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REVIEW

Transplantation in the patient with hepatitis C

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Summary

Hepatitis C virus (HCV) infection is the most frequent cause of liver disease after renal transplantation. Its clinical course is irrelevant in the short term, except for rare cases of fibrosing cholestatic hepatitis. However, in the long run, HCV infection can lead to major liver complications. Because interferon (IFN) is generally contraindicated in renal transplant patients, the best approach is to treat patients on dialysis. Until more information with pegylated-IFN is available, the use of alpha-IFN monotherapy is recommended. Most of the patients with sustained virological response remain HCV RNA negative after transplantation. HCV-positive renal transplant patients have a higher risk for proteinuria, chronic rejection, infections and post-transplant diabetes (PTDM). Long-term patient- and graft-survival rates are lower in HCV-positive patients. Mortality is higher, mainly as a result of liver disease and infections. HCV can contribute to the development of certain neoplasias such as post-transplant lymphoproliferative disease (PTLD). HCV infection is also an independent risk factor for graft loss. PTDM, transplant glomerulopathy and HCV-related glomerulonephritis can contribute to graft failure. Despite this, transplantation is the best option for end-stage renal disease in HCV-positive patients. Several measures to minimize the consequences of HCV infection have been recommended. Adjustment of immunosuppression and careful follow up in the outpatient clinic for early detection of HCV-related complications are mandatory.

Introduction

Liver disease is one of the leading causes of death in long-term survivors after renal transplantation [1,2]. Hepatitis C virus (HCV) infection is currently the main cause of chronic liver disease in renal transplant patients [1–7].

The special relationship between HCV infection and the kidney transplantation is exhibited concurrently also in the special relationship between this infection and dialysis therapy. Patients on haemodialysis had represented a high-risk group for HCV infection. This derives from the fact that not only the haemodialysis technique has usually implied a risk for a direct or indirect contact with contaminated blood, but also because of the frequent need for blood transfusions among these patients in the past. Fortunately, the frequency of HCV infection among dialysis patients has progressively decreased, as a result of the generalization of serological screening of blood donors, the use of erythropoietin and the application of universal precaution measures in haemodialysis units [6].

Therefore, it is easy to understand that HCV infection in kidney transplant patients usually starts with the presence of the infection while the patient is in the waiting list, as a consequence of the acquisition of the infection during dialysis therapy [1–4]. As the frequency of HCV infection has decreased in dialysis patients, its prevalence has also decreased among patients in the waiting list and therefore among kidney transplanted patients. In fact, a collaborative study performed in Spain which retrospectively reviewed the outcome of kidney transplant patients during the years 1990, 1994 and 1998, described a progressive and significant decline in the prevalence of anti-HCV antibodies, with values of 29.5%, 19% and 10% respectively [8].

A second *phenomenon* to be underlined when talking about HCV infection and kidney transplantation is the fact that HCV infection may be transmitted through transplantation itself [1,9]. Nevertheless, the routine serological screening of donors before transplantation today makes peritransplant transmission of HCV infection anecdotal when using HCV-negative donors. Finally, we have increasing information on the impact that kidney transplantation and the chronic use of immunosuppressive therapy have on the natural history of HCV infection and also on the impact that HCV infection itself has on the outcome of kidney transplantation [6–15].

In this article, we will review first the impact of kidney transplantation on HCV infection and liver disease. Second, the most important complications of this infection after transplantation such as glomerular diseases, diabetes mellitus etc., the influence they exert on rejection, infection and extrahepatic neoplasia will be summarized. Third, the impact of HCV infection on patient and graft survival will be reviewed. Finally, we will analyse the possibility of transplantation by using kidneys from donors with anti-HCV antibodies into HCV RNA-positive recipients. Several recommendations to minimize/prevent the consequences of HCV infection in renal transplant patients will also be provided. A summary of this review is provided in Table 1.

Table 1. Hepatitis C virus (HCV) infection and kidney transplantation. Most relevant data.

HCV-Related liver disease and kidney transplantation
Prevalence of anti-HCV antibodies (ELISA2/3): 10–49%
HCV RNA positive in serum of anti-HCV antibodies positive patients: 80–90%
Normal transaminase levels: 20–51%
Increased risk for cirrhosis and hepatocellular carcinoma: RR 1.79 [15]
Progression of liver disease slow. No progression in 50% [26]
Treatment with IFN in kidney transplant patients only in fibrosing cholestatic hepatitis [6]
Treatment with IFN or pegylated IFN and Ribavirin before transplantation
Other HCV-related complications after kidney transplantation
Glomerulonephritis: 5–8%
Post-transplant diabetes mellitus
Infections: More opportunistic infections such as tuberculosis
Transplant glomerulopathy: HCV infection is a risk factor for transplant glomerulopathy, but its incidence in HCV patients is unknown
Extrahepatic neoplasia: Prevalence of PTLD in HCV-positive patients is 3.6% [47]
Patient survival
Lower survival than HCV-negative patients at 10 years: 77.5% vs. 84.5%, respectively [8]
Better survival than HCV patients on the waiting list 95% vs. 85% respectively at 4 years [96]
Graft survival
Lower survival (censored-death) than HCV negative at 10 years 69% vs. 79% respectively [8]

Impact of kidney transplantation on HCV infection and liver disease

Epidemiology, prevalence and diagnostic tests of HCV infection after kidney transplantation

Although HCV infection may be acquired by preoperative transfusions and organ transplantation, most graft recipients with anti-HCV antibodies acquired the infection on dialysis, as we commented before [1–3]. Therefore, guidelines for renal transplantation [5,6] recommend that all transplant candidates should be evaluated for HCV infection; positivity for anti-HCV antibodies by immunoassay (EIA) requires HCV RNA determination for confirmation.

The prevalence of anti-HCV antibodies by EIA 2/3 varies between 10% and 49% depending on the centre, country, race, geographic origin of the recipient, mode of dialysis therapy (haemodialysis versus peritoneal dialysis), time on dialysis, number of blood transfusions, previous transplants, presence of anti-hepatitis B core antigen and history of intravenous drug abuse [1–6].

Most EIA 2/3 positive patients have detectable HCV RNA in the serum. This viraemic state persists in almost all transplanted patients. The viral load increases 1.8–30.3 times with respect to viral titres before kidney transplantation in HCV RNA-positive patients, suggesting that immunosuppressive therapy may facilitate viral replication [10,16]. In fact, it has been reported that Mycophenolate mofetil [17] and antithymocyte globulin [1] increase HCV viraemia. On the contrary, it has also been recently reported that Cyclosporin inhibits the replication of HCV in cultured hepatocytes [18]. HCV-RNA titres do not differ between patients with or without post-transplant liver disease [1] and are not clearly related to liver disease progression [19].

Clinical course of HCV infection after kidney transplantation

With the exception of patients developing fibrosing cholestatic hepatitis [20], HCV infection after kidney transplantation has a benign course, although biochemical and histological abnormalities appear in the long term [4,5,14]. Nevertheless, 20–51% of HCV-positive kidney transplant patients may have normal transaminase levels, although this does not necessarily mean a normal histology [4]. In any case, the state of the healthy carrier, with normal transaminase levels, a positive HCV RNA and a normal histology, has also been described in up to 10% of anti-HCV positive kidney transplant patients [21].

The risk of developing chronic liver disease after kidney transplantation seems to depend on several factors such as the duration and the severity of HCV infection before transplantation, the liver histopathology, the co-infection by hepatitis B virus, the time after transplantation and the kind of immunosuppression received [1–5]. The fact must be highlighted that the use of anti-lymphocyte preparations since 1991 seems to be related to a higher risk of developing a liver disease [1]. However, in a recent study from the US Registry, the use of antibody induction did not negatively influence patient survival in these patients [22]. In this context, in Spain our HCV-positive population treated with antibody induction showed similar liver disease outcome and mortality than HCV-positive patients treated without antibody induction [23].

In a recent meta-analysis, mortality caused by liver disease [cirrhosis or hepatocellular carcinoma (HCC)] in HCV-infected kidney transplant patients was increased in most of the included studies, with a RR of death of 1.79, when compared with HCV-negative recipients [15]. The risk of developing HCC was elevated in HCV-positive patients. In a report from the US registry, the incidence of HCC was 6.5 per 100 000 person-year among kidney transplants. The incidence of HCC among nonliver recipients was independently associated with hepatitis B antigen, HCV and diabetes mellitus [24].

Pathology of HCV infection after kidney transplantation

Liver biopsies in selected patients with chronic elevation of ALT have documented severe liver disease, e.g. chronic active hepatitis or cirrhosis, in up to 20% of HCV-positive transplant recipients [4]. The prevalence was lower when biopsies were performed in all HCV-positive patients, regardless of ALT levels. Glicklich and Kapoian reported in 164 liver biopsies performed soon after transplantation in HCV-positive patients that chronic hepatitis was common (81%), but cirrhosis infrequent (7%) [25].

When describing the histological evolution of HCV infection after kidney transplantation, the literature is scarce and few series have described such evolution on the basis of protocol liver biopsies, independently of transaminase values. In one study, a minimum of three sequential liver biopsies *per* patient was performed in 51 HCV RNA-positive kidney transplant patients. Time after kidney transplantation was over 6 years and none of the patients had previously received interferon (IFN) therapy. Three evolutive histological patterns were described: the degree of fibrosis remained stable in 20 patients, fibrosis increased in 21 patients and fibrosis progressively improved in the remaining 10 cases. In this study, baseline liver fibrosis and a high diversity of HVR 1 region in HCV genome behaved as independent risk factors for the regression of fibrosis. The authors concluded that HCV infection does not negatively influence liver histology in the long term in 50% of kidney transplant patients [26].

With regard to the comparison of the histological evolution of liver disease in HCV kidney transplant patients versus immunocompetent patients, contradictory results have been published. Zylberberg *et al.* [27] described a faster progression of the liver histological activity and fibrosis in kidney transplant patients than in nonimmunocompromised patients infected by HCV. On the contrary, Alric *et al.* [19] observed a slow progression of liver fibrosis in HCV-infected kidney transplant patients, which was also inferior to that observed in infected patients with a normal renal function. The authors suggested that the use of different immunosuppressive protocols by the two groups might explain these differences. Finally, a recent study compared the liver histology of 38 HCV-infected kidney transplant patients with that of a matched cohort of 38 HCV-infected patients with end-stage renal disease [28]. This group observed a higher proportion of cases with septal fibrosis, confluent necrosis and steatosis in transplanted versus nontransplanted patients, suggesting that kidney transplantation might modify the natural history of HCV infection in patients with end-stage renal disease.

In summary, on the basis of the current evidence, patients with HCV infection are at increased risk for progressive liver disease after renal transplantation, but the progression of liver disease seems to be slow and does not occur in all patients [6]. The role of Fibroscan in the follow up of liver fibrosis after renal transplantation is still to be defined [29].

Treatment of HCV infection and kidney transplantation

The therapeutic strategy for HCV infection in relation to kidney transplantation has been extensively reviewed by recently published international guidelines [6,7]. The problem of anti-HCV therapy is that IFN has been related to an increased risk of allograft dysfunction and loss. Even more, IFN can induce allograft rejection in failed grafts [30,31]. Therefore, its use in kidney transplantation has been contraindicated, with the exception of patients with fibrosing cholestatic hepatitis [3,32,33] or other conditions in which the benefits of treatment outweigh the risk of allograft loss. This general recommendation has been recently challenged by a pilot study published by Pageaux *et al.* [34] showing how treatment with IFN after transplantation might not be so risky as initially shown, although these findings should be corroborated in future research. On the other hand, Ribavirin and Amantadine monotherapies after transplantation have no apparent impact on HCV viraemia or liver histology [32].

Therefore, the best strategy is to treat HCV infection in patients on dialysis before transplantation [2,3,6,7,35–39].

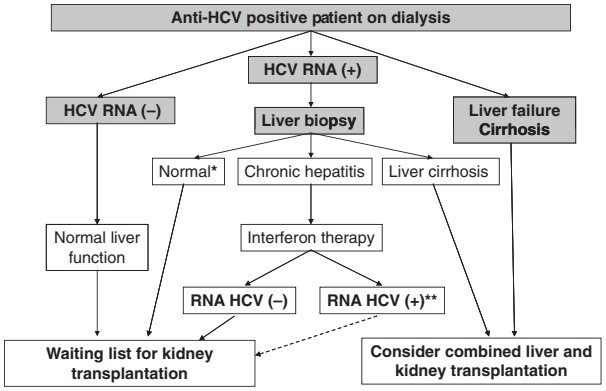

Figure 1 Proposed approach to treat anti-hepatitis C virus -positive patients on dialysis who are candidates for kidney transplantation. *Interferon therapy may be considered to prevent liver disease progression and decrease HCV related morbidity (PTDM, Post-transplant glomerulonephritis) after transplantation. **Interferon non responders patients and those refusing to be treated should be included in the waiting list, because HCV positive kidney transplant patients exhibit a better survival outcome when compared to HCV positive patients remaining in dialysis.

Taking into account the available literature, we suggest a therapeutic schema on the management of HCV infection in dialysis patients who are considered candidates for renal transplantation, which is represented in Fig. 1. In summary, cirrhosis should be ruled out by liver biopsy and if present patients should be considered for combined kidney-liver transplantation. IFN-based therapy should be offered to patients with an active viral infection (HCV RNA positive) and a biopsy-proven chronic hepatitis. However, current knowledge makes it advisable to offer anti-HCV therapy also to those patients with an active viral infection and no related liver disease [6,7]. The reason is that controlling HCV infection before transplantation could prevent liver disease progression [32] and HCV-related morbidity after transplantation such as glomerulonephritis [36] and post-transplant diabetes mellitus [32] although evidence in this regard is still weak. Finally, HCV RNA negative before transplantation seems to relate to a sustained virological response (SVR) in the long run [32], SVR being defined as HCV RNA clearance 6 months after completion of anti-HCV treatment.

This being a recommendation of general nature based on current results with anti-HCV therapy, final decision on whether treatment should be started or not before a patient is placed into the waiting list should be a matter of case-to-case individual assessment [6,7]. Consideration should be given to the cause of end-stage renal disease (glomerulonephritis), the overall clinical situation and vital prognosis of the patient as well as the existence of contraindications to IFN-based therapy. Additionally, full discussion with the patient clearly setting out the potential benefits and the risks associated with the treatment is mandatory. In this context, there could be a number of patients who will refuse to be treated, in whom physicians will decide treatment is not the preferred option or who will not achieve a SVR after therapy. Also, even treatment with IFN might not be affordable in some geographical settings with restricted resources, which are usually the ones with a higher prevalence and incidence of HCV infection. All these patients should be placed in the waiting list even in this situation, because their expectancy of life is better than that of HCV-infected patients who remain under dialysis [10,40–42].

The best therapeutic anti-HCV strategy before transplantation is still to be defined [43]. Long experience with standard-IFN therapy in patients under dialysis [44] now has to yield place to newer therapies as shown by recent results provided by dedicated centres with pegylated-IFN, whether combined with Ribavirin or not. In a controlled trial, Liu demonstrated the superior efficacy and safety profile of pegylated–IFN (135 μg/week) as compared with standard-IFN (3 million units three times a week) on dialysis-treated patients [45]. By using multivariate analysis, treatment with pegylated-IFN was independently predictive of SVR. Combined therapy with pegylated-IFN 135 μg/week and Ribavirin 200 mg/day, subsequent dose of the latter tailored according to plasma concentrations, showed impressive results in a recent study: 15 out of 16 patients infected by genotype 1 and 19 out of 19 infected with a different genotype achieved SVR [46]. However, tolerability was a matter of concern, 74% of the patients developing severe anaemia. Despite the case made out in the recent publications, the longer experience and better quality of published studies concerning standard-IFN in patients under dialysis therapy, makes standard IFN still the recommended option [6,7]. Concomitant use of ribavirin in these patients should be considered with caution because it induces haemolytic anaemia [30]. The treatment would consist of standard-IFN, 3 million units three times a week for 48 weeks for genotypes 1 and 4, and 24 weeks for genotypes 2 and 3. It is also recommended to determine whether an early response has been achieved at 12 weeks for deciding whether treatment is continued for 24 or even 48 weeks [6]. This treatment achieves SVR in around 40% of treated patients [30,44]. Interestingly, the early response to standard-IFN is a good predictor for a long-term SVR [30]. During this treatment, these patients should be 'on hold', out of the waiting list for transplantation.

Complications of HCV infection after renal transplantation

Among the most important complications induced by HCV infection after kidney transplantation are

glomerulonephritis and post-transplant diabetes mellitus (PTDM) [2]. HCV infection can also influence acute rejection, can clearly increase the incidence of infections and finally it can facilitate the presence of some types of extrahepatic neoplasia [47–49]. In this context, we could anticipate that these complications might constitute a direct or indirect explanation for the diminished graft and patient survival observed among HCV-infected kidney transplant patients.

Renal disease induced by HCV infection

HCV infection has been related to different extrahepatic problems, including haematological, dermatological, autoimmune and nephrological disorders [1–7]. Glomerular lesions have been described in native and transplanted kidneys of HCV-infected patients [50–57]. The most frequent glomerular lesions observed in HCV-positive kidney transplant patients are cryoglobulinaemic or noncryoglobulinaemic membranoproliferative glomerulonephritis (MPGN) [54,55] and membranous glomerulonephritis (MGN) [56]. Transplant glomerulopathy [2], anticardiolipin-related thrombotic microangiopathy [58] and fibrillary glomerulonephritis [59] have also been described. In fact, HCV infection is considered as a predictor for the development of proteinuria in kidney transplantation [60]. The most frequent clinical picture is MPGN, usually recurring after a second or a third kidney transplant, and the second in frequency is MGN. Notably, HCV-associated renal disease does not correlate with the severity of liver disease [51].

The pathogenesis of MPGN and MGN seems to be based on the deposition of immune complexes containing viral RNA in the glomerulus, paradoxically happening in immunocompromised patients [2,61]. Viral antigens have been detected by immunohistochemistry [62] and by *in situ* hybridization [63]. It has been also reported that laser capture microdissection is a useful method for measuring HCV RNA genomic sequences and HCV core protein in kidney structures such as glomeruli and tubules in patients with HCV-related glomerulonephritis [64]. Recently, a role in the pathogenesis of HCV-associated glomerulonephritis has been suggested for Toll-like receptors (TLRs), proteins expressed on immune and nonimmune cells as important components of the innate immunity. Wornle *et al.* [65] recently found that Toll-like receptor 3 (TLR3) mRNA expression was clearly elevated in mesangial cells in HCV-related glomerulonephritis and was associated with enhanced proinflammatory cytokines. They hypothesized that immune complexes containing viral RNA activate mesangial TLR3 during HCV infection inducing chemokine/cytokine release and effecting proliferation and apoptosis. This finding suggests a novel role of TLR3 in HCV-related glomerulonephritis that could establish a link between viral infections and glomerulonephritis.

Because IFN is generally not recommended in kidney transplant patients, there is no specific therapy for the treatment of HCV-related glomerular lesions after renal transplantation. Rituximab, an anti-CD20 antibody that selectively targets B cells has been effective in some cases of HCV-related post-transplant cryoglobulinaemic MPGN, but its definite role in this entity still remains to be determined [61,66–68]. In fact, severe infections associated with rituximab therapy have been reported [68].

The policy of our unit regarding HCV-associated glomerular lesions depends on the clinical presentation; if an abrupt clinical picture with nephrotic syndrome starts, with or without renal insufficiency, steroid boluses are applied. In case of developing non-nephrotic or nephrotic range proteinuria with preserved renal function, antiproteinuric agents, mainly ACEI and/or ARA II are used [69]. Finally, it has been recently observed that treatment with IFN before transplantation may decrease the incidence of post-transplant HCV-related glomerulonephritis [36].

Post-transplant diabetes mellitus

HCV infection seems to be related to a higher incidence of diabetes mellitus [2]. This observation applies to non-transplanted HCV-positive patients, to liver transplant patients whose cause of end-stage liver disease has been HCV infection itself and finally to HCV-infected kidney transplant patients [2]. In liver transplantation, insulin resistance is associated with HCV infection and plays a role in the progression of HCV-related liver disease and fibrosis [70]. In a recent meta-analysis of 13 observational studies including 30 099 renal transplant patients, Fabrizi *et al.* [71] observed a marked increase of the risk of PTDM in HCV-positive patients. They suggested that the excess risk of death in these patients might be at least partially attributed to PTDM. The administration of tacrolimus in HCV-infected kidney transplant patients has been described to increase the incidence of PTDM even more [71,72]. This post-transplant complication may be one of the factors explaining a decreased patient and graft survival among HCV-positive kidney transplant patients, as PTDM has been described as an independent risk factor for graft loss and patient death. In fact, it appears that HCV-positive patients with PTDM have a higher risk of mortality than non diabetic HCV-positive patients [6].

The mechanisms explaining the relationship between HCV infection and diabetes mellitus are likely to involve insulin resistance caused by inhibitory actions of the virus on insulin regulatory pathways in the liver [72]. Besides, regarding HCV infection and tacrolimus use, a pharmacokinetic explanation may be considered. Tacrolimus

pharmacokinetics is affected by HCV infection; in fact, HCV replication seems to slow down the tacrolimus metabolism [73,74]. Therefore, the use of a similar initial dose of tacrolimus in HCV-positive and -negative kidney transplant patients does probably induce an overexposure in the formers to tacrolimus, at least in the first days after transplantation. This overexposure could explain a higher frequency of PTDM in HCV-positive kidney transplant patients treated with tacrolimus. The practical attitude would be to avoid the use of tacrolimus in HCV-positive kidney transplant patients, to use lower initial doses of this calcineurin inhibitor or to apply steroid-sparing immunosuppressive strategies. In other words, the use of immunosupressive drugs that are clearly associated with PTDM should be balanced to optimize anti-rejection efficacy, while minimizing the risk of hyperglycaemia, as 2008 KDIGO guidelines recommended [6].

An early detection of PTDM in HCV-positive renal transplant patients is desirable to initiate therapy. The diagnosis of hyperglycaemia should be according to current ADA criteria (fasting blood glucose >125 mg/100 ml on two separate measures) [6]. Finally, patients with PTDM should be referred to a diabetologist [6].

Acute rejection

It is still a controversial issue whether HCV infection decreases or whether, on the contrary, enhances the risk of acute rejection. We described that HCV induces a state of immunodeficiency, based on a reduction in the rate of naive T-helper lymphocytes and an alteration in the proliferative responses to mitogens of T lymphocytes [75]. These alterations should relate to a decreased incidence of acute rejection, which in fact has been described by some groups [1–3].

On the contrary, other series found a similar [8,60] or even a higher incidence of acute rejection in HCV-positive patients [76]. Of note, the same conditions that related to the HCV infection are also the ones determining a higher risk for acute rejection. This means that a longer history of renal disease, previous transplants and blood transfusions are all risk factors for HCV infection in kidney transplant patients. Besides, these situations determine a higher immunological risk. This could be the reason why, despite a virus-related immunodeficiency, HCV-positive kidney transplant patients may exhibit a higher than expected risk of acute rejection in some series. As an example, Forman *et al.* [76] observed a higher incidence of antibody-mediated acute rejection in HCV-positive patients in a series of 354 kidney transplant patients. When adjusted for a PRA >20%, the Cox regression analysis did not identify HCV infection as an independent risk factor for the development of antibody-mediated acute rejection.

Because of the previous statements, one may wonder whether immunological damage of the graft in HCV-positive patients related to the coexistence of immunological high risk may be the reason why death-censored graft survival has been described to be lower in HCV-positive kidney transplant patients. As previously said, there are conflicting data regarding the incidence of acute rejection between HCV-positive and HCV-negative kidney transplant patients. However, information is lacking with regard to the incidence of subclinical acute rejection in these patients. In a recently published Spanish series of 435 kidney transplant patients with a protocol biopsy performed in the first 6 months after transplantation, it was described that subclinical acute rejection with chronic allograft nephropathy and hepatitis C infection were both independent risk factors for graft loss [77]. Therefore, we could conclude that the immunological damage of the graft does not explain on its own the higher incidence of graft loss in HCV-positive kidney transplant patients.

Infection

The immunocompromised status of the HCV-infected kidney transplant patient is also evident in some of the series, which identify infection as one of the main causes of death in HCV-positive kidney transplant patients in comparison with HCV-negative ones [11–13]. In fact, in the past it was reported that patients with non-A non-B hepatitis had 'a marked increase of life-threatening extrahepatic complications' [9]. This finding has been demonstrated in HCV-positive patients who had more frequent postoperative infections and potentially fatal infections of the central nervous system, lungs and blood stream (such as cytomegalovirus infection, tuberculosis, sepsis). Infections are enhanced by heavy immunosuppression [9,78,79]. In this way, our group recently reported that HCV infection is the most important risk factor for the development of tuberculosis in renal transplant patients [80]. Therefore a careful immunosuppressive regimen should be selected in these patients. Aggressive immunosupression as a routine should be avoided in HCV-positive patients, if possible. Unfortunately, the frequent condition of high immunological risk of the HCV-positive patient makes it difficult to find the ideal immunosuppressive strategy for these patients.

HCV infection and post-transplant extrahepatic neoplasia

The occurrence of post-transplant proliferative disorders (PTLD) after organ transplantation has been recently associated with HCV infection together with well known risk factors such as Epstein-Barr virus, induction immunosuppression and anti-rejection therapy. In a study from Italy, including 1101 liver-, heart- and renal transplant patients, the overall prevalence of PTLD was 1.4% (0.8%

in renal transplant patients) and significantly higher in HCV-positive (3.6%) than in HCV-negative patients (1.2%) [47]. In the French Registry of PTLD occurring after renal transplantation, HCV infection was a risk factor for mortality, among others [48]. In a single-centre experience from Taiwan, PTLD was the second cause of post-transplant neoplasia and it was observed in three out of four HCV-positive recipients [81]. In the American Registry including 66 169 recipients, 160 (0.24%) developed multiple myeloma and the incidence of HCV infection was higher in patients with myeloma, suggesting a possible association between HCV infection and myeloma for the first time [49]. Although these preliminary data should be corroborated with new studies, they suggest that HCV infection could play a role in the pathogenesis of PTLD and haematological neoplasias. Therefore this important topic deserves further investigation.

The impact of HCV infection in graft and patient survival after kidney transplantation

It has been documented that the survival of HCV-positive patients after renal transplantation is significantly better than that of matched patients who remain in the waiting list [10,40,41]. Therefore, it is not only clear that HCV infection is not a contraindication for renal transplantation, but that renal transplantation is the best therapy for patients with HCV infection and end-stage renal disease [1–7,41]. However, HCV-positive patients after renal transplantation have a lower patient and graft survival compared with HCV-negative patients [5–13,15,81,82].

Influence of HCV infection on patient survival

Several studies demonstrated that patients with HCV infection after renal transplantation exhibited a similar survival in the short term as compared to noninfected renal transplant patients [83–87]. However, in the long term, the situation is different in most of the series, showing that HCV-positive patients have a significantly lower survival than HCV-negative patients [3,11–13,15,81,83]. The experience of Hospital Necker is very illustrative: HCV did not adversely affect 5-year survival [86] but, after a longer follow up, survival was clearly lower [11]. As an example, Mathurin *et al.* [12] published in a case control study that 216 HCV-positive recipients matched with 216 control subjects that 10-year patient survival was significantly lower in HCV-positive patients: 65.5% vs. 85.3% ($P < 0.001$). In the multivariate analysis, HCV, biopsy-proven cirrhosis, age and year of transplantation were independent risk factors for 10-year survival in renal transplant patients. Twenty-one percent of deaths were caused by liver disease in HCV-positive patients. Interestingly, in patients with liver biopsies, patient survival in those with cirrhosis was not different at 5 years, but definitively lower at 10 years, when compared with patients with little fibrosis (85% vs. 77% and 26% vs. 62%, $P < 0.05$ respectively). In a multicentre study conducted in Spain including 488 HCV-positive from a total population of 3,365 patients transplanted between 1990 and 1998, we also found that HCV infection was an independent risk factor for patient death and the proportion of deaths caused by liver disease was higher than that in HCV-negative patients (13.85% vs. 0.6%; $P = 0.03$) [8]. In spite of this, 10-year patient survival was 77.5% vs. 84.5% in HCV-positive versus. HCV-negative patients, including only functioning grafts after 1 year. This survival figure is acceptable, taking into account that these HCV-positive patients are high risk patients. In fact, the mortality rate progressively increased; it was 10% at 10 years and 20% at 20 years [10].

In a meta-analysis of observational studies recently reported including 6,345 patients, the increased mortality in the HCV-positive population (RR 1.79; 95% CI 1.57–2.03) has been corroborated [15]. It was at least partially related to an increase in liver-related death and the frequency of cirrhosis and HCC as causes of death was significantly higher in HCV-positive as compared with HCV-negative patients in six out of the eight studies (from USA, France, Spain, Taiwan, Germany and Sweden) included in the analysis. Cardiovascular and infectious diseases were also important causes of death in these HCV-positive patients included in this systematic review. Extrahepatic complications of HCV infection, such as PTDM, can also contribute to mortality. In fact, HCV infection and PTDM are separately considered as independent risk factors for patient death. In this way, a study from USRDS registry showed that the presence of PTDM was associated with lower patient survival in HCV-positive patients [41]. Even in HCV patients in the waiting list for transplantation, diabetes mellitus is more prevalent and is a major factor for mortality [42]. A retrospective study also found that HCV infection in kidney-pancreas transplant patients significantly increased the risk of patient death [88].

As we commented before, a role for heavy immunosuppression, probably increasing HCV viral replication after renal transplantation was also suggested by the observation that quadruple therapy with monoclonal or polyclonal antibodies was associated with more frequent instances of liver disease [1]. However, a recent paper from the USA Registry focussing on the impact of immunosuppressive regimen on survival in HCV-positive renal transplant patients showed that antibody induction did not negatively affect patient survival [22]. Although comparative studies using different immunosuppressive protocols are not available, current information

regarding survival figures, incidence of acute rejection and infectious complications suggest that immunosuppression should be adjusted depending on liver histology [3]. In this way, all conventional current immunosuppressive drugs can be used in HCV-positive patients [6]. It has been described that Cyclosporin inhibits HCV viral replication in cultured hepatocytes [18] and renal transplant patients with HCV infection under Cyclosporin immunosuppression showed stabilization and regression of liver fibrosis in more than 50% of patients [19]. In the American analysis previously mentioned there was no difference between cyclosporine and tacrolimus [22]. However, it should be noted again that the risk of PTDM is higher in HCV-positive patients treated with tacrolimus [72]. In this context, whether HCV-infected kidney transplant patients should receive cyclosporine or tacrolimus is a hot topic, although there are no clinical trials underway. Our own policy is to use low-dose tacrolimus combined with MMF, together with an early steroid withdrawal. Notably, Mycophenolate mofetil as part of maintenance immunosuppressive regimen was associated with better patient survival [22]. The influence of m-TOR inhibitors (sirolimus and everolimus) on patient survival after renal transplantation is unknown.

Influence of HCV infection on graft survival

As in the case of patient survival, HCV infection did not influence graft survival in the short term [83–87]. However, in most of the recent studies with longer follow up, patients with HCV infection exhibited lower graft survival compared with HCV-negative patients [8,11–13,15,81–83]. In the Spanish study previously mentioned, as an example, 10-year death-censored graft survival was 69% in HCV-positive patients, significantly lower compared with HCV-negative patients 79% ($P < 0.0001$) including only functioning grafts after 1 year [8]. Although the lower graft survival may reflect lower patient survival in some reports [3], in several but not in all series HCV infection was an independent risk factor for graft loss [7,9,12,13,15,79,81–84]. In fact, in the meta-analysis above mentioned including 6345 patients, the presence of anti-HCV-positive antibodies was an independent and significant factor for graft failure (RR 1.56, 95% CI 1.35–1.80 $P = 0.019$) in four of the eight studies included in the analysis. It is important to note that these four significant studies included the majority of the patients used for this meta-analysis, which amounts to 4613 (73%) patients [15].

Several problems associated with HCV infection can contribute to a decreased death-censored graft survival after renal transplantation, such as the development of proteinuria because of chronic allograft nephropathy and/or HCV-associated glomerulonephritis and PTDM.

As previously mentioned, HCV infection is an independent risk factor for proteinuria after transplantation. Hestin *et al.* [60] reported that persistent proteinuria developed more frequently in HCV-positive than in HCV-negative patients. At 1 year, the probability of proteinuria was 19.5% in the HCV-positive and 7.5% in HCV-negative patients. At 3 years, proteinuria was 22.9% vs. 10.7% and at 5 years was 45.1% and 13.1% respectively. However, there was no difference in graft and patient survival at 5 years between the two groups. The histopathological study in patients with proteinuria (unfortunately few patients) demonstrated a nonsignificantly higher frequency of *de novo* glomerular lesions in HCV-positive patients. Notably, chronic rejection was the most frequent lesion in both groups, showing that nearly half of HCV-positive patients had transplant glomerulopathy. Although other experiences have found a similar incidence of transplant glomerulopathy among HCV-positive versus HCV-negative patients [57], other authors have suggested a possible association between HCV infection and transplant glomerulopathy [89,90]. In fact, Cosio *et al.* [89] found that compared with a group of 105 patients without transplant glomerulopathy, the prevalence of HCV antibodies was significantly higher in patients with chronic transplant glomerulopathy (1.9% vs. 33% respectively, $P = 0.0004$). These authors postulated that HCV, directly or indirectly, or by inducing the release of cytokines, such as interferon, may produce endothelial cell lesion leading to transplant glomerulopathy. Mahmoud *et al.* [91] also found a higher incidence of proteinuria and chronic rejection in a series of HCV positive with HCV RNA in the serum and Bruchfeld *et al.* [92] published that HCV infection was more important for graft loss than time on renal-replacement therapy.

Our experience is Spain is very illustrative: we studied the characteristics of 3365 renal transplants during the 1990s and risk factors associated with death-censored graft failure. Despite worsening of surrogate parameters of renal quality (donor age significantly increased) and poorer HLA-matching (HLA mismatches significantly increased), graft survival improved during this decade. Acute rejection decreased (from 39% to 25%; $P < 0.0001$) and the prevalence of HCV infection decreased from 29% to 10%; $P < 0.0001$) [93]. These two major time-dependent modifications may be related to this improvement: a reduction in the prevalence of acute rejection and a dramatic reduction in the prevalence of HCV-positive patients [93]. Both significantly contributed to counterbalance the detrimental effect of decreasing renal allograft quality and worsening of some recipient-dependent factors. The presence of HCV infection was an independent risk factor for graft loss and the follow-up data revealed a steady increase of serum creatinine between 3 months

and 1 year, an increase of proteinuria between 3 months and 1 year and the 1-year proteinuria was also higher in patients with HCV infection [8]. As described in other studies, chronic rejection was the most frequent cause of graft loss [83]. Therefore, HCV infection seems to be associated with greater rates of proteinuria, chronic rejection and graft loss. In fact, as we commented before, in a study with protocol biopsies at 6 months, subclinical acute rejection with chronic allograft nephropathy and HCV infection were both independent risk factors for graft loss [77]. Notably, in a recent study pretransplant IFN therapy in 50 HCV-positive patients significantly decreased the incidence of chronic allograft nephropathy; in other words absence of IFN therapy before transplantation was a significant risk factor for chronic allograft nephropathy [91].

The presence of post-transplant cryoglobulinaemic or noncryoglobulinaemic MPGN and MGN associated with HCV infection contribute to the development of graft failure [54–56]. Concerning type I MPGN, it has been reported to result in accelerated loss of the graft [54,55]. In MGN, the clinical course and the development of renal failure seem to be similar in patients with and without HCV infection [53]. The exact role of these glomerular lesions on graft loss is unknown because there are no prospective data focussing on this problem and the policy of graft biopsies is not uniform. However, retrospective data suggested that the prevalence of these glomerular lesions associated with HCV infection is, in our experience, around 6% (data not shown). An early diagnosis and therapy with steroids and/or ACEI/ARB may be beneficial. Results with IFN before transplantation to maintain HCV RNA negative after transplantation and to decrease the incidence of post-transplant glomerulonephritis are encouraging [36].

In renal transplant patients, the complications of PTDM on morbidity, mortality and graft survival are well established [41,94,95]. As previously said, there is clear evidence that HCV infection increases the incidence of PTDM [71]. Also, many studies have demonstrated separately that HCV infection and PTDM are independent risk factors, not only for patient death but for death-censored graft loss [41,94,95]. Therefore, it seems logical to think that both entities together can contribute to decrease graft survival after renal transplantation. Concerning tacrolimus therapy in these HCV-positive patients it is important to remark that although tacrolimus increases PTDM [72], it also has a protective effect on death-censored graft survival and patient survival [94]. Early detection and therapy of PTDM together with the use of an immunosuppressive regimen to minimize the risk of hyperglycaemia and to optimize anti-rejection efficacy in HCV-positive patients could be important to

Table 2. Main short-term results of center-based experiences with the transplantation of kidneys from Anti-HCV-positive donors (HCVD+) into Anti-HCV-positive recipients (HCVR+).

	Morales *et al.* [106]		Ali *et al.* [107]		Mandal *et al.* [108]		Woodside *et al.* [109]		Veroux *et al.* [111]	
	HCVD+/R+	HCVD−/R+	HCVD+/R+	HCVD−/R+	HCVD+/R+	HCVD−/R+	HCVD+/R+	HCVD−/R+	HCVD+/R+	HCVD−/R+
N	24	40	28	16	19	10	20	20	28	16
Follow up (months), [mean (SD)]	26 (8)	30 (10)	36 (range: 12–60)		15.4 (2)		Median 26.3	Median: 34.9	Median: 23 (range: 4–46)	
Acute rejection			50%	68%	42%	50%	20%	25%	10%	14.2%
Graft survival	96%	93%	86%		89%	70%	89% (1st year)	79% (1st year)	90%	88%
Patient survival	100%	98%	86%		89%	90%	89% (1st year)	94% (1st year)	100%	94%
Acute Liver Dysfunction			16%‡		16%¶	10%¶	–	–	–	–
Chronic Liver Dysfunction	8.3%†	7.5%†	9%§		11%**	10%**	–	–	–	–
Time on the waiting list (months) [mean (SD)]	–	–	–	–	9 (3)*	29 (3)*	9.9 (1.8)*	17.8 (3.3)*	9	24

*$P < 0.05$
†Level of ALT above 2.5 times the upper normal limit during more than 6 consecutive months.
‡Level of ALT above two times the upper normal limit during more than 2 weeks, but less than 6 consecutive months.
§Level of ALT above two times the upper normal limit during more than 6 consecutive months.
¶Level of ALT above two times the upper normal limit.
**Level of ALT above two times the upper normal limit during more than 3 months.

decrease graft loss [6,7,96]. Notably, pretransplant IFN therapy in HCV-positive patients may also decrease the incidence of PTDM [97].

Renal transplantation using kidneys from anti-Hepatitis C virus antibodies positive donors

Soon after the description of HCV [98], several series acknowledged that the infection was transmitted through organ transplantation [99–105]. For this reason, organ procurement organizations and international guidelines have strongly recommended that all organ donors should be tested for HCV infection [6,7]. There is also an almost universal consensus that kidneys from donors with a positive serology for HCV (HCVD+) should not be used into Anti-HCV-negative recipients (HCVR−) [106]. However, the use of kidneys from these donors into HCVR+ is still a matter of debate [3]. Several centre-based experiences have shown the safety and efficacy of this approach in the short term (Table 2) [106–111]. On the contrary,

Table 3. Recommended measures to miminize hepatitis C virus (HCV)-related complication after kidney transplantation.

Measures while patient is on waiting list
Isolate HCV-positive patients is not recommended as an alternative to strict infection-control procedures for preventing transmission of HCV [6]
Treat with alpha-interferon (IFN) monotherapy if chronic hepatitis is documented by biopsy in HCV RNA-positive patients [6,7,116]
Treatment with alpha-IFN monotherapy of HCV RNA-positive patients without chronic hepatitis to decrease post-transplant morbidity-associated with HCV infection (glomeruonephritis, diabetes) should be discussed [6,7,116]
Treatment with Pegylated-IFN with or without Ribavirin to be considered in dedicated and experienced centres [6,7,116]
Measures in the perioperative period of transplantation
Avoid blood transfusions, if possible
Do not transplant kidneys from HCV-positive donors into HCV-negative recipients
Measures after transplantation
'HCV-positive patients must be followed carefully to detect deterioration of liver function, infectious diseases, proteinuria, diabetes or neoplasia' [6]
Immunosuppression
Use a nonaggressive immunosuppressive protocol: no routine use of ATG, ALG or OKT3, except in immunologically high-risk patients
Immunosuppression in the maintenance phase depending on the severity of liver disease
All immunosuppressive drugs can be used in HCV-positive patients
Selected immunosuppressive regimen should be targeted to optimize anti-rejection efficacy, while minimizing the risk of post-transplant diabetes mellitus (PTDM) In immunologically high-risk patients, tacrolimus and MMF should be useful. However in other patients, cyclosporine and MMF or low doses of tacrolimus and MMF without steroids could be useful
Liver disease
At each visit, liver enzymes, bilirubin and prothrombin time should be measured. Antibodies anti-HCV and HCV RNA should be tested at least twice a year
Liver biopsy should be considered in patients with abnormal liver function (diagnosis, prognosis, modulation of immunosuppression, possible treatment)
Extremely important: if HCV-positive patients present severe cholestasis, liver biopsy should be performed immediately. If fibrosing cholestatic hepatitis is present, IFN therapy should be considered on a case-by-case basis
In patients with cirrhosis, ultrasonography and alpha-fetoprotein levels should be monitored frequently to early detect hepatocellular carcinoma
The use of Fibroscan to monitor liver fibrosis could be useful
In patients with end stage liver failure, liver transplantation should be considered
Avoid alcohol and potentially hepatotoxic drugs
Infections
Be on the alert for severe infections, such as tuberculosis, and opportunistic infections
In case of fever, start effective antibiotic treatment
HCV-related glomerulonephitis
Be on the alert for proteinuria and/or microhaematuria
In patients with proteinuria/ microscopic haematuria, a graft biopsy should be performed
In the case of HCV-related glomerulonephritis, anti-proteinuric drugs should be started
HCV-related post-transplant diabetes
Be on the alert for hyperglycaemia
Patients with hyperglycaemia should be referred to a diabetologist
HCV-related extrahepatic neoplasia
Be on the alert for post-transplant lymphoproliferative disease
Be on the alert for haematological neoplasia
Patients with neoplasia should be referred to an oncologist

data from the USRDS showed that recipients of kidneys from HCVD+ exhibited a significantly worse survival than those transplanted from HCVD−, regardless of HCV serology of the recipients [112]. A higher incidence of PTDM in the former group was considered a possible reason to justify this different outcome [113]. However, the authors still considered that the approach was appropriate as outcome after renal transplantation for patients with a positive serology for HCV was better than remaining in the waiting list [41].

In Spain, two units have been applying the policy of transplanting kidneys from HCVD+ into HCVR+ since March 1990 [106,114]. The policy was subsequently modified in 1993, by restricting the use of these kidneys to recipients with a positive HCV RNA before transplantation in order to increase the safety of this strategy [106]. In our experience, with a close follow-up care, mid-term outcome of these patients was similar to that of HCVR+ transplanted from HCVD−, in terms of patient and graft survival and clinical evolution of HCV-related liver disease [115]. Hence, we consider this is a safe strategy in order to face organ shortage for transplantation in a better manner, although long-term assessment of this policy is still needed [6,7,115]. In order to avoid the phenomenon of superinfection [116], matching donors and recipients according to their genotype should be recommended, although it is obviously limited by time constraints.

Conclusions

Hepatitis C virus infection is the most frequent cause of liver disease after renal transplantation. Although in the short term clinical course is irrelevant, HCV infection in the long term can lead to severe liver complications such as cirrhosis, hepatocellular carcinoma and death. Because Interferon is contraindicated after renal transplantation, treatment before transplantation with interferon monotherapy is recommended. Most of the patients with sustained virological response remain HCV RNA negative after transplantation and HCV-related post-transplant morbidity decreases. However HCV-positive patients without response or who refused Interferon therapy should also be transplanted because survival after transplantation is better than dialysis. HCV renal transplant patients have a higher risk for developing proteinuria, chronic rejection, infection and PTDM. Long-term patient and graft survival rates are lower in HCV-positive compared with HCV-negative patients. Mortality is higher because of liver disease and infections. Remarkably, HCV infection is an independent risk factor for graft loss and seems to be associated with greater rates of proteinuria and chronic rejection. The presence of PTDM and HCV-related glomerulonephritis can contribute to graft failure. Despite this, renal transplantation is the best option for the HCV-positive patient with end-stage renal disease. To minimize the consequences of HCV infection after renal transplantation several measures should be recommended (see Table 3): adjustment of immunosuppressive therapy and careful follow up for early detection of proteinuria, infection, diabetes or worsening of liver disease are mandatory.

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