Correlation of locus alleles of DRB1 II class of histocompatibility complex with clinical, immunological and virological parameters in HIV infection

Volikova Olga Aleksandrovna,
SE «Dnepropetrovsk Medical Academy of Health Ministry of Ukraine», teaching assistant
E-mail: ovolja@ukr.net

Summary: Associations between the presence in HIV infected patients of different variants of HLA DRB1 locus alleles and the risk of HIV-associated diseases development while receiving HAART are determined. There is a correlation between HLA DRB1 locus alleles of histocompatibility class II and levels of β2-microglobulin, neopterin, immune cell activation and HIV load in patients receiving HAART.

Keywords: HIV infection, HIV-associated diseases, the system of HLA II class, allele locus DRB1, viral load, CD4, HAART.

It was shown that the increase in viral load (VL) may promote systemic activation of the immune system in HIV infection, which is a strong predictor of disease progression in HIV infection. It was proved that increased level of β2-microglobulin (β2-MG) is associated with changes in the immune status and HIV viral load and is connected with HIV progression and survival of patients [2, 3].

There are literary data regarding positive associations of tuberculosis with specific HLA DRB1 locus that indicate susceptibility to tuberculosis [1].

Objective: Identify association between the presence of different variants of locus alleles of DRB1 in patients with HIV infection and the risk of HIV-associated disorders and changes in immunological and virological parameters in patients receiving highly active antiretroviral therapy (HAART).

Materials and methods. The study involved 102 patients with HIV aged 24 to 58 years, the average age of patients was 38 years. The term of infection of examined subjects was in averaged 7.4 ± 0.33 years. According to the clinical

course of HIV infection, all patients were divided into three groups. The 1st group included 32 patients (31.4 %) with I and II clinical stages, the 2nd group included 26 (25.5 %) patients with clinical stage III, the 3rd group included 44 (43.1%) patients with IV clinical stage. All patients were also divided into seven groups by the presence of locus alleles DRB1 of class II histocompatibility complex. Six research groups consisted of patients with alleles of genes that occur most frequently among persons in the Dnepropetrovsk region: HLA DRB1 *01, HLA DRB1 *04, HLA DRB1 *07, HLA DRB1 *11, HLA DRB1 *13, HLA DRB1 *15. The seventh group consisted of patients with alleles locus that is rarely found (HLA DRB1 *03, HLA DRB1 *08, HLA DRB1 *10, HLA DRB1 *12, HLA DRB1 *14, HLA DRB1 *16, HLA DRB1 *17, HLA DRB1 *18). Most examined patients (87.3%) received HAART for medical reasons, 12.7 % of patients in the study did not receive HAART for any other reason. The control group involved 15 healthy donors.

Specificities of 15 alleles of genes DRB1 were defined with amplified test systems. Determination of levels of neopterin (N) and β2-MG handled by ELISA with standard test systems (manufacturer Germany).

Statistical analysis of the obtained material used the methods of Fisher criterion and Student's test. Value of $p < 0.05$ was considered statistically significant. Statistical analysis of the results was performed using the software MathCad and Excel-2010. Considering the large range of VL data, for statistical analysis a log scale data were calculated.

Results. According to our observations the highest percentage of occurrence of various forms of HIV-associated tuberculosis (TB), including first diagnosed tuberculosis (FDTB) observed in the lungs of patients with locus alleles HLA DRB1 *13 *15 and rarely seen locus alleles. Also various forms of TB in a smaller percentage of cases developed in patients with locus alleles HLA DRB1 *04 *07 *11. TB never occurred in patients who had gene allele HLA DRB1 *01 (Table 1).

Table 1. Dynamics of HIV-associated diseases in patients with different alleles of HLA DRB1 locus in patients receiving HAART

Alleles HLA DRB1 locus	PGL, %	Oropharyngeal candidiasis, %	Recurrent bacterial infection of the URT, %	Pneumonia, %	FDTB lung	Various forms of TB, %	Herpetic infection, %
HLA DRB1 *01	31.6	67.7	31.6	31.6	-	-	-
HLA DRB1 *04	43.6	87.5	37.5	-	31.3	-	37.5
HLA DRB1 *07	-	50	37.5	-	-	26.9	34.6
HLA DRB1 *11	30.4	78.3	33.3	33.3	-	33.3	23.3
HLA DRB1 *13	37.5	79.2	-	41.7	37.5	45.8	-
HLA DRB1 *15	-	75	-	-	50	50	-
Rare alleles	20	80	30	-	35	40	30
P	<0.004	<0.003	<0.004	<0.005	<0.003	<0.004	<0.005

As shown in Table 1, recurrent bacterial infection of the upper respiratory tract (URT) occurred in patients with HIV locus with alleles HLA DRB1 *01, *04, *07, *11 and with rare alleles. Pneumonia developed in patients who have had locus alleles HLA DRB1 * 01, * 11, * 13. Concurrent herpetic infections in HIV-infected patients occurred in the presence of gene alleles HLA DRB1 *04 *07 *11 and rare alleles of locus. In HIV-infected examined patients of all groups regardless of the system of HLA DRB1 HIV-associated oropharyngeal candidiasis

developed. Persistent generalized lymphadenopathy (PGL) was seen in HIV infected patients with locus alleles HLA DRB1 *01 *04 *11 *13 and rare alleles.

Table 2. Dynamics of disease development in HIV-infected patients with different locus alleles of HLA DRB1 in patients receiving HAART

Alleles HLA DRB1 locus	CHCV, %	CHBV, %	CH unspecified (including toxic hepatitis), %	Cirrhosis, %	Anemia I, II, III degree, %
HLA DRB1 *01	63	42	84	-	-
HLA DRB1 *04	68.7	43.8	81.3	31.3	56.3
HLA DRB1 *07	41.7	-	58.3	-	-
HLA DRB1 *11	60.8	34.8	78.3	-	52.2
HLA DRB1 *13	62.5	-	79.2	-	33.3
HLA DRB1 *15	50	-	66.7	-	-
Rare alleles	52.5	37.5	72.5	-	30
P	<0.004	<0.003	<0.005	<0.004	<0.003

Chronic viral hepatitis C (CHCV) and chronic hepatitis (CH) unspecified (including toxic hepatitis) as concomitant disease, developed in HIV-infected patients irrespective of HLA class II. Chronic viral hepatitis B (CHBV) occurred in patients with gene alleles HLA DRB1 *01, *04, *11 and rare alleles. CH progressed into cirrhosis in patients with locus alleles HLA DRB1 *04. Anemia I, II, III degree accompanies patients with HIV infection who have locus alleles HLA DRB1 *04, *11, *13 and rare alleles. (Table 2)

Table. 3. Dynamics of biochemical and immunological parameters in HIV-infected patients with different locus alleles DRB1 II class while taking HAART

Alleles of HLA DRB1 locus	Groups of patients	N, nmol/l	β_2-MG, mcg/ml	$CD4^+$ T-helper cells	*P*
HLA DRB1 *01	I	33.444±29.479	6.578±1.676	426 ±185	<0.003
	II	53.5±3.536	9.25±0.355	340±4.95	<0.006
	III	56.714±10.847	9.429±1.117	323±200	<0.004
HLA DRB1 *04	I	65±42.509	9.2±45.197	428±115	<0.003
	II	68.4±1.709	9.44±2.389	422±184	<0.006
	III	77.125±10.062	25.039±1.432	127±123	<0.004
HLA DRB1 *07	I	29.125±14.055	7.05±1.623	552±191	<0.003
	II	53.333±33.399	8.6±2.245	279±59	<0.006
	III	50±10.583	8.14±0.876	193±89	<0.004
HLA DRB1 *11	I	24±9.899	6.45±0.636	468±145	<0.003
	II	56.222±14.292	9.389±1.013	359±86	<0.006
	III	68.1±30.658	10.06±1.831	130±92	<0.004
HLA DRB1 *13	I	46±9.077	8.3±1.011	533±238	<0.003
	II	56.333±37.033	8.7±2.573	387±146	<0.006
	III	61.083±24.839	9.042±1.215	171±129	<0.004
HLA DRB1 *15	I	31.875±13.943	7.238±1.48	551±172	<0.003
	II	79±8.888	9.663±1.212	211±69	<0.006
	III	83±33.141	9.757±1.427	201±201	<0.004
Rare alleles	I	31±12.423	7.757±1.176	447±183	<0.003
	II	50±20.255	8.531±1.284	344±117	<0.006
	III	74.706±32.247	9.641±1.855	162±130	<0.004

As shown in Tables 3, 4 in almost all patients in all examined groups there was an increase in VL, reduced levels of CD4 + T-helper cells and increased levels of N and β2-MG in the development of HIV from I till IV clinical stages in patients receiving HAART.

Table. 4.Dynamics of changes in viral load in HIV-infected patients with different gene alleles DRB1 II class on HAART

Alleles HLA DRB1 locus	Groups of patients	VL (ln)	*P*
HLA DRB1 *01	I	4.325±3.433	<0.004
	II	3.689	<0.007
	III	2.405±5.753	<0.005
HLA DRB1 *04	I	3.689	<0.004
	II	4.677±3.047	<0.007
	III	7.461±4.423	<0.005
HLA DRB1 *07	I	4.359±2.085	<0.004
	II	4.144±1.991	<0.007
	III	5.583±2.81	<0.005
HLA DRB1 *11	I	3.924±0.332	<0.004
	II	5.661±2.942	<0.007
	III	7.486±4.377	<0.005
HLA DRB1 *13	I	4.619±2.168	<0.004
	II	7.767±2.857	<0.007
	III	5.292±2.127	<0.005
HLA DRB1 *15	I	6.216±3.632	<0.004
	II	8.154	<0.007
	III	8.154±4.327	<0.005
Rare alleles	I	5.064±3.074	<0.004
	II	4.008±0.625	<0.007
	III	7.16±4.139	<0.005

In patients with the allele HLA DRB1 *01 reduction in VL 1.8-fold (between I and III groups) was observed and CD4+ T-helper cells were kept at a high level (up to 323±200) even taking into account the stage of HIV infection that was not observed in other alleles of the HLA DRB1 gene. In all other patients who had the allele HLA DRB1 locus *04, *07, *11, *13, *15 and rare alleles with IV clinical stage CD4+ T-helper cells were decreased to the level of ≤200 in 1 mm^3 and VL was increased 1.2 – 2.1 times. Increased levels of N and β2-MG were

observed in all patients with different alleles of the HLA DRB1 locus. However, the most significant increase in both N and β2-MG was seen in carriers of alleles of the locus HLA DRB1 *01, *11, *15. Thus, at HLA DRB1 *01 N was increased 1.7 times, β2-MG by 1.4 times; in HLA DRB1 *11 N was increased 2.8 times, β2-MG is 1.6; with HLA DRB1 *15 N was increased 2.6 times, β2-MG 1.4 times. A separate significant 1.7 times increase of N was observed in patients with alleles of the locus HLA DRB1 *07 and in rare alleles 2.4 times. A separate and significant increase of β2-MG 2.7 times was observed in patients who had the alleles of the locus HLA DRB1 *04.

Conclusions.

1. There was a correlation between alleles of DRB1 locus of HLA histocompatibility class II and β2-MG, N, cellular immune activation and HIV load in patients receiving HAART.

2. In the process of receiving HAART in patients with alleles of the locus HLA DRB1 *01 there was observed the 1.8 times decrease of VL, the content of CD4+ T-helper cells at a sufficiently high level, even taking into account the stage of HIV infection that was not observed in other alleles of the HLA DRB1 gene. With the alleles of the locus HLA DRB1 *04, *07, *11, *13, *15 and rare alleles even with HAART there was a sharp decrease in CD4+ T-helper cells to the level of $\leq$200 in 1 mm^3 and an increase in VL.

3. Increased levels of N and β2-MG were observed in all patients with different alleles of the HLA DRB1 locus. However, the most significant increase in both N and β2-MG was seen in alleles of the locus HLA DRB1 *01, *11, *15.

4. The highest percentage of occurrence of HIV-associated TB of various forms, including FDTB lung was observed in patients with alleles of the locus HLA DRB1 *13, *15 and with rare alleles. Also TB of various forms in a smaller percentage of cases developed in patients with alleles of the locus HLA DRB1 *04, *07, *11. In patients who had the allele of gene HLA DRB1 *01 TB did not develop.

5. Pneumonia developed in HIV-infected patients who had alleles of the locus HLA DRB1 *01, *11, *13.

6. The development of herpetic infection in HIV-infected patients occurred in the presence of gene HLA DRB1 alleles *04, *07, *11 and rare alleles.

7. Chronic HCV and chronic hepatitis unspecified (including toxic hepatitis) as a concurrent disease developed in HIV-infected patients regardless of the HLA class II. Chronic HBV was seen in patients with HLA alleles DRB1 *01, *04, *11, and rare alleles. Chronic hepatitis progressed to cirrhosis in patients with alleles of the locus HLA DRB1 *04.

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