Usage of HCV viremic organs in liver transplantation to anti-HCV negative recipients: The current status and review of literature

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ABSTRACT

Liver transplantation is the main curative therapy for end-stage liver disease. The number of transplanted organs is increasing globally. However, the number of available organs in the pool is insufficient, considering the excessive number of patients on the waiting list, which is a major concern for transplant programs. Hepatitis C infection (HCV) is a common indication for liver transplantation, and in recent years, a major progress has been made in its treatment with direct-acting antiviral (DAA) agents. HCV-positive livers have been transplanted to HCV-positive recipients for a long time. The high rate of sustained virologic response through DAA has brought new treatment options for the patients during the pre- and post-transplantation periods. Recently, there have been few reports of transplanting the available HCV-positive organs to HCV noninfected recipients. However, there is not yet an agreement on the optimal selection of patients who would benefit from such transplantation, and this has become a current topic of interest. Thus, we aim to review the current literature on this evolving topic.

Keywords: *Hepatitis C virus, transplantation, nucleic acid test, transmission infection, viremic donors, increased-risk donor*

INTRODUCTION

Liver transplantation (LT) is the curative treatment for end-stage liver disease (ESLD). However, an increasing imbalance between organ demand and supply is becoming a more crucial problem as the number of patients on the waitlist is trending upwards (1). Hepatitis C infection (HCV) is a leading cause of ESLD, and high sustained virologic response rates (SVR) were achieved in both pre- and post-LT settings, with the application of direct-acting antiviral agents (DAA) (2,3). Such high SVR may encourage to conduct transplantation from HCV-positive viremic donors to HCV-negative recipients. Recently, there have been reports of an increasing number of deaths from opioid abuse and drug overdose in the United States (4). The main rationale for including anti-HCV-positive viremic donors is to reduce the waiting time and eventually the waitlist mortality. However, a major drawback in this regard is the risk of potentially fatal post-LT complications, such as acute hepatitis, fibrosing cholestatic hepatitis, and eventual graft loss. Thus, the need for post-LT DAA treatment of the recipient is unquestionable.

The risk of HCV transmission from an HCV-positive donor to an HCV-negative recipient after solid organ transplantation has been known for a long time (5). The risk is significant, as it was historically shown that the replication of HCV within the graft may cause accelerated fibrosis and eventual cirrhosis in 44% of recipients within 5 years (6). The viral load of the donor is very important, especially to determine the risk of infection among recipients. Nucleic acid testing (NAT), which defines the HCV viral load, can detect positivity earlier than serologic testing. NAT can be positive 3-5 days following the exposure (7), thus allowing the differentiation of hepatitis C viremic donors from non-viremic donors.

Definitions used to describe donor's HCV status

Anti-HCV-positive NAT-negative donor: Such a donor exhibits spontaneous clearance or sustained virologic response after treatment. Spontaneous clearance is observed among 14%-26% of HCV-infected patients (8,9). In this group of patients, the HCV transmission risk to recipients is not zero, but it is very low.

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Anti-HCV-positive NAT-positive donor: In this type of donors, there is an indicator of active viremia and high-risk transmission.

Anti-HCV-negative NAT-positive donor: In this type of donors, there is an acute infection (within the past 2 months) and a high transmission risk. A negative anti-HCV antibody does not exclude an HCV virus infection, especially in increased risk-donors. NAT may be positive (anti-HCV negative) in donors with an increased risk because of the window period.

Anti-HCV-negative NAT-negative donor: In these donors, an unexpected transmission can be seen with this type of serologic results, especially in the eclipse-period in NAT-negative donors. The eclipse period is the period in the early phase (1st week) before the virus becomes detectable. The risk of meeting in the early period in the eclipse phase in increased-risk donors (injection drug users) was determined to be 32.4/10,000 in the United States, especially when the NAT assay was negative (10).

Increased-risk donors and HCV infection among them: In recent years, there has been a significant increase in deaths due to the ongoing opioid epidemic and drug overdoses, especially in the United States. The CDC reported that opiates caused more than 60% of drug-overdose-related deaths in the United States in 2014 (4). It was stated in Goldberg's review that drug overdose deaths increased by 350% between 2003 and 2014 (2003, n=138; 2014, n=625). The donors' ages ranged between 25 and 44 years in general (median age, 31), and they were younger compared to other donors who died of cardiovascular disease (median age, 47) or stroke (median age, 52). The organ donation rate was significantly higher in donors whose cause of death was drug overdose. These donors generally were young individuals with high-quality grafts because they lacked comorbid diseases. However, the number of transplanted organs from these donors was significantly lower when compared to donors with other causes of death (11). The most important factor for discarding organs from increased-risk donors who died from drug overdose was concern with disease transmission (12). Since 2011, the number of available high-risk donors has been rising. In 2014, the high-risk donor percentage was 65.0% among donors dying from drug abuse, compared to 12%-28% of donors with other causes of death (11). The term *increased risk* refers to the donor characteristics that reflect an increased risk of disease transmission. This terminology does not refer to organ quality, nor does it predict graft survival.

The HCV infection associated with use of the same needle was commonly seen in increased-risk donors, with a transmission rate of approximately 16.9% per 100 person years (10). Also, the incidence of acute HCV associated with the use of the injection drugs increased three times between 2011 and 2015 (13). The HCV infection spreads approximately to one-third of injection drug users in their first year of drug abuse (14). Increased use of opioid and intravenous drugs has altered the demographic structure of donors. There has been an increase in high-risk donors who are HCV positive; this in part may be attributed to the opioid epidemic that causes an increase in the number of deceased donors due to drug overdose (13).

Major progress has been made in the treatment of HCV with the use of DAA agents in recent years. A sustained virologic response with these agents is 95%-98% after transplantation (3). Even with the introduction of highly effective antiviral therapies in recent years, the discard rate of HCV-positive donor livers continues to be high. The most important factor in increasing the use of such livers may be the high success rates achieved with DAA.

Liver transplantation with anti-HCV-positive donors: Transplantation from an anti-HCV-positive donor to an anti-HCV-positive recipient has been implemented as a standard approach for many years, with no difference in graft survival between anti-HCV-positive and anti-HCV-negative donors. A large study with 934 HCV-positive recipients evaluated whether the post-transplant outcomes change with donors' HCV status, and they did not show a difference in the overall survival between recipients who received a transplant from Anti-HCV positive and negative donors (15).

With the emergence of DAA agents, there has also been a significant increase in the ratio of transplantation from anti-HCV-positive donors to positive recipients (16). The number of anti-HCV-positive recipients who received anti-HCV-positive livers has increased from 6.9% to 16.9% by 2015 (17). The authors have demonstrated that the allograft survival in HCV-positive recipients was similar for patients who received an HCV-positive liver and those who received an HCV-negative liver.

The number of organ donors showing antibodies against HCV has been estimated to be as high as 4.3% of all potential cadaveric donors in the United States and Europe (18, 19). According to the United Network for Organ Sharing data, anti-HCV-positive and NAT-negative donors in the United States constitute 1.8% of the donor pool, and

NAT-positive and HCV-positive donors constitute 4.2% of the donor pool (20). If anti-HCV-positive donors are included into the donor pool, this may increase the pool and potentially reduce the waitlist mortality.

Anti-HCV-positive donors with undetectable serum HCV RNA do theoretically carry residual virus risk transmission to anti-HCV-negative recipients, as shown in the liver tissue of interferon-treated chronic HCV patients many years ago (21). Suryaprasad et al. (22) reported 6 cases of HCV transmission from NAT-negative increased-risk donors to anti-HCV-negative recipients. Bari et al. (23) also reported HCV transmission (ratio of 16%) from anti-HCV-positive, NAT-negative donors to anti-HCV-negative recipients. All donors were male and increased-risk donors due to drug overdose.

Following the introduction of new DAA agents, the next question is, "Can we safely use the viremic HCV-positive donors in anti-HCV-negative recipients in liver transplantation?" The concerns regarding transplantation from HCV viremic donor to anti-HCV-negative recipient are HCV complications, graft failure, and HCV infection transmission risk to the partner. Considering the mortality on the wait list and the high SVR rate following the treatment with DAA agents, the transplantation from anti-HCV-positive viremic donor to negative recipient has been widely discussed recently in a consensus statement (24). The SVR with DAA agents, even among difficult-to-treat genotypes, with fewer side effects, have been reported in the literature, although multicenter clinical trials are highly recommended (25).

When planning transplantation from an HCV viremic donor to an anti-HCV-negative recipient, important questions that need to be answered are to which recipients and in which clinical scenarios. In hepatocellular carcinoma cases, who are at such an advanced illness stage that they cannot wait for an extended time on the waiting list, and in patients with a low MELD score, but with extrahepatic complications, transplantation from an HCV viremic donor can be considered.

In the literature, we see some case reports related to transplantation from HCV viremic donors to aviremic recipients. In a 2017 abstract, O'Dell et al. (26) presented their experience in transplantation of HCV-positive donors to 5 HCV-naïve recipients between March 2016 and April 2017. HCV recurrence was not detected among three recipients to whom transplantation was performed from NAT-negative donors, but HCV infection emerged in two recipients in whom transplantation was done from NAT-positive donors. The post-transplantation genotype in both cases was genotype 1a, and they were treated with ledipasvir/sofosbuvir for 12 weeks, starting within 30 days postop. A rapid virologic response was detected in both patients, and dose adjustment or immunosuppressive regimen change in neither patient was necessary.

Saberi et al. (27) reported a case of a 57-year-old HCV-cured patient with hepatopulmonary syndrome who was transplanted liver from an HCV-NAT-positive donor. Ledipasvir/sofosbuvir was prescribed, as per the repeat HCV genotype that was obtained on the postop Day 3, and the treatment was eventually initiated on the postop Day 25. Recipient achieved SVR, and a stable graft function was reported 2 years following transplantation. This case may signify the importance of considering patients with low MELD scores, but with clinical deterioration for earlier-transplantation HCV viremic donors.

The treatment and duration of post-transplantation DAA depend on recipient's newly acquired genotype. There is no optimal strategy for the starting time. Early pan-genotypic DAA treatment may be helpful in reducing the post-transplant HCV-related complications, that is, a potential acute hepatitis picture. In the United States, the experience also depends on the approval process of the DAAs by the health insurance companies. Although this can be a lengthy process, the medications are usually started within 4 weeks following transplantation.

Graft failure due to fibrosing cholestatic hepatitis (FCH) is the most serious complication of a recurrent HCV infection after liver transplantation and is encountered among <10% recipients, during the early post-LT period. Successful treatment with new oral DAA agents for FCH has been reported by Leroy et al. (28) They treated 23 F patients with DAA agents in a prospective cohort study. A complete clinical response and subsequent 12-week SVR were observed among 22 of 23 patients (96%); however, a rapid virologic response rate was lower than expected. This favorable experience is important to know during the follow-up of HCV-naïve recipients, who are potentially accepting HCV viremic donations.

Another important issue is the determination of donor's fibrosis stage with liver biopsy before transplantation (29). Early-stage fibrosis (≤2) may determine the long-term graft survival after LT (30). It is unknown at this time whether HCV-positive grafts with the fibrosis Stage 2 are acceptable or if only grafts with no fibrosis should be considered (29).

The interaction of DAA agents with immunosuppressive drugs is also an important consideration in this group of recipients. Sofosbuvir, ledipasvir, and daclatasvir can be used safely with tacrolimus and cyclosporine A, but simeprevir can increase the level of tacrolimus and cyclosporine. Also, tacrolimus dose needs to be reduced in patients who take glecaprevir/pibrentasvir, while its use with a cyclosporine dose >100 mg is not recommended (31-33). Many of the drugs can be used safely among liver transplant patients.

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