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NEW DEVELOPMENTS IN SOLID ORGAN TRANSPLANTATION

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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 were "emotionally related"). All ABO-compatible recipients were included in the present series : primary (37) and secondary (4) transplants, diabetics (2). We compared their results to those of 41 recipients of cadaver donor kidneys matched for age, sex, immunosuppressive regimen, rank and year of transplant, focusing the discussion on the subgroups of patients (24) under Cyclosporin A (CsA) therapy.

ULD transplantation is as successful as cadaver transplantation with a good HLA matching : at 3 years, graft survival rates are 81 % in ULD versus 86 % in the control group under CsA. 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 patiens without rejection).

Despite poor HLA matching, ULD tansplantation under CsA as the basic immunosuppressive agent, offers good results : benefitting from the quality of living donor kidney graft, it helps to alleviate the persisting shortage of cadaver donors.

Introduction

Despite many efforts to increase organs procurement, there is a persistant shortage of cadaver kidneys worldwide, justifying the continuing use of living donors (2, 7-9, 12, 17). The use of unrelated living donor (ULD) is however not widely accepted and only a few series have been reported (1, 3, 5, 11, 15). We previously reported our experience with ULD transplantation in 16 selected cases (primary graft in non diabetic recipients, most of them conventionnally treated) (14) and found that the results were as good as those obtained in well HLA-matched cadaveric (CDV) grafts (13).

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

Material and methods

Among 1800 grafts performed at our center between 1963 and March 1989, 342 originated from a living donor (fig. 1). The donor was genetically unrelated with the recipient in 41 cases. Donor to recipient relationship was as follows : wife-to-husband in 23 cases, husband to wife in 14 cases, friend-to-friend in 2 cases, anonymous donor in 2 cases.

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).

The group of ULD recipients was compared to a control group of cadaver graft (CDV) recipients selected as follows. For each ULD graft we selected from our patient population the cadaver grafts performed in patients of identical sex and age (± 4 years) and treated with the same basic immunosuppressive regimen (with or without CsA); we finally choose as control graft the one performed at the closest calendar date of the ULD graft, irrespective of the type of original nephropathy.

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

Since 1983, (24 transplants, cyclosporine era), CsA was given in continuation with steroïds and ALG and with or without azathioprine (Aza); maintenance therapy for all patients of both groups in this era included CsA, Aza and steroïds.

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

Charts were reviewed in July 89 sothat the minimum potential follow-up was 10 months. Death occurring less than 3 months after dialysis resumption was attributed to transplantation. Actuarial patient and graft survival curves were calculated by Kaplan-Meier product limit method and compared by log rank test. Chi-square and Student's t-test were used for other comparisons.

Results

As shown in table I, ULD and CDV groups differed for some characteristics. There was a greater proportion of patients with chronic glomerulonephritis and none with diabetes in the control group. As expected, duration of pre-transplant 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.

Actuarial patient (fig. 2) and graft (fig. 3) survivals in the whole ULD group did not significantly differ from that of the control group despite the inclusion in the former of two diabetics who died; at 5 years, it reached 61 and 56 % in the ULD, versus 75 and 58 % in the control group, respectivally.

As recipient conditioning was quite different between the groups during the conventional era (see methods), it is more appropriate to focus the comparison on the transplants performed during the cyclosporine era, where the only remaining difference between ULD and control group was the starting day of ALG. Patient and graft survivals are again similar in both groups, reaching, at three years, 90 and 81 % in ULD versus 96 and 86 % in the control group (fig 4 and table II). Grafts from ULD functioned more rapidly than those from CDV as witnessed both by the number of patients needing post-transplant dialysis (none in the former group versus 6 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 III). Graft tolerance, as assessed by calculating both graft survival without acute rejection (fig 5) and mean serum creatinine in currently functioning grafts (table III) appeared equivalent in both groups. One graft loss from chronic rejection in the ULD group was due to patient poor compliance.

Discussion

The use of unrelated living donors for kidney transplantation remains controversial (2, 4, 7-10, 12, 17). An important underlying question is to know whether ULD transplantation is as successful as cadaver transplantation with a good HLA matching. In a previous study restricted to primary transplantations in non diabetic 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 (13); only two of them had been receiving CsA. We have now reviewed our whole experience with ULD transplantation up to September 1988 including secondary

transplants, diabetic recipients and patients transplanted since 1984. Once again, results in the ULD group equal that of 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 role of thoracic duct drainage, splenectomy and donor specific transfusions have been discussed in our previous paper (13). During the cyclosporine 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 CsA therapy appears as good in ULD recipients than in well HLA matched CDV recipient : 50 % of the patients did not experience any rejection crisis in both groups and mean serum creatinine at the end of follow-up is similarly good. That the good HLA-compatibility did not confer additional benefit in CDV recipients may be interpreted in two ways. The role of HLA matching in pre-transfused, CsA 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 (18). Conversely, the earlier conditioning of the recipient with ALG and some other non immunologic 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 CsA as the basic immunosuppressive agent. Others have recently reported similarly excellent results (3-year graft survival of 89 %) using donor specific transfusions : an important drawback of such a protocol is however the 20 % rate of sensitization, mostly occurring in female recipients (11) and precluding transplantation from that donor. This is why we abandoned that protocol. Recent decision analysis comparing donor specific transfusions and CsA as two different strategies for living donor transplantation concludes that CsA is equally efficacious and may even be prefered (6, 16).

The general advantages of the use of living donors for kidney transplantation are numerous. It helps to alleviate the persisting shortage of cadaver donors; in the Eurotransplant network, despite many efforts to increase organ procurement, the waiting list for cadaver graft recipient is steadily increasing (Eurotransplant Newsletter 67). The quality of living donor kidney can be thoroughly evaluated, thus avoiding some hazards related to cadaver organ procurement (such as suboptimal function, undiagnosed infections, hypertension conveyed by the graft...). Living donor kidney functions without delay, thus facilitating post-transplant management of the patient.

The argument against the use of living donor must also be considered. The post-operative and long-term risks for the donor have been recently reviewed (2). None of the donors in our series had serious complications from the operation. Provided that careful evaluation of potential donor with strict criteria for

exclusion are respected, long-term survey of kidney donors is reassuring : despite slight increase of proteinuria, they do not develop progressive renal failure (2).

The benefit for the donor must not be ignored. Like others (9), we observe that donating kidney has a positive impact in the most majority of the donors, increasing self-esteem. The motivation of the donor must be carefully assessed; in our experience, motivation is often at least as strong in "emotionnally" related but genetically unrelated donor than in the genetically related donor. Nevertheless, our current policy remains to restrict ULD transplantation to selected cases meeting the following criteria : lack of a compatible living related donor, reasons to avoid waiting time for a cadaver kidney, full understanding and strong motivation of an "emotionally" related donor.

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Table I : Characteristics of transplants in ULD and control (CDV) groups

	ULD (n = 41)	CDV (n = 41)	p.
Original nephropathy : number of patients with			
- CGN	15(36 %)	24(58 %)	0.05
- CIN	11(27 %)	5(12 %)	NS
- Diabetics	2 (5 %)	0	
- Others	13(32 %)	12(30 %)	NS
Pretransplant dialysis :			
- mean duration (months)*	22.2 ± 26.5	40.9 ± 37.3	0.01
- no of non dialysed patients	5	0	0.05
HLA-compatibility :			
- no of AB-mismatches*	2.8 ± 1(37)	1.7 ± 1(37)	0.0001
- no of DR-mismatches*	1.4 ± 0.7(31)	0.5 ± 0.6(30)	0.0001
Donor Age (years)*	39.2 ± 8.1(39)	30.4 ± 16.2(39)	0.003
Total ischemia time	02h35 ± 01h16	32h16 ± 16h57(39)	0.0001

CGN : chronic glomerulonephritis; CIN : chronic interstitial nephritis

* Mean ± SD

Table II : Causes of graft losses in CsA treated ULD and control (CDV) groups (n = 24)

	ULD	CDV
Acute Rejection	-	1
Chronic Rejection	2	-
Recurrence of disease	-	1
Death with functionning graft		
Acute Hepatitis	-	1
Heart Failure	-	1
Lymphoma	1	-
Sepsis	2	-
Total	5	4

Table III : Immediate and long-term graft function in cyclosporine treated ULD and control (CDV) group (n = 24)

Post-transplant

No of patients	ULD	CDV	P
- with Serum Creatinine <2mg/dl within 3 days	17/24	7/24	0.001
- Needing dialysis	0/24	6/24	0.01

Currently

- no of patients with current serum creatinine <2mg/dl	19/19	18/20	NS
- Mean serum creatinine ± SD	1.45 ± 0.32	1.53 ± 0.54	NS

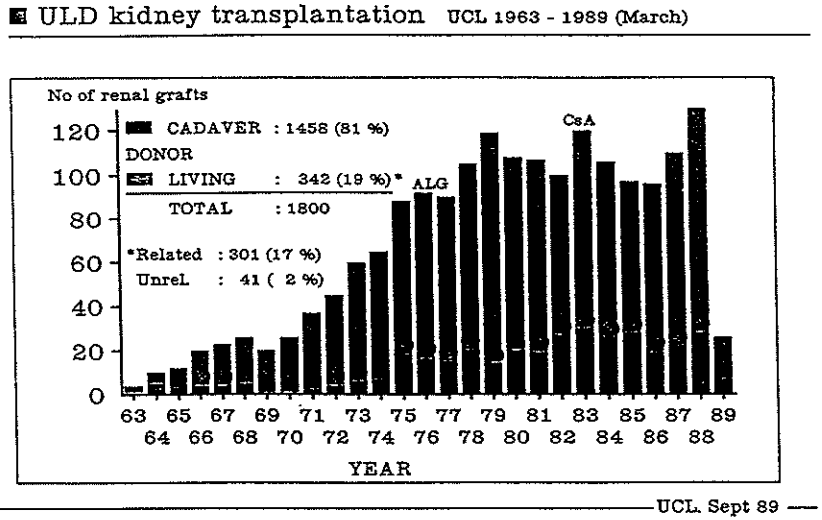

Fig. 1 : Kidney Transplantation Activity at the University of Louvain, Belgium (June 1963 - March 1989). Proportion of ULD and LRD donors.

ACTUARIAL PATIENT SURVIVAL IN ULD and CDV GROUPS

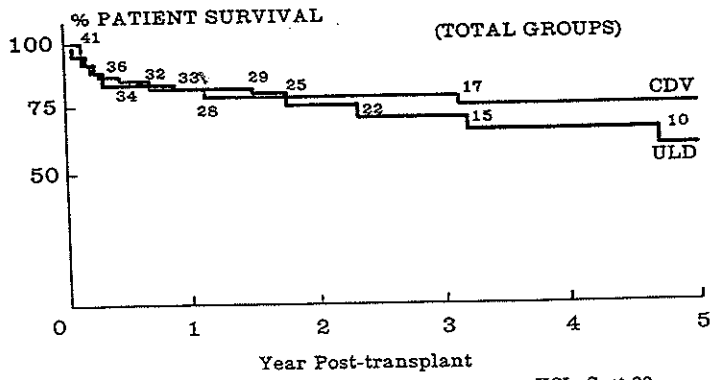

Fig. 2 : Actuarial Patient Survival in the whole ULD and control (CDV) groups.

ACTUARIAL RENAL GRAFT SURVIVAL IN ULD and CDV GROUPS

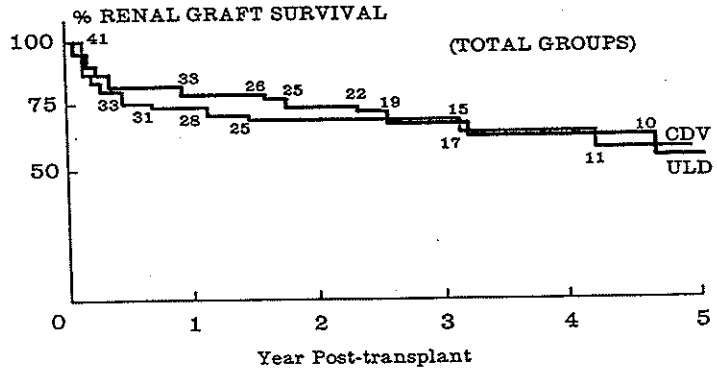

Fig. 3 : Actuarial graft survival in the whole ULD and control (CDV) groups.

ACTUARIAL PATIENT and RENAL GRAFT SURVIVAL IN ULD and CDV GROUPS UNDER CsA THERAPY

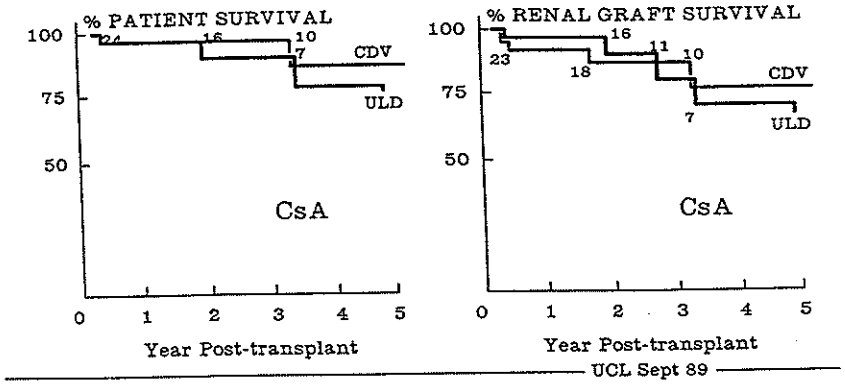

Fig. 4 : Actuarial Patient and Kidney graft Survivals in ULD and control (CDV) groups on CsA therapy (n = 24).

ACTUARIAL REJECTION FREE SURVIVAL IN ULD and CDV GROUPS UNDER CsA THERAPY

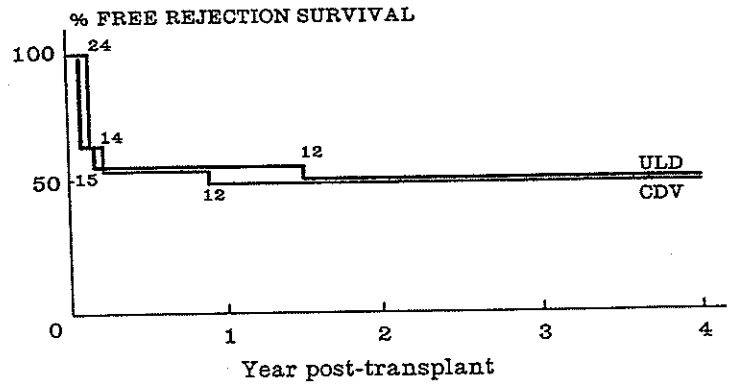

Fig. 5 : Actuarial Rejection Free Survival in ULD and control (CDV) groups on CsA therapy (n = 24).