Hepatitis C after renal transplantation: histopathological correlations

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Abstract. This study evaluates the correlations between liver histology, cytolysis, cryoglobulinaemia, co-infection with hepatitis B virus, and immunosuppressive treatment in renal transplant patients with HCV infection. Forty-five of 378 kidney recipients (January 1973–September 1993) had anti-HCV antibodies (prevalence = 11.9%) detected by second generation ELISA (Abbott Pasteur). Viral RNA was detected in those patients by RT-PCR in serum and liver. HCV-positive patients underwent liver biopsy to assess their liver tissue lesions according to Knodell’s score. Patients were also screened for Hbs, Hbc and Hbe antigens (ELISA, Abbott) and cryoglobulins (immunobinding, SEBIA). Of the 45 HCV+ patients, 38 (84.4%) had persistent viral replication in the serum and 29 of the 30 patients having undergone liver biopsy had PCR-positive liver tissue. The liver biopsies revealed no active hepatitis lesion in 14 patients (46.6%, Group CAH-), 16 (53.3%) had chronic active hepatitis (Group CAH+) and 3 (10%) had signs of cirrhosis. Comparing groups CH+ and CH- showed that viral replication was detected in all 16 patients with chronic active hepatitis, versus 10/14 patients in the CAH-group (P<0.05). Patients were more frequently treated with azathioprine in the CH+ group (12/16 vs 8/14; P<0.05). The duration of renal transplantation was significantly longer in patients with a Knodell score > 5 (58 ± 56 months vs 35 ± 29 months, P < 0.001). Incidence of co-infection with HBV was similar in both groups. The mean values of alanine aminotransferase correlated with the Knodell score (r = 0.4, P = 0.03). Mixed cryoglobulinaemia was more common in the replicant forms of HVC infection (12/38 vs 1/7, P < 0.0001). This study shows that liver histological lesions are correlated with HCV viral replication, are more frequent in patients treated with azathioprine and are more severe as the duration of transplant is longer.

Introduction

It has now been clearly established that hepatitis C virus (HCV) infection can account for a number of hepatic disorders after renal transplantation (RT) [1,2]. The prevalence of infection following RT ranges from 4 to 50% [3], and is linked to the prevalence of infection in the population of dialysis patients. The reciprocal consequences of RT on the natural history of the disease and of HCV infection on the graft function are now beginning to be discussed. The aim of this study was to determine the prevalence of HCV infection in a large series of RT patients and to determine the relationships that exist between biochemical liver abnormalities (cytolysis), liver pathology and the presence of cryoglobulinaemia, hepatitis B virus co-infection and immunosuppressive therapy.

Patients and methods

Anti-HCV antibody screening was performed in 378 patients who were transplanted between January 1, 1973 and September 1, 1993. Serological exploration consisted of second generation immunoenzymatic assay (ELISA II, Abbott, Sanofi Pasteur) validated by a confirmation test (RIBA II, Ortho). Anti-HCV-positive patients were explored for anti-HBs, anti-HBc and anti-HBe antibodies and antigens (ELISA). HCV-RNA screening was performed in serum and liver tissue by reverse transcription with DNA amplification techniques (RT-PCR). Liver cytolysis was assessed from the alanine aminotransferase (ALT) concentrations (the ALT peak was taken into consideration for statistical regression tests). Liver biopsy puncture (LBP) was systematically performed in patients who were HCV antibody-positive, in search for pathological lesions such as inflammation and necrosis, quantified according to Knodell’s modified index: KI-rated from 0 to 21. Chronic active hepatitis was defined as KI > 5. Cryoglobulinaemia was investigated by immunobinding assay (Hydragel SEBIA) with anti-sera specific for heavy and light chains. The immunosuppressive treatment was as follows: 26 patients (57.7%) were treated with azathioprine (A)—prednisone (P)—cyclosporin (CyA) or A-P and 19 patients were treated with CyA-P. The statistical tests used were the χ² test fitted for percentage comparisons and the linear regression test to study the correlations between KI and ALT.

Results

Forty-five patients of the 378 had anti-HCV antibodies (prevalence 11.9%). Thirty-eight out of 45 patients

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Hepatitis C after renal transplantation

Table 1. Correlations between chronic hepatitis (IK>5) and viral replication, HBV infection, immunosuppressive treatment and transplantation duration

<table>
<thead>
<tr>
<th></th>
<th>IK&gt;5 (n = 16)</th>
<th>IK&lt;5 (n = 14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT-PCR +</td>
<td>16/16 (100%)</td>
<td>10/14 (71%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Ag Hbs or Hbe +</td>
<td>3/16</td>
<td>1/14</td>
<td>NS</td>
</tr>
<tr>
<td>Aza-Pred-CsA</td>
<td>12/16</td>
<td>8/14 (57.1%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>RT duration (months)</td>
<td>58 ± 56</td>
<td>35 ± 29</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: IK = Knodell's index; RT = renal transplantation; Aza = Azathioprine; Pred = Prednisone; CsA = Cyclosporin.

(84%) had persistent viral replication, as demonstrated by serum HCV-RNA positivity (PCR+ group). The LBP results (30 patients) were as follows: 14/30 patients (46.6%) had no significant pathological abnormalities (KI <5); 16/30 (53.3%) had histologically verified chronic active hepatitis, defined by IK >5, including three patients (10%) with cirrhosis. Viral RNA on the liver biopsy was evidenced in 29/30 patients. Comparing between patients with and without chronic active hepatitis (KI >5) revealed that all patients with KI >5 were HCV-RNA-positive (PCR+). The incidence of hepatitis B virus co-infection was the same in both groups. RT duration was significantly longer in patients with chronic active hepatitis (KI >5). The proportion of patients treated with azathioprine was significantly greater in the group of patients with KI >5 (Table 1). The mean ALT value for the 30 patients biopsied was 62 ± 50 U/ml (range 12–150). There was a significant correlation between ALT and KI (R = 0.40; P = 0.03). Mixed cryoglobulinaemia was detected in 13 patients (28.9%): it was polyclonal anti-IgM IgG form in all cases with a monoclonal component in four cases. The existence of cryoglobulinaemia was significantly more frequent in the PCR+ group (12/38 [31.5%] vs 1/7 [14.3%] in the PCR− group, P < 0.0001).

Discussion

The proportion of HCV infection in renal transplantation patients varies from 4% to 50% between teams [1, 3]. In immunocompetent patients, chronic HCV infection is associated to an increased risk of chronic hepatitis, cirrhosis and hepatocellular liver carcinoma [4]. RT justification in patients with HCV chronic hepatitis should consider the consequences of immunosuppression on the prognosis of liver disease. To assess the role of HCV in the development of liver disease, it is necessary to have sufficient prospective follow-up and to repeat liver biopsies. Consistently with data reported by other authors, all patients in our study who had positive PCR exhibited signs of chronic active hepatitis [5]. The results from our study show that liver lesions are aggravated with the duration of RT, which may simply reflect the evolution of liver disease. The data regarding the relationship between biochemical disorders and histological damage are conflicting. Certain authors had established that cytolysis was a poor indicator of the existence of chronic hepatitis in transplanted patients [3, 5] or in healthy blood donors [4]. In our study, we noted a significant correlation between transaminase values and the Knodell score, consistently with Pereira et al.'s findings [6]. Regarding the effect of immunosuppressive treatment on liver histological lesions, we observed a greater proportion of chronic active hepatitis (KI >5) in patients administered triple therapy. It has been established that the chronic progression of hepatitis C is slower than that of hepatitis B [5]. It has recently been demonstrated that HBV-HCV co-infection had no additional deleterious effect on liver pathology [8]. Our results are not conclusive in that respect because of the small number of B/C virus co-infection observed. Hepatitis C is the first etiological agent of type II cryoglobulinaemia [10]. The occurrence of glomerulonephritis (membrano-proliferative) observed in cryoglobulinaemic HCV-infected patients may be related to the deposition of immunoglobulins in the glomeruli or by the direct cytopathological effect of the virus on renal tissue [11]. It would be interesting to study the prevalence of HCV-linked glomerular diseases in renal transplantation patients, as compared with non-transplanted subjects. In our study, cryoglobulin secretion was frequent (28.9%), often oligoclonal and with a monoclonal component in 4 cases. It could be classified as type II-III according to Schifferli's classification [12]. Intermediate oligoclonal forms reflect the dissequilibrium between the B and T lymphocytes. The emergence of a B cell clone is probably promoted by acquired immunosuppression in transplanted patients. This monoclonal proliferation should therefore be taken into account in adjusting the intensity of immunosuppressive therapy.

References