The influence of hepatitis B and hepatitis C virus infection in the recipient on late renal allograft failure

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Abstract

Background. Chronic liver disease is one of the most important complications after renal transplantation. Hepatitis B and mainly hepatitis C are the more frequent causes of liver disease. Although there are controversial results, in some series, hepatitis B and hepatitis C are associated with lower graft and patient survival.

Patients and methods. A total of 3365 adult patients who received a renal transplant in 1990 (N = 824), 1994 (N = 1075) and 1998 (N = 1466) with a functioning graft after the first year were included. Fifty-one (2.1%) with positive HbsAg were diagnosed with hepatitis B at transplantation; 488 (16.9%) presented positive anti-hepatitis C antibodies and were diagnosed with hepatitis C virus (HCV) infection and 25 patients (0.8%) were diagnosed with concomitant hepatitis B virus (HBV) and HVC infection. Demographic, immunosuppression, survival figures and post-transplant and follow-up data of these patients and negative HBV and HVC patients were recorded.

Results. The overall prevalence of HBV in the recipients was 2.1%. Patient survival was lower and liver disease was the main cause of death in HBV-positive patients. However, in the multivariate analysis the presence of positive HbsAg did not have an independent risk factor for graft loss and patient death. This finding was similar in patients with concomitant HBV and HVC infection. Graft and patient survival were lower in HCV-positive patients and liver disease was the main cause of death. Interestingly, proteinuria and serum creatinine were risk factors for graft loss and patient death. Fortunately, prevalence of HCV in the recipients significantly decreased from 29% in 1990 to 10% in 1998.

Conclusions. In the last decade in Spain, HBV infection in the recipients, showing an overall prevalence ~2%, did not influence graft and patient survival. However, HCV infection in the recipient was associated with lower graft and patient survival, although the prevalence of HCV clearly decreased from 29% in 1990 to 10% in 1998.

Keywords: hepatitis B; hepatitis C; late renal allograft failure; patient survival; proteinuria

Introduction

Chronic liver disease (CLD) is a frequent complication after renal transplantation, representing the fourth cause of death in most series [1]. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the most important causes of CLD in renal transplant patients [1–3]. Although the results are controversial, in some series both HBV and HVC infections have a deleterious effect on long-term graft and patient survival in the long run [3–5]. Also, liver disease is the first cause of death in these infected patients [4].

The aim of the present study is to analyse the influence of HBV and HVC infections on long-term graft survival after renal transplantation compared with non-infected patients and the changes in the prevalence of these infections over the last decade in Spain.

Patients and methods

Study design

We retrospectively analysed the patients included in the Spanish Chronic Allograft Nephropathy Study. As previously described [6], a cohort of 3365 adult patients who received a renal transplant in Spain in 1990, 1994 and 1998 with a functioning graft at 1 year were included.
Pre-transplantation, 51 (2.1%) of them tested positive for HbsAg and were HCV negative, 488 (16.9%) had positive anti-HCV antibodies and negative HbsAg and 25 (0.8%) had both HBV and HCV infections.

Clinical variables

The variables of the presence of HBV and HCV infections were recalculated, obtaining variables that identified patients with HBV without HCV and patients with HCV but without HBV. A new variable specified in more detail the situation of these patients in relation to their viral state; it was categorized as follows: no HbsAg, no HCV antibodies; with HbsAg, no HCV antibodies; no HbsAg, with HCV antibodies; with HbsAg and HCV antibodies.

In all infected and non-infected patients, different types of variables were evaluated before and after renal transplantation, focusing on survival figures and risk factors for graft loss and patient death. In these HBV and HCV patients we also analysed the changes of prevalence during 1990 and 1998. Immunosuppressive treatment was analysed on an intention-to-treat basis.

Definitions

Hepatitis B virus infection. The presence of pre-transplantation HBV infection was defined by the presence in the recipient of positive HbsAg.

Hepatitis C virus infection. The presence of pre-transplantation HCV infection was defined by the presence in the recipient of positive anti-HCV antibodies (ELISA1 in 1990 and ELISA2,3 in 1994 and 1998).

Combination of hepatitis B and hepatitis C infection. This was defined by the concomitant presence of both positive HbsAg and positive anti-HCV antibodies.

Statistics

Cox proportional hazards regression for analysing graft and patient survival was used. A backward procedure was used to exclude those not showing a significant effect. The survival models were calculated censoring for death. All graft survival models were adjusted by year of transplantation and for centre effect. For patient survival only the year of transplant was included as an adjustment variable because no deaths were observed in some of the centres and numerical problems would have arose when fitting the model.

Results

Hepatitis B virus infection

The prevalence of recipients with HBV infection was lower in 1994 and 1998 than in 1990, but this difference was not statistically significant (Figure 1).

Regarding recipient characteristics (gender, age, original renal disease, re-transplantation, hyperimmunization, HLA mismatches, smoking, the dialysis modality and time on dialysis) and donor data (gender, age, cause of death, non-heart beating) there were no significant differences comparing with HBV- and HCV-negative patients. All positive HbsAg patients received a cadaveric renal transplant.

The overall immunosuppressive treatment for recipients with HBV infection was significantly different from that of patients without HBV infection. The percentage of treatment with regimens with MMF was lower in HBV-positive patients (19.7 vs 31.8%, P = 0.001).

There were no differences in acute rejection, corticosteroid rejections, cytomegalovirus infection and surgical complications between both groups. However, delayed graft function was significantly more frequent and cold ischaemia time longer in HBV-positive than in HBV-negative patients (47.1 vs 28.6%, P = 0.01, and 33.3 vs 26.1 h, P = 0.02, respectively).

No significant differences were observed in the follow-up data (serum creatinine and proteinuria at 3 months and 1 year and in the 3 months to 1 year period; changes in both parameters in treatment with ACEI/ARAI and lipid-lowering therapy), graft survival (Figure 3) and cause of graft loss. Patient survival was lower (Figure 4) and the percentage of deaths due to liver failure was higher for patients with hepatitis B (44.4 vs 0.6%, P = 0.0000).

The multivariate analysis revealed that among the patients with HBV infection, five variables were independently associated with patient survival: recipient age (P = 0.0001), cause of donor death (P = 0.02), serum creatinine at 3 months (P = 0.011), proteinuria at 3 months (P = 0.0001) and proteinuria increase from 3 months to 1 year (P = 0.0001). However, the presence of positive HbsAg was not an independent risk factor for patient survival.

Hepatitis C virus infection

The prevalence of recipients with HCV infection was significantly lower in 1998 than in 1994, which in turn was lower than in 1990 (Figure 2).

Recipients with HCV infection were characterized by presenting a lower mean body weight, height and body mass index, lower proportion of polycystic disease, a
higher proportion of re-transplantation, increased mean peak and last panel reactive antibodies, a higher percentage of haemodialysis as renal replacement therapy and longer time on dialysis. Also, donor weight was significantly lower for recipients with hepatitis C. No significant differences were detected for the other donor and recipient variables comparing with patients without HCV infection.

The immunosuppressive protocols including MMF (with cyclosporine or tacrolimus) were less frequent in recipients with HCV \(17 \text{ vs } 31.8\% , \ P < 0.0001\). The presence of anti-HCV antibodies was found to be significantly associated with increased cold ischaemia time and higher frequency of delayed graft function. There were no differences with HCV-negative patients on acute rejections, cortico-resistant acute rejections, cytomegalovirus infection and surgical complications.

The follow-up data revealed a steady increase of serum creatinine between 3 months and 1 year; an increase in proteinuria between 3 months and 1 year, and the 1 year proteinuria was also higher in patients with HCV infection. Both treatments with ACEI/ARAI and lipid-lowering agents were less frequent in HCV-positive patients.

Patients with HCV infection had a higher risk for graft loss [RR 1.585, 95% CI (1.274–1.973), \( P < 0.0001\)] and patient death [RR 1.505, 95% CI (1.121–2.021), \( P < 0.0065\)] (Figures 3 and 4). Also, the proportion of deaths due to liver disease was higher (13.85 \text{ vs } 0.6\% , \ P = 0.03\). No significant differences were observed in the causes of graft loss.

In the multivariate analysis, the presence of HCV infection in the recipient was an independent risk factor for graft loss (Table 1) and for patient death (Table 2).

### Hepatitis B and hepatitis C

The percentage of recipients with concomitant HBV and HCV infections decreased significantly from 1990 to 1998 (Figure 1): a total of 25 patients with HBV and HCV infection were transplanted in this period.

The joint effect of HBV and HCV infections on survival showed that graft [RR 1.3, 95% CI (0.553–3.309), \( P > 0.05\)] and patient survival [RR 1.17, 95% CI (0.375–3.693), \( P > 0.77\)] were not statistically different in patients without these infections (Figures 3 and 4).

### Discussion

The present study explored the changes over the last decade in the prevalence of HBV and HVC infections in renal transplant recipients and their influence on late renal allograft failure.
Table 1. Graft survival vs presence of hepatitis C in the recipient, and other variables

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (ref. ‘&lt;60 years’)</td>
<td>1.788</td>
<td>(1.335, 2.395)</td>
</tr>
<tr>
<td>Last panel reactive antibodies (ref. ‘&lt;15%’)</td>
<td>1.412</td>
<td>(1.038, 1.921)</td>
</tr>
<tr>
<td>Acute rejection (ref. ‘no’)</td>
<td>1.638</td>
<td>(1.316, 2.040)</td>
</tr>
<tr>
<td>Triglycerides at 3 months (+1 mg/dl)</td>
<td>1.083</td>
<td>(1.009, 1.163)</td>
</tr>
<tr>
<td>Creatinine at 3 months (+1 mg/dl)</td>
<td>2.121</td>
<td>(1.855, 2.425)</td>
</tr>
<tr>
<td>Creatinine increase from 3 months to 1 year (+1 mg/dl)</td>
<td>2.748</td>
<td>(2.359, 3.203)</td>
</tr>
<tr>
<td>Proteinuria at 3 months (+1 g/24h)</td>
<td>1.108</td>
<td>(1.015, 1.210)</td>
</tr>
<tr>
<td>Proteinuria increase from 3 months to 1 year (+1 g/24h)</td>
<td>1.317</td>
<td>(1.221, 1.421)</td>
</tr>
<tr>
<td>Proteinuria increase from 3 months to 1 year (+1 g/24h) in 1990</td>
<td>1.498</td>
<td>(1.142, 1.966)</td>
</tr>
<tr>
<td>Proteinuria increase from 3 months to 1 year (+1 g/24h) in 1994</td>
<td>1.790</td>
<td>(1.550, 2.066)</td>
</tr>
<tr>
<td>Proteinuria increase from 3 months to 1 year (+1 g/24h) in 1998</td>
<td>1.349</td>
<td>(1.145, 1.588)</td>
</tr>
<tr>
<td>IECAS/ARAII during the first year (ref. ‘yes’)</td>
<td>1.425</td>
<td>(1.082, 1.877)</td>
</tr>
<tr>
<td>IECAS/ARAII during the first year (ref. ‘yes’) in 1990</td>
<td>3.053</td>
<td>(0.465, 20.049)</td>
</tr>
<tr>
<td>IECAS/ARAII during the first year (ref. ‘yes’) in 1994</td>
<td>1.279</td>
<td>(0.840, 1.947)</td>
</tr>
<tr>
<td>IECAS/ARAII during the first year (ref. ‘yes’) in 1998</td>
<td>1.821</td>
<td>(0.953, 3.544)</td>
</tr>
<tr>
<td>Recipient HCV positive</td>
<td>1.532</td>
<td>(1.170, 2.006)</td>
</tr>
</tbody>
</table>

Table 2. Patient survival vs presence of hepatitis C in the recipient (without hepatitis B) and other variables

<table>
<thead>
<tr>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age (ref. ‘&lt;60 years’)</td>
<td>4.220</td>
<td>(3.075, 5.790)</td>
</tr>
<tr>
<td>Cause of death (ref. ‘TCE’)</td>
<td>1.385</td>
<td>(1.037, 1.848)</td>
</tr>
<tr>
<td>Creatinine at 3 months (+1 mg/dl)</td>
<td>1.749</td>
<td>(1.441, 2.123)</td>
</tr>
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<td>Creatinine increase from 3 months to 1 year (+1 mg/dl)</td>
<td>1.433</td>
<td>(1.127, 1.821)</td>
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<tr>
<td>Proteinuria at 3 months (+1 g/24h)</td>
<td>1.330</td>
<td>(1.140, 1.552)</td>
</tr>
<tr>
<td>Proteinuria increase from 3 months to 1 year (+1 g/24h)</td>
<td>1.199</td>
<td>(1.034, 1.391)</td>
</tr>
<tr>
<td>Recipient HCV (ref. ‘HCV negative’)</td>
<td>1.549</td>
<td>(1.135, 2.114)</td>
</tr>
</tbody>
</table>

The prevalence of recipients with HBV infection was a little bit lower in 1994 and 1998 than in 1990, showing an overall prevalence of 2%. This percentage reflects the situation in Europe where vaccination and general measures against HBV infection are applied. In western Europe the prevalence of HBV infection decreased from 28% in 1978 to 3% in 1990 [7], and in Spain in 1990, 1994 and 1998 only 51 HBsAg-positive patients were transplanted.

The impact of HBV infection on survival figures after renal transplantation remains controversial [8–12]. In the multicentre study, the presence of positive HBsAg in the recipient had no significant impact on graft survival. Although patient survival was significantly lower and liver disease was the most important cause of death, the presence of positive HBsAg was not independently associated with patient death in the multivariate analysis. Therefore, over the last decade, HBV infection did not have a significant effect on graft survival in patients with a functioning graft at 1 year. This inclusion criterion possibly explains these results when they are compared with those obtained by Mathurin et al. [5] who included all HBsAg patients at transplantation and demonstrated that HBsAg positivity in the recipient was independently associated with patient and graft survival. On the other hand, due to the limitations of the database (focusing on late renal allograft failure), we were not able to show the possible influence of HBV replication on liver disease and survival figures. A recent study, however, showed that the presence of HBsAg was an independent predictor of death [13]. Also, we do not know if some patients were treated with Lamivudine or other antiviral agents.

The general characteristics of our HCV-positive patients were similar to those previously reported, and contained a higher proportion of re-transplantations, hyperimmunization and a longer time on haemodialysis. Some of these patients were considered as belonging to an immunologically high-risk group and they received quadruple immunosuppressive therapy. An immunosuppressive regimen including MMF was less frequent in these recipients. Perhaps, the scarce information about the effect of MMF on liver disease in 1998 could explain this difference.

Interestingly, the presence of HCV infection was significantly associated in both the univariate and the multivariate studies with a high risk for graft loss. Also, serum creatinine and proteinuria at 3 months and increases from 3 months to 1 year, were significant risk factors for graft loss. These data reinforce the concept that HCV infection is an independent risk factor for graft loss. It is well known that HCV induces glomerular diseases, mainly membranoproliferative or membranous glomerulonephritis [14]. The presence of proteinuria in our series as a significant risk factor in these patients suggests that it could be due, at least in part, to HCV-induced renal disease. This fact is further suggested by the frequency of de novo glomerulonephritis as a cause of graft loss that was slightly higher.
in HCV-positive patients (3.8 vs 2.7%, P NS). Recent encouraging results suggest that to prevent HCV-induced renal disease interferon therapy in dialysis could be started. Interferon can induce a sustained clearance of HCV RNA [15] and can also decrease the presence of de novo glomerulonephritis associated with HCV infection after transplantation [16].

Similar to most series, HCV infection (without HBV infection) was also a risk factor for patient death in the univariate and multivariate analysis. The possible role of the severity of liver disease in patient survival could not be established in our study. However, the patient survival at 10 years was 77.5%, a result that can be considered good for these high-risk patients. In fact, renal transplantation is considered as the best therapy for end-stage renal disease in HCV-positive patients [2,4].

It is of note that the prevalence of recipients with HVC infection significantly decreased from 29% in 1990 to 10% in 1998. This result reflects the current situation in Europe, where preventative measures against HCV infection are applied, including, avoiding transfusions, testing blood donors and general measures to avoid nosocomial transmission in dialysis [3,4]. This important reduction is especially relevant since HCV infection has been considered in several but not in all studies as an independent risk factor for graft survival and patient death [4,5,17,18]. This impressive reduction was a positive evolution that may have significantly contributed to the improved graft survival and half-life in our Spanish population in the last decade. This occurs in a changing background characterized by a decrease in the quality of the donor, an increase in patients’ age and the use of new immunosuppressive agents [6].

The combined effect of HBV and HCV has recently been a high risk of graft loss and mortality [13]. This was, however, not found in our study. Although these data should be interpreted with caution due to the small patient sample and the absence of information on the severity of liver disease, they can suggest that the clinical course of these patients is perhaps not as deleterious as has previously been described [19].

Our study has several limitations. It is a retrospective study focusing on late renal allograft failure and the database included mainly pre- and post-transplant risk factors for graft loss. Biochemical liver profiles, complete serology of HBV infection (HbsAg or DNA polymerase) and HCV infection (HCV RNA and genotype), clinical course and severity of liver disease and changes of immunosuppressive therapy or treatment (for instance, Lamivudine for replicating HBV infection) were not recorded. Also, only patients with graft functioning over 1 year were included. Therefore, in this analysis, the clinical impact of liver disease and the role of active viral diseases on survival results cannot be analysed. Despite these shortcomings, this is the first study exploring the prevalence and influence of HbsAg-positive and/or positive anti-VHC antibodies in the recipient on long-term graft survival over the last decade in a European country.

Conflict of interest statement. None declared.

References