Original Article

Effect of HLA on Hepatitis C Virus Clearance and Persistence in Anti-HCV-positive End-stage Renal Disease Patients

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ABSTRACT

Background/Aims: The efficacy of immune response against hepatitis C virus (HCV) is determined by human leukocyte antigen (HLA) molecules of the host which present HCV antigens to CD4 + and CD8 + T lymphocytes. In this study, we aimed to investigate the possible relationship between the frequencies of certain HLA class I–II alleles and the natural history of HCV in patients with end-stage renal disease (ESRD). **Settings and Design:** This is a retrospective cohort study conducted in a university hospital. **Patients and Methods:** The present study comprised 189 ESRD patients (candidates for renal transplantation) who had positive anti-HCV antibody test. The results concerning HCV and HLA status were gathered from patients' files. The viral persistence was compared between the groups that were determined by HLA sub-typing. **Statistical Analysis:** Statistical evaluation was performed using Mann–Whitney U-test, Chi-square test, and Fisher's exact test. Level of error was set at 0.05 for all statistical evaluations, and P values < 0.05 were considered statistically significant. **Results:** We found possible association between the course of HCV infection and specific HLA alleles. HLA class I Cw*6 and HLA class II DRB*10 alleles were observed more frequently in the viral clearance group ($P < 0.05$). The HLA class I B*38 allele group was more prone to develop chronic hepatitis C ($P < 0.01$). **Conclusions:** These findings suggest that HLA class I Cw*6 and HLA class II DRB*10 alleles may be associated with immunological elimination of HCV in Turkish patients on hemodialysis. HLA sub-typing could help predict the prognosis of HCV infection.

Key Words: End-stage renal disease, hepatitis C virus, human leukocyte antigen genotyping, viral clearance, viral persistence

Hepatitis C virus (HCV) is a leading cause of viral hepatitis. Acute infection is mild and asymptomatic in a great majority of patients. Persistent HCV infection is associated with a wide clinical spectrum ranging from mild hepatic injury to cirrhosis, chronic hepatitis, and hepatocellular carcinoma (HCC).[1] Worldwide, 170 million people were reported to have been infected with HCV.[2,3] Prevalence of HCV infection has been found to be significantly higher in patients receiving hemodialysis (HD) for end-stage renal disease (ESRD) compared to the general population.[4,5] Prevalence of anti-HCV positivity in HD centers has been

reported to be between 8.5% and 75%.[6] HCV prevalence in ESRD patients has been estimated to be between 14% and 82% in Turkey (varying by geographic region).[7]

Viral factors, such as viral heterogeneity and replication activity, together with host determinants, such as lack or deficiency of effective immune responses, play important roles in the pathogenesis of chronic hepatitis. Therefore, the heterogeneous clinical course of HCV infection in ESRD patients may be explained by both immunological and genetic characteristics of the host. Polymorphisms of the genes that regulate the immunity and the human leukocyte antigen (HLA) class I and II molecules are known to affect the clearance or persistence of viral antigens.[8] Many studies have demonstrated the relationship between HLA alleles and various infectious agents. Although HLA class I- and class II-dependent T cell–mediated immune responses play a major role in HCV pathogenesis, only a few studies have investigated the relationship between HLA class I and II alleles and HCV pathogenesis, yielding contradictory results.[9-11]

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The results of genetic studies revealed that different genes are responsible for the immunological reaction against HCV infection, but they also contribute to HLA class I and II variations.[12] Previous studies have investigated the effects of host genetic diversity on the natural history of HCV. The genetic diversity has been demonstrated on factors that play a role in the immune response, with CD8 + T cell response being the strongest genetic factor. These protective alleles may determine the success of overall antiviral immune response in the interaction between virus and host.[13]

Although HCV infection is moderate-high in the Turkish population, studies in this field are limited.[14,15] Therefore, we aimed to investigate whether there is a relationship between viral response and HLA subgroups in ESRD patients with HCV infection and to compare the results with those of similar studies.

PATIENTS AND METHODS

ESRD patients followed as outpatients at the Nephrology Department of Baskent University Faculty of Medicine (BUFM) between January 1994 and December 2010 were evaluated for this study. The hospital records of ESRD patients were reviewed in terms of demographic information of the cases, etiology of ESRD, positivity of anti-HCV antibody and HCV-RNA viral load, liver biopsies, treatments received and their duration, date of transplantation and changes during follow-up, presence of HCV relapses, and HLA groups. After collection of the data, all the patients aged between 17 and 65 years, with positive results of anti-HCV antibody test for 6 months, positive anti-HCV test detected at least 3 times during the outpatient follow-up visits, anti-HCV-positive/HCV-RNA-positive results, or with anti-HCV-positive/HCV-RNA-negative results in the presence of pathological findings of HCV infection on liver biopsy were included in the study. On the other hand, patients with lack of follow-up visits, positive HBsAg and/or anti-HIV antibody test, presence of autoimmune disease, thyroid disease, or malignant disease, patients with anti-HCV-positive/HCV-RNA-negative results without pathological signs of HCV infection on liver biopsy (lack of proof of chronic HCV infection), HCV-RNA-positive patients receiving immunosuppressive treatment, patients with comorbid conditions like porphyria, hemochromatosis, Wilson's disease, alcoholic hepatitis, alpha-1 antitrypsin deficiency, and autoimmune hepatitis, patients with a history of transplantation of organ other than kidney, and patients with alcohol or intravenous drug and substance addiction were excluded from the study. The control group consisted of 199 people randomly selected among renal transplantation donors, who have no line of descent with the patient group and were negative for anti-HCV antibodies. The control group was evaluated to detect the frequency of HLA alleles in the general population.

HCV status

Serum anti-HCV antibody tests were regularly performed beginning from the initial hospital visit and then at 6-month intervals. Serum HCV-RNA concentrations (tested at the same intervals) were determined in patients with positive anti-HCV test. Viral clearance was defined as obtaining negative HCV-RNA result after detection of anti-HCV antibodies (chronic HCV infection has been ruled out by repeated serologic analysis or by liver biopsy) or as presence of acute HCV infection with HCV-RNA which spontaneously disappeared during the follow-up period. Viral persistence was defined as persistent presence of anti-HCV antibodies plus positive HCV-RNA levels irrespective of the status of HCV treatment (including patients with no history of HCV treatment and patients with viral relapse or no response to previous treatment).

Serology analysis
HCV testing
Qualitative detection of antibodies against HCV was done using AxSYM HCV version-microparticle enzyme immunoassay (MEIA) and Architect System-chemiluminescent microparticle immunoassay (CMIA). HCV-RNA was detected by nested polymerase chain reaction (PCR) between 1994 and 2003, by the new LightCycler technology between 2003 and 2005, and by real-time PCR assay (quantitative real-time PCR within a linear interval between 10 and 20 IU/ml; Cobas Taqman 48 HCV, Roche Diagnostic Systems, Branchburg, N.J., USA) between the years 2005 and 2010.

HLA typing
HLA groups were identified in peripheral blood lymphocytes by a standard complement-dependent microlymphocytoxicity method between 1994 and 1998 and by PCR with sequence-specific primers (PCR-SSP) between the years 1998 and 2010. The patients were divided into two groups as spontaneous viral clearance and persistence (chronic HCV infection) groups.

Statistical analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Mann-Whitney U-test, Chi-square test, and Fisher's exact test were used to compare the groups. Level of error was set at 0.05 for all statistical evaluations, and a *P* value lower than 0.05 was considered statistically significant.

RESULTS

In the present study, hospital records of 268 ESRD patients were reviewed. A total of 189 (male/female: 130/59) ESRD patients [median age, 27 (17-56) years] who met the inclusion criteria were enrolled. The patients were followed for a mean period of 108 (36-204) months after the detection of anti-HCV antibodies.

In HLA class I-A group, prevalence of >3% was observed in 11 out of 20 sub-group alleles. However, there was no significant difference in the prevalence between HCV clearance and persistence groups.

In HLA class I-B group, prevalence of >3% was estimated for 15 out of 42 sub-group alleles. It was associated with the positivity of HLA class I B*38 allele in the HCV persistence group. The prevalence of HLA class I B*38 allele was 10.6% ($n = 20$) in anti-HCV antibody-positive group versus 11.5% ($n = 23$) in the control group; it was detected to be 14.7% ($n = 19$) in HCV persistence group and 1.7% ($n = 1$) in HCV clearance group ($P < 0.01$) (odds ratio: 10.018; confidence interval 1.308-76.728) [Table 1].

In HLA class I-C group, prevalence of >3% was determined for 7 out of 11 sub-group alleles. Our primary analysis revealed that it was quite likely to be associated with HCV clearance in the group positive for HLA class I Cw*6 allele. The prevalence of HLA class I Cw*6 allele was 42.3% ($n = 55$) in the anti-HCV–positive group versus 46.3% ($n = 67$) in the control group; it was 66.7% ($n = 22$) in the HCV clearance group compared to 33.0% ($n = 34$) in the persistence group ($P < 0.001$) (odds ratio: 0.258; confidence interval 0.112-0.595) [Table 2].

In HLA class II-DR group, only HLA-DR and -DQ genotypic alleles were studied from -DR, -DQ, and -DP loci. The prevalence was >3% in 13 out of 17 genotypic alleles for HLA-DR locus. We detected that positivity of HLA class II DR*10 allele was associated with HCV clearance. The

prevalence of HLA class II DR*10 allele was 4.7% ($n = 8$) in anti-HCV–positive group versus 4.5% ($n = 9$) in the control group; it was 11.5% ($n = 7$) in the HCV clearance group and 1.8% ($n = 1$) in the persistence group ($P < 0.01$) (odds ratio: 0.130; confidence interval 0.025-0.669) [Table 3]. In HLA class II-DQ group, the prevalence was >3% in eight out of nine sub-group alleles. However, there was no significant difference between HCV clearance and persistence groups.

We investigated whether specific HLA genotypes play a role in the clearance or persistence of HCV infection in Turkish HD patients. We compared the frequencies of HLA class I and class II alleles in 189 HCV-positive ESRD patients and 199 HCV-negative subjects. Our control group consisted of healthy individuals who were evaluated in detail as potential renal donors. No statistically significant difference was observed between patient and control groups regarding the frequency of certain HLAs sub-typed.

On the other hand, we observed that three allele classes (two-step) correlated with the course of HCV infection at high degrees. HLA class I Cw*6 ($P < 0.001$) and class II DR*10 ($P < 0.05$) were associated with HCV clearance, while HLA class I B*38 ($P < 0.01$) was related to viral persistence.

DISCUSSION

Prevalence of HCV infection is substantially higher in dialysis and renal transplant patients as compared to the general population,[16] and chronic HCV infection is one of the

Table 1: Comparison of the cases in terms of HLA-B tissue groups

Allele	General population % (n=199)	Patient group % (n=188)	HCV clearance % (n=57)	HCV persistence % (n=129)	P value[a]	Odds ratio		
						Volume	Lower	Upper
B*7	5.5 (11)	9.6 (17)	10.2	9.3	0.851	0906	0323	2544
B*8	6.0 (12)	112 (21)	16.9	8.5	0.089	0.457	0.182	1.145
B*13	4.0 (8)	4.8 (9)	5.1	4.7	1.000*	0.911	0.220	3.773
B*18	9.0 (18)	13.3 (25)	153	12.4	0.593	0.787	0.326	1.900
B*27	5.0 (10)	3.2 (6)	5.1	2.3	0.380	0.444	0.087	2.271
B*35	36.7 (73)	33 (62)	33.9	32.6	0.856	0.941	0.490	1.808
B*38	**11.6 (23)**	**10.6 (20)**	**1.7**	**14.7**	**0.007**	**10.018**	**1.308**	**76729**
B*39	2.0 (4)	4.8 (9)	5.1	4.7	1.000	0.911	0.220	3.773
B*41	4.0 (8)	3.7 (7)	1.7	4.7	0.437	2.829	0.333	24045
B*44	13.1 (26)	144 (27)	136	147	0.832	1.101	0.452	2.682
B*49	4.5 (9)	9.0 (17)	5.1	10.9	0.157	2.272	0.627	8.232
B*50	7.0 (14)	7.4 (14)	6.8	7.8	1.000	1.155	0.347	3.847
B*51	29.1 (58)	274 (50)	33.9	23.3	0.125	0.591	0.300	1.162
B*55	9.5 (19)	6.4 (12)	6.8	6.2	1.000	0.909	0.263	3.147
B*60	6.5 (13)	5.9 (11)	1.7	7.8	0.177	4.874	0.609	38.992
B*62	4.5 (9)	3.7 (7)	1.7	4.7	0.437	2.829	0.333	24.045
Bw*4	67.6 (188)	65.4 (127)	64.4	69.0	0.533	1.230	0.642	2.357
Bw*6	67.0 (188)	61.3 (118)	62.7	69	0.395	1.323	0.693	2.525

[a]*P* value has been calculated by Fisher's exact test, Significant allele has been bold texted

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Table 2: Comparison of the cases in terms of HLA class I-Cw tissue groups

Allele	General population % (n=199)	Patient group % (n=129)	HCV clearance % (n=33)	HCV persistence % (n=96)	P value[a]	Odds ratio		
						Volume	Lower	Upper
Cw*1	5.7 (10)	13.2 (17)	6.1	15.6	0.235	2870	0.620	13.287
Cw*2	9.6 (16)	9.3 (12)	3.0	11.5	0.294	4.141	0.514	33.384
Cw*3	17.1 (30)	14.0 (18)	15.2	13.5	0.818	0.877	0.287	2.608
Cw*4	38.3 (67)	49.6 (64)	42.4	52.1	0.338	1.475	0.664	3.277
Cw*5	5.1 (9)	3.1 (4)	3.0	3.1	1000	1.032	0.104	10.281
Cw*6	**46.3 (67)**	**42.3 (55)**	**66.7**	**34.0**	**0.001**	**0.258**	**0.112**	**0.595**
Cw*7	24.0 (42)	14.7 (19)	9.1	16.7	0.398	2.000	0.544	7.357

[a]*P* value has been calculated by Fisher's exact test, Significant allele has been bold texted

Table 3: Comparison of the cases in terms of HLA class II-DR tissue groups

Allele	General population % (n=199)	Patient group % (n=176)	HCV clearance % (n=54)	HCV persistence % (n=122)	P value[a]	Odds ratio		
						Volume	Lower	Upper
DR*1	13.1 (26)	10.8 (19)	13.0	9.8	0.538	0.732	0.271	1.977
DR*4	29.1 (58)	26.3 (46)	241	27.3	0.657	1.183	0.564	2.482
DR*7	15.1 (30)	13.1 (23)	14.8	12.3	0.647	0.806	0.320	2.033
DR*8	4.0 (8)	3.4 (6)	1.9	4.1	0.668	2.265	0.258	19.865
DR*10	**4.5 (9)**	**5.1 (9)**	**13.0**	**1.6**	**0.004**	**0.112**	**0.022**	**0.558**
DR*11	40.7 (81)	409 (72)	33.3	44.3	0.174	1.588	0.813	3.101
DR*12	4.0 (8)	3.4 (6)	5.6	2.5	0.373	0.429	0.084	2.195
DR*13	23.1 (46)	159 (28)	111	18.0	0.247	1.533	0.577	4.625
DR*14	10.1 (20)	10.8 (19)	7.4	12.3	0.435	1.752	0.553	5.550
DR*15	17.1 (34)	21.6 (38)	16.7	23.8	0.291	1.559	0.681	3.596
DR*16	6.5 (13)	4.0 (7)	5.6	3.3	0.440	0.576	0.124	2.668
DR*17	16.6 (33)	16.5 (29)	18.5	156	0.627	0.812	0.349	1.886
DR*52	0.0 (0)	5.1 (9)	9.3	3.3	0.135	0.332	0.086	1.290

[a]*P* value has been calculated by Fisher's exact test, Significant allele has been bold texted

leading causes of serious liver disease in ESRD patients.[4,5,17] The natural history and course of HCV infection in such patients have not been completely understood. Chronic HCV infection is mostly asymptomatic in HD patients, and successful elimination of HCV is observed in only 15% of HCV-infected patients. The main mechanism of viral elimination is through cytotoxic T-cell and natural killer (NK) cell–mediated pathways which are activated via expression of HLA class I and II gene products.[18] This antiviral immunological process can be influenced by other comorbid conditions like ESRD in which impaired T cell activity has been reported during HD treatment. Compared to increased counts of CD8 + and NK cells, interleukin (IL)-2 production as well as IL-4 and IL-10 humoral immunity are significantly lower in such patients.[19]

It is known that many viral and host-related agents influence the progression of HCV infection. In addition to direct cytopathic effect of the virus, absence of repetitive immune responses of the host plays an important role in HCV-related liver diseases. Immune response against HCV is polyclonal and multi-specific, which is also affected by a number of factors.[20] The activation of T helper (TH) 1 response is associated with spontaneous resolution of

viral infection compared to HCV persistence with a TH2 response. Although it is known that T cells, particularly TH CD4+, contribute to activation during HCV infection, the mechanisms which play a role in activation remain unclear.[21]

Previous studies suggest a relationship between HLA alleles and haplotypes and progression of HCV infection (in terms of treatment response, development of cirrhosis, and HCC).[22] However, the role of many HLA antigens in the development and progression of HCV infection remains debatable.[21,23] Studies investigating the relationship between HCV and HLA class I alleles have been conducted in people of various ethnic origins to outline the proclivity toward HCV infection in many countries. In Japan, Higashi *et al.* reported that those carrying HLA-B*61 and -Cw*3 alleles were more prone to chronic HCV infection.[24] Fanning *et al.* conducted a study in Ireland and reported a correlation between HLA-A*11, -Cw*04, and HCV persistence.[25] Additionally, HLA-A*01, -B*8, and-Cw*07 in Irish population,[26] HLA-A*3, -B*35, and-B*46 in Korean population,[27] HLA-B*14 in Italian population,[28] as well as HLA-Cw*04 and HLA-B*35 alleles in American Caucasians[29] were also observed to be correlated with HCV persistence. Hadhoud *et al.* conducted a common study in Saudi and Egyptian

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populations and investigated the correlation between HCV and HLA phenotypes in renal transplant patients positive for HCV infection. Frequency of HLA-A*19 phenotype was higher in HCV-positive patients of the Saudi population.[30] In our study, we found that HLA class I-A and-Cw alleles had no significant effect on HCV persistence.

The higher HLA class I B*38 allele frequency in HCV persistence group is an original finding since current literature review revealed no previous study showing such an association. On the other hand, the effect of HLA class I genotype on clearance of HCV infection was demonstrated in many studies. HLA-A*1101, HLA-B*57 (West African population),[31] Cw*4 allele (Russian population),[32] and Cw*0102 allele (American population)[29] were found to be protective against infection. In infants, HLA Cw*0602 and HLA Cw*07 alleles were protective against vertical HCV transmission.[33] We found that HLA class I-A and -B alleles had no significant effect on HCV clearance, while the frequency of HLA class I Cw*6 allele was significantly high in HCV clearance group.

Studies investigating the effect of HLA class II on HCV persistence reported that HLA DRB1*0405 and DQB1*0401/0402 (Japan),[24,34] HLA DQB1*0501 (America),[35] HLA DRB1*0301, DQB1*0201, and DQA1*0201 (Thailand and Europe),[36,37] as well as HLA DRB1*0701 (Europe)[38] were correlated with HCV persistence. The frequency of HLA DRB1*15-DQB1*0602 allele was higher in Irish families having chronic HCV infection with high viral load.[11] In an Italian study, DR*14 was correlated with hepatic cirrhosis and DR*17 and DQB1*0502 were correlated with progressive liver injury.[28]

In our study, HLA class II-DR and-DQ alleles had no significant effect on HCV persistence. Studies investigating the correlation between HCV viral clearance and HLA class II have shown a compatible relationship of HLA DRB1*11 and DQB1*0301 alleles with decreased disease severity of chronic HCV infection.[39,40] There was a strong relationship between HCV clearance and DQB1*0301 allele in French female population, DRB1*11 allele in French males,[41] DRB1*11 allele in French females,[42] and HLA DQB1*0301 allele in African-American population.[43] The HLA DR*11 and DQB1*0301 alleles, having a powerful presentation ability of antigenic HCV epitopes to CD4+ T cells, may offer effective viral clearance.[40] Viral clearance was also correlated with DRB1*0101 and DQ1*0501 alleles (American Caucasians)[43] and with DRB1*0101 allele (Irish and Saudi populations).[30,44] HCV-specific T-cell response was powerful in HLA DRB1*0101 alleles. DRB1*0701-DQB1*02 haplotypes were correlated with low HCV load in Ireland.[11] The lack of such an association in our study can be explained by the ethnic differences of our study population.

In Japan, DRB1 * 0901-DQB1*0303 haplotypes were detected as protective against cirrhosis,[45] whereas HLA B*44-DRB1 *1302-DQB1*0604 and DRB1*1302-DRB1*0604 were correlated with asymptomatic carrier phenotype.[34]

Yenigün et al. conducted a study in 49 patients with chronic HCV and 43 healthy controls to investigate HLA class II genotype profile and to determine the relation between HLA and HCV in chronic HCV infection. They reported that the frequency of HLA class II DRB1*11 allele was decreased in the patients with chronic hepatitis C.[14]

Various correlations have been found between HLA class II alleles and the natural history of HCV infection. Worldwide, population-based studies have indicated a correlation between DQB1*0301 and clearance of HCV infection.[42] Interestingly, there is an imbalance between DQB1*0301 and DRB1*1101 (non-randomized association between the polymorphisms in different loci). Moreover, DRB1*1101 was correlated with clearance of HCV infection in various studies.[13,24,37,41] In our study, we found that the frequency of HLA class II DR*10 allele was significantly high in the group with spontaneous clearance of HCV infection. We detected that HLA class II DQ alleles had no significant effect on HCV clearance.

Host–virus interaction in acute or chronic HCV infection is related to cellular immune response, which is regulated by HLA type and HLA-restricted viral "escape mutants." Genetically transferred HLA is one of the most important factors that determine the interpersonal differences in the immune response. Previous studies show different results concerning HLA serotypes between different ethnic groups, and even in the same ethnic group. Inappropriate design of the studies and inadequate sample size may lead to such conflicting results. While previous studies have been conducted in other ethnic or geographic populations, our study is the first one conducted in ESRD patients from different regions of Turkey.

In the present study investigating the correlation between specific HLA alleles and HCV infection in ESRD patients positive for anti-HCV antibody, it was determined that HLA-B*38 allele was an important risk factor for development of chronic HCV infection. On the contrary, we detected that HLA-Cw*6 and-DR*10 alleles provided viral clearance and prevented the development of chronic hepatitis C.

The data provided are not enough to clearly conclude that there is a correlation between the selected HLAs and the clearance or persistence of HCV infection. Further experiments, including functional studies, need to be performed to confirm that those HLA alleles are playing an

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important role in the clearance of HCV. Better understanding of the genetic infrastructure of the host in patients with HCV infection is of critical importance for the development of new prophylactic and immune-modulator antiviral strategies. The relationship between HCV infection and HLA can be enlightened with better designed studies conducted in larger patient groups.

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