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Shipping donor kidneys within Eurotransplant: outcomes after renal transplantation in a single-centre cohort study

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Abstract

Background. Shipment of organs during the allocation process aims to improve human leucocyte antigen (HLA) matching but can also have a detrimental effect by prolonging cold ischaemia. The overall effect of organ exchange on post-transplant outcomes in the Eurotransplant (ET) region has not been investigated.

Methods. This is a retrospective single-centre cohort study to investigate the effect of shipment of renal allografts on cold ischaemia times and the incidence of acute rejection (AR) and graft survival in 661 transplantations of deceased donor kidneys.

Results. Forty-six per cent ($N = 301$) of the patients received a locally procured and 54% ($N = 360$) a shipped donor kidney. Locally procured donors tended to be older, more often hypertensive and had less frequently died from trauma. Recipients of shipped kidneys were at higher immunological risk, being younger, more frequently retransplanted and immunized against HLA antigens. Shipped kidneys had a 2.2-h prolongation of cold ischaemia time (18.0 versus 20.2 h; $P < 0.0001$) but significantly less HLA A, B and DR mismatches (2.20 versus 2.84; $P < 0.0001$). Recipients of shipped kidneys had an increased incidence of first-year AR [19 versus 13%; odds ratio 1.62 (1.06–2.49); $P = 0.026$] and death-censored graft loss [hazard ratio 1.6 (1.1–2.4); $P = 0.01$] that was no longer statistically significant after adjustments for risk factors by multivariable modelling.

Conclusions. Shipment of kidneys in the ET region is associated with a modest increase in cold ischaemia time and significantly better HLA matching. This allows for successful transplantation of higher risk patients with no significant penalty with regard to AR rates or death-censored graft survival.

Keywords: acute rejection; cold ischaemia time; death-censored graft survival; kidney transplantation; organ allocation

Introduction

Mismatches between recipient and donor major histocompatibility antigens are well-documented risk factors for

the occurrence of acute rejection (AR) episodes [1–4] and graft loss after renal transplantation [5, 6]. Donor selection based on a minimal number of human leucocyte antigen (HLA) mismatches has therefore been a key priority of organ allocation systems [7, 8]. Multinational organ allocation organizations, such as Eurotransplant (ET), have been created to set up large donor and recipient pools to maximize the chance of finding HLA compatible donors [9].

The allocation of organs procured in foreign countries or distant locations of the same country raises important logistical challenges and is associated with a prolongation of cold ischaemia times as compared to locally used kidneys [10, 11]. Prolonged cold ischaemia time is an important cause of graft injury and delayed graft function (DGF), increases the risk of AR and has been shown to negatively impact graft survival [12–14]. Several large registry studies have clearly demonstrated that transplantation of fully matched kidneys is associated with a highly significant improvement in graft survival as compared to mismatched kidneys [7, 15–17] and is cost effective [18]. However, both in the USA and Europe, only a minority of shipped kidneys are transplanted into fully matched recipients [8, 10, 11, 18]. The overall effect of shipment on the prolongation of cold ischaemia time and post-transplant outcomes has only been investigated in a restricted number of studies [10, 11, 19]. These data suggest that the benefit of HLA matching in a subset of patients could be cancelled out by the increase in cold ischaemia in the overall population. The usefulness of shipping organs between transplant centres has therefore increasingly been put into question [20, 21].

The overall impact of organ exchange on cold ischaemia times and graft outcomes in the ET region has not been assessed up to now. We have conducted a single-centre retrospective cohort study on the effect of shipment of organs in Belgium and between Belgium and other ET member countries to address the following questions: (i) what is the effect of organ exchange in the ET region on cold ischaemia times? (ii) What is the effect of shipping on first-year AR and graft survival? (iii) To what extent can differences in outcomes be attributed to increased cold ischaemia time or are related to differences in donor quality and the immunological risk profile of the recipients?

Materials and methods

Study subjects

From March 1996 to 31 December 2006, 816 renal transplantations were performed at our institution. From this cohort, we excluded 48 paediatric transplants, 49 combined kidney plus other solid organ transplants performed on adults [pancreas ($N = 35$), liver ($N = 10$) and heart ($N = 4$)] and 58 adult living donor transplants. The remaining 661 transplants performed in 636 patients represent the study population of the present retrospective cohort study. The median follow-up was 5.1 years (interquartile range: 2.7–8.1 years).

Organ allocation procedure

All the organs transplanted were allocated by ET International in Leiden, the Netherlands, which is the official organ allocation organization in Belgium. Fifteen organs (2.3%) were preserved by hypothermic machine perfusion and 646 by cold storage. All kidneys were allocated after the implementation of the revised ET kidney allocation system in March 1996 as previously published [8]: (i) between 0 and 400 points for a decreasing number of HLA mismatches based on broad HLA A and B and split HLA DR antigens; (ii) up to 100 points to compensate for an increasing mismatch probability based on the recipients blood group, HLA frequencies and anti-HLA immunization; (iii) 33.3 points per year of waiting time with a maximum of 200 points; (iv) 200 points for a local, 100 points for a national and 0 points for a donor from another ET country; (v) a variable number of points based on the kidney balance between the country of the donor and the recipients.

Five per cent of kidneys were allocated by the ET special programmes or by rescue allocation after failure to find a suitable recipient by standard allocation: acceptable mismatch (AM) programme [22] ($N = 9$; 1.4%), ET Senior Programme [23] ($N = 14$; 2.1%) and rescue allocation ($N = 10$; 1.5%).

Immunosuppressive treatment

Patients received different types of immunosuppression during the 10-year-period. During the first period, until the end of 1998, the majority of patients received an immunosuppressive regimen based on induction with OKT3 anti-CD3 monoclonal antibodies, the microemulsion formulation of cyclosporine and azathioprine. During the year 1999, the three components of this regimen were progressively replaced by induction with anti-IL2 receptor monoclonal antibodies (aIL2R), calcineurin inhibitor therapy with either tacrolimus or the microemulsion formulation of cyclosporine and mycophenolic acid. Transplants were therefore subdivided into two periods of immunosuppression: from 1996 to 1998 ($N = 187$) and from 1999 to 2006 ($N = 474$). All patients received methylprednisolone intravenously at the dose of 250 and 125 mg on the day of transplantation and the first postoperative day, followed by tapered doses as previously described [3].

Exposures and outcomes of interest

The exposure of interest of the cohort study is the origin of the donor and the need for shipping the organs. Donors were stratified as 'local' if procured by the surgical team of the ULB-Erasme transplant centre, 'nationally shipped' if procured by another Belgian transplant centre ($N = 6$) or 'foreign shipped' if procured in another ET member country. The procurement centres were determined according to the relevant entry in the ET donor report form.

The outcomes of interest were the incidence of AR during the first year and death-censored graft survival. AR episodes were defined as any treated AR and were confirmed by biopsies in 95% of the cases. ARs were treated with intravenous methylprednisolone pulses at 3 mg/kg/day for 5 days followed by tapered prednisolone doses as first-line therapy in most patients. Thymoglobulin was used to treat cortico-resistant AR and as first-line therapy for selected patients with severe AR (BANFF IIb and III).

Data management and statistical methods

All recipient data were extracted from a computer database that collects data on all renal transplantations at the Université Libre de Bruxelles since 1965. Donor data were extracted from the database of the ET International Foundation (Leiden, The Netherlands).

Hypothesis testing of differences between nominal variables was done by Fisher's exact test or the chi-square test (when more than two groups were compared). Normally distributed continuous variables were compared by one-way analysis of variance and variables that were not normally distributed by the non-parametric Kruskal–Wallis and Wilcoxon rank-sum tests.

The main measure of the effect of donor origin on AR was expressed as the odds ratio (OR) with 95% confidence interval (95% CI). The association between donor origin and AR after adjustment for multiple risk factors was assessed by multivariate logistic regression modelling. Estimates of overall and death-censored graft loss were calculated by the Kaplan–Meier method with hypothesis testing using the log-rank test. The effect of donor origin on death-censored graft loss was assessed by Cox's proportional hazard modelling. Both the logistic regression model and the multivariate Cox model were built by forward selection and backward elimination of the predictor variables with an alpha error for entry into and elimination from the model of 0.2. The following

predictor variables were tested in these models: immunosuppressive period (≥1999 versus <1999), retransplantation, history of pre-transplant transfusion, duration of pre-transplant dialysis, recipient and donor gender and age, cold and warm ischaemia time, number of HLA A, B and DR mismatches, maximum historic panel reactive antibodies (PRA) (%), PRA at transplantation (%), donor origin (shipped versus locally procured). Both for the logistic regression and the Cox proportional hazard's model, the same final models were obtained using the forward and backward stepwise procedures. There were no missing data for the variables in the final logistic regression and Cox models. The proportional hazards assumption for variables in the final Cox model was tested using Schoenfeld residuals and by graphically displaying (for categorical variables) the estimate of $-\ln[-\ln\{S(t)\}]$ versus ln(t). Interaction between variables was tested by creating product terms that were entered into the logistic and Cox proportional hazard models.

Ethical considerations

The procedures of data collection and measures taken to maintain data confidentiality of the database of renal transplant recipients have been reviewed and approved by the ULB Hopital Erasme Ethics committee. Patients were orally informed at the moment of listing for renal transplantation about the fact that their medical data were to be collected in the centre and ET databases for medical and research purposes.

Results

Patient and donor characteristics

Among 661 renal transplantations, 301 (45.5%) recipients received organs from the local donors, whereas 360 transplants used organs either procured in the other Belgian transplant centres (national shipped, $N = 120$; 18.2%) or in the other ET member countries (foreign shipped, $N = 240$; 36.3%; Table 1).

Recipients of shipped donor kidneys were significantly younger, more frequently retransplanted, had higher historic and current HLA immunization, there were more frequent pre-transplant transfusions and had a longer duration of pre-transplant dialysis (Table 1).

Donor characteristics of locally procured and shipped kidneys were comparable except that local donors tended to be slightly older, more often hypertensive and had less frequently died from traumatic causes than donors of shipped kidneys (Table 1).

Table 1. Patient and graft characteristics according to origin of the donor[a]

	Local	National shipped	Foreign shipped	P[b]	Any shipped[c]	P[d]
Total	$N = 301$	$N = 120$	$N = 240$		$N = 360$	
Recipient characteristics						
Age (years, mean ± SD)	47.9 ± 11.9	44.6 ± 12.6	44.3 ± 11.8	0.0008	44.4 ± 12.1	0.0002
Male	176 (58.5%)	81 (67.5%)	153 (63.8%)	0.18	234 (65%)	0.09
>1st transplant	42 (14%)	31 (25.8%)	69 (28.8%)	<0.0001	100 (27.8%)	<0.0001
Dialysis (months; IQR)	27 (15–42)	31 (13–52)	46 (23–88)	0.0001	39 (20–73)	0.0001
PRA current >5%	28 (9.3%)	15 (12.5%)	43 (17.9%)	0.01	58 (16.1%)	0.01
PRA maximum ≥50%	18 (6.0%)	14 (11.7%)	34 (14.2%)	0.005	48 (13.3%)	0.002
Transfusion ≥5 PRC units	36 (12.0%)	11 (14.2%)	55 (22.9%)	0.002	72 (20.8%)	0.005
Donor characteristics						
Age (years, mean ± SD)	43.8 ± 15.3	41.5 ± 16.4	41.4 ± 15.7	0.18	41.4 ± 15.9	0.06
Male	187 (62.1%)	71 (59.2%)	139 (57.9%)	0.6	210 (58.3%)	0.3
Donor diuresis (mL/h, median with IQR)	250 (140–350)	200 (100–300)	200 (120–310)	0.003	200 (110–300)	0.001
Donor creatinine (mg/dL, mean ± SD)	0.92 ± 0.32	0.93 ± 0.36	0.90 ± 0.35	0.46	0.91 ± 0.35	0.37
Donor cardiac arrest[e]	47/170 (28%)	23/51 (45%)	27/109 (25%)	0.02	50/160 (31%)	0.47
Donor hypotension[e]	131/223 (59%)	59/80 (74%)	72/135 (53%)	0.01	131/215 (61%)	0.64
Donor hypertension[e]	62/263 (31%)	22/101 (22%)	48/178 (37%)	0.12	70/279 (25%)	0.07
Donor diabetes[e]	3/128 (2%)	0/32 (0%)	1/75 (1%)	0.2	1/107 (1%)	0.38
Donor smoking[e]	107/230 (47%)	33/85 (39%)	63/165 (38%)	0.2	96/250 (38%)	0.08
Donor death by cerebrovascular accident	149 (50%)	51 (43%)	104 (43%)	0.2	155 (43%)	0.1
Donor death by trauma	81 (27%)	46 (38.3%)	83 (35%)	0.04	129 (36%)	0.01
Transplantation characteristics						
Cold ischaemia (total cohort) (h, mean ± SD)	18.0 ± 5.8	19.5 ± 6.4	20.5 ± 5.8	<0.0001	20.2 ± 6.0	<0.0001
Cold ischaemia (<1999) (h, mean ± SD)[f]	22.2 ± 5.6	21.7 ± 6.0	23.6 ± 6.0	0.16	22.9 ± 6.1	0.44
Cold ischaemia (≥1999) (h, mean ± SD)[g]	16.7 ± 5.2	18.2 ± 6.4	19.2 ± 5.1	0.0001	18.9 ± 5.5	<0.0001
Warm ischaemia (min, mean ± SD)	32.4 ± 8.5	33.9 ± 8.4	32.5 ± 8.0	0.2	33.0 ± 8.1	0.32
DGF	41 (14%)	19 (16%)	44 (18%)	0.3	63 (17.5%)	0.17
HLA mismatches						
0 HLA MM	12 (4%)	16 (13%)	47 (20%)	<0.0001	63 (18%)	<0.0001
0 HLA DR MM	77 (26%)	45 (38%)	110 (46%)	<0.0001	155 (43%)	<0.0001
HLA ABDR MM	2.84 ± 1.04	2.62 ± 1.45	1.99 ± 1.32	<0.0001	2.20 ± 1.39	<0.0001
Period ≥1999	234 (77.7%)	75 (62.5%)	170 (70.8%)	0.005	245 (68.1%)	0.006
TRL/CSA/other (%)	61%/33%/6%	43%/49%/8%	50%/46%/3%	0.002	48%/47%/5%	0.001
aIL2R/OKT3/ATG/none (%)	45%/18%/17%/21%	32%/27%/24%/18%	42%/24%/18%/16%	0.07	38%/25%/20%/17%	0.05
MMF/AZA/other (%)	75%/19%/6%	64%/31%/5%	68%/25%/7%	0.07	67%/27%/6%	0.03

[a]IQR, interquartile range; PRC, Packed red cells.
[b]P of null hypothesis of no difference between local, national shipped and foreign shipped categories.
[c]The 'shipped' category corresponds to all transplantation with either national shipped or foreign shipped organs.
[d]P of the null hypothesis of no difference between local and shipped categories.
[e]The donor data for these characteristics were incomplete. Difference between denominator and column total indicates the number of patients with missing values.
[f]<1999: $N = 187$.
[g]≥1999: $N = 474$.

In the overall cohort, cold ischaemia time was modestly but significantly prolonged by shipping of organs in Belgium (19.5 ± 6.4 h) or from another ET member country (20.5 ± 5.8 h) as compared to locally procured organs (18.0 ± 5.8 h, P < 0.0001). Overall, shipment of donor kidneys was associated with a 2.2-h increase in cold ischaemia time (Table 1). Cold ischaemia time decreased significantly between 3.5 and 5.5 h in all donor categories when comparing the more recent (≥1999) to the previous (<1999) immunosuppressive period, with the largest reduction occurring in locally procured kidneys (Table 1). This resulted in a reduction in the proportion of kidneys with cold ischaemia times ≥24 h from 40 to 19 and 16%, respectively, in national and foreign shipped kidneys and from 31 to 9% in locally procured kidneys (P < 0.0001 for all donor categories). Interestingly, we observed no significant difference in cold ischaemia time between locally procured (22.2 ± 5.6 h) and shipped kidneys (22.9 ± 6.1 h) in the period before 1999 (P = 0.44).

Shipment was associated with a trend to a higher incidence of DGF that did not reach statistical significance. Shipping of kidney grafts allowed for a significantly higher proportion of patients receiving fully HLA-matched kidneys (20% with foreign shipped and 13% with national shipped kidneys versus 4% with locally allocated organs; P < 0.0001). Shipped organs were also more frequently fully HLA DR matched and had a significantly lower overall frequency of HLA A, B and DR mismatches (Table 1). Finally, recipients of locally transplanted organs were more frequently transplanted in the more recent immunosuppressive period and more frequently received tacrolimus and mycophenolic acid as primary immunosuppressive agents (Table 1).

Effect of donor origin on the incidence of first-year AR episodes

Overall, 109 of 661 patients (16.5%) developed at least one episode of AR during the first year after transplantation. Thirteen per cent of recipients of local kidneys experienced first-year AR versus 19.4% of recipients of shipped kidneys [OR 1.62 (95% CI 1.06–2.49) P = 0.026]. Nationally shipped and foreign shipped transplants did not differ in the overall incidence of first-year AR (Table 2). Multivariate logistic regression modelling showed that the presence of historic HLA immunization, the older immunosuppressive regimen, an increasing number of HLA mismatches, longer pre-transplant dialysis and younger recipient age were independent predictors for the development of AR episodes during the first year of transplantation (Table 3). Cold ischaemia time was a highly significant predictor of AR in the univariate analysis. Adjustment for cold ischaemia alone reduced the OR of AR in shipped kidneys from 1.62 to 1.43 which was close to the OR in the full model (1.42). This is compatible with partial confounding by the longer cold ischaemia times in shipped kidneys but does not fully account for the effect of shipment on AR. There was no difference in the effect of shipment on AR between the two immunosuppressive periods (<1999: OR 1.54 versus ≥1999: OR 1.46, P for homogeneity in OR = 0.9). In spite of the higher incidence of AR, shipped kidneys had similar graft function at 1 year (Modification of Diet in Renal Disease glomerular filtration rate 54.9 ± 18.3 mL/min) as locally procured kidneys (53.4 ± 14.8 mL/min; P = 0.27).

Effect of donor origin on death-censored graft loss

Recipients of shipped kidneys had similar overall graft loss (Figure 1a) but significantly higher death-censored graft loss as compared to patients transplanted with locally procured organs (18.0% at 5 years versus 12.8%, P = 0.01, Figure 1b). The effect of shipment differed markedly between the two immunosuppressive periods (Figure 2). Under cyclosporine and azathioprine-based immunosuppression (<1999), death-censored graft loss was significantly higher for shipped kidneys (20% at 5 years versus 9% for locally procured kidneys, P = 0.01, Figure 2a), whereas no significant effect of shipment on

Table 2. Association of shipping kidneys with the occurrence of first-year AR

	Patients with treated first-year AR (%)	OR (95% CI)	P
Local kidneys (*N* = 301)	39 (13)	1	
Total shipped kidneys (*N* = 360)	70 (19.4)	1.62 (1.06–2.49)	0.026
National shipped kidneys (*N* = 120)	25 (20.8)	1.77 (1.01–3.08)	0.04
Foreign shipped kidneys (*N* = 240)[a]	45 (18.8)	1.55 (0.97–2.48)	0.06

[a]P = 0.65 as compared to national shipped kidneys.

Table 3. Logistic regression model of the effect of shipment on first-year AR

	Univariate OR (95% CI)	P	Multivariate OR (95% CI)	P
Shipping kidney	1.62 (1.06–2.5)	0.026	1.42 (0.87–2.33)	0.16
Historic PRA (per % PRA)	1.02 (1.01–1.025)	<0.0001	1.02 (1.01–1.03)	<0.0001
Transplant ≥1999	0.43 (0.28–0.65)	<0.0001	0.44 (0.27–0.73)	0.001
HLA (per ABDR MM)	1.25 (1.06–1.49)	0.009	1.38 (1.14–1.67)	0.001
Dialysis (per year)	1.11 (1.06–1.16)	<0.0001	1.05 (1.0–1.1)	0.048
Recipient age (>55 years)	0.36 (0.2–0.65)	0.001	0.49 (0.26–0.93)	0.03
Cold ischaemia time (per hour)	1.07 (1.03–1.1)	<0.0001	1.03 (0.99–1.07)	0.11

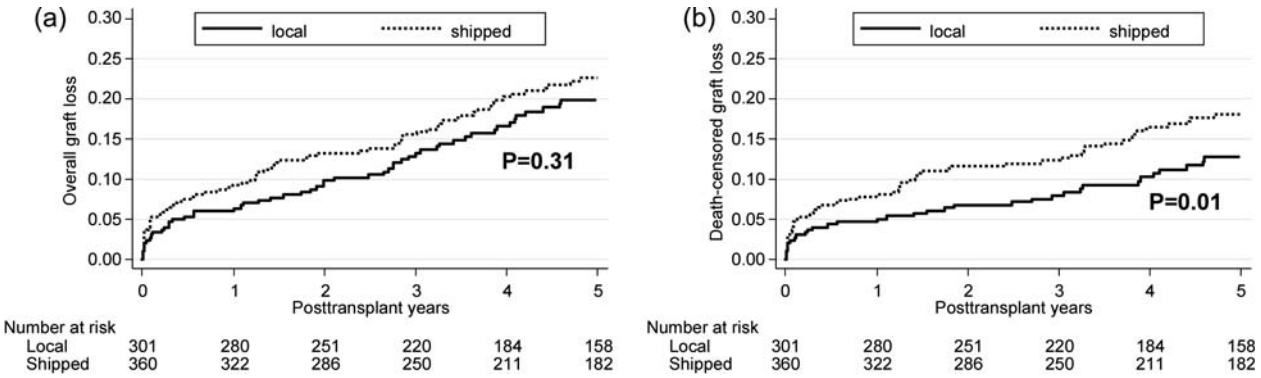

Fig. 1. Kaplan–Meier estimates of graft loss in recipients of locally procured as compared to shipped kidney transplants. Numbers of patients at risk are indicated in the table below the graphs. (**a**) Overall graft loss (P = 0.31) and (**b**) death-censored graft loss (P = 0.01) by log-rank test.

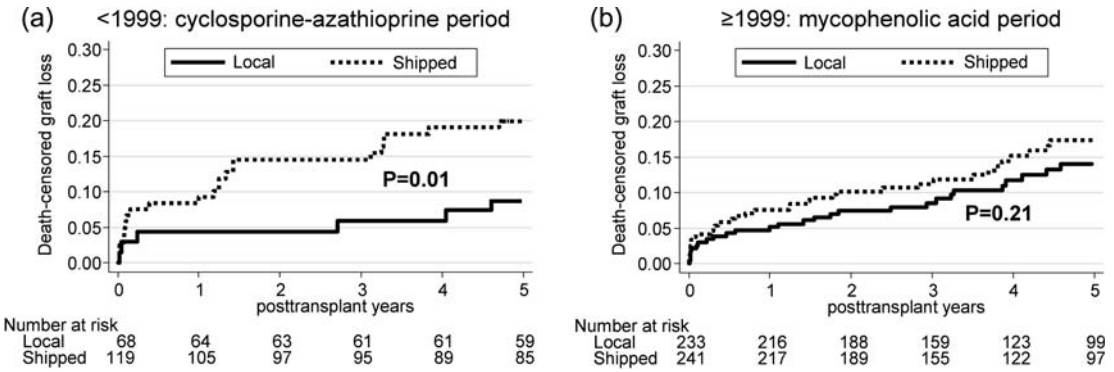

Fig. 2. Kaplan–Meier estimates of death-censored graft loss after transplantation of locally procured and shipped grafts during two successive immunosuppressive periods. (**a**) <1999: cyclosporine and azathioprine-based immunosuppression (P = 0.01) and (**b**) ≥1999: calcineurin inhibitor and mycophenolic acid-based immunosuppression (P = 0.21).

graft loss was observed under the more recent mycophenolic acid-based regimen (17.4% at 5 years versus 14.4% for locally procured kidneys, P = 0.21, Figure 2b).

In a univariate Cox model, shipment was associated with a 62% increase in the hazard of death-censored graft loss [hazard ratio (HR) 1.62, 95% CI 1.11–2.38] but was no longer significant in the multivariate model. Recipient age (HR 0.96 per year, P < 0.0001), historic peak HLA immunization (HR 1.09 per 10% PRA, P = 0.007) and older donor age (HR 1.02 per year, P = 0.009) were the only significant predictors of death-censored graft loss. HLA incompatibilities tended to increase the adjusted hazard of graft loss by 15% per mismatch (P = 0.07).

A large majority of both highly immunized patients (48 of 66 with PRA ≥50%) and patients transplanted with well-matched kidneys (76 of 93 patients with 0 HLA B and DR mismatches) received shipped kidneys. Highly immunized recipients of shipped kidneys had a significantly higher incidence of first-year AR (42.7%, 95% CI 27.2–56.1%) and 5-year death-censored graft loss (29.4%, 95% CI 17.6–46.5%) than the overall cohort (first-year AR 16.5% and 5-year death-censored graft loss 15.6%). On the contrary, recipients of well-matched shipped organs had a lower incidence of AR (9.2%, 95% CI 2.6–15.9%) and 5-year death-censored graft loss (9.9%, 95% CI 4.8–19.9%) than the overall cohort.

Discussion

Shipping organs between the procurement and transplantation centre is susceptible to prolong the need for cold storage before transplantation thereby potentially increasing the risk of DGF, AR and graft loss [12–14, 24]. In our cohort, shipment was associated with a 2.2-h increase in cold ischaemia time. This compares favourably with prolongations of 4–7 h previously reported in other studies [10, 11, 16]. The 18.0-h mean cold ischaemia time of locally procured kidneys in the present study is comparable to previously reported 19.7 h in a large US registry study and 19.2 h in a French multicentre trial [10, 11].

Shipped kidneys did not experience a higher incidence of DGF in spite of the significant longer cold ischaemia times and greater recipient HLA immunization, two potent risk factor of DGF [25]. This might be due to the younger donor age and to improved HLA matching in shipped kidneys, which has recently been shown to reduce the risk of DGF [25, 26].

In the present cohort, transplantation of a shipped kidney was associated with an ∼60% increase in the odds of first year AR and an equivalent increase in the hazard of death-censored graft loss. These results were in accordance with cohort studies from the USA and France showing a significant association between shipment of

organs and graft loss [10, 11]. However, adjustment for cold ischaemia time only slightly reduced the observed association between donor origin and AR. In addition, shipping of organs was only associated with increased death-censored graft loss in patients receiving the older cyclosporine- and azathioprine-based immunosuppressive regimen, although cold ischaemia times were similar in shipped and locally procured organs during this period. This suggests that transport-related prolongation of cold ischaemia plays only a minor role in the increased risk of adverse outcomes observed in recipients of shipped kidneys.

We therefore carefully analysed the donor and recipient characteristics for locally procured and shipped kidneys in order to identify additional risk factors for rejection and graft loss. Overall donor characteristics of locally procured and shipped kidneys were similar, although, in spite of the better outcomes, locally procured donors tended to be older and with more frequent arterial hypertension and death from cerebrovascular accidents.

Recipients of shipped organs had a significantly higher prevalence of immunological risk factors such as younger age, a previous history of transplantation, more frequent transfusion as well as HLA immunization. Our subgroup analysis showed that hyperimmunized patients were transplanted with shipped kidneys in >70% of cases and also were at very high risk of AR and graft loss, thereby acting as a confounding variable in the association between organ shipment and adverse outcome. Furthermore, shipment was associated with a longer period of pre-transplant dialysis which is a potential risk factor for AR and graft loss [3, 27, 28]. The lesser detrimental effect of shipment on graft loss in the more recent era is also compatible with a better prevention of alloimmune organ damage with the modern tacrolimus and mycophenolate-based immunosuppression in this high-risk population.

The differences in recipient characteristics appear as a logical consequence of the ET point system. Indeed, recipients of shipped kidneys do not get 200 points for local procurement which have to be compensated by the other three criteria that are better HLA matching, longer waiting time and higher HLA sensitization [8]. Our data thus confirm that the allocation algorithm, at least to a certain extent, fulfilled its purpose of employing the extended donor pool to select well-matched kidneys for patients at high immunological risk.

Several authors have advocated the local use of kidneys to shorten cold ischaemia times and to abandon kidney allocation based on HLA matching in the current context of efficient immunosuppressive regimens [20, 21]. This approach has been challenged by data from the Collaborative Transplant Study database indicating that the relative risk of graft loss due to incremental numbers of HLA mismatches has not been reduced by the introduction of our current immunosuppressive regimens [6]. This is in agreement with the data of our present cohort and our previous observation that HLA mismatches remain independent risk factors for AR in patients receiving current immunosuppressive regimens [3]. The EuroTransplant Old-to-Old program has also clearly documented that HLA mismatches remain a risk factor for AR even in older recipients who are considered at lower immunological risk [23].

Data from UNOS and the Collaborative Transplant Study indicate that the relationship between cold ischaemia and graft survival is not linear and that cold ischaemia up to 18–20 h has no or only minimal impact on graft outcomes [12, 13, 24]. In the course of our cohort study, the proportion of kidneys shipped from other ET member countries with cold ischaemia time ≥24 h has decreased from 41 to 16%. This suggests that, provided the necessary organizational effort, most shipments and transplantations can be realized in the ET area within an acceptable time frame. On the other hand, many of our locally procured kidneys also had surprisingly long ischaemia times, mostly due to delays in kidney transplantation until surgical teams had completed heart, lung or liver transplants from the same multi-organ donor. Significant improvements occurred during the study period with a reduction in local kidneys transplanted with cold ischaemia times of ≥24 h from 31 to 9%. The present experience demonstrates that transplantation of locally procured kidneys does not necessarily result in shorter cold ischaemia times, unless organizational obstacles to rapid transplantation are successfully addressed.

A limitation of this single-centre study is the relatively small size of our cohort which precludes detailed subgroup analysis to identify donor and recipient combinations with maximal survival benefit from organ exchange. However, we confirmed that transplantation of well-matched shipped kidneys results in very low rejection rates and excellent long-term survival. Furthermore, it is likely that without organ exchange, waiting time and AR due to worse HLA matching would have increased in immunized patients, although these effects cannot be quantified in this retrospective analysis. Longer waiting time is one of the most potent predictors for adverse post-transplant outcomes and increases the risk of death on the waiting list [28]. Data from the US registries show that 40–50% of shipped fully matched kidneys are transplanted into hyperimmunized recipients [29]. In the ET region, the AM programme has been shown to shorten waiting time and to improve post-transplant outcomes in immunized patients [22]. Organ shipment to improve HLA matching and targeting short cold ischaemia times should therefore not be seen as opposing and irreconcilable paradigms but be considered as being both part of a comprehensive effort to improve outcomes after renal transplantation.

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