HBsAg as Predictor of Outcome in Renal Transplant Patients

Ezequiel Ridruejo1, María del Rosario Brunet2, Ana Cusumano2, Carlos Díaz2, Mario Davalos Michel2, Luis Jost2, Luis Jost (h.2), Oscar G. Mando1, Antonio Vilches2

1Sección Hepatología, 2Sección Nefrología, Departamento de Medicina; Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno, (CEMIC), Buenos Aires

Abstract

Chronic liver infections related to hepatitis B and C viruses are a common problem in renal transplant patients with a prevalence of 1.5 to 50% in different countries. There is no uniform agreement regarding their influence on the incidence of acute rejection, graft outcome and survival of renal transplant patients. We retrospectively evaluated the influence of antiHBc, antiHCV and HBsAg positive status; gender; age over 50 years of age at the time of transplantation; pre and postransplantation alaninaminotransferase (ALT) elevation; acute rejection; type of graft; number of transplants; and maintenance and induction immunosuppression treatment on the incidence of acute rejection and both graft and patient survival in the population transplanted in our center between 1991 and 1998. The univariate analysis showed that antiHCV, HBsAg and antiHBc status, more than one renal transplant and one or more episodes of acute rejection were associated with diminished graft survival; and being over the age of 50 at the time of transplantation was also associated with diminished patient survival. In the multivariate analysis HBsAg positive and one or more episodes of rejection were associated with a diminished graft survival, and none of the variables studied was associated with diminished patient survival. In conclusion antiHCV and HBsAg positive status was associated with an increased risk of losing the transplanted kidney, and HBsAg positivity was associated with an increased risk of death, but this was not a statistically significant association.

Key words: chronic viral hepatitis, outcome, renal transplantation

Chronic liver diseases related to hepatitis B and C viruses are a frequent problem in renal transplant recipients, and there is no agreement regarding their impact upon both patient and allograft survival. Viral hepatitis prevalence in dialysis patients on the transplant waiting list varies between 1.5 to 50% according to different series1-6. The most relevant risk factors for these infections in the dialysis population are the number of transfusions, the time on dialysis and the dialysis modality, as they are much more frequent in hemodialysis than in peritoneal dialysis.

The aim of this study was to retrospectively determine the incidence of acute rejection, graft outcome and overall survival of renal transplant patients with a positive serology for hepatitis C (antiHCV positive) and B (HBsAg positive) when compared with our seronegative population.
Materials and Methods

The clinical records of the 254 renal transplants (252 adult patients) performed at CEMIC between January 1st 1991 and December 31st 1998 were systematically reviewed. All the information gathered up to July 31st 1999 was included in the analysis and the variables considered were the following: graft survival was the period (in days) elapsed between renal transplantation up to the return to dialysis or to the end of the evaluation; rejection: an episode of acute renal dysfunction treated with anti-rejection drugs, regardless of whether or not a biopsy was performed to establish the diagnosis; patient survival: the time (in days) elapsed between renal transplantation up to the patient’s death with a functioning graft, or up to the end of the evaluation.

We also analyzed the influence of the following variables (dependent) upon the previously mentioned (independent) variables: gender; age over 50 years at the time of transplantation; pretransplantation anti-HCV (hepatitis C virus antibody), HBsAg (hepatitis B surface antigen) and anti-HBc (hepatitis B core antibody) positivity; pre and posttransplantation alaninaminotransferase (ALT) elevation; rejection; type of graft; number of transplantations; and induction and maintenance immunosuppression treatment.

All these variables were subjected to a univariate and multivariate data analysis, using the Cox proportional hazard model and the hazard ratio (HR) associated with patient survival, graft survival and incidence of acute rejection with their corresponding 95% confidence intervals (CI) and p values. P values ≤ 0.05 were considered statistically significant. Cumulative patient and graft survival rates were calculated using the Kaplan Meier method and the comparisons were performed using the log rank method. For statistical analysis STATA® software, statistics data analysis version 7.0 (Stata Corporation, Tx., USA), was used.

Results

We evaluated all 252 adult recipients transplanted during the study period. All were Caucasian, 61% were men, 92% were on hemodialysis before renal transplantation, 62% were cadaveric transplantations, and the average age at the time of the evaluation was 38 years (Table 1). Twenty one patients (9%) were excluded because of insufficient data (moved to another country, transferred to another center, or lost to follow up for other reasons). Of the 231 remaining patients, 106 were anti-HCV positive and 17 HBsAg positive. The number of HBsAg positive patients receiving a transplant each year, remained stable during the study period. The median time of follow up was 1199 days (range 1-3125). The median time on hemodialysis before transplantation was 67.26 months (SD 47.69 months) for anti-HCV positive patients and 25.4 months (SD 23.04 months) for anti-HCV negative patients (p < 0.001). In HBsAg positive patients the time on dialysis was 57.18 months (SD 61.63 months) and in the HBsAg negative group the time was 43.42 months (SD 23.04 months) for anti-HCV negative patients and 54% in positive patients (p=0.0147) (Fig. 1). In anti-HCV positive patients the risk of returning to dialysis was 5.51/100 patients year, whilst in the HBsAg negative this risk was 2.83. HBsAg positive patients had a risk of 12.53/100 patients year, whilst in the HBsAg negative the risk was 2.83.

Cumulative graft survival rate at 7 years was 86% in HBsAg negative patients and 54% in positive patients (p=0.0147) (Fig. 1). In anti-HCV positive patients cumulative graft survival rate was 74% versus 91% in those who tested negative (p= 0.0347) (Fig. 2).

We found that only being over the age of 50 at the time of transplantation was associated with an increase in the risk of acute rejection (HR 2.39, p=0.001 CI 95% 1.45-3.93). In the multivariate analysis none of the variables studied were associated with an increased risk of rejection.

Being older than 50 at the time of transplantation was also associated with an increased risk of death (HR: 4.64, p >0.001, CI 95% 2.07-10.75), whilst transplantation using a living donor was associated with a lower mortality.
(HR: 0.308, p=0.031, CI 95% 0.109-0.89). HBsAg positive patients showed a higher mortality, but this was not statistically significant (HR: 2.02, p= 0.258, CI 95%: 0.597-6.838). AntiHCV positive status (HR: 1.11, p= 0.805, CI 95%: 0.481-2.564) and all the other variables studied did not have an impact upon the risk of death. In the multivariate analysis none of the variables studied was associated with an increased risk of death. In HBsAg positive patients cumulative survival rate was 76% and in the HBsAg negative population it was 88% (p= 0.24). In antiHCV positive patients this rate was 86% versus 87% in the negative group (p= 0.80).

**Discussion**

In this study antiHCV and HBsAg positive status was associated with an increased risk of losing the transplanted kidney, although the correlation attained significance only in the case of the B virus infection. HBsAg was also associated with an increased risk of death, but this was not statistically significant. Since chronic viral infections of the liver are diseases with a long term course, with a longer follow up period positive serologies might show a statistically significant association with patient death.

The present study has various limitations. It is a retrospective study and data from a small number of patients is missing. We did not have HCV viremia confirmation by the detection of HCV RNA by PCR in the antiHCV positive patients; given that other studies found a concordance of 75 and 98% between antiHCV and PCR positivity\(^4,5\), we believe that our population would...
show similar results. Although it has been shown that alterations in liver function tests do not predict patient outcome\textsuperscript{6, 7}, considering that less than 10% of our patients had liver biopsies performed, it is not possible to be certain if the group of patients with more severe liver disease had a different outcome from the group of patients with milder disease, as various publications suggest\textsuperscript{6, 8, 9, 10}. The results of the many studies dealing with these issues are controversial. Some indicate that antiHCV/HBsAg positive renal transplant patients have a lower survival and/or a higher risk of graft failure than negative patients\textsuperscript{6, 7, 10-13, 20}, but other studies found contradicting results\textsuperscript{14-20} on the other hand data from third world countries, especially from Latin America are virtually non-existent.

Based in series demonstrating a greater long term survival in chronic renal failure patients receiving a renal transplantation when compared with patients remaining on dialysis\textsuperscript{21}, two studies showed that even though mortality of antiHCV positive renal transplant patients is higher than in negative ones, the positive group’s mortality is still lower than that of patients remaining on dialysis\textsuperscript{22, 23}. There are multiple explanations for the difference in the results of the published studies: a short time of follow up, usually less than 10 years, for a disease which evolves over decades; most series have included a small number of patients from a single center; and the greatest difficulty in the interpretation of the data is that patients have usually not been adequately studied in relation to the severity of their liver disease. Also, some groups do not include patients with viral hepatitis in their transplant list and patients with severe comorbidities are generally not transplanted, thus generating a selection of patients which makes comparisons virtually impossible.

The results in our population suggest that antiHCV and HBsAg positive renal transplant patients have a worse outcome than negative ones. In spite of these results, and considering the diversity of the conclusions of the published studies, it is difficult to make general recommendations about the inclusion or exclusion of these patients in the renal transplantation list. Such recommendations, based upon uniform evaluation criteria, must be individualized\textsuperscript{4, 5} in order to avoid transplanting a patient with severe liver disease and allowing transplantation of patients with mild chronic viral hepatitis, who are unlikely to have complications in the long term.

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