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Clinical response and temporal patterns of acute cellular rejection: relationship to chronic transplant nephropathy

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Abstract The association between acute cellular rejection (ACR) and the development of chronic rejection has been the subject of much debate. Studies have suggested that the two phenomena may be linked, or, conversely that there may be no association at all. In order to clarify this relationship the outcome of 284 renal allografts were examined. The transplants were all performed at a single institution between April 1989 and December 1991, allowing a minimum follow up of 5 years. ACR was classified into three clinical response groups: (1) fully responsive to therapy (type 1 ACR), (2) partially responsive (type 2) and (3) ACR requiring treatment with ATG or OKT3 (type 3). Acute and chronic rejection were determined by histological (Banff) criteria. Chronic transplant nephropathy (CTN) occurred significantly more frequently in those with late ACR after day 60 than in those who had early rejection (53.5% versus 17.3%, respectively, $P < 0.00001$). Acute rejection that was fully responsive to therapy (type 1) had no association with CTN, but partially responsive rejection and rejection requiring second-line treatment were both significantly associated with CTN ($P < 0.0001$ and $P < 0.001$, respectively). This study suggests that it is the clinical behaviour and response to treatment of ACR that is paramount in determining the onset of chronic rejection, and not the mere presence or absence of the clinical phenomenon.

Key words Kidney transplantation · Acute rejection · Chronic transplant nephropathy · Long-term kidney transplant survival

Introduction

In the last decade, there can be few areas of clinical medicine that have advanced so rapidly as transplantation in all its forms and varieties. The advent of cyclosporin A (CsA) was of course associated with a huge improvement in the results of transplantation of all organs and, more recently, newer drugs such as FK506, mycophenolate mofetil and rapamycin have demonstrated that acute rejection can be reduced even further. Despite all these advances however, there has been depressingly little change in chronic allograft rejection, with late losses of renal allografts remaining between 3 and 5% per annum [1, 2]. A decade ago acute rejection was regarded as the sword of Damocles that hung over transplantation. This is less true in the late 1990's, and attention has now focused on those factors that determine the presence of chronic transplant nephropathy (CTN), and result in the gradual and relentless loss of grafts in later years. Late graft loss encompasses a wide variety of entities. In a large study of late graft loss, Schweizer et al. [3] examined the outcome of 2396 grafts over 20 years and concluded that 'chronic rejection' accounted for 24% of late graft loss. This agrees with a number of other studies [4, 5]. In more recent data from Milan, 'chronic rejection' accounted for 63% of

all late graft losses [6]. In all studies, death of the patient with a functioning graft featured high in the list of causes of late graft loss. Thus there is considerable interest in determining those factors that are associated with 'chronic rejection'. They are multifactorial and include histoincompatability [7], the frequency and intensity of acute rejection attacks [8–10] and inadequate immunosuppression [11]. Other non-immunological factors possibly associated with CTN include prolonged cold ischaemia time [12], donor age [13], lipid abnormalities [14], CMV, hypertension and diabetes [15]. It is the relationship between acute rejection and chronic graft loss that is the subject of this study. Acute cellular rejection (ACR) has often been erroneously regarded a single clinical entity. In this study the phenomenon has been subdivided to account for clinical response to therapy, and then related to the onset of chronic transplant nephropathy. Other factors including time of acute rejection episode, donor and recipient ages, transplant number, infection (bacterial and viral), transplant type (living related donor versus cadaver), ischaemia time and HLA match have been correlated with CTN in this single centre study.

Materials and methods

All patients receiving cadaver renal transplant in the Manchester renal transplant unit between 1 April 1989 and 30 September 1991 were considered for inclusion in this study. All had a minimum follow up of 5 years, or up to the date of their graft failure or death. Demographic data, tissue typing and matching details had been stored on a database in the North West Regional Tissue Typing Laboratory. Data on serum creatinine and cyclosporin levels were gathered from renal flow charts. All data were stored in a Paradox database.

Acute and chronic rejection

In all cases, CTN was determined using the Banff criteria [16], and in every instance there were histopathological data to confirm the presence of CTN. ACR was also determined histologically and classified according to Banff. In a small number of cases (10%), there was no biopsy confirmation of the acute rejection episode. In these circumstances, the presence of ACR was assumed by the following criteria: (a) serum CsA levels in the therapeutic range, (b) rising serum creatinine in the absence of obstruction or infection and (c) serum creatinine responsive to therapy for the rejection episode. If all of the above were present, this was regarded as 'clinically diagnosed' acute rejection, although they were in the vast minority.

Classification of acute rejection

Acute rejection was subdivided into three types depending entirely on the response of the episode to treatment. In those cases where the serum creatinine returned to $\leq 10\%$ of the prerejection value the episode was classified as clinical 'type 1' rejection, where the serum creatinine remained $\geq 10\%$ above the pretreatment value the episode was classified as 'type 2' and those cases where the episode was not responsive to treatment with steroids and required the use of OKT3 or ATG the episode was classified as 'type 3'.

Table 1 Actuarial 1- and 3-year patient and graft survival subdivided according to the presence or absence of chronic transplant nephropathy (CTN)

	1 Year		3 Years	
	Patient	Graft	Patient	Graft
CTN	93%	80%	88%	69%
No CTN	96%	92%	93%	88%

Statistical analysis

Chi-squared analysis was used to find an association between CTN and the following variables; transplant number (primary versus retransplant), donor gender, donor age (< 50 years versus > 50 years), all infections (yes versus no), total ischaemia time (< 24 h versus > 24 h), origin of kidney (cadaver versus living related donor), timing of an acute rejection episode (> or < 60 days) and severity of the episode (no rejection versus types 1, 2 or 3). Correlation coefficients were determined by Spearman's test. Kolmogorov-Smirnov's goodness test for normality was found to be $P < 0.00$ for all variables. Correlations were determined between CTN and HLA mismatches at A, B and DR loci, as well as between acute rejection and HLA-A, -B and -DR loci. Mann-Whitney U Wilcoxon tests were performed to find any association between CTN and the variables mean creatinine (at or over what time?), and cyclosporin dosage. Patient and graft survival curves were produced using Kaplan-Meier survival analysis. The software used was SPSS for Windows.

Results

For the unadjusted group of 284 patients the 1- and 3-year actuarial patient survival was 95.4% and 90.8%, respectively. For the whole population, 1- and 3-year actuarial graft survival was 87.3% and 80.7%, respectively. Subdividing the population into those with or without biopsy-proven CTN gave 1- and 3-year graft survival as shown in Table 1. Out of the 284 patients, there were 104 who had no rejection episodes (36.6%), 137 patients (48.2%) having rejection within the first 60 posttransplant days and 43 (15.1%) having rejection after 60 years. The incidence of late CTN was 17% in those with either no rejection or rejection that occurred in the early posttransplant period. In those having rejection later, the incidence of CTN was three times greater (Fig. 1). The difference achieved a highly significant statistical difference (X^2, $P < 0.0001$). When the data was subdivided using the clinical response to antirejection treatment, patients having fully reversible acute rejection (type 1) were no more likely to have subsequent CTN than those patients having no acute rejection at all. However, those patients having incompletely revers-

Table 2 The relationship between the clinical response of rejection to treatment and the late onset of CTN

Rejection	No CTN	CTN	Total
No acute rejection	86 (82.7%)	18 (17.3%)	104
Type 1 rejection	105 (88.2%)	14 (11.8%)	119
Type 2 rejection	7 (30.4%)	16 (69.6%)*	23
Type 3 rejection	20 (54.1%)	17 (45.9%)**	37

* $P < 0.0001$ versus no acute rejection, $P < 0.0001$ versus type 1
** $P < 0.001$ versus no acute rejection, $P < 0.001$ versus type 1

Table 3 The Banff histological grading of acute rejection and its relationship to CTN

	No CTN	CTN	Total
No acute rejection	71 (80.7%)	17 (19.3%)	88
Mild acute rejection (Banff 4-1)	20 (76.9%)	6 (23.1%)*	26
Moderate acute rejection [Banff 4-2 (A)]	13 (68.4%)	6 (31.6%)**	19
Moderate acute rejection [Banff 4-2 (B)]	15 (60%)	10 (40%)***	25
Severe acute rejection (Banff 4-3)	6 (75%)	2 (25%)****	6

* $P = 0.89$ versus no rejection
** $P = 0.38$ versus no rejection
*** $P = 0.06$ versus no rejection
**** $P = 1.00$ versus no rejection

Table 4 Univariate analysis of other non-immunological factors and CTN (CAD cadaver, LRD living related donor)

Risk factor	No CTN versus CTN *P* value
Transplant number (primary versus retransplant)	1.00
Donor gender (male versus female)	0.122
Donor age (< 50 years versus > 50 years)	0.072
All infections (yes or no)	0.70
Total ischaemia time (< 24 h versus > 24 h)	0.386
Origin of kidney (CAD versus LRD)	0.867

Table 5 Correlation between acute or chronic rejection and HLA-A, -B and -DR mismatches

Rejection	Spearman's coefficient	Significance
Chronic (CTN)		
HLA-A mismatches	0.002	0.972
HLA-B mismatches	− 0.053	0.373
HLA-DR mismatches	0.026	0.657
Acute		
HLA-A mismatches	− 0.006	0.919
HLA-B mismatches	− 0.09	0.128
HLA-DR mismatches	− 0.151	0.01

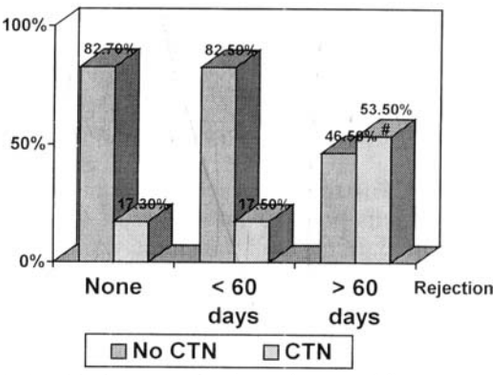

Fig. 1 Relationship between the time of onset of first acute rejection episode and subsequent chronic transplant nephropathy (CTN) (# $P < 0.0001$ versus no rejection or versus < 60 days)

ible rejection (type 2) or those requiring treatment with OKT3 or ATG were significantly more likely to have subsequent CTN ($P < 0.00001$ and $P < 0.001$), respectively; Table 2). When the data were subdivided to categorise grafts by the Banff grading of acute rejection, there was no significant association between Banff grading and subsequent CTN in the majority of the groups, with the exception of moderate (type B) acute rejection, where the late incidence of CTN was 40% (Table 3).

Other risk factors for the development of chronic rejection were also examined including transplant number, donor gender, donor age, infection, ischaemia time and origin of kidney. None of these factors was found to be associated with CTN (Table 4). Correlation of HLA-A, -B and -DR mismatches with either acute or chronic rejection are summarised in Table 5. There was no significant association between any of the HLA mismatches and CTN, although as expected there was a statistically significant association between mismatches at the DR locus and ACR. Finally mean serum cyclosporin levels were compared in those patients with or without CTN (Mann-Whitney U-Wilcoxon Rank Sum W Test). The mean rank of CsA levels in the CTN patients was 125.12, and 146.31 in the non-CTN patients. Although higher in the latter group, this was not a statistically significant difference.

Discussion

With the improving 1-year graft survival following renal transplantation most transplant centres may expect to achieve a 1-year graft survival of the order of 90%. Recent studies with new immunosuppressives such as FK506 and mycophenolate mofetil (MMF) have so far failed to have any significant impact on 1-year graft survival [17–19]. Indeed the 3-year graft survival in the randomised trials with MMF has not been statistically dif-

ferent either [20] (although the original trial design was not powered to show a difference in graft survival). Whilst the newer immunosuppressives have not impacted on graft survival, they all have the capability of reducing 6-month and 1-year graft rejection rates by as much as 50%.

As waiting lists for cadaver renal transplants grow and donor organs become more scarce, an increasing percentage of patients on transplant waiting lists are those whose previous grafts have failed. This group of patients is now one of the most numerous on such lists, and any effort directed at reducing late graft loss from chronic rejection (CTN) may have a beneficial effect on reducing our waiting lists. Much attention has focused on the role of acute rejection in the aetiology of CTN, and yet many studies have analysed 'acute rejection' as if it were a single clinical entity, without reference to the severity of that episode. In a series of 1347 renal transplants, Lindholm et al. [21] confirmed that acute rejection was associated with CTN. In their study, graft half-life was 6.6 years in those with acute rejection, but 12.5 years in those without ($P < 0.0001$). In contrast, the study by Vanrenterghem [22], failed to show any difference in 5-year survival when comparing those patients with or without a single episode of acute rejection, but multiple episodes were significantly associated with poor late graft function. However, their data did not examine the severity of the acute rejection episode. Cecka and Terasaki [11] have indirectly examined the severity of the acute rejection episode by assessing the magnitude of increase of serum creatinine during the rejection episode. If the rise in serum creatinine was < 133 μmol/l, no significant effect on graft survival was noted. However, if the serum creatinine elevated by ≥ 310 μmol/l during the rejection episode, then graft survival was less than 50% at 1 year.

From the data presented in this study, there are a number of unusual findings that require some consideration. There is little doubt that ACR may be associated with a poor long-term prognosis, but it is unusual and unexpected that the Banff grading of the rejection episode did not appear to be a statistically significant correlate of CTN. There is, however, a marked trend (Table 3) with increasing frequency of CTN as the Banff gradings are elevated. It is most probable that the subdivision of data into smaller groups for the Banff analysis has resulted in a type 2 statistical error due to smaller numbers in the multiple groups. Similarly, in the data presented here, there appears to be no association between CTN and HLA mismatch (for all loci). The lack of any expected association may be more of a reflection of the Manchester Philosophy of tissue matching than anything else. In this centre, 80–90% of all grafts are of zero HLA-DR mismatch, and the data are thus heavily skewed. The principal aim of this study was to examine the interrelation between acute and chronic rejection. Our data agree with the findings of Basadonna et al. [9] and others, in that the timing of an acute rejection episode has a significant impact on late function. Acute rejection occurring in the first few weeks is of much less importance than rejection occurring after 60 days. Why this is so is unclear? It may be that the diagnosis of acute rejection is made in a much less expeditious manner after the first few weeks as the patient has been discharged, the deterioration in function may be more insidious and there may be natural reluctance to readmit the patient after their recent discharge. It may also be that the pathological process of rejection is different at this time point; there may be a greater 'vascular' component to the rejection with more dire implications for the graft. An important observation of these data is that acute rejection is clearly not a homogeneous entity. Early, fully resolved acute rejection has little or no impact on late graft function, but poorly, or incompletely treated rejection has a significant detrimental effect. In the data presented here, amalgamation of all grades of rejection into one group would not have revealed any association with CTN; an erroneous assumption. We would recommend that any analysis of acute rejection should take account of the clinical response pattern of that rejection to treatment. It is the latter that is of prime importance and may influence the later well-being of the graft.

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