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BRIEF REPORT

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Experience with the Wujciak-Opelz allocation system in a single center: an increase in HLA-DR mismatching and in early occurring acute rejection episodes

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Abstract The present single-center, retrospective study was undertaken to assess the impact of the Wujciak-Opelz allocation system (XCOMB), currently used within Eurotransplant for renal allografts, on the incidence of early occurring rejection episodes (RE). Implementation of the system resulted in an increase of HLA-DR mismatches (MM), while the incidence of HLA-A + B + DR MM remained unchanged. During the 1st post-transplant month, the total number of RE, expressed per patient-months, increased by 64 % (0.326 vs 0.199, $P = 0.007$); when considering only severe and irreversible RE, the increase was 76 % (0.158 vs 0.090, $P = 0.011$). In contrast, from the 2nd to the 12th post-transplant month, the incidence of RE, regardless of severity, was similar before and after implementation of XCOMB. As early occurring RE have detrimental effects on long-term graft outcome, these observations, if confirmed on a larger scale, would justify changes in the allocation algorithm.

Key words Kidney transplantation, HLA-DR mismatches, Wujciak-Opelz allocation system · Wujciak-Opelz allocation system, HLA mismatches, kidney transplantation · HLA mismatches, Wujciak-Opelz allocation system, kidney transplantation · Acute rejection, kidney transplantation, Wujciak-Opelz allocation system

Introduction

The Wujciak-Opelz allocation system (XCOMB) for renal allografts [9] was implemented by Eurotransplant on 11 March 1996. Until that date, the grafts had been distributed within Eurotransplant mainly according to the best achievable HLA match to guarantee the highest possible success rate. During the last years, however, attention has turned to several other equally important factors, such as the time on the waiting list, the distance between donor and recipient centers, and the imbalance between imported and exported kidneys that exists within some local, regional, or national transplant centers. This led Wujciak and Opelz to elaborate an allocation system that would take these different factors into account. Computer simulations indicated that this new selection procedure would not affect graft survival. Preliminary results from Eurotransplant after 9 months of working with XCOMB [2] showed that it succeeded in decreasing the time the recipient had to be on the waiting list, in providing a better exchange rate among centers, and in reducing the average imbalance between imported and exported kidneys. These benefits were obtained without affecting the mean number of HLA mismatches (MM). It must be pointed out, however, that XCOMB does not discriminate between HLA-A, -B, or -DR antigens, whereas HLA matching before XCOMB was based mainly on HLA-B and -DR antigens. Thus, the present system, even though it does not affect the mean number of HLA-A + B + DR MM, may result in a poorer quality of matching for DR antigens. Indeed, at our center, we were struck by a considerable increase in the number of HLA-DR MM since the implementation of XCOMB, and we were worried

Table 1 Demographic characteristics of grafts before and after implementation of the Wujciak-Opelz allocation system (*PRA* panel-reactive antibodies, *DGF* delayed graft function, *ATG* antithymocyte globulin, *OKT3* OKT3 monoclonal antibody)

	Before (n = 214)	After (n = 106)	P value
Gender: Recipient (M/F)	133/81	70/36	NS
Donor (M/F)	129/85	66/40	NS
Age: Recipient (mean ± SEM)	35.4 ± 0.8	40.6 ± 1.2	< 0.001
Donor (mean ± SEM)	35.6 ± 1.0	39.2 ± 1.6	0.052
Graft number: 1/2–3 (% regrafts)	182/32 (15)	88/18 (17)	NS
HLA sensitization: ≤ 5%/> 5% PRA (% > 5% PRA)	201/13 (6)	98/8 (8)	NS
No. of blood transfusions (mean ± SEM)	3.6 ± 0.4	4.6 ± 1.3	NS
Preservation time (h, mean ± SEM)	22.4 ± 0.4	22.3 ± 0.6	NS
2nd warm ischemia time (min, mean ± SEM)	34.9 ± 0.5	35.5 ± 0.9	NS
Patients with DGF (% total)	17.1	20.4	NS
Antilymphocyte therapy (ATG/OKT3)	23/191	17/89	NS
No. of HLA mismatches (%)			
A locus 0:	54 (25)	37 (35)	0.002
1:	96 (45)	56 (53)	
2:	64 (30)	13 (12)	
B locus: 0:	42 (20)	19 (18)	NS
1:	132 (61)	68 (64)	
2:	40 (19)	19 (18)	
DR locus 0:	163 (76)	47 (44)	< 0.001
1:	49 (23)	55 (52)	
2:	2 (1)	4 (4)	
No. of A + B + DR (mean ± SEM):	2.29 ± 0.09	2.37 ± 0.13	NS

about its effect on the incidence of early occurring severe acute rejection episodes (RE), which are known to affect long-term graft outcome [8]. A retrospective study was thus undertaken to address this issue.

Materials and methods

Patients

From 1 January 1993 to 31 August 1997, 320 cadaver kidney transplantations performed on 270 patients were studied after exclusion of those patients (n = 29) who were not subjected to the same immunosuppressive protocol, i.e., triple therapy combining steroids, azathioprine, and cyclosporin (introduced on the 6th postoperative day) together with a 2-week therapy with either antithymocyte globulin (ATG, Merieux, 1–3 mg/kg per day, n = 40) or OKT3 monoclonal antibody (Janssen-Cilag, 5 mg/day, n = 280) [1]. All but five patients had received at least one pretransplant blood transfusion.

Rejection episodes

RE occurring during the 1st post-transplant year were graded according to their severity, which was assessed by comparing serum creatinine at its nadir value before the episode with that after the completion of antirejection therapy [8]. Three grades of rejection were defined: benign (no loss of graft function at all), severe (partial loss of graft function), and irreversible (return to regular dialysis treatment). If a RE occurred during the 1st post-transplant month at a time when the patient was still on dialysis, it was considered benign if the nadir creatinine value after completion of antirejection therapy and discontinuation of dialysis was lower than 1.5 mg/dl; otherwise it was considered severe. RE were treated with intravenous methylprednisolone pulses (3 mg/kg per day for 5 days), followed by tapered prednisolone doses. Corticoresistant RE were treated either with ATG or OKT3. Ninety-five percent of all RE were biopsy-proven.

Statistical methods

The chi-square or Fisher's exact test was used for nominal variables and an analysis of variance with *a posteriori* Bonferroni-Dunn tests for continuous variables. Patient and graft survival rates were calculated by the actuarial method [6], and differences between survival curves were assessed by the Breslow Gehan-Wilcoxon test [4]. Differences were considered to be significant when two-tailed P values were lower than 0.05.

Results

Demographic characteristics of grafts before and after implementation of XCOMB (Table 1)

First, both recipient and donor age were increased. Indeed, most centers, including ours, have accepted older

Table 2 Acute rejection episodes distributed according to their severity (*B* benign, *S* severe, *I* irreversible) and time of occurrence within the 1st post-transplant year, before and after implementation of the Wujciak-Opelz allocation system (XCOMB). Rejections are expressed as number of episodes *(R)* and as number of episodes per patient-months *(R/PM)*. Patient-months are the product of the number of patients at risk during a post-transplant period *(Pat)* by its duration in months

Months post-transplant	Before starting XCOMB			After starting XCOMB			*P* value
	Pat	R	R/PM	Pat	R	R/PM	
1							
B	211	23	0.109	95	16	0.168	0.052
S		15	0.071		12	0.126	0.050
I		4	0.019		3	0.032	NS
S + I		19	0.090		15	0.158	0.011
B + S + I		42	0.199		31	0.326	0.007
2–12							
B	194	42	0.020	58	2	0.005	NS
S		33	0.016		10	0.016	NS
I		11	0.005		2	0.003	NS
S + I		44	0.021		12	0.019	NS
B + S + I		86	0.041		14	0.024	NS

recipients and donors for transplantation in recent years, and this change has been even more pronounced since implementation of XCOMB. It should be noted, however, that these differences were rather small: 5.2 years for recipient age and 3.6 years for donor age. Second, as suspected, the implementation of XCOMB resulted in a shift towards fewer HLA-A and more HLA-DR MM, whereas the number of HLA-B and HLA-A + B + DR MM remained unaffected.

Patient and graft survival before and after implementation of XCOMB

Survival was not significantly affected by XCOMB: 1 year patient survival rates were 99.0% and 100%, and graft survival rates 91.0% and 90.4% before and after implementation of XCOMB, respectively.

Rejection episodes during the 1st post-transplant year

As the number of grafts at risk of rejection was very different before and after implementation of XCOMB, acute RE, distributed according to their severity, were expressed per patient-months to validate comparisons between the two groups (Table 2). During the 1st post-transplant month, the overall incidence of RE was 64% greater after implementation of XCOMB than before (0.326 vs 0.199 episodes per patient-months, $P = 0.007$), and this difference reached 76% (0.158 vs 0.090 episodes per patient-months, $P = 0.011$) when only severe and irreversible RE were taken into account. It should be noted that, during this 1st month, mean daily doses and whole blood trough levels of cyclosporin were significantly greater after implementation of XCOMB than before (6.60 ± 0.18 vs 5.86 ± 0.12 mg/kg per day, $P = 0.005$, and 245 ± 5 vs 221 ± 4 ng/ml, $P = 0.001$, respectively). This was due to the recent replacement of the standard formulation (Sandimmune) with the micro-emulsion formulation (Neoral) of cyclosporin. However, at the end of the 1st month, there was no difference in serum creatinine level between the two groups (2.39 ± 0.24 and 2.09 ± 0.12 mg/dl, respectively).

In contrast, from the 2nd to the 12th post-transplant month, the differences in rejection incidence coincident with XCOMB were much smaller than during the 1st month when considering either the total number of RE (0.024 vs 0.041) or only severe and irreversible RE (0.019 vs 0.021). Theses differences were far from statistically significant.

Discussion

The differences in the incidence of acute RE occurring during the 1st post-transplant month, especially those resulting in impaired functional recovery (severe and irreversible RE), observed after implementation of XCOMB arouse some concern about the consequences of this allocation system on graft outcome. Indeed, these RE have a detrimental influence on long-term graft survival [8]. Although overall HLA matching was not affected by XCOMB, HLA-DR MM have been more than twice as frequent since implementation of this system.

The differential impact of MM at each particular HLA locus on graft survival is still a matter of debate. However, it is commonly accepted that HLA-DR MM are more deleterious than HLA-B MM and that HLA-A MM have the smallest effect on graft outcome [3, 5,

7,10]. Thus, the increase in severe, early occurring acute RE, inducing poorer long-term graft outcome [8], may be causally related to poorer HLA-DR matching coincident with XCOMB. Moreover, this increase is observed despite higher mean daily doses and trough levels of cyclosporin and in the absence of any other factor that could be responsible for it (Table 1).

If these observations were confirmed on a larger scale and for longer follow-up periods than 1 year post-transplant, one would be justified in making some changes to the system currently in use. This could be achieved by introducing into the allocation algorithm a rule eliminating those patients who do not meet the minimum requirements for HLA compatibility. This is, of course, assuming it is possible to reach a consensus about these minimum requirements. If the allocation rules used by Eurotransplant before implementation of XCOMB and based mainly on HLA-B + DR compatibility (no more than 2 MM and, preferably, no DR MM) were reactivated, it might be calculated that, given a waiting list of some 11,000 kidney patients, which is what Eurotransplant has at the present time [2], about 30 candidates would be eligible for each random allograft. There could be a further selection, according to the other criteria of XCOMB. Thus, such a revised allocation system would take into account both requirements: optimal HLA matching, particularly at the DR locus, thereby guaranteeing long-term graft success, and an equitable distribution of the organs, thereby solving problems not related to HLA matching.

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