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Aggressive treatment of the first acute rejection episode using first-line anti-lymphocytic preparation reduces further acute rejection episodes after human kidney transplantation

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Abstract The detrimental effect of acute rejection episodes on long-term outcome of renal allografts in cyclosporin-treated patients is well established, although has not been seen by all investigators. To analyse the possibility that aggressive treatment of the first episode may ameliorate this detrimental effect, we performed an open label, randomised prospective trial in cyclosporin-based, immunosuppressed recipients of postmortem renal allografts in order to compare two different treatment protocols during primary acute rejection episodes: (1) group 1 of 25 patients received 3 × 250 mg methylprednisolone (MP) i.v.; (2) group 2 of 25 patients received 7 × anti-thymocyte globulin (ATG)-Fresenius i.v. (4 mg/kg body weight). During a period of 4 years, the following clinical observations were made: (1) The incidence of an acute re-rejection episode was significantly reduced in the ATG-treated study group (16%) compared to the MP-treated study group (72%); (2) The severity of the first acute rejection episode (intensity of renal dysfunction measured in terms of 10-day creatinine area under curve) showed no significant difference between the groups (37 mg × 10-d/dl to 58 mg × 10-d/dl); and (3) The half-lives of allografts in both groups have not shown any significant differences so far. In conclusion, aggressive treatment of the first rejection episode of renal allografts with the use of ATG reduced the incidence of re-rejection episodes which, however, are not reflected so far by improvement of the 4-year survival rate of these allografts. Since it could be observed that re-rejection is an even worse predictor for chronic transplant failure, a better long-term outcome of renal allografts in ATG-treated patients may be expected during a longer observation period. The incidence of a third episode was also reduced in the ATG-treated group (0%) compared to the MP-treated group (12%).

Key words Acute rejection episodes · Chronic transplant failure

Introduction

In the context of postmortem kidney transplantation, the occurrence of acute rejection episodes is one of the most important risk factors for the development of chronic transplant failure. The more episodes of acute rejection a patient suffers, the greater is the likelihood that he or she will subsequently develop chronic transplant failure [1–3]. In addition, there is recent evidence from the Collaborative Transplant Study data (G. Opelz, personal communication) and from our own clinical analyses suggesting that those acute rejection episodes of great severity and intensity are particularly worse predictors for chronic transplant failure [4, 5].

Table 1 *Demographics of the trial patients (group 1 treated with methylprednisolone for the first acute rejection episode, group 2 treated with anti-thymocyte globulin for the first acute rejection episode, HD haemodialysis, PRA panel-reactive antibodies, KTx number of kidney transplants, MM mismatch, CIT cold ischaemia time, WIT warm ischaemia time, ATN acute tubular necrosis, ns not significant)*

Parameter	Group	Mean	Standard deviation	Significance Two-tailed *t*-test
Equality of means				
Recipient age (years)	1	47.4	9.0462	ns
	2	42.8	10.0913	
Donor age (years)	1	41.4	12.3929	ns
	2	43.68	11.6573	
Time on HD (years)	1	7.636	4.6893	ns
	2	7.608	5.4876	
PRA	1	5.84	18.4925	ns
	2	11.48	28.3021	
KTx	1	1.24	0.4359	ns
	2	1.16	0.3742	
HLA-MM-A	1	0.72	0.7371	ns
	2	0.92	0.6403	
HLA-MM-B	1	0.56	0.5831	$P = 0.03$
	2	0.96	0.6758	
HLA-MM-DR	1	0.44	0.5831	ns
	2	0.72	0.6782	
CIT (h)	1	21	7.1063	ns
	2	21.96	5.6235	
WIT (h)	1	32.2	8.775	ns
	2	33.92	7.4157	
Frequencies (percentage)				Pearson chi-squared test
Male donor	1	52		ns
	2	6		
Male recipient	1	6		ns
	2	68		
ATN	1	4		$P = 0.089$
	2	64		

Therefore, prevention of re-rejection episodes and/or reduction of rejection severity by means of aggressive treatment of the first episode, may result in improved long-term outcomes of renal allografts reflected by better half-lives of the transplanted organs.

In the light of this analysis, we conducted a clinical trial in kidney-transplanted patients under cyclosporin-based immunosuppressive protocols, in whom the first acute rejection episode was treated with a course of an anti-lymphocytic preparation instead of administering the traditional steroid-pulse therapy. The study started 4 years ago, however, the data already allow our first preliminary conclusions, which seem to us to be worthwhile reporting.

Materials and methods

Study design

The study was designed as an open label, prospective, randomised trial in recipients of a postmortem kidney allograft under cyclosporin-based immunosuppression.

Randomisation

In the case of a suspected (later: biopsy-proven) first acute rejection episode, patients were randomised into one of two groups: group 1 ($n = 25$) received an anti-rejection treatment consisting of 3×250 mg methylprednisolone (MP) i.v. on 3 consecutive days; group 2 ($n = 25$) received an anti-rejection treatment consisting of $7 \times$ anti-thymocyte globulin (ATG)-Fresenius (4 mg/kg body weight) i.v. over a period of 7 days. This protocol served as an aggressive anti-rejection treatment.

Demographics

The patients' demographics are listed in Table 1. Statistically significant differences in both patients groups were only observed in regard to the HLA-B locus and the incidence of acute tubular necrotic kidneys (i.e. initially non-functioning kidneys).

Immunosuppressive maintenance treatment

Maintenance immunosuppressive treatment of patients in both groups followed the same protocol: cyclosporin (through levels 50–150 ng/ml) and steroids (4 mg–8 mg MP daily) up to 6 months posttransplant and, thereafter, steroid withdrawal attempts.

Table 2 Trial results: severity of acute rejection episodes and occurrence of second and third acute rejection episodes *(ARE)* in the two study groups *(AUC* area under curve)

Parameter	Group	Mean	Standard deviation	Significance *(P)* Two-tailed *t*-test
Equality of means				
Ten-day creatinine AUC (mg · 10 d/dl)	1	37.996	33.3076	0.047
	2	58.42	37.2874	
Incidence (percentage)				Pearson chi-squared test
Second ARE	1	72		0.0001
	2	16		
Third ARE	1	12		
	2	0		

Measurement of severity of acute rejection episodes

As based on experimental work of the Helsinki group [6], the severity of the episodes as reflected by the intensity of renal dysfunction was measured by the 10-day creatinine area under curve (AUC), the first day counted as the day of first anti-rejection treatment. The creatinine AUCs were calculated using the linear trapezoidal method. The borderlines of the area were the creatinine levels measured and the basic creatinine level of 1.5 mg/dl.

Re-rejection episodes and infection

The occurrence of re-rejection episodes was diagnosed clinically, always associated with histological evaluation of biopsy material.

Definitions of viral infections were made clinically, always confirmed by adequate laboratory investigations; any need for hospitalisation to apply antiviral treatment was considered as a viral infection.

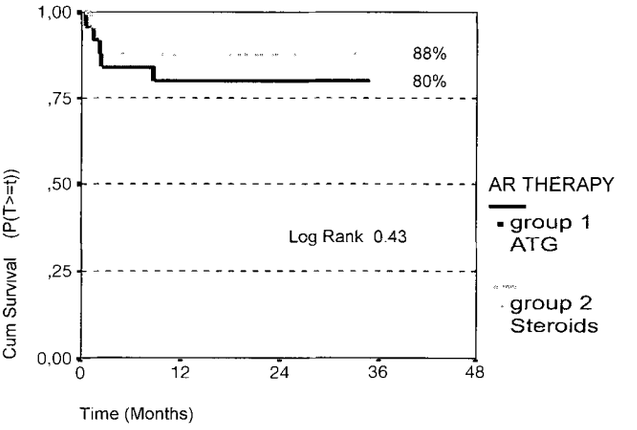

Fig. 1 Four-year graft survival rates of renal allografts in the two study groups *(AR* anti-rejection, *ATG* anti-thymocyte globulin, *Cum Survival* cumulative survival)

Results

Severity of rejection, occurrence of re-rejection episodes and 4-year graft survival rates

As shown in Table 2, ATG treatment of the first acute rejection episode did not result in a reduction of the severity of the acute renal dysfunction (as reflected by 10-day creatinine AUCs) compared to MP treatment. However, the occurrence of a second and third acute rejection episode was significantly reduced by ATG treatment of the first episode compared to MP treatment.

As shown in Figure 1, the projected 4-year allograft survival rates in both patient groups (88%/80%) are not significantly different. Remarkably, in both groups there is no event of chronic transplant failure observed so far.

Infections

The incidence of viral infections [cytomegalovirus (CMV) disease requiring ganciclovir and herpes infection requiring aciclovir therapy] was similar in both patient groups and did not show any significant difference.

Discussion

An attempt aggressively to treat the first acute rejection episode in kidney-transplanted patient under cyclosporin-based immunosuppression using AGT resulted in a significant reduction in incidence of the second and third acute rejection episodes when compared to MP therapy. Surprisingly, however, we did not observe an amelioration of the degree of intensitiy of renal dysfunction associated with the episode. The infection rate (CMV disease or Herpes infection) in these ATG-treated patient was not detectably increased, as might been expected.

Our aim in adopting this kind of aggressive treatment of the first acute rejection episode, namely to improve the long-term outcome of the renal allografts, has not been conclusively reached since the long-term results

in the control group of MP-treated patients are also excellent so far. Thus, a longer clinical observation period is needed to make a valid conclusion on this issue.

Nevertheless, we have already observed a reduction in the incidence of second and third acute rejection episodes, which represent even worse risk factors for the development of chronic transplant failure. We assume, therefore, that the patients administered primary ATG treatment of their first acute rejection episode are at a minor risk for these chronic events.

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