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Study of Il-28b Gene Polymorphism among Pregnant Women with Chronic Viral Hepatitis B

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SUMMARY: The genetic marker IL-28B, which allows partly to predict the course of the disease and the effectiveness of treatment, polymorphism of the interleukin 28B gene determines to a certain extent the sensitivity of the patient's immune system to the viral load and determines the course and outcome of the disease. Thus, the study of the IL-28B gene polymorphism will provide information on the functional activity of various types of immunocompetent cells; the severity of the inflammatory process, its transition to the systemic level and prognosis; on the ratio of the processes of activation of T-helpers of types 1 and 2, which is very important in the diagnosis and treatment of immunopathological processes. The analysis of genetic studies in a healthy population for two alleles showed that OPN rs12979860 of the IL-28B gene: CC - 38%, CT - 51%, TT - 12%; OPN rs8099917 of the IL-28B gene: TT - 56%, TG - 38%, GG - 7%. Analysis of polymorphism of the IL-28B gene in the group of pregnant CHBV showed that ARF rs12979860 of the IL-28B gene: CC - 32%, CT - 66%, TT - 4%; ARF for rs8099917 of the IL-28B gene: TT - 65%, TG - 25%, GG - not detected (0%). The frequency of occurrence of IL-28B gene haplotypes among healthy individuals and pregnant women with CVHB showed that among healthy individuals in 36% of cases there was a CC / TT haplotype, in 31% of cases - CT / TG, 21% - CT / TT, 7% - TT / TG, 4% - TT / GG, 1% - CT / GG and 0% each - TT / TT, CC / -, CT / -, - / TT. Analysis of haplotypes in groups of pregnant women with hepatitis B showed that in 25.7% of cases the CC / TT haplotype was encountered, in 27% of cases - CT / TG, 31.1% - CT / TT, 1.4% - TT / TG, 2.7% - TT / TT, 5.4% - - / TT, 5.4% - CC / -, 1.4% - CT / - and 0% each - TT / GG and CT / GG.

Key words: interferons, immunity, gene polymorphism, antiviral action, interferon system, antiviral defense of immunity, viral hepatitis B.

Topicality. According to the World Health Organization (WHO), viral hepatitis B (HBV) is a global problem that affects not only poor and developing countries, but also countries of the world's leading economies [1,5]. Currently, about 240 million people are infected with the hepatitis B virus, and in the last two decades, the prevalence of infection has ceased to depend on the economic status of the country [2,12]. Globalization and associated migration processes have led to the fact that the incidence of HBV in such prosperous European countries as Italy, Germany, France, has increased due to migrants and refugees from poor countries, and national vaccination programs in these countries have failed to prevent the spread of acute viral infections, especially in high-risk groups [3, 4]. Uzbekistan faced the same problems, the prevalence of HBV in which, according to expert estimates, reaches up to 18% per population [6].

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HBV proceeds as an acute and chronic infection, and in all cases is caused by the parenteral mechanism of transmission of the pathogen. Acute infection occurs in the form of cyclic parenchymal hepatitis with or without jaundice, which ends in recovery in 95% of patients. The remaining 5% develop chronic HBV, and it is in this group of patients that a high risk of developing HBV-associated complications is realized - cirrhosis of the liver and hepatocellular carcinoma, from which more than half a million people die every year in the world, and the costs of treatment, including liver transplantation, are estimated at billions of dollars [7,9,10,11]. The prevalence of HBsAg in pregnant women is not well established. For example, in the United States, infection is detected in 0.7-0.9% [8.9], in European countries, the prevalence ranges from 0.1 to 5.6% [9], in Russia it reaches 0.5% [10]. In recent studies, it has been shown that pregnancy can be regarded as a factor that potentially increases the risk of chronic HBV formation [12]. In a study by Han Y.T. (2014) found that pregnant women with acute HBV had prodromal fever, serum ALT levels were lower, bilirubin levels were higher, and HBsAg disappearance and seroconversion were less common than in non-pregnant women [13, 14]. Despite this, specific antiviral therapy in pregnant women with acute HBV is not recommended, except for the severe form of the disease, accompanied by the development of hepatic coma [14]. Several epidemiological studies have suggested that chronic HBV can cause trophoblast dysfunction and increase the incidence of placenta previa and premature abruption of the normally located placenta [15]. The leading problem of HBV during pregnancy is the vertical transmission of the virus from mother to child. Until now, it was believed that the parenteral route of transmission of the hepatitis B virus is the main one [9,15]. In the last decade, studies have emerged showing that perinatal, intrapartum and postnatal mother-to-child transmission is becoming the leading source of hepatitis B virus infection in some countries. It is believed that in regions with high endemicity (HBsAg prevalence> 8%), vertical transmission of infection prevails, while in countries with low endemicity (HBsAg prevalence <1%), sexual and parenteral transmission of the virus predominates [13].

In recent years, the influence on the course of the chronic process and the effectiveness of therapy of immunological factors of immunity and genetic variability in the region adjacent to the IL-28B gene located on the 19th chromosome, which encodes the translation of the antiviral interferon lambda-3, has been actively discussed in the literature. According to WHO forecasts, in the next 10-20 years the number of patients with liver cirrhosis is expected to increase by 60%, patients with hepatocarcinoma - by 68%, by 280% - patients with hepatic decompensation and 2 times - mortality from liver diseases. Therefore, the issue of genetic study of immunogenetic factors affecting the course and prognosis of the disease is relevant. In this regard, the aim of the study is to study the immunopathogenetic mechanisms involved in the formation, course and prognosis of the chronic viral process in pregnant women with chronic hepatitis B.

MATERIAL AND RESEARCH METHODS.

The study involved 54 pregnant women with chronic viral hepatitis B, who were at the gestational age from 4 to 22 weeks. All women were admitted with complaints of general weakness, malaise, severe toxicosis. PCR diagnostics for hepatitis B showed that 25% of women had PCR positive. The epidemiological history showed that the majority of patients

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(52%) were infected after undergoing surgical and dental procedures, 8% had a clear indication of transfusion of blood and blood products, 5% were medical workers, and 35% of patients had unknown causes. In 38% of patients, concomitant diseases were identified, in the structure of which diseases of the gastrointestinal tract (cholecystitis, gastritis, cholangitis) predominated, diseases of the genitourinary system (cystitis) were found in 7.5%, and diseases of the endocrine system in 14%. The sex-matched control group included 32 practically healthy (donors) individuals with an average age of 32.5 ± 1.7 years, who did not have liver diseases.

The diagnosis was established by infectious disease doctors and hepatologists based on the results of a clinical examination, data from laboratory and instrumental research methods. The diagnosis was verified by clinical and laboratory data on the basis of orders of the Ministry of Health of the Republic of Uzbekistan No. 560 dated 30.10.2000 and No. 5 dated 05.01.2012. The complex of primary examination included a traditional set of clinical and biochemical laboratory parameters, ultrasound, studies of serological markers.

The majority of the examined showed a moderate and low degree of biochemical activity. When collecting anamnestic data, great attention was paid to the history of interferon therapy and complaints of patients (general weakness, rapid fatigue, slight severity in the right hypochondrium). The duration of the disease with chronic viral hepatitis B averaged 6.5 ± 0.8 years, the diagnosis was established by infectious disease doctors and hepatologists based on the results of a clinical examination, laboratory and instrumental research methods.

According to the order of the Ministry of Health of the Republic of Uzbekistan No. 5 dated 01/05/2012, the following degrees of biochemical activity are distinguished: - the minimum activity of the infectious process - 1.5-2 ALT norms; - low activity of the infectious process - 2-3 ALT norms; - moderate activity of the infectious process - 3-5 ALT norms; - pronounced activity of the infectious process - over 5 ALT norms.

Determination of the main interferons in the serum of peripheral blood was carried out by the method of enzyme immunoassay using commercial test systems "Vector-Best" and "Human" on the analyzer "Stat-Fax" (USA). The test systems are based on the sandwich method of enzyme-linked immunosorbent assay using horseradish peroxidase as an indicator enzyme. The quantitative assessment of the results was carried out using Excel 2004, reflecting the dependence of optical density on concentration for a standard antigen. The sensitivity of the method when using these test systems is 2.5 pg / ml.

Serological method of identification of the marker of viral hepatitis B was carried out according to the instructions using the test systems “Serodia FN JIREBIO INC. JAPAN ”, based on the method of passive agglutination of sensitive gelatinous particles. The sensitivity of the method was 2.7 ng / ml.

Polymerase chain reaction (PCR) is an in vitro DNA amplification method, with which within a few hours a specific DNA sequence can be isolated and multiplied billions of times. The principle of the method consists in multiple copying (amplification) in a test tube of certain relatively small regions of RNA, tDNA, ranging in length from several tens to several hundred base pairs in the course of repeated temperature cycles.

For typing of polymorphic variants of the studied genes, we used DNA preparations obtained from 5 ml of venous blood. DNA isolation from human venous blood leukocytes was carried out using a modified alcohol-salt method. Genotyping was performed by pyrosequencing

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(PyroMark Q24, PyroMark Gold Q24 Reagents, Qiagen, Germany). Replication genotyping was performed using the HRM-qPCR method (Stratagene M * 3005P, Agilent Technologies, Germany; DT-Prime, DNA-Technology, Russia). HCV genotypes (1a, 1c, 2a, 2c, 3a) and the nucleotide polymorphism of the IL-28B gene were determined by PCR using specific primers. To identify polymorphic variants of the rs12979860 marker of the IL-28B gene, allele-specific PCR with the detection of products in real time was used. The design of primers and probes was carried out by employees of CJSC "Syntol" (Moscow). Thermal cycling was carried out on a detecting amplifier "CFX-96" Bio-Rad Laboratories, Inc. (USA). To determine the genotypes of this gene in all patients with CHB and 32 healthy donors, DNA was isolated from whole venous blood previously stabilized with EDTA. Determination of IL-28B gene polymorphism for two main alleles: rs12979860 and rs8099917. The structure of primers and decoding of genetic studies is shown in Figure 2.2.6.1. The structure of the primers used for the detection of rs12979860 and rs8099917 of the IL-28B gene: rs12979860 (forward - TGTACTGAACCAGGGAGCTC; reverse - GCGCGGAGTGCAATTCAAC; rs8099917 (forward - GTGCATATATGT reverse nucleus GCC.GCGCGC; -rs8099917 (430 bp).

The research results were statistically processed using the Student-Fisher test. Statistical processing of the data obtained was carried out using standard programs for calculating the arithmetic mean (M), the mean error for indicators and groups (m) and the standard deviation (σ). According to the calculated values in relation to the control and the corresponding value of the degree of freedom, the probability of error was determined according to the Student-Fisher table (t).

RESULTS OBTAINED AND DISCUSSION.

Within the framework of the Human Genome project, the relationship of simple nucleotide polymorphism (PNP) of the interleukin-28B gene with the rate of development of liver fibrosis and prognosis of the disease in chronic viral hepatitis B was revealed. In 2009, single nucleotide substitutions at two loci were found in the 19th chromosome re12979860 (replacing cytosine with thymine) and re 8099917 (replacing thymine with guanine) [4,5,12,14]. Studies have shown that the presence of an allelic variant (genotype) of the CC locus re12979860 (located in the gene encoding K28B) and TT locus re8099917 (located near the gene encoding K28B) indicates a high probability of achieving a sustained virological response (SVR) to antiviral therapy [3,6,9,12]. Thus, we have studied the polymorphism of the IL-28B gene, which is involved in antiviral protection. We set the goal to analyze the value of genetic polymorphisms of the IL-28B gene at loci rs8099917 and rs12979860 for assessing the prognosis of disease □ 15□ . For this purpose, a study of genetic polymorphisms of the IL-28B gene was carried out in a group of pregnant women. As recommended by the European Association for the Study of the Liver (EASL). We have studied the distribution of genotypes of the IL-28B gene in our region among the healthy population. Thus, the analysis of genetic studies in a healthy population for two alleles showed that OPN rs12979860 of the IL-28B gene: CC - 38%, CT - 51%, TT - 12%; OPN rs8099917 of the IL-28B gene: TT - 56%, TG - 38%, GG - 7%.

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Analysis of polymorphism of the IL-28B gene in the group of pregnant CHBV showed that ARF rs12979860 of the IL-28B gene: CC - 32%, CT - 66%, TT - 4%; ARF for rs8099917 of the IL-28B gene: TT - 65%, TG - 25%, GG - not detected (0%).

Thus, the analysis showed that in a healthy population of rs12979860 OPN of the IL-28B gene: that OPN rs12979860 of the IL-28B gene: CC - 38%, CT - 51%, TT - 12%; OPN rs8099917 of the IL-28B gene: TT - 56%, TG - 38%, GG - 7%.

Consequently, the most common genotypes of the IL-28B gene in a healthy population at the rs12979860 locus are the CT genotype - 51% of cases, and at the rs8099917 locus - the TT genotype - 56%.

Analysis of polymorphism of the IL-28B gene in the group of pregnant women with CVHB showed that ARF rs12979860 of the IL-28B gene: CC - 32%, CT - 66%, TT - 4%; ARF for rs8099917 of the IL-28B gene: TT - 65%, TG - 25%, GG - not detected (0%). Consequently, the most common genotypes of the IL-28B gene among the examined pregnant women with CVHB at the rs12979860 locus is the CT genotype - in 66% of cases, and at the rs8099917 locus - the TT genotype - 65%.

Further, the frequency of occurrence of IL-28B gene haplotypes was assessed among healthy individuals and pregnant women with CVHB. The results of the analysis of haplotypes of healthy individuals showed that in 36% of cases the CC / TT haplotype was encountered, in 31% of cases - CT / TG, 21% - CT / TT, 7% - TT / TG, 4% - TT / GG, 1% - CT / GG and 0% each - TT / TT, CC / -, CT / -, - / TT.

Analysis of haplotypes in groups of pregnant women with hepatitis B showed that in 25.7% of cases the CC / TT haplotype was encountered, in 27% of cases - CT / TG, 31.1% - CT / TT, 1.4% - TT / TG, 2.7% - TT / TT, 5.4% - - / TT, 5.4% - CC / -, 1.4% - CT / - and 0% each - TT / GG and CT / GG.

Of particular interest is the study of the recently discovered S.V. Kotenko and P. Sheppard of a new class of interferons - type III interferons [1,3,6]. There are 3 type III IFN molecules: IFN-X1 (IL-29 gene), IFN-X2 (IL-28A gene), IFN-X3 (IL-28B gene) [1,9]. It was found on cell culture that IFN-X inhibits the replication of hepatitis B and C viruses [4,5]. In relation to the IFN-X genes, the first report on the presence of a genetic predisposition to spontaneous HCV clearance and the prognosis for a permanent cure was published in the journal Nature in 2009 by D.L. Thomas et al. [6]. Thereafter, four independent studies established an association between SNPs in the region close to the IFN-X3 gene and the likelihood of HCV clearance. One study found a connection with the rs12979860 loci, and three others - with the rs8099917 locus [2,5,6,7]. Favorable genotigotes for the major T allele (T / T genotype) [12]. Individuals with genotypes C / C rs12979860 and T / T rs8099917 differ in the high probability of recovery from hepatotropic virus [18]. The frequency of occurrence of C- and T-alleles of IFN-X3 differs significantly in different ethnic groups [1,2]. Among SNPs of the IFN-X3 gene, loci were considered: rs12980275, rs8099917, rs12972991, rs8109886, G84803223, G812980602, G88105790, G811881222, G88103142, G828416813, G848066819, G87 However, the majority of researchers in assessing the prognosis of treatment of chronic viral hepatitis B prefer two main polymorphisms: G812979860 and G88099917 [11,12].

It has been established that the interferon system is a key mediator of the inflammatory process and the implementation of the immune response, especially in chronic prolonged

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inflammatory process, which includes chronic viral hepatitis B [10,15,17,18]. Consequently, the study of the interferon system of various types of action, as well as the changes to which the imbalance of cytokines leads, will allow a deeper understanding of the immunopathogenesis of the chronic viral process. This will naturally be important in the diagnosis and prognosis of therapy, as well as the immunological response to therapy. Moreover, the knowledge gained from the analysis of immunological values will allow improving the schemes of antiviral and immunotropic therapy. As you know, today there is practically no understanding of the direction of action of inflammatory mediators, their behavior and the severity of changes to which they can lead. As you know, IFN-α and IL-28B are powerful antiviral mediators, the inducer of which are viruses (RNA and DNA containing) [9,10]. In sufficiently high doses, interferons suppress both humoral and cellular immune responses, but at more moderate concentrations they have an immunoregulatory effect, which is most likely realized in vivo in vivo [5,7,8,12,14]. Moreover, excessive apoptosis against the background of a chronic inflammatory process in combination with activation of the humoral immunity and deep T-cell immunodeficiency contributes to the progression of the disease [13, 14, 16, 18].

According to the literature, the study did not establish a statistically significant difference in the frequencies of genotypes and alleles of the IL-28B marker (rs12979860) between the groups of healthy individuals and those with chronic viral hepatitis. Our results also did not reveal significant differences in the prevalence of IL-28B genotypes in the examined population of pregnant women with chronic viral hepatitis B.

In general, the revealed relationships of the minor allele of the T gene with the studied tests indicate the fact that the genetic polymorphism of IL-28B can be realized indirectly through a number of parameters involved in the pathogenesis of CHB and affecting the effectiveness of antiviral therapy. These factors include the presence of cytolysis and cholestasis syndromes, the severity of liver fibrosis, activation of hepatocyte regeneration and the level of VL [6,7,9,10,14,21].

Also, it was found that the IL-28B gene polymorphism (rs12979860) is associated with the severity of liver damage in patients with viral hepatitis, which must be taken into account in order to decide on the optimization of treatment with an unfavorable combination of these factors, especially in patients with the carriage of the minor T allele [3, 8,12,15]. Thus, the data obtained indicate that the genetic factors we studied are independent and reliable factors predicting the course and outcome of the disease, which can contribute to a personalized approach to the treatment and prediction of the pathological process.

Moreover, in recent years, several independent genomic studies have demonstrated the relationship of variants of human IL28B gene polymorphism (interferon lambda-3) with spontaneous elimination of viral hepatitis from the body, and response to treatment [2,6]. The nucleotide polymorphism of the IL-28B gene was determined by genotyping at two main loci: rs12979860 and rs8099917. According to modern literature, the role of genetic polymorphism in the studied regions has a positive predictive value, which is higher than other basic characteristics - predictors that guarantee the success of therapy (metabolic syndrome, viral load, stage of fibrosis, age) [1,5,8,12,15,16, 17.21]. The data obtained indicate that genetic factors, including the genotype of the hepatitis B virus and the genotypes of the IL-28B gene, are independent and reliable factors predicting the frequency of the

virological response and conducting a comprehensive examination with the determination of the patient's genotype according to IL28B will help to adopt a personalized treatment algorithm as a standard course of therapy. which will achieve greater effectiveness of therapy [6,9,10,11]. Some authors indicate that when analyzing the viral load indicators in patients with the compared rs12979860 genotypes of the IL-28B gene, it was determined that with the CC genotype the average viral load was 2.9x106 copies / ml of blood serum, and with the CT genotype - 1.2x106 copies / ml of blood serum. When comparing these indicators, significant differences were revealed, which is consistent with the literature data, which indicates that the viral load is much lower in individuals with the same genotype polymorphism [4,9].

Thus, our data can be said to be preliminary, it is necessary to continue research in this area, due to the fact that in Uzbekistan there is a high level of infection and incidence of viral hepatitis B. Moreover, it is necessary to consider a personalized approach to therapy, especially in pregnant women. It has been proven that an individual approach to treatment, timely prevention and correction of adverse events increase the effectiveness of treatment [5,8]. In this regard, the genetic marker, which partly allows predicting the course of the disease and the effectiveness of treatment, polymorphism of the interleukin 28B gene determines to a certain extent the sensitivity of the patient's immune system to viral load and determines the course and outcome of the disease. Thus, the study of the IL-28B gene polymorphism will provide information on the functional activity of various types of immunocompetent cells; the severity of the inflammatory process, its transition to the systemic level and prognosis; on the ratio of the processes of activation of T-helpers of types 1 and 2, which is very important in the diagnosis and treatment of immunopathological processes.

Conclusions. The analysis of genetic studies in a healthy population for two alleles showed that OPN rs12979860 of the IL-28B gene: CC - 38%, CT - 51%, TT - 12%; OPN rs8099917 of the IL-28B gene: TT - 56%, TG - 38%, GG - 7%.

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REFERENCES

[1] Abdo A.A., Al-Ahdal M.N., Khalid S.S., et al. IL28B polymorphisms predict the virological response to standard therapy in patients with chronic hepatitis C virus genotype 4 infection // Hepatology international. - 2013. - Vol. 7. №2. -P.533-538.

[2] Bordi L., Caglioti C., Garbuglia A.R., et al. IFNL4 and IFNL3 associated polymorphism strongly influence the spontaneous IFN-alpha receptor-1 expression in HCV-infected patients // PloS One. - 2015. - Vol. 10. №2. - e0117397.
[3] De Re V., Gragnani L., Fognani E., et al. Impact of immunogenetic IL28B polymorphism on natural outcome of HCV infection // BioMed research international. - 2014. - Vol. 2014. - 710642. doi: 10.1155/2014/710642.
[4] Domagalski K., Pawlowska M., Tretyn A., et al. Impact of IL-28B polymorphism on pegylated interferon plus ribavirin treatment response in children and adolescents infected with HCV genotypes 1 and 4 // European journal of clinical microbiology & infectious diseases. - 2013. - Vol. 32. №6. - P.745-754.
[5] Eslam M., Leung R., Romero-Gomez M., et al. IFNL3 polymorphisms predict response to therapy in chronic hepatitis C genotype 2/3 infection // Journal of hepatology. - 2014. - Vol. 61. №2. - P.235-241.
[6] Kotenko S.V., Gallagher G., Baurin V.V., et al. IFN-lambda mediate antiviral protection through a distinct class II cytokine receptor complex // Nat. Immunol. - 2003. - Vol. 4. - P.69-77.
[7] Lampertico P., Vigano M., Cheroni C., et al. IL28B polymorphisms predict interferon-related HBsAgseroclearance in genotype D HBeAg-negative patients with chronic hepatitis B // Hepatology. - 2013. - Vol. 57. №3. - P.890-896.
[8] Lopusna K., Rezuchova I., Betakova T., et al. Interferons lambda, new cytokines with antiviral activity // Actavirologica. -2013. - Vol. 57. №2. - P.171-179.
[9] Matsuura K., Tanaka Y., Nishida N., et al. Genetic polymorphism in IL28B gene associated with clinical course of hepatitis C virus infection in Japanese population // Hepatology international. - 2011. - Vol. 5. №1. - P.262.
[10] Miyamura T., Kanda T., Nakamoto S., et al. Roles of ITPA and IL28B genotypes in chronic hepatitis C patients treated with peginterferon plus ribavirin // Viruses. - 2012. - Vol. 4. №8. -P. 1264-1278.
[11] Mizokami M. Discovery of critical host factor, IL-28B, associated with response to hepatitis C virus treatment // Journal of gastroenterology and hepatology. - 2012. - Vol. 27. №3. -P.425-429.
[12] Muchmore B. Tang W., Porter-Gill P., et al. Identification and characterization of interferon- \4 (INF- \4), a novel class-2 cytokine which impairs clearance of hepatitis C virus // Cytokine. 2013. - Vol. 63. №3 - P.286.
[13] Orlent H., Reynaert H., Bourgeois S., et al. IL28B polymorphism and the control of hepatitis C virus infection: ready for clinical use? // Acta Gastro-EnterologicaBelgica. - 2011. Vol. 74. №2. - P.317-322.
[14] Peng L.J., Guo J.S., Zhang Z., et al. IL28B ra12979860 polymorphism does not influence outcomes of hepatitis B virus infection // Tissue antigens. - 2012. - Vol. 79. №4. - P.302-305.
[15] Rangnekar A.S., Fontana R.J. IL-28B polymorphisms and the response to antiviral therapy in HCV genotype 2 and 3 varies by ethnicity: a meta-analysis // Journal of viral hepatitis. - 2013. -Vol. 20. №6. - P.377-384.
[16] Robek M.D., Boyd B.S., Chisari F.V. Lambda interferon inhibits hepatitis B and C virus replication // J.Virology. - 2005. - Vol. 79. №6. - P.3851-3854.

[17] Schweitzer C.J., Liang T.J. Impact of host and virus genome variability on HCV replication and response to interferon // Current opinion in virology. - 2013. - Vol. 3. №5. - P.1-7.
[18] Sonneveld M.J., Wong V.W., Woltman A.M., et al. Polymorphisms near IL28B and serologic response to peginterferon in HBeAg-positive patients with chronic hepatitis B // Gastroenterology. - 2012. - Vol. 142. №3. - P.513-520.
[19] Sun Y., Lu Y., Xie L., et al. Interferon gamma polymorphism and hepatitis B virus-related liver cirrhosis risk in Chinese population // Cancer cell international. - 2015. - №15 - P.35.
[20] Thompson A.J., Muir A.J., Sulkowski M.S., et al. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus // Gastroenterology. - 2010. - Vol. 139. №1. - P.120-129.
[21] Zhou H., Wang L., Li X., et al. Interferon-y +874 A/T polymorphism and hepatocellular carcinoma risk: a meta-analysis // Medical science monitor. - 2015. - Vol. 21. - P.689-693.