Impact of Hepatitis C Virus Infection on Kidney Transplantation

Yasser Soliman
Internal Medicine and Nephrology Department, Ain Shams University.

Abstract

Hepatitis C virus (HCV) infection increases morbimortality in renal transplantation. Hepatitis C virus positive kidney transplant candidates who remain on the waiting list show a greater risk of mortality than those who are transplanted. The aim of this study was to examine the impact of HCV infection on patient and allograft survival after kidney transplantation. Eighty two patients with end stage renal disease underwent kidney transplantation were included in this study. The patients were classified into group I including 46 HCV negative patients (HCV-) and group II including 36 HCV antibody and HCV-RNA positive patients (HCV+). The immunosuppressive protocols were similar in both groups. All recipients were followed up for 3 years. Results: There were statistically insignificant differences (P>0.05) between both groups as regard age, gender and donor type (living related or unrelated). Hemodialysis duration before transplantation was highly significant (P<0.01) longer among HCV+ group (4.9± 3.7 years) compared to HCV- patients (2.4± 4.3 years). One patient died from each group showing insignificant difference (P>0.05); 2 grafts (4.3%) lost in HCV- group and 3 (8.3%) in HCV+ group with also insignificant difference (P>0.05). Five recipients (10.9%) in group I experienced delayed graft function compared to 2 (5.6%) recipients in group II with statistically insignificant difference. There was a significantly (P< 0.05) more number of acute rejection episodes among HCV+ patients (11=30.6%) than HCV- patients (5=10.9%). New onset diabetes mellitus occurred more among HCV+ (19.4%) than HCV- (8.7%) recipients, however the difference was insignificant. There was a significant (P<0.05) higher incidence of cytomegalovirus disease among HCV+ (11.1%) than HCV- (2.2%) recipients. Conclusion: This study suggested that HCV positivity does not significantly affect patient and graft survival despite the significant increased incidence of acute rejection episodes and cytomegalovirus disease. Lastly, all measures should be taken to prevent HCV transmission in dialysis population.

Introduction

Since hepatitis C virus (HCV) was identified in 1989 by Choo et al, as a main cause of non-A non-B hepatitis, HCV infection has achieved a great relevance in nephrology on the basis of its high prevalence among dialysis patients, renal allograft recipients as well as in essential mixed cryoglobulinemia with associated membranoproliferative glomerulonephritis (1,2,3). Renal transplantation confers an overall survival benefit in HCV + hemodialysis patients with similar 5-year patients and graft survival to those without HCV infection (4). Unfortunately, there is no safe treatment for HCV infection after renal transplantation. It has been reported recently that ribavirin monotherapy improved liver enzymes levels, had no effect on HCV viremia, but seems also not to have a beneficial effect on liver fibrosis (5).

Aim Of The Work

The aim of this study was to evaluate the effect of HCV infection among end stage renal disease (ESRD) patients after undergoing kidney transplantation.

Patients And Methods

This prospective study included 82 patients with ESRD. All were receiving their first living kidney transplants at Naser Institute, and Ain Shams University.
Yasser Soliman

Specialized Hospital. The patients were classified according to HCV status into 2 groups. Group I: included 46 HBs Ag, and HCV antibody negative (HCV–) patients, 28 (60.9%) males and 18 (39.1%) females; 31 (82.6%) patients received living related grafts and the rest 14(17.4) were unrelated. Eight patients of group I were preemptive transplantation. Group II: Included 36 HBs Ag negative HCV antibody and RNA positive patients, 20 (55.6%) males and 16 (44.4%) females, 30 (83.3%) patients received related and 6 (16.7) unrelated grafts.

All patients were exposed to history taking including the etiology of renal failure, duration on hemodialysis, blood transfusion, and antiviral treatment (in group II). All patients underwent blood testing for serum alanine transferase (ALT), aspartate transferase (AST), albumin, prothrombin time, creatinine, blood urea nitrogen (BUN), and blood glucose level. Anti-HCV antibodies were determined with a third generation enzyme linked immunoassay (Abbott-laboratories, Chicago, IL, USA). HCV-RNA was detected by qualitative polymerase chain reaction (PCR) using Amplicor Kits (Roche Diagnostic System, Indianapolis, USA). A liver biopsy was indicated for all HCV-RNA positive patients, irrespective of transaminases levels. All recipients were having ≤4 HLA mismatch with their donors, and the immunosuppressive protocols were similar in both groups in the form of triple therapy with steroids, cyclosporine, and azathioprin.

The patients were followed up for 3 years as regard renal function tests, liver function tests, occurrence of delayed graft function (DGF)-defined as the transient requirement for dialysis beginning in the first week after the transplant operation, acute rejection, new onset diabetes mellitus (DM), and cytomegalovirus disease.

**Statistical Methods**

SPSS statistical software package, v.9.02, Echosoft Corp, USA, 1998 was used for data analyze. Dates were expressed as Mean ±SD for quantitative measures and both number and percentage for categorized data. Wilcoxon Rank sum test was used for comparison between two independent mean groups for non parametric data. Lastly, Chi-square test was used for correlation between each 2 independent techniques. The probability of error at 0.05 was considered significant, while at 0.01 highly significant.

**Results**

Table-1 shows the characteristics of patients in group I (HCV-) and group II (HCV+). The mean age in group I was (42.4 ± 11.2 years) with non significant difference (P>0.05) from group II (44 ± 10.5 years). Also, there was no significant difference between both groups as regard gender (P> 0.05). Though 30.4% of patients in group I received kidneys from unrelated donors compared to 16.7% only in group II, the difference was insignificant (P>0.05). There was a highly significant (P<0.01) longer duration of hemodialysis before transplantation in group II than group I (4.9 ± 3.7 & 2.4 ± 4.3 years respectively).

Table-2 Shows non significant (P>0.05) difference between group I and group II as regard serum creatinine level during the follow up period, while a highly significant (P<0.001) higher level of BUW in group II (38.2 ±11.7 mg/dl ) compared to group I ( 21 ± 13.1 mg/dl ).One patient died in each group (both from infection) resulting in non significant difference (P>0.05) in patient survival between the two groups after 3 years, and the relative risk was 1.3 with HCV positivity. Also, there was insignificant difference (P>0.05) as regard three years graft survival between HCV – (95.7%) and HCV + (91.7 %) and the relative risk of graft loss is 1.9 with HCV positively. Five recipients (10.9%) experienced delayed graft function in group I compared to 11 recipients (5.6%) in group II but the difference was insignificant (P>0.05).There was a significant (P<0.05) higher incidence of acute rejection episodes (all were steroid sensitive) in group II (30.6%) than group I (10.9%) with a relative risk of 2.8. There was a higher
Impact of Hepatitis C Virus Infection on……

incidence of new onset DM in group II (19.4%) than group I (8.7%), however the difference was insignificant and the relative risk of developing DM with HCV positively was 2.2. There was a significantly (P<0.05) higher incidence of cytomegalovirus disease in HCV+ group II (11.1%) in comparison to group I (2.2%) with 5.1 relative risk.

Table 1: Patients Demographic Characteristics, and clinical metrics in group I (HCV-) and group II (HCV+).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I N = 46</th>
<th>Group II N = 36</th>
<th>Z</th>
<th>P-Value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years) mean ± SD</td>
<td>42.4 ± 11.2</td>
<td>44 ± 10.5</td>
<td>-0.7</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 28 (60.9%)</td>
<td>20 (55.6%)</td>
<td>0.63</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Female 18 (39.1%)</td>
<td>16 (44.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor Type</td>
<td>LR 32 (69.6%)</td>
<td>30 (83.3%)</td>
<td>1.44</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>LUR 14 (30.4%)</td>
<td>6 (16.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis Duration (Years) mean ± SD</td>
<td>2.4 ± 4.3</td>
<td>4.9 ± 3.7</td>
<td>-2.8</td>
<td>&lt;0.01</td>
<td>HS</td>
</tr>
</tbody>
</table>

SD : Standard deviation  NS : Non significant.
LR : Living related     HS : Highly significant.
LUR : Living unrelated

Table 2: Patients and Graft survival during the follow up period (3 years)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I N = 46</th>
<th>Group II N = 36</th>
<th>Z</th>
<th>P-Value</th>
<th>Significance</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN (mg/dl) mean ± SD</td>
<td>21±13.1</td>
<td>38.2±11.7</td>
<td>-6.2</td>
<td>&lt;0.001</td>
<td>HS</td>
<td></td>
</tr>
<tr>
<td>S. Creatinine (mg/dl) mean ± SD</td>
<td>1.7±1.1</td>
<td>1.8±1.4</td>
<td>-0.4</td>
<td>&gt;0.05</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Death n ( %)</td>
<td>1(2.2%)</td>
<td>1(2.8%)</td>
<td>-0.2</td>
<td>&gt;0.05</td>
<td>NS</td>
<td>1.3</td>
</tr>
<tr>
<td>Graft Failure n ( %)</td>
<td>2(4.3%)</td>
<td>3(8.3%)</td>
<td>-0.8</td>
<td>&gt;0.05</td>
<td>NS</td>
<td>1.9</td>
</tr>
<tr>
<td>Delayed Graft Function n ( %)</td>
<td>5(10.9%)</td>
<td>2(5.6%)</td>
<td>0.85</td>
<td>&gt;0.05</td>
<td>NS</td>
<td>2</td>
</tr>
<tr>
<td>Acute Rejection n ( %)</td>
<td>5(10.9%)</td>
<td>11(30.6%)</td>
<td>-2.2</td>
<td>&lt;0.05</td>
<td>S</td>
<td>2.8</td>
</tr>
<tr>
<td>Diabetes Mellitus n ( %)</td>
<td>4(8.7%)</td>
<td>7(19.4%)</td>
<td>-1.4</td>
<td>&gt;0.05</td>
<td>NS</td>
<td>2.2</td>
</tr>
<tr>
<td>Cytomegalovirus Disease n ( %)</td>
<td>1(2.2%)</td>
<td>4(11.1%)</td>
<td>-1.7</td>
<td>&lt;0.05</td>
<td>S</td>
<td>5.1</td>
</tr>
</tbody>
</table>

SD : Standard deviation  HS : Highly significant
RR : Relative risk     NS : Non significant

Discussion

This study showed no significant difference between both groups as regard age, gender, and donor type. There was a significant longer duration of hemodialysis before transplantation in group II (HCV+) implicating hemodialysis in the prevalence of HCV among ESRD patients. A similar finding was reported by Bruchfeld et al(7).
The present study showed a slightly increased incidence of patient mortality and graft loss in HCV+ group compared to HCV- group during the 3 years follow up period, however the differences were insignificant. Pereira study showed that graft and patient survival were not significantly different after 3.5 years between HCV+ and HCV- kidney transplant recipients\(^9\). Also, Lee et al, reported that graft losses and death rates were not significantly different between HCV+ and HCV- kidney recipients\(^9\). In contrast, Legendre et al, Gentil et al, and Bruchfeld et al, observed a significantly higher percentage of graft loss among HCV+ than HCV- renal recipients\(^{(10,11,7)}\). Batty et al, claimed a 13% mortality rate in HSV+ and 8.5% in HCV- patients\(^{(12)}\). Nevertheless, Bezard-Beahbani et al, evaluated the impact of HCV infection occurring after kidney transplantation, and they suggested that HCV infection (in a previously HCV- recipient before transplantation) did not cause or contribute to renal dysfunction during the one year follow-up period of the study\(^{(13)}\). The frequency of new onset DM was significantly higher in HCV+ (19.4%) than HCV- (8.7%) patients. A similar finding was observed by Stehman - Breen et al, resulting in 18% prevalence of DM in an HCV infection cohort\(^{(14)}\). There was unexplained statistically insignificant higher incidence of delayed graft function among HCV- than HCV+ group. On the other hand, there was a significant (P<0.05) increased number of acute rejection episodes among HCV+ (11=30.6%) compared to HCV- (5=10.9%) recipients. This study showed a significantly increased incidence of cytomegalovirus disease in group II (11.1%) with a RR 5.1 in comparison to HCV- group. Till publishing this work, there were no trials in the literature correlating HCV status and cytomegalovirus disease after kidney transplantation.

**Conclusion & Recommendations**

This study suggested that HCV infection among ESRD patients does not affect significantly patient and renal allograft survival after kidney transplantation despite the significant increased incidence of acute rejection episodes and cytomegalovirus disease during the first 3 years following transplantation. A more extended study is advisable to identify the impact of HCV infection on the long term patient and graft survival. Lastly, all measures should be taken to prevent HCV transmission in dialysis population.

**References**

Impact of Hepatitis C Virus Infection on…….


تأثير عدوى فيروس الالتهاب الكبدى (سي) على زراعة الكلى
ياسر سليمان
قسم الباطنة - كلية الطب - جامعة عين شمس

ان الإصابة بالالتهاب الكبدى الفيروسى (سي) يزيد من معدلات الوفيات والإعاقة في مرضى زراعة الكلى. أن المرضى المصابين بالفيروس الكبدى (سي) يكونون أكثر عرضة للوفاة من المرضى الذين لا يعانون من هذا الفيروس. إن هدف هذه الدراسة هو دراسة تأثير الإصابة بالفيروس (سي) على المرضى وعلى الكلى المنقولة بعد عملية الزراعة تتضمن هذه الدراسة 28 مريضاً مصاباً بفشل الكلوي المزمن، وتبين هذه الدراسة أن الانتظار المزمن والذين تم لهم عملية زراعة الكلى. وقد تم تقسيم المرضى إلى مجموعتين:

المجموعة الأولى: تتضمن 46 مريضاً غير مصابين بالفيروس الكبدى (سي).
المجموعة الثانية: تتضمن 36 مريضاً مصابين بالفيروس (سي).

وقد تم تتابع المرضى لمدة 3 سنوات.

أظهرت الدراسة فرق ليس له دلالة إحصائية بين المجموعتين بالنسبة للعمر والجنس ونوع المتغير ( قريب للمرضى أو غير ذلك. وأظهرت النتائج دلالة إحصائية عالية القيمة بالنسبة لمدة الاستنساخ الدموى قبل عملية الزراعة ، حيث وجد أن مدة الاستنساخ الدموى أطول (4.9 ± 3.7) في المرضى المصابين بالفيروس (سي) مقارنة بالمرضى الذين لا يعانون من فيروس (سي) (2.4 ± 4.3) . لم تظهر نتائج ذو دلالة إحصائية لوفاة أدى المرضى من كل مجموعة . أيضاً لم تظهر نتائج ذو دلالة إحصائية لإثنيين (4.3%) من مرضى زراعة الكلى في المجموعة المصابين بفيروس (سي) وثلاثة (8.3%) في المجموعة المصابين بتصلب العامة (سي) وذلك لفقر الدم المزروع 0 و قد أصيب 5 من المرضى الذين تم لهم عملية الزراعة بتأخير في وظيفة الكلى المزروعة من المجموعة الأولى (10.9%) وذلك بالمقارنة باثنين (5.6%) من المجموعة الثانية ولكن الفرق ليس له دلالة إحصائية. أظهرت النتائج وجود عدد أكبر من حالات الوفاة في المرضى الذين لا يعانون من فيروس (سي) (30.6%) ولم يدخل في المجموعة المصابين بالفيروس (سي) (11.9%) وذلك بالمقارنة بالمرضى الذين لا يعانون من فيروس (سي) (5%).

و هذا الفرق ذو دلالة إحصائية عالية القيمة وقد ظهرت نتائج حالات مرض الزوائد عدة علامة دلالة إحصائية عالية القيمة وقد ظهرت نتائج حالات مرض الزوائد عدة علامة دلالة إحصائية عالية القيمة وقد ظهرت نتائج حالات مرض الزوائد عدة علامة دلالة إحصائية عالية القيمة. هذه النتائج أيضًا يوجد فرق ذو دلالة إحصائية عالية القيمة بالنسبة لمصابي الالتهاب الكبدى الفيروسى (سي) (19.4%) وذلك بفضل عملية الاستئصال الدموى. في منتجات الفيروسات المزروعة وذلك يوجد نسبة أعلى في المرضى المصابين بالفيروس (سي) (11.1%) بالمقارنة بالمرضى الذين لا يعانون من فيروس (سي) (2.2%)

النتائج: أظهرت النتائج أن الإصابة بالفيروس (سي) لا يوثر بشكل واضح على كل من نجا المرضى ومعدل الوفيات بعد عملية زراعة الكلى وذلك على الرغم من وجود زيادة في معدل حالات الوفاة للمرضى المصابين بالإصابات. و أخيراً يجب اتخاذ كل الإجراءات لمنع انتشار مرضي الفيروس الكبدى (سي) بين مرضى الاستئصال الدموى.