SANAMED
2013; 8(1): 11–18
ISSN-1452-662X

UDK: 616.36-002-085 ; 616.98:578.828
Originalni naučni rad

ACTIVATION OF BLOOD T-CELLS IN HIV/HCV CO-INFECTED PATIENTS

Matsiyeuskaya V. Natallia, Tsyrkunov M. Vladimir

Grodno State Medical University, Grodno, Belarus

Primljen/Received 04. 01. 2013. god.

Prihvaćen/Accepted 01. 03. 2013. god.

Abstract: Expression of HLA-DR which is immune response activation marker on T-cells and their subpopulations (CD4+ and CD8+ lymphocytes) and number of $CD4^+/CD25^+$ cells with immune suppression properties in blood of HIV/HCV coinfected patients depending on HIV viral load, AIDS and receiving of antiretroviral therapy were studied. It was detected that HLA-DR expression on T-cells was significantly higher in patients with detectable HIV viral load, AIDS, and in patients not receiving antiretroviral therapy. Antiretroviral therapy leads to significant reduction of immune system activation markers expression, though it doesn't allow to reach the level of healthy individuals. Number of $CD4^+/CD25^+$ cells had inverse correlation with activated CD3+ and CD3+CD8+ lymphocytes and HIV viral load.

Key words: HIV, HCV, immunity activation, HLA-DR, $CD4^+/CD25^+$ T-cells.

INTRODUCTION

At present chronic activation of immune system is the crucial aspect of HIV infection pathogenesis. Hyperimmune response leads to synthesis of proinflammatory cytokines, increased production of new HIV virions, loss of central IS cellular elements: CD4+ and CD8+ lymphocytes. IS activation is more significant factor than CD4 lymphocytes level in survival rate prognosis of HIV infected patients (1, 2, 3).

There are various mechanisms, providing chronic IS activation in HIV infection. One of the mechanisms is associated with massive loss of CD4+ T-cells in the intestinal lymphoid tissue of HIV infected patients, which takes place from the first days of HIV infection. This leads to disturbance of the intestinal wall barrier properties, creates conditions for translocation into the systemic circulation of intestinal flora microorganisms, proinflammatory cytokines, lipopolysaccharides produced by gram-negative intestinal bacterias (vigorous stimulator of immune system cells), promoting activation of immune system via innate pattern recognition (2, 4).

Another important mechanism of immune system activation is interaction of HIV-1 with T-cells and macrophages in the process of virus replication in an infected organism. It was detected that HIV ability to induce immune activation creates conditions for HIV replication in human cells, as far as productive HIV infection can be realized only in activated human cells. It should be added that various coinfections (bacterial, viral, fungous, parasitic etc.) occurring in HIV infected patients were proved to be factors of immune system activation in HIV infection. A number of studies show that immunization of HIV infected patient may induce immune system activation (2, 5).

Chronic immune system activation is associated with some negative consequences for a patient: increased level of HIV in blood and tissues, high variability of HIV, virus resistance to ART, increased ability of virus for transmission by sexual and transplacental routes, etc. Eventually immune system activation provides HIV infection progression and promotes unfavorable disease prognosis (1, 6).

Cellular activation markers of the immune response are such molecules as HLA-DR, CD38+, CD71+ (6). Membrane molecules HLA-DR, concerning to MCH–II class, are represented on antigen presenting cells (dendritic cells, macrophages/monocytes, B-lymphocytes, vascular endothelium, etc.). Besides, from the side of T-cells, participating in HLA-DR identification, the connection with CD4-molecule is necessary as it acts as a coreceptor for class II MHC molecules (1).

CD25 — is a receptor to one of the main T tropic cyrokines — interleukin 2. CD127 low CD25 high is subpopulation which represents FoxP3-expressing regulatory CD4+ T-cells (7, 8).

It was proved, that population of regulatory CD4+CD25+ T cells, inhibit activity of effector T-cells with CD4+CD25- phenotype. Number of CD4+CD25+ cells in blood of healthy donors makes up 0.7–5.5% from peripheral mononuclear cells. In HIV infected patients Treg cells induce suppression of HIV specific and general cellular immune response (9, 10).

AIM OF THE RESEARCH

To detect content of T-cells, expressing HLA-DR and content of CD4+/CD25+ T-cells in HIV/HCV co-infected patients depending on HIV viral load, AIDS, receiving of antiretroviral therapy.

MATERIALS AND METHODS

The patients included in the study were divided into two groups. The 1st group included 51 patients with HIV/HCV coinfection, the 2nd group consisted of 10 patients with HCV infection. To determine the clinical stage of HIV infection WHO classification was used (2006). Control group consisted of 16 healthy individuals (3 men and 13 women negative for the markers of viral hepatitis type B and C and HIV infection, aged 32.5±15.1 years old on average). All patients were tested for HBV and HCV serological markers using ELISA kits. RNA load and HCV genotype was studied using "Amplisens" kits (Russia). The diagnosis of HIV infection was verified by detection of antibodies to HIV using ELISA and immunoblot. Plasma viral load (VL) of RNA HIV were detected using Ampisens monitor (Russia). Detectable level of RNA was defined as 500 copies/mL.

Clinical characteristic of patients included in the study is given in Table 1.

As seen in Table 1, the age of patients in groups didn't differ significantly, with men prevalence. Parenteral way of HIV transmission due to intravenous drug use was detected in 55% of cases in group 1 and in 10% of cases in group 2. AIDS was established if level of CD4+ T lymphocytes was less than 200 cells/mkl and/or if patient had the fourth stage of HIV infection according to WHO classification, 2006.

In the current investigation the following monoclonal antibodies were used ("Becton Dickenson", USA):

1) CD3 (SK7, FITC) / CD16 (B73.1, PE) + CD56 (NCAM 16.2, PE) / CD45 (2D1, PerCP) / CD19 (SJ25C1, APC)

2) CD4 (SK3, FITC) /CD8 (SK1, PE) /CD3 (SK7, PerCP)

3) HLA-DR (L243, APC)

4) CD4 (SK3, APC)

5) CD25 (M-A251, FITC).

The cells were analyzed using "FACSCalibur" flow cytometer ("Becton Dickenson", USA). Cell acquisition and analysis were performed using "CellQuest" version 3.3 and "Weasel" version 2.9 software (WEHI, Australia).

Statistical Analysis

Differences between groups were analyzed via Kruskal-Wallis test and two-tailed unpaired nonpara-

Table 1. *Characteristics of patients in study groups*

Index	group 1 HIV/HCV n = 51	group 2 HCV n = 10
Age, years	34.1 ± 5.9	40.3
Men. abs. (%)	39 (76.5)	7 (70.0)
Women. abs. (%)	12 (23.5)	3 (30.0)
IDU n (%)	28 (54.9)	1 (10.0)
1 genotype HCV. n (%)	17 (51.5)*	7 (70.0)
Not 1 genotype HCV. n (%)	16 (48.5)	3 (30.0)
1 clinical category. n (%)	22 (43.1)	
2 clinical category. n (%)	23 (45.1)	
3 clinical category. n (%)	4 (7.8)	
4 clinical category. n (%)	2 (3.9)	
AIDS. n (%)	11 (23.5)	
ART recipients. n (%)	17 (33.3)	

Note: * – $p < 0.05$ in comparison with the patients of group 2; test χ^2; (IDU) — injecting drug users; ART — antiretroviral therapy.

Table 2. *HLA-DR expression on T-cells in groups of patients*

Parameter. Median (ranges)	Control n = 16	1A group HIV/HCV n = 17	1B group HIV/HCV n = 34	2 group HCV n = 10
HLA-DR (%)	21.2 (15.6–36.3)	33.6 (21.1–71.5)*,****	46.8 (17.3–71.6)*,****	17.2 (11.3–42.5)
HLA-DR cells/μL	574.9 (225.9–1269.2)	629.2 (140.3–1227.6)	837.5*,**** (224.1–1669.7)	379.0 (120.5–1534.3)
CD3+/HLA-DR (%)	8.6 (2.2–18.7)	19.5 (12.0–67.6)*,****	33.9 (10.8–63.8)*,****	7.7 (4.3–22.73)
CD3+ /HLA-DR cells/μL	176.8 (60.9–652.8)	387.7 (74.3–1159.8)*,***,****	585.0 (174.1–1626.5)*,****	138.8 (77.2–796.6)
CD4+/HLA-DR (%)	5.0 (2.9–9.9)	3.4 (1.9–6.4)*,***,****	4.1 (1.6–10.0)*	3.7 (2.4–9.1)
CD4+ /HLA-DR cells/μL	101.5 (64.5–345.4)	55.8 (29.0–146.7)*	72.6 (10.0 – 274.5)*	81.8 (29.0–186.1)
CD8+/HLA-DR (%)	5.4 (2.3–17.0)	23.0 (11.0–59.2)*,****	31.7 (12.8–60.6)*,****	6.7 (3.6–18.4)
CD8+ /HLA-DR cells/μL	114.7 (63.9–577.9)	366.4 (100.0–1015.4)*,***,****	518.9 (173.3–1655.3)*,****	124.0 (62.8–664.7)

Note: * – $p < 0.05$ in comparison with control; ** – $p < 0.05$ in comparison with 1A group patients; *** – $p<0.05$ in comparison with 1B group patients; **** – $p<0.05$ in comparison with 2 group patients; Mann-Whitney test.

Table 3. *CD4+/CD25+ cell in the studied groups*

Parameter. Median (ranges)	Control n = 16	1A group HIV/HCV n = 17	1B group HIV/HCV n = 34	2 group HCV n = 10
CD25+ (%)	5.5 (3.5–8.5)	3.6 (1.8–8.0)*	3.8 (0.5–9.5)*	5.1 (2.8–14.0)
CD25+ cells/μL	128.3 (54.8–243.1)	49.6 (19.9–187.1)*,****	68.9 (7.6–260.5)*	108.8 (35.3–170.2)
CD4+/CD25+ (%)	3.6 (2.2–6.0)	2.0 (1.1–4.1)*,****	1.8 (0.3–6.7)*,****	3.9 (1.4–8.1)
CD4+/CD25+ cells/μL	87.8 (40.9–162.1)	31.6 (11.3–95.0)*,****	34.7 (1.0–224.0*,****	87.7 (22.2–126.4)

Note: * – $p < 0.05$ in comparison with control; ** – $p < 0.05$ in comparison with 1A group patients; *** – $p < 0.05$ in comparison with 1B group patients; **** – $p < 0.05$ in comparison with 2 group patients; Mann-Whitney test.

metric Mann–Whitney's test. The correlation between variables was evaluated using Spearman rank coefficient (r). A value of $p \leq 0.05$ was considered significant. All calculations were performed using the Statistica (StatSoft, USA) and StatPlus (AnalystSoft) software.

RESULTS

In group 1, 17 (33,3%) patients received ART. So, the immunological parameters were compared in 2 subgroups of group 1. Patients receiving ART were included in group 1A and ones not receiving, in group 1B (table 2). ART lasted from 6 months to 5 years. In most patients ART scheme was represented by combination of 2 nucleoside reverse transcriptase inhibitors and 1 non-nucleoside reverse transcriptase inhibitors, schemes with protease inhibitors were received by 2 patients. The genotypes of HCV were detected in 33 patients in the group 1 and in all patients (n = 10) of the group 2. The proportion of 1 genotype HCV was significantly higher in the patients of the 2nd group in comparison with the 1 st group.

As seen in Table 2, the highest expression of HLA--DR on T-cells was detected in 1B group patients

Table 4. *CD3+/HLA-DR (%) and CD8+/HLA-DR (%) correlations with other parameters in HIV/HCV coinfected patients*

Activated T-cells	Parameters	1A group HIV/HCV. n = 17	1B group HIV/HCV. n = 34
CD3+/ HLA-DR(%)	CD3+/CD4+ (%)	NS	R = – 0.80; p < 0.0001
	CD3+/CD8+ (%)	R = 0.5. p < 0.0001	R = 0.70; p < 0.0001
	IRI	NS	R= – 0.79; p < 0.0001
	CD8+/HLA-DR (%)	R= 0.91. p < 0.0001	R= 0.95; p <0.0001
	CD4+/CD25+ (%)	NS	R= – 0.73; p < 0.0001
	HIV VL	NS	R = 0.53; p = 0.005
	AIDS	NS	R = 0.42; p = 0.01
CD8+/ HLA-DR	CD3+/CD8+ (%)	R = 0.52. p = 0.03	R = 0.71; p < 0.0001
	IRI	R = – 0.56. p = 0.02	R = – 0.82; p < 0.0001
	CD3+/CD4+ (%)	NS	R = – 0.84; p < 0.0001
	CD4+/CD25+ (%)	NS	R = – 0.70; p < 0.0001
	AIDS	NS	R = 0.41; p = 0.02
	HIV VL	NS	R = 0.56; p = 0.003

Note: R — Spearman's rank correlation coefficient; NS — absence of significant differences (p > 0.05); IRI — immunoregulatory index (CD4+/CD8+)

Table 5. *Parameters of HLA-DR expression in HIV/HCV co-infected patients with detectable and undetectable HIV VL*

Parameter. Median (ranges)	HIV/HCV VL < 500 cp/ml n = 22	HIV/HCV VL > 500 cp/ml n = 22	P
HLA-DR (%)	33.0 (20.5–64.2)	50.7 (17.3–71.6)	0.02
HLA-DR cells/μL	595.8 (140.3–1305.6)	842.0 (224.1–1669.7)	NS
CD3+/HLA-DR (%)	19.0 (12.0–52.0)	36.7 (10.8–63.8)	0.006
CD3+/HLA-DR cells/μL	373.0 (74.3–1023.3)	603.1 (174.1–1626.5)	0.04
CD4+/HLA-DR (%)	4.1 (1.9–10)	4.2 (1.6–6.7)	NS
CD4+/HLA-DR cells/μL	62.6 (29.0–274.5)	67.2 (10.0–163.6)	NS
CD8+/HLA-DR (%)	21.1 (11.0–48.8)	34.4 (12.9–60.3)	0.005
CD8+/HLA-DR cells/μL	384.5 (100.0–926.8)	582.3 (173.3–1655.3)	0.04

Note: * — p, Mann-Whitney test.

Table 6. *CD4+/CD25+ indices in HIV/HCV infected patients with detectable and undetectable HIV VL*

Parameter. Median (ranges)	HIV/HCV VN < 500 cp/ml. n = 22	HIV/HCV VN > 500 cp/ml. n = 22	P
CD25+ (%)	4.9 (1.8–9.5)	3.1 (0.5–6.7)	0.005
CD25+ cells/μL	82.0 (19.9–260.5)	48.9 (7.6–197.3)	0.05
CD4+/ CD25+ (%)	2.7 (0.7–6.7)	1.4 (0.3–3.2)	0.002
CD4+/ CD25+ cells/μL	38.8 (11.3–224.0)	29.8 (1.0–81.3)	0.02

Note: Mann-Whitney test.

Table 7. *HLA-DR expression in patients with undetectable HIV VL (< 500 cp/ml.) depending on receiving of antiretroviral therapy*

Parameter. Median (ranges)	1A group HIV/HCV n = 13	1B group HIV/HCV n = 9	P
HLA-DR (%)	32.8 (21.1–64.2)	42.52 (20.5–63.2)	NS
HLA-DR cells/μL	456.4 (140.3–1108.1)	910.3 (443.3–1305.6)	0.02
CD3+/HLA-DR (%)	18.3 (12.0–40.8)	30.4 (13.0–52.0)	NS
CD3+/HLA-DR cells/μL	350.2 (74.3–765.0)	724.3 (287.8–1023.3)	0.02
CD4+/HLA-DR (%)	3.3 (1.9–6.4)	4.39 (3.0–10)	0.06
CD4+/HLA-DR cells/μL	41.1 (29.0–146.7)	113.4 (59.8–274.5)	0.003
CD8+/HLA-DR (%)	21.0 (11.0–48.3)	29.5 (12.8–48.8)	NS
CD8+/HLA-DR cells/μL	327.4 (100.0–733.0)	511.8 (289.7–926.8)	0.02

Note: * – p, Mann-Whitney test; patients didn't receive (–) and received (+) ART.

Table 8. *HLA-DR expression on T-cells and CD4+/CD25+ content in HIV/HCV coinfected patients in absence and presence of AIDS*

Parameter. Median (ranges)	HIV/HCV AIDS (–), n = 28	HIV/HCV AIDS (+), n = 6	P*
HLA-DR (%)	44.8 (17.3–67.2)	62.6 (49.8–71.6)	0.006
HLA-DR cells/μL	843.9 (387.6–1669.7)	733.5 (224.1–1470.1)	NS
CD3+/HLA-DR (%)	30.5 (10.8–59.8)	48.4 (34.7–63.8)	0.01
CD3+/HLA-DR. cells/μL	603.1 (243.7–1626.5)	562.1 (174.1–1023.8)	NS
CD4+/HLA-DR (%)	4.1 (1.7–10.0)	4.1 (1.6–6.8)	NS
CD4+/HLA-DR cells/μL	79.9 (48.4–274.5)	51.5 (10.0–75.7)	0.004
CD8+/HLA-DR (%)	30.0 (12.8–59.0)	44.1 (32.3–60.3)	0.02
CD8+/HLA-DR cells/μL	540.1 (283.7–1655.3)	512.9 (173.3–952.4)	NS
CD4+/CD25+ (%)	2.3 (0.7–6.7)	1.0 (0.3–1.7)	0.004
CD4+/CD25+ cells/μL	43.4 (13.8–224.0)	10.6 (1.0–34.2)	0.002

Note: * – p, Mann-Whitney test. NS – not significant (p > 0.05); presence (+) and absence (–) of AIDS stage

(HIV/HCV co-infection without ART), but percentage of CD4+ lymphocytes and absolute value CD3+ and CD8+ T-cells expressed HLA-DR in 1B group were significantly higher in comparison with 1A group patients, receiving ART. At the same time indices of HLA-DR expression on CD3+ and CD8+ T-cells in patients of 1A and 1B groups were higher in comparison with the control group and group 2 (HCV infection). Percentage of activated T-helpers in both groups of HIV infected patients was lower in comparison with control group, and absolute content of activated T-helpers was lower in comparison with the control group as well as group 2.

Percentage and absolute number of CD4+/CD25+ Treg cells in studied groups are given in Table 3.

As seen in Table 3, CD25+ and CD4+/CD25+ indices content didn't significantly differ in patient groups receiving ART or not receiving ART. At the same time significant differences were detected in both parameters with the control group. Besides, in both groups with HIV/HCV coinfection percentage and absolute value of CD4+/CD25+ cells were significantly lower in comparison with HCV group.

A number of significant correlations of activated CD3+ and CD8+ T-cells with other immunological parameters, viral serum load of HIV, AIDS in the groups with HIV/HCV coinfected patients were detected (Table 4).

As seen in Table 4, activated CD3+ and CD8+ lymphocytes had opposite correlations with major T-cells subpopulations (CD4+ and CD8+). Direct correlation of activated CD3+/HLA-DR and CD8+/HLA-DR cells indices were observed with CD3+/CD8+ (%) in both

groups, while these indices had opposite correlation with CD3+/CD4+ (%) in group 1B. In group 1B negative correlation between activated CD3+ and CD8+ and Treg CD4+/CD25+ (%) was detected as well as direct correlation with presence of AIDS and HIV VL, while in group 1A these correlations were absent. In both groups with coinfection strong correlation was detected between activated CD3+ and CD8+ lymphocytes.

HIV VL was detected in 44 patients with HIV/HCV coinfection: in 15 patients of 1A group and 29 of 1B. Undetectable HIV VL (<500 cp/ml) was established in 13 patients of 1A group and in 9 patients from 1B group. Detectable HIV VL (>500 cp/ml) was established in 2 patients of 1A group and in 20 patients from 1B group.

As it is known HIV VL correlates with level of HIV replication, which is one of the main mechanisms of IR activation (6). In Table 5 indices of activation markers expression in HIV/HCV co-infected patients in group 1 are given according to level of HIV VL.

As seen in Table 5, percentage and absolute value of activated CD3+ and CD8+ lymphocytes in patients with detectable HIV VL were significantly lower than in patients with undetectable HIV VL, which proves correlation of T-cells activation with HIV replication and increase of HIV VL. At the same time indices of activated T-helpers didn't significantly differ in the compared groups.

Parameters of CD25 expression on blood lymphocytes and CD4+/CD25+ content in HIV/HCV co-infected patients in group 1 with detectable and undetectable HIV VL are given in Table 6.

As seen in Table 6, CD25+ expression on blood lymphocytes and CD4+/CD25+ cells in blood of patients with undetectable HIV VL was significantly higher than in patients with detectable HIV VL.

It is known, that in HIV-infected patients before the development of evident immunosuppression HIV VL can stay at a low, undetectable level without ART for a long time. In 13 patients from 1A group, receiving ART, HIV VL was at an undetectable level which indicates the presence of virological response on ART. At the same time in 1B group HIV undetectable level had been detected in 9 patients by the time of the research. Expression of HLA-DR on T-cells of HIV/HCV coinfected patients with undetectable HIV VL was compared in patient groups receiving and not receiving ART (Table 7).

As seen in Table 7, despite approximately equal percentage of activated CD3+ and CD8+ T-cells, absolute value of activated cells was significantly higher in patients in group 1B, though HIV level was undetectable. Number of CD4+/HLA-DR in group 1A was significantly lower in comparison with patients in group 1B.

At the same time in comparison of activation markers expression in patients with undetectable HIV VL on ART with the control group significantly higher indices of activated CD3+ and CD8+ of T-cells and lower CD4+/HLA-DR ($p < 0,05$) were detected in HIV/HCV patients in group 1A. This fact indicates imbalance in the immune system of HIV infected patients, despite virological response (VR) on ART. Comparison of these indices with HCV infection group showed significantly higher parameters of CD3+/HLA-DR and CD8+/HLA-DR (percentage and absolute value) in HIV/HCV coinfection with undetectable HIV VL on ART ($p < 0,05$).

Expression of CD25 on blood lymphocytes and content of CD4+/CD25+ cells in HIV/HCV coinfected patients with undetectable HIV VL depending on ART receiving did not differ significantly ($p > 0,05$), unlike the content of activated T-cells. These facts indicate correlation of CD4+/CD25+ cells with HIV replication and, respectively, HIV VL more closely than with parameters of immune system activation.

Activation of T-cell immune response in HIV infection is more informative predictor of the disease prognosis, than HIV replication level. Recent research proved that SIV in natural conditions is a nonpathogenic virus, despite high replication activity due to minimal immunity activation (3). In this connection we compared parameters of T-cell mediated immunity activation in HIV/HCV coinfected patients, not receiving ART with absence and presence of AIDS (Table 8).

As seen in Table 8, percentage of CD3+/HLA-DR and CD3+CD8+/HLA-DR was higher in patients with AIDS in comparison with patients without AIDS. Relative CD4+/HLA-DR indices did not significantly differ in the compared groups but absolute CD4+/HLA-DR index in AIDS was significantly lower. Percentage and number of CD4+/ CD25+ cells was significantly lower in AIDS, which was additionally proved by negative correlation of CD4+/ CD25+ index with HIV VL (Spearman's R correlation = –0,75; $p < 0,0001$).

DISCUSSION

Numerous researches displayed that ART reduces IS activation by inhibiting of different HIV replication stages (5, 9). The results of our research prove this fact, as a significant reduction of activated T-cells in HIV/HCV coinfected patients receiving ART was detected. It was proved that the patients not receiving ART despite an undetectable HIV level had a higher absolute level of HLA-DR activation markers expression on T-cells, than the patients with an undetectable HIV VL receiving ART. This fact points that even at undetectable HIV VL in the HIV infected patient active

HIV replication in organs and tissues takes place; it stresses the important role of ART in control of HIV replication.

At the same time virological response on ART in the form of HIV VL reduction to an undetectable level does not guarantee restoration of IS function. It is proved by increase of non-AIDS-related cancers frequency, such as non-Hodgkin lymphoma, papillomavirus anorectal dysplasia and other manifestations of inflammatory immune reconstitution syndrome in patients receiving ART (1). In our research HLA-DR expression on blood T-cells in patients receiving ART was considerably higher in comparison with the control group and HCV infected patients. Continuing immune system activation despite virological response on ART can be explained by numerous mechanisms, including HIV ability to "avoid" ART effect (6). Besides, presence of various coinfections in HIV infected patients can support IS activation.

The disease progress and AIDS development was associated with relative increase of HLA-DR expression on blood T-cells. At the same time absolute value of these indices did not statistically differ in the compared groups, which can be associated with the development of pancytopenia in AIDS.

It was detected, that binding of HIV with CD4+CD25+ Treg cells increases their life span and functional activity as well as induces redistribution of these cells in human organism: migration from the peripheral blood and accumulation in the lymphoid tissue, where the most intensive HIV replication occurs. Due to CD4+CD25+ immunosuppressive activity in the lymphoid tissue HIV-infected cells "avoid" immune control, which provides persistent HIV replication and promotes disease progression (9, 10). One of the immunosuppression mechanisms in HIV infection is HIV ability to cause proliferation of CD4+/CD25+ T-cells by HIV specific antigenic stimulation. So, CD4+/CD25+ T-cells are suppressors of immune response in HIV-infected patients (8, 11).

In both HIV/HCV co-infection groups receiving and not receiving ART CD4+/ CD25+ content was significantly lower in comparison with control group and HCV group. Besides, opposite correlations between activated CD3+ and CD8+ T-cells and Treg lymphocytes were received.

This can be associated with the fact that the majority of CD4+/CD25+ cells in HIV infected patients is localized in the lymph nodes, where the most intensive HIV replication, correlating with HIV VL occurs (8, 9). In this connection HIV VL reduction due to inhibition of HIV replication under ART is associated with the increase of CD4+/CD25+ cells in patients' blood.

Therefore, in natural disease course immunity activation in HIV infected patients is most evident at AIDS stage and correlates with high level of HIV VL. Reduction of CD4+/CD25+ lymphocytes content is associated with high HIV VL. So, in HIV/HCV co-infected patients at AIDS stage considerably lower level of absolute and relative CD4+/CD25+ content was detected in blood in comparison with patients without AIDS.

CONCLUSIONS

In natural disease course immunity activation in HIV/HCV infected patients is more evident at AIDS stage, as patients at AIDS stage had considerably higher level of HLA-DR expression on blood CD3+ and CD8+T-cells in comparison with patients without AIDS. It was detected that HLA-DR expression on T-cells and cytotoxic blood lymphocytes is considerably higher in patients with the detectable HIV VL. Virological response on ART lead to significant reduction of immune system activation markers expression, though it was significantly higher in comparison with the level of healthy individuals. Reduction of CD4+/CD25+ lymphocytes in blood is associated with high HIV VL. In the patients with AIDS stage a lower index of CD4+/CD25+ blood lymphocytes was detected compared to those patients without AIDS. Regulatory T-cells had an opposite correlation with content of activated CD3+ and CD8+ lymphocytes and HIV VL.

CONFLICTS OF INTEREST

We declare that we have no conflicts of interest

Abbreviations

AIDS — acquired immunodeficiency syndrome
ART — antiretroviral therapy
HCV — Hepatitis C virus
HIV — Human immunodeficiency virus
IR — immune response
IS — immune system
SIV — Simian immunodeficiency viruses
VL — viral load

FINANCIAL DISCLOSURE/FUNDING

The study was funded by Public Health Ministry of Belarus in the frame of Governmental Research and Practical Program "Infectious diseases and Microbiology Biotechnology" provided by Republican Research & Practical Center for Epidemiology & Microbiology, Minsk, Belarus, 2009–2010.

Sažetak

AKTIVACIJA T-ĆELIJA U KRVI HIV/HCV KOINFICIRANIH PACIJENATA

Matsiyeuskaya V. Natallia, Vladimir M. Tsyrkunov

Grodno State Medical University, Grodno, Belarus

U studiji je ispitivana ekspresija HLA-DR receptora na T-ćelijama i njihovim subpopulacijama (CD4+ i CD8+ limfocitima), kao i broj CD4+/CD25+ ćelija sa imunosupresivnim svojstvima, u krvi HIV/HCV koinficiranih pacijenata u zavisnosti od nivoa HIV virusa u serumu, AIDS-a i primanja antiretrovirusne terapije. Otkriveno je da je ekspresija HLA-DR na T-ćelijama značajno veća kod pacijenata sa detektabilnim nivoom HIV u serumu, AIDS-om, i kod pacijenata koji ne primaju antiretrovirusnu terapiju. Antiretrovirusna dovodi do značajne redukcije ekspresije markera aktivacije imunog sistema, iako se međutim ne dostiže nivo kao kod zdravih osoba. Broj CD4+/CD25+ ćelija ima negativnu korelaciju sa aktiviranim CD3+ i CD3+CD8+ limfocitima, kao i sa virusnim nivoom HIV u serumu.

Ključne reči: HIV, HCV, aktivacija imunog sistema, HLA-DR, CD4+/CD25+ T-ćelija.

REFERENCES

1. Levy JA. HIV pathogenesis: 25 years of progress and persistent challenges. AIDS. 2009; 23: 147–60.

2. Lawn SD, Butera ST, Folks TM. Contribution of Immune Activation to the Pathogenesis and Transmission of Human Immunodeficiency Virus Type 1 Infection. Clinical microbiology reviews. 2001; 14 (4): 753–77.

3. Chakrabarti LA. Immune mechanisms of HIV control. Curr Opin Immunol. 2010; 22 (4): 488–96.

4. Gonzalez VD, Falconer K, Kim G et al. High Levels of Chronic Immune Activation in the T-Cell Compartments of Patients Coinfected with Hepatitis C Virus and Human Immuno - deficiency Virus Type 1 and on Highly Active Antiretroviral Therapy Are Reverted by Alpha Interferon and Ribavirin Treatment. Journal of virology. 2009; 83 (21): 11407–11.

5. Zhang ZN, Shang H, Jiang YJ et al. Activation and coreceptor expression of T lymphocytes induced by highly active antiretroviral therapy in Chinese HIV/AIDS patients. Chin Med J. 2006; 119 (23): 1966–71.

6. Fuse S, Molloy MJ, Usherwood EJ. Immune Responses Against Persistent Viral Infections: Possible Avenues for Immunotherapeutic Interventions. Critical Reviews in Immunology. 2008; 28 (2): 159–83.

7. Orendi JM, Bloem AC, Borleffs JC et al. Activation and Cell Cycle Antigens in CD4+ and CD8+ T Cells Correlate with Plasma Human Immunodeficiency Virus (HIV-1) RNA Level in HIV-1 Infection. The Journal of Infectious Diseases.1998; 178: 1279–87.

8. Kinter A, McNally J, Riggin L, Jackson R, Roby G, Fauci AS. Suppression of HIV-specific T cell activity by lymph node CD25–regulatory T cells from HIV-infected individuals. PNAS. 2007; 104 (9): 3390–5.

9. Ji J, Cloyd MW. HIV-1 binding to CD4 on CD4/CD25 regulatory T cells enhances their suppressive function and induces them to home to, and accumulate in, peripheral and mucosal lymphoid tissues: an additional mechanism of immunosuppression. International Immunology. 2009; 21 (3): 283–94.

10. Dunham RM, Cervasi B, Brenchley JM et al. CD127 and CD25 Expression Defines CD4+ T Cell Subsets That Are Differentially Depleted during HIV Infection. J Immunol. 2008; 180 (8): 5582–92.

11. Jonuleit H, Schmitt E, Stassen M, Tuettenberg A, Knop J, Enk AH. Identification and Functional Characterization of Human CD4/CD25 T Cells with Regulatory Properties Isolated from peripheral blood. J Exp Med. 2001; 193 (11): 1285–94.

Correspondence to/Autor za korespondenciju
Natallia V. Matsiyeuskaya
Department of infectious diseases,
Grodno State Medical University, Grodno, Belarus
Ul. Gorkogo 80, 230009 Grodno, Belarus.
Tel: +375295804208,
fax: +375152434286,
e-mail: natamati@mail.ru