Hepatitis C virus infection in patients on renal replacement therapy

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Abstract
Hepatitis C virus infection is a frequent clinical problem in patients on dialysis and renal transplant recipients. The local prevalence rates of hepatitis C virus infection in patients on peritoneal dialysis, hemodialysis, or after kidney transplantation are 2%, 9%, and 6%, respectively. Conventional diagnosis of hepatitis C virus infection is by anti-hepatitis C virus immunoassays. However, up to 10% of immunosuppressed patients may be negative for anti-hepatitis C virus but positive for hepatitis C virus RNA. Repeated blood transfusions and a long duration of dialysis are major risk factors for hepatitis C virus infection among patients with renal failure. Although the risk of acquiring hepatitis C virus infection through transfusions has decreased considerably with the advent of screening tests for anti-hepatitis C virus, precautionary measures should be instituted rigorously at renal units to prevent nosocomial transmission. Hepatitis C virus infection in dialysis patients often assumes a relatively mild course. In contrast, renal allograft recipients can develop potentially life-threatening exacerbations, as exemplified by fibrosing cholestatic hepatitis. Liver disease of variable severity can be observed in about two thirds of hepatitis C virus-positive renal allograft recipients. In the majority of patients, however, the adverse effect of hepatitis C virus infection on survival may not be evident in the first decade after renal transplantation. Hepatitis C virus-positive patients with renal failure should not be excluded from kidney transplantation, but should be assessed individually with regard to the severity of liver disease before transplantation. Dialysis patients with hepatitis C virus infection, especially those with a potential for kidney transplantation, should be considered for treatment with interferon, because the risk of interferon in inducing renal allograft dysfunction is too high to justify its routine use in renal allograft recipients.

Key words: Chronic disease, Hepatitis/diagnosis, Kidney transplantation, RNA, Viral/analysis

中文摘要
丙型肝炎病毒感染在透析患者及接受腎臟移植者中十分常見。在本港，丙型肝炎病毒感染在患者間的流行率分別為2%、9%及6%。丙型肝炎病毒感染的傳統診斷以丙型肝炎病毒感染測定進行；然而，約10%免疫抑制患者可能對丙型肝炎病毒抗原呈性，但對丙型肝炎病毒 RNA 呈陽性。在腎功能衰竭患者中，重複輸血及長期透析是感染丙型肝炎病毒的主要危険因素。爾後隨著對丙型肝炎病毒抗原的篩查試驗的進步，輸血感染丙型肝炎病毒的風險已顯著減少，腎科部門仍應嚴格執行預防措施，以預防醫院傳播感染。在透析患者中，丙型肝炎病毒感染的病程通常較輕微；與之相比，在接受腎臟移植者中，丙型肝炎可能出現對患者的生約構成威脅的惡化，如纖維膽小管性肝炎。約有三分之二丙型肝炎病毒陽性，曾接受腎臟移植者患有不同程度的肝臟疾病；然而在大部份患者中，丙型肝炎病毒感染對存活的不良影響，在腎臟移植的首10年內不會出現。丙型肝炎病毒安徽香港醫學會

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Liver disease due to infection by the hepatitis C virus (HCV) or the hepatitis B virus (HBV) has an important impact on the outcome of patients on renal replacement therapy, and accounts for up to 30% of mortality in long-term renal allograft recipients (1-3). The hepatitis C virus was cloned in 1989, and has been identified as the major cause of non-A non-B hepatitis (4,5). The problem of HCV infection has continued to escalate because of the lack of an effective vaccine.

Patients on long-term dialysis and renal allograft recipients have increased risk of HCV infection, consequent to their transfusion requirement and the repeated risks of parenteral exposure in the former group, as well as the possibility of transmission via the transplanted organ. In addition, the course of HCV-related liver disease might exacerbate upon immunosuppression.

This article will review the current knowledge on the incidence and prevalence, the diagnostic approach, the major risk factors, and the measures to prevent HCV infection in patients with end-stage renal failure. The clinicopathological features of HCV-related liver disease in dialysis patients and those after renal transplantation will be discussed, although the impact of HCV infection on the long-term outcome of renal allograft recipients remains to be elucidated. Despite the improved efficacy of treatment for HCV infection with pegylated interferon with or without ribavirin in non-immunosuppressed individuals, these results may not be extrapolated to dialysis patients or those who have undergone kidney transplantation, in view of differences in tolerability to these therapeutic agents.

### Table 1. Prevalence of HCV infection in patients on renal replacement therapy.

<table>
<thead>
<tr>
<th></th>
<th>Anti-HCV+, %</th>
<th>HCV RNA+, %</th>
<th>Year/location</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>17</td>
<td>1991/Hong Kong</td>
<td>(6)</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td>1993/Hong Kong</td>
<td>(7)</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td>1997/Spain</td>
<td>(8)</td>
</tr>
<tr>
<td>27</td>
<td></td>
<td>23</td>
<td>1998/Miami, FL, US</td>
<td>(9)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>2001/Hong Kong</td>
<td>(10)</td>
</tr>
<tr>
<td>Peritoneal dialysis patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>1991/Hong Kong</td>
<td>(6)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>1992/Taiwan</td>
<td>(11)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>1995/Singapore</td>
<td>(12)</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>1996/Spain</td>
<td>(13)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>2001/Hong Kong</td>
<td>(10)</td>
</tr>
<tr>
<td>Renal allograft recipients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>12</td>
<td>1993/Hong Kong</td>
<td>(14)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>2001/Hong Kong</td>
<td>(10)</td>
</tr>
</tbody>
</table>
The incidence of new HCV infection has declined since the late 1980s due to the increasing use of erythropoietin and the screening of blood products and patients for HCV status (19). However, we have recently observed a disproportionately high incidence of new HCV infection among patients who have received kidney allografts from a neighboring region(s), especially in patients who have undergone hemodialysis or have received blood transfusions in these regions before transplantation. These observations strongly suggested suboptimal precautionary measures and/or screening of blood products at the respective renal units.

**Prevention of hepatitis C virus infection in dialysis units**

In view of the strong evidence for nosocomial transmission, universal precautions and procedures specific to hemodialysis units are crucial to minimize the risk of infection. These include:

1. wearing or changing gloves and aprons before contact, and washing hands after contact with patients, dialysis equipment, or potentially infectious surfaces or materials;
2. wearing a goggle or face mask and apron when exposure to blood or body fluids is expected;
3. routine cleaning and disinfection procedures—the dialysis circuit should be disinfected by standard procedures, and the surfaces of dialysis machines should be cleaned with an appropriate agent(s) after each session;
4. prohibition of sharing instruments or medications among patients, including multiuse vials; preparing and distributing medications from a centralized area, and avoiding the use of medication supply carts from patient to patient.

The renal unit should have an established program for regular surveillance of blood-borne viral infections in dialysis patients. In the event of new HCV infections, other susceptible patients who have shared the same dialysis sessions and/or machines with the index patient should be tested for HCV infection. Testing in high-risk susceptible individuals should be performed weekly for 3 months. Susceptible patients who have returned to the renal unit after receiving hemodialysis or a blood product transfusion in high- or unknown-risk areas should be tested for HCV infection covering the window period and, before the results are known, managed as potentially infected with the use of dedicated hemodialysis machines until the risk is discounted.

Hepatitis C virus carriers should receive hemodialysis using dedicated machines (20,21). Although the benefit of segregating hemodialysis rooms has remained doubtful provided that other precautionary measures are strictly maintained, it is still advisable, particularly in units with a high prevalence of HCV infection. Although the re-use of hemodialyzers has not been associated with an increased risk of viral hepatitis in patients or staff, it is common practice to exclude dialyzers from HCV-positive patients from re-use programs. Similarly, in view of the detection of HCV in peritoneal dialysis effluent, this should be handled as potentially infectious material (22).

**Transmission of hepatitis C virus through organ transplantation**

Data from the New England Organ Bank studies (23,24) have shown that about half of the recipients of organs from HCV-positive donors acquired the infection, and that life-threatening acute or chronic liver diseases could develop. Other investigators have reported variable rates of infection or the development of clinical manifestations (25-27). As in renal allograft recipients with a pre-existing HCV infection, it is difficult to predict the clinical outcome in individual patients who acquire de novo HCV infection after organ transplantation. Nevertheless, it is imperative that HCV-positive organs should not be transplanted into HCV-negative recipients. However, data to date suggest that the transplantation of HCV-positive kidneys into recipients who have a pre-existing HCV infection may not have a detrimental effect on the clinical outcome of the recipients up to 5 years after transplantation (28). The clinical consequence of superinfection with different genotypes of HCV remains to be established.

**DIAGNOSIS**

Hepatitis C virus is a single-stranded linear RNA virus from the *Flaviviridae* family. It has a lipid envelope, and the genome contains approximately 9400 nucleotides. Six major genotypes and more than 50 subtypes of HCV have been identified to date, some of which have been reported to be related to the clinical course and the response to therapeutic interventions. The virus also shows marked genetic heterogeneity, especially in the amino terminal end of the hypervariable region 1, and this has significant implications on serological diagnosis and the development of vaccines (29,30).
Antibodies to hepatitis C virus

Testing for circulating non-neutralizing antibodies to HCV (anti-HCV) is commonly used for the diagnosis of HCV infection. The viral genome encodes, from the N-terminal, the basic nucleocapsid (C), the first envelope glycoprotein (E1), the second envelope/nonstructural-1 glycoprotein (E2/NS1), followed by the other non-structural regions NS2, NS3, NS4, and NS5 (31). Different generations of enzyme-linked immunosorbent assays and recombinant immunoblot assays (RIBA) have evolved for the detection of antibodies to different components of HCV. Enzyme-linked immunosorbent assays are more often used to screen a large number of samples, whereas RIBA can be used for confirmation in view of its higher specificity. First-generation immunoaasys, which detect antibodies directed toward a recombinant NS4 antigen c100, are associated with high false-positive and -negative rates, and have become obsolete. Second-generation anti-HCV assays, which detect antibodies directed toward the c22 antigen from the nucleocapsid and the c200 antigen from the NS3/NS4 regions (as well as the 5-1-1 antigen in RIBA2 assays), have improved sensitivity and specificity, both of which approach 95%, and they detect anti-HCV at 4 weeks after exposure, compared with the 16-week window period for the first-generation tests (32). An additional recombinant antigen from the NS5 region is incorporated in third-generation tests, which have sensitivity and specificity rates of 97% and 100%, respectively (9,33).

Hepatitis C virus RNA

Hepatitis C virus RNA in blood samples can be detected qualitatively by reverse transcription and polymerase chain reaction (RT-PCR), using primers directed toward the highly conserved 5’ end of the viral genome (34). The presence of circulating HCV RNA provides the earliest evidence for HCV infection, often within 2 weeks of infection. The test is highly sensitive, and can detect HCV RNA at concentrations down to 2000 copies/mL. In view of the technical complexity, the requirement for careful handling of specimens, and the protocol variations among different laboratories, this test is usually reserved for confirmation of HCV infection status or for research purposes, but not for routine clinical diagnoses. Nevertheless, testing for HCV RNA is particularly useful in patients who have tested negative for anti-HCV when there is a high degree of suspicion based on clinical manifestations. In this regard, 10% to 20% of dialysis or transplant patients with HCV infection may be negative for anti-HCV by second-generation immunoaasys (32, 35-39). Furthermore, the presence of anti-HCV may not indicate persistent infection in patients who have been treated with interferon, where testing for HCV RNA is required to indicate success or failure of treatment.

With regard to quantitative assays for HCV RNA, quantitative PCR requires considerable technical expertise, whereas the branched-chain DNA assay shows better standardization and reproducibility. In this assay, the HCV RNA is captured to a solid phase by probes to the 5’ untranslated and core regions, after which the signal is amplified with the use of amplification multimers (40). The test is less sensitive than RT-PCR, and detects HCV RNA at concentrations down to 350,000 copies/mL. Nevertheless, the procedure is automated and reproducible, and provides useful information in patients under treatment. In this context, studies with quantitative assays have demonstrated that circulating levels of HCV RNA were higher in patients with end-stage renal failure compared with non-uremic patients (41).

Hepatitis C virus genotypes

In contrast to the 5’ non-coding region, the E1 and E2/NS1 regions of the HCV genome demonstrate much genetic heterogeneity. Convention classification divides HCV first into six major types, then into subtypes and isolates (42). Sequence analysis, PCR with genotype specific primers, restriction fragment length polymorphism analysis, and commercial line probe assays can be used for the typing of HCV at corresponding levels of precision (43-45). Infection with the 1b genotype has been associated with more severe liver disease and a less favorable response to interferon therapy, although the pathogenetic role of genetic heterogeneity in HCV-related liver disease remains to be defined (46-50). Our previous study (51) showed that the common genotypes in local patients on renal replacement therapy were 1b (78%), 1a (10%), and 6a (8%).

CLINICAL MANIFESTATIONS

Hepatitis C virus infection can lead to acute or chronic hepatitis. Acute hepatitis C is often asymptomatic or associated with mild clinical manifestations. The incubation period ranges from 1 to 26 weeks. Jaundice is uncommon, and it is rare for patients to have significant impairment of liver function (52). In view of the relatively minor clinical manifestations, regular surveillance of HCV infection in high-risk groups is indicated. It is to be noted that the development of anti-HCV may be delayed, and testing for circulating HCV RNA may be required for early diagnosis (53).

Hepatitis C virus infection is characterized by the propensity for chronicity, which has been reported to affect more than 80% of patients (54). The infection can persist despite normalization of elevated transaminase levels. Genetic heterogeneity and rapid mutation are important factors contributing to the persistence of HCV infection (55,56). Progression of liver disease in non-
immunosuppressed individuals with chronic hepatitis C is usually slow, with 20% to 50% of patients eventually developing cirrhosis after 20 to 30 years (57,58). Nevertheless, with the reduced incidence of HBV infection after the introduction of vaccination programs, chronic HCV infection has assumed increasing importance as a major cause of chronic liver disease. In this regard, more than 10 000 deaths in the United States are attributable to HCV infection annually. It has been reported that, annually, 1% to 2% of patients with compensated cirrhosis caused by HCV experience hepatocellular carcinoma (59,60), whereas 5- and 10-year survival rates have been reported as 91% and 79%, respectively, in non-immunosuppressed individuals (59). Disease progression can be affected by multiple host or viral factors (Table 3). It is interesting to note that the load of viral inoculum does not seem to have an effect on disease progression (67). In addition, the course of HCV-related liver disease can be modulated by the immune responsiveness of the host, so that accelerated disease progression can occur in immunosuppressed patients, as exemplified by fibrosing cholestatic hepatitis (68).

**Patients on dialysis and kidney transplant recipients**

Although the level of transaminases is related to the activity of HCV-induced liver disease in general, the correlation between biochemical and histological manifestations is weak in individual patients. The normal range of serum transaminases for patients without liver disease is lower for dialysis patients compared with non-dialyzed patients. An abnormal level of transaminases has been noted in a variable proportion of HCV-positive dialysis patients, ranging from less than 10% to 70%, and is not a reliable indicator of the severity of liver disease (7,69-71). Data from histological investigations showed that the pathology of HCV-induced liver disease in most patients on dialysis was relatively mild, and similar to non-renal failure patients with persistently normal transaminase levels (41).

We have reported that the level of circulating HCV RNA increased upon immunosuppression (72). Although there is a general trend that HCV-related liver disease also becomes more severe after kidney transplantation, the relationship between increased viral replication and disease progression is again not absolute (73-75). A small proportion of patients can develop fulminant exacerbation of HCV-induced liver disease, as exemplified by fibrosing cholestatic hepatitis, whereas others can retain apparent clinical stability over an extended period, even without elevation in the level of liver enzymes (68,76,77). Genotypic variations cannot totally account for the heterogeneity in clinical manifestations (78). Our previous study in local patients (14) showed that 70% of HCV-positive renal allograft recipients developed abnormal levels of liver enzymes, and 50% demonstrated recurrent or persistent abnormalities. In addition to elevated serum transaminase levels, these patients can have prominent increases of the ductal enzymes. Half of the patients showed histological evidence of chronic hepatitis with varied degrees of cirrhosis, and histological abnormalities were more severe in patients with persistent biochemical derangements. Our results also showed that early onset of biochemical derangements after kidney transplantation was associated with an unfavorable liver prognosis (14).

Fibrosing cholestatic hepatitis can complicate HBV or HCV infection in immunosuppressed patients, and is characterized by periporal fibrosis, ballooning of hepatocytes, marked cholestasis, yet relatively mild inflammatory infiltration on histological examination, in the face of markedly accelerated viral replication so that the hepatocytes contain abundant virus particles (76). This complication has been associated with a high mortality, but can respond favorably to interferon therapy (79). The pathogenesis is related to the suppressed host immune responsiveness, thereby resulting in unabated

### Table 3. Factors that may modulate the rate of progression or the severity of HCV-related liver disease.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic polymorphisms with TGF β1 and angiotensin II</td>
<td>hepatic fibrosis</td>
<td>(61)</td>
</tr>
<tr>
<td>Age of patient</td>
<td>progression</td>
<td>(57,62)</td>
</tr>
<tr>
<td>40-55 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geographic locality</td>
<td>Different incidences of liver cancer</td>
<td>(63)</td>
</tr>
<tr>
<td>Host immune response</td>
<td>Varied severity of chronic hepatitis</td>
<td>(64)</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>progression</td>
<td>(65)</td>
</tr>
<tr>
<td>HCV genotype</td>
<td>Varied severity</td>
<td>(48-50)</td>
</tr>
<tr>
<td>Coinfection with HBV</td>
<td>severity</td>
<td>(66)</td>
</tr>
<tr>
<td>Histologic inflammation and bridging fibrosis</td>
<td>progression</td>
<td>(58)</td>
</tr>
</tbody>
</table>

TGF = transforming growth factor
viral replication. With regard to the immunopathogenetic mechanisms of HCV-induced liver disease in kidney transplant recipients, we reported that peripheral blood suppressor/cytotoxic T lymphocytes were increased, whereas activated helper/inducer T lymphocytes and natural killer cells were reduced in HCV-positive renal allograft recipients (80). Furthermore, increased non-major histocompatibility complex-restricted cytotoxic T cells and reduced natural killer cells were associated with the presence or absence of liver disease, respectively, suggesting that immune mechanisms were involved in the pathogenesis of chronic hepatitis C after renal transplantation.

In view of the slow disease progression in the majority of patients, long-term studies are required to examine the impact of HCV infection on the morbidity and mortality of kidney transplant recipients. In the majority of renal allograft recipients, HCV infection per se does not seem to reduce patient survival up to 7 years after transplantation (69,73,78,81-83). Increased morbidity and mortality attributable to liver disease have been reported, especially in series with prolonged follow-up, and it is likely that a significant proportion of patients will ultimately experience liver complications (84,85).

Assessment of hepatitis C virus-positive dialysis patients before kidney transplantation

Although the risk of developing liver-related complications is likely to increase with increasing time after transplantation in HCV-positive renal allograft recipients, the magnitude of such long-term risks may still compare favorably to keeping HCV-positive patients on dialysis. Indeed, it was demonstrated that the outcome of HCV-positive renal allograft recipients was better than their counterparts who had remained on long-term dialysis (86). There have been conflicting observations on whether HCV positivity had a negative impact on patient survival after kidney transplantation (87,88). In addition to death from liver disease, some authors have reported a higher incidence of severe infections in HCV-positive individuals (87). The apparent discrepancies could be partly accounted for by the heterogeneous severity of liver disease before transplantation and the different immunosuppressive regimes. There is general agreement that HCV infection per se should not be regarded as a contraindication against kidney transplantation, but that prospective kidney transplant recipients must be carefully assessed with regard to the severity of liver disease, preferably with the aid of liver biopsy. The role of genotyping and monitoring the virus load after transplantation in the clinical management of patients has not been established. The latter theoretically may allow earlier detection of disease exacerbation and thus therapeutic intervention. Patients must be counseled before transplantation about the subsequent risk of liver complications, and the possible requirement for interferon therapy, because the latter might have a detrimental effect on the renal allograft.

Hepatitis C virus-related renal diseases after kidney transplantation

Membranoproliferative glomerulonephritis, with or without cryoglobulinemia, is the most common form of HCV-related allograft disease, affecting up to 5% of HCV-positive renal allograft recipients (89,90). Associations between allograft membranous nephropathy or thrombotic microangiopathy and HCV infection have also been reported (91,92). The onset of clinical manifestations attributed to these complications can vary from months to years after transplantation. Whether these complications might respond to interferon therapy has not been elucidated, but allograft survival could be reduced by the immunological actions of interferon per se.

MONITORING AND TREATMENT

In view of the increased propensity for liver complications, HCV-positive patients should be monitored with regard to their hepatic activity, the development of cirrhosis, and the development of hepatocellular carcinoma. Regular measurement of the levels of liver enzymes and alpha fetoprotein is mandatory. It is noteworthy that the normal upper limits of liver enzymes are lower in dialysis patients compared with non-dialyzed individuals. The prothrombin time should be measured when there is suspicion of liver disease that might result in significant functional impairment, when surveillance for other complications of portal hypertension is also indicated. The levels of calcineurin inhibitors need to be closely monitored in renal allograft recipients with chronic active hepatitis, in view of their predominant metabolism by the liver.

Interferon, pegylated interferon, and ribavirin

About 5% to 15% of non-uremic patients with chronic hepatitis C can achieve sustained virologic response to interferon monotherapy given at 3 to 6 MU three times weekly for 6 to 12 months, with concomitant improvement in liver abnormalities (93). The response rate increases 30% to 40% after combination therapy with ribavirin. Factors that affect the response rate include:

1. hepatitis C virus genotype—genotype 1 responds less well to therapy compared with genotypes 2 or 3;
2. liver histology—the response rate may be lower in patients with bridging fibrosis or cirrhosis;
3. virus load—high baseline levels of HCV RNA have been associated with lower response rates.

The attachment of polyethylene glycol to interferon reduces its rate of absorption after subcutaneous injection, reduces its renal and cellular clearance, and decreases its immunogenicity, thereby resulting in prolongation of its half-life. A controlled study with pegylated interferon in non-uremic patients has demonstrated better sustained response rates of up to 23%, compared with 12% in patients receiving standard interferon-α therapy (94). Early results from ongoing studies that examine combination therapy of pegylated interferon with ribavirin have shown significantly improved virologic response rates exceeding 50% (95).

In contrast to non-renal-failure patients, where interferon therapy is well tolerated in the majority, dialysis patients have a higher incidence of adverse effects, which include malaise, reduced appetite, malnutrition, exacerbation of anemia, and resistance to erythropoietin therapy, thereby resulting in a high drop-out rate (96-98). Such differences from non-uremic patients may be related to the reduced clearance of interferon as well as the underlying uremic state. Interferon therapy in HCV-positive renal allograft recipients has been associated with a high incidence (exceeding 46%) of renal allograft dysfunction or acute graft failure, because of acute rejection or tubulointerstitial disease (99-102). These patients may also be less likely to have a sustained response. Whether ribavirin may have a role in the treatment of HCV-positive renal transplant recipients has not been investigated, but it is probably wise to avoid using ribavirin in dialysis patients, because anemia will be exacerbated by drug-induced hemolysis (103).

The optimal timing, the choice of therapeutic agents, the duration of therapy, and above all, the decision on which patients should be treated, are the critical issues pertaining to the treatment of HCV infection in patients on dialysis or after kidney transplantation. Many of these issues have remained unresolved. Although there is increasing promising data on the use of pegylated interferon in the treatment of HCV infection in non-uremic patients, and favorable results with the concomitant use of interferon and ribavirin have been reported, these agents have substantial adverse effects in patients on renal replacement therapy. Therefore, the decision whether to start treatment has to be individualized, and the risks incurred by the therapeutic agents need to be weighed against those from HCV-induced liver complications. Notwithstanding, about 20% of HCV-positive dialysis patients can achieve sustained clearance of HCV with interferon therapy (97). It is reasonable to attempt treatment before transplantation, because the administration of interferon in renal allograft recipients is associated with a high risk of renal allograft dysfunction, and should be reserved for patients who demonstrate progressive and severe HCV-related liver disease (99).

**CONCLUSIONS**

Much information on the virologic and clinical aspects of HCV infection in patients on renal replacement therapy has accumulated since the virus was cloned in 1989. The long-term effects of HCV infection on clinical outcome, especially in immunosuppressed renal allograft recipients, remain to be elucidated. Treatment of HCV infection in dialysis patients or renal allograft recipients still presents a difficult clinical problem, because there is as yet no effective and safe agent that is applicable to these patients. The prevention of new HCV infections by rigorously following measures that have proven efficacy is therefore important.

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