Hepatitis C virus (HCV) infection remains frequent in patients on renal replacement therapy and has an adverse impact on survival in infected patients on chronic hemodialysis as well as renal transplant (RT) recipients. Nosocomial spread of HCV within dialysis units continues to occur. HCV is also implicated in the pathogenesis of renal dysfunction often mediated by cryoglobulins leading to chronic kidney disease as well as impairing renal allograft function. The role of antiviral therapy for hepatitis C in patients with renal failure remains unclear. Monotherapy with conventional interferon (IFN) for chronic hepatitis C is probably more effective in dialysis than in non-uraemic patients but tolerance is lower. Limited data only are available about monotherapy with pegylated interferon and combination therapy (pegylated IFN plus ribavirin) for chronic HCV in the dialysis population. Clinical experience with antiviral therapy for acute HCV in dialysis population is encouraging. Interferon remains contraindicated post-RT because of concerns about precipitating graft dysfunction. Sustained viral responses obtained by antiviral therapy in renal transplant candidates are durable after renal transplantation and may reduce HCV-related complications after RT (post-transplant diabetes mellitus, HCV-related glomerulonephritis, and chronic allograft nephropathy).

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Keywords: Hepatitis C virus; Renal failure; Dialysis; Renal transplantation; Glomerulonephritis; Interferon; Ribavirin

1. Introduction

Patients with chronic kidney disease (CKD) on renal replacement therapy especially hemodialysis (HD) continue to have a higher prevalence of hepatitis C virus (HCV) infection than the general population. The prevalence of anti-HCV seropositivity in patients undergoing regular dialysis in developed countries ranges between 7% and 40% [1–3].

Important insights gained in the last decade include more accurate diagnostic testing for HCV in CKD and prevention of nosocomial HCV transmission [4]. A detrimental effect of HCV on survival in dialysis patients and renal transplant recipients has been confirmed [4]. Despite these advances, the management of hepatitis C virus-infected patients with CKD is complex and there are several issues, such as the role of antiviral therapy in dialysis patients and post-renal transplant that remain unresolved. In addition, at least some patients develop CKD as an extrahepatic manifestation of HCV. In transplant recipients, renal injury has been described in renal and hepatic recipients.

The aim of this paper is to review recent data on HCV infection and CKD.

2. Diagnosis of HCV infection

Serologic detection of antibody to HCV antigens by enzyme-linked immunoassay (ELISA) remains the
initial test for HCV diagnosis in CKD. With older serological techniques there were some important concerns about accurate diagnosis of HCV in patients with CKD. The first- and second-generation tests lead to frequent false-negative results; Bukh et al. [5] reported that 2.6% of dialysis patients seronegative by second-generation ELISA were viremic by polymerase chain reaction (PCR). The third-generation ELISA test however is more specific and sensitive in patients with CKD. In one series of 81 dialysis patients, no false-negative serology were found [4]; however, in another report of 2576 patients, 6 (0.23%) were seronegative but PCR positive [6]. Although the serological diagnosis of HCV in CKD is now accurate, management decisions however requires confirmation of viremia and identification of specific genotype as well as assessment of viral load. RIBA testing in CKD has generally been surpassed by PCR-based technology which has been extensively evaluated in patients with CKD especially in the HD population. Samples for HCV-RNA testing in dialysis patients should be obtained prior to the HD procedure; heparin used during dialysis sessions can interfere with the PCR technique. In addition, the HD procedure can lower HCV RNA levels by adsorption of HCV RNA onto the inner surface of dialyzers and destruction of viral particles by the hydraulic pressure exerted by the blood for dialysis [7]. The HCV RNA qualitative assay based on transcription mediated amplification (TMA) will probably increase sensitivity but it has been studied in a relatively small number of CKD patients. The largest series included 366 hemodialysis patients from Greece [8]. The detection of HCV infection increased with the use of sensitive HCV RNA (TMA) by 33.3% (44/132). In another study, 22 HD patients (7%) were negative by second-generation EIA but TMA positive [9]. The development of two commercial real-time PCR assays has facilitated the reproducible highly sensitive detection of HCV RNA among different laboratories [10]. The clinical significance of reduction in HCV RNA levels during dialysis requires further evaluation but has been suggested to be of potential benefit if antiviral therapy is used [11].

3. Epidemiology of HCV in CKD patients (dialysis population)

The advent of the serologic screening of blood for HCV, the routine use of erythropoietin for CKD patients with anemia, and the implementation of infection control procedures to prevent spread of HCV within dialysis units has helped to reduce transmission of HCV infection among patients on maintenance hemodialysis in the developed world. The prevalence of HCV infection patients on hemodialysis is variable but is consistently higher than in the general population. Anti-HCV seropositive rate among patients on chronic HD in the United States in 2002 was 7.8% ($n = 164,845$), having been 10.4% in 1995 [1]. The prevalence of anti-HCV seropositive patients among patients undergoing regular dialysis in Western Europe currently ranges between 3% and 20% [1–4].

As shown in Table 1, information on the prevalence and incidence of HCV infection in patients on long-term dialysis in developing countries is limited but single-center surveys show continued high prevalence and incidence rates [12–14]. 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.

4. Nosocomial transmission of HCV within HD units

The transmission of acute HCV among patients on maintenance HD, despite the absence of typical parental risk factors, is supported by various observations: an independent association between time on HD and HCV seroprevalence [15], the relationship between prevalence and incidence of anti-HCV in individual HD units [16], a higher frequency of anti-HCV seropositivity in patients on HD at a hemodialysis center compared with patients on peritoneal dialysis [17] and home-HD treatment [18], and the relative homogeneity of HCV isolates in patients receiving treatment in the same HD unit [19]. The small but definite incidence of acute HCV infection detected in chronic HD patients, after the elimination of post-transfusion HCV, also confirms nosocomial HCV transmission.

Nosocomial HCV transmission among patients dialyzed simultaneously in the same room has been unequivocally shown [20–24]. A total of 49 HD cases of acute HCV were identified over a 3-year follow-up in a Japanese study [20]. The investigators observed that some nurses withdrew needles for dialysis access in several consecutive HD patients without changing gloves between patients. After education of staff members and application of an

| Table 1 |
|---------------------------------|-----------------|----------------|
| Country                     | Anti-HCV positives | Reference year |
| Moldavia                   | 75% (111/148)   | 1999          |
| Egypt                      | 80% (169/210)   | 2000          |
| Saudi Arabia               | 43.4% (86/198)  | 2004          |
| Iran                       | 24.8% (74/298)  | 2005          |
| Turkey                     | 19% (83/437)    | 2005          |
| Morocco                    | 76% (141/186)   | 2005          |
| Tunisia                    | 20% (79/395)    | 2006          |
| Brazil                     | 16.4% (180/1095) | 2007         |
| Sudan                      | 23.7% (56/236)  | 2007          |
adhesive pad at the time of needle withdrawal, no further cases of acute HCV were recognized for more than 1 year in 730 patients on regular HD. Kokubo et al. [21] suggested that sharing of contaminated multidose vials of heparin-saline solutions was responsible for an HCV outbreak in their HD unit. Poor hand washing before and, less frequently, after activities which involved a risk of nosocomial transmission was described by Arenas et al. [25] as an important cause of HCV spread in HD. These authors also carried out a multicenter survey to evaluate the extent of compliance with standard precautions by HD staff in nine Spanish HD units [26]. Hand washing was performed only 13.8% of the time before patient contact, and 35.6% of the time after patient contact. Gloves were actually used on 92.9% of occasions indicated by unit policy.

The transmission of HCV between patients receiving hemodialysis on the same day on different shifts but sharing the same HD machine is consistent with transmission possibly via dialysis machines but appears uncommon [27]. Dialyzer reuse has been identified as a risk factor for seroconversion for HCV in a Portuguese study. In units that reprocessed dialyzes, centers that used a separate room to reprocess dialyzers from anti-HCV-positive patients, and those that did not reprocess dialyzers from anti-HCV-positive patients had significantly lower incidence rates compared with those that did not follow any specific precautions [28]. It remains unclear whether this reflected a causal relationship or a better adherence to infection control practices in centers with a separate room for reuse (or no reuse) in HCV-infected dialysis patients.

There is no consensus about the need to isolate HCV-infected patients on maintenance HD by rooms, machines and staff analogous to HBsAg positive patients on regular hemodialysis. Hepatitis C and B (HBV) viruses are parenterally transmitted, and the isolation of HBsAg positive patients has been successful in limiting spread of HBV within HD units. However, a need to isolate is not universally accepted. The infectivity of HCV is lower than HBV, and the virus is not viable at room temperature. Two large prospective studies have addressed the impact of isolation measures on HCV transmission to hemodialysis patients [2,22]. No significant link between nosocomial transmission of HCV to hemodialysis patients and absence of isolation was noted. A Belgian prospective multicenter study eliminated nosocomial spread of HCV (from 1.4% to 0%) over a 54-month follow-up in the absence of any isolation policy but by close attention to blood-borne precautions [29]. A similar reduction was achieved by others [30]. The CDC does not recommend designated machines or patient isolation; no ban on dialyzer reuse has been advocated [31,32]. A strict adherence to standard precautions and routine HD unit precautions fully prevents HCV transmission to HD patients.

5. Natural history of HCV in CKD patients (dialysis population)

Accurate assessment of the natural history of HCV in dialysis patients and renal transplant recipients has been difficult as infection in these patients is typically asymptomatic with an apparently indolent course. Dialysis patients generally have high morbidity and mortality rates reflecting age and comorbid conditions making the long-term consequences of HCV infection difficult to determine. Routine evaluation of HCV infection is further complicated in CKD by aminotransferase values which are typically lower in the dialysis than in the non-uraemic population. Dialysis patients with HCV viremia have aminotransferase levels greater than those who do not, although values remain within the so-called ‘normal range’ [33].

However, studies with appropriate size and follow-up have shown an independent and significant association between anti-HCV positivity and diminished patient survival [34–37]. A recent meta-analysis on the impact of HCV on mortality (seven observational studies involving 11,589 unique patients on maintenance hemodialysis) showed that the summary estimate for adjusted relative risk (RR) of all-cause mortality with anti-HCV was 1.34 with a 95% confidence interval of 1.13–1.59 [38]. Liver dysfunction has been implicated in a lower survival of seropositive patients; the summary estimate for RR of liver-related mortality with anti-HCV was 3.75 (95% CI, 1.93; 17.99) [38].

A more recent association with cardiovascular mortality has been identified with an independent and significant link between anti-HCV serologic status and cardiovascular mortality; the relative risk was 1.80 (95% CI, 1.1–2.95) in the subset of patients younger than 65 years [37]. This multivariate analysis was adjusted for case-mix and malnutrition-inflammation complex syndrome variables, which are associated with mortality.

6. Natural history of HCV in CKD patients (renal transplant recipients)

The most important causes of death after RT are cardiovascular disease, infection, and malignancy but liver-related deaths also play a role in increased mortality after renal transplant. Initial studies did not show a significant difference in survival for anti-HCV-positive RT recipients, particularly when 5-year but not 10-year survival rates were reported. Mathurin et al. [39] retrospectively studied 834 RT recipients over a 10-year follow-up period. No survival differences were seen at 5 years. However, at 10 years, patient and graft survival of HCV-infected patients were significantly lower than those described in uninfected matched RT controls,
been linked to an increased incidence of diabetes mellitus [49]. A recent meta-analysis of observational studies [40] has confirmed that positive anti-HCV antibody status was an independent and significant risk factor for death and graft failure after RT; the summary estimate for RR was 1.79 (95% CI, 1.57; 2.03) and 1.56 (95% CI, 1.35; 1.80), respectively.

In addition to an increased disease burden due to liver disease, HCV infection in the kidney transplant recipient has been implicated in the pathogenesis of acute glomerulopathy [41], de novo immune complex glomerulonephritis in the allograft [42–44], and a higher rate of chronic allograft nephropathy [45]. HCV has also been linked to an increased incidence of diabetes mellitus following renal transplantation (PTDM) [46].

7. Liver biopsy data in CKD

There is a lack of liver biopsy data in patients with HCV and CKD. Glicklich et al. [47] found that the total histological score and stage were similar between 22 patients on the waiting list for RT and 45 RT recipients seropositive for anti-HCV. There were no patients with cirrhosis, and only three with stage 3 fibrosis in the sub-group of renal transplant candidates. In 37 anti-HCV seropositive patients with chronic renal failure who were referred for kidney or kidney/liver transplantation, cirrhosis was present in 25% (9/37), and some degree of fibrosis in 81% (30/37). No relationship between severity of histologic changes and HCV viral load or genotype or aminotransferase activity was apparent. In this study [48], there was a high frequency of patient referral for combined kidney/liver transplantation perhaps accounting for the frequency of advanced fibrosis. Sterling et al. [49] evaluated liver histology in 50 consecutive patients with chronic HCV awaiting RT. Bridging fibrosis or cirrhosis was present in 22%, which was not significantly different from a control group of HCV-positive patients with intact renal function and normal ALT, although there was a trend towards more fibrosis in the dialysis group. These studies suggest that advanced fibrosis is a common histologic finding in individuals otherwise believed to be acceptable RT candidates despite ‘normal’ aminotransferase values. As in other studies of HCV in CKD, patients evaluated for possible RT are generally a more robust cohort than dialysis-dependent patients as a whole. Patients with clinically overt liver disease might be precluded from RT evaluation, perhaps helping to underestimate the consequences of HCV in CKD. The role of non-invasive evaluation of liver fibrosis in HCV-infected patients with CKD requires further study. The Fibroscan machine which is currently undergoing clinical evaluation appears useful at excluding cirrhosis in patients with chronic liver disease [50] and may have a role in CKD patients with HCV infection.

As cirrhosis constitutes an important risk factor for death and renal dysfunction after renal transplantation alone, combined kidney/liver transplantation should be considered for renal transplant candidates with cirrhosis even without overt hepatic decompensation. The recently published KDIGO guidelines from the International Society of Nephrology suggest that isolated renal transplant may be a reasonable consideration in patients with well compensated cirrhosis [51].

8. Kidney donor with HCV-positive serology

HCV can also be transmitted from infected donors to recipients by kidney transplantation [52,53]. A number of mechanisms have been suggested to explain the variance in reported transmission rates: prevalence of HCV viremia among cadaveric donor pools, viral load, and recipient susceptibility. The rate of HCV transmission has been much higher using slush perfusion of organs than in those using pulsatile perfusion [54].

The prevalence of a positive second-generation anti-HCV test among U.S. cadaver organ donors was 4.2% in 1992 [55]. The high prevalence of HCV among dialysis patients awaiting RT and the shortage of cadaveric kidneys led some groups to evaluate efficacy and safety of using kidneys from HCV-infected donors in recipients already infected with HCV [56,57]. This approach shortened waiting times for these patients and did not affect a short-term survival or invariably lead to progressive liver disease. In contrast, a large registry analysis demonstrated that use of grafts from HCV-infected donors was associated with a high rate of mortality, regardless of the anti-HCV antibody status of the recipient [58]. This study, although large, is limited by the absence of information on recipient baseline liver disease or comorbidity, or the rationale for use an HCV-infected donor kidney. Transplantation of kidneys from donors infected with HCV should be restricted to recipients with positive HCV viremia at the time of transplant. The UNOS database indicates that the use of kidneys from anti-HCV-positive deceased donors in HCV-infected recipients is associated with superior patient survival compared to remaining on dialysis [59]. The potential risks of superinfection with an HCV donor genotype different from that of the recipient is unknown. Genotype superinfection through transplantation has been reported in a few cases and a 10-fold increase in transaminase levels was observed [60,61]. Recently, a multicenter survey found no impact on patient or graft survival [62]. In contrast, use of organs from HCV-positive donors has been unequivocally associated with severe acute hepatitis in HCV naïve recipients and is contraindicated [52].
9. Therapy of chronic hepatitis C in CKD population (dialysis patients)

9.1. Monotherapy with standard interferon

Monotherapy with standard IFN in HCV-infected patients on maintenance hemodialysis has been evaluated in numerous albeit generally small clinical trials [63–79] Table 2, only a few of which were controlled [66,69,73]. A recent meta-analysis identified 24 trials (529 unique patients) demonstrating that the summary estimate of the sustained virological response (SVR) was 39% (95% CI, 32; 46), and 33% (95% CI, 19; 47) for genotype 1 [80]. Paradoxically sustained viral responses are higher in patients on maintenance hemodialysis compared to patients with intact kidney function. Several mechanisms may account for this observation: dialysis patients with HCV usually have a lower viral load, liver disease may be milder [46], and a release of endogenous interferon during hemodialysis sessions has been described [81]. Further, there is impaired clearance of standard interferon in patients on maintenance hemodialysis [82,83].

However, tolerance to interferon monotherapy is lower in patients on maintenance hemodialysis with a drop-out rate of 19% (95% CI, 13; 26) [80]. The profile of side-effects to interferon therapy in dialysis patients seems different from normal controls; in addition to flu-like symptoms (17%), other common side-effects leading to interruption of interferon therapy in dialysis patients are neurological (21%), and gastrointestinal (18%).

It is unproven whether achieving an SVR translates into improved survival in the CKD population with HCV infection. However, SVR results in improved liver histology [63,73]. Huraib et al. [73] observed that histology activity index (HAI) score decreased from 4.27 ± 1.19 to 1.64 ± 0.67 (P = 0.0001) after IFN-alpha treatment in 15 hemodialysis patients on a cadaveric renal transplant list who underwent repeated liver biopsy (before and at the end of IFN-α treatment). Pol et al. have recently given standard IFN to three dialysis patients with HCV-related cirrhosis; tolerance to treatment was satisfactory and liver histology in two of them improved significantly [84].

However, there is concern about the applicability of these results to all dialysis patients since most subjects in these studies were on the waiting list for RT and were probably more robust than the general HD population. Only limited information is available from North American centers where many CKD patients are African-American which is a predictor of impaired response to interferon [85].

9.2. Combined (standard interferon plus ribavirin) antiviral therapy

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. A lack of information about appropriate ribavirin dosing and concerns about side-effects, i.e. severe hemolytic anemia, have limited the use of ribavirin in dialysis patients [86–88]. In a concentration-controlled study, Bruchfeld et al. [87] used combined therapy in six dialysis patients: the SVR was 17% (one of six). Average daily doses were 170–300 mg ribavirin. Ribavirin-induced anemia was treated with high doses of erythropoietin (20,000–30,000 IU/week).

Others [88] have given standard IFN plus ribavirin (200 mg × 3/week) for 24 weeks to nine patients on maintenance HD with a SVR of 66% (six out of nine). In another 11 patients the SVR rate was 55% (six out of 11). No additional side-effects were reported at this lower ribavirin dose.

9.3. Monotherapy with pegylated interferon

No significant differences 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 vs. 20–40 mL/min) have been detected [89]. However, pharmacokinetics of pegylated interferon α-2a during hemodialysis may vary reflecting permeability and dialyzer pore size [90].

A single dose pharmacokinetic study of pegIFN α-2b found its mean area under the serum concentration-time curve and C_max (maximum concentration in serum) was increased up to twofold in patients with renal failure compared with controls; mean half-life increased by up to 40% [91]. In a separate analysis of hemodialysis patients in the same study, it was observed that the HD procedure had negligible effects on clearance. A single dose study in patients on maintenance hemodialysis identified no additional toxicity although there was a 30% reduction in IFN clearance [92].
The largest series to date of anti-HCV-positive patients on chronic HD (n = 78) treated with pegIFN-α2a (135 mcg s.c. weekly) was reported by Covic et al. [93]. The SVR rate was 14.1% (11/78) and a high rate of adverse effects (83%) was recorded.

As listed in Table 3, the use of pegylated interferon is mostly based on small uncontrolled clinical trials [94–102].

9.4. Combined (pegylated interferon plus ribavirin) antiviral therapy

Information on combined antiviral therapy is even more preliminary in nature [103–106]. Bruchfeld et al. [103] administered pegIFN plus ribavirin to dialysis patients, four patients were given pegIFN-α2b and two pegIFN-α2a. Average ribavirin dose was 170–300 mg/day. The SVR and drop-out rate were 50% (three out of six) and 50% (three out of six), respectively.

The successful management of ribavirin-induced anemia in dialysis patients has been described by Rendina et al. [104] in a prospective, controlled trial. The SVR rate was 97.5% (34/35) in chronic hemodialysis patients receiving peginterferon alfa-2a (135 mcg/week) plus ribavirin (200 mg/day) for 24 or 48 weeks (according to HCV genotype). One patient discontinued therapy prematurely due to anemia, and 26 (74%) required the epoietin-alfa dose to be increased to 40,000 IU/week up to the end of the study. Eleven (31%) patients required reduction of the ribavirin dosage (from 200 mg/day to 200 mg on every other day). The high SVR and tolerance reflected several factors including study design. Only young patients on the waiting list for renal transplant were included; most patients had mild liver disease [52% (12/23)].

Table 3
Antiviral therapy based on pegylated IFN (alone or with ribavirin) for chronic hepatitis C in dialysis patients: SVR rate (sustained virological response) according to ITT (intention-to-treat) analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>SVR</th>
<th>Antiviral agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annichiarico et al. (2004)</td>
<td>33.3% (2/6)</td>
<td>Peg-IFNα-2b</td>
</tr>
<tr>
<td>Teta et al. (2005)</td>
<td>66.6% (2/3)</td>
<td>Peg-IFNα-2a</td>
</tr>
<tr>
<td>Russo et al. (2006)</td>
<td>12.5% (2/16)</td>
<td>Peg-IFNα-2b</td>
</tr>
<tr>
<td>Sporea et al. (2006)</td>
<td>30% (3/10)</td>
<td>Peg-IFNα-2a</td>
</tr>
<tr>
<td>Mukherjee et al. (2003)</td>
<td>22.2% (2/9)</td>
<td>Peg-IFNα-2b</td>
</tr>
<tr>
<td>Covic et al. (2006)</td>
<td>14.1% (11/78)</td>
<td>Peg-IFNα-2a</td>
</tr>
<tr>
<td>Casanovas-Taltavull et al. (2007)</td>
<td>25% (3/12)</td>
<td>Peg-IFNα-2a</td>
</tr>
<tr>
<td>Ayaz et al. (2008)</td>
<td>50% (11/22)</td>
<td>Peg-IFNα-2a</td>
</tr>
<tr>
<td>Li et al. (2008)</td>
<td>48% (12/25)</td>
<td>Peg-IFNα-2a</td>
</tr>
<tr>
<td>Bruchfeld et al. (2006)</td>
<td>50% (3/6)</td>
<td>Peg-IFNα-2a + R (n = 2)</td>
</tr>
<tr>
<td>Rendina et al. (2007)</td>
<td>97% (34/35)</td>
<td>Peg-IFNα-2a + R</td>
</tr>
<tr>
<td>Van Leusen et al. (2008)</td>
<td>71% (5/7)</td>
<td>Peg-IFNα-2a + R</td>
</tr>
</tbody>
</table>

* Study limited to patients with chronic renal failure (not on dialysis) with recurrent hepatitis C after OLT.

Less impressive results were reported by Carriero et al. [106] in a prospective, cohort trial with pegIFN-α2a plus low-dose ribavirin (200 mg/day) for chronic HCV in 15 patients receiving long-term dialysis. The SVR and drop-out rate were 29% (4/14) and 71% (10/14), respectively. The most frequent side-effect was anemia which required ribavirin discontinuation in three patients; seven (47%) patients received blood transfusion.

10. Therapy of chronic HCV in CKD population (renal transplant recipients)

No safe and effective therapy exists for the treatment of chronic HCV post-RT [107–110]. A meta-analysis of clinical trials of IFN-based therapy (interferon alone or with ribavirin) in RT recipients with chronic hepatitis C showed that the summary estimate for SVR and drop-out rate was 18.0% (95% CI, 7.0–29%) and 35% (95% CI, 20–50%), respectively [111]. The most frequent side-effect requiring interruption was graft dysfunction, typically acute rejection refractory to corticosteroid therapy.

Combined antiviral therapy (interferon plus ribavirin) has been used in a few studies. Shu et al. [109] treated 11 RT recipients with chronic HCV with a very low dose of IFN-α (1 MU by subcutaneous route three times weekly) for 48 weeks. Three patients terminated the therapy prematurely because of acute graft failure (one case) and urosepsis (two cases). Antiviral therapy with interferon needs to be considered only in patients [i.e., fibrosing cholestatic hepatitis (FCH)] in whom the risk of not treating justifies the possible loss of the allograft. Alternative regimens based on drugs other than interferon have been described but no proof of their efficacy has been provided. Amantadine [112], ribavirin monotherapy [113,114] or their combination [115] had no impact on viral levels or liver histology.

11. Therapy of chronic HCV in CKD population (renal transplant candidates)

There is increasing interest in treating HCV infection in RT candidates. Kamar et al. [116] treated 55 anti-HCV positive/HCV RNA positive hemodialysis patients with standard interferon monotherapy, 21 (38%) had an SVR. Of these, 16 (76%) underwent renal transplantation and received immunosuppressive therapy, including antithymocyte globulin. At 22.5 months after renal transplantation, HCV viremia was absent in all patients, and no patient developed PTDM. A case report also reported a patient with a durable SVR post-RT [117].

Pre-transplant interferon may also reduce the occurrence of post-transplant de novo or recurrent glomerulo-
nephritis. In a study [118], of 15 HCV-positive renal transplant recipients who received pre-renal 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 positive at transplantation). Among untreated controls, 12 out of 60 (19%) developed de novo HCV RNA positive at transplantation). Among untreated controls, 12 out of 60 (19%) developed de novo HCV RNA positive at transplantation. Pre-transplant antiviral therapy of HCV may lower the incidence of post-transplant diabetes mellitus (PTDM) in allograft recipients. In a controlled trial, Gursoy et al. [119] observed that the frequency of PTDM in allograft recipients who had not received IFN than in those who had been treated with IFN before transplantation, 25% (10/40) vs. 7.1% (1/14), P = 0.009.

An additional benefit of pre-transplant antiviral therapy may be a reduced incidence of chronic allograft nephropathy (CAN) as HCV infection has been implicated in its pathogenesis. In a large group of kidney transplant recipients with chronic HCV, Mahmoud et al. [45] found that a higher proportion of untreated controls developed chronic allograft nephropathy compared with IFN patients, 40.6% (13/32) vs. 5.6% (1/18), P = 0.009. The SVR rate was 44% (8/18) and 0% (0/32), in IFN-treated and control group, respectively (P < 0.05). By multivariate analysis, absence of IFN therapy before RT was a risk factor for chronic allograft nephropathy with an odds ratio of 11.6 (P = 0.020).

12. Therapy of acute HCV in CKD population (dialysis patients)

Acute HCV progresses to chronic infection in more than 90% of uremic patients [120,121]. Recent recommendations to monitor ALT in HD population may facilitate detection of cases of acute HCV [122–128].

In a prospective, controlled clinical trial Gursoy et al. [123] administered low- (3 MU) and high-dose (6–10 MU) IFN-α2a three times weekly for 3 months to 36 patients on regular hemodialysis with acute HCV. The SVR rate was 53% (19/36); six (16%) patients discontinued therapy as a result of side-effects. Three (50%) patients in the high-dose group had to stop therapy as a result from severe flu-like symptoms (n = 2), and leukopenia (n = 1). Viral clearance was observed in one patient (5.6%) of the control group.

In a controlled clinical trial, Al-Harby et al. [127] administered IFN-α (3 MU three times per week) for 12 weeks to nine adult patients with acute hepatitis C – six (67%) achieved an SVR. Two patients in the treatment group dropped out; one due to colitis and another because of non-compliance. No patients in the control group had RNA clearance. Based on these data, treatment of acute HCV if recognized should be attempted.

13. Therapy of HCV in CKD patients (HCV-associated glomerulonephritis)

Recent information at a population-based level has shown a significant link between HCV seropositivity and an increased risk for developing ESRD [129]. The role of HCV infection in glomerular diseases has been confirmed in both native and transplanted kidneys [130]. The most common form of glomerular diseases associated with HCV is type I membranoproliferative glomerulonephritis (MPGN) in patients with type II cryoglobulinemia. The majority of trials of antiviral therapy for HCV-related GN have confirmed a relationship between SVR and improvement in kidney function [131–135]. Rossi et al. [132] treated using combined therapy (standard IFN plus ribavirin, 12 months) three patients with HCV-related cryoglobulinic GN. All patients achieved an SVR and a decrease of daily proteinuria (3.47 ± 1.5 vs. 0.17 ± 0.12, P = 0.02) and rheumatoid factor [1320 (210–2142) vs. 112 (99–266) IU/mL on follow-up.

A recent meta-analysis of clinical, controlled trials of the two treatments (antiviral versus immunosuppressive) described for HCV-related GN [136] identified six studies involving 145 unique patients with HCV-associated GN [137–142]. The majority of patients had cryoglobulinic glomerulonephritis. The primary endpoint was the frequency of patients with reduction of proteinuria (return of proteinuria to normal or decrease >50%) at the end of therapy. Pooling of study results demonstrated that proteinuria decreased more commonly after standard IFN-doses than corticosteroid therapy, OR was 3.86 (95% CI, 1.44; 10.33; P = 0.007). The conclusion was that standard-IFN doses were more effective than immunosuppressive therapy in lowering proteinuria of patients with HCV-related cryoglobulinic GN at least in the short term.

Preliminary data support the use of rituximab, a human-mouse chimeric monoclonal antibody that is highly effective for in vivo B-cell depletion, for the treatment of HCV-associated GN. It has been suggested that rituximab interferes with monoclonal IgM production, cryoglobulin synthesis, and renal deposition of immune complexes (ICs). Two uncontrolled, pilot trials have been conducted (n = 11 patients) [143,144]. A decrease in proteinuria was found in both the trials with a concomitant reduction of serum levels of rheumatoid factor. No acute or delayed severe side-effects were seen. However, clinical relapses of glomerular disease after completion of rituximab therapy were found. Response is not universal [145].
14. Conclusions and recommendations

Despite screening of blood products nosocomial transmission of HCV continues to occur in HD units. HCV infection diminishes patient and graft survivals. Therapy of HCV in CKD is complicated but SVR can reduce post-RT complications. Antiviral treatment of HCV-related GN can result in improvement in renal function.

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