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Organ transplantation from donors infected with blood-borne viruses. A foreign experience

M.Sh. Khubutiya, S.A. Solonin, M.A. Godkov

N.V. Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia

Correspondence to: Mogeli Sh. Khubutiya, Acad. of RAS, Professor, Director of N.V. Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia, e-mail: sklifos@inbox.ru

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We have analyzed the foreign experience of organ transplantation from donors infected with blood-borne viral infections (BBVIs). Lifting ban on the transplantation of organs positive for BBVI markers contributes to the expansion of the donor pool and reduces time spent on waiting lists. At the same time, the use of donor organs positive for BBVI markers is often associated with an increased risk of complications and deaths among recipients.

Keywords: HIV, HBV, HCV, liver transplantation, kidney transplantation, blood-borne viral infections.

Introduction

In 2013, according to the Global Observatory on Donation and Transplantation, more than 117 000 organ transplants were made worldwide. Of these, about 79 000 were accounted for kidney transplants, 25 000 – for liver, 6000 – for heart 4800 – for lungs, 2400 – for pancreas [1]. Despite the high rates of transplant activity, the real need in such operations remains ten times higher. For example, in the United States by the end of 2012 in the transplant waiting lists (TWL) countrywide were 76 047 people, in 2016 their number increased to 120 921 (Based on OPTN data as of 19.04.16). According to the United Network for Organ

Sharing (UNOS) data, it continues to increase the proportion of persons with viral-induced cirrhosis and hepatocellular carcinoma [2]. The number of chronic renal diseases and chronic renal failures are increasing [3].

The most common cause of enlarged incidence of chronic diseases is associated with the wide prevalence blood-borne viral infections (BBVIs), which include HIV, HBV and HCV infections. By the end of 2014 there were about 36.9 million HIV-infected persons, 240 million with chronic HBV and from 130 to 150 million people living with HCV-infection worldwide [4-6].

The high prevalence of BBVIs associated with severe medical and social consequences in the form of a predictable increase of patients who require transplantation. This type of specialized high-tech medical care is often the only radical method for treatment, the success of which largely depends on the quality of the donor's organ.

Currently, the indications for organ transplantation, the criteria for inclusion in TWL, as well as the order of rendering this type of assistance have been determined. However, the inclusion in TWL does not guarantee obtaining of a donor's organ because of the shortage. UNOS and Eurotransplant data is showing that the actual necessity for organs exceeds the existing capabilities of the pool of living and deceased donors [2, 7]. The continuously growing demand for organs in conditions of the existing deficit pushed scientists and doctors to carry out scientific researches aimed at the revision of existing contraindications to organ donation. The research concerned, first of all, the revision of the enumeration of relative and absolute contraindications. Today there is a trend to use organs from older donors and ones with extended criteria. In some countries, the pool of such donors could exceed 25% [8]. The use of

organs from these donors carries a high risk of kidney allograft loss and death [9, 10].

In recent years, the transplant community have been discussed issues and attempted to change the generally accepted selection criteria for potential organ donors (POD) in order to expand the pool primarily for account of donors infected with BBVIs [11]. It became possible due to the achievements of modern medicine, clinical pharmacology, and acceptable results of 3 and 5-year survival rates of recipients. Considering the extremely high need in organs, as well as success in the treatment of BBVIs, a reasonable question arises: "Is it possible to use organs and tissues from donors with positive laboratory tests of BBVIs?"

Actuality of this problem determined the large proportion of recipients, infected BBVIs, and that fact that the current screening algorithm for BBVIs among potential donor does not completely exclude the risk of transmission of these infections through organ transplantation from the donor to the recipient [12].

Aim: to analyze the foreign experience of the use of donor organs infected with BBVIs.

The use of organs with HBV infection

According to several studies performed in the United States, between 847 000-2 200 000 people are infected with HBV, from 2 700 000 to 3 500 000 people have chronic HCV infection, and more than 1 200 000 people living with HIV [13-16]. In the countries of the European Union, these indices are 4.2, and 5.7 to 10.8 per 100,000 populations, respectively [17].

Previously, it was thought that the presence in the serum of patients antibodies to capsid antigen (HBcAb) in the absence of HBsAg and HBV DNA is an evidence of acute resolving or chronic hepatitis B. In 1978, J.

N. Katchaki et al. [20] described a case of acute HBV-infection in the recipient after a blood transfusion containing HBcAb in the absence of HBsAg. Further, it was shown that viral DNA can be detected in the blood serum and liver tissue of patients who do not have the surface antigen to detect by available methods. Such cases have become considered as "occult" HBV-infection. In 2008 experts of the European Association for the study of liver diseases (EASL) defined the notion of occult HBV-infection as "presence of HBV DNA in the liver (with detectable or undetectable HBV DNA in the serum) of individuals testing HBsAg negative by currently available assays". This phenomenon is based on the mechanism of viral replication. Genetic material of the virus is present in hepatocytes in the form of covalently closed circular DNA (cccDNA) with the possibility of further integration into the host cell genome [19].

The prevalence of HBcAb among liver donors varies from 5-15% in the US and European countries to 53% in Southeast Asia [20-22]. It has been shown that more than half of cases (58%) liver transplantations from donors with isolated anti-HBc end with *de novo* HBV and has a negative impact on post-transplant survival [23]. The probability of HBV transmission via heart and kidney transplantation from HBc positive donor is significantly lower, but not completely excluded [24, 25]. The likelihood of HBV transmission is manifold decrease if the recipient has antibodies to hepatitis B (HBsAb) or carry out a prophylaxis of specific immunoglobulin (HBIg) and (or) antiviral medication, e.g. lamivudine [25-28].

The application of non-specific prevention allows reducing the risk of *de novo* HBV and recurring infection, as well as to increase 5-year clinical outcomes of patient and graft at a level exceeding 80% [28, 29]. Taking drugs prophylaxis reduces the risk of *de novo* HBV-infection by

using HBIg up to 19%, lamivudine – up to 2.6%, combinations of medicines (HBIg + analogue nucleos(t)ides) up to 2.8%, respectively [30]. Modern antiviral drugs allows to use a pool of donors with HBsAg "+". A group of researchers under the leadership of Y. Choi at al. [31] demonstrated the possibility of the normal functioning of liver graft for 2 years in 62.5% of patients after transplantation from HBsAg positive donors to recipients with chronic liver disease HBV etiology. Several studies have shown that the administration of antiviral therapy is not always accompanied by the disappearance of HBsAg and a decrease in HBV replication activity [32, 33]. The utilization of HBsAg "+" graft in patients with hepatic cirrhosis HBV/HDV leads to the retransplantation within 2 years [34]. Prolonged antiviral therapy, primarily lamivudine, associated with a high risk of developing drug (secondary) resistance [35]. New antiviral drugs such as entecavir, tenofovir and adefovir which have a high level of genetic barrier and a low resistance rate, makes it possible to minimize the possibility of recurrent HBV-infection. It should be noted that the variants of HBV with mutations in P-gene (primary resistance) could be detected among patients prior to nucleos(t)ides analogues therapy. According Mirandola S. at al. data, the proportion of such patients can reach 5% [36].

Liver graft recipients with markers of resolved HBV-infection (the presence of anti-HBc in serum only) during post-transplant period may have a reactivation of HBV as a result of application of immunosuppressive therapy. The risk of reactivation in case immunosuppressive therapy is undefined and depends on the number of factors – patient age, presence of concomitant diseases etc. Especially high probability of reactivation HBV-infection when use corticosteroids and anticancer drugs, specifically rituximab [37]. Cases of HBV reactivation are rare in patients receiving immunosuppressive therapy and

who have a titer of HBsAb higher than 100 IU/L [38]. As a rule, cases of reactivation of HBV during treatment with immunosuppressive drugs effectively amenable to therapy with analogues of nucleos(t)ides.

The clinical guidelines for management patients with transplanted organs developed by the International Society of Transplantation permit the use of organs from HBsAg "–" and anti-HBc "+" deceased donors to recipients with HBV or to patients in UNOS's 1st class urgency list.
Performing such operations is possible only with the full informed consent of the recipient (and/or relatives) [39].

The use of organs with HCV-infection

Hepatitis C is the most common cause of chronic terminal liver disease and hepatocellular carcinoma. Patients with terminal stages of liver cirrhosis in the outcome of HCV account for up to 25% in WTL for liver [2].

According to one of the surveys, the number of potential organ donors with antibodies to hepatitis C, depending on the risk group varies from 3,45 to 18,20% [40]. It has been shown that graft reinfection with HCV occurs in 100% of cases among recipients who had HCV RNA at the time of transplantation and did not get an antiviral treatment. Recurrent HCV-infection is the leading cause of graft loss and recipient death. The faster becomes the graft reinfection, the worse postoperative results. In most patients after surgery the viral load of HCV RNA may exceed the pre-transplantation level and the infection is progressing faster than in non-transplanted [41].

Controversial results have been published regarding the impact of the use of organs with HCV markers on the survival of recipients. Thus, a group of researchers led by P.G. Northup et al. [42] have been analyzed UNOS and Organ Procurement and Transplantation Network scientific

registry data for the period from 1994 to 2008 and showed that the detection of anti-HCV among deceased organ donors should not be an absolute contraindication to transplantation. The application of modern antiviral therapy makes it possible to level the differences in clinical outcomes and functional activity of grafts after transplantation from anti-HCV "+" donor to anti-HCV "+" recipient compared to results from anti-HCV "-" donor to anti-HCV "+" recipient. Similar results were obtained by A. T. Burr et al. [43]. The utilization of renal grafts from donors with anti-HCV "+" allows to reduce the term in WTL an average of 1 year and reach 1 and 3-year survival rates in patients at the level of 91% and 77%, respectively [44]. In the absence of adequate antiviral therapy, hepatic graft cirrhosis develops in 20-30% of transplant recipients [45].

A multicenter cohort study (J. C. Lai et al.) [46] showed that using a liver from a donor with anti-HCV "+", advance the risk of fibrosis if the donor was over 45 years old. The usage of organs from anti-HCV "+" donors to anti-HCV "-" recipients can significantly ($p = 0.002$) reduce patient survival rates [47]. A group of researchers led by M. I. Montenovo pointed out that 1, 5 and 10-year survival rates among HCV infected recipients who got an organ from donor with anti-HCV "+" and without them did not have statistically significant differences [48]. At the same time, it was noted that the survival rate for recipients without HCV-infection was higher ($p < 0.0001$) than those who had no hepatitis C [49]. On survival rate of recipients and grafts can influence social and economic factors – race, median family income [50].

Active use of modern antiviral drugs can reduce the risk of graft loss. Currently proposed several groups of medicines with high efficacy: recombinant and pegylated interferons, ribavirin, inhibitors of NS3 serine protease (boceprevir), NS3/4A protease (telaprevir, simeprevir) and RNA polymerase HCV NS5B (sofosbuvir), etc [49, 51]. New drugs with direct

antiviral action for hepatitis C treatment have 97% efficiency [52]. Administration of modern antiviral medicines for HCV treatment requires consideration of their interactions with immunosuppressors (cyclosporine and tacrolimus), as it affects their pharmacokinetics [51].

The active use of antiviral therapy after transplantation is limited by the large number of side effects, variety of the used treatment regimens and drug interactions require careful pharmacological control [53]. The widespread introduction of modern medicines with direct antiviral action into the clinical practice is hindered by their high cost. For example, if a 48-week course of pegylated interferons in combination with ribavirin costs an average of about $ 35 000, the administration of new drugs with direct antiviral action in combination therapy can range from $ 92 000 to $155 000 for 12-week course [54].

The decision to transplant organs from a donor with HCV-infection is balance between the risk of transmission of the virus that can lead to the morbid affection of transplanted organ, and the effectiveness of patient care, which is in emergency condition. Taking into account the high prevalence of hepatitis C in the population, the complexity of treating patients after transplantation and low availability of modern therapy, the utilization of organs from donors with HCV is still debate. The basic conditions for the possible use of the donor's pool with HCV-infection are absence of hepatitis C replication and thorough histological examination of the graft prior to transplantation [46].

The use of organs with HIV-infection

In April 2016, surgeons from the Johns Hopkins University performed the first liver and kidneys transplantation in the US history from HIV-infected donor to two HIV-infected recipients [55]. This was made possible by the adoption of relevant law (HIV Organ Policy Equity

Act, HOPE) in 2013 and UNOS approval in February 2016. Until then, the presence of HIV was an absolute contraindication to donation since 1988. The presence of HIV in recipients previously was considered as ban since it was assumed that such patients had an extremely high risk of developing opportunistic infections and oncologic diseases. In 2008, M. E. Roland et al. [56] published data on transplantation to HIV-infected recipients for the period from 2000 to 2003.

The study included 11 liver and 18 kidney recipients with HIV-infection. Results of 1 and 3-year survival of recipients after liver and kidneys transplantation were 91%, 64% and 94%, 94%, respectively. The authors noted that the results of 3-year survival in kidney recipients were comparable to the cohort of uninfected recipients who underwent a similar operation, according to the UNOS national database for the period 1999-2004.

Dr. Elmi Muller is the surgeon from the University of Cape Town (South Africa) and the founder in the field of organ transplantation from HIV-infected donors. Since 2008, as part of a prospective non-randomized study she performed 27 kidney transplants from deceased HIV-infected donors to HIV-infected recipients. The main conditions for inclusion to the study for donors were the absence in medical history an antiretroviral therapy, for recipients – receiving antiretroviral therapy, CD4 cell count > 200 cells/mm^3, HIV RNA < 50 copies/ml. In the first year after transplantation the survival rates of patients was 84%, 3 and 5-year survival rates were 84% and 74%, respectively; rejection of kidney graft recorded in 8% cases in the 1st year, 22% in the 3rd year after transplantation. In most cases, the rejection was stopped due to correction immunosuppressive drugs dosage and use plasmapheresis in combination with a rabbit anti-thymocyte immunoglobulin. In spite of the fact that the somatic condition recipients and grafts were satisfactory after surgery,

HIV-associated nephropathy, not requiring dialysis, was recorded in 11.1% of cases [57]. According to P. G. Stock et al. data [58], HIV-infected recipients have an extremely high risk of graft rejection. The transplant rejection was recorded during 1 and 3 years of observation in 31% and 41% of cases, respectively. For the time being there are no clear explanations of such reactions. Perhaps this could be linked with pharmacological interactions between antiretroviral drugs and immunosuppressors. Also there is alertness about the possibility of infection HIV-infected recipient with donor's antiretroviral drug-resistant strains. The research results E. Muller and P. G. Stock indicate the need for further studies aimed at assessing safety and efficacy of organ transplantation from HIV-infected donors. An early resolution of these problems will increase the pool of potential donors in the US only, according to B.J. Boyarsky, on an average 500 people per year [59]. And if the effectiveness of modern antiretroviral therapy allows a significant increase life expectancy, the presence of co-infection will inevitably lead to the need for a repeated transplantation.

Conclusion

In 1994, US health service officials prepared guidelines for preventing transmission of HIV via organs and tissues by transplantation. In 2013, this document was supplemented; it included recommendations for avoidance the transmission of hepatitis B and C viruses from the donor to the recipient [60]. At the same time in Europe and in the United States, thanks to different research programs, it has been shown that the presence HIV, HBV and HCV infections are not an absolute contraindication to donation. The use of modern medical technologies combined with effective antiviral therapy provides economic justification for transplantation. For example, the cost of hemodialysis in patients with

chronic renal failure may significantly exceed the cost of transplant care and concomitant medication. For patients with chronic terminal heart, liver and lung diseases, the use of BBVIs infected organs are a chance to get the necessary organ. For such patients, there are no other types of substitution therapy, without transplantation they will inevitably perish. The utilization of organs from donors with BBVIs has many “pitfalls” ethical and medical nature and requiring a complex and comprehensive study. For example, the use of donors with current or recovered HBV infection is unlikely to have a significant effect on the actual deficit in regions that are not endemic for HBV infection, such as North America and Western Europe, where the prevalence of this infection is less than 1-2%. It can be safely asserted that this problem is more relevant for mid- and highly endemic regions, such as the Mediterranean and South-East Asia countries, where 5-15% of the population have chronic HBV-infection and where a significant number of potential donors are carriers of laboratory markers HBV. The lifting the ban on organ transplantation from people infected HIV and HCV can contribute to the expansion of the donor’s pool and in the future will reduce the length of stay in WTL, and improve the quality of life. However, at the moment there are a number of restrictions regarding the access and drug monitoring of modern immunosuppressive and antiviral medicines for recipients, as well as difficulties with additional expensive laboratory testing potential organ donors with BBVIs. Organ transplantation is often associated with a greater risk to the life of patients, and treatment protocols of BBVIs in recipients are still in the category of experiments and have not always been included in clinical practice.

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