLA-A11	11 (28.2)	3 (25)	14 (27.5)	1
HLA-A23	2 (5.1)	2 (16.7)	4 (7.8)	0.232
HLA A24	10 (25.6)	5 (41.7)	15 (29.4)	0.303
HLA-A25	3 (7.7)	0 (0)	3 (5.9)	1
HLA-A26	3 (7.7)	1 (8.3)	4 (7.8)	1
HLA-A29	2 (5.1)	1 (8.3)	3 (5.9)	0.561
HLA-A30	3 (7.7)	0 (0)	3 (5.9)	1
HLA-A31	2 (5.1)	0 (0)	2 (3.9)	1
HLA-A32	5 (12.8)	2 (16.7)	7 (13.7)	0.662
HLA-A68	2 (5.1)	1 (8.3)	3 (5.9)	0.561
HLA-B7	3 (7.7)	2 (16.7)	5 (9.8)	0.580
HLA-B8	1 (2.6)	0 (0)	1 (2)	1
HLA-B13	2 (5.1)	1 (8.3)	3 (5.9)	0.561
HLA-B15	2 (5.1)	0 (0)	2 (3.9)	1
HLA-B18	3 (7.7)	0 (0)	3 (5.9)	1
HLA-B27	4 (10.3)	0 (0)	4 (7.8)	0.561
HLA-B35	10 (25.6)	4 (33.3)	14 (27.5)	0.715
HLA-B37	4 (10.3)	0 (0)	4 (7.8)	0.561
HLA-B38	2 (5.1)	1 (8.3)	3 (5.9)	0.661
HLA-B39	1 (2.6)	0 (0)	1 (2)	1
HLA-B40	**4 (10.3)**	**5 (41.7)**	**9 (17.6)**	**0.024**
HLA-B41	1 (2.6)	0 (0)	1 (2)	1
HLA-B44	8 (20.5)	1 (8.3)	9 (17.6)	0.666
HLA-B48	1 (2.6)	0 (0)	1 (2)	1
HLA-B49	5 (12.8)	2 (16.7)	7 (13.7)	0.662
HLA-B50	2 (5.1)	2 (16.7)	4 (7.8)	0.232
HLA-B51	9 (23.1)	3 (25.0)	12 (23.5)	1
HLA-B52	6 (15.4)	1 (8.3)	7 (13.7)	1
HLA-B55	2 (5.1)	0 (0)	2 (3.9)	1
HLA-B57	0 (0)	1 (8.3)	1 (2)	0.235
HLA-B58	2 (5.1)	1 (8.3)	3 (5.9)	0.561

Table 3. The frequencies of HLA class II alleles in HepB vaccine responders and no responders

HLA class II alleles	Responders (39) N, (%)	Nonresponders (12) N, (%)	Total (51) N,(%)	p
DRB1*01	3 (7.7)	0 (0)	3 (5.9)	1
DRB1*03	5 (12.8)	3 (25)	8 (15.7)	0.372
DRB1*04	8 (20.5)	4 (33.3)	12 (23.5)	0.442
DRB1*07	6 (15.4)	3 (25)	9 (17.6)	0.424
DRB1*08	1 (2.6)	0 (0)	1 (2)	1
DRB1*10	3 (7.7)	0 (0)	3 (5.9)	1
DRB1*11	14 (35.9)	5 (41.7)	19 (37.3)	0.743
DRB1*12	3 (7.7)	1 (8.3)	4 (7.8)	1
DRB1*13	4 (10.3)	3 (25)	7 (13.7)	0.334
DRB1*14	6 (15.4)	1 (8.3)	7 (13.7)	1
DRB1*15	8 (20.5)	1 (8.3)	9 (17.6)	0.666
DRB1*16	4 (10.3)	0 (0)	4 (7.8)	0.561
DQB1*02	7 (25)	5(45.5)	12 (30.8)	0.262
DQB1*03	15 (53.6)	6 (54.5)	21 (53.8)	1
DQB1*04	1 (3.6)	0 (0)	2 (3.9)	1
DQB1*05	**14 (50)**	**1 (9.1)**	**15 (38.5)**	**0.028**
DQB1*06	9 (32.1)	4 (36.4)	13 (33.3)	1
DQA1*01	**23 (85.2)**	**5 (45.5)**	**28 (73.7)**	**0.019**
DQA1*02	3 (11.1)	3 (27.3)	6 (15.8)	0.329
DQA1*03	3 (11.1)	4 (36.4)	7 (18.4)	0.161
DQA1*04	1 (3.7)	0 (0)	1 (2.6)	1
DQA1*05	15 (55.6)	7 (63.6)	22 (57.9)	0.729

DISCUSSION

Various studies so far on healthy populations revealed that several host related risk factors, such as advanced age, male gender, low birth-weight, obesity, malnutrition, smoking, and illicit drug addiction contribute negatively on the immune response to vaccines.[5-6,19] Additionally, the presence of other immune-compromising conditions like diabetes, cancers, HIV and/or HCV infections, vitamin D deficiency, and chronic kidney disease affects the immune response unfavourably.[3,6] The impact of genetic factors on the immune response to HepB vaccine has not been clearly established yet but in different ethnic groups, specific HLA class I and II proteins were found to play an essential role in presenting antigens to specific T cells, and thus modulate the response to vaccination.[5,19,21-24]

In this study, which is the first to our knowledge in Turkish hemodialysis patients, we found that specific HLA alleles, namely HLA B40, DQA1*01, and DQB1*05, correlated with antibody response to HepB vaccine. HLA B40 was significantly associated with vaccine unresponsiveness whereas HLA DQA1*01 and HLA DQB1*05 allelles significantly increased the probability of responsiveness to HepB vaccination in our study population. Recently HLA-B*40 as a predictor for nonresponse has been reported in Taiwanese chronic hepatitis patients with low HBsAg levels who were administered HBsAg-based recombinant vaccine.[25] Theoretically, HLA B40 allele products are more or less ineffective than other alleles in conveying antigen processing and presentation. Their study also indicated that the frequency of HLA DQB1*05 allele in responders was more prevalent than no responders albeit not significant.

However, we found a significant relation with HLA DQB1*05 and HepB vaccine responsiveness. In a previous study conducted in end stage renal disease patients from our country, the presence of HLA A3 allele was reported to correlate significantly with responsiveness.[4] Although we couldn't demonstrate that relation in our study, as a novel finding the presence of HLA DQA1*01 and HLA DQB1*05 allelles were encountered significantly more in responders in our study.

Uremia related both cellular and humoral immune dysfunctions in hemodialysis patients negatively influence antibody response to vaccines. Defective B7-2 (CD86) expression in dialysis patients is an important cause of cellular immune dysfunction, and this defect may result in dysfunctions in the initiation and maintenance of CD4+ T-cell proliferation after activation through attenuation of co-stimulation of effector T cells, impairment in antigen presentation-antibody response pathway, and hence vaccine unresponsiveness.[16,26-27] In a recent study in hemodialysis patients from Poland, a remarkable relation between interferon-λ3 (IFN- λ3) levels and responsiveness to HepB vaccines was assessed. [28] Their results indicated that responders to HepV vaccination as well as hemodialysis patients who produce anti-HBs after HepB infection have significantly higher plasma concentrations of IFN-λ3 than no responders.

Major limitations of the study include a short number of the study population, inadequacy for accurate recordkeeping, and inadequacy of the data. We could not determine the specific cause of end stage renal disease in each patient and therefore could not conduct statistical analysis and establish any association between etiology of CKD and responsiveness to HepB vaccination.

In conclusion, although the interplay between HLA class I and II proteins and immune response to HepB vaccination has not been elucidated clearly, there has been accumulating reports that HLA gene expression and specific genotypes played a role in vaccine responsiveness in various ethnic groups. The relation of HLA-B40, DQA1*01, and DQB1*05 with HepB vaccination response in Turkish hemodialysis patients is such a novel finding. Upregulated HLA-B40 gene expression in such patients may anticipate innovations in more immunogenic vaccine development. The findings also suggest that determination of pre-immunization genetic profile background may help reconfigure vaccination scheme in the future.

Conflict of interest: Authors declare no conflict of interest.

Acknowledgements: We express our gratitude to Fatma Liv, M.D., Arif DEMİR, M.D. from the dialysis center for their consent in collecting the participants' data.

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Recibido en su forma original: 27 de febrero de 2019
En su forma en corregida: 18 de abril de 2019
Aceptación final: 2 de mayo de 2019
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