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Acute rejection relapses posttransplant: definition of risk group and evaluation of potent therapeutic regimens

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Abstract A group of 113 patients were investigated after allogenic cadaver renal transplantation to analyse whether the small number of patients presenting acute rejection relapses could be defined by risk factors and whether there is an efficacious regimen for the safe therapy of recurrent rejection episodes. According to these results we are aware of a group of "highly reactive rejectors" especially within the younger recipients and there are further characteristics which can be identified as being associated with an elevated risk of recurrent acute rejection. By adequate antirejection therapy we can achieve a favourable transplant survival rate of 97 % in the critical first year. An additional benefit may result from ALG consolidation related to suppression of the remaining CD8-positive human natural killer cells.

Key words Acute rejection relapses · Risk factors · Transplant outcome · ALG

Introduction

Despite potent and intense antirejection therapy with repeated triple combinations of cyclosporine A (CsA), cortisone and antithymocyte globulin, (ATG), and consecutive CD3 monoclonal antibodies (OKT3) in acute rejection, there still remain transplant recipients presenting acute rejection (AR) relapses. In a group of patients after allogenic transplantation, we investigated whether a recipient group could be defined by risk factors and if there is an efficacious regimen for the safe therapy of recurrent rejection episodes.

Patients and methods

In a group of 113 patients after allogenic cadaver renal transplantation (Tx), we analysed pre- and posttransplant risk factors for the recurrence of > 2 AR episodes and evaluated short-term efficacy of the antirejection regimen. Simultaneously, we analysed lymphocyte subsets before and weekly after Tx and while on antirejection treatment. We compared patients with ≤ 2 ($n = 95$; 84 %) with patients with 3 or 4 ($n = 18$; 16 %) AR episodes. Rejection was diagnosed uniformly by one referential pathologist using the histological triple technique.

Therapeutic regimen

All patients received CsA, cortisone and ATG for 7 days. In patients at risk of rejection this was followed by CsA, cortisone and azathioprine. In acute clinical rejection, cortisone pulses were given (500 mg, 3 days). AR diagnosed histologically could be classified as interstitial or vascular. Patients with interstitial AR were treated with OKT3 and plasmapheresis (6 ×). If patients responded to OKT3, a second course was given, but if they did not respond (13 patients) the ATG therapy was given. Antilymphocyte globulin (ALG) (5 ml/kg per day) consolidation was given for a 5-day period to patients at risk of recurrent AR episodes.

Cytomegalovirus (CMV) monitoring

Simultaneously, patients were monitored for cytomegalovirus (CMV) disease [weekly CMV IgM titre (ELISA), virus culture from urine and throat swabs, pp-65-CMV-early antigen (+PCR)] in order that virustatic therapy with ganciclovir could be instituted prophylactically.

Cytoimmunological monitoring

The following lymphocyte subsets were analysed by a flourescent-activated cell sorter (FACS): CD2 (T11, SRBC-rec), CD3 (T3, T-cell antigen), CD4 (helper inducer T-cells), CD8 (suppressor T-cells), CD25 (interleucin-2 receptor), CD57 (human natural killer cells), CD56 (natural killer, LGL cells), CD20 (B-cells, B1), HLA-DR+ (monocytes, B-, activated T-cells), CD11b (monocytes, granulocytes, CR3), CD8+/HLA-DR+ (activated T-cells), CD3+/CD25+ (interleucin-2+ T-cells), HLA-DR+ monocytes, HLA-DR/CD11b (monocytes), CD8+/HNK-1+ (CD8-Subset) and CD8+/NKH-1+ (CD8-Subset).

Bioimmunological monitoring

The following were monitored: circulating immunocomplexes C1q, circulating immunocomplexes IgG, IgM and IgA, immunoglobulins IgG, IgM, IgA and IgE, C3 and C4 complement, C-reactive protein quantitative, and β-2-microglobulin.

Clinical variables

The pre- and posttransplant variables that were analysed are detailed in Table 1.

Statistical analysis

Data were analysed by Student's t-test, the Mantel-Haenszel procedure and the chi-squared test.

Table 1 Clinical variables analysed to define risk factors associated with acute rejection episode relapses

Pretransplant	Posttransplant
Recipient age	–
Donor age	–
Histocompatibility	–
Cytotoxic antibodies	Cytotoxic antibodies
Cold ischemia time	Acute renal failure
CMV status donor/recipient	CMV disease
Blood transfusions	Blood transfusions
Duration of dialysis	Duration of dialysis
Renal disease	Urinary tract infection
Blood group	–
Sex	–
Body weight index	–

Table 2 Clinical and immunological risk factors associated with recurrence of acute rejection after renal allografting

1. Younger recipient age	$P < 0.0001$
2. Elder donor age	$P = 0.0264$
3. Duration of preceding dialysis	$P = 0.0265$
4. Transfusions before Tx	$P = 0.0179$ (negative CC)
5. Cytotoxic antibodies	$P = 0.0327$
6. Body weight index before Tx	$P = 0.05$
7. CD8+/HLA-DR+ after Tx	$P = 0.0003$
8. CD8+/HNK+ after Tx	$P = 0.0324$
9. C4-complement after Tx	$P < 0.0001$ (negative CK)
10. β-2-microglobulin after Tx	$P = 0.0094$
Number HLY-B matches	statistical trend (negative CC)
Number of HLA mismatches	statistical trend
Transfusions after Tx	statistical trend

Results

The occurrence of AR episodes was as follows: none in 19 patients (17 %), one in 45 patients (40 %), two in 31 patients (27 %), three in 11 patients (10 %) and four in 7 patients (6 %) (Fig. 1). The mean number of AR episodes was 1.5 ± 1. Statistically significant clinical and immunological risk factors associated with the occurrence of more than two AR episodes are as follows (see also Table 2): younger recicipient age ($P < 0.0001$), elder donor age ($P = 0.0264$), duration of preceding haemodialysis ($P = 0.0265$), transfusions before Tx ($P = 0.0179$, negative CC), cytotoxic antibodies ($P = 0.0327$), body weight index before Tx ($P = 0.05$), CD8+/HLA-DR+ after Tx ($P = 0.00039$), CD8+/HNK+ after Tx ($P = 0.0324$), C4 complement after Tx ($P < 0.0001$, negative CK) and β-2-microglobulin after Tx ($P = 0.0094$) (Fig. 2). The number of HLA-B matches (negative CC), the number of HLA mismatches and the number of transfusions after only showed a statistical trend. Differences of cold ischemia time or histocompatibility could be excluded.

With our therapeutic regimen 1-year graft survival improved up to 97 %. In all except 1 patient the severe recurrent AR was finally overcome and transplant (TP) function stabilised after ALG consolidation with

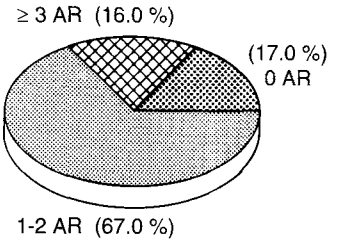

Fig. 1 Prevalence of acute rejection episodes in a group of 113 patients analysed after renal allotransplantation

a resulting serum creatinine level of 1.74 ± 0.77 mg/dl (> 2 AR episodes) vs 1.38 ± 0.48 mg/dl (< 2 AR episodes) (follow-up 2.7 ± 1.2 years). Cytoimmunologically, the risk group was characterised by an enhanced expression of CD8+HLA-DR+ (activated T-cells) and CD8/HNK+ (CD8 positive human natural killer cells) that finally could be significantly reduced only by ALG ($P = 0.0155$). An additional immunological effect of ALG consolidation after > 3 AR episodes was observed in patients characterised by a significant increase of CD8+/HLA-DR+ ($P = 0.0095$), in patients with vascular AR without decrease of CD3 after OKT3 plus in-

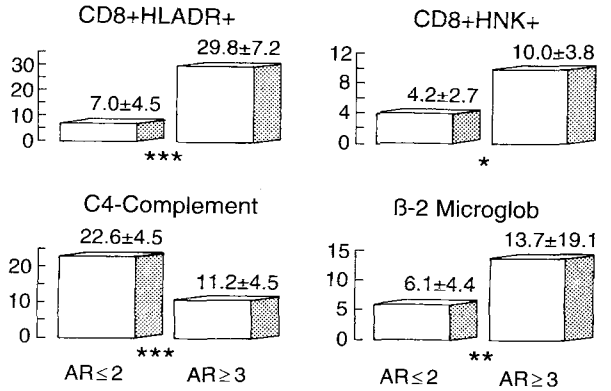

Fig. 2 Immunological differences between the group with ≤ 2 acute rejection (AR) episodes vs the group with ≥ 3 AR episodes. (Mean values post Tx during recurrence of rejection)

crease of HLA-DR+ ($P = 0.0450$) prior to ALG. In 3 patients severe AR was complicated by TP rupture, all could be revised operatively. OKT3-enhanced incidence of CMV disease, defined as the manifestation of one virologic parameter plus organ deterioration, was up to 50 % vs 31 % for the entire study group but early treatment with ganciclovir (+ hyperimmunoglobulins) was safe and without any remaining complications. There were no lymphoproliferative disorders in the highly immunosuppressed group. In patients with > 2 AR episodes the survival rate was 100 %. In a follow-up we evaluated our results with regard to long-term TP function. After 2.7 ± 1.2 years there was only a difference in actual serum creatinine as a parameter of long-term TP function (1.74 ± 0.77 vs 1.38 ± 0.48 mg/dl), but no difference in TP survival comparing the two groups (Table 3).

Discussion

According to these results and especially within the younger recipient group, we have to be aware of "highly reactive rejectors". Further factors can be identified as being associated with a significantly elevated risk of recurrent acute rejections. The adequate antirejection therapy results in a very high transplant survival rate of 97 % in the critical first year. Our immunological data conceivably elucidate a beneficial effect of ALG consolidation upon suppression of the remaining CD8-positive human natural killer cells even after OKT3. In patients with AR relapses after OKT3 we should focus on the cells referred to as non-T- and non-B-cells and they probably respond neither to ATG nor to CD3 antibodies but more likely to ALG as was demonstrated by our data. It is also noteworthy that in patients with vascular rejection treated with OKT3 plus plasmapheresis, there may remain a risk group characterised by an insufficient reduction of CD3 cells after OKT3 in whom finally ALG could succeed in lowering the expression of these cells. Thus this agent turned out to be of additional therapeutic and consolidating value in a small group of patients presenting acute rejection episodes not responding sufficiently to so-called OKT3 rescue as do most of the patients with < 2 AR. These unanticipated immunological results may elucidate observations with undefined ALG effect noticed by others [1]. As expected, OKT3 results in an enhanced risk profile of symptom-

Table 3 Summary of patients' characteristics (*AR* acute rejection episode, *TP* transplant)

		Patients with ≥ 3 AR ($n = 18$)	Patients with ≤ 2 AR ($n = 95$)
Pretransplant status			
Recipient age	***	35 ± 11 years	42 ± 13 years
Donor age	*	42 ± 14 years	34 ± 13 years
HLA mismatches	n.s.	4 ± 1	4 ± 2
Cold ischemia	n.s.	19.3 ± 6.6 h	17.5 ± 5.7 h
Duration of dialysis	*	4.5 ± 4.4 years	3.9 ± 4.4 years
Transfusion	*	2.8 ± 2.7	5 ± 7
Posttransplant status			
Number of acute rejections		2.5 ± 1	1.5 ± 1
TP rupture		2 patients	1 patient
OKT3 incidence		18 patients	25 patients
ALG incidence		13 patients	None
Patients' survival		100 %	100 %
Transplant lost		1	2
After 2.7 ± 1.2 years follow-up			
Actual serum creatinine	*	1.74 ± 0.77	1.38 ± 0.48 mg/dl
Actual proteinuria		0.54 ± 0.62	0.39 ± 0.55 g/day
CMV disease		23 %	34 %
Malignancies		1 patient	3 patients

Statistics: Student's *t*-test; * $P < 0.05$; *** $P < 0.001$; n.s. = non significant

atic CMV infection justifying ganciclovir prophylaxis in the CMV-risk group according to serostatus donor/recipient. As is known from the literature, the number of AR episodes affects long-term TP outcome with regard to the increased risk of so-called "chronic rejection": in renal TP we could demonstrate the same effect in patient groups studied [2–5]. Besides overall improvements in the results of cadaveric renal transplantation, the literature still focuses on high-risk renal TP recipients who experience excessive graft loss [6–8]. Our immunosuppressive antirejection regimen provides a highly effective therapy yielding favourable success rates even in these patients. Long-term results of this regimen including neoplastic potentiation addressed at a follow-up of 2.7 ± 1.2 years do not show differences between the two groups studied.

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