The Long-Term Effect of Hepatitis C Virus on the Outcome of Live-Donor Kidney Transplant Recipients. A Retrospective Study


Abstract

Objectives: Hepatitis C virus infection occurs frequently among end-stage renal disease patients. Moreover, its effect on long-term patient and renal graft survival is controversial. This study was performed to assess the long-term effect of hepatitis C virus on the outcome of kidney allografts

Materials and Methods: We retrospectively analyzed 273 hepatitis B negative renal transplant recipients who were transplanted at Mansoura Urology and Nephrology Center, for whom hepatitis C virus RNA polymerase chain reaction results were available before transplant, and followed them for at least 17 years after transplant. We compared graft and patient survival rates between viremic group (study group) and nonviremic group (control group). We also studied posttransplant hepatic function, graft performance, and incidence of posttransplant diabetes mellitus.

Results: Hepatitis C virus was detected in sera of 195 patients (71%). No statistically significant increased risk for graft failure ($P = .29$) or patient death ($P = .47$) was found among the groups. Hepatitis C virus viremic transplant recipients had significantly greater frequencies of biochemical chronic liver disease ($P = .01$). However, we did not report significant differences regarding incidence, quantity of proteinuria, biopsy-proven acute rejection, chronic allograft nephropathy, and incidence of posttransplant diabetes mellitus between the studied groups.

Conclusions: Hepatitis C virus infection was shown to increase the incidence of chronic hepatitis posttransplant. However, no statistically significant adverse effect on long-term renal graft and patient survival was noted.

Key words: Kidney transplantation, Hepatitis C virus, Patient survival and graft survival

Introduction

Renal transplant represents the optimal treatment for patients with end stage kidney disease.\(^1\) Patients with end-stage kidney disease (ESKD) who undergo renal replacement therapy (RRT) are at high potential risk of infection with hepatitis C virus. In the past, blood transfusions have played a major role in the transmission of hepatitis C virus (HCV) to hemodialyzed patients that was substituted, from the late 1980s onwards, by erythropoietin prescription. Thus, the vast majority of seroconversions for HCV in hemodialysis patients are currently due to nosocomial transmission.

Early detection, prevention, and treatment of complications caused by chronic HCV infection may improve the outcomes of infected kidney transplant recipients.\(^3\) Moreover, kidney transplant candidates should undergo antiviral treatment before a kidney transplant.\(^4\) However, posttransplant treatment of HCV infection is not routinely recommended because of the potential increased risk of acute rejection.

Several real-world data\(^5\) have demonstrated that eligibility for and tolerability of triple therapy against HCV infection with a first-wave protease inhibitor is
limited. With the approval of sofosbuvir, effective
treatment with and without pegylated interferon has
become available for most genotypes. However, no
data are available regarding the added benefit
concerning dialysis and transplant candidates, but
many prospective and promising studies are ongoing.

Hepatitis C virus-positive kidney transplant
recipients have a significantly increased risk of
posttransplant liver disease. Chronic active hepatitis
and its sequelae are the principal forms of liver
involvement in these patients. In addition, an unusual
form of liver disease with severe cholestasis and
rapidly progressive liver failure has been described.6
Several studies have examined the incidence, type,
and manifestations of renal disease among renal
transplant recipients with HCV infection. The most
common manifestations are proteinuria, membrano-
proliferative glomerulonephritis, and membranous
nephropathy.7 So, proteinuria has been used as a
marker of disease in the renal allograft among
anti-HCV positive transplant recipients.8 A renal
thrombotic microangiopathy may be observed in
HCV-infected renal transplant recipients, particularly
among those with anticardiolipin antibodies. Several
reports have suggested an association between HCV
infection and posttransplant diabetes mellitus
(PTDM), which has a deleterious effect on patient and
graft survival, 9 especially in tacrolimus-treated
patients.10

Many studies have been adopted to evaluate effect
of HCV on renal transplant recipients, but most of
them were short term and comprised relatively small
numbers of patients. This study was designed to
evaluate the long-term effect of HCV on the outcome
of Egyptian live-donor renal transplant recipients after
at least 17 years follow-up.

Materials and Methods

The material of this work comprised 317 patients with
end-stage renal disease who were transplanted in
Mansoura Urology and Nephrology Center from
beginning of April 1993 to the end of December 1996.
Forty-four patients were excluded either because of
presence of HBsAg (11 patients), died of graft failure
within the first 6 months posttransplant, because of
causes other than hepatitis C (10 patients) or lost to
follow-up (23 patients). The remaining 273 patients
were divided into 2 groups, viremic (195 patients) and
nonviremic (78 patients), as detected by HCV RNA
PCR. The viremic group was retrospectively analyzed
after an average 17 years follow-up and compared
with the control nonviremic group.

The following variables were compared between
both groups: recipient age, gender, donor age and
relation, duration of hemodialysis, number of blood
transfusion episodes and antischistosomal treatment
pretransplant, posttransplant liver status (judged by
ALT behavior, synthetic functions and sonographic
appearance), frequency of biopsy-proven rejection
(acute and chronic, cellular and humoral), mean
serum creatinine levels at comparable times, effect of
HCV infection on azathioprine therapy, frequency of
PTDM, proteinuria, hypertension, patient survival
and graft survival in both groups. Bivariate techniques
were used for initial evaluation of contrasts. Thus, the
chi-square and Fisher exact tests were used for
comparisons of frequencies of qualitative variables;
the Mann-Whitney U test and the unpaired t test were
used for comparisons of means of 2 quantitative
variables. A P value < .05 was considered significant.

Graft and patient survival rates were assessed using
the Kaplan-Meier method. Statistical analyses were
performed with SPSS software (SPSS: An IBM
Company, version 16.0, IBM Corporation, Armonk,
NY, USA).

Results

This study was adopted to identify effect of hepatitis
C virus posttransplant regarding liver status, its
effect on azathioprine therapy as an hepatotoxic
drug, incidence of graft acute and chronic rejection,
mean serum creatinine at certain times, incidence of
proteinuria and its degree, PTDM, as well as its effect
on patient and graft survival. Patients transplanted
at Mansoura Urology and Nephrology Center
between 1993 and 1996 were included in this study
and divided into viremic (195 patients) and
nonviremic group (78 patients) according to hepatitis
C status as detected by PCR. These 2 groups were
followed up and compared retrospectively after at
least 17 years posttransplant. The study was
approved by the Ethical Review Committee of the
Institute. All of the protocols conformed to the
ethical guidelines of the 1975 Helsinki Declaration.
Written informed consent was obtained from all
subjects.

Table 1 shows the patients’ characteristics and
demographic differences between both groups of renal
Liver status posttransplant was evaluated biochemically using ALT as a marker of hepatitis (Table 2), significantly higher proportion of viremic patients had evidence of transaminitis (transient and persistent) compared with nonviremic ones \((P = .01)\). The overall frequencies and number of rejection episodes (acute and chronic) and the type of rejection among both groups of recipients were statistically comparable (Tables 3). Also, mean serum creatinine levels at comparable time points were statistically insignificant (Table 4).

Although the frequency of PTDM was higher in the viremic recipients, the difference however was not significant statistically \((P = .19)\). Presence of proteinuria as well as the amount of this proteinuria was not affected by presence of HCV (Table 5). Regarding graft and patient survival, the same insignificant results were obtained as shown in

**Table 1.** Pretransplant Characteristics of 273 Recipients According to Their Hepatitis C Virus RNA Detected By Polymerase Chain Reaction Before Transplant

<table>
<thead>
<tr>
<th>Pretransplant Characteristics</th>
<th>HCV RNA Positive</th>
<th>HCV RNA Negative</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M ± SD, y</td>
<td>(n = 195)</td>
<td>(n = 78)</td>
<td></td>
</tr>
<tr>
<td>Gender (M/F, frequency)</td>
<td>164/39</td>
<td>50/28</td>
<td>.05</td>
</tr>
<tr>
<td>Donor age, M ± SD, y</td>
<td>35 ± 9.7</td>
<td>32 ± 11.1</td>
<td>.19</td>
</tr>
<tr>
<td>Donor sex, M/F, frequency</td>
<td>87/11</td>
<td>52/26</td>
<td>.29</td>
</tr>
<tr>
<td>Duration of HD, M ± SD, mo</td>
<td>18 ± 12</td>
<td>7 ± 4</td>
<td>.001</td>
</tr>
<tr>
<td>Number of transfused blood units, M ± SD</td>
<td>1.5 ± 1.2</td>
<td>1.1 ± 1.1</td>
<td>.16</td>
</tr>
<tr>
<td>Positive history of antischistosomal treatment, frequency (%)</td>
<td>30.3%</td>
<td>13.6%</td>
<td>.13</td>
</tr>
<tr>
<td>Patients never dialyzed (frequency, %)</td>
<td>62 (31.8%)</td>
<td>19 (24.4%)</td>
<td>.39</td>
</tr>
<tr>
<td>Patients never received blood (frequency, %)</td>
<td>95 (48.7%)</td>
<td>57 (73.3%)</td>
<td>.14</td>
</tr>
<tr>
<td>Patients received neither blood nor dialysis (frequency, %)</td>
<td>2 (1%)</td>
<td>12 (15.3%)</td>
<td>.18</td>
</tr>
</tbody>
</table>

**Abbreviations:** HD, hemodialysis; HCV, hepatitis C virus; M/F, male/female; M ± SD, mean ± standard deviation

**Table 2.** Posttransplant Liver Status (Judged by Alanine Aminotransferase Behavior) in 273 Recipients According to Their Viremic State (Polymerase Chain Reaction)

<table>
<thead>
<tr>
<th>Liver Status</th>
<th>HCV RNA Positive ((n = 195))</th>
<th>HCV RNA Negative ((n = 78))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistently normal ALT</td>
<td>145 (74%)</td>
<td>86 (78.7%)</td>
<td>.62</td>
</tr>
<tr>
<td>Transient ALT elevation</td>
<td>7 (3.6%)</td>
<td>17 (21.8%)</td>
<td>.16</td>
</tr>
<tr>
<td>Persistently high ALT (acute and chronic hepatitis)</td>
<td>44 (22.2%)</td>
<td>7 (9%)</td>
<td>.01</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALT, alanine aminotransferase; HCV, hepatitis C virus

**Table 3.** Frequency and Types of Biopsy-proven Rejection Episodes in 273 Recipients According to Their Hepatitis C Virus RNA Viremic State

<table>
<thead>
<tr>
<th>Rejection Episodes</th>
<th>HCV RNA Positive ((n = 195))</th>
<th>HCV RNA Negative ((n = 78))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of acute rejections:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No rejection</td>
<td>57 (29.2%)</td>
<td>19 (24.4%)</td>
<td>.51</td>
</tr>
<tr>
<td>One rejection episode</td>
<td>62 (31.8%)</td>
<td>28 (35.9%)</td>
<td>.89</td>
</tr>
<tr>
<td>Two rejection episodes</td>
<td>46 (23.6%)</td>
<td>21 (26.9%)</td>
<td>.67</td>
</tr>
<tr>
<td>Three rejection episodes</td>
<td>21 (10.8%)</td>
<td>7 (9%)</td>
<td>.91</td>
</tr>
<tr>
<td>Four rejection episodes</td>
<td>9 (4.6%)</td>
<td>2 (2.6%)</td>
<td>.66</td>
</tr>
<tr>
<td>Five rejection episodes</td>
<td>0 (0%)</td>
<td>1 (1.3%)</td>
<td>.63</td>
</tr>
<tr>
<td>Type of acute rejection:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute cellular rejection</td>
<td>83 (42.6%)</td>
<td>29 (37.2%)</td>
<td>.49</td>
</tr>
<tr>
<td>Acute humoral rejection</td>
<td>14 (7.2%)</td>
<td>7 (9%)</td>
<td>.80</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>68 (34.9%)</td>
<td>24 (30.8%)</td>
<td>.51</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCV, hepatitis C virus

**Table 4.** Mean Serum Creatinine Levels at Comparable Time Points in Renal Allograft Recipients According to Their Viremic State (Polymerase Chain Reaction)

<table>
<thead>
<tr>
<th>Rejection Episodes</th>
<th>HCV RNA Positive ((n = 195))</th>
<th>HCV RNA Negative ((n = 78))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One month</td>
<td>1.2 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>.70</td>
</tr>
<tr>
<td>One year</td>
<td>1.3 ± 0.5</td>
<td>1.4 ± 0.7</td>
<td>.28</td>
</tr>
<tr>
<td>Two years</td>
<td>1.5 ± 0.7</td>
<td>1.4 ± 0.5</td>
<td>.58</td>
</tr>
<tr>
<td>Three years</td>
<td>1.6 ± 0.7</td>
<td>1.6 ± 0.8</td>
<td>.80</td>
</tr>
<tr>
<td>Four years</td>
<td>1.6 ± 0.6</td>
<td>1.6 ± 0.7</td>
<td>.39</td>
</tr>
<tr>
<td>Five years</td>
<td>1.7 ± 0.9</td>
<td>1.6 ± 0.8</td>
<td>.96</td>
</tr>
<tr>
<td>Last follow-up</td>
<td>2.6 ± 1.9</td>
<td>2.6 ± 2.6</td>
<td>.11</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCV, hepatitis C virus

**Table 5.** Posttransplant Medical Disorders in Recipients With or Without Hepatitis C Viremia as Detected By Polymerase Chain Reaction

<table>
<thead>
<tr>
<th>Rejection Episodes</th>
<th>HCV RNA Positive ((n = 195))</th>
<th>HCV RNA Negative ((n = 78))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTDM</td>
<td>54 (27%)</td>
<td>15 (19.2%)</td>
<td>.19</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No proteinuria</td>
<td>53 (27.2%)</td>
<td>34 (43.6%)</td>
<td>.28</td>
</tr>
<tr>
<td>Non nephrotic range proteinuria</td>
<td>105 (53.8%)</td>
<td>40 (51.3%)</td>
<td>.80</td>
</tr>
<tr>
<td>Nephrotic range proteinuria</td>
<td>37 (19%)</td>
<td>11 (14.1%)</td>
<td>.44</td>
</tr>
</tbody>
</table>

**Abbreviations:** HCV, hepatitis C virus; PTDM, posttransplant diabetes mellitus

**Figure 1.** Kaplan-Meier Curve for Demonstrating Graft Survival

No statistically significant difference was found between both viremic and nonviremic recipients \((P = .29)\).
Figures 1 and 2 even after adding ALT, as a marker of chronic hepatitis, as a variable (Figures 3 and 4).

Discussion

Liver disease is an important cause of morbidity and mortality among recipients of transplanted organs. In 1989, HCV was cloned and identified as parenterally transmitted non-A, non-B hepatitis. Hepatitis C virus infection remains an important health problem that is associated with deleterious consequences in kidney transplant recipients. Besides hepatic complications, several extrahepatic complications contribute to reduced patient and allograft survival in HCV-infected kidney recipients. However, HCV infection should not be considered as a contraindication for kidney transplant because patient survival is better with transplant than on dialysis.

To evaluate the long-term effect of hepatitis C on the outcome of live-donor kidney transplant recipients as regard patient and graft, we conducted this long-term retrospective study among 273 kidney transplant recipients. The positive correlation between blood transfusion on hemodialysis and the risk for HCV infection obtained in this study was similar to results reported by others, which may be explained by longer dialysis duration that necessitates multiple blood transfusions at that time. Also, endemicity of hepatitis C in Egypt is also a cofactor that is mostly attributed to receiving antischistosomal treatment through multidose Tartar emetic vials, multiple blood transfusions during dialysis for correction of anaemia before erythropoietin prevalence in this time. Transmission of HCV to sequential patients using the same hemodialysis machine, however, has not been widely reported. Peter and coworkers have reported a case where viral gene sequencing and phylogenetic analysis strongly suggest HCV transmission from a patient of low infectivity to a patient who shared the same hemodialysis machine. Fifty patients (25%) from HCV positive group developed either transient or persistent transaminitis after a transplant. This was significantly higher than that traced in HCV-negative patients (12.8%) (P = .01). This confirms the previously reported critical role of HCV infection as a leading cause of liver disease posttransplant.

We did not find any association between the presence of HCV and incidence of acute rejection, chronic rejection, or mean serum creatinine levels at all studied times. These findings run in concordance with findings traced by other studies. In contrast, other studies reported significantly higher incidence of acute rejections in recent transplant hepatitis C positive recipients. These contradictions may be related to either the duration of follow-up, method of detection of HCV, or detection through ELISA or nucleic acid testing by PCR, and the number of recipients followed up.

In this long-term study, we found higher incidence of posttransplant diabetes mellitus in viremic group in comparison to the nonviremic one (27% vs 19.2%), but that percentage was statistically insignificant (P = .19). In contrast, most of studies document significantly higher incidence of PTDM in...
viremic group.\textsuperscript{23,24} Also Baid-Agrawal\textsuperscript{25} suggests that impaired peripheral insulin sensitivity is associated with HCV infection irrespective of the transplant status, and is the most likely pathogenic mechanism involved in the development of type 2 diabetes mellitus associated with HCV infection. This variation in reported incidence may be related to the varying definitions of diabetes used in the literature, duration of follow-up, presence of other modifiable, and nonmodifiable risk factors. Immunosuppression protocols also may explain this difference in results as corticosteroids and the calcineurin inhibitors, tacrolimus, and to lesser extent cyclosporine; neither azathioprine nor MMF, are diabetogenic. Mycophenolate mofetil may mitigate the diabetogenic effect of tacrolimus possibly by allowing clinicians to use lower doses. Sirolimus is now recognized to be associated with reduced insulin sensitivity and defect in compensatory β cell response. Also, acute rejection episodes, \textit{cytomegalovirus} infection and male gender of recipients also play a role.\textsuperscript{24}

Chronic HCV has been associated with glomerular disease in native and transplanted kidneys. The obtained results evaluating the difference in incidence and/or quantity of proteinuria among viremic and nonviremic groups were insignificant. The same results have been reported by other authors.\textsuperscript{25} Conversely, others document a higher incidence of proteinuria among the viremic group than the nonviremic one.\textsuperscript{8,19,26}

Regarding the long-term effect of HCV on patient and graft survival, there was no significant difference between the groups. This agrees the majority of published short-term series\textsuperscript{27-29} and long-term ones.\textsuperscript{20,30} Conversely, her short-term\textsuperscript{26} and long-term studies\textsuperscript{18,23} have demonstrated significantly inferior graft survival in viremic recipients. Other studies document lower graft survival in nonviremic recipients.\textsuperscript{31} Even after reanalyzing the data after adding ALT as a marker of active liver disease, the same results were found.

Our study has some limitations: it is a retrospective study, and there is a deficiency of histopathologic data about hepatic affection by HCV.

**Conclusions**

There is a high prevalence of HCV infection in ESRD patients waiting for renal transplant. The long-term effect of HCV viremia on patient and graft survival in live-donor kidney transplant recipients was not statistically significant. Also, the frequency of biopsy-proven chronic allograft rejection among the 2 groups of was not statistically significant. So, HCV infection is not an absolute contraindication for transplant. Moreover, all HCV positive patients should be treated pretransplant to avoid HCV-related complications. Also, immunosuppression in those patients should be tailored on individual basis to minimize complications. We recommend larger and longer randomized controlled studies to evaluate the effect of HCV on patient and graft survival.

**References**


