DOI: 10.15825/1995-1191-2022-2-31-38

POST-LIVER TRANSPLANT HBV INFECTION (REVIEW)

A.D. Nikogosova[1], D.V. Umrik[1], O.M. Tsirulnikova[1, 2]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

[2] Sechenov University, Moscow, Russian Federation

Chronic hepatitis B virus (HBV) infection is common throughout the world. According to the World Health Organization, about 300 million people around the world are living with the HBV infection markers, with prevalence ranging from 0.4% to 8.5%, depending on the region. Untreated HBV infection results in severe liver disease, including cirrhosis and hepatocellular carcinoma (HCC), in at least one third of patients. While vaccination and new antiviral drugs are effective in preventing the severe consequences of HBV infection, liver transplantation remains the ultimate therapy for patients with HBV in cirrhosis. In patients with HBV replication, recurrence in the graft occurs in 100% of cases, which requires antiviral therapy combined with immunosuppressive therapy. According to the literature, de novo HBV infection after orthotopic liver transplantation (OLTx) in patients without replication and even in patients negative for hepatitis B surface antigen is between 1.7% and 5% [Castells L. et al., 2002]. After OLTx, liver recipients with baseline chronic HBV infection and patients with de novo HBV infection occurring after transplantation are indicated for long-term antiviral therapy.

Keywords: HBV infection, de novo, liver transplantation, nucleos(t)ide analogues, entecavir, tenofovir.

MAIN CHARACTERISTICS OF HBV INFECTION

HBV is the prototype member of a steadily growing family of viruses called hepadnaviruses. It is a partially double-stranded circular virion DNA (cDNA). According to the different genome sequence, there are 10 genotypes of HBV (A–J) [1]. The HBV genome basically encodes four types of antigens – HBsAg, HBcAg, HBeAg and HBxAg. The virus envelope consists of a double lipid bilayer and various proteins. The lipid bilayer contains the S antigen as well as the pre-S1 and pre-S2 antigens, which together make up the large, medium, and small protein forms on the envelope known collectively as hepatitis B surface antigen (HBsAg). Beneath the lipid bilayer is the viral capsid consisting of the bovine HBV antigen (HBcAg). The capsid contains circular, partially double-stranded DNA and DNA polymerase (encoded by the P gene). In addition, the serum contains a related nucleocapsid soluble E antigen called HBeAg. This antigen may be absent in some mutant strains. Gene X encodes a protein closely associated with the ability of HBV to cause virus-associated primary liver cancer [2].

HBV infection is widespread throughout the world. According to WHO, about 300 million people worldwide live with HBV, with a prevalence ranging from 0.4% to 8.5%, depending on the region.

The outcome of acute HBV infection depends on age. About 95% of infected infants, 20–30% of children infected at age 1–5 years, and less than 5% of adult patients develop chronic infection [3]. Untreated chronic HBV infection in at least one-third of patients leads to severe liver disease, including cirrhosis, hepatocellular carcinoma, and risk of hepatitis D virus (HDV) co/superinfection [4, 5]. The overall prevalence of HDV is about 0.98% (95% CI 0.61 to 1.42). In the HBsAg-positive population, HDV pooled prevalence was 14.57% (95% CI 12.93 to 16.27) [6].

While vaccination and new antiviral drugs are effective in preventing the severe consequences of HBV, liver transplantation (LTx) remains the ultimate therapy for patients with severe HBV-infected liver [7]. Besides, due to shortage of donor organs, in the clinical practice of some countries, especially in HBV endemic areas, organs from donors with HBV-infection markers are used for transplantation [8]. According to the literature, de novo HBV infection after OLTx is observed in 1.7–5% of cases [9]. After LTx, long-term antiviral therapy is indicated in patients with chronic hepatitis B and in patients with de novo HBV developing after LTx.

FEATURES OF HBV INFECTION AFTER LIVER TRANSPLANTATION

HBV reactivation after LTx is associated with various pre-transplant factors such as viral load at the time of transplantation, presence of HBeAg, and development of hepatocellular carcinoma. Various studies have demonstrated that certain HBV genotypes may be associated with a higher risk of recurrent infection. For example, genotype D has been shown to have this potential compared to genotype A [10]. If the viral load at the time of transplantation is above 10^5 copies/ml or 20,000 IU/ml,

Corresponding author: Anna Nikogosova. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (958) 828-32-09. E-mail: benevolenskaya.a@gmail.com

the patient is classified as being at high risk of recurrent HBV infection [10]. The virus cDNA is quite stable in infected cells and can persist in the latent state as a source for reactivation of the infection. It has long been known that hepatitis B virus cDNA can persist in the liver of patients decades after clinical and laboratory recovery from infection [11–13]. This persistence occurs despite an active immune response against the virus. In addition, clinical studies have demonstrated that therapy with nucleos(t)ide analogues can strongly suppress HBV DNA replication, but the decrease in the number of cDNA after one year of treatment was negligible [14]. Due to this peculiarity, HBV is rather difficult to eradicate, and its persistence, though at a low level, explains the reason for the possibility of hepatitis reactivation in any person infected with the virus, including after LTx.

Virus elimination occurs with the development of a sustained, polyclonal, multispecific CD4+ and CD8+ T cell response, as well as through B cell response and production of neutralizing anti-HBs antibodies. HBV-specific T cells both directly target infected cells for elimination through cytopathic mechanisms and suppress viral replication through interferon-mediated pathways [15, 16]. The neutralizing antibodies produced by activated B cells further limit the spread of HBV. Although these immune mechanisms are sufficient to control active HBV replication, they are probably not effective enough to destroy the entire pool of infected cells containing either "latent" HBV cDNA or low-replication HBV, which avoid exposure to HBV-specific immune cells [17]. Thus, these cells represent a reservoir of persistent HBV. Although the size and nature of this reservoir in individuals with serologic signs of HBV convalescence are unknown, it is clear that it is a source of HBV reactivation following disruption or suppression of immune control mechanisms. HBV reactivation after LTx is associated with suppression of the immune response by immunosuppressive drugs. Glucocorticoids suppress cell-mediated immunity by inhibiting the production of interleukins necessary for T and B cell proliferation [17]. Calcineurin inhibitors such as cyclosporine and tacrolimus suppress T cells by binding to immunophilin proteins and inhibiting interleukin production [18]. Thus, it is not surprising that after LTx and initiation of immunosuppressive therapy, the risk of potential reactivation of HBV infection increases.

DE NOVO HBV INFECTION AFTER LIVER TRANSPLANTATION

De novo HBV infection after LTx represents the development of infection in a patient without previous HBV markers and who has undergone surgical treatment for another liver disease. The source of HBV infection, as in the general population, can be transfusions of blood components, surgical interventions including dental surgery, sexual partners, etc. Also, in patients after LTx, a donor who is HBsAg negative but has HBc antibodies in serum and HBV cDNA in hepatocytes may be a source. After transplantation of such an organ to a recipient, the virus is reactivated against the background of immunosuppressive therapy, which leads to chronic inflammation of the graft [19].

LONG-TERM OUTCOMES OF LIVER TRANSPLANTATION IN HBV PATIENTS

Recurrent HBV infection after OLTx is an important factor that reduces graft and recipient survival, significantly worsening the long-term prognosis. Without prophylactic treatment, the HBV recurrence rate is very high, reaching 80–100%. Recurrence usually occurs between 6 and 12 months after LTx [20].

According to the European Liver Transplant Registry, 5,822 surgeries for Virus B related cirrhosis were performed from 1988 to 2016 [21]. This represents 5% of the total number of transplants during this period. Over the past 15 years, the role of HBV infection in cirrhosis requiring transplantation has decreased to 4%. The 1-, 5-, 10- and 15-year graft and patient survival rates were 82% and 86%, 72% and 76%, 66% and 70%, and 57% and 62%, respectively. Interestingly, the 1- and 5-year graft and patient survival rates after transplantation for alcoholic cirrhosis was similar to those of patients with baseline HBV, while the 10- and 15-year survival rates were significantly lower in patients with alcoholic cirrhosis – 55% and 59% and 40%, 43%, respectively. Graft and patient survival in patients with cirrhosis in HCV infection was lower than in patients with HCV infection (Table).

Table

Indications for liver transplantation and corresponding graft and recipient survival. European Liver Transplant Registry, data from January 2002 to December 2016 [21]

Reason for liver transplantation	Number of patients	% of total number of transplant surgeries	1-year graft and patient survival rates, %	5-year graft and patient survival rates, %	10-year graft and patient survival rates, %	15-year graft and patient survival rates, %
HBV	3826	4	82, 86	72, 76	66, 70	57, 62
HBV + HDV	1431	2	89, 93	84, 89	79, 83	75, 78
HCV	10495	12	78, 81	59, 64	46, 51	36, 40
Alcoholic cirrhosis	18135	20	83, 86	71, 75	55, 59	40, 43
Autoimmune diseases	2027	2	83, 88	74, 80	63, 72	45, 57

1,939 liver transplants were performed for Virus BD related cirrhosis, which accounted for 2% of the total number of operations. Transplant and patient survival rates were higher than those for hepatitis B monoinfection: The 1-, 5-, 10- and 15-year graft and patient survival rates were 89% and 93%, 84% and 89%, 79% and 83%, 75% and 78%, respectively. HBV accounted for 16% of etiologies of the underlying cirrhosis in HCC patients [21].

Patients without HBV replication after transplantation thanks to effective antiviral therapy have been shown to have a higher survival rate compared to recipients with persisting viremia. Providing effective antiviral therapy is essential to significantly improving long-term transplant outcomes in this category of patients [22, 23].

RISK FACTORS FOR PROGRESSION OF HBV AFTER LIVER TRANSPLANTATION

The following are risk factors for the development and progression of HBV after LTx [21]:

- Viral load at the time of LTx (more/less than 10^5 copies/mL of HBV DNA in serum)
- Presence/absence of HBeAg
- Presence/absence of resistance to antiviral medications
- Use of immunosuppressive drugs

The risk of reactivation is conventionally divided into high (if HBV infection reactivation rate is ≥10%), moderate (if risk of reactivation is 1–10%), and low (if risk of reactivation is <1%), depending on the type of immunosuppressive therapy and on the presence/absence of HBsAg, but positive anti-HBcAb. Treatment with calcineurin inhibitors is a moderate risk factor for reactivation (HBV reactivation rate of 1–10%) [24]. Low-dose corticosteroid therapy (prednisolone 10 mg orally daily for 4 weeks) can increase the risk of reactivation up to 10% in HBsAg-positive individuals. Medium-dose corticosteroids (10–20 mg orally daily) may increase the risk of seroconversion in HBsAg-negative and anti-HBc-positive individuals [25]. Therefore, these individuals require close monitoring. Routine screening for HBV infection, in the form of HBsAg and anti-HBs testing, is recommended for all patients at risk of HBV reactivation [26]. Prophylactic therapy with oral anti-HBV drugs is highly recommended for patients at high or intermediate risk of reactivation. For patients at low risk of reactivation, either proactive therapy or wait-and-see approach is recommended. Among HBsAg-negative and anti-HBc-positive patients, data on the risk of HBV reactivation and anticipatory therapy are very inconsistent in many situations. In general, the risk of HBV reactivation is much lower in HBsAg-negative and anti-HBc-positive patients than in HBsAg-positive patients. The greatest risk of reactivation requiring proactive therapy is associated with the use of B-cell depleting treatment regimens or transplantation. In most other cases in HBsAg-negative and anti-HBc-positive patients, close monitoring is recommended.

ANTIVIRAL THERAPY AFTER LIVER TRANSPLANTATION

In the late 1980s and early 1990s, there were studies showing that patients after LTx for HBV, without antiviral therapy, had a high risk of recurrent infection in the graft. Moreover, in patients without HBeAg replication and in the absence of HBeAg, the rate of recurrence is as high (50% to 75%) as in patients without these viral replication markers [27]. Liver recipients on immunosuppressive therapy and with persistent HBV developed aggressive chronic hepatitis, turning into cirrhosis or graft rejection within 1–2 years. In 1991, Davies et al. introduced the term “fibrosing cholestatic hepatitis” to describe a unique and fatal form of recurrent HBV infection. Histologically, fibrosing cholestatic hepatitis is characterized by balloon degeneration of hepatocytes, moderate or no inflammation, varying degrees of perisinusoidal fibrosis and cholestasis, and marked expression of HBsAg and HBcAg on immunohistochemistry [28]. Increased intracellular expression of HBV antigens is largely the result of immunosuppressive drugs, which weaken the immune response against infected liver cells and can directly stimulate viral replication. The 3-year survival rate of hepatitis B patients who underwent transplantation in the United States from 1987 to 1991 was only 55%, compared with 68–78% in patients who underwent LTx for other indications [29, 30]. A multicenter study in 1994 showed that LTx for HBV was associated with rapid graft infection and high mortality [31]. Therefore, the presence of HBsAg and HBeAg in patients was an absolute contraindication for LTx, and the presence of HBsAg without HBeAg as a relative contraindication [32].

Since the development of protocols for long-term prevention of human hepatitis B immune globulin (HBIg), which contains antibodies to hepatitis B surface antigen, in 1987, HBV-related liver disease has been included in the indications for OLTx in Europe [33]. However, the presence of hepatitis B was a relative contraindication for transplantation in the United States until the mid-1990s.

Interferon medications were once the basis of antiviral therapy for HBV infection before LTx, and were also used after LTx, as graft survival was very low without antiviral therapy [34]. Binding of type 1 interferon alfa to the interferon alpha receptor initiates a signal transduction pathway leading to the induction of multiple genes called interferon-stimulated genes. These genes encode multiple proteins that mediate the antiviral effects of interferon as well as its side effects. The number and severity of side effects, together with the injectable route of administration and the low efficacy of this therapy, are

the main reasons as to why interferon medications are hardly used today. In clinical trials, almost all patients had at least one adverse event. Serious adverse events were occurred in 10% of patients r treated with peginterferon alfa-2a and in 17% of patients treated with peginterferon alfa-2b. About 40% of patients needed dose adjustments due to adverse reactions. The most common reasons for dose modifications were neutropenia (27% for peginterferon alfa-2a and 18% for peginterferon alfa-2b) and thrombocytopenia (4% and 3%, respectively). About 14% and 10% of patients had to discontinue therapy because of adverse events [35]. The most common reasons for discontinuation of therapy were psychiatric (depression and irritability), systemic (e.g., fatigue, headache), or dyspepsia. Most patients experienced a flu-like syndrome, such as fatigue, fever, chills, myalgias, arthralgias, backache, headache, anorexia, nausea, diarrhea, impaired concentration, difficulty sleeping, weight loss, decreased libido, hair loss, and bone marrow suppression [36]. Interferon therapy also stimulates the body's immune response, increasing the risk of graft rejection, averaging 5%. After transplantation there are also hematological manifestations – cytopenia, anemia – requiring not only dose modification but also introduction of stimulants of hemopoiesis and leukopoiesis and even hemotransfusions (up to 50% of recipients) [37].

Human HBIg, which contains antibodies to hepatitis B surface antigen, is still used in many transplant centers. Some studies have shown that the combination of HBIg and direct-acting antivirals (DAAs) is effective in preventing HBV reactivation [38, 39]. In a meta-analysis including 1484 patients, a combination therapy of HBIg with nucleos(t)ide analogues was more effective in reducing HBV recurrence than monotherapy with DAAs, but the vast majority of included studies used lamivudine, adefovir or their combination [40].

At the same time, there is sufficient data showing that a monotherapy with DAAs has high efficacy in patients after LTx. A 53-month study of 362 patients who underwent LTx for cirrhosis resulting from HBV infection was conducted. None of the patients received HBIg. Half of the patients were placed on lamivudine (LAM), 39% received entecavir (ETV), and 12% received combination therapy (predominantly lamivudine + adefovir). The HBV recurrence rate at 3 years for LAM, ETV, and combination group was 17%, 0%, and 7%, respectively [41].

With the appearance of new nucleoside analogues (entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide) with high resistance threshold, the concept of the need for lifelong use of HBIg to prevent HBV relapse, due to its high cost, lack of standard protocols and inconvenience in the long term (parenteral administration only), began to undergo significant changes: dose reduction, shortened course of administration, intraoperative administration only, which was not accompanied by an increased risk of HBV recurrence when coadministered with potent nucleoside analogues. At present, further studies on the possibility of completely excluding HBIg from antiviral therapy and preventing HBV recurrence after LTx are continuing [42–44].

Antiviral drugs for HBV infection can be divided into three classes:

- interferons
- Nucleoside reverse transcriptase inhibitors (lamivudine, telbivudine, entecavir)
- Nucleotide reverse transcriptase inhibitors (adefovir, tenofovir disoproxil fumarate, tenofovir alafenamide)

At present, interferons, as well as lamivudine, telbivudine and adefovir, are practically not used, especially after LTx, due to the high risk of side effects, resistance and low efficacy of these drugs. Several meta-analyses have shown the lamivudine to have a less favorable outcome for treatment and prevention of HBV reactivation than entecavir or tenofovir [45–47]. Tenofovir and entecavir are the most powerful antiviral drugs, characterized by a high genetic barrier to resistance and are used as monotherapy. The goal of antiviral therapy is to achieve and maintain a negative HBV DNA level.

Entecavir, an oral nucleotide analogue, is phosphorylated to form active triphosphate. By competing with its natural substrate, deoxyguanosine triphosphate, entecavir triphosphate inhibits all 3 functional activities of viral polymerase: 1) HBV polymerase priming, 2) reverse transcription of negative strand from pregenomic iRNA and 3) synthesis of positive strand HBV DNA. Entecavir triphosphate is a weak inhibitor of cellular DNA polymerases. The presence of mutations of HBV resistance to lamivudine increases the risk of entecavir resistance. Due to this, frequent monitoring of viral load in lamivudine-resistant patients and, if necessary, change of antiviral therapy are required. The drug is used in a 0.5–1 mg/day dose.

Tenofovir disoproxil fumarate is converted in the body to tenofovir, a nucleoside monophosphate (nucleotide) analogue of adenosine monophosphate. Tenofovir is subsequently converted to its active metabolite, tenofovir diphosphate. It is a nucleotide inhibitor of reverse transcriptase. The drug is used in a 300 mg/day dose.

Tenofovir alafenamide is a tenofovir phosphonoamidate prodrug (analog of 2'-deoxyinosine 5'-monophosphate). It penetrates primary hepatocytes by passive diffusion and is transported by hepatic capture transporters – organic anion transporting polypeptides. In primary hepatocytes, tenofovir alafenamide is primarily hydrolyzed by carboxylesterase-1 to form tenofovir. Intracellular tenofovir is subsequently phosphorylated to the pharmacologically active metabolite tenofovir diphosphate. Tenofovir diphosphate inhibits hepatitis B virus replication by introducing it into viral DNA via hepatitis B reverse transcriptase, resulting in DNA strand breakage. The drug is used in a 25 mg/day dose.

Another strategy for preventing HBV recurrence is the induction of active immunity through vaccination [48]. A study by Bienzle et al. showed the possibility of successful vaccination after LTx [49]. Vaccines targeting the preS1 domain, which can potentially overcome immune tolerance to HBV, have shown promising efficacy in developing an immune response in clinical trials. On the other hand, HBV vaccines may be more effective in preventing de novo hepatitis B infection in HBsAg-negative patients. In a study of 71 HBsAg-negative patients who received anti-HBc-positive grafts, de novo HBV infection did not develop in 54 patients who were vaccinated [50].

ADVERSE EVENTS THAT OCCUR WITH ANTIVIRAL THERAPY

The possibility of antiviral therapy with entecavir and tenofovir disoproxil fumarate for treatment of HBV infection in the post-transplantation period may be limited by resistance to a long-term drug, renal dysfunction against the background of combined administration with nephrotoxic drugs, especially with calcineurin inhibitors, as well as the presence of osteoporosis.

In patients with impaired renal function, the tenofovir disoproxil fumarate dose should be adjusted if creatinine clearance is <50 mL/min. In patients with 30–49 mL/min creatinine clearance, the interval between doses should be doubled. Patients with 10–29 mL/min creatinine clearance should use tenofovir disoproxil fumarate once or twice a week. For patients on hemodialysis, tenofovir disoproxil may be used after each hemodialysis session or every 7 days.

Studies investigating the efficacy and safety of tenofovir alafenamide in patients with chronic kidney disease (CKD) have shown the superiority of the drug over tenofovir disoproxil fumarate in influencing renal function and bone remodeling at weeks 48 and 96. A significant difference in glomerular filtration rate (GFR) reduction was demonstrated: 0.6 mL/min versus 5.4 mL/min in HBeAg-positive patients ($p < 0.0001$), 1.8 mL/min versus 4.8 mL/min in HBeAg-negative patients ($p = 0.004$). A significantly lower percentage reduction in bone mineral density in the hip was also reported compared with patients treated with tenofovir disoproxil fumarate (0.10% vs. 1.72% in HBeAg-positive patients ($p < 0.0001$) and 0.29% vs. 2.16% in HBeAg-negative patients ($p < 0.0001$) and spine (0.42% vs. 2.29% in HBeAg-positive patients, 0.88% vs. 2.51% in HBeAg-negative patients [51]. Studies have also been conducted on the use of tenofovir alafenamide in patients after LTx in the presence of chronic kidney disease (ID NCT02862548). There was demonstrated a significant increase in GFR in 48 weeks after the start of tenofovir alafenamide in patients after LTx taking calcineurin inhibitors, a decrease in alanine aminotransferase (ALT) levels compared with its activity on the background of tenofovir disoproxil fumarate [52].

CONCLUSION

The risk of HBV recurrence after liver transplantation in the absence of antiviral therapy is high, which is an important prognostic factor that reduces graft and patient survival. There is also a certain risk of de novo HBV infection after LTx requiring an antiviral therapy.

Based on analysis of published studies on HBV reactivation and de novo HBV infection in liver transplant patients, it can be stated that effective antiviral therapy is necessary to improve transplant outcomes and patient survival.

Given the lack of generally accepted protocols describing the treatment specifics for HBV infection developing after LTx, as well as the small number of studies on the use of DAAs after LTx, this study attempts to combine available data on the course of post-LTx HBV infection, effectiveness of antiviral therapy, and long-term outcomes (graft and patient survival rates).

The authors declare no conflict of interest.

REFERENCES

1. *Schaefer S.* Hepatitis B virus taxonomy and hepatitis B virus genotypes. *World J Gastroenterol*. 2007; 13 (1): 14–21.
2. *Jiang Y et al.* The Mechanisms of HBV-Induced Hepatocellular Carcinoma. *J Hepatocell carcinoma*. 2021; 8: 435–450.
3. *Beasley RP.* Rocks along the road to the control of HBV and HCC. *Ann Epidemiol*. 2009; 19 (4): 231–234.
4. *Lin CL, Kao JH*. Natural history of acute and chronic hepatitis B: The role of HBV genotypes and mutants. *Best Pract Res Clin Gastroenterol*. 2017; 31 (3): 249–255.
5. *Chen Y, Tian Z*. HBV-Induced Immune Imbalance in the Development of HCC. *Front Immunol*. 2019 Aug; 10: 2048.
6. *Chen HY et al*. Prevalence and burden of hepatitis D virus infection in the global population: a systematic review and meta-analysis. *Gut*. 2019; 68 (3): 512–521.
7. *Terrault NA et al*. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016; 63 (1): 261–283.
8. *Vodkin I, Kuo A*. Extended Criteria Donors in Liver Transplantation. *Clin Liver Dis*. 2017; 21 (2): 289–301.
9. *Castells L et al*. Clinical impact and efficacy of lamivudine therapy in *de novo* hepatitis B infection after liver transplantation. *Liver Transpl*. 2002; 8 (10): 892–900.
10. *Devarbhavi HC et al*. Preliminary results: outcome of liver transplantation for hepatitis B virus varies by hepatitis B virus genotype. *Liver Transpl*. 2002; 8 (6): 550–555.
11. *Marzano A et al*. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. *Liver Transpl*. 2005; 11 (4): 402–409.

12. *Roche B, Samuel D*. Withdrawal of posttransplant hepatitis B virus prophylaxis: A blind test. *Liver Transpl*. 2016; 22 (9): 1183–1185.
13. *Faria LC et al*. Hepatocellular carcinoma is associated with an increased risk of hepatitis B virus recurrence after liver transplantation. *Gastroenterology*. 2008; 134 (7): 1890–1899.
14. *Rehermann B et al*. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. *Nat Med*. 1996; 2 (10): 1104–1108.
15. *Werle-Lapostolle B et al*. Persistence of cccDNA during the natural history of chronic hepatitis B and decline during adefovir dipivoxil therapy. *Gastroenterology*. 2004; 126 (7): 1750–1758.
16. *Sung JJY et al*. Intrahepatic hepatitis B virus covalently closed circular DNA can be a predictor of sustained response to therapy. *Gastroenterology*. 2005; 128 (7): 1890–1897.
17. *Guidotti LG, Chisari FV*. Immunobiology and pathogenesis of viral hepatitis. Annu. Rev. Pathol. 2006; 1: 23–61.
18. *Löwenberg M et al*. Glucocorticoid signaling: a nongenomic mechanism for T-cell immunosuppression. *Trends Mol Med*. 2007; 13 (4): 158–163.
19. *Azzi JR, Sayegh MH, Mallat SG*. Calcineurin inhibitors: 40 years later, can't live without. *J Immunol*. 2013; 191 (12): 5785–5791.
20. *Shu-Sen Zheng et al*. Prophylaxis and treatment of hepatitis B virus reinfection following liver transplantation. *Hepatobiliary Pancreat Dis Int*. 2002; 1 (3): 327–329.
21. *Adam R et al*. 2018 Annual Report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. *Transpl Int*. 2018; 31 (12): 1293–1317.
22. *Li MS et al*. The strategy and efficacy of prophylaxis against hepatitis B virus recurrence after liver transplantation for HBV-related diseases in the era of potent nucleos(t)ide analogues: A meta-analysis. *J Dig Dis*. 2021; 22 (2): 91–101.
23. *Saidy RRO et al*. Clinical and Histological Long-Term Follow-Up of *De Novo* HBV-Infection after Liver Transplantation. *Medicina (Kaunas)*. 2021; 57 (8): 767.
24. *Adil B et al*. Hepatitis B Virus and Hepatitis D Virus Recurrence in Patients Undergoing Liver Transplantation for Hepatitis B Virus and Hepatitis B Virus Plus Hepatitis D Virus. *Transplant Proc*. 2016; 48 (6): 2119–2123.
25. *Calabrese LH, Zein NN, Vassilopoulos D*. Hepatitis B virus (HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. *Ann Rheum Dis*. 2006; 65 (8): 983–989.
26. *Perrillo RP, Martin P, Lok AS*. Preventing hepatitis B reactivation due to immunosuppressive drug treatments. *JAMA*. 2015; 313 (16): 1617–1618.
27. *Lok ASF, McMahon BJ*. Chronic hepatitis B: update 2009. *Hepatology*. 2009; 50 (3): 661–662.
28. *O'Grady JG et al*. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. *J Hepatol*. 1992; 14 (1): 104–111.
29. *Davies SE et al*. Hepatic histological findings after transplantation for chronic hepatitis B virus infection, including a unique pattern of fibrosing cholestatic hepatitis. *Hepatology*. 1991; 13 (1): 150–157.
30. *Harrison RF et al*. Recurrent hepatitis B in liver allografts: a distinctive form of rapidly developing cirrhosis. *Histopathology*. 1993; 23 (1): 21–28.
31. *Belle SH, Beringer KC, Detre KM*. Trends in liver transplantation in the United States. *Clin Transpl*. 1993; 19: 35.
32. *Crippin J et al*. Retransplantation in hepatitis B – a multicenter experience. *Transplantation*. 1994; 57 (6): 823–826.
33. *Van Thiel DH et al*. Medical aspects of liver transplantation. *Hepatology*. 1984; 4 (1 Suppl): 79S–83S.
34. *Lauchart W, Müller R, Pichlmayr R*. Long-term immunoprophylaxis of hepatitis B virus reinfection in recipients of human liver allografts. *Transplant Proc*. 1987; 19 (5): 4051–4053.
35. *Gara N, Ghany MG*. What the infectious disease physician needs to know about pegylated interferon and ribavirin. *Clin Infect Dis*. 2013; 56 (11): 1629–1636.
36. *Terrault NA et al*. Interferon alfa for recurrent hepatitis B infection after liver transplantation. *Liver Transpl Surg*. 1996; 2 (2): 132–138.
37. *Crespo G et al*. Viral hepatitis in liver transplantation. *Gastroenterology*. 2012; 142 (6): 1373–1383.e1.
38. *Karasu Z et al*. Low-dose hepatitis B immune globulin and higher-dose lamivudine combination to prevent hepatitis B virus recurrence after liver transplantation. *Antivir Ther*. 2004; 9 (6): 921–927.
39. *Takaki A, Yagi T, Yamamoto K*. Safe and cost-effective control of post-transplantation recurrence of hepatitis B. *Hepatol Res*. 2015; 45 (1): 38–47.
40. *Wang P et al*. Is hepatitis B immunoglobulin necessary in prophylaxis of hepatitis B recurrence after liver transplantation? A meta-analysis. *PLoS One*. 2014; 9 (8): e104480.
41. *Fung J et al*. Oral nucleoside/nucleotide analogs without hepatitis B immune globulin after liver transplantation for hepatitis B. *Am J Gastroenterol*. 2013; 108 (6): 942–948.
42. *Gautier SV et al*. One hundred deceased donor liver transplantations at a single center. *Russian Journal of Transplantology and Artificial Organs*. 2012; 14 (1): 6–14.
43. *Malomuzh OI, Chekletsova EV, Khizroyev XM, Pets VA, Fokin SV, Taranov VA et al*. HBV-infection *de novo* after orthotopic liver transplantation: clinical and virological characteristics, assessment of antivirus therapy effectiveness. *Russian Journal of Transplantology and Artificial Organs*. 2012; 14 (3): 24–30.
44. *Tsirul'nikova OM, Umrik DV, Monakhov AR, Zubenko SI.* Profilaktika retsidiva gepatita B posle transplantatsii pecheni: a tak li neobkhodim immunoglobulin? *Vestnik transplantologii i iskusstvennykh organov*. 2021; 23 (S): 60–61.
45. *Huang KW et al.* Efficacy and Safety of Lamivudine Versus Entecavir for Treating Chronic Hepatitis B Virus-

related Acute Exacerbation and Acute-on-Chronic Liver Failure: A Systematic Review and Meta-Analysis. *J Clin Gastroenterol*. 2017; 51 (6): 539–547.
46. *Govan L et al.* Comparative effectiveness of antiviral treatment for hepatitis B: a systematic review and Bayesian network meta-analysis. *Eur J Gastroenterol Hepatol*. 2015; 27 (8): 882–894.
47. *Chun Yang et al.* Meta-analysis of prophylactic entecavir or lamivudine against hepatitis B virus reactivation. *Ann Hepatol*. 2016; 15 (4): 501–511.
48. *Fung J.* HBV therapeutic vaccines and cccDNA inhibitors – emergence of a cure. *Liver Transpl*. 2016; 22 (S1): 52–56.
49. *Bienzle U et al*. Immunization with an adjuvant hepatitis B vaccine after liver transplantation for hepatitis B-related disease. *Hepatology*. 2003; 38 (4): 811–819.
50. *Wang SH et al*. Active immunization for prevention of *de novo* hepatitis B virus infection after adult living donor liver transplantation with a hepatitis B core antigen-positive graft. *Liver Transpl*. 2017; 23 (10): 1266–1272.
51. *Chan HLY et al*. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016; 1 (3): 185–195.
52. *Sripongpun P et al*. Potential Benefits of Switching Liver Transplant Recipients to Tenofovir Alafenamide Prophylaxis. *Clin Gastroenterol Hepatol*. 2020; 18 (3): 747–749.

The article was submitted to the journal on 7.04.2022