REVIEW PAPER

Renal Disease and Transplantation Forum
2024, vol. 17, no. 3, 71–75

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/rdatf.101557

VIA MEDICA

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Hepatitis C virus and kidney transplantation

Abstract

Kidney transplantation is the treatment of choice in patients with end-stage kidney disease. Hepatitis C virus infection in kidney transplant recipients is associated with numerous complications. Apart from hepatitis and consecutive cirrhosis, patients with HCV infections are more prone to develop severe infections, post-transplant diabetes mellitus, and recurrence of HCV-induced glomerulonephritis in transplanted kidneys. Patients after kidney transplantation with HCV infection are at higher risk of death. Previously used treatment based on interferon and ribavirin was poorly tolerated by this group and had low efficacy. Introducing direct-acting antivirals (DAA) was a breakthrough for patients with kidney disease, including kidney transplant recipients. DAA treatment rarely has side effects and prevents many complications associated with HCV infection.

Renal Disease and Transplantation Forum 2024, vol. 17, no. 3, 71–75

Keywords: hepatitis C, kidney transplantation

INTRODUCTION

The prevalence of hepatitis C virus (HCV) in patients with chronic kidney disease (CKD) is higher than in the general population. Numerous medical procedures, including hemodialysis and blood transfusion, contribute to a higher risk of acquiring the infection. Patients with end-stage kidney disease require renal replacement therapy — hemodialysis, peritoneal dialysis, or kidney transplantation (KT). KT is the optimal choice that gives the best survival results. HCV infection decreases survival rates in kidney transplant recipients and is an independent risk factor for losing graft function [1]. HCV is a hepatotropic virus, but it can also trigger autoimmune processes, including glomerulonephritis. Due to its influence on the immunological system, HCV infection may also have numerous extrahepatic manifestations — the most common is cutaneous vasculitis in the course of mixed cryoglobulinemia. Others include lymphoproliferative disorders, neurological disorders, or autoimmune thyroiditis. The risk of developing CKD in HCV-positive patients is 40% higher compared to HCV-negative patients [2].

Treatment of HCV infection has been a challenge for many years. Treatment based on interferon and ribavirin was poorly tolerated by CKD patients and less efficient than in the general population. Introducing direct-acting antivirals (DAA) was critical in this group of patients. The influx of refugees from Ukraine in recent years has probably increased the number of patients infected with HCV, including those with CKD, which is why this subject is of great importance [3]. Another potential threat to patients previously infected with HCV is occult HCV infection (occult hepatitis C). This phenomenon involves the presence of the viral genetic load in hepatocytes and peripheral blood mononuclear cells (PBMC) after the virus has been eliminated from the serum and is detected only by using ultrasensitive methods. The frequency of occult hepatitis C is unknown. Still, it seems that patients undergoing immunosuppressive treatments are more likely to suffer from its consequences, such as lymphoproliferative disorders, as in a previously described case report [4]. However, this topic requires further research because clinical implications of occult hepatitis C have not yet been established.

HCV INFECTION IN KIDNEY TRANSPLANT RECIPIENT

HCV infection in kidney transplant recipients might be an infection acquired de novo or reactivation of a pre-existing infection. In

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patients after kidney transplantation, it is recommended to screen for HCV infection using the nucleic acid amplification test (NAT) to determine the presence of HCV RNA. Most patients with HCV infection in the post-transplantation period do not produce anti-HCV antibodies despite high viral loads [5]. The presence of HCV RNA in the absence of anti-HCV antibodies suggests acute infection. De novo HCV infections in patients after kidney transplantation may initially be asymptomatic, as in the general population. Unfortunately, over time, the infection leads to liver cirrhosis and/or hepatocellular carcinoma (HCC). Patients after kidney transplantation receive immunosuppressive treatment, which facilitates viral replication and might promote liver fibrosis. Zylberberg et al. [6] showed that the progression of liver fibrosis is faster in patients after liver transplantation than in immunocompetent patients. It is optimal to test HCV RNA within the first month after transplantation to initiate treatment early in the case of HCV infection [5]. HCV RNA testing also allows for shortening the immunological window in comparison to HCV-antibodies testing.

Liver complications are not the only ones faced by kidney transplant recipients with HCV infection. HCV infection also increases the risk of post-transplant diabetes, which further increases cardiovascular risk in this group. Moreover, HCV infection, which is often the cause of glomerulonephritis and might lead to end-stage kidney disease, may also be the cause of recurrence of glomerulonephritis associated with HCV in the transplanted kidney. It rarely occurs in the case of previous HCV eradication. Typical glomerulonephritis associated with HCV infection is membranoproliferative glomerulopathy (MPGN) with the presence of immune complexes, often accompanied by mixed cryoglobulinemia. HCV may also induce membranous nephropathy, but recurrence of this glomerulopathy in transplanted kidneys occurs rarely [7].

Generally, HCV infection among kidney transplant recipients is associated with a higher incidence of proteinuria, which is an indication for graft biopsy [8]. In the case of diagnosis of HCV-related glomerulonephritis after kidney transplantation, antiviral treatment should be initiated immediately if the patient has not yet been cured. In the majority of cases, effective treatment prevents the recurrence of HCV-related glomerulopathy. If glomerulopathy is active despite antiviral treatment, it may be necessary to enhance immunosuppressive treatment, including initiating of rituximab therapy [9].

Renal transplant recipients with active HCV infection are also at greater risk of severe infections, such as sepsis than patients without present viremia [10, 11]. Some authors believe that the hepatitis C virus acts as an immunosuppressant by influencing the function of helper lymphocytes [12].

QUALIFICATION FOR KIDNEY TRANSPLANTATION IN AN HCV-POSITIVE RECIPIENT

Kidney transplantation is the best therapeutic option for renal replacement therapy regardless of the presence of HCV infection. Potential candidates for kidney transplantation with anti-HCV antibodies should be screened for HCV RNA to determine HCV status and, if necessary, start antiviral therapy. Before kidney transplantation, patients with HCV infection should be evaluated for liver complications and the presence of portal hypertension. Currently, elastography has become the gold standard for assessing fibrosis, which has largely replaced the invasive test of liver biopsy. In the case of patients with decompensated liver cirrhosis, i.e., those in whom the pressure gradient in the hepatic vein exceeds 10 mmHg, and with signs of portal hypertension such as esophageal varices, ascites, encephalopathy or collateral circulation, simultaneous kidney and liver transplantation should be considered. Simultaneous transplantation gives better results than kidney transplantation preceding liver transplantation. The genetic material comes from a single donor, and it has also been observed that simultaneous transplantation reduces the risk of kidney rejection [13]. In cases of mild-to-moderate portal hypertension without decompensated cirrhosis, this decision must be made on an individual basis.

HCV TREATMENT IN KIDNEY TRANSPLANT RECIPIENTS

Interferon and ribavirin-based therapies that have been used for many years have been associated with very poor tolerance by CKD patients, including those on dialysis and after kidney transplantation. Interferon therapy was also associated with an increased incidence of severe humoral rejection. As mentioned, HCV infection reduces survival in patients after kidney transplantation; therefore, introducing DAA drugs was a breakthrough of

exceptional importance in this group of patients. DAA therapy involves a combination of 2 to 4 drugs that directly inhibit viral proteins at different points of viral protein metabolism. Available agents include drugs that inhibit the activity of proteins at various stages of virus replication: NS5B polymerase inhibitors, NS3 protease inhibitors, and NS5A protein inhibitors. Therapy lasts from 12 to 24 weeks, depending on the protocol and previous treatment history. Tolerance of treatment in kidney transplant recipients is very good, as in the general population. The goal of treatment is to achieve a sustained virologic response (SVR), which is defined as the absence of HCV RNA 12 weeks after the end of treatment. DAA treatment regimens are divided into pangenotypic (effective against all virus genotypes) or genotype-specific types. Both pangenotypic and genotype-specific protocols are safe for kidney transplant recipients. The effectiveness of both types reaches 95–100%, similar to the general population, without being associated with a higher incidence of side effects or rejection of transplanted kidneys.

According to the 2022 Kidney Disease: Improving Global Outcomes (KDIGO) recommendations, DAA therapy in kidney transplant candidates may be initiated before or after transplantation, depending on the expected waiting time for the transplant and donation type (living *vs.* deceased). Twelve weeks of therapy may be initiated in patients whose expected waiting time for a kidney transplant will be longer than 24 weeks [9]. This allows assessing SVR 12 weeks after treatment completion. In the case of live donation, DAA therapy can be performed before or shortly after transplantation. The choice of therapy depends on local protocols and the experience of centers. According to the 2023 recommendations for the treatment of hepatitis C from the Polish Expert Group, patients whose GFR is > 30 mL/min/1.73 m^2 may be treated following the general principles of HCV therapy. However, in patients with GFR < 30 mL/min/1.73 m^2, including dialysis patients waiting for transplantation, the preferred therapies include glecaprevir with pibrentasvir, elbasvir with grazoprevir (in the case of genotypes 1 and 4), and sofosbuvir with velpatasvir. In the case of previous ineffective therapy based on interferon or ribavirin, DAA therapy should be extended [3]. In the case of previous decompensated cirrhosis, sofosbuvir with velpatasvir should be considered. According to the 2022 KDIGO guidelines, sofosbuvir is also safe in all CKD stages. It is worth emphasizing that protease inhibitors are contraindicated in patients with Child-Pugh scores of B or C.

During grazoprevir with elbasvir treatment, more frequent monitoring of tacrolimus levels is recommended. The combination of these drugs with cyclosporine is not recommended. Generally, during DAA therapy, it is important to frequently monitor the level of immunosuppressive drugs, especially calcineurin inhibitors, due to their common metabolism by cytochrome P450.

Three months after achieving SVR, as well as in the case of an increase in transaminases, the patient requires control HCV RNA testing regardless of the time of completion of DAA therapy.

Before starting treatment with DAA, the presence of HBV (hepatitis B virus) should be assessed. In the case of active HBV infection, its treatment should be initiated before starting DAA therapy because, during DAA therapy, reactivation of HBV DNA may occur. In the event of an increase in transaminases in patients with anti-HBc antibodies (Hepatitis B core antibody), HBV DNA viremia should be reassessed.

Patients with cirrhosis caused by HCV have a risk of developing HCC of up to 4% annually [14]. In recent years, there have been studies suggesting an increase in the incidence of HCC after DAA treatment. Nevertheless, subsequent studies, including a meta-analysis from 2017, did not confirm this observation [15]. In the general population, the introduction of DAA therapy in patients with HCV infection significantly improves survival. The long-term results of DAA treatment in pre- and post-kidney transplant patients are unknown, but this treatment is also suspected to reduce mortality.

There are no recommendations that would suggest initiating DAA therapy in patients with a very short life expectancy.

HEPATITIS C IN KIDNEY DONOR

It is estimated that 0.5–18.5% of donors may be infected with HCV (5). HCV virus may be transmitted through organ transplantation, as described by Pereira et al. in 1991 [16]. This discovery prompted routine HCV testing of potential donors. It has been known for years that the bottleneck for kidney transplantation is, among others, the availability of donor organs. To expand the donor

pool, transplant surgeons in many countries began to consider kidneys from donors infected with HCV. Initially, they were transplanted only to HCV-positive recipients, which allowed for significant shortening of transplantation waiting times. Such transplants were associated with good outcomes for both patients and graft survival. This solution, however, is not free from risks — there remains the possibility of superinfection with a different genotype, as well as reinfection in people who have eliminated the virus, as the presence of anti-HCV antibodies does not mean immunocompetence. Currently, due to new effective therapeutic options, some countries allow transplantation of a kidney from an HCV-positive donor to an HCV-negative recipient. This significantly shortens the waiting time for transplantation. To avoid acute and severe hepatitis, DAA treatment is initiated immediately. Of course, the patient must be informed about the risks and consequences of kidney transplantation from an HCV-positive donor. In Poland, given the relatively short waiting time for a transplant, which is about a year, this practice is not used. It cannot be ruled out that kidney transplantation from a donor who has eliminated the virus and achieved SVR will be associated with infection of the recipient because of occult HCV infection in the donor. Although there is no evidence yet of transmission of infection in this way, the potential recipient must be informed about the risk and the need to monitor HCV RNA and implement DAA therapy if indicated.

If a potential living donor is diagnosed with HCV infection, it is necessary to start DAA antiviral treatment, and the procedure should be postponed until SVR is confirmed. The potential donor should undergo extended diagnostics because advanced liver fibrosis is a contraindication to kidney donation.

CONCLUSION

In summary, HCV infection carries many risks for CKD patients, including kidney transplant recipients. The co-occurrence of CKD and viral hepatitis C is associated with a particularly high risk of liver disease progression and increased cardiovascular mortality. Although HCV infection reduces the survival rate of patients after kidney transplantation, the mortality rate is still lower than in patients with HCV infection who did not receive a kidney transplant but remained on dialysis [17]. DAA treatment has good results in the general population and transplanted patients — it is safe, effective, and well-tolerated. Initiating treatment before kidney transplantation helps avoid many risks in the peri- and post-transplant period, including acceleration of liver disease. If treatment is initiated after transplantation, the effectiveness of DAA does not decrease despite increased viral load in the post-transplant period. Curing HCV infection increases the survival rate of patients after kidney transplantation compared to patients with active infection. For optimal patient care, close cooperation between nephrologists and infectious disease specialists is recommended.

Author contributions:
Both authors contributed equally.

Funding:
None.

Acknowledgments:
None.

Conflict of interest:
Authors declare no conflict of interest.

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