

# Influence of selected HLA tissue compatibility antigens on the course and efficacy of viral hepatitis C treatment – actual knowledge position

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## ABSTRACT

Hepatitis C virus (HCV) infection is a common problem. Combined treatment with interferon and ribavirin improved treatment efficacy, but still high percentage of infected patients has not reached virus elimination. It was found that HCV infection course, but also treatment efficacy among other things can depend on patient's individual factors, including MHC genes structure for HLA tissue compatibility antigens. Many connections between HLA system and HCV infection course were noted. There are some reports concerning connections between MHC structure and results of chronic hepatitis C treatment with interferon. In future, results of investigations connected with this problem can allow to verify qualification criteria for treatment with  $\alpha$ -interferon, because actual knowledge position has been too inconspicuous to have practical significance.

**Key words:** HLA, HCV, interferon alfa

## INTRODUCTION

Infection with virus C hepatitis (HCV) is a general problem – it is estimated that about 3% of world population is infected with this virus, not excluding children [1,2]. So great infections occurrence emerges from the facts that up to this time it has not been managed to elaborate effective antiviral vaccine and infection has often asymptomatic course that can favour its spread [1,3]. Children are usually asymptomatic HCV carrier, but the only not specific symptom can be feeling of fatigue [1,3]. Interferon  $\alpha$  has been used in treatment of viral hepatitis since years. Therapy efficacy was not satisfactory and that is why during last years combined therapy with interferon and ribavirin has been used and that fact has improved therapy efficacy [3-5]. However, there is still high percentage of infected patients in whom virus elimination has not been achieved [4,5]. It was stated that natural course of HCV infection, but also therapy efficacy can depend on so called patient's individual factors (for example MHC genes structure for HLA tissue compatibility antigens, patient's age, race) and viral factors (for example virus genotype, its antigens) [6-11]. It was noted that immune system can efficiently eliminate

virus even among 15% of patients with acute hepatitis [10]. The conclusion was proposed that particular HLA alleles can present epitopes for Th CD4 lymphocytes more effectively that can cause more vivid organism response to infection and virus elimination [10,12].

HCV is characterized by low immunogenicity and furthermore anti-HCV antibodies often do not recognize appropriate virus epitopes due to pseudotypes formation [3]. Greater role is performed by cellular immunity that includes MHC tissue compatibility antigens class I, but especially class II. Common occurrence of MHC class I causes that every infected cell can be recognized by cytotoxic T lymphocytes which are the main effectors of virus elimination. Therefore persons with various structure of MHC class I genes can have different features of HLA antigens, but their different structure can influence on individual response to infection. In turn, lymphocytes T CD4 recognize peptides connected with MHC class II and can influence directly cytotoxically, but mainly they have immunomodulative features. They increase cytokines secretion and that is why proliferation of lymphocytes B, cytotoxic lymphocytes CD8 and other inflammatory cells is induced [1,3].

**Table 1. Influence of selected genes of MHC complex, haplotypes and tissue compatibility antigens on viral hepatitis C course.**

	Advantageous influence	Disadvantageous influence
Barrett et al., 2005	B1*0101	
Hamed et al., 2003	DRB1*0101	DRB1*0301
Harcourt et al., 2001	DQB1*0301	
Hong et al., 2005	DQB1*0301 DRB1*1101	
Hüe et al., 2002	DR11 DRB1*11	DR3 DRB1*03 DQB1*0201
López-Vázquez et al., 2004	DR11	B18 MICA-A4 DR3/MICA-A4/B18
Neumann-Haefelin et al., 2006	B27	
Patel et al., 2006		B18
Thio et al., 2001	DQB1*0301 DRB1*0101 DRB1*0101/DQB1*0501	DRB1*0301.
Tokushige et al., 2003	DRB1*0901 Alleles B1B1 for TNF	
Wawrzynowicz-Syczewska et al., 2000	DQB1*0301	
Yoon et al., 2005	DRB1*0301 DQA1*0501 DQB1*0201 DQA1*0501-DQB1*0201 connection DRB1*0803, DQB1*0604 z B46	A3, B23 B46 DRB1*0803 DQB1*0604 DRB1*0803-DQB1*0601
Yoshizawa et al., 2003	DRB1*12 (*1201 and *1202) DRB1*0301 DRB3*03	

## REVIEW

Many connections between HLA system and HCV infection course were found. (*Tab.1*) Concerning tissue compatibility antigens class I, Neumann-Haefelin et al. noted that HLA-B27 is connected with spontaneous virus elimination [13]. In turn, Yoon et al. in their widely planned studies observed that HCV chronic carrier state is connected with the presence of antigens HLA-A3, HLA-B23 and HLA-B46 that occur in healthy persons significantly statistically more rarely [14]. On the base of studies in the group of patients infected with HCV, López-Vázquez A et al. stated that HLA-B18 antigen often occurs in patients with liver cancer, in turn they do not occur at all in asymptomatic HCV carriers [8]. The same authors ascertained that MICA-A4 antigens occurred more frequently among patients with liver cancer in comparison with virus carriers. Patel et al. stated that heterogeneity tissue compatibility antigens class I are of less consequence in comparison with class I antigens during the course of HCV infection, particularly in relation to progression to cirrhosis and liver cancer [15]. However, these authors observed more frequent HLA-B18 occurrence in patients with liver fibrosis in comparison with

group of patients not infected with HCV. HLA-B18 did not occur statistically significantly more frequent among patients with advanced cirrhosis. Barrett et al. claim that the presence of HLA-B1\*0101 can have an influence on spontaneous virus elimination [16].

Khakoo et al. stated that structure of tissue compatibility antigens class I has an influence on the course of HCV infection, but particularly in connection with suitable genes structures coding cellular receptors of NK cells for HLA class I molecules controlling their activity (KIRs) [17]. Results of studies published by these scientists, indicate that possession of two copies of HLA-C1 (HLA-C1C1) among some of these structures, occurs more frequently in the group of patients who eliminated virus, but HLA-C2C2 – in patients with persistent infection. Differences concerning HLA-B alleles prevalence in compared groups were not observed [17]. Spanish investigators, who analysed genes structures for KIRs and HLA in connection with themselves established that the presence of HLA- Bw4I80 epitope and KIR3DS1 gene is more common among HCV carriers in comparison with patients suffering from hepatocellular carcinoma [18].

There are more evidences of significant influence of tissue compatibility antigens class II on HCV infection course.

**Table 2. Influence of selected genes of MHC complex, haplotypes and tissue compatibility antigens on the therapy efficacy of viral hepatitis C.**

	Advantageous influence	Disadvantageous influence
Airoldi et al., 2004	DRB1*11 DRB1*0602 homozygosity of TAP1*0101	DRB1*02
Dincer et al., 2001		DRB1*13
Harcourt et al., 2001	DQB1*0301	
Jiao et al., 2005	DRB1*07	DRB1*04
Kikuchi et al., 1998		B54 A24-B54-DR4
Korenaga et al., 2001	Cw1 and B51	DR9
Muto et al., 2004		DR6
Som et al., 1998	DRB1*0404	
Sugimoto et al., 2002	LMP 7K	
Wawrzynowicz-Syczewska et al., 2000	DRB1*1501-DQA1*01-DQB1*0602 DRB1*0701-DQA1*0201-DQB1*02	
Yu et al., 2003	A11 B51 Cw15 DRB1*15 DRB1*15-DQB1*05 A11-DRB1*15	A24

Yoshizawa et al., comparing the group of patients with cirrhosis in the course of HCV infection with the group of patients who are many years' asymptomatic HCV virus carriers, proved that alleles DRB1\*12 (\*1201 and \*1202), DRB1\*0301 and DRB3\*03 are more frequently found in asymptomatic HCV virus carriers [19]. Harcourt et al. ascertained that patients infected with HCV with alleles DQB1\*0301 show better antiviral defence [20]. Also Polish researchers from Szczecin proved that allele DQB1\*0301 occurs rarely among patients with chronic viral hepatitis C [21]. Hong et al. stated that alleles DQB1\*0301 and DRB1\*1101 have protective significance [22]. They are connected with more effective presentation of HCV virus epitopes and therefore the risk of persisting infection in chronic form is lower among persons with such genes structure. Tokushige et al. ascertained that the presence of DRB1\*0901 is connected with low activity of inflammatory processes in the liver [23]. Spanish scientists proved that among patients infected with HCV, the presence of HLA-DR11 occurs more frequently in the group of asymptomatic virus carriers in comparison with group of patients in terminal phase of liver disease, particularly with liver cancer [8].

Scientists from France investigated influence of HLA system on liver fibrosis in patients chronically infected with HCV and stated that DRB1\*11 occurs statistically significantly more rarely among patients with cirrhosis, but DRB1\*03 and DQB1\*0201 are found statistically significantly more frequently [24]. The same authors also noted that the medium degree of liver fibrosis is higher among patients with HLA-DR3 in comparison with patients with HLA-DR11.

Egyptian studies compared prevalence of selected HLA-DR alleles in patients infected with HCV and suffering from haemophilia and liver carcinoma. It became evident that allele DRB1\*0101 more frequently occurs among patients without neoplastic disease, but DRB1\*0301 more frequently occurs among patients with liver carcinoma, but differences indicate the possibility of the influence concerning these alleles presence on the course of HCV infection [12].

There are also reports about influence concerning not only single genes, but also particular genes systems on HCV infection course. Spanish investigators found that the presence of haplotype DR3/MICA-A4/B18 shows relation with liver carcinoma development and can be an important prognostic factor for disease progression [8]. Also Yoon et al. proved many interdependences, not only concerning the single genes presence in the HLA class II system, but also among particular haplotypes and HCV infection [14]. So they proved that among persons who are chronically infected with hepatitis C virus, alleles DRB1\*0803, DQB1\*0604 and also haplotype DRB1\*0803-DQB1\*0601 are the most frequently present among genes coding antigens of tissue compatibility antigens class II in comparison with healthy persons, but, in turn, more rarely occur alleles DRB1\*0301, DQA1\*0501 and DQB1\*0201, but also haplotype DQA1\*0501-DQB1\*0201. These authors also stated that association of alleles DRB1\*0803, DQB1\*0604 with the presence of HLA-B46 class I is more frequently present among patients with chronic HCV infection.

Very interesting interdependences concerning the HCV infection course and individual factors of the host were

described on the base of their studies by Thio et al. [10]. They noted that the presence of allele DQB1\*0301 is connected with virus elimination. This dependence is already noticeable in the group that is ethnically heterogeneous, but more evident in the group of dark-skinned patients. Viraemia elimination among dark-skinned patients was connected with the presence of allele DRB1\*0101 and haplotype DRB1\*0101/DQB1\*0501, but its survival – with the presence of allele DRB1\*0301.

Tokushige et al. stated that the presence of alleles B1B1 for TNF are connected with low activity of inflammatory processes in the liver and that is why there are some connections between infection course and HLA class III [23]. Constantini et al., searching for relations concerning HCV infection course and selected genes of MHC complex class III, particularly concerning genome influence on probability of spontaneous or induced by the treatment viraemia elimination, stated that such interdependences should not be expected in this class [25].

There are also reports concerning connections between MHC system and results of treatment with interferon of chronic hepatitis C (Tab.2). HLA classes I - Cw1 and B51 are connected with persistent response to treatment in patients infected with HCV genotype 2 [26]. Yu et al. ascertained that patients with antigens HLA-A11, B51, Cw15 better respond to treatment with interferon, but worse response is presented by patients with HLA-A24 [27]. Moreover, they supposed that homozygosity of A24 and DQB1\*05 exerts an accumulated influence on persistent response.

Harcourt et al. noted that patients with alleles DQB1\*0301 better respond to combined treatment with interferon and ribavirin [20]. Yu et al. stated that patients with alleles DRB1\*15 better respond to treatment with interferon [27]. Airoidi et al., investigating the influence concerning the presence of various tissue compatibility antigens, noted that although DRB1\*11 and DRB1\*0602 are found statistically non significantly, but they are more frequently present among patients responding persistently (shortage of viraemia for minimum 3 years from treatment ending) to treatment with interferon as monotherapy [28]. Furthermore it was proved that the presence of allele DRB1\*0404 is connected with persistent response [29]. In turn, Chinese authors proved that patients with DRB1\*07 better respond to combined treatment with interferon and ribavirin in comparison with patients with DRB1\*04 [6]. Muto et al. stated that patients without antigen HLA-DR6 better respond to treatment with interferon [7].

Wawrzynowicz-Syczewska et al. noted that haplotypes DRB1\*1501-DQA1\*01-DQB1\*0602 and DRB1\*0701-DQA1\*0201-DQB1\*02 are more frequently found among patients with chronic viral hepatitis C, who respond well to treatment with interferon [21]. Yu et al. acknowledge also haplotypes DRB1\*15-DQB1\*05 and A11-DRB1\*15 as a beneficial prognosis for treatment [27].

However, patients not responding to treatment with interferon more frequently than among other groups reveal the presence of alleles and haplotypes HLA-B54 and HLA-A24-B54-DR4 [30], DR9 [26], DRB1\*13 [31], DRB1\*02 [28].

The connection shortage between selected alleles of MHC system and efficacy of treatment with interferon was proved, for example considering range of alleles DRB1 and DQB1 – loci different than DRB1\*0404 [29]. The connection shortage between prevalence of HLA-A and HLA-C alleles and efficacy of treatment with  $\alpha$  interferon was found [30]. Polish authors from Łódź also did not confirm connection between HLA system and efficacy of treatment with interferon, concerning adult patients with HCV infection and alleles HLA-DRB1\* [32]. Airoidi et al. proved that alleles system TAP 1 TAP 2 does not influence statistically significantly on probability of efficacy concerning treatment with interferon in patients with chronic hepatitis C. However they observed more frequent (statistically not significant) homozygosity occurrence of TAP1\*0101 in patients with persistent response to interferon [28]. Also Sugimoto et al. stated that there is no connection between genes structure (TAP 1 and TAP 2, but also LMP 2) and efficacy of the treatment with interferon [33]. However these the same authors found the relation concerning efficacy of this treatment and possession of the LMP 7K allele (patients with this allele more frequently persistently responded to treatment).

The dependence concerning efficacy of treatment with INF and system of selected tissue compatibility antigens class III was investigated. Airoidi et al. did not reveal relationship concerning genes for TNF  $\alpha$  and  $\beta$  [28]. Also researchers from United Kingdom did not confirm dependence induced by treatment of viraemia elimination on tissue compatibility antigens class III [25].

Few authors undertake a problem concerning influence of MHC complex genes systems on prevalence and course of extrahepatic manifestations of HCV infection, connected complications or extrahepatic complications that have connection with treatment of this infection with interferon. Hwang et al. stated that HLA-DR3 more frequently occurs among group of patients with cryoglobulinaemia comparing with patients without this complication and healthy persons [34]. In turn, HLA-DR4 more frequently occurs among patients in whom the presence of autoantibodies is found [34]. Not great amount of patients infected with HCV can show predisposition to develop dilated and hypertrophic cardiomyopathy [35]. Mechanism concerning formation of such predisposition is not explained. Japanese investigators attempted to search its connection with HLA system among rather large, as consisted of 59 persons, group of patients with these diseases. However they did not confirm such connections [35].

Italian authors proved that HLA system can also have an influence on course of treatment with interferon in patients infected with HCV and complications formation during its course in the form of thyroid gland diseases, such as: transient thyreotoxicosis, autoimmune hypothyroidism or subacute thyroiditis [36].

## CONCLUSIONS

Studies results concerning HLA polymorphism in population infected with HCV will complete knowledge of hepatitis C immunogenetics and relations of response to treatment with interferon  $\alpha$  depending on features of studied HLA antigens. It can allow in future to verify evaluation criteria for treatment with interferon  $\alpha$ . This fact has both economical aspect – it will allow to avoid bearing costs of ineffective treatment, just as ethical aspect - it will allow to avoid ineffective treatment that is burdening, not devoid of side effects and diminishes patients' quality of life.

However it seems that actual knowledge position in this subject is still too inconspicuous to have a practical significance at the present time and that is why this problem needs further research.

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