Acute rejection and late renal transplant failure: Risk factors
and prognosis

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Abstract

Background. Acute rejection episodes are a major
determinant of renal allograft survival, and the
improvement of the transplantation results in the last
two decades is largely due to a progressive decrease in
the incidence of acute rejection. These results are
explained by the incorporation of new immunosuppres-
sive agents since the introduction of cyclosporine.
Because the detrimental effect of acute rejection on
graft survival is not limited to the early post-transplant
period, we have focused on the impact of acute
rejection episodes on late transplant failure in patients
with the graft functioning 1 year after transplantation.

Methods. We have retrospectively analysed in 3365
renal transplants performed in adults in Spain during
1990, 1994 and 1998 the incidence and severity of the
acute rejection episodes, their risk factors, and their
influence on graft and patient survival.

Results. The incidence of rejection episodes in the
whole series was 32.5%, decreasing in 1998 (25.1%)
compared with the previous years (38%) (P < 0.0001).
Corticoid-resistant rejection episodes also decreased
from 8% in 1990 and 1994 to 3.4% in 1998 (P <
0.0001). Multivariate analysis showed that patients
< 60 years old (P < 0.0001), sensitized recipients
(P = 0.038), patients with delayed graft function
(P < 0.0001), cytomegalovirus infection (P = 0.0060),
and those transplanted in 1990 or 1994 (P <
0.0001) had an increased incidence of rejection episodes. In
the univariate analysis, induction treatment with antilymphocyte globulines or OKT3
(P = 0.0002), and traumatic donor death (P = 0.042) were associated with a lower incidence of acute rejection. In the
univariate analysis of the transplants performed in 1998, addressed to evaluate the effect of the new

Introduction

Acute rejection episodes in renal transplantation are
considered a risk factor for short-term and long-term
allograft survival [1–4]. Since the introduction of
cyclosporine two decades ago a progressive decrease in
the incidence of rejection episodes and a subsequent
improvement in graft survival, partly derived from the
introduction of new immunosuppressive agents, has
been observed [5,6]. However, these beneficial effects
on early graft survival have had less effect on the late
attrition rate, mainly due to chronic transplant
nephropathy and patient death with a functioning
graft [7,8]. Because estimation of long-term allograft
survival is influenced by the early failures, we have
performed an analysis of the late transplant failures,
excluding the losses during the first year after trans-
plantation, in order to assess the risk factors of
acute rejection and how these episodes influence late
transplant survival.
Subjects and methods

In a series of 3365 kidney transplants recipients, transplanted in Spain in the 1990s, and with a functioning graft 1 year after transplantation, the prevalence of acute rejection episodes during the first 2.5 years after transplantation has been studied, because this was the follow-up period for the patients transplanted in 1998 at the time of analysis. We analysed the patient’s risk factors and their impact on graft and patient survival. Acute rejections were diagnosed based on the clinical and analytical data, and by the administration of anti-rejection treatment. The treatment consisted of steroid boluses, at least three doses of 250 mg of methyl prednisolone, and when the episodes were considered corticoid-resistant, the patients received antilymphocyte globulines (AtgamR, Pharmacia or ThymoglobulinR, Sangstat®) or OKT3. Biopsy-proven acute rejection was increasingly obtained in the three consecutive periods analysed. Univariate and multiple linear regression analysis, adjusting for year of transplant and centre, were performed in order to analyse the risk factors for acute rejection in the whole series. In addition, in order to assess the impact of the new immunosuppressive agents mycophenolate mofetil, tacrolimus and anti-IL2 antibodies, introduced in the last period, the risk factors in the transplants performed in 1998 were also analysed. Graft and patient survival in relation to rejection episodes were analysed using the Cox proportional hazards regression model. Comparison of patient survival between subjects with or without acute rejection, stratified for each year of transplantation could not be adjusted for centre effect because too few deaths were observed in 1998.

The evolution of renal allograft function in the patients with acute rejection episodes, measured by serum creatinine and daily proteinuria, was compared with the function in patients without rejection. Systolic and diastolic blood pressures as well as cholesterol and triglyceride levels were also compared in the two groups. Mann-Whitney U-test was applied to test the differences between these two groups of independent observations. The significance level was 0.05 for all statistical tests.

Results

Incidence and severity of acute rejection

In the whole series, 32.5% of the patients experienced acute rejections, and 27.2% suffered from them during the first year. The prevalence of acute rejection decreased in the patients transplanted in 1998 compared with those transplanted in 1990 or 1994 (P < 0.0001), with no significant differences between these two last years. The percentages of patients free of acute rejection 2.5 years after transplantation were 61.3, 62 and 74.9% for those transplanted in 1990, 1994 and 1998, respectively (P < 0.0001) (Figure 1). The percentage of patients with one rejection episode decreased from 32.3% in 1990 and 31% in 1994 to 21.5% in 1998, and those with recurrent rejection episodes were 6.4, 7 and 3.6% of the patients transplanted in the three consecutive periods (P < 0.0001). The fraction of patients with a corticoid-resistant acute rejection, who required antilymphocyte globulines or OKT3, also decreased from 8.1% in 1990 and 8.4% in 1994 to 3.4% in 1998 (P < 0.0001). The percentage of patients with acute rejection that were biopsy proven increased from 28.4% of the treated episodes in 1990 to 33.9% in 1994, and 47% of the acute rejections diagnosed in 1998 (P < 0.0001). There were no significant differences in the Banff grading of acute rejection diagnosed in the three periods: in 1990, 55.6% of the acute rejection episodes were graded Banff I, 40% grade II and 4.4% grade III; in 1994 the percentages were 51.4, 39.9 and 8.7%, and in 1998 the corresponding percentages were 52.3, 43 and 4.7%, respectively (P = 0.429).

Risk factors for acute rejection

Factors that significantly increased the risk of acute rejection in the logistic regression analysis were the recipient’s age (reference >60 years; RR 1.582; P < 0.0001), sensitization of the recipients (reference <15% peak panel reactive antibodies; RR 1.173; P = 0.038), presence of delayed graft function (RR 1.417; P < 0.0001) and cytomegalovirus (CMV) infection (RR 1.260; P = 0.0060) (Table 1). Patients transplanted in 1998 had a reduced risk of acute rejection compared with transplants performed in 1990 (RR 0.645; P < 0.0001), with no differences between patients transplanted in 1990 and 1994 (P = 0.920). In the univariate analysis an increase in the risk of acute rejection was observed in the patients who did not receive induction treatment with polyclonal antilymphocyte antibodies or OKT3 (RR 1.393; P = 0.0002), and in recipients of a kidney from a donor whose cause of death was of traumatic origin (RR 1.158; P = 0.0425).

In order to assess the impact of the new immunosuppressive agents introduced after 1994, a separate analysis of the risk factors for acute rejection was
performed considering exclusively the patients transplanted in 1998. In the multiple regression analysis, the presence of delayed graft function [RR 1.427; 95% confidence interval (CI) (1.355, 2.126); \( P < 0.0001 \)] and a recipient age < 60 years [RR 1.425; 95% CI (1.059, 1.925); \( P = 0.019 \)] correlated again with the rejection episodes. In the univariate analysis, an increased risk of acute rejection was observed in patients not receiving mycophenolate mofetil treatment at the moment of transplantation compared with those who received this drug [RR 1.367, 95% CI (1.176, 1.590); \( P < 0.0001 \)], as well as with immunosuppressive protocols containing cyclosporine compared with those containing tacrolimus [RR 1.568; 95% CI (1.133, 2.170); \( P = 0.0068 \)]. Treatment with anti-IL2 antibodies was not followed by a reduced incidence of acute rejection (\( P = 0.853 \)), but very few patients were treated with these antibodies. As in the whole series, HLA sensitization [RR 1.280, 95% CI (1.095, 1.496); \( P = 0.0019 \)], and CMV infection [RR 1.367, 95% CI (1.053, 1.419); \( P = 0.0082 \)] correlated with an increased risk of rejection in the univariate analysis.

**Table 1. Risk factors for acute rejection (adjusting for year of transplant and centre)**

<table>
<thead>
<tr>
<th></th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Recipient age (ref. ‘≥60 years’)</td>
<td>1.572 (1.273, 1.941)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Recipient sex (ref. ‘male’)</td>
<td>1.093 (0.958, 1.246)</td>
<td>0.1847</td>
</tr>
<tr>
<td>Time on dialysis (+1 month)</td>
<td>0.999 (0.998, 1.001)</td>
<td>0.2113</td>
</tr>
<tr>
<td>Type of dialysis (ref. ‘DP’)</td>
<td>1.294 (0.975, 1.718)</td>
<td>0.0742</td>
</tr>
<tr>
<td>HLA mismatches (+1 mismatch)</td>
<td>1.048 (0.987, 1.114)</td>
<td>0.1267</td>
</tr>
<tr>
<td>Peak panel reactive antibodies (ref. ‘≤15%’)</td>
<td>1.235 (1.049, 1.454)</td>
<td>0.0114</td>
</tr>
<tr>
<td>Last panel reactive antibodies (ref. ‘≤15%’)</td>
<td>1.207 (0.960, 1.519)</td>
<td>0.1077</td>
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<tr>
<td>Prior transplantation (ref. ‘no’)</td>
<td>1.051 (0.865, 1.279)</td>
<td>0.6153</td>
</tr>
<tr>
<td>HbA1c (ref. ‘yes’)</td>
<td>1.059 (0.680, 1.650)</td>
<td>0.3003</td>
</tr>
<tr>
<td>HCV Ab (ref. ‘yes’)</td>
<td>1.172 (0.979, 1.404)</td>
<td>0.0847</td>
</tr>
<tr>
<td>Donor age (ref. ‘&lt;60 years’)</td>
<td>1.004 (0.832, 1.212)</td>
<td>0.9651</td>
</tr>
<tr>
<td>Donor sex (ref. ‘male’)</td>
<td>1.030 (0.900, 1.179)</td>
<td>0.6687</td>
</tr>
<tr>
<td>Source of the organ (ref. ‘living donor’)</td>
<td>1.037 (0.557, 1.933)</td>
<td>0.9085</td>
</tr>
<tr>
<td>Cause of death (ref. ‘TCE’)</td>
<td>1.158 (1.005, 1.335)</td>
<td>0.0425</td>
</tr>
<tr>
<td>Donor type (ref. ‘heart beating’)</td>
<td>1.183 (0.824, 1.699)</td>
<td>0.3614</td>
</tr>
<tr>
<td>Cold ischaemia time (&gt;1 h)</td>
<td>1.001 (0.993, 1.010)</td>
<td>0.7452</td>
</tr>
<tr>
<td>Delayed graft function (ref. ‘no’)</td>
<td>1.430 (1.243, 1.644)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ALG/ATG or OKT3 at the time of transplantation (ref. ‘yes’)</td>
<td>1.393 (1.168, 1.662)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mycophenolate at the time of transplantation (ref. ‘yes’)</td>
<td>1.129 (0.889, 1.434)</td>
<td>0.3191</td>
</tr>
<tr>
<td>CMV infection (ref. ‘no’)</td>
<td>1.349 (1.127, 1.615)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Cyclosporine vs tacrolimus (ref. ‘tacrolimus’)</td>
<td>1.141 (0.810, 1.606)</td>
<td>0.4515</td>
</tr>
<tr>
<td>Year of transplantation(^\text{a})</td>
<td>– &lt;0.0001 – – – – – – – –</td>
<td>– – – – – – – – – – –</td>
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<tr>
<td>1990</td>
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<tr>
<td>1994</td>
<td>1.025 (0.870, 1.208)</td>
<td>0.7683</td>
</tr>
<tr>
<td>1998</td>
<td>0.620 (0.523, 0.734)</td>
<td>&lt;0.0001</td>
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Ref., reference.
\(^\text{a}\)Only 2.5 years of follow-up were taken into account for the univariate analysis. For the multivariate analysis all available follow-up (11.5 years) was employed.

Effect of acute rejection on late graft and patient survival

Patients with acute rejection showed a worse renal function, expressed by higher serum creatinine levels and 24 h proteinuria, in comparison with those without rejection episodes, and the differences were statistically significant during the whole follow-up. Correspondingly, Cox proportional hazards regression analysis showed that acute rejection was followed by a significantly reduced allograft survival (RR 2.083; \( P < 0.0001 \)) (Figure 2 and Table 2). Risk of graft loss

![Fig. 2. Graft survival attending to acute rejection.](https://academic.oup.com/ndt/article-abstract/19/suppl_3/iii38/1826921)
increased with recurrent rejections (RR 3.804; P < 0.0001) compared with those with a single rejection episode (RR 1.822; P < 0.0001) and, in those with biopsy proven acute rejection, with the severity of the histological findings according to the Banff criteria. The relative risk of graft failure increased from 1.832 in patients with Banff I acute rejection to 3.063 in those graded Banff III. This detrimental effect of acute rejection on graft survival was homogeneous in the three periods analysed, and did not decrease in 1998 (P = 0.129). The relative risk of graft failure for patients with acute rejection, compared with those without rejection, was in 1990, 1.977 [95% CI (1.523, 2.567), P < 0.0001]; in 1994, 1.806 [95% CI (1.371, 2.379), P < 0.0001], and in 1998, 3.387 [95% CI (2.037, 5.632), P < 0.0001]. Patient survival, however, was not significantly influenced by acute rejection in the whole series (P = 0.132) or when analysed separately in the three periods (P = 0.737).

Blood pressure values showed significantly higher systolic and diastolic levels during the two first years, with no differences afterwards. Triglycerides levels were higher 1 and 2 years after transplantation in the patients with acute rejection, while cholesterol was higher at 3 months in patients free of acute rejection. No differences were observed after the second year between both groups.

**Discussion**

This analysis was performed to define the changing profile of acute rejection in adult kidney transplant recipients over the 1990 decade in Spain, and its repercussions on late transplant survival. A major finding was the marked reduction of the incidence of acute rejections observed in kidney transplants performed in 1998 compared with the patients transplanted in 1990 and 1994. In addition, a reduction of recurrent rejection episodes was also observed. Accordingly, corticoid-resistant acute rejection was less commonly diagnosed and treated in 1998 than in the previous years. This is even more relevant taking into account that in 1998 patients were transplanted with higher HLA mismatching, higher HLA sensitization levels, and a greater percentage of patients receiving a re-transplant than in the two previous years [9]. These three conditions are well recognized risk factors of increased rejection and lower graft survival [10,11]. Altogether these findings suggest that a more effective prevention of the immune response was obtained in the last period analysed.

Addition of mycophenolate mofetil to immunosuppressive regimens with cyclosporine has uniformly reduced the incidence and severity of acute rejection [5,6]. Although this reduction has not been followed by a better graft survival in the short term, a longer follow-up has shown that mycophenolate mofetil could improve allograft survival [12]. This has been attributed not only to a reduction of the incidence and severity of acute rejection, but also to mechanisms independent of the rejection episodes [13]. This was also observed in this study, as a reduction of the acute rejection incidence in 1998 coincided with the widespread introduction of mycophenolate in the immunosuppressive protocols in Spain that year. In this series, 59.1% of the patients transplanted in 1998 received immunosuppressive protocols containing mycophenolate, mostly associated with cyclosporine [9]. Tacrolimus was also introduced that year, but it was only given to 11.7% of the patients. Although not significant in the logistic regression analysis, in the univariate analysis of the patients transplanted in 1998, treatment with mycophenolate or tacrolimus was associated with a reduced incidence of acute rejection. Anti-IL2 monoclonal antibodies were only given to 4.1% of the patients transplanted in 1998 with no apparent effect on the incidence of acute rejection, but more patients need to be treated before drawing any conclusion.

As has been reported in other series, we also observed an increased risk of acute rejection in younger recipients compared with older ones, and in patients with delayed graft function [14,15]. The logistic regression analysis showed that compared with 1990 the year 1998 was an independent risk
factor of reduced acute rejection, with no differences between 1990 and 1994. This could be due to changes in the immunosuppressive protocols, the inclusion of older recipients, and the practice of more frequent kidney biopsies to diagnose the cause of an allograft dysfunction. CMV infection was associated with an increased risk of acute rejection in the multivariate analysis. Although it is much debated whether CMV infection precedes or follows acute rejection, a recent paper found that CMV seromismatching (donor positive, recipient negative) was followed by an increased incidence of acute rejection, suggesting that CMV infection or disease is in itself a risk factor for rejection [16].

Acute rejection episodes had a deleterious impact on graft survival in the whole series, an effect that was also observed when acute rejection was analysed separately in each of the 3 years studied. These findings are in accordance with most series showing the negative impact of acute rejection on long-term allograft survival, and stress the importance of effectively preventing acute rejection to avoid chronic transplant nephropathy [3,17]. Moreover, the administration of the new immunosuppressants mycophenolate and tacrolimus in 1998, although followed by less acute rejection, did not prevent, in the patients with these episodes, the decline of graft survival, compared with patients free from rejection, at least in the first 2.5 years of follow-up studied.

Patients with acute rejection episodes showed a persistent worse renal function, expressed by an increased serum creatinine level and daily proteinuria. Coincidently, patients with rejection episodes also showed higher blood pressure levels during the first 2 years, probably an expression of the worse renal function. The negative impact of higher blood pressures and proteinuria [18] on renal allograft survival is well established; as a consequence, early measures conducted to control these findings are indicated in order to improve long-term graft survival and reduce cardiovascular risks in the transplant population. In the same way, hyperlipidaemia is a frequent finding in transplant recipients, and both hypercholesterolaemia, as well as, in our case, hypertriglyceridaemia have been associated with a deteriorating renal allograft function [2].

In conclusion, we found a decrease in the incidence and severity of acute rejection in the late 1990s in renal adult transplants, probably related to the introduction of the new immunosuppressive agents, particularly mycophenolate mofetil and tacrolimus. However, the negative impact of rejection episodes on renal function and graft survival remained unchanged. Avoiding acute rejection is still a major target in the prevention of the development of chronic transplant nephropathy and in the reduction of late transplant failure.

Conflict of interest statement. None declared.

References