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Worse outcome in younger adult renal graft recipients with HCV infection. An 8-year prospective study

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Introduction

Late morbidity remains one of the mot important problems in renal transplantation, and chronic liver dysfunction (CLD) is one of the main factors that may contribute to it. The majority of long-term data about liver disease in renal transplant patient concerns HBsAg positive patients. Since 1989, however, it has become evident that the most frequent cause of liver disease was hepatitis C virus (HCV) infection. Considering that in Italy 20–40% of dialyzed patients have been found to be anti-HCV positive [3], the contribution of HCV infection to long-term morbidity of transplant patients may be relevant.

In this study, we evaluated whether renal transplant patients with HCV infection were at higher risk of death when compared with HCV negative recipients.

Patients and methods

In 1989, 320 patients alive with a functioning kidney, transplanted between 1983 and 1989, on cyclosporine A (CsA) basal protocols, were tested for anti-HCV. Serum samples stored at –70°C, were tested for anti-HCV by a second generation ELISA. Anti-HCV positive patients were further investigated by qualitative reverse-transcriptase polymerase chain reaction in order to evaluate the viral replication. CLD was defined by abnormal liver test for more than 60 months.

Patients positive for hepatitis B surface antigen were excluded from this study.

Results

Anti-HCV antibodies were detected in sera of 130 (40.62%) out of the 320 CsA-treated patients. Patient age (35 ± 11 versus 32 ± 12) and gender (M/F 73/57 versus 111/79) did not differ between anti-HCV positive and negative patients. When compared with antiHCV negative recipients, anti-HCV positive patients had a longer time on dialysis (54 ± 44 versus 25 ± 25, $P = 0.0001$), a shorter follow-up after transplantation (85 ± 30 versus 90 ± 26, $P = 0.02$), more patients received blood transfusion (yes/no 100/18 versus 52/125, $P = 0.0001$), second transplants (1°/2° 114/16 versus 186/4, $P = 0.0002$) and more patients received the kidney from cadaveric donor (cadaver/LRD 122/8 versus 162/28, $P = 0.01$). No differences were observed in the incidence of acute rejection, (yes/no 42/88 versus 63/127) and in the type of immunosuppression (mono/double/triple therapy 23/57/50 versus 44/83/63).

When the cumulative hazard of developing CLD was taken into account, HCV positive patients had more probability of CLD within 10 years from transplantation than HCV negative patients ($P = 0.0000$).

After transplantation, CLD developed in 63 out of the 130 HCV positive patients (48.46%). We compared the 63 HCV positive patients who develop biochemical abnormalities with the 67 HCV positive patients who did not show biochemical abnormalities throughout the postransplant follow-up of 133 ± 33 months. The pres-

ence of genotype 1b was more frequent (yes/no 29/28 versus 13/33, $P = 0.02$) and the follow-up was significantly longer (89 ± 26 versus 80 ± 33, $P = 0.008$). Instead, there were no differences between patients with our without CLD as far as age, gender or pretransplant blood transfusions. The study of genotypes showed that 1b was present in 42 patients (40%), 2a in 36 (35%), 1a in 14 (13%), 4a in six (6%), 3a in four (4%), 4b in one (1%) and 2b in one (1%) patient. In our series, HCVRNA was detected in the serum of 103 out of 104 (99%) patients who were HCV positive.

Liver biopsy was performed in 39 patients with chronically abnormal liver enzymes in a mean 70 ± 39 months after transplantation. Histologic changes of chronic persistent hepatitis were present in five, a lobular pattern in five, chronic active hepatitis in 23 (mild to moderate in 19 and severe in four), cirrhosis in four and fibrosing cholestatic hepatitis in two patients.

Graft survival (including death) at 14 years in the HCV positive group (55%) did not differ from HCV negative (59%).

The 14-year actuarial patient survival rate was significantly lower (77%) in antiHCV positive patients than HCV negative patients (85%) ($P = 0.01$). In antiHCV positive patients the causes of death were related to extra-hepatic sepsis in six (31%), to liver failure in four (21%) and to cardiovascular accidents in nine patients (48%), whereas in antiHCV negative patients, death was related to neoplasia in five (45%), cardiovascular accidents in five (45%) and infection in one (10%) patient.

At univariate analysis antiHCV status, age, blood transfusions, dialysis duration, rejection episodes, CLD were tested. Among these variables, only age ($P = 0.0006$) and antiHCV status ($P = 0.008$) were significantly associated with patient survival.

The same variables were analyzed by the multivariate analysis. Age at transplant was the only significant parameter correlated with long-term patient survival at 14 years ($P = 0.0006$), whereas antiHCV was no longer significant ($P = 0.69$).

When patients were divided according to the age at transplant, in patients younger than 40 years, antiHCV remained an independent factor associated with patient survival ($P = 0.0366$), whereas in patients older than 40 years it lost significance ($P = 0.248$).

Discussion

In this study we found a high prevalence of HCV infection in transplanted patients. This was probably due to the fact that before 1989 there was no test to recognize whether a blood or a transplant donor could be a carrier of C virus. In fact, we found that there were more transfused patients among HCV positive patients than among negative patients. Moreover, the risk of HCV positivity was higher in patients who had received a renal allograft from a cadaver than from a living related donor, and had a longer period of dialysis.

As already reported by previous papers [1, 2], this study confirms that renal transplant patients with HCV positivity had significantly more probability of developing CLD, with about half of HCV positive patients with biochemical abnormalities, severe histological lesions were seen in 25% of patients. In this series too, the genotype 1b was found more frequently in patients who developed CLD than in patients without CLD.

There is some controversy about the influence of HCV status on the long-term outcome of renal transplant patients; Roth et al. [2] found no difference in patients and graft survival rates at 5 years between HCV positive and negative patients, while Periera et al. [1] reported a higher risk of mortality in HCV positive patients. In this study, we found that the graft survival rate was similar in HCV positive and negative patients. However, the mortality rate was significantly higher in HCV positive patients. At multivariate analysis, age was the only variable associated with death, independently of the HCV status. However, if we consider only patients younger than 40 years, HCV positive patients had a significantly higher probability of dying than HCV negative patients. Most younger patients died from extra-hepatic sepsis and/or liver failure. These data suggest an ominous impact of HCV status in the long term.

In conclusion, this study shows that HCV positive transplanted patients had a high risk of developing CLD within 10 years. This risk is more elevated in carriers of the subtype 1b. There is a consistent risk of mortality in HCV positive patients younger than 40 years.

References

1. Periera BJ, Wright TL, Schmid CH, Levey AS (1995) The impact of pretransplantation hepatitis C infection on the outcome of renal transplantation. 60: 799–805
2. Roth D, Zucker K, Cirocco R, DeMattos A, Burke GW, Nery J, Esquenazi V, Babischkin S, Miller J (1994) The impact of hepatitis C virus infection on renal allograft recipients. Kidney Int 45: 238–244
3. Vosnides GG (1997) Hepatitis C in renal transplantation. Kidney Int 52: 843–861