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# Hepatitis B and C in Kidney Transplantation

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## Abstract

The prevalence of chronic hepatitis B and C virus infection has declined among the dialysis population during the past decades. However, it still comprises a major health problem with high morbidity and mortality. Renal transplantation is the optimal treatment for patients with end-stage renal disease and hepatitis B or C, although it is associated to lower patient and allograft survival compared to seronegative kidney recipients. Novel therapeutic strategies with the use of new antiviral agents, especially direct-acting antiviral agents in hepatitis C, have significantly changed the natural history of both hepatitis B and C not only in the general population but also in renal-transplant recipients. We believe that future research should focus on the impact of new antiviral medications in this specific subset of patients.

**Keywords:** hepatitis B, hepatitis C, transplantation, direct-acting antiviral agents

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## 1. Introduction

Though the prevalence of both hepatitis B and C is decreasing at least in developed countries, it still ranges from 0.1 to 20% for hepatitis B and from 2.5 to 13% for hepatitis C. General hygiene measures as well as specific measures in dialysis units and vaccination programs contributed to the reduction of hepatitis B and C prevalence in the dialysis population. However, hepatitis B and C seropositivity still remain an important clinical problem in this patient population associated with a high risk of morbidity and mortality. Although kidney transplantation is the treatment of choice for hepatitis B- and C-infected dialysis patients, morbidity and mortality are worse compared to seronegative patients. Major causes of death are liver cirrhosis and hepatocellular carcinoma.

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This review focuses on pretransplant and posttransplant evaluation of prospective donors and recipients emphasizing the optimal use of grafts from hepatitis B- or C-seropositive donors and the impact of hepatitis B or C infection in patient and allograft survival. Additionally, it focuses on the role of novel antiviral agents.

## 2. Kidney transplantation and hepatitis B virus infection

### 2.1. Epidemiology

The human hepatitis B virus (HBV) is a small enveloped DNA virus causing acute and chronic hepatitis. Although a safe and effective vaccine has been developed and it has been available for the last two decades, HBV infection still represents a major global health problem. It is estimated that approximately 30% of the world's population has had contact with or are carriers of the HBV. An estimated 350 million of them are HBV carriers [1]. Around one million persons die of HBV-related causes annually. HBV prevalence varies from 0.1% in Western Europe, United States, Canada, Australia, and New Zealand, up to 20% in southern Asia, China, and sub-Saharan Africa. Intermediate prevalence (3–5%) is the Mediterranean countries, Japan, Central Asia, the Middle East, and South America. Acute infection occasionally results in fulminant hepatitis, but more importantly can progress to a chronic state, with decompensation, cirrhosis, and hepatocellular carcinoma being the most serious complications. The progression rate is approximately 90% for an infection acquired perinatally, and decreases to 5% for infections acquired during adulthood [2].

Hemodialysis (HD) patients are at an increased risk of acquiring HBV. Reasons include increased exposure to blood products, shared hemodialysis (HD) equipment, breaching of skin, and immunodeficiency. Hemodialysis, which requires access to the bloodstream, also may favor transmission of HBV between patients, and between patients and staff.

The prevalence of hepatitis B virus infection in hemodialysis patients has significantly decreased over the past few years. This is due to the implementation of effective prevention measures, such as general hygiene rules, separation during hemodialysis, and hepatitis B vaccination. The most important measure to prevent HBV infection is immunization against the virus. Chronic dialysis patients should receive vaccination against hepatitis B. Ideally, patients with chronic kidney disease (CKD) should receive vaccination against hepatitis B at earlier stages of the disease, before starting dialysis, since vaccine immunogenicity is low in dialysis patients (70%) compared to 90% in the general population. Intensified vaccination protocols have been used in hemodialysis patients with good responses. The presence of an adequate hepatitis B antibody (anti-HBs) titer should be checked annually. If the antibody titer is lower than 10 IU/ml, a booster dose of the vaccine should be administered [3].

Although rates of new infection are decreasing [4], hepatitis B still remains a problem in dialysis populations. According to data from the United States Renal Data System (USRDS) in 2002, 1% of dialysis patients were seropositive for HBsAg [3]. A registry study of Asia-Pacific countries found the prevalence of hepatitis B surface antigen (HBsAg) positivity ranging from

1.3 to 14.6% [5]. Despite the decrease of HBsAg prevalence in dialysis patients, 350 million people worldwide are chronic HBV carriers and a large number of them will need transplantation in the future [6].

Hepatitis B virus–infected patients are at risk of exacerbation of the infection, progressive liver disease, and development of hepatocellular carcinoma after kidney transplantation. Renal transplantation offers higher survival and better quality of life compared to hemodialysis, which also applies to HBV patients, providing that they are receiving antiviral prophylaxis, since it is easier to prevent than treat HBV reactivation [7].

## **2.2. Evaluation of HBV-infected dialysis patients before transplantation**

All dialysis patients should be checked routinely for HBsAg and when indicated with HBV DNA. HBV infected kidney transplant candidates should be tested for hepatitis B e antigen (HBeAg) and serum HBV DNA prior to transplantation. Patients who are HBeAg positive or have high levels of HBV DNA should receive antiviral treatment before transplantation with one of the available agents (lamivudine (LAM), entecavir (ETV), adefovir, tenofovir, and telbivudine (LdT)) until HBeAg becomes negative and viral replication is suppressed.

According to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines, it is recommended that a liver biopsy is performed in HBsAg-positive hemodialysis patients on the waiting list for transplantation in order to evaluate liver disease status. If there is ongoing viral activity, candidates should repeat liver biopsy every 3–5 years [8]. Noninvasive testing for liver stiffness as fibroscan (elastography), which tends to replace liver biopsy in the general population, has not yet been validated neither in HBV-positive patients nor in patients on hemodialysis or after transplantation [9]. So, liver biopsy while on the waiting list still remains the “gold standard” for kidney transplant candidates.

Liver cirrhosis has for long been considered as an absolute contraindication for kidney transplantation alone; combined liver kidney transplantation is the treatment of choice in these patients. However, with the use of new nucleos(t)ide analogs, some dialysis patients with compensated cirrhosis achieve sustained viral response (SVR). If a follow-up biopsy after 12 months reveals partial reversibility of cirrhosis, those patients can be after that included in the waiting list and undergo kidney transplantation alone. This has been reported for HBV- and hepatitis C virus (HCV)-positive patients after SVR with the new antivirals [10].

HBsAg-positive renal transplant candidates should start antiviral treatment immediately after transplantation, regardless of the HBV DNA status or the findings of liver histology, due to the risk of severe reactivation, fibrosing cholestatic hepatitis, and rapid histological deterioration after the induction of immunosuppression.

## **2.3. Transmission of HBV infection from the donor**

Besides HBV reactivation, HBV may be transmitted from the donor to the recipient. Renal transplantation from HBsAg-positive donors to HBV-naïve recipients is not recommended because it carries a significant risk of de novo infection, most often with an aggressive course

[11]. On the other hand, as shown by Jiang et al., allografts from HBsAg-positive donors can safely be transplanted into HBsAg-negative recipients with natural or acquired immunity (anti-HBs positive, titer above 10 IU/ml), with concurrent administration of hepatitis B hyperimmune globulin (HBIG) with or without booster vaccination [12]. In such cases, although the risk of transmission is relatively low, it is mandatory to inform patients and to obtain written consent in order to proceed with kidney transplantation. In a study by Singh et al., the successful procedure was described in 104 anti-HBs-positive recipients [13]. Prevention strategies included booster vaccination and concomitant administration of HBIG in combination with antiviral agents while vaccination alone was used in 27 patients.

In our center, we perform kidney transplantations from HBsAg-positive donors to HBsAg negative/HBsAb positive, that is, immunized either from past infection or from vaccination recipients. Those transplantations are performed only if the antibody titer of the recipient, measured immediately before transplantation, is at least 10 IU/ml and with concomitant administration of one dose of booster vaccination in combination with hepatitis B hyperimmune globulin (HBIG) while most of the recipients are started on antiviral prophylaxis postoperatively. The need and the duration of antiviral treatment in this patient population have not been investigated; moreover, data about monitoring long term are lacking. It seems logical to assume that antibody titer should be checked and booster vaccination should be administered when the titer falls below 10 IU/ml, since transplant recipients receiving immunosuppression are at risk for viral reactivation—if it has been transmitted from the donor—for long. However, to the best of our knowledge, current evidence is so sparse that only suggestions can be made.

Another issue regarding donor to recipient HBV transmission is that there is a very low but substantial risk of HBV transmission from HBsAg-negative, anti-HBc-positive, anti-HBs-negative donors to HBV-naïve recipients. In a recent review of 1385 HBsAg-negative kidney recipients from anti-HBc-positive donors, seroconversion to HbsAg positivity occurred in 0.28% (4/1385) and to anti-HBc positivity in 2.3% (32/1385) [14–16]. Ideally, those donors should be checked for anti-HBc IgM presence, indicating a more recent infection rather than ineffective immune response. Unfortunately, in the case of transplantation from deceased donors, this is impossible, due to the shortness of time. Given the organ shortage and the survival advantage of transplantation over remaining on hemodialysis, kidney transplantation could be considered in these cases too, since the risk for transmission is even lower than from HBsAg-positive donors. Again without data supporting the evidence, one may suggest that, in this case too, transplant candidates should be immunized and receive prophylaxis with booster vaccination and HBIG administration, while antiviral prophylaxis may not be indicated in this setting.

#### **2.4. Outcome of HBV-infected patients after kidney transplantation**

HBV-infected renal allograft recipients have worse survival compared to their seronegative counterparts. A meta-analysis of six observational studies, which included 6050 HBsAg-positive patients after kidney transplantation, showed that the relative risk of death and graft loss were 2.49 and 1.44, respectively [17].

The widespread use of antiviral agents since 1986 has significantly improved survival of HBV-infected kidney transplant recipients. In a small study from Italy, 42 HbsAg-positive patients who have been transplanted between 1976 and 1982 had a 12-year survival rate of 67% [18]. In a more recent study from Hong Kong, a 10-year survival of 63 HbsAg-positive renal transplant recipients who were treated with nucleoside/nucleotide analogs reached 81% [19]. However, liver failure remains the leading cause of death in this patient population. HBsAg-seropositive recipients who are HBeAg-negative have undetectable viral load, and for mild changes in liver biopsy they should receive preventive antiviral therapy immediately posttransplantation, in order to avoid viral reactivation due to immunosuppressive therapy. The only study that evaluated serial biopsies after kidney transplantation found histological deterioration in 85% of HBsAg-positive patients. No patient had cirrhosis before kidney transplantation while 28% of them had biopsy-proven liver cirrhosis after transplantation. Among those with cirrhosis, hepatocellular carcinoma was found in 23% [20].

## 2.5. Antiviral agents

The goal of treatment is suppression of viral replication and prevention of hepatic fibrosis, while minimizing resistance to the drugs. HBV DNA levels need to be measured systematically to assess response to therapy, because of the poor likelihood of seroconversion to anti-HBs and because of low reliability of alanine aminotransferase (ALT) as a marker of liver disease activity.

Treatment must be initiated before or immediately after transplantation. In a study of 15 patients, seven were started on lamivudine at the time of kidney transplantation. All patients had normal transaminase levels preoperatively. Half of those who were not treated initially showed transaminase elevations in the first year of follow-up requiring lamivudine therapy at that time. By contrast, all seven individuals who had received lamivudine at the time of transplantation remained negative for HBV DNA throughout the follow-up [21].

Currently, there are several medications available for the treatment of hepatitis B: interferon alfa-2b, pegylated interferon (PEG-IFN) alfa 2a, and the nucleos(t)ide analogs lamivudine, adefovir, tenofovir, telbivudine, and entecavir.

### 2.5.1. Interferon and PEG-IFN

In the current era of potent antiviral drugs as nucleoside analogs, the use of interferon- $\alpha$  (IFN) and PEG-IFN after transplantation is not recommended anymore. IFN- $\alpha$  has known immunomodulatory effects and its use in case series of kidney transplant recipients in the past has been associated with increased rates of graft loss due to rejection and with relapse rates approaching 80% after therapy discontinuation [22].

### 2.5.2. Lamivudine (LAM)

Lamivudine is a cytosine analog that inhibits HBV reverse transcriptase. The prophylactic use of lamivudine posttransplantation has proven efficacy long term. Since LAM was the first nucleoside analog approved for clinical use, most of the available data on the management of HBsAg-positive renal transplant recipients are with this agent. A meta-analysis of 14 clinical

studies, which included 184 patients, showed that LAM administration results in undetectable viral load in 91% and a normalization of alanine aminotransferase (ALT) in 81% of patients, for a prolonged period of time [23]. Lamivudine has for long been the cornerstone of therapy in HBV-infected kidney transplant recipients and has increased survival rates. HBsAg-positive kidney recipients treated with lamivudine reached 10-year survival rates of 81%, comparable to HBsAg-negative patients [24].

Since it is eliminated by the kidney, its dose should be adapted to renal function: recommended dose is 100 mg/day in patients with estimated glomerular filtration rate (eGFR) >50 ml/min and 100 mg every other day in patients with less-preserved renal function.

The major problem with prolonged lamivudine treatment is the development of resistance. The presentation of the resistance varies. Some patients show only reappearance of serum HBA DNA, while others present with elevated liver enzymes. In most cases, resistance occurs due to a mutation in the tyrosine-methionine-aspartate-aspartate (YMDD) locus of the HBV DNA polymerase [25].

In a series of studies, the rates of lamivudine resistance vary from 20 up to 60% [26, 27]. In a study of 29 renal transplant recipients, after a mean follow-up of 69 months, 14 patients (48%) developed lamivudine resistance. Among them, 79% presented with a hepatitis flare. The YMDD mutation was found in all cases of resistance [25]. A meta-analysis of 2004 showed that increased duration of lamivudine therapy was positively associated with lamivudine resistance [22].

Patients with lamivudine resistance should be treated with adefovir, tenofovir, entecavir, or telbivudine.

### 2.5.3. *Tenofovir disoproxil fumarate (TDF)*

Tenofovir disoproxil fumarate (TDF) is a nucleotide analog and a potent inhibitor of human immunodeficiency virus type 1 reverse transcriptase and hepatitis B virus polymerase. Tenofovir is a potent antiviral agent for treatment-naïve patients and for patients with lamivudine resistance [28, 29]. Data for patients who have undergone kidney transplantation are limited and there are concerns for the development of kidney injury. Daude et al. conducted a study, which showed effective suppression of viral replication after 12 months of follow-up and preservation of stable kidney function in seven hepatitis B virus-positive solid-organ transplant recipients, with three renal-transplant recipients among them [30]. In a study of patients from the general population with HBV infection, tenofovir was effective in lamivudine-resistant cases, and did not induce resistance after up to 48 months of treatment [31].

### 2.5.4. *Telbivudine (LdT)*

Telbivudine is not effective in kidney transplant recipients with lamivudine-resistant HBV, because it shows cross-resistance to lamivudine and entecavir, since the virus develops the same mutations for both medications. Data about the use of telbivudine in renal transplantation are lacking.

### 2.5.5. Entecavir (ETV)

Entecavir, a guanosine analog, is 30 times more potent than lamivudine in suppressing viral replication and nowadays it is used as first-line prophylactic treatment in renal transplant recipients. This drug has a high antiviral potency, a high genetic barrier for resistance, and a good safety profile. There is sufficient evidence that it can effectively clear the viral load for a prolonged period. A recent prospective study included 27 renal transplant recipients, 18 (67%) were treatment naïve and 9 (33%) had been previously treated with LAM but had no resistant mutations. Entecavir cleared HBV DNA in 70, 74, 96, and 100% of patients after 12, 24, 52, and 104 weeks, respectively. Furthermore, entecavir reached higher rates of undetectable HBV DNA compared to lamivudine (32, 37, 63, and 63% at 12, 24, 52, and 104 weeks, respectively;  $P < 0.005$ ) [32]. However, in patients with lamivudine-resistant HBV, complete response to entecavir can be delayed for more than 6 weeks, or not be achieved at all. The use of entecavir in renal transplant recipients who had developed lamivudine—or adefovir—resistance has been examined in a small study of 10 solid-organ-transplant recipients, with 8 kidney-allograft recipients among them, who were treated with entecavir for 16.5 months. There was a significant decrease in HBV DNA viral load (50%) without any significant adverse events [33]. Resistance to entecavir has not been documented in renal transplant recipients. In the general population, the rate of entecavir resistance is minimal (1.2%) in treatment-naïve patient after 5 years of therapy. However, in lamivudine-resistant patients, the probability of entecavir resistance at years 1–5 rises from 6 to 15, 36, 46, and 51%, respectively [34].

### 2.5.6. Adefovir dipivoxil (ADV)

Adefovir is an acyclic nucleotide adenosine analog. Adefovir is effective as monotherapy or in combination with entecavir in the general population with HBV infection and lamivudine resistance [35–38]. The problem with this agent is that it is potentially nephrotoxic. Studies in human immunodeficiency virus (HIV) patients show that high daily doses of adefovir (60–120 mg) may cause renal tubular injury. The drug is mainly used in lamivudine-resistant HBV cases [39]. Fontaine et al. studied the efficacy of adefovir as monotherapy at 11 renal-transplant recipients with lamivudine resistance. After 12 months, a satisfactory decline in serum HBV DNA and an absence of hepatitis flares were observed. Importantly, there were no significant clinical and laboratory adverse events [35]. In another study of 11 renal-transplant recipients with lamivudine resistance, adefovir was given at very low doses (10–2.5 mg/day) and it showed good efficacy, without nephrotoxicity [38]. In another study, evidence of nephrotoxicity implementing treatment discontinuation despite dosage adjustment was observed in 29% of patients [39].

## 2.6. Treatment duration

In the general population, the duration of treatment depends on the HBeAg status. HBeAg-positive patients should be treated until HBV DNA and HBeAg are cleared and anti-HBe seroconversion occurs. Additional treatment is needed for at least 6–12 months after anti-HBe seroconversion to prevent virological reactivation. Patients without HBeAg should be treated until HBsAg clearance. The duration of antiviral therapy for renal transplant recipients



remains unclear, because outcomes after nucleos(t)ide analogs withdrawal in immunosuppressed patients allograft recipients are unknown.

One small retrospective study [40] evaluated the course of 6 out of 14 HBsAg(+) kidney-transplant recipients, in whom antiviral treatment had been discontinued after a median of 14 months. All of the six patients in whom antiviral agents had been discontinued were on stable, low-dose maintenance immunosuppression with undetectable HBV DNA and serological negativity for HBeAg. In four out of the six patients (67%), antiviral withdrawal was successful, without any sign of reactivation after a median follow-up of 60 months. In the remaining two patients, who had reactivated HBV, antiviral therapy was reintroduced immediately, with subsequent HBV clearance. Though the number of patients is indeed small, the study provides promising results for future investigation.

In the absence of robust data, we can suggest that antiviral treatment after kidney transplantation may be discontinued only in a subset of carefully selected patients who meet the following criteria: stable renal function and low immunological risk for rejection, low-dose maintenance immunosuppression for at least 6–9 months, no serological or biochemical evidence for HBV activity and previous antiviral treatment without resistance to any antiviral agent for at least 12 months. Close monitoring of HBV DNA every 3–6 months is essential, while antivirals should be reintroduced whenever immunosuppression must be intensified, that is, in the case of anti-rejection treatment.

## **2.7. Reactivation of HBV after renal transplantation: the role of immunosuppression**

Immunosuppression is associated with hepatitis B virus reactivation not only in HBsAg-positive recipients but also in patients seropositive for anti-HBc/anti-HBs, usually in low titers, that is, past infection (reverse seroconversion) [41].

The majority of data come from studies in HBV patients treated for solid-organ or hematological malignancies [41, 42].

The main factors associated with HBV reactivation posttransplantation are the immunocompetence of the recipient, the total amount of immunosuppression, and finally the characteristics of the virus.

The status of immunosuppression changes the interaction between the HBV virus and the host, leading to potentially severe liver injury. Liver damage in the setting of immunosuppression may occur through two different mechanisms. The first mechanism is direct hepatotoxicity after the introduction of immunosuppression due to uncontrolled viral replication as a consequence of reduced immunosurveillance of the host. The second mechanism involves indirect, immune-mediated liver damage occurring after cessation of immunosuppression, during immune reconstitution. The second mechanism has been described in patients with solid-organ or hematologic malignancies even up to 6–12 months after completion of chemotherapy [43].

Since renal transplant recipients receive lifelong immunosuppression, hepatotoxicity in this setting may mostly be attributable to the first mechanism with the highest risk for viral

reactivation being during the induction period, when the total amount of immunosuppression is high or whenever immunosuppression is intensified after that, as, for example, during anti-rejection treatment.

## 2.8. Immunosuppressive agents

Corticosteroids (CSs), calcineurin inhibitors (CNIs) (cyclosporine and tacrolimus), antimetabolites (mycophenolate mofetil (MMF) or mycophenolic sodium and azathioprine), and mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) are the main immunosuppressants used in various combinations in kidney transplantation. Monoclonal antibodies (Rituximab, anti-IL2 Basiliximab) and polyclonal antibodies as antithymocyte globulin (ATG) are also part of the immunosuppressive regimen used for the induction or for the treatment of rejection. All of them are implicated in alterations of viral replication, mostly by inducing increased viral replication and enhance the risk of HBV reactivation. The risk of HBV reactivation according to specific immunosuppressive drug classes has been estimated by the American Gastroenterological Association (AGA) [44].

### 2.8.1. Rituximab

According to the AGA guidelines, Rituximab has the highest risk estimate of HBV reactivation (high >10%) from all immunosuppressants used in kidney transplantation. Moreover, the risk of HBV reactivation may persist up to 12 months, since the antibody has a prolonged phase of immune reconstitution.

Rituximab administration has been associated with HBV reactivation not only in HBsAg-positive but also in anti-HBc-positive and anti-HBs-positive patients (reverse seroconversion). In a prospective study of 314 HBsAg-negative patients with B-cell lymphoma treated with Rituximab, 16.2% were HBV carriers. All of them were anti-HBc positive, whereas half of them were also anti-HBs positive. Virus reactivation occurred in 12% of patients. HBV DNA clearance with the use of entecavir permitted readministration of Rituximab [45].

### 2.8.2. Polyclonal antibodies (antithymocyte globulin, ATG)

Increased viral replication following ATG administration has been described for herpes viruses, Epstein-Barr virus (EBV), and, to a lesser degree, cytomegalovirus (CMV). In those cases, ATG has been administered to patients with severe aplastic anemia concomitantly with cyclosporine [46]. Data about HBV reactivation after treatment with ATG are lacking.

### 2.8.3. Corticosteroids (CS)

Corticosteroids are the oldest and commonest immunosuppressants worldwide. Its use is undoubtedly associated with increased viral replication. Since they are used in many dosages, the risk of HBV reactivation depends on the dose and duration of CS administration. High corticosteroid doses increase viral replication, while ALT may be decreased. The opposite is observed during steroid tapering with elevated aminotransferases 4–6 weeks after steroid discontinuation [40]. According to the AGA guidelines, high CS doses (up to 20 mg/d of

prednisone) and/or prolonged (>3 months) administration are considered as high risk for HBV reactivation while rapid tapering may also increase the risk for viral reactivation due to immune reconstitution.

In kidney transplantation, high CS doses are administered during the first weeks post transplantation; thereafter, they are tapered during a period of 3–6 months to a maintenance dose of 5 mg of prednisone daily or every other day. In stable, low-immunological risk patients they may be avoided completely (steroid-avoidance protocols) or they may be withdrawn after 4–6 weeks or even later (steroid-withdrawal protocols) with excellent outcomes. High CS doses, including intravenous pulses of methylprednisolone up to 500 mg/d, are used for the treatment of acute rejection.

In HBV kidney transplant recipients, steroids must be used at the lowest possible doses and preferably be discontinued or even completely avoided in patients with low immunological risk.

#### 2.8.4. Calcineurin inhibitors

Calcineurin inhibitors are still the cornerstone of immunosuppression in kidney transplantation. It has been shown that cyclosporine reduces viral replication *in vitro*. Nowadays, most immunosuppressive regimens are tacrolimus based. Although there are no definite conclusions or guidelines, some suggest that cyclosporine may be preferable to Tacrolimus in HBV kidney transplant recipients. Nevertheless, since there are no definite conclusions, the choice of one of the two calcineurin inhibitors depends on the center's practice. Some others may argue that it is easier to withdraw steroids from a Tacrolimus-based regimen and would prefer this choice [47, 48].

#### 2.8.5. Antimetabolites

Azathioprine, though hepatotoxic *per se*, has not been associated with an increased risk of HBV reactivation when given as monotherapy. Nevertheless, after the introduction of the more selective and more potent antimetabolites as the mycophenolic acids (MPAs), the use of azathioprine in kidney transplantation has been restricted to patients with special indications [49].

##### 2.8.5.1. Mycophenolate acid derivatives

Mycophenolate mofetil and the newer mycophenolate sodium have nowadays replaced azathioprine in most immunosuppressive regimens. Data about MPAs and HBV reactivation are lacking, but in general they are considered safe for HBV kidney-transplant recipients.

#### 2.8.6. Mammalian target of rapamycin (mTOR) inhibitors

The reactivation of HBV with the use of mTOR inhibitors has not been studied in renal-transplant recipients and generally they are considered safe. Some case reports of HBV reactivation related to everolimus when used as a chemotherapeutic agent have been reported

but everolimus dosage in this setting is much higher than the usual doses given as maintenance immunosuppression in kidney transplantation [50].

In conclusion, all immunosuppressants given in kidney transplantation can be used in HBV-positive recipients. The most important issue is the total amount of immunosuppression long term. It is crucial to maintain the lowest level of immunosuppression that is necessary to prevent rejection and to closely monitor the HBV status. Prophylactic antiviral treatment should be initiated immediately after transplantation and continued at least for 1 year after stable and low maintenance immunosuppression. In the carefully preselected patients in whom antivirals may be discontinued, close monitoring for HBV reactivation is mandatory.

## **2.9. In summarizing the existing evidence about kidney transplantation and HBV**

- Though decreasing, HBV still remains a considerable problem in dialysis patients and kidney transplant recipients.
- Chronic kidney disease patients should be vaccinated before the initiation of dialysis.
- Intensified vaccination protocols should be applied to hemodialysis patients and antibody titer checked regularly.
- HBV-positive dialysis patients need monitoring with HBV DNA, viral serology (including HBeAg), and liver enzymes.
- HBsAg-positive candidates for kidney transplantation should be evaluated thoroughly with HBV DNA, liver enzymes, and liver biopsy.
- Antiviral treatment with tenofovir or entecavir (preferably to lamivudine) should be introduced to HBsAg-positive patients with viral activity on the waiting list.
- Patients with decompensated cirrhosis are candidates for combined liver-kidney transplantation, while compensated cirrhosis is no more an absolute contraindication for kidney transplantation alone.
- Kidney transplants from HBsAg-positive and from HBsAg-negative/anti-HBc-positive donors can be safely transplanted into immunized, HBsAg-negative recipients with concomitant prophylaxis.
- HBsAg-positive kidney transplant recipients should receive antiviral prophylaxis immediately after transplantation.
- In the current era of new antivirals, outcomes after transplantation are improving and long-term patient and graft-survival rates are approaching those of HBsAg-negative-matched recipients.
- The duration of antiviral prophylaxis after transplantation is unknown.
- Antivirals can be withdrawn in subsets of patients after transplantation.
- All immunosuppressants can be used in HBsAg-positive recipients.

- The total amount of immunosuppression must be kept at the lowest possible levels for the given donor/recipient.

In conclusion, with growing knowledge and evolving evidence in both fields, hepatitis B and transplantation, in the era of potent antivirals as nucleoside analogs, HBsAg-positive kidney-transplant candidates and recipients can be successfully treated and monitored and reach survival rates comparable to their HBsAg-negative counterparts.

### 3. Kidney transplantation and hepatitis C virus infection

#### 3.1. Epidemiology of hepatitis C virus (HCV) infection

The prevalence of hepatitis C virus (HCV) infection worldwide is 3% and infected people are estimated to be approximately 170 millions. Prevalence rates in Africa, America, Europe, and South-East Asia are less than 2.5%. In the Western Pacific regions, the prevalence ranges between 2.5 and 4.9% while in some parts of the Middle East, it reaches 13% [51–53].

The prevalence of hepatitis C in patients with end-stage renal disease (ESRD) presents great variation worldwide. In northern Europe, it is below 5%, whereas in the US and southern Europe, it stands at 10%. In several North African, Asian, and Latin American countries, the relative disease prevalence varies between 10 and 70% [54]. In Greece, a 2003 collaborative study of the Hellenic Center for Infectious Diseases Control and the Hellenic Society of Nephrology showed that the percentage of patients with hepatitis C was 7.5% in a total of 7016 patients on dialysis [55].

Prior to 1990, the main routes of HCV transmission were blood-product transfusions, intravenous drug use, and unsafe medical procedures. Since the systematic screening of blood products, the risk of HCV infection related to transfusions is extremely low (1/20000000) [56]. Currently, the main routes of HCV infection are intravenous drug use, unsafe medical procedures, mother-to-child transmission, and the use of unsterilized materials in activities such as acupuncture and tattooing. Household and sexual transmission is extremely low. The dialysis-related risk is estimated at 2% per year. With the screening of blood products and the use of erythropoiesis-stimulating agents, the risk of transfusion-related HCV infection in dialysis patients has dramatically declined; however, they continue to comprise a “high-risk” group. In several studies, the prevalence of HCV infection correlated strongly with the time on dialysis, independently of the burden of transfusions and it was higher in HD than in home HD or peritoneal dialysis patients. These data strongly suggest that nosocomial transmission is of major importance [57].

Therefore, the KDIGO workgroup for the prevention of HCV transmission in dialysis patients focused on the implementation of hygienic precautions regarding the staff of HD units and the sterilization of the dialysis machines. Of major importance is the fact that the isolation of HCV-infected patients does not seem to protect against HCV transmission in HD units and therefore it is not recommended [53].

#### **4. Kidney transplantation versus dialysis for HCV-infected dialysis patients**

A meta-analysis of observational studies tried to establish the impact of hepatitis C virus infection on survival in dialysis patients. It showed that HCV-positive patients on dialysis have an increased risk of mortality compared with their HCV-negative counterparts, which is mainly attributed to liver-associated disease and its complications (relative risk, 5.89) [58].

Kidney transplantation is the treatment of choice for HCV-positive patients with ESRD. Three retrospective studies showed that transplantation offered a survival advantage in HCV-seropositive patients compared to those who remained on the waiting list [59–61]. A recent systematic review that included 9 studies with a total number of 2274 HCV-infected renal-transplant candidates and recipients showed that 5 years posttransplantation, anti-HCV-positive patients who had undergone kidney transplantation had approximately 55% lower risk of death compared to wait-listed patients [62].

#### **5. Diagnosis and assessment of liver disease in HCV-positive kidney-transplant candidates**

The clinical tools that are used for the assessment of liver damage for patients with ESRD do not differ from those used for the general population. Several studies have shown that aminotransferase (AST, ALT) levels are low in patients on dialysis and this reduction appears to occur in patients with advanced chronic kidney disease even before the initiation of renal-replacement treatment [63, 64].

All patients on the waiting list for a kidney allograft should be tested for hepatitis C, initially with an anti-HCV enzyme-linked immunosorbent assay (ELISA) and after a positive result by polymerase chain reaction assay (PCR) for the quantification of HCV RNA. Identification and classification of HCV genotype should follow. Screening for HCV must be a clinical routine and it must be performed once a year in all dialysis patients, since they are at constant risk of acquiring HCV infection. Dialysis units with a high prevalence of HCV should adopt a more strict protocol by examining their patient population for the presence of viremic activity, regardless of the result of the ELISA test [53].

Liver biopsy is recommended by the KDIGO guidelines as the “gold standard” for assessing the severity of hepatic damage and the prognosis of the disease. Furthermore, it can provide valuable assistance in planning the future treatment strategy [65]. A study on percutaneous liver biopsy in chronic hepatitis C patients found the procedure to be safe without increased risk in patients with ESRD [66]. The necessity of a liver biopsy is underlined by the following factors:

- There is no reliable correlation between the fluctuation of aminotransferases levels or the measurements of HCV RNA and the severity of liver injury as shown by histological findings in this group of patients [67].

- The percentage of HCV-positive renal transplant recipients that develop liver disease in the course of transplantation varies in different studies between 19 and 64% [59, 60].
- Studies have shown that up to 25% of ESRD patients with chronic hepatitis C infection have subclinical pre-cirrhotic disease in liver biopsy [68].
- The finding of advanced fibrosis in liver biopsy is a contraindication for renal transplantation, because 10-year survival is lower than 26% [52]. Patients with adequately compensated hepatic disease should be referred for simultaneous liver-kidney transplantation.

Novel, noninvasive, simple radiographic and serologic tests are used to validate hepatic fibrosis. Transient elastography (TE) evaluates the severity of fibrosis by liver-stiffness measurement. It has been used in non-uremic patients for the staging of fibrosis with satisfactory results [69]. In the dialysis population with chronic HCV infection, TE, performed with a Fibroscan machine, seemed to be efficient in estimating fibrosis in one study available [70]. Aspartate aminotransferase-to-platelet ratio index (APRI) is a serologic marker of fibrosis, easy to calculate. APRI is useful in diagnosing the degree of fibrosis [71], although it has a lower diagnostic accuracy than TE especially in cases of cirrhosis, in HD as well as in non-uremic patients with HCV [70]. Larger cohort studies are needed before noninvasive techniques can replace liver biopsy. Nevertheless, they can be useful when the biopsy cannot be performed because of contraindications or patient refusal.

## 6. Kidney donation from HCV-positive donors

All prospective donors should be evaluated for the risk of HCV infection based on blood tests, medical history, and lifestyle habits. Prior to transplantation, deceased and living donors should be screened for anti-HCV antibodies, preferably using ELISA third generation. However, the presence of antibodies against HCV in the donor may indicate a previous cleared infection and nontransmissibility. Thus, conducting PCR for HCV RNA is the next step for anti-HCV-positive donors. In the setting of cadaveric kidney transplantation, the results of HCV RNA will be available after transplantation. Therefore, the KDIGO guidelines advise against transplantation from HCV-positive donors to HCV-negative recipients [53], since it is well established that hepatitis C can be transmitted by solid-organ transplantation with a high frequency that approaches 100% in some studies [72, 73]. Viral transmission results in the occurrence of liver disease in the immunocompromised recipient, leading eventually to poor clinical outcomes due to infectious complications, development of cholestatic syndrome, and progression to hepatic failure [74].

Allocation of HCV-positive kidneys is controversial. The strategy of many transplant centers, including ours nowadays, is to accept kidneys from HCV-positive-deceased donors for HCV-positive-transplant candidates. According to the latest KDIGO guidelines [53], seropositive recipients should be tested by PCR for HCV RNA and must have an active viremia. This practice is based on the fact that kidney transplantation of HCV-infected dialysis patients from HCV-positive donors reduces the time in the transplant waiting list and is associated with

superior survival compared to those who remain on the list waiting for a seronegative donor [75]. Additionally, a retrospective study by Morales et al. examined the differences between HCV-positive recipients who were transplanted either from HCV-positive donors or from HCV-negative donors. In terms of decompensated liver disease, no differences were observed between the two groups (10.3 vs. 6.2%). Moreover, 5- and 10-year patient survival were similar in the two groups, namely 84.8 and 72.7% in the subset of recipients from HCV-positive donors versus 86.6 and 76.5%, respectively, in those who received an HCV-negative renal allograft. Five- and ten-year graft survivals were decreased in the HCV-positive donor group (58.9% at 5 years and 34.4% at 10 years) compared to the HCV-negative donor group (65.5% at 5 years and 47.6% at 10 years,  $p: 0.006$ ). However, this difference was not associated to HCV seropositivity in the multivariate regression analysis [76]. Ideally, donors and recipients should be matched for HCV genotype to minimize the risk of super-infection, even if this procedure is rarely performed during a deceased donor evaluation. However, two retrospective studies showed that the number of HCV genotypes has no significant effect on patient survival [77, 78]. In the new era of HCV treatment with the direct-acting antiviral agents (DAAs), the knowledge of the donors' genotype will be useful for the assessment of future treatment strategies.

Living donors with HCV infection and viremia should preferably receive appropriate treatment prior to donation, since the duration of therapy is short and it leads to sustained SVR [79]. On the other hand, prior to donation the transplant team should carefully consider and explain to the donor the risk for developing HCV-associated renal disease or diabetes mellitus in the future.

Based on the aforementioned data, the policy of transplanting a kidney from an anti-HCV-positive donor to an anti-HCV-positive recipient is considered to be a safe approach with good clinical outcomes in the long term. In any case prior to receiving an allograft, the HCV-infected-transplant candidate should be informed in detail about the HCV status of the donor, the risk of super-infection or other complications, the data regarding patient and graft survival, as well as the new treatment options.

## **7. Impact of HCV infection on posttransplant outcomes**

Hepatitis C adversely affects the survival of both patients and grafts. Numerous, predominantly retrospective cohort studies report inferior 10-year survival rate of HCV-positive patients in comparison to uninfected kidney recipients [80–82]. Age at transplantation and the presence of anti-HCV antibodies were independently associated with patient survival [81]. However, a serious limitation of these studies is that histological data regarding the severity of hepatic disease pretransplantation were not available in the majority of them.

A recent meta-analysis of 18 observational trials that included 133,530 renal allograft recipients revealed an increased rate of all-cause mortality in HCV-positive patients after transplantation, regardless of the year of transplantation and thus the immunosuppressive regimen that was used, the country of origin or the number of patients. The main causes of death were cirrhosis



and hepatocellular cancer. It is worth noting that hepatic disease developed late after transplantation. Cardiovascular mortality and cardiovascular disease were also more prevalent in this study group [83]. Additional extrahepatic causes of morbidity and mortality were new onset diabetes after transplantation (NODAT), de novo and recurrent glomerular diseases (mainly de novo type I membranoproliferative GN), and sepsis [84–86].

The abovementioned studies demonstrated also that graft survival is decreased in seropositive patients posttransplantation. More specifically, the meta-analysis by Fabrizi et al. showed that the adjusted relative risk of graft loss in these patients compared to those who are not infected was 1.76 [83]. Allograft failure has been attributed to the aforestated morbidity factors, namely diabetes and glomerulonephritides, as well as to the occurrence of transplant glomerulopathy and chronic allograft injury [83–87].

## 8. Therapy

Treatment of patients infected with HCV comprises the traditional approach with interferon and ribavirin, as well as novel regimens, interferon- $\alpha$ -free that consist of the direct-acting antiviral agents. Therapeutic regimens aim at the elimination of the virus. The viral load, based on HCV RNA quantification in serum, must be undetectable (10–15 IU/ml) 12 weeks after the end of treatment (SVR).

### 8.1. Traditional therapy

In the past decade, interferon and ribavirin were considered to be the cornerstone of HCV antiviral treatment. Nonetheless, these drugs were associated with considerable toxicity. More specifically, the use of interferon after kidney transplantation induced acute kidney injury, episodes of rejection resistant to steroid therapy, and graft loss [88, 89]. Therefore, before 2013 transplant candidates could only be treated prior to transplantation as the KDIGO guidelines recommended, with the exception of patients with fibrosing cholestatic hepatitis [53]. However, the Dialysis Outcomes Practice Patterns Study demonstrated that only a minority of ESRD patients on dialysis were treated for HCV [90]. Among 4589 HCV-positive HD patients who were observed from 1996 to 2011, only 48 (1%) were treated for HCV, whereas among the subset of patients waiting on the list for transplantation, only 3.7% were treated for HCV. The reasons for this approach were as follows:

- The use of ribavirin in this patient population aggravated anemia that was already present due to chronic kidney disease.
- Pegylated interferon- $\alpha$  (PegIFN- $\alpha$ ) as monotherapy resulted in poor outcomes, with SVR 30–35% [91].
- Addition of ribavirin in low doses increased the SVR to 55% after 6 months, but also increased side effects [92].
- A substantial percentage of patients (18–30%) dropped out of therapy.

Nevertheless, HCV clearance when achieved was maintained posttransplantation in the vast majority of patients despite the use of immunosuppression [93].

## 8.2. Novel therapeutic agents

Thorough understanding of the HCV structure, replication mechanism, and cell cycle has led to the development of the DAAs. These drugs are small molecules that target nonstructural (NS) viral proteins and inhibit HCV replication. Four classes of DAAs exist, namely NS3/4A protease inhibitors (PIs) simeprevir, paritaprevir, and grazoprevir, NS5B nucleoside polymerase inhibitors (NPIs) and non-nucleoside polymerase inhibitors (NNPIs) sofosbuvir and dasabuvir, respectively, and NS5A inhibitors ledipasvir, daclatasvir, ombitasvir, and elbasvir [94].

The introduction of these new agents has modernized the therapeutic ammunition and has radically changed the treatment of patients with HCV infection; ongoing trials are expected to prove the safety and efficacy of DAAs in patients with impaired renal function and ESRD and establish proper dosing regimens. Besides the spectacular effectiveness of these drugs (SVR over 95%) in patients who had not received prior therapy [95], another important issue is the improved tolerance to treatment, due to reduced treatment duration and fewer side effects.

Different combinations of DAAs are administered based on the different HCV genotypes (Table 1).

<b>Genotype 1a and 1b</b>	<b>Genotype 4</b>
PegIFN- $\alpha$ , RBV, and Sofosbuvir	PegIFN- $\alpha$ , RBV, and Sofosbuvir
PegIFN- $\alpha$ , RBV, and Simeprevir	PegIFN- $\alpha$ , RBV, and Simeprevir
Sofosbuvir and Ledipasvir	Sofosbuvir and Ledipasvir
Ritonavir, Paritaprevir	Ritonavir, Paritaprevir, Ombitasvir
Ombitasvir and Dasabuvir	Sofosbuvir and Simeprevir or Daclatasvir
Sofosbuvir and Simeprevir or Daclatasvir	Grazoprevir, Elbasvir $\pm$ Ribavirin
Grazoprevir, Elbasvir $\pm$ Ribavirin	
<b>Genotype 2</b>	<b>Genotype 5</b>
PegIFN- $\alpha$ , RBV, and Sofosbuvir	PegIFN- $\alpha$ , RBV, and Sofosbuvir
Sofosbuvir and RBV	Sofosbuvir and Ledipasvir
Sofosbuvir and Daclatasvir	
<b>Genotype 3</b>	<b>Genotype 6</b>
PegIFN- $\alpha$ , RBV, and Sofosbuvir	PegIFN- $\alpha$ , RBV, and Sofosbuvir
Sofosbuvir and Daclatasvir	Sofosbuvir and Ledipasvir

**Table 1.** Treatment recommendation (EASL 2015) for chronic hepatitis C patients without liver cirrhosis.

The first studies that evaluated the effectiveness of DAAs excluded patients with estimated glomerular filtration rate (eGFR) less than 30 ml/min/1.73m<sup>2</sup>, patients on dialysis, and renal-transplant recipients. It is worth noting that sofosbuvir is contraindicated for patients with

eGFR <30 ml/min/1.73m<sup>2</sup> and for dialysis patients [94, 95]. Therefore, treatment options for this study group with HCV infection from genotypes 2, 3, 5, and 6 of HCV are limited, because all regimens include sofosbuvir. Severe, urgent cases should receive treatment after careful expert consultation. On the other hand, results are very promising for patients with genotypes 1 and 4 in comparison with the general population. Ruby-I is a single-arm multicenter study, in which 20 patients with HCV genotype 1 and CKD stage 4,5 or in dialysis were given ombitasvir co-formulated with paritaprevir and ritonavir, administered with dasabuvir for 12 weeks. Patients with HCV genotype 1a infection also received ribavirin (n:13), whereas those with genotype 1b infection did not (n:7). The majority of patients, 90%, achieved the primary end point which was SVR 12 weeks after the end of treatment (SVR12). One patient did not achieve an SVR12 because of a relapse and another one died from causes not related to treatment. The most common adverse event was anemia (69%) due to ribavirin treatment, which led to drug discontinuation in nine cases [96]. C-Surfer is a multicenter, phase 3, randomized study of safety and observational study of efficacy regarding the combination of grazoprevir and elbasvir (both approved by the Food and Drug Administration (FDA) and wait to be approved by the European Medicines Agency (EMA) in 2016) for patients with genotype 1 infection and stage 4–5 CKD. The treatment group consisted of 111 patients, who received grazoprevir and elbasvir for 12 weeks. The results were remarkable. The SVR12 was 99%, with only one patient relapsing, whereas the drugs were well tolerated with minor adverse events that did not lead to drug discontinuation [97].

The use of interferon-free treatment regimens is of major importance in renal transplantation because it eliminates the risk of acute allograft rejection and subsequent graft loss. An important question that arises is when is the proper timing of treatment, pre- or post transplantation? The introduction of DAAs permits us to exceed the narrow timeframes before transplantation and treat our patients after transplantation. Thus, we have the advantage of using allografts from HCV-positive donors for recipients willing to accept them. This practice minimizes the time on the waiting list and subsequently the time on dialysis and all its deleterious effects as we have already mentioned, but it cannot be applied in small countries such as Greece with extremely long waiting time on the list. On the other hand, treatment with DAAs prior to transplantation may offer the advantage of increasing the overall survival of patients by diminishing the risk of hepatic and extrahepatic complications especially severe, evolving liver disease, glomerulonephritis and NODAT. Another important issue to consider when deciding the timing of treatment is the virus genotype. Eradication of the virus in patients infected with genotype 1 or 4 is plausible before transplantation, since sofosbuvir-free regimens are available.

In renal transplantation, the DAAs are used according to the guidelines applied to the general population and the liver-transplant recipients. Until 2016, there were no data to guide the use of these agents in kidney transplant patients and to demonstrate their efficacy and safety to this subpopulation of patients. The policy of many transplant centers, including ours, is that all kidney-transplant patients with chronic HCV infection and eGFR >30 ml/min/1.73m<sup>2</sup> receive appropriate therapy with a new, interferon-free antiviral regimen based on the detected genotype (**Table 1**). The dose of DAAs is not adjusted when eGFR is greater than 30 ml/min/

1.73m<sup>2</sup>. Ribavirin is not recommended with eGFR <30 ml/min/1.73m<sup>2</sup> although it has been used in patients after renal transplantation with a close monitoring of hemoglobin levels [98].

Of great importance are the drug-drug interactions between the DAAs and the immunosuppressive agents and the mandatory dose adjustments (**Table 2**).

	Daclatasvir	Sofosbuvir&Ledipasvir	Ritonavir, Paritaprevir, Ombitasvir&Dasabuvir	Simeprevir	Sofosbuvir
Everolimus	Orange	Orange	Orange	Orange	Green
Azathioprine	Green	Green	Green	Green	Green
Ciclosporin	Green	Orange	Orange	Red	Green
Mycophenolate	Green	Green	Orange	Green	Green
Sirolimus	Green	Orange	Orange	Orange	Green
Tacrolimus	Green	Orange	Orange	Orange	Green

**Green:** No significant interaction is expected.

**Orange:** Possible interaction which requires close monitoring, changing the dosage, and/or drug-delivery time.

**Red:** Avoid concomitant use of drugs.

This table is based on data by the University of Liverpool on the site <http://www.hep-druginteractions.org> (University of Liverpool). For additional drug-drug interactions and for a more extensive range of drugs, detailed pharmacokinetic interaction data, and dosage adjustments, refer to the abovementioned website.

**Table 2.** Interactions between immunosuppressive drugs and DAA agents.

Since 2016, several studies have emerged. Kamar et al. tried to assess the efficacy and safety of an interferon-free regimen based on sofosbuvir. Twenty-five renal-transplant recipients with HCV infection (19/25 Genotype 1, 2/25 Genotype 2, 1/25 Genotype 3, 3/25 Genotype 4) received various combinations of sofosbuvir with other agents; ribavirin (n:3), daclatasvir (n:4), simeprevir (n:6), simeprevir and ribavirin (n:1), ledipasvir (n:9), ledipasvir and ribavirin (n:1), pegylated interferon and ribavirin (n:1). At week 12, an impressive SVR of 100% was recorded. During therapy, no significant adjustments in the dose of immunosuppressive drugs were required and kidney function remained stable [109]. However, after virus clearance, trough levels of tacrolimus decreased without any dose change. It is already known that HCV infection alters the pharmacokinetics of CNIs and results in increased drug exposure [99]. Therefore, we must be cautious after HCV clearance and adjust the dose of CNIs accordingly. A case series study of 20 HCV-infected kidney recipients (85% Genotype 1, 15% Genotype 2) who were treated off-label with sofosbuvir in combination with simeprevir (n:9), ribavirin (n:3), ledipasvir (n:7), and daclatasvir (n:1) demonstrated a sustained virological response of 100% at week 12 and it was maintained for a short median follow-up period of 8.6 months [100].

These impressive results show that the efficacy and safety of DAAs in renal transplant recipients is comparable with the general population. It remains to be determined if viral clearance after transplantation will improve long-term patient and kidney-allograft outcomes. The optimal timing of HCV therapy (posttransplantation or pretransplantation) has not clearly been determined. Taking into account that based on clinical trials the DAAs will be available for patients with eGFR  $<30$  ml/min/1.73m<sup>2</sup> in the near future, treating these patients before transplantation may prevent posttransplantation complications and improve the overall outcomes. For the time being, ESRD patients infected with HCV Genotypes 2, 3, 5, 6 can be treated with DAAs only after transplantation or when it is absolutely obligatory in life-threatening conditions.

## 9. Immunosuppression in HCV-positive kidney transplant recipients

Immunosuppression may increase hepatitis C viral proliferation after transplantation and thus accelerate the evolution of hepatic damage [101]. Information regarding the use of immunosuppressive drugs in seropositive allograft recipients comes mostly from liver transplantation, as well as from the experience in the field of oncology-hematology. Large, prospective studies examining the effect of immunosuppressive drugs in HCV-seropositive recipients are lacking. However, the total amount of induction and maintenance immunosuppression may play an important role in the reactivation of the virus post transplantation.

## 10. Immunosuppressive agents

### 10.1. Rituximab

The use of anti-CD20 monoclonal antibody rituximab has been reported in a small number of seven HCV-positive patients after kidney transplantation. It was not related to the recurrence of the infection in a follow-up period of 19 months [102]. Larger studies in the field of hematology have shown a high incidence of hepatic flares in HCV-seropositive patients following treatment with Rituximab for lymphoma [103].

### 10.2. Induction therapy

Data from the Scientific Registry of Transplant Recipients (SRTRs) demonstrated that induction therapy, with polyclonal or monoclonal antibodies, has been associated with a lower risk of death. This finding could probably be attributed to lower rejection rates in patients receiving induction treatment [104]. Anti-CD3 monoclonal antibody OKT3, however, has been associated with recurrence of HCV in liver transplantation [105]. It is therefore avoided in HCV-infected patients after transplantation. On the other hand, the administration of the polyclonal antibody antithymocyte globulin (ATG) as induction therapy in 104 HCV-infected kidney-transplant patients did not induce viral replication [106], a finding that was confirmed by subsequent studies [107]. Contradictory data exist regarding monoclonal anti-IL2 antibodies,

such as daclizumab. A single-center study in a small number of patients showed that therapy with daclizumab is followed by faster progression of liver fibrosis compared to ATG [108]. Large studies based on data from the United Network for Organ-Sharing UNOS base indicate that liver-transplant recipients with chronic HCV infection exhibit satisfactory graft and patient survival after receiving induction with daclizumab [109, 110].

### **10.3. Corticosteroids (CS)**

High pulses of corticosteroids can cause up to 100 times increase of the viral load, but this has only been demonstrated in liver transplantation [107]. Although rapid steroid discontinuation leads to lower rates of diabetes and HCV recurrence, it has been associated with worst outcomes in liver transplantation [111, 112]. In the aforementioned study by Luan et al., in a total of 3708 HCV-positive kidney transplant patients, mortality rates were similar between those who received CS and those who did not [104].

### **10.4. Calcineurin inhibitors (CNIs)**

In vitro studies have shown that cyclosporine may have an antiviral effect by suppressing HCV replication and the expression of proteins [113]. Moreover, cyclosporine is less diabetogenic in comparison with tacrolimus. However, in a cohort of 71 patients with HCV infection posttransplantation, liver fibrosis and viral replication were similar regardless of the CNI used [114]. Additionally, data from the Scientific Registry of Transplant Recipients (SRTR) [104] did not confer a survival advantage of cyclosporine over tacrolimus in renal allograft recipients.

### **10.5. Antimetabolites**

MPAs appear to be safe in HCV-seropositive individuals after kidney transplantation. Notably, MMF administration was related to a reduced risk of death (hazard ratio (HR): 0.77,  $p$ : 0.005) in the study by Luan et al., implying a possible advantageous effect of the drug in renal recipients with chronic HCV infection [104].

### **10.6. Mammalian target of rapamycin (mTOR) inhibitors**

Data regarding the use of mTOR inhibitors in transplant patients with HCV infection are limited. Sirolimus was associated with decreased evolution of hepatic fibrosis and cell proliferation in vitro, in an animal model of hepatic fibrosis [115]. This finding was not confirmed in a small cohort study of HCV-infected kidney recipients, where switch from CNI to sirolimus was not followed by lower viral load [116].

In conclusion, almost all immunosuppressive agents can be used in HCV-positive renal recipients. As in the case of HBV, the most important issue is the total level of immunosuppression, which should be kept as low as possible based on the specific conditions of transplantation and the immunological profile of the recipient. Close monitoring of HCV RNA is mandatory.

## 11. In summarizing the existing evidence about kidney transplantation and HCV

- The prevalence of hepatitis C in patients with ESRD presents great variation worldwide and is correlated with the time on dialysis.
- Kidney transplantation is the choice of therapy for HCV-infected patients with ESRD.
- Mortality is lower among patients who undergo kidney transplantation compared to those remaining on the waiting list.
- Liver biopsy should be performed in all HCV-infected renal transplant candidates.
- Systematic screening for HCV should be routinely done in all ESRD patients. Dialysis units with a high prevalence of HCV should preferably test all patients for HCV RNA, regardless of the presence of anti-HCV antibodies.
- Well-compensated cirrhosis is not a contraindication to kidney transplantation.
- Renal transplant recipients with chronic HCV infection have lower patient and allograft survival post transplantation compared with noninfected renal transplant recipients.
- Major causes of mortality in HCV-infected renal transplant recipients are cirrhosis and hepatocellular cancer. Additional causes of morbidity following kidney transplantation are de novo and recurrent and glomerular diseases and NODAT.
- Transplantation of a renal allograft from an HCV-infected donor may cause HCV infection to the recipient.
- All potential kidney donors, deceased and living, should be evaluated for the risk of HCV infection based on blood tests, medical history, and lifestyle habits.
- Kidneys from HCV-positive donors are donated to anti-HCV–positive recipients.
- Interferon should not be administered in renal transplant recipients with chronic HCV infection because it is associated with rejection episodes and graft loss.
- We suggest the following approach regarding antiviral treatment in HCV-infected renal allograft recipients:
  - All patients with eGFR >30 ml/min/1.73 m<sup>2</sup> should receive a new, interferon-free antiviral regimen based on the virus genotype.
  - Patients with eGFR <30 ml/min/1.73 m<sup>2</sup> should not be treated with sofosbuvir. Treatment options for genotypes 2, 3, 5, and 6 of HCV are limited. In severe conditions, treatment should be discussed with experts.
  - In the case of HCV genotype 1 or 4, the combination grazoprevir-elbasvir can be administered.

- Potential drug-drug interactions of antivirals with immunosuppressive agents present an important issue in selecting the appropriate immunosuppressive regimen after kidney transplantation.
- Immunosuppressive agents can safely be used in HCV-positive renal recipients with close monitoring of HCV RNA and minimization of immunosuppression.

In conclusion, the development of direct-acting antiviral agents (DAAs) may change the natural history of HCV infection in renal allograft recipients. Randomized, prospective trials are expected to prove the safety and efficacy, as well as the optimal dose of DAAs in patients with impaired renal function, ESRD, and kidney transplantation.

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