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Unrelated living donor kidney transplantation

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Abstract. Since 1966, we have performed 41 renal transplants from unrelated living donors (ULD), 39 of which were "emotionally related". All donor-recipient pairs included in the present series were ABO-compatible. Recipients included 37 with primary and 4 with secondary transplants; 2 of the latter were diabetics. We compared these results to those of 41 recipients of cadaver donor kidneys matched for age, sex, immunosuppressive regimen, rank, and year of transplant, focusing our attention on the subgroups of patients under cyclosporin A (CyA) therapy ($n = 24$). We found that ULD transplantation was as successful as cadaver transplantation with good HLA matching: at 3 years, graft survival rates were 81% in ULD versus 86% in the control group under CyA. Moreover, grafts from ULD functioned more rapidly (no post-transplant dialysis and 70% of the patients with serum creatinine below 2 mg/dl within 3 days post-transplant). Graft tolerance was equivalent in both groups (50% of the patients experienced no rejection). We conclude that despite poor HLA matching, ULD transplantation with CyA as the basic immunosuppressive agent offers good results: benefiting from the quality of living donor kidney grafts, it helps to alleviate the persistent shortage of cadaver donors.

Key words: Kidney transplantation, unrelated donor – Donor, unrelated, in kidney transplantation – Unrelated donors, in kidney transplantation

Despite many efforts to increase organ procurement, there is a persistent shortage of cadaver kidneys worldwide, justifying the continuing use of living donors [2, 8–10, 13, 18]. The use of unrelated living donors (ULD) is, however, not widely accepted, and only a few series have been reported [1, 3, 6, 12, 16]. We previously reported our experience with ULD transplantation in 16 selected cases (primary graft in nondiabetic recipients, most of them conventionally treated) [14] and found that the results were as good as those obtained in well HLA-matched cadaveric (CDV) grafts [15].

We now review our entire experience with ULD transplantation in 41 patients and focus our analysis on the subgroup of the last 24 patients treated with cyclosporin A (CyA). In order to know whether ULD transplantation is as successful as cadaver graft transplantation with good HLA compatibility, especially under CyA treatment, we compare the data of ULD transplants with those of CDV grafts matched for age, sex, rank of transplant, basic immunosuppression regimen, and period of transplantation.

Materials and methods

Of the 1800 transplants performed at our center between June 1963 and March 1989, 342 came from a living donor (Fig. 1). The donor was genetically unrelated to the recipient in 41 cases; all donor-recipient pairs were ABO-compatible in this series. The donor-to-recipient relationships were as follows: wife-to-husband ($n = 23$), husband-to-wife ($n = 14$), friend-to-friend ($n = 2$), and finally anonymous donation ($n = 2$).

There were 23 male and 18 female recipients. Their mean age was 41.6 ± 7.6 years. The graft was the first in 37 patients and the second in 4 patients. Two patients were diabetics (both recipients of a second graft).

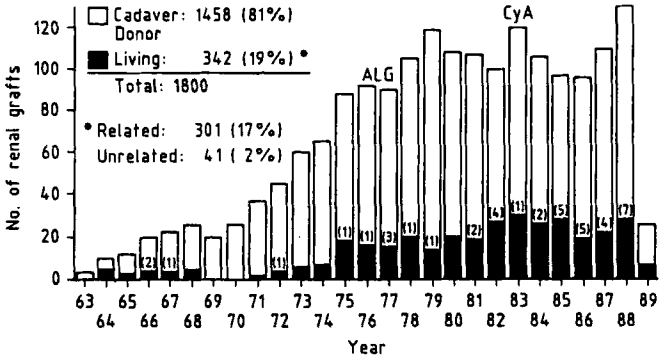

Fig. 1. Kidney transplantation activity at the University of Louvain, Belgium from June 1963 to March 1989. Proportion of unrelated living donors *(ULD)* and living related donors *(LRD)*

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Table 1. Characteristics of transplants in unrelated living donor (ULD) and control cadaver (CDV) groups

	ULD ($n = 41$)	CDV ($n = 41$)	P
Original nephropathy			
Chronic glomerulonephritis	15 (36%)	24 (58%)	0.05
Chronic interstitial nephritis	11 (27%)	5 (12%)	NS
Diabetes	2 (5%)	0	
Other	13 (32%)	12 (30%)	NS
Pretransplant dialysis			
Mean duration (months)[a]	22.2 ± 26.5	40.9 ± 37.3	0.01
Number of nondialysed patients	5	0	0.05
HLA-compatibility			
Number of AB-mismatches[a]	2.8 ± 1 (37)	1.7 ± 1 (37)	0.0001
0 AB-MM	1	5	
1 AB-MM	3	11	
2 AB-MM	8	13	
3 AB-MM	14	7	
4 AB-MM	11	1	
Number of DR-mismatches[a]	1.4 ± 0.7 (31)	0.5 ± 0.6 (30)	0.0001
0 DR-MM	3	15	
1 DR-MM	13	14	
2 DR-MM	15	1	
Donor age (years)[a]	39.2 ± 8.1 (39)	30.4 ± 16.2 (39)	0.003
Total ischemia time	02h35 ± 01h16 (39)	32h16 ± 16h57 (39)	0.0001

[a] Mean ± SD

The group of ULD recipients was compared to a control group of CDV graft recipients selected as follows. Each ULD graft was sex and age (±4 years) -matched with a CDV graft from our patient population; grafts were also matched in terms of basic immunosuppressive regimen (with or without CyA). The control graft that was finally chosen was the one performed on the calendar date closest to that of the ULD graft, irrespective of the type of original nephropathy.

After 1976, all patients in both groups were prepared with at least three pretransplant blood transfusions and were given a prophylactic 2-week course of antilymphocyte globulin (ALG), started 3 days before transplantation in the ULD group and on the day of the operation in the CDV group. From 1963 to 1982 (17 transplants, conventional era), additional conditioning included donor-specific transfusions, a 5-day course of preoperative thoracic duct drainage, and splenectomy in 4, 9, and 13 patients, respectively, in the ULD group and in none of the patients in the CDV group.

After 1983 (24 transplants, cyclosporin era), CyA was given in combination with steroids and ALG, and with or without azathioprine (Aza); maintenance therapy for all patients in both groups in this era included CyA, Aza, and steroids.

The only prerequisite for ULD transplantation was a negative T-cell crossmatch, irrespective of the HLA-matching, whereas CDV grafts were dispatched by the Eurotransplant Foundation according to the best HLA-A, B match until 1979 and HLA-A, B, and DR match thereafter.

Charts were reviewed in July 1989 so that the minimum potential follow-up was 10 months. Death occurring less than 3 months after resumption of dialysis was attributed to transplantation. Actuarial patient and graft survival curves were calculated by the Kaplan-Meier product limit method and compared by log rank tests. Chi-square and Student's t-test were used for other comparisons.

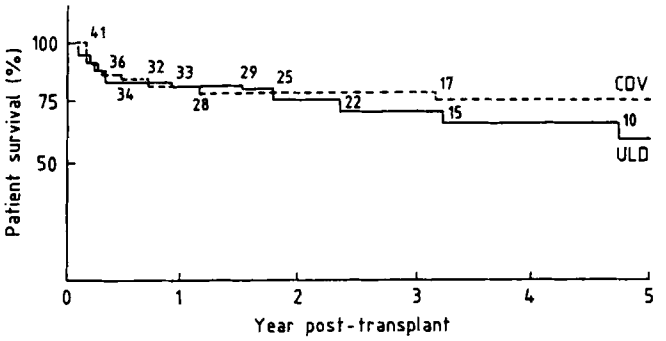

Fig. 2. Actuarial patient survival in the entire *ULD* and control cadaver *(CDV)* groups

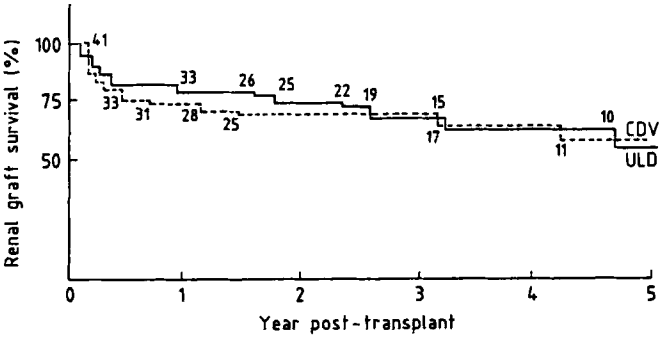

Fig. 3. Actuarial graft survival in the entire *ULD* and control *CDV* groups

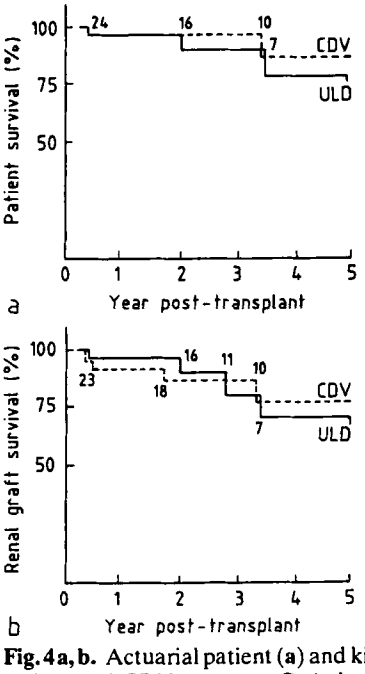

Fig. 4a, b. Actuarial patient (**a**) and kidney graft survival (**b**) in *ULD* and control *CDV* groups on CyA therapy ($n = 24$)

Results

As shown in Table 1, ULD and CDV groups differed with regard to some characteristics. There was a greater proportion of patients with chronic glomerulonephritis and none with diabetes in the control group. As expected, duration of pretransplant dialysis was longer, HLA compatibility was better, and graft ischemia time was longer in the control group. Finally, donors were younger in the control group.

Table 2. Causes of graft loss in CyA-treated ULD and control CDV groups ($n = 24$)

	ULD	CDV
Acute rejection	–	1
Chronic rejection	2	–
Recurrence of disease	–	1
Death with functioning graft		
Acute hepatitis	–	1
Heart failure	–	1
Lymphoma	1	–
Sepsis	2	–
Total	5	4

Table 3. Immediate and long-term graft function in cyclosporin-treated ULD and control CDV groups ($n = 24$)

	ULD	CDV	*P*
Post-transplant			
Number of patients With serum creatinine < 2 mg/dl within 3 days	17/24	7/24	0.001
Needing dialysis	0/24	6/24	0.01
Currently			
Number of patients with current serum creatinine < 2 mg/dl	19/19	18/20	NS
Mean serum creatinine ± SD	1.45 ± 0.32	1.53 ± 0.54	NS

Actuarial patient (Fig. 2) and graft (Fig. 3) survival rates in the entire ULD group did not differ significantly from those in the control group, despite the inclusion in the former of two diabetics who died; at 5 years, the rates reached 61% and 56% in the ULD group versus 75% and 58% in the control group, respectively.

As recipient conditioning was quite different between the groups during the conventional era, it is more appropriate to focus any comparisons on the transplants performed during the cyclosporin era, where the only remaining difference between ULD and control groups was the starting day of ALG. Patient and graft survival rates were, again, similar in both groups, reaching 90% and 81% in the ULD group versus 96% and 86% in the control group at 3 years (Fig. 4, Table 2). Grafts from ULD functioned more rapidly than those from CDV donors, as witnessed by both the number of patients needing post-transplant dialysis (none in the former group versus six in the latter) and the proportion of recipients with serum creatinine below 2 mg/dl within 3 days post-transplant (70% in the former versus 29% in the latter; Table 3). Graft tolerance, assessed by calculating both graft survival without acute rejection (Fig. 5) and mean serum creatinine in currently functioning grafts (Table 3), appeared equivalent in both groups. One graft loss from chronic rejection in the ULD group was due to poor compliance on the part of the patient.

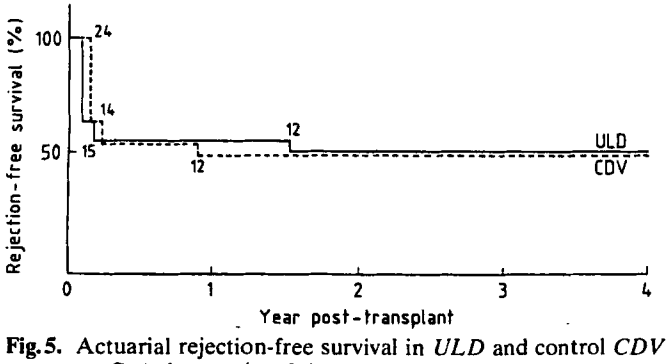

Fig. 5. Actuarial rejection-free survival in *ULD* and control *CDV* groups on CyA therapy ($n = 24$)

Discussion

The use of unrelated living donors in kidney transplantation remains controversial [2, 5, 8–11, 13, 18]. An important underlying question is whether ULD transplantation is as successful as cadaver transplantation when there is good HLA matching. In a previous study restricted to primary transplantations in nondiabetic recipients, we observed that the outcome of 16 such patients was equivalent to that of a control group of HLA well-matched cadaveric graft recipients [15], only two of whom had been receiving CyA. We have now reviewed our entire experience with ULD transplantation up to March 1989, including secondary transplants, diabetic recipients, and patients transplanted since 1984. Once again, results in the ULD group equal those in the control group, despite the inclusion of higher risk patients.

Several differences in the conditioning of the ULD recipients compared to the CDV recipients during the conventional era could have contributed to the good results observed in the former group: the respective roles of thoracic duct drainage, splenectomy, and donor-specific transfusions have been discussed in our previous paper [15]. During the cyclosporin era, the management of recipients was more uniform and more comparable between ULD and control groups, as the only difference was the starting time of ALG therapy. We have thus focused our analysis on this subgroup of patients. Graft tolerance under CyA therapy appears as good in ULD recipients as in well HLA-matched CDV recipients: 50% of the patients did not experience any rejection crisis in either group, and mean serum creatinine at the end of follow-up was equally good. That the good HLA compatibility did not confer any additional benefit upon CDV recipients may be interpreted in two ways. The role of HLA matching in pretransfused, CyA-treated patients may be minimal in the short term, as suggested in several recent series, and could only be appreciated in large groups of patients [19]. Conversely, the earlier conditioning of the recipient with ALG and some other nonimmunological characteristics of living donor transplantation (i.e., quality of graft, elective surgery) may have counterbalanced the poor HLA matching in the ULD group.

Whatever the explanation, our experience with ULD transplantation shows that very good results can be obtained using our current protocol with CyA as the basic immunosuppressive agent. Others have recently reported

similarly impressive results (3-year graft survival of 89%) using donor-specific transfusions. An important drawback of such a protocol, however, is the 20% rate of sensitization, occurring mostly in female recipients [12] and precluding transplantation from that donor. This is why we abandoned that protocol. Recent decision analysis comparing donor-specific transfusions and CyA as two different strategies for living donor transplantation concludes that CyA is equally efficacious and may even be prefered [7, 17].

The general advantages of using living donors in kidney transplantation are numerous. First, and perhaps foremost, it helps to alleviate the persistent shortage of cadaver donors; in the Eurotransplant network, despite many efforts to increase organ procurement, the waiting list for cadaver grafts is steadily increasing [4]. The quality of living donor kidneys can be thoroughly evaluated, thus avoiding some hazards related to cadaveric organ procurement (e.g., suboptimal function, undiagnosed infections, hypertension conveyed by the graft). Living donor kidneys function without delay, thus facilitating post-transplant management of the patient.

The argument against the use of living donors must also be considered. The postoperative and long-term risks for the donor have recently been reviewed [2]. None of the donors in our series had serious complications from the operation. Provided there is careful evaluation of potential donors and the strict criteria for exclusion are respected, long-term prospects for kidney donors is reassuring: despite a slight increase in proteinuria, they do not develop progressive renal failure [2].

The benefit for the donor must also not be ignored. Like others [10], we have observed that donating a kidney has a positive impact on the majority of donors, increasing their self-esteem. The motivation of the donor must be carefully assessed; in our experience, motivation is often at least as strong in the "emotionally" related, but genetically unrelated, donor as in the genetically related donor.

Nevertheless, our current policy remains to restrict ULD transplantation to selected cases that meet certain criteria. In the absence of a compatible living related donor, in order to avoid waiting for a cadaver kidney, and with the full understanding and strong motivation of an "emotionally" related donor, we find ULD transplantation totally justifiable.

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