Journal of Renal and Hepatic Disorders

CODON PUBLICATIONS

COMMENTARY

Direct-Acting-Antivirals Anti-hepatitis C Virus in Renal Transplant Patients: Relevance of Pharmacologic Interaction

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Abstract

Renal transplantation in patients affected by hepatitis C virus (HCV) infection has been a serious problem because of the use of immunosuppressants. HCV virus may be more aggressive in both the liver and the kidney. Several posttransplantation pathologies are known to be ascribed to the HCV virus. Virus eradication has been historically attempted with interferon (IFN) and ribavirin with poor results. In addition, IFN given posttransplantation may cause severe acute rejection. The introduction of direct antiviral agents (DAA) has revolutionized the treatment, and now it is possible to treat renal transplant patients with these agents leading to a HCV-free status in 3 months without the use of IFN. The major problem caused by these agents is their interference with the immunosuppressive agents. The pharmacokinetics of DAA and immunosuppressants often meet the same metabolic pathways and use the same cytochromes or proteic complexes. In some cases, this may lead to high or low immunosuppressant levels with the risk of rejection. In other cases, the DAAs are interested and they may be increase or decrease in a dangerous way. Therefore, a strict monitoring is always recommended.

Keywords: direct antiviral agents; HCV-related diseases; immunosuppressants; metabolic pathways; posttransplant complications

Received: 30 June 2020; *Accepted after Revision*: 23 July 2020; *Published*: 03 August 2020

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How to cite: Salvadori M et al. Direct-Acting-Antivirals (DAA) Anti HCV in Renal Transplant Patients: Relevance of Pharmacologic Interaction. J Ren Hepat Disord. 2020;4(2):29–33.

Doi: https://doi.org/10.15586/jrenhep.v4i2.79

Introduction

Carta et al. published an interesting article on the use of some direct antiviral agents (DAAs) in renal transplant (RT) recipients affected by hepatitis C virus (HCV) infection.

The issue is relevant and presents several aspects that need to be highlighted.

Clinical Problems of HCV in RT Patients

The persistence of HCV infection after RT is a severe risk factor for graft and patient survival. Complications may involve the liver or the kidney.

Liver disease

The immunosuppression is associated with an increase in viral replication and with a progression of hepatic fibrosis (1). The same study documented that the evolution toward cirrhosis was 21.4% in transplant patients versus 3.6% in nontransplant patients.

Renal disease

1. Secondary infections
   RT patients HCV+ have a higher incidence of systemic infections, in particular affecting the central nervous system and the respiratory tract. These infections in these patients represent the second most common cause of patient deaths after hepatic disease (2).
2. Posttransplant diabetes mellitus (NODAT)
   In one meta-analysis on 30,099 RT patients, the prevalence of diabetes mellitus was higher in HCV+ patients (3).
3. *Lymphoproliferative disorders*
   Several studies documented an increase of lymphoproliferative disorders in HCV+ RT patients (4).
4. *Glomerulonephritis*
   HCV with associated cryoglobulinemia frequently causes membranoproliferative glomerulonephritis (MPGN) after RT (5). In this study, MPGN was found in 45.4% of RT patients who were HCV+. HCV+ is also associated with membranous nephropathy (MN) after RT (6). Both MPGN and MN can be ascribed to the deposition of immunocomplexes containing viral RNA (7).
5. *Transplant glomerulopathy*
   One study from the Boston study group (8) studied 29 HCV+ RT patients and found that transplant glomerulopathy (the marker of chronic rejection) developed significantly earlier posttransplantation in HCV+ RT patients with respect to HCV – patients (P = 0.02). The authors documented an overlapping of chronic humoral rejection, HCV infection, and thrombotic microangiopathy.

   Finally, it is important to remember the high incidence of acute rejection in transplant patients receiving interferon (IFN) (9).

   All these findings support the relevance of treating HCV infection in RT patients and the need to find alternative and more effective therapies with respect to IFN.

DAA-Based Therapies

The improved knowledge of the vital cycle of HCV and of the virus structure and its proteins allowed the development of highly efficient DAA (Figure 1).

To date, the DAAs may be divided into four classes according to the mechanism of action (Table 1). The first DAAs for the treatment of HCV were the protease inhibitors against NS3/SA, such as telaprevir and boceprivir (10, 11). These drugs are used for the treatment of genotype 1 in association with IFN and ribavirin. In 2013, three new DAAs were approved in the United States: simeprivir (IP-NS3/NS4A), daclatasvir (inhibitor of NS5A), and sofosbuvir (inhibitor of polymerase NS5B). The use of these DAAs allowed for avoiding the use of IFN. New strategies in the use of DAAs have been the use of combinations of DAAs (12), such as sofosbuvir and ledipasvir. More recently, new DAAs have been added, such as elbasvir, glecaprevir, ritonavir, ombitasvir, dasabuvir, and voxilaprevir (13, 14).

The introduction of these drugs allowed for obtaining efficacy against all genotypes, to reduce the duration

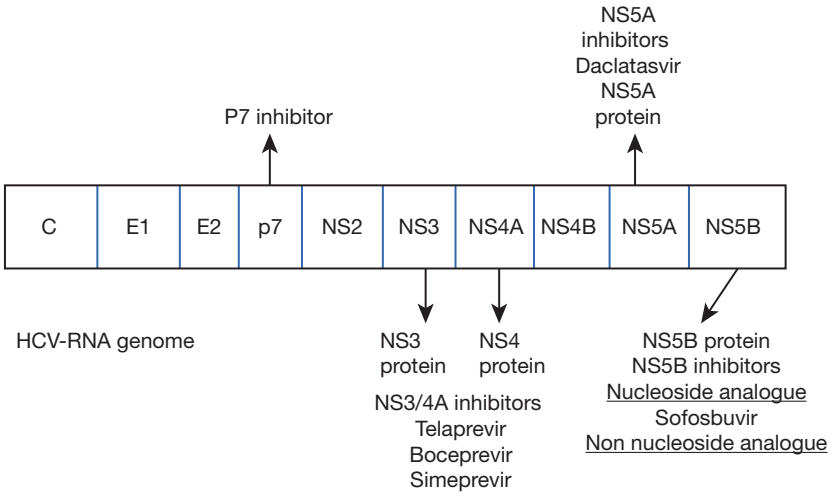

Figure 1. Development of new drugs for HCV infection. HCV, hepatitis C virus.

Table 1: The four classes of DAAs.

The four classes of DAAs	Mechanism of action	Drugs (targeted genotypes in brackets)
NS3/4A protease inhibitors (PIs)	Block a viral enzyme (protease) that enables the hep C virus to survive and replicate in host cells	• Glecaprevir (1–6) • Paritaprevir (1,4) • Voxilaprevir (1–6) • Grazoprevir (1,3,4)
Nucleoside and nucleotide NS5B polymerase inhibitors	Target the hep C virus to stop it from replicating itself in the liver, thereby blocking the virus from multiplying	• Sofosbuvir (1–4)
NS5A inhibitors	Block a virus protein, NS5A, that HCV needs to reproduce and for various stages of infection	• Ombitasvir (1,4) • Pibrentasvir (1–6) • Daclatasvir (3) • Elbasvir (1,4) • Ledipasvir (1) • Ombitasvir (1) • Velpatasvir (1–6)
Nonnucleoside NS5B polymerase inhibitors	Stop HCV from reproducing by inserting themselves into the virus so that other pieces of the hep C virus cannot attach to it	• Dasabuvir (1)

DAA, Direct-Acting-Antivirals; HCV, hepatitis C virus; hep C, hepatitis C.

of treatment, and to increase the safety and efficacy of the treatment (15).

The new KDIGO guidelines recommend that all patients with HCV who are candidates for kidney transplantation should be considered for DAA therapy, either before or after transplantation. The same recommendation applies to HCV candidates with a living donor (16).

Pharmacological Interactions

Pharmacokinetic interactions are the most important, primarily because of the role of cytochrome P450 (CYP450). The interactions with glycoprotein P (P-gp) are also important in limiting the drug bioavailability (17, 18).

The use of drugs inducing CYP450 or P-gp carries the risk of reducing the DAA concentrations. On the other hand, the use of the protein inhibitor, NS3-4A, is contraindicated in patients with severe liver disease. Similarly, the use of the polymerase inhibitor, sofosbuvir, is not indicated in patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 because of its renal elimination (19).

In addition to inhibiting cytochrome CYP3A, cyclosporine (CyA) also inhibits the organ anion transporter family 1B1/3 (OATP1B1/3), the breast cancer resistance protein (BCRP), and P-gp. As a consequence, its administration with a protease inhibitor IPNSA3-4A is not recommended because of the increase in blood CyA. On the contrary, the administration of simeprevir with tacrolimus (TAC) causes only a small decrease of the latter and requires monitoring (20, 21).

The new combinations with an IPNS3-4A as grazoprevir–elbasvir or glecaprevir–pibrentasvir or sofosbuvir–ledipasvir–voxilaprevir may cause a mild TAC modification and require monitoring (22–24).

No data are available for the inhibitors of mammalian target of rapamycin (mTORIs).

Daclatasvir and sofosbuvir may be safely administered together with TAC and mTORIs (25).

The association between ombitasvir–paritaprevir–ritonavir and the immunosuppressants may be dangerous because ritonavir causes inhibition of CYP3A4 and of P-gp. This may cause an increase of the calcineurin inhibitors and of the mTORIs. In one study (26), CyA doses were reduced to one-fifth and TAC doses were reduced to 0.5 mg/week.

Table 2 shows the modifications of immunosuppressant doses in patients receiving DAA.

In conclusion, the availability of new IFN-free DAA offers the possibility of efficiently treating RT patients with HCV infection.

The possible important interactions between these drugs and the immunosuppressants often require strict monitoring to reduce the risks of rejection or immunosuppressants-related toxicity.

Table 2. Adjustments and monitoring of immunosuppressants in patients on treatment with DAA.

Antiviral	Azathioprine	Mycophenolic acid	CyA	TAC	Sirolimus	Everolimus
Sofosbuvir	–	–	–	–	–	–
Simeprevir	–	–	Not to be given	Monitoring	Monitoring	Monitoring
Daclatasvir	–	–	–	–	–	–
Sofosbuvir/ Ledipasvir	–	–	Monitoring	Monitoring	Monitoring	Monitoring
Paritaprevir/ Ombitasvir/ Ritonavir	–	Monitoring	Monitoring	Monitoring	Monitoring	Monitoring
Sofosbuvir/ Velpatasvir	–	–	Not to be given	Monitoring	Monitoring	Monitoring
Sofosbuvir/ Velpatasvir/ Voxilaprevir	–	–	Not to be given	Monitoring	Monitoring	Monitoring
Grazoprevir/ Elbasvir	–	–	?	?	?	?

–No clinical interaction.

DAA, Direct-Acting-Antivirals; CyA, cyclosporine; TAC, tacrolimus.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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