REVIEW

Management of hepatitis C in patients with chronic kidney disease

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Abstract

Hepatitis C virus (HCV) infection is highly prevalent among chronic kidney disease (CKD) subjects under hemodialysis and in kidney transplantation (KT) recipients, being an important cause of morbidity and mortality in these patients. The vast majority of HCV chronic infections in the hemodialysis setting are currently attributable to nosocomial transmission. Acute and chronic hepatitis C exhibits distinct clinical and laboratorial features, which can impact on management and treatment decisions. In hemodialysis subjects, acute infections are usually asymptomatic and anicteric; since spontaneous viral clearance is very uncommon in this context, acute infections should be treated as soon as possible. In KT recipients, the occurrence of acute hepatitis C can have a more severe course, with a rapid progression of liver fibrosis. In these patients, it is recommended to use pegylated interferon (PEG-IFN) in combination with ribavirin, with doses adjusted according to estimated glomerular filtration rate. There is no evidence suggesting that chronic hepatitis C exhibits a more aggressive course in CKD subjects under conservative management. In these subjects, indication of treatment with PEG-IFN plus ribavirin relies on the CKD stage, rate of progression of renal dysfunction and the possibility of a preemptive transplant. HCV infection has been associated with both liver disease-related deaths and cardiovascular mortality in hemodialysis patients. Among those individuals, low HCV viral loads and the phenomenon of intermittent HCV viremia are often observed, and sequential HCV RNA monitoring is needed. Despite the poor tolerability and suboptimal efficacy of antiviral therapy in CKD patients, many patients can achieve sustained virological response, which improve patient and graft outcomes. Hepatitis C eradication before KT theoretically improves survival and reduces the occurrence of chronic graft nephropathy, *de novo* glomerulonephritis and post-transplant diabetes mellitus.

Key words: Hepatitis C virus; Chronic kidney disease; End-stage renal disease; Hemodialysis; Kidney transplantation; Diagnosis; Conservative management; Therapy

Core tip: In this review, we discuss the most recent and relevant literature regarding diagnostic aspects, clinical features, outcomes and therapy of chronic hepatitis C

in subjects with chronic kidney disease, in the context of conservative management, hemodialysis, and kidney transplantation. In addition, antiviral regimens are summarized and treatment algorithms are proposed.

INTRODUCTION

Over the last two decades, there has been a large body of evidence that supports an intimate relationship between liver and kidney diseases. In the same way that several causes of renal injury can occur in patients with acute liver failure or chronic liver disease, a variety of hepatic lesions can develop in subjects with chronic kidney disease (CKD). Although drug-induced liver injuries, non-alcoholic fatty liver disease and hepatic iron overload are relatively frequent in CKD patients, hepatitis C virus (HCV) infection remains the most common and severe cause of liver disease in this population[1].

HCV infection is a major public health issue, which affects approximately 2.8% of the world's population[2,3]. HCV infection is highly prevalent among CKD subjects and, consequently, in kidney transplant (KT) recipients[4,5]. In spite of the reduction in HCV seroconversion rates in hemodialysis units, prevalence is still substantially higher than in general population, ranging from 10% to as high as 59%, according to the geographic area[6,7]. A recent meta-analysis performed by Su *et al*[8] on the incidence of HCV infection in hemodialysis patients confirmed this high variability of incidence rates across regions, with most of this heterogeneity probably related to the level of country development and differences in the primary prevalence of HCV infection in hemodialysis units. By evaluating 22 studies, these authors found a pooled incidence rate of HCV infection of 0.97 (95%CI: 0.66-1.29) in developed countries, and of 4.44 (95%CI: 2.65-6.23) per 100 patients in developing countries[8]. Patients under renal replacement therapy, particularly hemodialysis, are exposed to blood borne pathogens, given the need for intravenous access, and frequent catheter manipulation[9]. These patients are frequently treated in close proximity to one another and share supplies or equipment that can become contaminated. Furthermore, breaches in infection control practices can result in episodes of patient-to-patient HCV transmission[10]. Time in hemodialysis, previous renal transplant and presence of anti-HBc antibodies are associated with HCV infection while use of erythropoietin (EPO) and adherence to universal precaution measures seem to protect against HCV infection[11]. While transfusion of blood products still

plays a significant epidemiological role in developing countries, the vast majority of HCV chronic infections in the hemodialysis setting are currently attributable to nosocomial transmission through hand-borne transmission or by the use of contaminated medication vials, such as saline, anesthetic drugs and unfractionated heparin (UFH)[6,9,12]. Although single dose low molecular weight heparin (LMWH) has been increasingly used (particularly in Western Europe), UFH provided in multidose vials is the anticoagulant of choice for most maintenance hemodialysis units all over the world, which possibly contributes to HCV transmission when standard precautions are not strictly adopted[13,14].

Since there is a paucity of data for individuals on peritoneal dialysis, this review will focus on diagnostic aspects, clinical outcomes and therapeutic options for hepatitis C in CKD patients receiving conservative management, undergoing hemodialysis, and after kidney transplantation.

ACUTE HEPATITIS C

With the introduction of EPO and the consequent reduction of blood transfusions in hemodialysis patients, the main route of HCV infection is related to environmental transmission of the virus[15,16].

In hemodialysis patients, acute infections are usually asymptomatic and anicteric. Despite the lower levels of alanine aminotransferase (ALT) levels observed in CKD patients[17,18], acute infections are often accompanied of moderate ALT elevations (typically inferior to 10 times the upper limit of normality), followed by anti-HCV seroconversion in 90% of cases, one to seven months after ALT elevation[16,19-21]. Systematic screening of ALT and anti-HCV in hemodialysis patients are strongly recommended (monthly for ALT and 6-monthly for anti-HCV), and even small unexplained increase in serum ALT levels should raise the suspicion of acute HCV infection. The infection is confirmed by the detection of HCV RNA in serum by polymerase chain reaction (PCR) assay, which precedes the appearance of anti-HCV antibodies by several weeks or months[22,23]. In the study of Moreira *et al*[24], serum samples were collected monthly for 1 year from 281 patients admitted for hemodialysis; six patients seroconverted during the study (incidence = 3.1/1000 person-month). In 1.8% (5/281) of cases, RNA was detected before the appearance of antibodies (up to 5 mo), and in 1.1% (3/281) of cases, RNA was the unique marker of HCV infection.

Viral clearance is very uncommon in hemodialysis patients, occurring in less than 5% of patients[16,19], and therefore acute infections should be treated as soon as the diagnosis is established, whenever possible. Given that documentation of anti-HCV seroconversion is generally feasible in the context of hemodialysis, a pretreatment liver biopsy is seldom necessary, unless a differential diagnosis is required.

In non-uremic patients, data about treatment of

Table 1 Studies on acute hepatitis C treatment in hemodialysis patients

Ref.	Süleymanlar *et al*[26] (1998)	Gürsoy *et al*[27] (2001)	Urbánek *et al*[28] (2004)	Al-Harbi *et al*[29] (2005)	Rocha *et al*[30] (2007)	Engel *et al*[32] (2007)	Liu *et al*[33] (2010)	Ferreira *et al*[31] (2011)
n	3	36	18	9	23	10	35	26
Interferon type	IFN	IFN	IFN	IFN	IFN	PEG-IFN α2b	PEG-IFN α2a	IFN PEG-IFN α2a
Schedule	4.5 MU *tiw*	3 MU or 6-10 MU *tiw*	10 MU + 3 MU *tiw*	3 MU *tiw*	3 MU or 6 MU *tiw*	1 µg/kg *qw*	135 µgv *qw*	3 MU *tiw* or 135 µg *qw*
Duration	16 wk	12 wk	3 wk + 12 wk	12 wk	48 or 24 wk	24 wk	24 wk	48 wk
SVR	100%	39%	72%	67%	43%	40%	89%	54%

IFN: Interferon; PEG-IFN: Pegylated interferon; MU: Million units; *tiw*: Three times a week; *qw*: Once a week; SVR: Sustained virological response rate by intention-to-treat analysis.

Table 2 Treatment regimens for hepatitis C virus infection in chronic kidney patients

Stage of CKD	Estimated GFR	Target dosage of ribavirin	Dosage of Interferon
1	⩾ 90	800 to 1200 mg *qd*[1]	PEG-IFN α2a 180 µg *qw*
2	60 to 89	600 to 800 mg *qd*[1]	or PEG-IFN α2b 1.5 µg/kg *qw*
3	30 to 59	400 to 600 mg *qd*[1]	
4	15 to 29	200 mg *qd*	PEG-IFN α2a 135 µg *qw*
5	< 15 or HD	Titrated according to patient tolerability[2]	or PEG-IFN α2b 1.0 µg/kg *qw*

[1]Divided in two doses; [2]See text for details. GFR: Glomerular filtration rate expressed in mL/min per 1.73 m²; *qd*: Once a day; PEG-IFN: Pegylated interferon; *qw*: Once a week; HD: Hemodyalisis.

acute hepatitis C are limited and heterogeneous regarding studied populations, regimens and duration of treatment[25]. In hemodialysis patients data are even scarcer, with small sample sizes. In addition, most studies report results with standard interferon[26-31]. Only two studies reported data of pegylated interferon (PEG-IFN) in hemodialysis patients[32,33]. These two and six other studies were evaluated in a meta-analysis about treatment of acute hepatitis C in hemodialysis patients[34] (Table 1). The global rate of sustained virological response (SVR) was 59%, with 9% of dropouts. Although there were no clear differences in efficacy or safety between PEG-IFN and standard IFN, we suggest that PEG-IFN with adjusted doses (Table 2) should be preferentially used, for the sake of better patient compliance and comfort. In non-uremic patients there is no evidence of additional benefit of association with ribavirin[35] but there is no data regarding its use in uremic patients. Nevertheless, the recommendation is to treat HCV acute infection with monotherapy PEG-IFN for six months, regardless of the genotype. It is not recommended to wait 12 wk for spontaneous clearance, since this occurrence is very uncommon in CKD subjects.

In KT recipients, the occurrence of acute hepatitis C can be associated with a more severe course, with a rapid progression of fibrosis towards cirrhosis, including the development of fibrosing cholestatic hepatitis or vanishing bile duct syndrome[36-39]. For this reason, antiviral therapy should be rapidly introduced, even if poor tolerability and efficacy are expected. Although there are no comparative studies with IFN monotherapy, the better option would be the treatment with PEG-IFN

in combination with ribavirin for 24 to 48 wk, with doses adjusted according to estimated glomerular filtration rate (eGFR) (Table 2).

CHRONIC HEPATITIS C BEFORE KIDNEY TRANSPLANTATION

CKD patients under conservative management

The prevalence of HCV infection is higher in conservative management CKD patients than in general population, being mainly related to parenteral exposure[40-44]. Clinical and laboratory features of chronic HCV infection in CKD individuals under conservative management are not well known, and additional studies are needed to better understand the natural history and clinical impact of chronic HCV infection in this population. Nevertheless, the accuracy of ALT in detecting HCV infection is high[43,44], suggesting that ALT is a good marker of this infection among pre-dialysis patients, in contrast to individuals under hemodialysis[17]. In one study, 39 pre-dialysis patients with chronic HCV infection were compared to HCV-infected hemodialysis subjects[43]. Pre-dialysis patients were older, showed a higher proportion of elevated aminotransferases levels, higher inflammatory activity and more advanced fibrosis on liver histology. However, since comparable fibrosis progression rates were observed, there is no evidence suggesting that chronic hepatitis C exhibits a more aggressive course in CKD subjects under conservative management. Interestingly, high HCV viral loads seems to be common in these patients[43], in contrast to what is
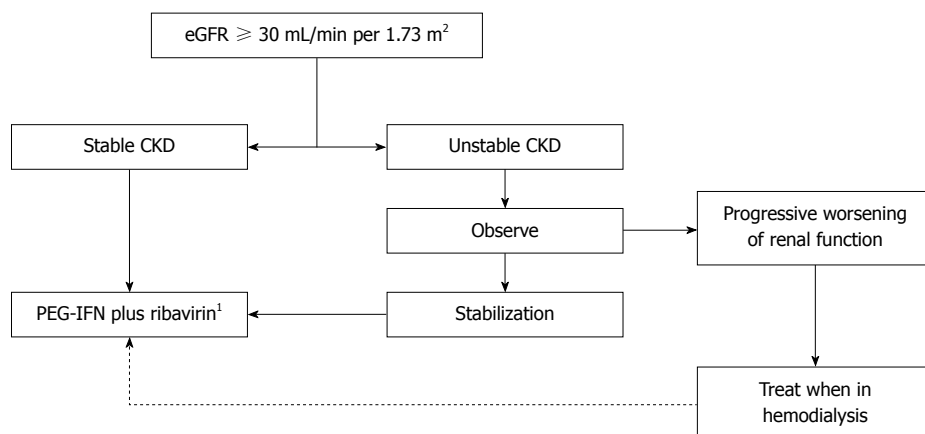
Figure 1 Treatment decision algorithm for hepatitis C virus-infected chronic kidney disease patients under conservative management. [1]Adjusted doses according to eGFR. eGFR: Estimated glomerular filtration rate; CKD: Chronic kidney disease; PEG-IFN: Pegylated interferon.

observed in hemodialysis subjects, who typically present low levels of serum HCV RNA, a finding possibly related to the clearance of HCV particles during dialysis[45-47].

Treatment decision relies on the CKD stage (based on eGFR), rate of progression of renal dysfunction and the possibility of a preemptive transplant. A treatment decision algorithm is proposed in Figure 1. Although antiviral therapy is feasible for subjects in all CKD stages, for most patients with CKD stage 4 (eGFR of 15 to 29 mL/min per 1.73 m^2) it is preferable to wait until there is indication for initiation of dialysis. This waiting attitude for CKD stage 4 patients is proposed only for those without significant liver fibrosis, considering the particularly low fibrosis progression rate and the poor tolerability of these subjects, as well as the high risk of further deterioration of kidney function and early indication for renal replacement therapy[48,49].

Treatment schedule consists of PEG-IFN α2a and ribavirin, with doses tailored to eGFR (Table 2), for 24 to 48 wk. Dose adjustment according to renal function is particularly needed for ribavirin[50], which concentrates in circulating red blood cells (RBCs)[51,52], causes a relative adenosine triphosphate deficiency and increased susceptibility to oxidative damage, leading to accelerated RBC turnover and hemolytic anemia[53]. Therefore, in CKD subjects, renal function and hemoglobin levels should be carefully monitored during antiviral therapy, due to the increased risk of ribavirin-induced anemia, which can be severe in patients who frequently have multifactorial anemia and other comorbidities (like coronary artery disease). The use of EPO (up to 40000 IU/wk) improves tolerability and promotes the stability of hematological parameters during treatment.

CKD patients under hemodyalisis
HCV infection is an important cause of morbidity and mortality in dialysis patients and has been associated with both liver disease-related deaths (due to complications of cirrhosis and hepatocellular carcinoma) and cardiovascular mortality[54-56]. It is possible that HCV contributes to atherogenesis through aggravation of

metabolic syndrome factors and/or by leading to a chronic inflammatory state[57].

In CKD patients undergoing hemodialysis, HCV infection has distinct clinical and laboratory features as compared to the non-uremic population and KT recipients, which can affect the management of those subjects. The prevalence of advanced liver fibrosis is lower (4% to 10%)[58,59], and progression to cirrhosis during hemodialysis seems to be uncommon[60]. In addition, as mentioned above, for yet unknown reasons, ALT levels are lower than those observed in non-uremic patients, even in the presence of significant histological damage, which hampers its utility as a marker of HCV infection[18,61].

Anti-HCV has proven to be a reliable screening test for HCV chronic infection in CKD patients[62]. Although false-negative tests have been observed with first and second generation kits, this became rather unusual with third generation enzyme immunoassays and chemiluminescence assays[62,63].

It should be noted that, although these patients are immunocompromised due to the underlying disease, low HCV viral loads are typically observed[45-47]. The mechanisms involved in this phenomenon are poorly understood and are probably multifactorial. Filtration of viral particles into the dialysate, adherence of the virus to the surface of the dialysis membrane, and destruction of viral particles during the dialysis procedure have been proposed as potential mechanisms[46,47]. It is not clear whether the type of dialysis would significantly affect the clearance of HCV particles. However, it has been suggested that HCV viral load is lower in CKD patients under chronic hemofiltration[64]. Moreover, the phenomenon of intermittent HCV viremia, characterized by low levels of serum HCV viral load intercalated with episodes of undetectable HCV RNA, has been commonly reported in CKD patients under hemodialysis[46,65-68]. This event is responsible for false-negative results in HCV RNA assays in 33% to 67% of anti-HCV-reactive patients[46,65-68], which not only can result in delayed treatment (or no treatment at all), but

Table 3 Meta-analyses on the treatment of chronic hepatitis C in hemodialysis patients

Ref.	Year	Trials (*n*)	Therapy	*n*	SVR[1]
Russo *et al*[95]	2003	11	IFN	213	33% (21%-51%)
Fabrizi *et al*[96]	2003	14	IFN	269	37% (28%-48%)
Gordon *et al*[97]	2008	20	IFN	459	41% (33%-49%)
		5	PEG-IFN	87	37% (9%-77%)
Fabrizi *et al*[99]	2008	24	IFN	529	39% (32%-46%)
		4	PEG-IFN	116	31% (7%-55%)
Gordon *et al*[98]	2009	20	IFN	428	45%
Alavian *et al*[100]	2010	21	IFN	491	39% (32%-46%)
		12	PEG-IFN	279	39% (27%-52%)
Fabrizi *et al*[101]	2010	16	PEG-IFN	254	33% (24%-43%)
Fabrizi *et al*[102]	2011	10	PEG-IFN + RBV	151	56% (28%-84%)
Fabrizi *et al*[103]	2014	11	PEG-IFN + RBV	287	60% (28%-97%)

[1]Mean overall estimate for sustained virological response (range). IFN: Interferon; PEG-IFN: Pegylated interferon; RBV: Ribavirin.

also contributes to environmental transmission of HCV in dialysis units. Several physiopathogenetic mechanisms have been proposed to explain the intermittent HCV viremia, like heparin interference with the PCR assay used for the detection of HCV RNA[69], mechanical extraction of viral particles adhering to dialyzer membrane[47,70], and induction of interferon production, hepatocyte growth factor, or other cytokines with antiviral properties by the hemodialysis procedure[71-73].

Therefore, isolated undetectable results of HCV RNA should not be interpreted as absence of replication. To better clarify HCV viral kinetics in this population, it is recommended for all anti-HCV-positive CKD patients on hemodialysis to perform sequential HCV RNA monitoring by using a highly sensitive detection method like reverse transcriptase-polymerase chain reaction (RT-PCR) or transcription-mediated amplification[74-77].

Occult HCV infection could conceivably also represent a risk for nosocomial transmission of HCV within hemodialysis units, as well as an additional risk of reactivation and progressive liver disease after KT. However, a study evaluating 417 hemodialysis subjects found only a single case of HCV RNA detectable in peripheral blood mononuclear cells in the absence of HCV RNA in serum, suggesting that occult HCV infection is very rare in CKD patients in hemodialysis[63].

Although widely performed and accepted as the gold-standard method to evaluate hepatic fibrosis, liver biopsy is an invasive technique with associated morbidity[78]. CKD individuals frequently exhibit major hemostatic disorders and hemorrhagic complications, posing additional risks for patients undergoing invasive procedures[79]. Transjugular liver biopsy is an alternative procedure for obtaining liver specimens that has already been evaluated in the CKD population[80,81]. Although safe, this procedure is not widely available and frequently provides small samples, which might underestimate fibrosis staging. Hence, there is a need for the develop-

ment of accurate noninvasive tests to estimate liver fibrosis, especially among dialysis patients, in whom a higher risk for liver biopsy complications has been observed in most, but not all, studies[80,82-84]. Noninvasive tests such as APRI (AST-to-platelet ratio index), Fibro-Test® and transient hepatic elastography have shown good diagnostic performance to predict the severity of liver fibrosis in hemodialysis patients with chronic hepatitis C, and can be used as alternative methods to liver biopsy for subjects with contraindications to the procedure or for those who refuse to be biopsied[58,85-87].

Hepatitis C eradication before KT theoretically improves survival and reduces the occurrence of chronic graft nephropathy[88], *de novo* glomerulonephritis[89] and post-transplant diabetes mellitus[90]. After transplantation, viremia increases significantly[9] and progression of liver fibrosis occurs[91,92], with an evident negative impact on survival after 10 years of transplantation[93]. Moreover, given the risk of treatment-induced graft dysfunction and poor tolerance of interferon-based therapy, antiviral therapy has limited indications in HCV-infected KT subjects[94]. Thus, in KT candidates, treatment should be offered regardless of the degree of histological injury, with the goal of viral eradication. It is highly recommended that common clinical comorbidities such as anemia, retinopathy and cardiovascular disease should be identified and controlled before treatment.

There have been several trials of hepatitis C treatment in hemodialysis patients, mostly uncontrolled and with different therapeutic regimens. These trials have been included in many meta-analysis[95-103], which are listed in Table 3.

Overall SVR rates derived from meta-analysis appear not to be very different for the use of standard IFN or PEG-IFN. However, in a randomized, controlled trial, viral load and use of PEG-IFN (*vs* standard IFN) were predictive of SVR[104]. The addition of ribavirin seems to provide a significant increase in SVR, but demands greater care in pretreatment evaluation and in monitoring and managing of anemia (including EPO supplementation). Studies evaluating combined therapy with interferon and ribavirin used ribavirin doses from 200 mg 3 times a week up to 300 mg/d[105-115]. Dropout rates were highly heterogeneous, ranging from 0% to 71%.

Given its easier dosing schedule and possible higher efficacy, it is recommended to use PEG-IFN (preferably PEG-IFN α2a 135 μg) once a week, after dialysis session, in combination with ribavirin. The ribavirin dose should be titrated according to patient tolerability, as follows: an initial dose of 200 mg once a week is given, followed by increments of 200 mg every two weeks until the maximum dose tolerated (stable levels of hemoglobin above 10 g/dL are often required). After stabilization of ribavirin dosage (usually between 400 to 1200 mg/wk), PEG-IFN is initiated and used for 24 to 48 wk (Figure 2).

HCV viral kinetics can be used to support clinical decisions during treatment. Early virological response has a positive predictive value of 67% to predict SVR
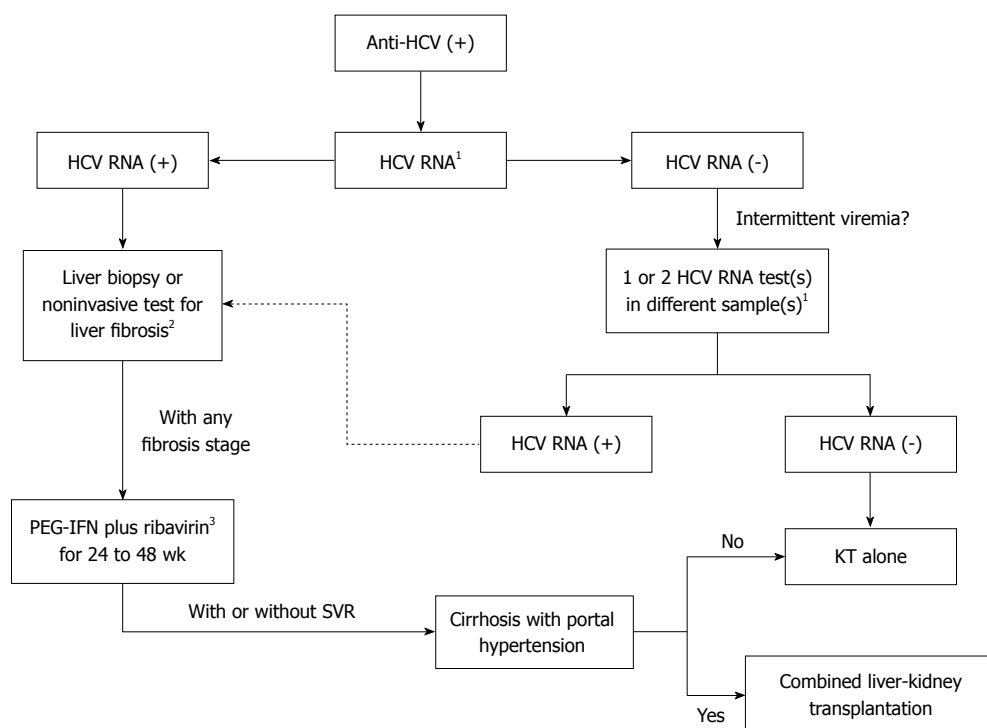
Figure 2 Treatment decision algorithm for hepatitis C virus-infected chronic kidney disease patients under hemodialysis who are candidates for kidney transplantation. [1]By real-time PCR or transcription-mediated amplification; [2]APRI, FibroTest or transient hepatic elastography; [3]Adjusted doses (see text for details). PEG-IFN: Pegylated interferon; KT: Kidney transplantation; SVR: Sustained virological response; HCV: Hepatitis C virus; KT: Kidney transplantation.

and a negative predictive value (NPV) of 75% in patients receiving interferon monotherapy[98]. More recently, it has been observed a NPV of 100% for SVR if HCV RNA is detectable on week 12 of treatment[116].

Preliminary reports have suggested that first wave HCV NS3/4A protease inhibitors telaprevir and boceprevir could be used in CKD patients, with good efficacy and safety profile[117-120]. There is no need for dose adjustments for telaprevir or boceprevir since dialysis does not exert a substantial influence on the pharmacokinetics of the drugs[121,122]. It is possible that the next generations of anti-HCV direct-acting antiviral agents (DAAs), such as second and third waves NS3/4A protease inhibitors, NS5A polymerase inhibitors, NS5B polymerase inhibitors and cyclophillin inhibitors will overcome the therapeutic barrier in this population, especially when interferon-free and ribavirin-free regimens become available.

Patients with cirrhosis, particularly those with portal hypertension, may have a decreased survival and increased morbidity after renal transplantation[123]. In these cases, a renal transplantation alone is contraindicated and combined liver-kidney transplantation should be considered. For patients with compensated cirrhosis and without significant portal hypertension, isolated renal transplant appears to be safe[124,125]. In these subjects with advanced fibrosis or cirrhosis, imaging monitoring and upper endoscopy are recommended for the screening of hepatocellular carcinoma and esophageal varices, respectively.

CHRONIC HEPATITIS C AFTER KIDNEY TRANSPLANTATION

Although some studies have failed to find a negative impact on clinical outcomes after KT[126,127], the majority of studies so far reported indicate that HCV infection is associated with increased liver-related mortality and fibrosis progression among HCV-infected KT patients, with a significant reduction in patient and graft survival, possibly related to accelerated fibrogenesis and increased liver damage induced by the use of immunosuppressive regimens[88,91-93,123,128-133]. Recent evidence also suggests that KT recipients with chronic HCV infection have an increased risk of post-transplant *de novo* glomerulonephritis[89,90,134], diabetes mellitus[90,135], and azathioprine hepatotoxicity[136].

In contrast to what is observed in CKD patients under dialysis, HCV-positive KT recipients more often present with false-negative anti-HCV results, even with newer immunoassays[63,137]. In a recent study, 19 out of 417 KT recipients were HCV RNA-positive and 3 of those patients (16%) were anti-HCV-negative by using chemiluminescence immunoassays[63]. This inability to mount an antibody response against HCV is probably related to the immunosuppressive therapy. Another consequence of immunosuppression is the significant increase in HCV viral load, with no reports of intermittent viremia so far[9,138]. Interestingly, similarly to hemodialysis subjects, there is a very low prevalence of occult HCV infection in KT recipients[63].

Table 4 Studies on the treatment of chronic hepatitis C in kidney transplant recipients

Ref.	Year	*n*	Therapy	Interferon dose	Duration (mo)	SVR
Harihara *et al*[154]	1994	3	IFN	3-6 MU *biw*	NA	NA
Therret *et al*[155]	1994	13	IFN	3-5 MU *tiw*	About 4	NA
Magnone *et al*[156]	1995	11	IFN	1.5-5.0 MU *tiw*	6	NA
Rostaing *et al*[157]	1995	14	IFN	3 MU *tiw*	About 5	0%
Ozgür *et al*[158]	1995	5	IFN	4.5 MU *tiw*	6	NA
Yasumura *et al*[159]	1997	6	IFN	6 MU *tiw*	About 7	33%
Durlik *et al*[160]	1998	11	IFN	3 MU *tiw*	About 6	0%
Hanafusa *et al*[161]	1998	10	IFN	9 MU *tiw*	6	10%
Tokumoto *et al*[162]	1998	6	IFN	9 MU *tiw*	6	50%
Baid *et al*[163]	2003	12	IFN + RBV	3 MU *tiw*	Variable	33%
Tang *et al*[164]	2003	4	IFN + RBV	3 MU *tiw*	12	50%
Shu *et al*[165]	2004	11	IFN + RBV	1 MU *tiw*	12	27%
Izopet *et al*[166]	1997	15	IFN	3 MU *tiw*	About 5	0%
Sharma *et al*[167]	2006	6	IFN + RBV	3 MU *tiw*	About 12	33%
Pageaux *et al*[168]	2009	8	PEG-IFNα2a	180 µg *qw*	6-12	50%
Aljumah *et al*[169]	2012	19	PEG-IFN + RBV	90-180 µg *qw*	12	42%
Sanai *et al*[170]	2013	32	PEG-IFN + RBV	135-180 µg *qw*	12	38%

IFN: Interferon; MU: Million units; *biw*: Two times a week; NA: Not available; *tiw*: Three times a week; PEG-IFN: Pegylated interferon; RBV: Ribavirin; SVR: Sustained virological response rate by intention-to-treat analysis.

There is still no consensus on the best immunosuppressive strategy in HCV-positive KT recipients. Antiviral activity of cyclosporine A (CsA), probably acting by antagonizing the effect of cyclophilin B on HCV replication[139], has been demonstrated both *in vitro* and *in vivo*[139-143], and it is possible that CsA may exert a beneficial effect on necroinflammatory activity in HCV-related liver disease among KT recipients[144-146].

Additional differences from hemodialysis patients are the higher prevalence of advanced liver disease in KT recipients[59,91,92], and the better accuracy of aminotransferases for the prediction of significant histological lesions[147-149]. Although liver biopsy is still recom-mended to evaluate the severity of hepatic lesions in patients on hemodialysis patients as well as in transplant recipients[150,151], several noninvasive methods for the assessment of liver fibrosis have been studied in HCV-positive KT patients, including simple blood tests[58], Fibro Test[85,152], and liver elastography[152,153], with fair diagnostic performances. In selected cases, these methods can be used as alternatives to liver biopsy. Screening for hepatocellular carcinoma and esophageal varices is indicated for patients with advanced fibrosis or cirrhosis.

As for antiviral therapy, there are several heterogeneous studies including small series of HCV-infected KT patients (ranging from 3 to 32 subjects), treated with standard or pegylated IFN alone or in combination with low dose ribavirin[154-170] (Table 4). Seventeen studies have been compiled in 2 meta-analyses[94,171], and the mean overall estimates for SVR with IFN monotherapy (10 studies), IFN plus ribavirin (4 studies) and PEG-IFN plus ribavirin (3 studies) were 16%, 36% and 43%, respectively.

Despite initial concerns about increased risk of graft dysfunction and loss, ranging from 0% to 40% in early studies[159-162,166], more recent series have shown lower graft rejection rates, between 0 and 5%[167-170]. Advances in immunosuppression therapy and the use of the less immunogenic PEG-IFN are possible explanations for this observation. However, dropout rates remain high (mean incidence of 28%) and do not differ greatly between early and recent studies[154-170], probably due to the worse anemia found in those receiving IFN in combination with ribavirin.

AASLD and KDIGO guidelines recommend against antiviral therapy for HCV-infected KT recipients, with the exceptions of fibrosing cholestatic hepatitis or life-threatening vasculitis[150,172]. Nevertheless, treatment with PEG-IFN and ribavirin should be considered for patients with advanced fibrosis, always taking into account time after transplantation, eGFR and renal function stability.

With the aid of EPO supplementation (doses up to 40000 IU/wk to maintain hemoglobin levels $\geq$ 10 g/dL), an initial ribavirin dose of 200 mg once a day is given, followed by increments of 200 mg every two weeks until the maximum dose tolerated, with target dosage of ribavirin defined according to eGFR (Table 2). After stabilization of ribavirin dosage (usually between 400 to 800 mg/d), interferon is initiated and used for 48 wk, irrespective of HCV genotype. Even in absence of comparative trials, it is suggested to use PEG-IFN (preferably PEG-IFN α2a 135-180 µg) once a week, in combination with ribavirin (see Figure 3). There are no studies supporting the use of DAAs for the treatment of KT HCV-positive recipients, but it is expected that these patients will benefit from interferon-free regimens.

SIDE EFFECTS OF ANTIVIRAL THERAPY

Treatment with IFN (standard or pegylated) and ribavirin is associated with frequent and sometimes serious side effects[173,174]. Among the latter are autoimmune diseases (worsening or *de novo* thyroid disorders, diabetes mellitus, psoriasis, *etc*.), significant hemolytic anemia and severe
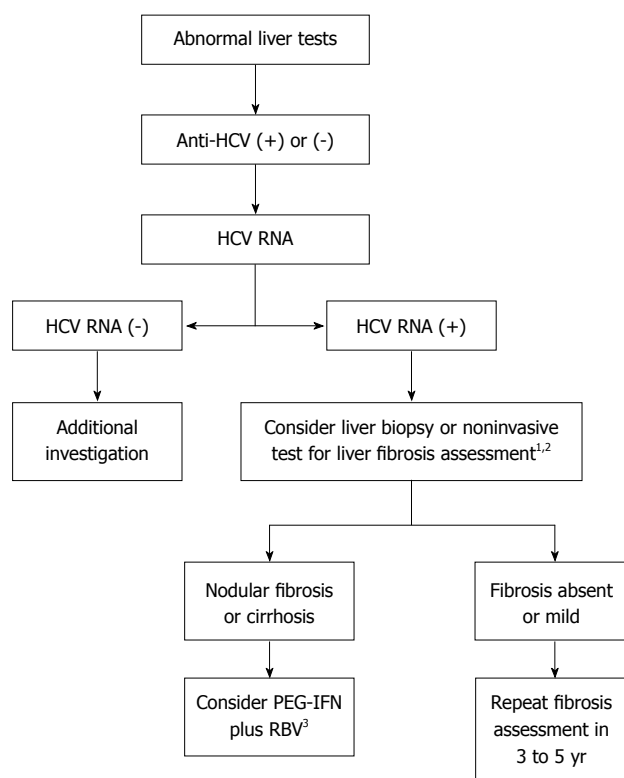
Figure 3 Treatment decision algorithm for hepatitis C virus-infected kidney transplantation recipients. [1]Particularly if time after transplantation > 5 years; [2]APRI, TX3, FibroTest or transient hepatic elastography; [3]Adjusted doses according to eGFR. PEG-IFN: Pegylated interferon; RBV: Ribavirin; eGFR: Estimated glomerular filtration rate.

depression. In a recent meta-analysis of eleven clinical studies published by Fabrizi *et al*[103], the summary estimate for dropout rate was 0.18 (95%CI: 0.08-0.35), with a large heterogeneity across studies, mainly due to anemia (24%) and infections (13%).

Except from hemolytic anemia, side effects are mainly related to IFN. The majority of the patients receiving IFN presents with a flu-like syndrome, characterized by diffuse myalgia, headache, fatigue and fever. Generally, these symptoms are self-limited and managed by common analgesics. Depression can be induced by IFN in 20% to 30% of the cases, usually after three months of treatment[175]. Being mild to moderate in intensity, IFN-induced depression can generally be handled with conservative measures, by non-psychiatrist professionals. However, if severe depression develops, HCV treatment must be stopped and the patient should be immediately referred to a psychiatrist. IFN-induced cytopenias (thrombocytopenia and leucopenia), are relatively common, typically dose-dependent and rarely associated with clinically significant complications, even in CKD patients. IFN dose reductions and the use of growth factors usually allow the continuation of therapy[173,174].

On the other hand, as previously discussed, the ribavirin-induced hemolytic anemia is very common and troublesome in CKD patients, due to its severity and potential noxious consequences in these subjects with high cardiovascular risk. Initial low doses of ribavirin,

early dose reductions, and EPO supplementation are the main strategies for the management of anemia in this context. It should be mentioned that ribavirin can carry an increased risk of birth defects, and proper contraception during and up to six months after therapy must be adopted. Minor side effects like cough and skin rash also seem to be mostly associated with ribavirin[173,174].

With the first-generation HCV protease inhibitors (PIs), boceprevir and telaprevir, complex drug-to-drug interactions and tolerability issues remain a concern[176,177]. Boceprevir is associated with an increased incidence of anemia and dysgeusia and telaprevir is associated with an increased incidence of dermatological disorders, anemia, and anorectal symptoms[178-181]. An approximately 15% to 26% increase in anemia incidence in patients under triple therapy with boceprevir or telaprevir has been observed[178-181]. In these patients, anemia is considered the consequence of the combined effects of ribavirin-induced hemolysis and the bone marrow suppression of IFN and PI. In the same manner of dual therapy, ribavirin dose reductions and EPO are used for the management of anemia, although blood transfusions are also frequently required. Dysgeusia and anorectal symptoms are infrequently severe and often improve under conservative measures and dietetic modifications. A wide spectrum of dermatological disorders has been described in approximately 50% of the patients treated with first-generation PIs, particularly with telaprevir, ranging from simple pruritus with or without rash to severe skin reactions like Stevens-Johnson's syndrome or DRESS syndrome[182]. Emollients/moisturizers and topical corticosteroids are sufficient for most cases (90% to 95%), but dermatological consultations are frequently needed for more severe cases. Treatment discontinuation is required in about 6% of patients[182].

NEW PERSPECTIVES FOR HCV THERAPY IN CKD PATIENTS

In spite of the increment in SVR rates with the use of the first-generation PIs telaprevir and boceprevir in subjects with preserved renal function, the higher incidence of significant side effects (mainly severe anemia and dermatological reactions) and the frequent drug-drug interactions have hampered their widespread use in difficult-to-treat populations, such as CKD patients. Newer DAAs, like sofosbuvir (a nucleotide NS5B polymerase inhibitor), simeprevir (a second generation PI), and daclatasvir (a NS5A replication complex inhibitor), with or without PEG-IFN and/or ribavirin, or used in different combinations with one another, produces SVR rates superior to 90%[183-188]. Besides leading to the highest SVR rates ever seen, these emerging DDAs seems to exhibit a reduced potential for drug-drug interactions and a better safety profile, which will probably facilitate their use for the treatment of HCV infection in CKD subjects. However, the

appropriate dose of sofosbuvir has not been identified for subjects with severe renal impairment (eGFR < 30 mL/min per 1.73 m^2) or hemodialysis patients and dose adjustments might be necessary[189]. Likewise, although simeprevir is primarily metabolized by the liver and its renal elimination is minimal, the safety of the drug has not been evaluated in patients with CKD stages 4 and 5. Conversely, unpublished data suggested that dose reduction would not be needed for the use of daclatasvir in patients with any stage of renal impairment. Finally, a phase 3 study will evaluate the safety and efficacy of the all-oral and IFN-free combination therapy with ombitasvir (a NS5A replication complex inhibitor), ABT-450 (a second-generation PI) and dasabuvir (a non-nucleoside NS5B polymerase inhibitor), with or without ribavirin, for the treatment of genotype 1-infected CKD patients (ClinicalTrials.gov identifier NCT02207088)[190].

CONCLUSION

HCV infection is highly prevalent among CKD subjects and, consequently, in KT recipients, exerting a significant negative impact on clinical outcomes both before and after KT. Although interferon-based antiviral therapy in CKD patients is associated with poor tolerability and suboptimal efficacy, there has been mounting evidence that many patients can benefit from treatment. In those individuals, accurate characterization of liver disease and adequate assessment of comorbidities are mandatory for optimal management and therapeutic decisions.

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