PRELIMINARY COMMUNICATION

Clinical Results From Transplanting Incompatible Live Kidney Donor/Recipient Pairs Using Kidney Paired Donation

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Context First proposed 2 decades ago, live kidney paired donation (KPD) was considered a promising new approach to addressing the shortage of organs for transplantation. Ethical, administrative, and logistical barriers initially proved formidable and prevented the implementation of KPD programs in the United States.

Objective To determine the feasibility and effectiveness of KPD for the management of patients with incompatible donors.

Design, Setting, and Patients Prospective series of paired donations matched and transplanted from a pool of blood type or crossmatch incompatible donors and recipients with end-stage renal disease (6 conventional and 4 unconventional KPD transplants) at a US tertiary referral center (between June 2001 and November 2004) with expertise in performing transplants in patients with high immunologic risk.

Intervention Kidney paired donation and live donor renal transplantation.

Main Outcome Measures Patient survival, graft survival, serum creatinine levels, rejection episodes.

Results A total of 22 patients received transplants through 10 paired donations including 2 triple exchanges at Johns Hopkins Hospital. At a median follow-up of 13 months (range, 1-42 months), the patient survival rate was 100% and the graft survival rate was 95.5%. Twenty-one of the 22 patients have functioning grafts with a median 6-month serum creatinine level of 1.2 mg/dL (range, 0.8-1.8 mg/dL) (106.1 μmol/L [range, 70.7-159.1 μmol/L]). There were no instances of antibody-mediated rejection despite the inclusion of 5 patients who were highly sensitized to HLA antigens due to previous exposure to foreign tissue. Four patients developed acute cellular rejection (18%).

Conclusions This series of patients who received transplants from a single-center KPD pool provides evidence that recipients with incompatible live donors, even those with rare blood type combinations or high degrees of HLA antigen sensitization, can receive transplants through KPD with graft survival rates that appear to be equivalent to directed, compatible live donor transplants. If these results can be generalized, broader availability of KPD to the estimated 6000 patients with incompatible donors could result in a large expansion of the donor pool.

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THE NUMBER OF PATIENTS WAITing for a kidney transplant continues to grow at an alarming pace[1] and any significant gains in closing the gap between organ supply and demand are likely to come from the increased use of live donors. The 2 most significant barriers to greater use of live donors are blood type incom-

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patibility and HLA antigen sensitization. Based on blood group frequencies in the United States, there is a 36% probability that any 2 individuals will be blood type incompatible, eliminating up to one third of the potential live donor pool.[2,3] In about 30% of the patients on the deceased donor waiting list, HLA antigen sensitization is present due to exposure to foreign tissue in the form of previous transplants, pregnancies, or blood transfusions. Approximately 7000 of these patients have a wide breadth of response to common HLA antigens as measured by a panel reactive antibody (PRA) assay and are described as being highly sensitized (PRA >80%).[1] Patients who are highly sensitized are likely to have a positive crossmatch with any given donor, which would indicate that they harbor cytotoxic antibodies against the donor that can result in an immediate, irreversible hyperacute or acute antibody-mediated rejection (AMR).[4-6]

Successful protocols for enabling incompatible transplants by removing or neutralizing blood group or HLA-specific antibodies with plasmapheresis and intravenous immunoglobulin (desensitization) are being performed at several specialized centers but these procedures are expensive, labor intensive, and have a variable response rate.[7-12] An alternative strategy is kidney paired donation (KPD) transplantation. In KPD transplants, incompatible donor/recipient pairs exchange kidneys so that each recipient receives a compatible organ.

In this study, we present the results of our single-institution experience with 22 patients involved in 10 live KPD transplants. The KPD transplant represents a cost savings compared with desensitization, which in its own right is significantly less costly than if an individual continues to undergo dialysis.[13] While logistically challenging, a broader implementation of KPD on a regional or national scale could provide compatible organs for a substantial number of the estimated 6000 patients on the waiting list who currently have incompatible donors.[13-16]

METHODS

Study Group

The KPD protocol was approved by the ethics committee and legal office at Johns Hopkins University, Baltimore, Md. All operations for each KPD transplant were performed simultaneously to reduce the possibility that 1 operation would need to be aborted while the others were completed. All participants agreed to the uncertainties inherent in a kidney donor exchange and to remain anonymous to each other until after the operation. Johns Hopkins Hospital is a referral center for patients with blood type and HLA antigen incompatibilities. All patients were given the option of entering the KPD pool. However, some of the patients with barriers that were more amenable to desensitization received transplants successfully under a regimen of plasmapheresis and intravenous immunoglobulin. Thus, patients who were more difficult to match because of their blood types or broad HLA antigen reactivity were overrepresented in our KPD pool, reducing the overall number of possible matches. Race/ethnicity of the patients was recorded by the attending physician or nurse.

Immunosuppression

Twenty recipients received 0.1 mg/kg of tacrolimus daily (Prograf, Fujisawa Healthcare Inc, Deerfield, Ill), 2 g of mycophenolate mofetil administered in twice daily divided doses (Cellcept, Hoffmann-La Roche Inc, Nutley, NJ), and 500 mg of methylprednisolone intraoperatively and then 125 mg every 6 hours for 6 doses, followed by 20 mg of prednisone daily beginning on the day of transplantation. In addition, 8 patients who were considered to be at higher risk for rejection (received previous transplants and/or patients with high PRAs) also received induction therapy with 2 mg/kg of daclizumab prior to reperfusion and then 1 mg/kg every other week for 5 total doses (Zenapax, Hoffman-La Roche Inc). The target serum levels for tacrolimus were 8 to 10 ng/dL. The prednisone was rapidly tapered so that by 6 months most patients were taking 5 mg/d. Unconventional KPD patients 2 and 9 were given sirolimus daily (Rapamune, Wyeth Pharmaceuticals, Madison, NJ) due to complications associated with tacrolimus during previous transplants.

Plasmapheresis/Cytomegalovirus Immunoglobulin Preconditioning Protocol

One patient (unconventional KPD patient 8) received plasmapheresis using a COBE Spectra (Gambro BCT, Lakewood, Colo) as previously described.[9] This was a fourth transplant for this patient and 2 of his previous grafts were lost in the first week after transplantation due to severe AMR. A splenectomy was performed 11 days prior to transplantation and a single dose of anti-CD20 monoclonal antibody (375 mg/m^2 of rituximab [Rituxan], Genentech Inc, San Francisco, Calif) was administered 1 day prior to transplantation.

Diagnosis and Treatment of Rejection

Recipients underwent percutaneous renal transplant biopsy for clinical suspicion of acute rejection based on a decline in renal function. Standard Banff criteria[17,18] for acute cellular and acute AMR were used for diagnosis. Patients with acute cellular rejection were treated with 100 mg/d of dexamethasone for 3 days and then a steroid taper or 1.5 mg/kg per day of antithymocyte globulin for 7 days (Genzyme, Cambridge, Mass). There were no cases of AMR.

Antibody Testing

Isoagglutinin titers were determined by doubling dilutions of serum using standard serological techniques.[10] Crossmatch techniques, including anti–human globulin-enhanced lymphocytotoxicity crossmatch with T cells, one wash for lymphocytotoxicity with B cells, and flow cytometry with T and B cells were performed as previously described.[19] When present, anti-HLA antigen class I and class II donor-

specific antibody were identified by enzyme-linked immunosorbent assay using soluble HLA antigens as targets (GTI Quik-ID and GTI Quik-ID Class II; GTI Diagnostics, Waukesha, Wis). All titers for donor-specific antibody represent IgG antibodies.

Statistical Analysis

Probability calculations of highly sensitized patients receiving a kidney from the deceased donor pool were performed using a previously published algorithm.[20] The probability of finding an acceptable donor was calculated as the frequency of donors with an acceptable blood type (column 2, TABLE 1), multiplied by the frequency of donors with an acceptable maternal haplotype, multiplied by the frequency of donors with an acceptable paternal haplotype. To calculate the frequency of an acceptable maternal or paternal haplotype (column 5, Table 1), the summed allele frequencies of each unacceptable antigen were subtracted from 1 (column 3, Table 1). However, during this process, frequencies of haplotypes bearing 2 or more unacceptable antigens (column 4, Table 1) would be subtracted twice because an individual may carry unacceptable antigens encoded by more than 1 locus. Therefore, these frequencies were added back to the equation (column 5, Table 1).

RESULTS

Between June 2001 and November 2004, 6 conventional and 4 unconventional KPD transplants were performed (FIGURE 1). The term *conventional* is applied to KPD transplants in which a blood type A and B donor/recipient is matched to a pair with the opposite incompatibility. In an *unconventional* KPD, recipients with blood type O can participate and derive mutual benefit, overcoming incompatibilities of blood type and positive crossmatch or positive crossmatch alone.

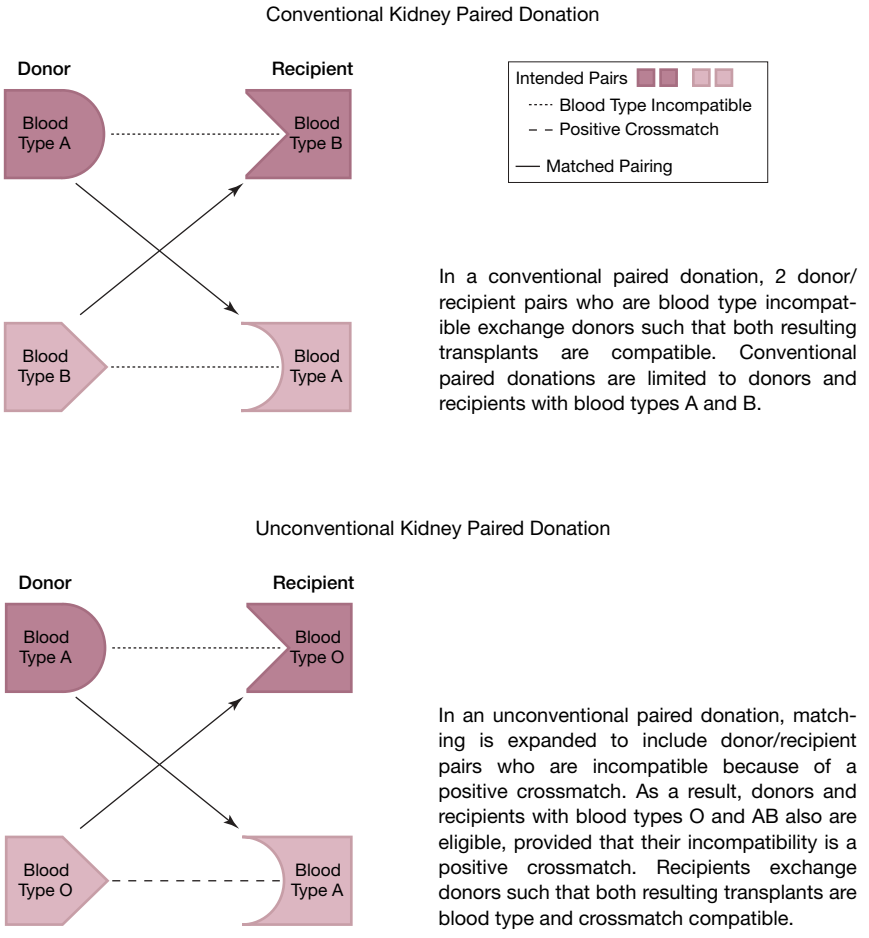
Eight of the KPD transplants, including all 6 conventional and 2 unconventional, involved 2 donor/recipient pairs, while 2 unconventional KPD trans-

Table 1. Calculated Probability of 3 Highly Sensitized Patients Receiving a Kidney From the Deceased Donor Pool

	Frequency				
Patient No.*	Acceptable Blood Types	Unacceptable Alleles	Incompatible Haplotypes	Acceptable Maternal or Paternal Haplotype	Final Probability†
U8	O = 0.4476	DR5 = 0.1111	DQ3 haplotypes bearing DR5, DR10, or DR53 = 0.085	(1 – 0.1111 – 0.0082 – 0.3084 – 0.401 + 0.085) = 0.2563	0.4476 × 0.2563 × 0.2563 = 0.0294
		DR10 = 0.0082			
		DR53 = 0.3084			
		DQ3 = 0.401			
U9	O = 0.4476	A2 = 0.2895	Bw4 haplotypes bearing A2, A28, A9, A25, or A32 = 0.1752	(1 – 0.2895 – 0.0423 – 0.1038 – 0.01956 – 0.03651 –0.4105 + 0.1752) = 0.2730	0.4476 × 0.2730 × 0.2730 = 0.0334
		A28 = 0.0423			
		A9 = 0.1038			
		A25 = 0.01956			
		A32 = 0.03651			
		Bw4 = 0.4105			
U10	A or O = 0.8538	A1 = 0.1591		(1 – 0.1591 – 0.2895 – 0.1038 – 0.00039 – 0.1532 –0.06434 – 0.00417 – 0.04177 – 0.1511 – 0.12852 – 0.0893 – 0.0971 + 0.3791) = 0.0969	0.8538 × 0.0969 × 0.0969 = 0.0080
		A2 = 0.2895	All 96 haplotypes bearing combinations of unacceptable alleles = 0.3791		
		A9 = 0.1038			
		A36 = 0.00039			
		B12 = 0.1532			
		B62 = 0.06434			
		B63 = 0.00417			
		B27 = 0.04177			
		DR2 = 0.1511			
		DR7 = 0.12852			
		DR11 = 0.0893			
		DR13 = 0.0971			

*The "U" indicates unconventional paired donation.
†Calculated as frequency of acceptable blood type (column 2) multiplied by frequency of acceptable maternal haplotype (column 5) multiplied by frequency of acceptable paternal haplotype (column 5).

Figure 1. Depictions of Kidney Paired Donations



plants included 3 donor/recipient pairs each. The KPD transplants were performed to avoid blood group incompatibility (14 patients), eliminate a positive crossmatch (4 patients), improve HLA antigen matching (1 patient who participated in KPD primarily for altruistic reasons), avoid HLA antigens shared with a previous transplant recipient (2 patients), or reduce the amount of donor-specific anti-HLA antigen antibody (estimated by the strength of crossmatch reactivity) to a level that could be easily removed by plasmapheresis (1 patient). In the cases of 4 patients with a positive crossmatch, extremely high titers of donor-specific antibody (dilution >1:1024) rendered desensitization using plasmapheresis unfeasible based on our experience (R.A.M. et al, unpublished data, 2005). Of the 4 patients, 3 were highly sensitized (PRA >80%).

Twenty-one of 22 recipients ultimately received a blood type compatible, negative-flow cytometric crossmatch organ transplant. One patient (unconventional KPD patient 8, PRA = 100%), whose cytotoxic crossmatch with the intended donor had a titer of greater than 1024, had a much lower level of anti-HLA antigen antibody (titer = 4) with his exchange donor but required some pretransplant desensitization treatments. Patient characteristics for all KPD exchanges appear in TABLE 2. The median number of HLA antigen mismatches was the same between the intended donor and the paired donor. However, 5 of the 22 patients had PRAs higher than 80% and were matched on the basis of avoiding unacceptable antigens.

Outcomes and renal function are summarized in TABLE 3. One graft (conventional KPD patient 1) was lost on the night of surgery due to renal vein thrombosis after the kidney had sustained an injury to the hilar portion of the vein during the laparoscopic donor nephrectomy. Four patients developed acute cellular rejection (18%) and all have responded to a steroid pulse or antithymocyte globulin treatment. At a median follow-up of 13 months (range, 1-42 months), the patient survival rate was 100%. Twenty-one of the 22 patients currently have functioning grafts (95.5%) with a median 6-month serum creatinine level of 1.2 mg/dL (range, 0.8-1.8 mg/dL) (106.1 µmol/L [range, 70.7-159.1 µmol/L]). Conventional KPD patient 9 (PRA = 73%) was the only recipient of a conventional KPD transplant that had a PRA of higher than 10%. However, the median peak PRA of the unconventional KPD transplant cohort was 54.5% (range, 0%-100%) and 5 of the 10 patients had a PRA of higher than 80%. Despite constituting a higher immunologic risk group, recipients of an unconventional KPD transplant continue to display excellent graft function with a median 6-month serum creatinine level of 1.4 mg/dL (range, 0.8-1.8 mg/dL) (123.8 µmol/L [range, 70.7-159.1 µmol/L]). There were no episodes of hyperacute or acute AMR.

The complexity and potential benefits of an unconventional KPD transplant are demonstrated by the triple exchange illustrated in FIGURE 2. All 3 patients in the exchange had high levels of donor-specific antibody (titer >1024) on a cytotoxic crossmatch with their intended donor. Furthermore, based on blood type and HLA antigen antibody reactivity, we calculated the probability of finding a suitable donor in the deceased donor pool was 0.029 for unconventional KPD patient 8, 0.033 for unconventional KPD patient 9, and 0.008 for unconventional KPD patient 10 (Table 1).

Table 2. Patient Characteristics*

Patient No./ Sex/Age, y	Race/ Ethnicity	Etiology	No. of Failed Renal Transplants Prior to Current Match	Incompatibility	Benefits of Match	No. of HLA Antigen Mismatches		Panel Reactive Antibody, %†
						Matched Donor	Intended Donor	
Conventional Paired Donation								
1/M/45	White	Hypertensive nephrosclerosis	0	ABO-I	ABO-C	5	6	0
2/M/54	White	Alport syndrome	0	ABO-I	ABO-C	5	3	2
3/F/44	Black	Diabetes mellitus	0	ABO-I	ABO-C	5	3	0
4/M/66	White	Unknown	0	ABO-I	ABO-C	5	4	0
5/M/62	White	Diabetes mellitus	0	ABO-I	ABO-C	3	5	0
6/M/66	White	Polycystic kidney disease	0	ABO-I	ABO-C	4	2	0
7/F/53	White	Hypertensive nephrosclerosis	1	ABO-I	ABO-C	4	4	0
8/F/60	Hispanic	Hypertensive nephrosclerosis and urinary reflux	0	ABO-I	ABO-C	4	6	0
9/M/35	White	Hypertensive nephrosclerosis	1	ABO-I	ABO-C	3	5	73
10/F/39	White	Diabetes mellitus	1	ABO-I	ABO-C	5	3	0
11/F/55	White	Unknown	0	ABO-I	ABO-C	5	6	6
12/M/61	White	Hypertensive nephrosclerosis	0	ABO-I	ABO-C	6	6	2
Unconventional Paired Donation								
1/M/31	White	Polycystic kidney disease	0	ABO-I	ABO-C	5	1	33
2/F/37	White	Chronic glomerulonephritis	1	Historic positive crossmatch, repeat mismatch‡	No repeat mismatch§	1	5	99
3/M/13	White	Congenital dysplasia	1	Repeat mismatch‡	No repeat mismatch§	5	3	0
4/F/38	White	Congenital disease	0	Positive crossmatch titer >1024‖	Negative crossmatch with matched donor and 1 antigen mismatch¶	1	3	50
5/F/29	Black	Focal segmental glomerulosclerosis	0	ABO-I	ABO-C	4	4	42
6/F/63	White	Bilateral renal cell carcinoma	0	5 Antigen mismatch	3 Antigen mismatch	3	5	0
7/M/44	White	Unknown	0	Positive crossmatch titer >1024‖	Negative crossmatch with matched donor	4	3	82
8/M/42	White	Diabetes mellitus, hypertensive nephrosclerosis	3	Positive crossmatch titer >1024‖	Low–titer-positive crossmatch#	5	4	100
9/F/31	White	Diabetes mellitus	0	Positive crossmatch titer >1024	Negative crossmatch	3	2	98
10/M/34	White	IgA nephropathy	1	Positive crossmatch titer >1024	Negative crossmatch	2	5	82

Abbreviations: ABO-C, blood type compatible; ABO-I, blood type incompatible.
*For all patients, the median (range) age is 44 years (13-66 years); the median (range) number of HLA antigen mismatches for both matched donor and intended donor columns is 4 (1-6); and the median (range) panel reactive antibody is 2% (0%-100%).
†Indicates the patient's degree of sensitization.
‡Indicates prior antibody response to an antigen seen in the current donor.
§Antigen that had caused an antibody response in the recipient in the past and was present in the intended donor is not present in the matched donor.
‖Indicates the strength of the antibody response.
¶Indicates HLA antigen concordance.
#Antibody response to matched donor HLA antigen is weaker than antibody response to intended donor, indicating amenability to desensitization.

Pair 1

Unconventional KPD patient 8 was a 42-year-old white man with blood type A and end-stage renal disease as a result of diabetes mellitus and hypertensive nephrosclerosis. He had received 3 previous kidney transplants. His first allograft lasted 3 years. The second and third grafts were lost during the first week after transplant due to severe AMR. He had spent a total of 14 years undergoing dialysis. His stepsister, who is blood type O, agreed to serve as the donor for a fourth transplant but a positive cytotoxic crossmatch with a titer greater than 1024 was identified. He had a PRA of 100% with strong reactivity against common HLA antigens A1, A2, and A11. His intended donor was mismatched at HLA antigens A1 and A11. Given the strength of the crossmatch, the patient was deemed unsuitable for desensitization and was offered the opportunity to participate in the KPD transplant program. Although our database of potential exchange participants currently includes 86 donors and 71 recipients, we could not identify any combination of donors and recipients that would provide this patient with a negative crossmatch. However, he had a low titer (dilution = 1:4) positive cytotoxic crossmatch against the intended donor of unconventional KPD patient 10 (HLA antigen A3), a reactivity strength amenable to desensitization. Five pretransplant and 9 posttransplant plasmapheresis treatments were performed. He received both splenectomy and anti-CD20 prior to transplantation.[21] The patient eliminated his donor-specific antibody and at 9 months after transplan-

Table 3. Creatinine Levels Prior to Transplantation and at 1 Week, 3 Months, and 6 Months

Patient No. (Rejection Type and Banff[17,18] Score)	Creatinine Level, mg/dL (µmol/L)*				Follow-up After Transplant, mo
	Prior to Transplantation	1 wk	3 mo	6 mo	
Median (range) of all patients					13 (1-42)
mg/dL	6.5 (3.0-11.6)	1.1 (0.6-2.8)	1.1 (0.7-1.6)	1.2 (0.8-1.8)	
µmol/L	574.6 (265.2-1025.4)	97.2 (53.0-247.5)	97.2 (61.9-141.4)	106.1 (70.7-159.1)	
Conventional Paired Donation					
1	6.4 (565.8)	NA	NA	NA	NA
2	5.8 (512.7)	1.5 (132.6)	1.3 (114.9)	1.1 (97.2)	42
3	6.5 (574.6)	1.0 (88.4)	1.0 (88.4)	1.2 (106.1)	30
4	7.5 (663.0)	2.8 (247.5)	1.1 (97.2)	1.2 (106.1)	30
5	5.1 (450.8)	1.2 (106.1)	0.8 (70.7)	1.1 (97.2)	23
6 (cellular 2A)	11.6 (1025.4)	2.2 (194.5)	1.2 (106.1)	1.4 (123.8)	23
7	3.5 (309.4)	1.2 (106.1)	1.6 (141.4)	1.5 (132.6)	6
8	7.7 (680.7)	0.9 (79.6)	0.9 (79.6)	1.0 (88.4)	6
9	8.9 (786.8)	1.0 (88.4)	1.0 (88.4)	NA	4
10	3.2 (282.9)	1.1 (97.2)	1.3 (114.9)	NA	4
11	3.3 (291.7)	2.8 (247.5)	NA	NA	1
12	5.1 (450.8)	0.9 (79.6)	NA	NA	1
Overall median (range)					6 (1-42)
mg/dL	6.1 (3.2-11.6)	1.2 (0.9-2.8)	1.1 (0.8-1.6)	1.2 (1.0-1.5)	
µmol/L	539.24 (282.9-1025.4)	106.1 (79.6-247.5)	97.2 (70.7-141.4)	106.1 (88.4-132.6)	
Unconventional Paired Donation					
1	8.8 (777.9)	1.4 (123.8)	1.3 (114.9)	1.5 (132.6)	19
2	5.3 (468.5)	1.1 (97.2)	1.4 (123.8)	1.4 (123.8)	19
3	4.8 (424.3)	0.9 (79.6)	0.7 (61.9)	0.8 (70.7)	16
4 (cellular 1A)	9.3 (822.1)	1.1 (97.2)	1.1 (97.2)	1.1 (97.2)	16
5	6.0 (530.4)	0.6 (53.0)	0.8 (70.7)	1.1 (97.2)	16
6	9.8 (866.3)	0.9 (79.6)	0.9 (79.6)	1.0 (88.4)	13
7	11.5 (1016.6)	1.7 (150.3)	1.6 (141.4)	1.8 (159.1)	13
8	9.1 (804.4)	1.5 (132.6)	1.2 (106.1)	1.4 (123.8)	9
9 (cellular 1A)	3.0 (265.2)	1.6 (141.4)	1.4 (123.8)	1.5 (132.6)	9
10 (cellular 2B)	9.0 (795.6)	2.7 (238.7)‡	1.5 (132.6)	1.7 (150.3)	9
Overall median (range)					14.5 (9-19)
mg/dL	8.9 (3.0-11.5)	1.1 (0.6-2.7)	1.2 (0.7-1.6)	1.3 (0.8-1.8)	
µmol/L	786.8 (265.2-1016.6)	97.2 (53.0-238.7)	106.1 (61.9-141.4)	114.9 (70.7-159.1)	

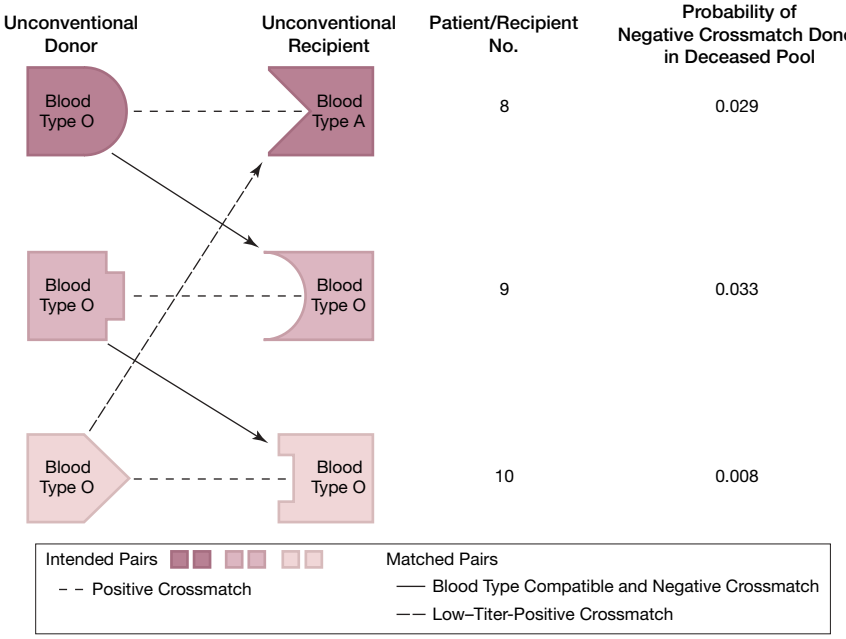
Abbreviation: NA, data not available.
*Unless otherwise indicated.

tation had a creatinine level of 1.1 mg/dL (97.2 µmol/L).

Pair 2

Unconventional KPD patient 9 was a 31-year-old white woman with blood type O and end-stage renal disease secondary to type 1 diabetes mellitus. She continued to undergo dialysis for 2 years. She had a PRA of 98% and had a high titer positive crossmatch (dilution >1:1024) with her father, the intended donor. Among others, the patient had antibodies to HLA antigen A2 and Bw4. She presented with 9 potential donors, all of whom had HLA antigens A2 or Bw4. However, the intended donor of unconventional KPD patient 8 carried neither HLA antigens A2 nor Bw4. The final flow crossmatch was negative and unconventional KPD patient 9 underwent an unremarkable transplant. She had 1A cellular rejection and was successfully treated with pulse steroids. At 9 months after transplantation, she did not have additional episodes of rejection and had a stable serum creatinine level of 1.3 mg/dL (114.9 µmol/L).

Figure 2. Use of a Triple Match



Three intended unconventional donor/recipient pairs are shown. Each recipient has a positive crossmatch to the intended donor, with a titer of 1024 or greater indicating a strong antibody response not amenable to desensitization. The 3 recipients exchange donors such that 3 feasible scenarios are created: 2 negative crossmatches and 1 low–titer-positive crossmatch that can be overcome by desensitization.

Pair 3

Unconventional KPD patient 10 was a 34-year-old white man with blood type O and end-stage renal disease secondary to IgA nephropathy. He had a previous deceased donor renal transplant in 1985 that was lost to chronic rejection. He was highly sensitized due to his previous transplant and multiple blood transfusions. His PRA was 82% and he had continued to undergo dialysis for 4 years. He had high titer antibodies against HLA antigens DRw51, w53, DQ1, and DQ3 and a positive cytotoxic crossmatch (dilution >1:1024) with his wife, the intended donor, was identified. However, he was identical to the father of unconventional KPD patient 9 at the HLA class II loci and had a negative flow crossmatch with this donor. Following an unremarkable transplant, the patient's serum creatinine level increased on day 4 and a biopsy revealed a 2B cellular rejection for which he received a course of anti–human thymocyte globulin. He did not have any additional episodes of rejection and at 9 months after transplantation had a stable serum creatinine level of 1.7 mg/dL (150.3 µmol/L).

COMMENT

The results of 6 conventional (blood groups A and B incompatible donor/recipient pairs) and 4 unconventional (2 double and 2 triple exchanges) KPD transplants performed at a single center were presented herein. The patient and graft survival in this cohort was 100% and 95.5%, respectively, with a median follow-up of 13 months. This compares favorably with the 2001 United Network for Organ Sharing live donor 1-year adjusted patient and graft survival of 98.3% and 94.3%.[1] For unconventional KPD transplants in which the average PRA was higher than 50%, our graft survival was 100% compared with the US Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients 2004 rate of 92% for patients with similar levels of sensitization. There was an 18% acute cellular rejection rate and no episodes of AMR. This compares favorably with the 30% acute cellular rejection rate reported by Fuller et al[22] for living unrelated transplant recipients. Seven (32%) of the 22 recipients had prior transplants. All patients with positive crossmatches with their intended donors had high titer donor-specific antibodies making them ineligible for desensitization by our current acceptance criteria. Through the KPD transplant program, 4 of 5 highly sensitized recipients were successfully paired with donors for whom they had no reactivity on a flow crossmatch and required no preconditioning. The remaining patient was matched with a donor who did not have HLA molecules for which he showed strong reactivity but persisted with a low–titer-positive crossmatch amenable to desensitization.

The concept of the KPD transplant was first described by Rapaport in 1986.[23] Ross et al[24] provided the ethical construct for KPD transplant in 1997. Further refinements of the ethics of various types of exchanges were introduced in subsequent publications by this group.[25-27] The ethical concerns abated and barriers to implementation were administrative and logistical. Single centers did not have enough incompatible pairs to provide a large enough pool to generate a significant number of matches and it became clear that regional or national systems of listing and matching would be necessary. The challenges inherent in organizing complex cooperative programs between transplant centers (eg, should donors travel or kidneys be shipped) have dominated the landscape and as a result only 53 patients have received a transplant through KPD in the United States to date.[1]

Two types of paired donation have been performed by our group and others.[26] In the conventional live KPD transplant, individuals with blood types A and B are matched with a pair who have the opposite incompatibility. Unfortunately, this is the rarest blood type combination and only affects about 3% to 5% of the live donor/recipient pairs.[2]

The unconventional live KPD transplant, however, allows blood type O donors and recipients to benefit from paired donation. This significantly increases the impact of the KPD transplant on the live donor pool. In this type of exchange, a blood type O recipient who has a positive crossmatch or incompatible blood type with his/her intended donor is matched with a blood type O donor of another crossmatch incompatible pair. More than 2 donor/recipient pairs can participate in this exchange.[28] This type of KPD transplant solves the problem of the excess of blood type O recipients with incompatiable blood type donors. It also allows patients who are broadly sensitized to common antigens to have the opportunity to receive a kidney with a negative crossmatch.

Immunologic risk varies depending on the donor/recipient profile (repeat HLA antigen mismatches from previous transplants or strength of crossmatch reactivity) between a sensitized patient and the intended donor.[21] Likewise, factors such as donor blood group (A1 vs A2 or B) and recipient blood group antibody titers define immunologic risk for a patient undergoing desensitization for an incompatible blood type transplant. When a patient presents with an incompatible donor, the risk of AMR and graft loss can be estimated. In some cases, this risk is so high that the patient would benefit from receiving a kidney from another donor with more favorable HLA antigens or blood type. By eliminating the requirement for a negative crossmatch or blood type compatibility for all participants in a KPD transplant, patients could be matched with a paired donor against whom they have lower immunologic risk and undergo pretransplant desensitization. We are not aware of any other instances other than the one presented herein in which the KPD transplant has been performed to facilitate desensitization. We think this could have a dramatic impact on the field of desensitization, yielding better results and lower cost of therapy.

This study demonstrates that KPD transplants can be performed with outcomes similar to compatible living donor kidney transplants. The cost savings and decrease in waiting time that could be realized by a wider application of this concept are substantial.[14] Because the likelihood of finding a suitable match is dependent on the size of the pool, a national list could enable many more transplants.[13,29] We estimate that about half of the incompatible pairs could receive transplants using a national KPD transplant scheme with blood type compatible, negative crossmatch kidneys, including as many as 14% of the highly sensitized patients.[13] Patients unable to be matched by KPD could undergo desensitization with their intended donor. Those who were not deemed acceptable for desensitization due to high titer or immunologic risk could participate in a less restricted KPD search in which a more favorable, but not completely compatible, donor could be identified. This single-center experience demonstrates that KPD is feasible, successful, and if applied to larger donor pools, capable of expanding access to renal transplantation.

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Study concept and design: Montgomery, Ratner.
Acquisition of data: Montgomery, Zachary, Hiller, Houp, Cooper, Kavoussi, Jarrett, Burdick, Maley, Melancon, Kozlowski, Leffell, Warren.
Analysis and interpretation of data: Montgomery, Zachary, Segev, Houp, Simpkins, Phillips, Desai, Collins, Reeb, Kraus, Rabb, Leffell, Warren.
Drafting of the manuscript: Montgomery, Segev, Phillips, Desai, Collins, Warren.
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Study supervision: Montgomery, Ratner, Warren.
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REFERENCES

1. United Network for Organ Sharing Web site. Organ procurement and transplantation network data. Available at: http://www.unos.org. Accessed March 10, 2005.
2. Terasaki PI, Gjertson DW, Cecka JM. Paired kidney exchange is not a solution to ABO incompatibility. *Transplantation*. 1998;65:291.
3. Zenios SA, Woodle ES, Ross LF. Primum non nocere: avoiding harm to vulnerable wait list candidates in an indirect kidney exchange. *Transplantation*. 2001; 72:648-654.
4. Terasaki PI. Humoral theory of transplantation. *Am J Transplant*. 2003;3:665-673.
5. Williams GM, Hume DM, Hudson RP Jr, Morris PJ, Kano K, Milgrom F. 'Hyperacute' renal-homograft rejection in man. *N Engl J Med*. 1968;279:611-618.
6. Kissmeyer-Nielsen F, Olsen S, Petersen VP, Fjeldborg O. Hyperacute rejection of kidney allografts associated with pre-existing humoral antibodies against donor cells. *Lancet*. 1966;2:662-665.
7. Glotz D, Antoine C, Julia P, et al. Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIg). *Am J Transplant*. 2002;2:758-760.
8. Jordan SC, Vo AA, Nast CC, Tyan D. Use of high-dose human intravenous immunoglobulin therapy in sensitized patients awaiting transplantation: the Cedars-Sinai experience. *Clin Transpl*. 2003;193-198.
9. Montgomery RA, Zachary AA, Racusen LC, et al. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory hu-

moral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation*. 2000;70:887-895.
10. Sonnenday CJ, Warren DS, Cooper M, et al. Plasmapheresis, CMV hyperimmune globulin, and anti-CD20 allow ABO-incompatible renal transplantation without splenectomy. *Am J Transplant*. 2004;4:1315-1322.
11. Warren DS, Zachary AA, Sonnenday CJ, et al. Successful renal transplantation across simultaneous ABO incompatible and positive crossmatch barriers. *Am J Transplant*. 2004;4:561-568.
12. Gloor JM, Lager DJ, Moore SB, et al. ABO-incompatible kidney transplantation using both A2 and non-A2 living donors. *Transplantation*. 2003;75:971-977.
13. Segev DL, Gentry SE, Warren DS, Reeb B, Montgomery RA. Kidney paired donation and optimizing the use of live donor organs. *JAMA*. 2005;293:1883-1890.
14. Segev DL, Gentry SE, Melancon JK, Montgomery RA. Characterization of waiting times in a simulation of kidney paired donation. *Am J Transplant*. 2005;5:2448-2455.
15. Gentry SE, Segev DL, Montgomery RA. A comparison of populations served by kidney paired donation and list paired donation. *Am J Transplant*. 2005;5:1914-1921.
16. Roth AE, Sönmez T, Ünver MU. Kidney exchange. *Q J Econ*. 2004;119:457-488.
17. Racusen LC, Halloran PF, Solez K. Banff 2003 meeting report: new diagnostic insights and standards. *Am J Transplant*. 2004;4:1562-1566.
18. Racusen LC, Solez K, Colvin RB, et al. The Banff 97 working classification of renal allograft pathology. *Kidney Int*. 1999;55:713-723.
19. Zachary AA, Montgomery RA, Ratner LE, et al. Specific and durable elimination of antibody to donor HLA antigens in renal-transplant patients. *Transplantation*. 2003;76:1519-1525.
20. Zachary AA, Braun WE. Calculation of a predictive value for transplantation. *Transplantation*. 1985;39:316-318.
21. Montgomery RA, Zachary AA. Transplanting patients with a positive donor-specific crossmatch: a single center's perspective. *Pediatr Transplant*. 2004;8:535-542.
22. Fuller TF, Feng S, Brennan TV, Tomlanovich S, Bostrom A, Freise CE. Increased rejection in living unrelated versus living related kidney transplants does not affect short-term function and survival. *Transplantation*. 2004;78:1030-1035.
23. Rapaport FT. The case for a living emotionally related international kidney donor exchange registry. *Transplant Proc*. 1986;18(suppl 2):5-9.
24. Ross LF, Rubin DT, Siegler M, Josephson MA, Thistlethwaite JR Jr, Woodle ES. Ethics of a paired-kidney-exchange program. *N Engl J Med*. 1997;336:1752-1755.
25. Ross LF, Woodle ES. Ethical issues in increasing living kidney donations by expanding kidney paired exchange programs. *Transplantation*. 2000;69:1539-1543.
26. Ross LF, Zenios S. Restricting living-donor-cadaver-donor exchanges to ensure that standard blood type O wait-list candidates benefit. *Transplantation*. 2004;78:641-646.
27. Ross LF, Zenios S. Practical and ethical challenges to paired exchange programs. *Am J Transplant*. 2004;4:1553-1554.
28. McLellan F. US surgeons do first "triple-swap" kidney transplantation. *Lancet*. 2003;362:456.
29. Park K, Moon JI, Kim SI, Kim YS. Exchange donor program in kidney transplantation. *Transplantation*. 1999;67:336-338.

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