

Review Article

Hepatitis C and Kidney Transplantation

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Hepatitis C virus (HCV) infection is relatively common among patients with end-stage kidney disease (ESKD) on dialysis and kidney transplant recipients. HCV infection in hemodialysis patients is associated with an increased mortality due to liver cirrhosis and hepatocellular carcinoma. The severity of hepatitis C-related liver disease in kidney transplant candidates may predict patient and graft survival after transplant. Liver biopsy remains the gold standard in the assessment of liver fibrosis in this setting. Kidney transplantation, not haemodialysis, seems to be the best treatment for HCV+ve patients with ESKD. Transplantation of kidneys from HCV+ve donors restricted to HCV+ve recipients is safe and associated with a reduction in the waiting time. Simultaneous kidney/liver transplantation (SKL) should be considered for kidney transplant candidates with HCV-related decompensated cirrhosis. Treatment of HCV is more complex in hemodialysis patients, whereas treatment of HCV recurrence in SLK recipients appears effective and safe.

1. Introduction

Hepatitis C is one of the commonest chronic viral infections world-wide and has major healthcare and health economic implications [1] (Figure 1). However, with recent advances in treatment, clearance of the virus is achieved in selected cases and a reduction in the rate of progression of liver disease and its complications occurs in others. Kidney disease is a major public health problem; over 10% of the adult population has chronic kidney disease (CKD) [2], and up to 350 pmp/yr of the adult population develop ESKD and require treatment with renal replacement therapy (RRT) by dialysis or transplantation. The prevalence of HCV infection in people with ESKD is very high, and when present has implications both for dialysis patients and for kidney transplant (KT) recipients [3, 4].

HCV infection is challenging both in dialysis patients and KT recipients, but there are differences between these two groups in terms of the effect of HCV infection on long-term survival, the natural history of the disease, and differential benefits and risks associated with available treatments both of the HCV and the renal failure. As kidney transplantation is the treatment of choice for many people with ESKD,

the clinical assessment and the management of HCV infection are important clinical considerations in this setting.

In this paper, we report the current status of HCV infection and kidney transplantation. After a brief presentation of the natural history of hepatitis C virus infection in immunocompetent host, we assess: (i) HCV infection in end-stage kidney disease (ii) the impact of HCV on clinical outcomes (iii) the assessment of the disease and (iv) the disease management of HCV+ve kidney transplant recipients.

2. Natural History of Hepatitis C Virus (HCV) Infection

The worldwide burden of chronic hepatitis C (CHC) infection is enormous. In 1999, the World Health Organization estimated that the worldwide prevalence of CHC ranges from 0.1% to more than 12%. This equates to approximately 170 million chronic carriers worldwide with an incidence of 3 to 4 million new cases annually [6].

After initial exposure, HCV RNA can be detected in blood within 1 to 3 weeks. Acute infection is usually asymptomatic; it can be severe but rarely fulminant. In general, 60 to 85% of

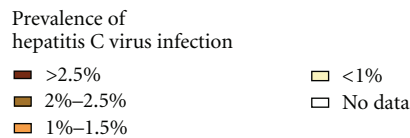
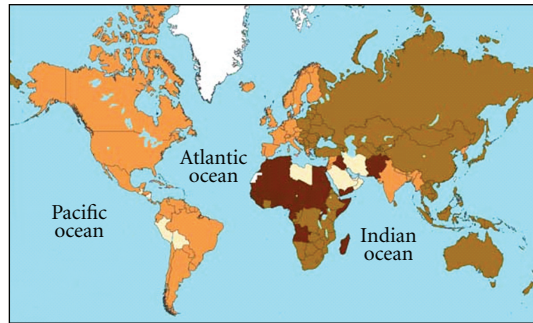


FIGURE 1: Prevalence of Hepatitis C Infection. Data source: World Health Organization. (Modified from [5].)

HCV-infected persons develop chronic infection, defined as the continued presence of HCV RNA for 6 months or longer after the estimated onset [7].

The spectrum of the disease ranges from mild to severe chronic hepatitis, cirrhosis, and hepatocellular carcinoma. The disease is complex, and predictions about long-term prognosis for individual patients remain difficult. Hepatitis C can be extremely slow to progress and usually does so without liver-specific symptoms or physical signs during the first decade of infection. Estimates of the proportion of chronically infected persons who develop cirrhosis 20 years after initial infection vary from 10 to 15% [7]. When liver cirrhosis is established, the transition to decompensated cirrhosis occurs when complications secondary to liver failure arise, such as jaundice, variceal hemorrhage, ascites, and encephalopathy. Decompensated cirrhosis is associated with increased risk of mortality and necessitates liver transplantation.

Identifying the group of patients at greatest risk of fibrosis progression remains a primary challenge for clinicians. Older age at time of infection, duration of infection, degree of liver inflammation at first biopsy, and cofactors such as alcohol abuse and coinfection with human immunodeficiency virus (HIV) or hepatitis B virus (HBV) all appear to be predictors of a poorer prognosis.

The most reliable tools for examining the natural history of hepatitis C are those which examine a change in the histopathological status. Although this necessitates repeated liver biopsies, it does enable the physician, within the space of a few years, to examine possible disease progression or lack of it. The typical histological features of chronic hepatitis C are variable degrees of hepatocellular necrosis and inflammation, referred to as the activity or grade of disease, and fibrosis, referred to as stage of disease.

While the activity of the liver disease can fluctuate, fibrosis is believed to be progressive and largely irreversible. Importantly, it is the progression of fibrosis that ultimately

leads to architectural distortion of the liver and cirrhosis. For these reasons, the rate of progression of fibrosis is the defining feature of the natural history of chronic hepatitis C.

Several systems for scoring liver fibrosis have been proposed, each based on visual assessment of collagen staining of liver biopsy samples, and the more frequently used systems are the histology activity index (HAI: Knodell score) [8, 9] and the Metavir system [10].

In 2001, Poynard reported that the median estimated duration of infection for progression to cirrhosis was 30 years, ranging from 13 years in men who drank and were infected after the age of 40 to 42 years in women who did not drink alcohol and were infected before the age of 40 [11]. This average rate of progression of fibrosis is consistent with those reported in more recent studies [12–14]. It should be highlighted, however, that these studies were performed in referral centers, and the patients who were studied may not have been representative of the average patient with chronic hepatitis C.

3. HCV Infection in End-Stage Kidney Disease (ESKD): Prevalence and Impact on Survival

Hepatitis C virus (HCV) infection is very common in patients with ESKD [15]. The reported prevalence in hemodialysis (HD) patients is variable, but is considerably greater than in the general population. There are some indications that the overall prevalence of HCV infection in dialysis patients is falling, as reported by data from the USA, Western Europe, and Australia and New Zealand [3, 16–19].

Information on the incidence and prevalence of HCV infection in patients on long-term dialysis in developing countries is limited, but single-center surveys show that these rates are high [20–22]. This probably reflects nosocomial transmission of HCV in the HD environment, incomplete anti-HCV screening of blood and blood products, and a higher prevalence of HCV in the general population in developing countries.

Irrespective of the baseline prevalence in the general population, the key underlying determinants of an increased relative risk of HCV infection in dialysis patients are age, overall exposure to blood products, and the duration of dialysis treatment [15–17]. Therefore, the widespread use of erythropoiesis-stimulating agents (ESAs) with a consequent decrease in blood transfusions and progressive improvements in infection control on dialysis units are likely major contributors to a decreasing prevalence of HCV infections in HD patients in the developed world.

In those patients who undergo renal transplantation, in developed countries, the reported prevalence of HCV infection is usually higher than that seen in HD patients, ranging from 11% to 49% [23–30].

Where there are differences reported in HCV infection prevalence between dialysis patients and KT recipients, the reasons may include the length of time on dialysis before transplantation, the duration of the dialysis that the transplant recipient received, and a history of and/or the number of blood transfusions. As transplant recipients usually

TABLE 1: Summary Estimates for Adjusted Relative Risk of Mortality among HCV+ve Dialysis Patients.

	Cohort Size	RR	P-value
Goodkin et al. [4]	16 720	1.17	.016
Fabrizi et al. [31]*	2 341	1.57	—
Fabrizi et al. [33]**	11 589	1.34	—
Scott et al. [3]	23 046	1.25	.04

* Meta-analysis of four clinical trials [34, 35]. A test for homogeneity of the relative risks across the four studies gave a *P*-value of .77.

** Meta-analysis of seven clinical trials [36]. Tests for homogeneity of the aRR across the seven studies gave *R*_i value of 0.48.

RR: relative risk.

survive longer than patients who remain on dialysis, a higher proportion of transplant recipients may have been exposed as a consequence of receiving blood products or dialysis in a period of less rigorous infection control.

HCV infection has been independently associated with an increased mortality in maintenance HD patients. The DOPPS (Dialysis Outcomes and Practice Patterns) study, conducted over three continents, showed an independent association between positive anti-HCV antibody status and mortality in dialysis patients [4]. These results have been confirmed in other studies [31–33].

Scott et al. (the ANZDATA registry study) [3] reported similar survival at 5 years (48% versus 47%) and 10 years (22% and 20%) for HCVAb+ve and HCVAb–ve patients, however, when the differential age distribution and other patient characteristics were incorporated, the adjusted hazard ratio (aHR) for mortality was increased in the HCVAb+ve population Table 1.

4. Outcome of Renal Transplantation in HCV+ Patients

Kidney transplantation (KT) is associated with improved long-term survival in the ESRD population [37], and whilst there is evidence in some studies of a detrimental impact of HCV infection on the outcome of KT, the survival of HCV infected recipients is excellent when considered against that those of HCV infected patients who remain on dialysis [38, 39].

Initial studies focused on short-term outcomes and showed similar patient and graft survival in HCV+ and HCV– recipients at 5 years [27, 40–42], and a low prevalence of cirrhosis HCV-related even after 10 years post-KT [43]. Similar findings were reported by Einollahi et al. in 2002, who showed no differences in terms of survival between HCV+ve and HCV–ve recipients at 7 years post-KT [44].

These findings could reflect the comparatively short period of followup as well as the low numbers of patients as some studies have indicated that the difference in survival was significant only in the second decade after transplantation [45].

These single studies were pooled by Fabrizi et al. in a meta-analysis [46], which showed that positive anti-HCV antibody status was an independent and significant risk

factor for death and graft failure after renal transplantation; the summary estimate for the relative risk was 1.79 (95% CI, 1.57; 2.03) and 1.56 (95% CI, 1.35; 1.80), respectively (Table 2).

In their recent study, Scott and colleagues [3] evidenced a prevalence of HCV infection among kidney transplant recipients of 1.8%, and found that patient survival among HCVAb+ve and HCVAb–ve groups was 77% versus 90% and 50% versus 79% at 5 and 10 years, respectively, with an adjusted HR for patient death of 2.38 (95%CI, 1.69–3.37). The most common causes of death among the HCVAb+ve kidney recipients were cardiovascular disease (aHR = 2.74), malignancy (aHR = 2.52), and hepatic failure (aHR = 22.1).

Despite the negative impact of HCV infection on long-term survival after KT, three retrospective studies [34, 39, 53] of HCV-infected patients have demonstrated that survival is improved with transplantation compared to the remaining wait-listed on dialysis in HCV-infected patients with kidney failure. There are no published studies demonstrating a worse outcome with transplantation compared to dialysis for these patients. Therefore, it is recommended that HCV infection should not be considered a contraindication to KT [54].

While mortality is the most significant end-point in the natural history of HCV after KT, other outcomes have also been assessed in HCV-infected KT recipients with variable conclusions. In a case-control, retrospective survey, Zylberberg et al. [55] found that the yearly progression rate of hepatic inflammation and fibrosis was significantly higher in the KT recipients as compared with the immunocompetent group. In contrast, Alric et al. [56] found that the progression of liver fibrosis per year was significantly lower for KT recipients than for matched patients with HCV and normal renal function. Reasons for the differences are not clear.

4.1. De Novo Glomerulonephritis and Chronic Allograft Nephropathy after Kidney Transplant in HCV+ve Recipient. In addition to an increased disease burden due to liver disease and an association with all-cause and cardiovascular disease mortality, HCV infection in kidney transplant recipients has been implicated in the pathogenesis of acute glomerulopathy [57], *de novo* immune complex glomerulonephritis in the allograft [58–60], and, in some reports, a higher rate of chronic allograft nephropathy (CAN) [61].

HCV infection is one of the most important factors predisposing to the development of glomerulonephritis (GN) in the native kidney and in the renal allograft [62] and the high prevalence of HCV infection in renal allograft recipients places this group at high risk of immune-mediated glomerular diseases. In *de novo* membranoproliferative glomerulonephritis (MPGN) and *de novo* membranous glomerulopathy (MGN), with or without mixed cryoglobulinemia, are the most most frequent glomerular lesion associated with chronic HCV infection in renal allografts [58, 60, 63].

In 2001, Cruzado et al. [64] reported a prevalence of *de novo* MPGN and MGN in HCV+ve kidney recipients of 45.4% and 18.2%, respectively, versus a lower rate in

TABLE 2: Death rate in HCV+ve versus HCV−ve patients after Kidney Transplantation.

	Year of publication	Followup after KT in months (mean)*	HCV-positive Death	HCV-negative Death	P-value
Pereira et al. [23]	1995	68/70	11/29 (38%)	26/72 (36%)	n.s.
Pereira et al. [47]	1995	68/83	9/22 (41%)	16/78 (20.5%)	n.s.
Legendre et al. [48]	1998	79/81	15/112 (13.4%)	19/387 (5%)	.01
Gentil et al. [49]	1999	62/57	13/85 (15.3%)	11/235 (4.7%)	.003
Lee et al. [50]	2001	72	31/151 (20.5%)	46/326 (14%)	n.s.
Breitenfeldt et al. [51]	2002	110.4	38/130 (29%)	164/797 (20.6%)	.001
Einollahi et al. [44]	2003	n.a.	2/41 (5%)	34/868 (4%)	.74
Bruchfeld et al. [52]	2004	130	29/51 (57%)	170/520 (32.7%)	.001
Scott et al. [3]	2010	62.4	32/140 (23%)	743/7432 (10%)	.0001

* Data are given for anti-HCV+ve/anti-HCV−ve patients when appropriate. n.a.: not available; n.s.: not statistically significant.

HCV−ve recipients of 5.7% and 7.7%, respectively. These data have been confirmed in 2006 by Ozdemir et al. [59] who reported a prevalence of *de novo* GN in HCV-infected recipients of 34%, compared to 6.6% in HCV−ve recipients. In both studies, this higher prevalence of autoimmune GN was associated with a poor graft outcome, even worse than *de novo* GN in HCV−ve.

HCV infection has also been associated with CAN. This was first suggested in 2005 by Mahmoud who reported a higher rate of CAN in patients HCV+ve who had not received interferon therapy before KT, compared with a population of HCV+ve patients who received IFN for the treatment of HCV infection (with a 100% of biochemical response and 55% of clearance of the virus), after controlling for other biases that may contribute to the development of CAN [61]. Recently, the analysis of the ANZDATA has shown an increased rates of graft failure due to chronic allograft nephropathy (aHR = 1.87) in HCV+ve recipients compared to HCV−ve patients [3]; also, the analysis of 4304 renal transplant recipients (with 587 of them HCV+ve) in the period 1990–2002, performed by the Spanish Chronic Allograft Nephropathy Study Group [65], evidenced HCV infection was associated with early greater rates of proteinuria, lower renal function, chronic rejection, *de novo* GN, graft loss, and lower survival, compared with HCV−ve recipients.

The pathogenesis of CAN could be explained by a multitude of alloantigen-dependent and -independent factors which have been extensively reviewed [66–68].

It has been proposed that a higher incidence of acute rejection due to higher viral-induced immune reactivity according to previous studies [27] and a chronic suboptimal immunosuppression might be a possible explanation for the relationship between HCV infection and CAN. However, this association has not been confirmed in other studies [69].

HCV infection has also been associated with the development of early graft dysfunction due to acute glomerular lesions, such as acute transplant glomerulopathy and *de novo* renal thrombotic microangiopathy [57, 70]. Hepatitis C infection has also been linked to an increased incidence of posttransplant diabetes mellitus (PTDM) [71], which

is an important determinant of worse outcome following transplantation.

4.2. HCV Replication and Immunosuppression Regimen after Kidney Transplant. Levels of viremia after transplantation are higher compared to pretransplantation values [72]. The marked increase in serum HCV-RNA levels, which usually develops within the first months after renal and liver transplantation, has been closely associated with the immunosuppressive therapy, and a more aggressive immunosuppression enhances HCV replication [73], although the relationship between posttransplantation viral kinetics and severity of recurrence of HCV remains unclear.

Pelletier in 2000 found no correlation between HCV-RNA blood levels and the intrahepatic viral replication rate in the posttransplant period [74], suggesting that the elevated levels of serum HCV-RNA typically observed post-transplantation are not a result of increased replication but rather of decreased clearance in the setting of immune suppression [75].

Di Martino et al. [76] evidenced a progression to chronic active hepatitis after liver transplantation, despite a reduction in immunosuppression and a decrease of intrahepatic HCV-RNA levels, suggesting an immune-mediated injury behind the liver damage, although there are reports of an association between high levels of viral replication and a rapid progressive histologic course suggesting a cytopathic mechanism of HCV-induced allograft injury [77–80]. High levels of viremia have been described in the setting of fibrosing cholestatic hepatitis (FCH) after liver transplantation [81], suggesting that during the early phase of recurrent hepatitis C or in the setting of this particular syndrome, liver damage may be due to the direct cytopathic effect of HCV. Fibrosing cholestatic hepatitis has been sporadically described in kidney transplant recipients with a severe, and often fatal, course [82–85].

At the present time, there are relatively few studies that examine the impact of immunosuppression on HCV-related outcomes in kidney transplant patients, and it is not clear whether the impact of immunosuppression on outcomes in liver transplant patients with HCV infection can be

extrapolated to HCV-infected kidney transplant recipients. Therefore, all currently available maintenance immunosuppressive therapies can be used in kidney transplant recipients with HCV infection [54].

Cyclosporin, but not tacrolimus may inhibit HCV viral replication, although whether this has any clinical consequences is not validated in kidney transplant patients. However, a recent report of 71 HCV+ve KT recipients [86] showed, during long-term immunosuppression, cyclosporine when compared with tacrolimus, resulted in no significant differences in viral replication and development of liver fibrosis. However, the function of the renal graft was significantly better preserved in patients receiving tacrolimus.

Mycophenolate mofetil (MMF) has shown to have an inhibitory effect on viral replication in the nontransplant setting [87] and there is no convincing evidence of a specific deleterious effect on either graft or patient outcomes in kidney transplant recipients with HCV infection [88, 89].

Among antibody therapies commonly used for induction or for treating acute rejection, unfavorable outcomes have been frequently reported in the literature concerning liver transplant patients with HCV infection. In contrast, recent registry data of 3708 patients from the United States indicate that antibody induction with the use of a biological agent, either depleting (OKT3, ATGAM, or rabbit thymoglobulin) or nondepleting antibodies (IL-2 R blocking antibodies), did not negatively affect patient survival in HCV-infected kidney transplant recipients [90].

Regarding the use of sirolimus in HCV-infected kidney transplant recipients, there are only limited data.

5. Assessment of Liver Fibrosis in HCV+ Renal Transplant Candidates

There is evidence that the severity of hepatitis C-related liver disease may predict worse patient and graft survival [91, 92] after KT. The most accurate method to assess liver inflammation and fibrosis is with liver histology, using the Knodell score [8]. Single-center retrospective cross-sectional studies have reported that up to 25% of HCV-infected patients being evaluated for kidney transplantation have bridging fibrosis or cirrhosis on biopsy [93–98]. Some investigators have suggested that presence of advanced fibrosis (bridging fibrosis or cirrhosis) should preclude kidney transplantation [99, 100]. However, we feel that currently there are insufficient data to support such a recommendation.

Recently, the accuracy of liver biopsy in staging liver disease has been a focus of discussion. Because a biopsy represents 1/50,000 of the liver, the heterogeneity of liver fibrosis in HCV infection and the inadequacy of liver sample size can cause considerable bias in the assessment of liver histology [100–102]. Also, liver biopsy is associated with clinical risks.

Currently, a variety of noninvasive tests may be used to estimate liver fibrosis in HCV patients with normal renal function, using either individual markers (such as procollagen) or a panel of tests, such as the Enhanced Liver Fibrosis (ELF) that includes hyaluronic acid, tissue inhibitor of matrix metalloproteinases-1, aminoterminal propeptide

of procollagen type III (which are involved in the synthesis and degradation of extracellular matrix) [103], and present the advantage of providing frequent fibrosis evaluation. However, few data are available regarding the utility of those tests in ESRD patients with HCV chronic infection (Table 3).

The AST/ALT ratio was studied as a noninvasive marker of liver fibrosis in 49 ESRD patients with HCV infection. Despite the significant differences in AST/ALT ratio found between different fibrosis stages, the usefulness of this index may be limited by the absence of adjusted cutoffs in ESRD patients where lower aminotransferase activity is expected. The lack of association between AST/ALT ratio and the degree of liver fibrosis has been also confirmed in a more recent study [103, 108].

The FibroTest, a composite marker of fibrosis, has been evaluated in both HD patients and KT recipients with HCV infection, but its reliability in this setting is controversial [106, 107].

APRI (AST-to-platelets ration index) with adjusted cutoffs has been proposed as a valid alternative to liver biopsy in a significant proportion of HCV+ HD patients [103, 104] although further large studies are needed to confirm these findings.

Others markers of liver fibrosis have also been evaluated in patients with chronic hepatitis C, including YKL-40 and hyaluronic acid (HA), but the performance of these tests was lower than that observed for others noninvasive markers previously evaluated such as APRI [105].

Transient elastography (TE, FibroScan) is a novel non-invasive technique that has been validated in patients with chronic hepatitis C for the assessment of hepatic fibrosis, by measuring liver stiffness. Although it has not been validated yet in CKD patients with HCV infection, it may represent a new and noninvasive tool to assess the stage of liver disease in this setting.

In conclusion, liver biopsy represents the gold-standard in the assessment of liver fibrosis in HCV+ patients with ESKD and might be considered part of the pretransplant evaluation for HCV+ patients; despite the increased role of noninvasive tests for the evaluation of liver fibrosis in HCV-infected patients with CKD, this requires further study.

5.1. Kidney or Liver and Kidney Transplantation?

Should patients found to have advanced fibrosis or cirrhosis be excluded from kidney transplantation alone? This is a key question as the mortality in HCV+ patients with advanced kidney disease is more commonly related to other comorbidities than liver disease both pre- and posttransplantation [39, 109]. The data in this area are conflicting.

The presence of compensated liver cirrhosis before kidney transplantation has the potential to increase the risk of recipient mortality in terms of operative procedure because of marginal posttransplant reserve and nutritional state, and increased susceptibility to post-transplant infectious and metabolic complications, as well as evolution to decompensated liver disease and the subsequent need for a liver transplant.

TABLE 3: Predictive value of serological markers for advanced liver fibrosis in HCV+ patients with end-stage renal disease.

	Components of the test	Cutoffs	Authors	Sample Size	AUROC	PPV	NPV
APRI	AST-to-Platelets-Ratio	<0.4 = no advanced fibrosis >0.9 = advanced fibrosis	Schiavon et al. [103]	203	0.8	66%	93%
			Liu et al. [104]	279	0.83	85%	82%
			Schiavon et al. [105]	185	0.78	66%	93%
Fibrotest	α 2 macroglobulin, haptoglobin, γ -glutamyl transpeptidase, total bilirubin and apolipoprotein A1 levels	<0.2 = no advanced fibrosis >0.6 = advanced fibrosis	Varaut et al. [106]	50	0.47	71%	77%
			Canabakan et al. [107]	33	0.46	20%	45%
Hyaluronic Acid	Unbranched, high-molecular weight polysaccharide that is widely distributed in the extracellular spaces	<64 = no advanced fibrosis >205 = advanced fibrosis	Schiavon et al. [105]	185	0.65	42%	86%
YKL-40	Glycoprotein with function in the remodelling of the extracellular matrix or in tissue inflammation	<290 = no advanced fibrosis >520 = advanced fibrosis	Schiavon et al. [105]	185	0.6	35%	84%

There are no data available to determine whether patients with early cirrhosis on liver biopsy but well-compensated clinical disease do better if they are transplanted or remain on dialysis.

In 2006, Campbell et al. [109] evaluated the association between advanced liver fibrosis and survival among HCV+ patients evaluated for KT.

Among 108 HCV+ patients, eighteen (6%) had advanced fibrosis (bridging fibrosis or cirrhosis) before KT. Fifty-eight patients subsequently underwent KT, and 10 of these had advanced fibrosis. Rates of transplantation were similar between those with advanced fibrosis (56%) and those without (53%; $P = .1$). Survival was similar in those with and without advanced fibrosis both among all patients ($P = .92$) and among those patients who underwent kidney transplantation ($P = .83$); nonliver disease comorbidities seemed to be the most important outcome determinants in this population.

In 2007, Maluf et al. [38], analyzing forty-three HCV+ KT recipients, identified Knodell score >6 in the pre-KT biopsies (without mentioning if it was prevalently related to inflammation or fibrosis) as a predictor of mortality after KT in HCV+ve patients and, therefore, raised concerns about the benefits of KTx in this group of patients, although prospective studies are necessary to confirm these findings.

There are very limited outcome data regarding transplantation of a kidney alone in HCV-infected recipients with pre-existing compensated cirrhosis of the liver; therefore, the KDIGO (Kidney Disease: Improving Global Outcomes) clinical guidelines 2008 recommends that HCV-infected kidney transplant candidates with compensated liver cirrhosis on biopsy only be considered for kidney transplantation under investigational protocol. HCV-infected patients with evidence of decompensated liver disease should be evaluated for simultaneous kidney liver transplantation [54].

6. Use of Kidney Allografts from Anti-HCV+ Donors

Shortly after the introduction of the first-generation anti-HCV tests, studies conducted at the New England Organ Bank unequivocally demonstrated that HCV could be transmitted by organ transplantation [110–112]. This may occur as a new infection in a previously uninfected recipient or superinfection with a different genotype in an HCV-infected recipient [113]. Studies conducted in the 1980–1990s evidenced as, among recipients of organs from anti-HCV+ve donors, 35% (range 0–55%) developed posttransplant liver disease, 50% (14–100%) became anti-HCV+ve after transplantation, and 73% (14–96%) developed HCV viremia [111, 112]. The wide variations in the rate of transmission of HCV infection by anti-HCV+ve donors reported by different centers could be due to several factors, such as failure to test recipients at some centers, different prevalence of HCV infection among donors, and differences in organ preservation; the use of pulsatile pump perfusion may reduce the viral load in the donor kidney and seems to have the potential to reduce viral transmission from HCV-infected organs [114]. The extrapolated prevalence of anti-HCV among cadaver organs by ELISA-2 was calculated to be 4.2% and that of HCV-RNA to be 2.4% [112]. This seems to be higher than the prevalence of anti-HCV among healthy blood donors, and it could reflect the higher prevalence of risk factors, among cadaver organ donors, associated with the spread of viral infections, such as unsuspected intravenous drug use or sexual promiscuity.

The high prevalence of HCV among dialysis patients awaiting KT and the shortage of cadaveric kidneys led some groups to evaluate efficacy and safety of using kidneys from HCV+ donors in recipients infected with HCV [115, 116].

A large registry analysis in 2002 demonstrated that use of grafts from HCV+ donors was associated with an increased mortality, regardless of the anti-HCV antibody status of the recipient [117]. However, the use of kidneys from anti-HCV+ deceased donors in HCV+ recipients has been associated with superior patient survival compared with dialysis [118]. Also, Maluf et al. [119], using the Organ Procurement and Transplantation Network (OPTN) database, reported a shortened waiting time of nearly 300 days for HCV+ve recipients received a graft from HCV+ donors compared with HCV–ve recipients, though this was balanced by a significantly decreased patient and graft survival. It is unknown whether the survival reduction was due to other donor factors, a direct effect of the virus on the kidney itself, or related to superinfection with competing viral strains.

A larger analysis of the same OPTN database recently performed by Northup et al. [120], including 19 496 HCV+ve recipients and 934 HCV+ve donors, showed that the adjusted hazard ratio for death was similar for HCV+ recipient/HCV– donor compared with HCV+ recipient/HCV+ donor (1.176 versus 1.165, $P = .91$); the worst survival was in the HCV– recipient/HCV+ donor group (55.1%).

Use of organs from HCV+ donors has been associated with severe acute hepatitis in HCV-ve recipients (fulminant or fibrosing cholestatic hepatitis), perhaps related to acute infection under maximal immunosuppression [121–123], increased prevalence of chronic liver disease, and worse survival [35, 124–126]; therefore, transplantation of kidneys from HCV+ donors should be restricted to recipients who have a HCV viremia at the time of transplant.

The potential risks of superinfection with an HCV donor genotype different from that of the recipient is unknown. Genotype 1 is the most common genotype of hepatitis C virus in the western countries in both patient with and without ESRD, and it is known to be less responsive to the antiviral therapy with Peg-interferon plus Ribavirin. Genotype superinfection through transplantation has been reported in a few cases, and an increase in transaminase levels was observed [127–130]. Some authors argued that genotyping should be routine, and that HCV genotype 1 kidneys should not be used in patients with other genotypes. However, data do not exist for this strategy beyond anecdotal reports, recommendations, and case reports.

In conclusion, these data provide strong evidence that access to this “extra” pool of organs may confer a waiting time advantage in the HCV-positive population, but the conflicting data on graft and patient survival in this group requires further thought.

7. Therapy of Chronic Hepatitis C in the Chronic Kidney Disease Population

In those without kidney disease, the current standard of care for the treatment of HCV infection is with pegylated interferon and ribavirin. The response is dependent on many factors, including HCV genotype, HCV viral load, age and

gender, degree of liver impairment, and duration of therapy. Treatment is limited by many factors, especially toxicity. New agents, such as protease inhibitors, are in clinical development and early studies suggest that these will revolutionize the treatment of HCV infection. Thus, for some patients with histologically early liver disease and little inflammatory activity, delay of therapy may be appropriate.

Despite the increased prevalence of HCV infection in CKD patients compared to that of the general population, the indications for treatment and optimal antiviral regimens in terms of safety and efficacy in CKD are not well defined. Also, all major RCTs for the treatment of HCV infection have specifically excluded patients with abnormal kidney function. A variety of IFN-based regimens with differing treatment durations have been used in CKD, which makes comparison among studies more difficult. The KDIGO Clinical Practice Guidelines 2008 on “Treatment of HCV infection in patients with CKD” were based on the best available information from the CKD population together with data from the general population, where extrapolation was considered to be appropriate.

The decision to treat HCV infection in the CKD patient should be based on liver histology, age, comorbidities, ability to tolerate therapy, probability of achieve a sustained viral response (SVR), life expectancy, and candidacy for kidney transplantation [54].

Potential benefits of successful therapy include slowing the progression of liver disease and reducing the risk of post-transplant complications associated with HCV. However, given the generally indolent progression of HCV, treatment is not recommended for the patient with less than a 5-year estimated survival due to comorbidities such as cardiovascular disease. In some patients, such as in the pretransplant patient or in the patients with HCV-associated GN with or without cryoglobulinemia, there are good data to support treatment. For patients with HCV infection and CKD Stages 1–4, it might be reasonable to adapt the recommendations for treatment that apply to the general population, as there are no studies available that target this specific population [54]. Considering that HCV infection after kidney transplantation is implicated in the pathogenesis of acute glomerulopathy, *de novo* graft HCV-associated GN, diabetes mellitus, and the higher incidence of CAN, the strength of the recommendation to treat HCV+ve kidney transplant candidate is greater than in the general HCV+ve population on HD; moreover, in this setting antiviral therapy is recommended even for those with a pattern of histologic injury that does not meet the recommended degree of fibrosis to qualify for therapy in the general population (that is, Metavir score <2 and Ishak score <3). In patients with well-compensated cirrhosis, the decision of whether to treat is difficult, and the benefit of treatment in this setting is difficult to measure.

Conventional IFN monotherapy in dialysis patients with chronic hepatitis C is associated with dismal results [61, 131–136]. Two separate meta-analyses analyzing HCV+ patients on hemodialysis showed SVR rates of 33% to 37% with standard IFN-alpha with drop-out rates of 17% to 30% [137, 138].

The combination of Pegylated IFN (PEG-IFN) and ribavirin (RBV) in chronic HCV patients with normal kidney function gives reported SVR rates of 54% to 61% [139].

Few studies have evaluated combined therapy in HD patients and the quality of this evidence is very low [140–147]. Patients with renal dysfunction are particularly vulnerable to the tolerability issues associated with therapy with PEG-IFN α plus ribavirin. The elimination rate of ribavirin in patients with impaired renal function is reduced, and only a small fraction of the drug is eliminated by hemodialysis. In patients with creatinine clearance between 10–30 mL/minute and 30–60 mL/minute, the AUC for ribavirin is threefold and twofold greater, respectively, than for patients with CrCl > 90 mL/minute. As a result of this increase in drug exposure and the accompanying elevated risk for drug-related toxicity, for example, severe hemolytic anemia, ribavirin is contraindicated in patients with CrCl < 50 mL/minute [148–150].

The use of PEG-IFN monotherapy in patients with ESRD, compared with traditional IFN, is more convenient with once a week dosing, but only small studies have been published to date [36, 151–160].

There is no significant difference in apparent body clearance of PEG-IFN α -2a between patients with normal kidney function and those with significant reductions in kidney function (creatinine clearance >100 mL/min versus 20–40 mL/min (CKD 3b/4)) [161]. However, with ESKD patients receiving HD, the pharmacokinetics of pegylated interferon α -2a may vary reflecting differences in dialyzer permeability and pore size [162]. Recently Fabrizi et al. [163] attempted a systematic review of the literature with a meta-analysis of clinical trials performed to assess efficacy and safety of PEG-IFN monotherapy in CKD patients with chronic hepatitis C. They analyzed 16 clinical trials (5 controlled studies) with a total of 254 patients. The results showed that SVR was achieved by around one-third of patients on HD, the same response seen with standard IFN monotherapy. However, the viral response to monotherapy with standard or pegylated IFN in maintenance HD patients remains higher than that observed in patients with chronic hepatitis C virus and normal kidney function (7–29%) who received standard IFN monotherapy [164]. There may be several reasons for this including: low HCV viral load in HD patients [165] reduced clearance of IFN in HD patients [166] and the observation that HCV-related chronic hepatitis in HD patients is usually milder [167]. The data reported in this meta-analysis are limited by heterogeneity between studies and the small numbers in each study population. Furthermore, the applicability of these results to clinical practice is uncertain because patients included in these studies were on the waiting list for renal transplantation and were younger and probably healthier than the general dialysis population.

More encouraging results regarding the effectiveness of PEG-IFN come from the recent single-center report by Werner et al. [168] who showed a SVR of 45% among a population of 22 naïve HCV patients on HD listed for KT, but confirmation with larger samples is required (Table 4).

Interferon therapy pretransplant has been associated to a reduced incidence of post-transplant *de novo* or recurrent glomerulonephritis. Cruzado et al. in 2003 [169] found that of 15 HCV+ KT recipients who received prerenal transplantation interferon, 10 (67%) became negative at the time of renal transplantation, and only one of 15 (6.7%) developed *de novo* glomerulonephritis (this patient was HCV RNA+ at transplantation). Among untreated controls, 12 out of 60 (19%) developed *de novo* glomerulonephritis post-KT, all 12 had detectable HCV RNA at transplantation.

Pretransplant antiviral therapy of HCV may also reduce the incidence of post-transplant diabetes mellitus (PTDM) in allograft recipients. In a controlled trial, Gursoy et al. [170] observed that the frequency of PTDM was higher in the group of HCV+ recipients who had not received IFN than in those who had been treated with IFN before transplantation, 25% (10/40) versus 7.1% (1/14), $P = .009$.

8. Therapy of Chronic HCV Infection in Kidney Transplant Recipients

The efficacy and safety of IFN-based therapy of hepatitis C after KT is unsatisfactory [144, 171–174]. The potential benefits need to be weighed against the risk of allograft rejection.

The administration of IFN after kidney transplantation can be deleterious to the allograft and should generally be avoided in kidney transplant recipients unless there is indication of worsening hepatic injury on biopsy or clinically decompensating liver disease. Reported rates of kidney graft dysfunction after IFN treatment range from 9 to 100%, with most episodes occurring between 0.3 and 8 months after initiation of therapy. Most kidney graft dysfunction was related to increased rates of acute rejection, which is frequently steroid resistant and irreversible and could lead to graft loss [54].

Apart from the antiviral effects mediated through the Jak-Stat signaling pathway, IFN is a potent immunomodulator affecting both the innate and the adaptive immune system [175–181].

The association between ACR and antiviral therapy was initially described in renal transplant recipients and was subsequently reported in liver transplant patients [182, 183]. Interferon alpha (IFN α) activates a large number of interferon stimulated genes (ISGs), which combined with the upregulation of MHC antigen expression results in increased antigen presentation, T-cell activation, and dominance of a Th1 response including release of TNF α , IL2, IL12, IFN γ , FasL, perforin, and GrzB activities, and decrease on IL10 and T-reg activity, collectively leading to tissue damage and inflammation. Also, ribavirin potentiates ISGs expression skewing toward TH response. IFN α also enhances recruitment and activity of other nonspecific cell types such as natural killer (NK) cells, macrophages, neutrophils, and monocytes.

While expansions of T-cell clones directed to viral antigens contribute to viral load reduction and clearance, expansions of T-cell clones to alloantigens may trigger immune-related disorders including acute cellular rejection and

TABLE 4: Clinical trials of monotherapy with conventional IFN or pegylated IFN in hemodialysis patients with chronic hepatitis C.

	Period	Patients number	Antiviral Agent	Doses of IFN or Peg-IFN	SVR
Degos et al. [132]	2001	37	IFN α	3 MU three times weekly	19%
Mukherjee et al. [152]	2003	9	Peg-IFN- α 2b	1 mcg/kg/week	22%
Ozdemir et al. [133]	2004	20	IFN α	3–6 MU three times weekly	40%
Rivera et al. [134]	2005	27	IFN α ($n = 20$) Peg-IFN- α 2a ($n = 7$)	3 MU three times weekly 135 mcg/week	40%
Mahmoud et al. [61]	2005	18	IFN α	3 MU three times weekly	44%
Grgurevic et al. [135]	2006	15	IFN α	3 \times 3 MU/week ($n = 8$) 3 \times 5 MU/week for 3 months, then 1 \times 5 MU/week for another 3 months ($n = 7$)	40%
Rocha et al. [136]	2006	46	IFN α	3 MU three times weekly	22%
Sporea et al. [153]	2006	10	Peg-IFN- α 2a	180 mcg/week	30%
Russo et al. [151]	2006	16	Peg-IFN- α 2b	1 mcg/kg/week ($n = 9$), 0.5 mcg/kg/week ($n = 7$)	12.5%
Covic et al. [154]	2006	78	Peg-IFN- α 2a	135 mcg/week	14%
Espinosa et al. [36]	2007	16	Peg-IFN- α 2a ($n = 7$) Peg-IFN- α 2b ($n = 9$)	1.5 mcg/week ($n = 9$), 135 mcg/kg/week ($n = 7$)	25%
Casanovas-Taltavull et al. [155]	2007	12	Peg-IFN- α 2a	135 mcg/week	25%
Ucmak et al. [156]	2008	12	Peg-IFN- α 2a	135 mcg/week	50%
Sikole et al. [157]	2008	14	Peg-IFN- α 2a	135 mcg/week	41%
Liu et al. [158]	2008	25	Peg-IFN- α 2a	135 mcg/week	48%
Ayaz et al. [159]	2008	22	Peg-IFN- α 2a	135 mcg/week	50%
Akhan et al. [160]	2008	12	Peg-IFN- α 2a	135 mcg/week	50%
Werner et al. [168]	2010	22	Peg-IFN- α 2a ($n = 9$) Peg-IFN- α 2b ($n = 13$)	180 mcg/week 1.5 mcg/kg/week 1 mcg/kg/week (1 patient)	45%

IFN: interferon; MU: million units; Peg-IFN: pegylated interferon; SVR: sustained virological response.

chronic ductopenic rejection as well as *de novo* autoimmune hepatitis.

ACR is often associated with concomitant low or negative serum HCV RNA. It has been suggested that HCV clearance during IFN-based therapy improves hepatic microsomal function, which in turn leads to lower immunosuppressant levels in blood putting patients at higher risk of development of ACR.

The American Association for the Study of the Liver Disease (AASLD) specifically recommends that kidney transplantation is a contraindication to IFN therapy for HCV infection. However, controlled and cohort (prospective or retrospective) studies have addressed this issue in kidney transplant recipients.

A meta-analysis of clinical trials of IFN-based therapy (interferon alone or with ribavirin) in KT recipients with chronic hepatitis C showed that the summary estimate for SVR rate was 18.0% (95% CI, 7.0–29%) with a drop-out rate of 35% (95% CI, 20–50%) [174]. The most frequent side-effect requiring discontinuation was acute rejection refractory to corticosteroid therapy. Combined antiviral therapy (interferon plus ribavirin) has been evaluated in a few studies [172, 173]. Shu et al. [173] in 2004 reported

an SVR of 27% (3/11) and a drop-out rate of 27% (3/11) due to graft dysfunction ($n = 1$) and urosepsis ($n = 2$) during antiviral therapy with very low dose IFN- α (1 MU s.c. three times weekly) for 48 weeks.

Thus, antiviral therapy with IFN, as state in KDIGO clinical practice guidelines 2008, should only be considered in patients with fibrosing cholestatic hepatitis or life-threatening vasculitis in whom the risk of not treating justifies the possible loss of the allograft [54].

Alternative regimens based on amantadine, RBV monotherapy, or their combination have been proposed, but no proof of their efficacy has been provided [184–187], and therefore they are not recommended.

9. Combined Kidney-Liver Transplantation in Patients with Hepatitis C

As cirrhosis and the development of liver cell cancer constitute an important risk factor for death and renal dysfunction after KT alone, combined kidney/liver transplantation should be considered for KT candidates with cirrhosis.

Since the adoption of the Model for End-Stage Liver Disease (MELD) score for allocating organs in the US in

2002, there has been a significant increase in simultaneous liver kidney (SLK) transplantation [188]. However, data are controversial and do not identify which patient should be offered SLK transplantation [189–194].

In 2008 an American consensus conference [195] convened to establish guidelines for evaluation, listing and transplantation of patients with end-stage liver disease (ESLD) and renal failure. The consensus agreed that the following conditions represent clear indications for listing for SKL:

- (i) End-stage renal disease with cirrhosis and symptomatic portal hypertension or hepatic vein wedge pressure gradient ≥ 10 mm Hg.
- (ii) Liver failure and CKD with GFR ≤ 30 mL/min.
- (iii) AKI or hepatorenal syndrome with serum creatinine ≥ 2.0 mg/dL and dialysis ≥ 8 weeks.
- (iv) Liver failure and CKD with a renal biopsy demonstrating $>30\%$ glomerulosclerosis or 30% fibrosis.

There are many data supporting the effectiveness of SKL. One year patient survival seems to be better than liver transplantation alone (LTA) [190, 196]. Some evidence suggests the kidney allograft lasts longer in liver transplant recipients from the same donor [197, 198]. Moreover, dialysis seems to be tolerated poorly in liver transplant recipients compared with matched kidney failure only dialysis patients [199].

However, if patients with cirrhosis receive a liver and kidney transplant, this may disadvantage those who require a kidney alone. Many recent studies have reported a lower survival of renal allografts in SLK compared to KTA recipients without liver disease [189, 197, 200].

As HCV-related cirrhosis is the leading indication for liver transplantation in western countries [201] and because HCV is associated with increased morbidity and mortality among both liver and kidney transplant recipients [202–207], there is a clear need to obtain data on the natural history and management of recurrent hepatitis C in the SKL setting.

In 2009, Del Pozo [208] compared outcomes among HCV+ and HCV– recipients of SLK with HCV+ recipients of isolated liver transplant, but did not find any significant difference in terms of 1-, 2-, and 5-years survival ($P = .6$). They found that HCV+ patients undergoing SKL were significantly older than HCV– patients (61 versus 51 years, $P = .01$). Diabetes after SLK was significantly more prevalent in the HCV+ group (78% versus 28%, $P = .01$). There were no significant differences between HCV+ and HCV– SKL recipients in terms of kidney graft function and kidney and liver rejection.

Van Wagner and colleagues [209], in the largest study reported to date, analyzed the outcome of patients with HCV infection undergoing SLK transplant, compared to that of HCV+ patient underwent LTA.

Despite many limitations, such as the retrospective nature of the studies, the heterogeneity of the indication for SKL, the lack of a control group of HCV-SLK recipients, and the choice of a control group of LTA patients with a lower median MELD score lower (17.4 versus 38, LTA, and SLKT, resp.), reflecting less advanced liver disease.

The 1-, 3-, and 5-year overall survival rates for the SLK group were 73.7%, 61.8%, and 68.1%, and in the LTA group the rates were 91.9%, 78.8%, and 73.2%, respectively. However, once adjusted for age, gender, and MELD, there were no statistical differences ($P = .298$). Also, there was no difference in liver graft survival between SLK and LTA groups.

There were more early posttransplant infection episodes in the SLK (56.3%) compared with LTA (21.6%) ($P = .001$) and there was a trend towards increased early mortality in the SLK group ($P = .08$), as reported in others studies [197, 200, 210–212].

There was no difference in the time to HCV recurrence, the proportion with \geq stage 2 fibrosis, renal function, and graft function between the groups. This study does not report posttransplant diabetes.

Ten of the 17 SLK recipients with HCV recurrence underwent antiviral therapy with pegylated IFN and RBV. Of these 10 SKL patients, two achieved SVR and 5 discontinued therapy; of the 14 liver only recipients, 5 achieved SVR and seven discontinued therapy. There were no episodes of liver or kidney rejection while on treatment in the SKL group, while one episode of liver rejection was documented in the LTA group. The authors speculated that the simultaneous transplantation of kidney and liver may protect the kidney graft against acute rejection induced by PEG-IFN alpha treatment; this is in keeping with evidence that the liver transplant provides some level of immunologic protection to the kidney allograft [197, 200].

Similar findings were reported in two case reports [213, 214] and in a small case series by Schmitz et al. [215], who showed, among 6 recipients of combined kidney-liver transplant (4 simultaneous, 2 consecutive), one episode of liver rejection after antiviral treatment with PEG-IFN alfa2b, but no episodes of kidney rejection were reported; the rate of SVR was 50% (3/6).

Based on these data, antiviral treatment for HCV recurrence in SLK recipients appears safe, but additional prospective studies with larger patient populations are needed to further validate the feasibility of such antiviral treatment.

10. Conclusion

The prevalence of hepatitis C in patients with chronic kidney disease (CKD) on hemodialysis (HD) is higher than that in the general population. Hepatitis C reduces survival both in dialysis patients and renal transplant recipients. Liver biopsy performed before KT is an important tool to determine the severity of liver disease in HCV+ patients and may help to assess the prognosis and the management of the patients both before and after transplantation. Transplantation of kidneys from HCV+ donors restricted to HCV+ recipients may confer an advantage in terms of waiting time in this population although the results on outcome seem to be controversial. Monotherapy with conventional IFN or Pegylated-IFN for chronic hepatitis C seems to be effective in patients on haemodialysis. Data available about combination therapy with pegylated interferon plus ribavirin are limited.

While IFN treatment in HCV+ kidney transplant candidates is recommended, treatment post-KT should be restricted to patients in whom the risk of not treating justifies the possible loss of the allograft (such as fibrosing cholestatic hepatitis). Otherwise, it is contraindicated, because of the high risk of rejection and consequent graft loss. Simultaneous kidney/liver transplantation should be considered for renal transplant candidates with decompensated cirrhosis.

Treatment of HCV recurrence in SLK recipients appears effective and safe, although further studies are needed to validate this data.

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