Severe evolution of chronic hepatitis C in renal transplantation: a case control study

Hervé Zylberberg1,*, Bertrand Nalpas1,*, Françoise Carnot3, Habib Skhiri2, Hélène Fontaine1, Christophe Legendre4, Henri Kreis2, Christian Bréchot1 and Stanislas Pol1

1Service d’Hépatologie et INSERM U-370, 2Service de Transplantation Rénale, Hôpital Necker, 3Laboratoire d’Anatomopathologie Hôpital Européen G. Pompidou and 4Service de Transplantation Rénale, Hôpital Saint-Louis, Paris, France

Abstract

Background. To evaluate the impact of kidney transplantation on histopathological progression of hepatitis C virus (HCV)-related liver disease.

Methods. In a retrospective study, 28 HCV-positive renal transplant patients, who underwent two sequential liver biopsies with a mean of 7.1±4.0 years, were compared with 28 matched immunocompetent controls.

Results. According to the Metavir score, the initial and final activity scores (from 0 to 3) increased from 0.2±0.4 to 1.4±1.1 (P<0.001) and those of fibrosis (from 0 to 4) from 0.5±0.5 to 2.0±1.4 (P<0.001) in the transplanted group, respectively, whereas the respective differences were not significant in the control group. The yearly progression rate of activity and fibrosis was significantly higher in the renal transplant group as compared with the immunocompetent group: 0.26±0.41 vs 0.01±0.19 (P<0.01) and 0.26±0.35 vs 0.05±0.21 (P<0.03), respectively. Twenty (71.5%) and 14 (50.0%) of the renal allograft recipients had activity and fibrosis progression as compared with four (16%) (P<0.01) and four (16%) (P<0.01) in immunocompetent patients; six kidney recipients (21.4%) evolved to cirrhosis vs only one in the control group (3.6%) (P=0.07). Liver-related mortality was significantly higher during the follow-up period in renal transplant patients than in the control group (10 vs 0%) (P<0.05).

Conclusion. Using conventional immunosuppressive regimen, renal transplantation is associated with a more severe evolution of chronic hepatitis C as compared with HCV-infected immunocompetent subjects. Thus, the histopathological evaluation should be performed and anti-viral therapy discussed before renal transplantation.

Keywords: HCV; immunocompromised; renal transplantation

Introduction

Hepatitis C virus (HCV) infection is frequent in patients with end-stage renal disease managed with peritoneal dialysis, haemodialysis, or kidney transplantation [1–4]. It is presumed to be transmitted via transfusion of blood products in most cases or by other nosocomial means [5–8]. Throughout the world, the frequency of anti-HCV antibodies in patients with renal failure varies according to the geographic area from 6 to 64%. Epidemiological, serological, and virological data of HCV infection in kidney allograft recipients have been widely reported [9–17]. Most liver histology studies available in HCV-infected kidney recipients are transversal [14] and longitudinal analyses on the basis of sequential liver biopsies have not been performed so far. In order to better evaluate the impact of kidney transplantation on HCV-related liver lesions, we have compared longitudinal histopathological progression and liver-related mortality in HCV-infected renal transplant recipients and immunocompetent untreated patients who underwent serial liver biopsies.

Subjects and methods

Patients

Our retrospective study was performed on the HCV-infected renal transplant patients with functioning allograft who were referred to the Liver Unit of the Necker Hospital. Among
the 150 patients who fulfilled these inclusion criteria, we selected the 28 HBsAg- and anti-HIV-negative, non-alcoholic (alcohol consumption <40 g/day) patients who had undergone two sequential liver biopsies without any anti-viral treatment. Such a surveillance protocol, implemented in agreement with the local transplantation unit team, is currently proposed to all HCV-positive kidney recipients. They were compared with 28 immunocompetent subjects matched for age, gender, duration of HCV infection, age at contamination, HCV genotype, and interval time between liver biopsies as best as possible.

The main characteristics of the two groups of patients are given in Table 1. All were HCV RNA-positive. The initial liver biopsy was performed within the first 6 months after renal transplantation in 22 of the 28 and later in the remaining six patients (1–21 years). The mean interval between initial and final liver biopsy in the two groups was 7.1 ± 4.0 and 6.1 ± 3.2 years, respectively. The median time elapsed between renal transplantation and final liver biopsy was 13.6 years (range 2.6–23.9 years). The mean number of allograft rejections during the observation period was 1.6 ± 1.0. Renal transplant patients received standard immunosuppressive regimens, which have previously been detailed [18], combining low doses of steroids (10–17.5 mg/day) and azathioprine (75–150 mg/day). None had symptomatic mixed cryoglobulinaemia or HCV-related membrano-proliferative glomerulonephritis.

The presumed source of HCV contamination in transplanted patients was blood transfusion of which frequency broadly varied among the studied patients (from three to 34, median = 9). As most acute hepatitis C infection remains asymptomatic, the date of HCV contamination, in the absence of known acute hepatitis, was arbitrarily assumed to be the date of starting dialysis.

In the renal transplant group, activity and fibrosis progression were analysed according to clinical (duration of infection, number of rejections, immunosuppressive regimen), virological (genotype), and histological (initial activity and fibrosis scores) parameters.

### Table 1. General characteristics of HCV-infected kidney recipients and control groups

<table>
<thead>
<tr>
<th></th>
<th>Kidney recipients (n = 28)</th>
<th>Controls (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>28</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>M/F</td>
<td>18/10</td>
<td>18/10</td>
<td>NS</td>
</tr>
<tr>
<td>Age at first biopsy* (years)</td>
<td>34 ± 9</td>
<td>36 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Age at contamination* (years)</td>
<td>28 ± 10</td>
<td>26 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of infection* (years)</td>
<td>6.8 ± 4.9</td>
<td>10.5 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Interval between biopsies* (years)</td>
<td>7.1 ± 4</td>
<td>6.1 ± 3.2</td>
<td>NS</td>
</tr>
<tr>
<td>ALT (IU/l)</td>
<td>64 ± 57</td>
<td>101 ± 70</td>
<td>0.06</td>
</tr>
<tr>
<td>AST (IU/l)</td>
<td>65 ± 55</td>
<td>57 ± 50</td>
<td>NS</td>
</tr>
<tr>
<td>HCV genotypes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a + 1b</td>
<td>39.3%</td>
<td>44%</td>
<td>NS**</td>
</tr>
<tr>
<td>3</td>
<td>7.1%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>3.6%</td>
<td>16%</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>50%</td>
<td>24%</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± SD; **HCV genotype distribution was not statistically different between groups.

### Methods

**Serological anti-HCV assays.** Serum antibodies to HCV were detected with the third-generation HCV enzyme-linked immunosorbent assay from Ortho Diagnostic (Raritan, NJ, USA), according to the manufacturer’s instructions. All these tests were performed routinely at time of first visit in our unit. HCV genotyping was done using commercial kits (Innolipa, Innogenetics, Gent, Belgium). HCV viral loads had not been measured as frozen sera were not available for all patients and had been kept at −30°C, a storage temperature not confident for the measurement of quantitative HCV viraemia.

**Histopathological analysis.** Chronic liver disease was classified as chronic hepatitis or cirrhosis in all patients. Activity (from 0 to 3) of the liver disease and fibrosis (from 0 to 4) were semi-quantitatively assessed according to the Metavir score [19]. Histological analyses were done using current technical conditions by the same pathologist unaware of the date of biopsies and the group to which the patients belonged. Score variation between repeated biopsies were classified: in three groups for the necrotico-inflammatory activity: ‘decrease’ when the difference between the second and the first liver biopsy was equal to or less than −1; ‘plateau’ when the difference was nil; ‘increase’ when the difference was equal to or greater than +1; in two groups for fibrosis: less and equal to or more than 2 units difference. The progression per year of the liver lesions was defined as the ratio between the scores difference (between final and initial biopsies) and the interval time between the two biopsies, as recently established in various populations of HCV-infected patients [20–22].

**Statistical analysis.** Comparisons of qualitative variables were based on the χ² and Fisher exact tests; quantitative values were compared using the Student’s t-test, non-parametric tests (Mann–Whitney, Wilcoxon). All analyses were done using the SPSS 9.0 software (SPSS Inc., Chicago, IL, USA).

### Results

The initial activity scores were significantly lower in the transplanted than in the control groups, 0.2 ± 0.4 vs 1.3 ± 0.5 (P < 0.001) as well as the fibrosis scores 0.5 ± 0.5 vs 1.2 ± 0.7 (P < 0.01), respectively (Table 2); all the kidney recipients thus had a non-severe hepatitis at initial evaluation. However, the mean progression rate of activity and fibrosis expressed by year were significantly higher in the kidney recipients: 0.26 ± 0.41 vs 0.01 ± 0.19 (P < 0.001) and 0.26 ± 0.35 vs 0.05 ± 0.21 (P < 0.03), respectively. As a consequence, final activity and fibrosis scores did not differ between the groups, the fibrosis score being even slightly higher in kidney recipients (1.9 ± 0.4 vs 1.7 ± 1.0, NS).

In kidney recipients, activity increased, plateaued, and decreased in 71.4, 21.4, and 7.1%, respectively, whereas the corresponding percentages in controls were 16.1, 60.0, and 24.0% (P = 0.001) (Figure 1).
Similarly, a net increase in fibrosis was observed in 50% of the kidney recipients compared with 16% in controls (P = 0.009) (Figure 2). Moreover, while no cirrhosis was observed at the first biopsy in any group, six kidney recipients (21.4%) evolved to cirrhosis within the first 13 years of infection vs only one (28 years after contamination) in the control group (3.6%) but the difference was not statistically significant (P = 0.07). Altogether, at the final histological evaluation, up to 40% of the kidney recipients had progressed to a severe hepatitis.

There was no correlation between the activity or fibrosis progression and the number of graft rejections or the type of immunosuppression regimen (i.e. with or without OKT3).

Three kidney recipients and none of the controls died during the observation period (10.7 vs 0%) (P < 0.05). In these three patients, the cause of death was liver-related; all three patients were characterized by a very high yearly progression rate of fibrosis (0.41 ± 0.19) as compared with 0.24 ± 0.37 in those who remained alive; the difference was close to the significance limit (P = 0.08 using non-parametric test).

**Discussion**

Our results provide strong evidence that kidney transplantation and/or immunosuppressive regimen worsen the natural course of chronic hepatitis C. Indeed, up to 70% of renal transplant patients as compared with only 19% of immunocompetent patients had a histopathological deterioration and 21% evolved to cirrhosis within 13 years after HCV contamination. These results are at variance with those recently obtained in 36 HCV-infected renal transplant recipients who underwent two liver biopsies 45 and 81 months after transplantation: 13 had progressing liver fibrosis (fibrosers) while 23 did not (non-fibrosers) [23]. The discrepancies between these two series may reflect differences in the overall follow-up which was longer in our study, in our definition of pathological deterioration as we analysed the pathological evolution according to activity and fibrosis (and not fibrosis alone) and differences in the potency of drug-related immunosuppression.

The reasons for the severe liver disease deterioration that we observed in kidney recipients should be carefully analysed. First of all, the known factors of liver deterioration such as age at contamination, duration of HCV infection, HCV genotype, and alcohol consumption [20,24] could reasonably be excluded as cases and controls were carefully matched. One can suggest that the lower hepatitis severity in the cases at initial evaluation (i.e. close to the renal transplantation), a figure which is in accordance with the usual low activity of HCV-related liver disease in dialysis patients [3], could favour a faster worsening but several arguments can be raised against such hypothesis. First, in a series of HCV-infected immunocompetent patients we observed that a high, and not a low, activity of the hepatitis was associated with an increase in the yearly progression rate of fibrosis score while the initial fibrosis score had no any impact on this progression [25]. Second, the yearly progression rate of fibrosis observed in our control group was similar

**Table 2.** Comparisons of pathological results between HCV-infected kidney recipients and immunocompetent patients

<table>
<thead>
<tr>
<th></th>
<th>Kidney recipients (n = 28)</th>
<th>Controls (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial activity</td>
<td>0.2 ± 0.4*</td>
<td>1.3 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Initial fibrosis</td>
<td>0.5 ± 0.5</td>
<td>1.2 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Final activity</td>
<td>1.4 ± 1.1</td>
<td>1.3 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Final fibrosis</td>
<td>1.9 ± 0.4</td>
<td>1.7 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Yearly progression rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td>0.26 ± 0.41</td>
<td>0.01 ± 0.19</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.26 ± 0.35</td>
<td>0.05 ± 0.21</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Initial cirrhosis</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Final cirrhosis</td>
<td>6 (21.4%)</td>
<td>1 (3.6%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Mean ± SD.
to that reported by other authors [20]. Third, we analysed the progression of the disease using sequential liver biopsies and the time elapsed between the two evaluations was similar in both groups.

Although viral loads were not measured owing to the retrospective design of our work, we speculate that liver deterioration could be partly related to immunosuppression, which enhances viral replication. In our experience, kidney recipients have a 3-fold increase in viral load as compared with dialysis patients (S. Pol, unpublished data) and a link between pathological deterioration and high HCV viraemia is suggested by results observed in HIV/HCV-coinfected patients [24]. By using a similar methodology to evaluate fibrosis progression, it has been demonstrated that HIV infection, usually associated with a high HCV viraemia, resulted in a rapid progression of cirrhosis [22] whereas, in contrast, HCV-infected patients with normal transaminase activity have a low progression [21]. Furthermore, the potential link between HCV viral load and fibrosis progression is also suggested by the extremely high rate of the so-called ‘hepatic cholestatic fibrosis’ syndrome in allograft recipients (6% in liver recipients and 1.5% in kidney recipients) [26,27]. An argument against this hypothesis may come from the absence of significant differences of the increases in serum HCV RNA or genotype distribution between fibrosers and non-fibrosers in the study by Izopet et al. [23]; however, these authors compared the figures obtained within their series of kidney recipients according to the rapidity of fibrosis accumulation and did not provide any comparison with those obtained in a control group and there is no direct demonstration of a statistical link between serum and intrahepatic viral load, especially in immunocompromised patients. Finally, besides a possible quantitative difference in HCV viraemia as a cause of fibrosis, a qualitative impact of immunosuppression on HCV could also exist; indeed a slower diversification of the hypervariable (HVR)-1 region of the HCV genome (namely, the diversification of quasi-species) was significantly associated with liver fibrosis progression, suggesting the selection of more aggressive variants in fibrosers [23]. Finally, we cannot exclude that the renal insufficiency, which may be observed in kidney recipients may participate in the deterioration by modifying the profile of cytokine expression or the specific lymphocytotoxicity. Altogether, prospective studies in renal recipients including HCV viral load determination and quasi-species analysis are needed in order to verify our hypothesis.

Initial studies dealing with the impact of HCV infection in kidney recipients suggested that HCV infection did not modify patient survival [9,11]; nevertheless, recent studies, which included a higher number of patients and a longer follow-up, have clearly indicated a decreased survival rate in HCV-positive as compared with HCV-negative kidney recipients [12,15–17]. Our results are in accordance with the latter conclusion: indeed we observed a higher, although not significant, rate of cirrhosis development and a higher mortality rate in kidney recipients. Moreover, in our series, the cause of deaths was always liver-related and those who died were characterized by a high yearly progression rate of fibrosis.

Our results raise the question of anti-viral therapies in dialysis patients who are candidates to renal transplantation. Such a treatment may result in a long-term virological response [28,29] while it is clear that it is inefficient and deleterious (induction of allograft rejection) once transplantation is performed [30,31]. On the other hand, in HCV-infected kidney recipients, a liver biopsy should be performed every 3–5 years in order to identify patients who are at risk of deterioration: as interferon is clearly contra-indicated, other anti-viral therapeutic schemes should be discussed, including single-drug therapy by ribavirin [32] even if its potential histopathological benefit is not yet proven in kidney recipients but has been reported to significantly decreased the necrotico-inflammatory score in immunocompetent patients with HCV-related chronic hepatitis [33]. Another question, which has no answer to date, is that of a potential benefit in decreasing immunosuppression, which could limit the pathological worsening in HCV-infected kidney recipients.

In conclusion, our data show that in kidney graft recipients, evolution of chronic hepatitis C is more severe than in HCV-infected immunocompetent subjects. Therefore, in HCV-positive haemodialysis patients, liver histopathological evaluation should be performed and anti-viral therapy discussed before renal transplantation.

References

2. Chan TM, Lok ASF, Cheng IKP, Chan RT. Prevalence of hepatitis C virus infection in hemodialysis patients: a longitudinal study comparing the results of RNA and antibody assays. Hepatology 1993; 17: 5–8
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