ORIGINAL ARTICLE

Crossing borders to facilitate live donor kidney transplantation: the Czech-Austrian kidney paired donation program – a retrospective study

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SUMMARY

Kidney paired donation (KPD) is a valuable tool to overcome immunological barriers in living donor transplantation. While small national registries encounter difficulties in finding compatible matches, multi-national KPD may be a useful strategy to facilitate transplantation. The Czech (Prague) and Austrian (Vienna) KPD programs, both initiated in 2011, were merged in 2015. A bi-national algorithm allowed for ABO- and low-level HLA antibody-incompatible exchanges, including the option of altruistic donor-initiated domino chains. Between 2011 and 2019, 222 recipients and their incompatible donors were registered. Of those, 95.7% (Prague) and 67.9% (Vienna) entered into KPD registries, and 81 patients received a transplant (95% 3-year graft survival). Inclusion of ABO-incompatible pairs in the Czech program contributed to higher KPD transplant rates (42.6% vs. 23.6% in Austria). After 2015 (11 bi-national match runs), the median pool size increased to 18 pairs, yielding 33 transplants (8 via cross-border exchanges). While matching rates doubled in Austria (from 9.1% to 18.8%), rates decreased in the Czech program, partly due to implementation of more stringent HLA antibody thresholds. Our results demonstrate the feasibility of merging small national KPD programs to increase pool sizes and may encourage the implementation of multi-national registries to expand the full potential of KPD.

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Key words
ABO incompatibility, histocompatibility, immunogenetics, kidney clinical, kidney paired donation, live donors, pre-sensitisation

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Introduction

Living donor (LD) kidney transplantation is currently the best treatment option for patients with end-stage renal disease, allowing for excellent outcomes in terms of patient and graft survival. Transplantation across major immunological barriers, in particular preformed anti-HLA donor-specific antibodies (DSA), however, may confer a significant risk of rejection and graft failure, despite use of intense desensitization protocols [1,2]. For such situations, kidney paired donation (KPD) has emerged as a valuable tool to minimize immunological risks and facilitate successful transplantation [3–6]. In KPD, incompatible donor-recipient pairs exchange kidneys with other incompatible pairs, so that all recipients receive compatible or at least better-matched organs. Since its first description in 1986 by Rapaport [7], KPD has been implemented in many countries around the world [8–11] with the Dutch, UK, and Spanish multicenter registries being the largest in Europe [12–14].

A critical determinant of program efficiency is the size of KPD pools. Small pool sizes, as in single-center or small national programs, may substantially limit matching probabilities, especially for patients with broad HLA sensitization [4,5,13]. Computer simulations based on real data from the UK program have revealed that a pool of 50 patients would yield a match rate of 38%, but in order to reach match rates approximating 50% inclusion of more than 100 patients would be necessary [13]. Apart from pool size, the composition of KPD registries (proportions of ABO- vs. HLA-incompatible pairs; broadness and strength of HLA sensitization) may play a key role, and match rates were reported to strongly decrease upon accumulation of broadly sensitized hard-to-match recipients [4,5]. Enlarging pool size may thereby markedly increase match rates for this disadvantaged group of patients [15].

In recent years, several European countries have started their own KPD programs or plan to do so within the European Network for Collaboration on Kidney Exchange Programs (ENCKEP) [14]. In the Czech Republic (Prague) and Austria (Vienna), first LD kidney donor exchanges were realized already in 2003 and 2000, respectively; however, systematic KPD registries were implemented a decade later. The Czech program was implemented in 2011, and, later on, a new in-house computer-algorithm was developed for virtual cross-match-based donor-recipient matching [16]. At the same time, the Austrian program was initiated in close collaboration with the Australian KPD program after trans-national validation of the Australian national organ matching system [17]. In an effort to enlarge KPD pools, the two KPD programs were merged in 2015, yielding a first cross-border kidney exchange - the first in Europe - in September 2016 [18].

The objective of the present retrospective evaluation was to provide a detailed descriptive analysis of KPD in our two countries, in an effort to better understand the impact of inherent differences in patient characteristics and algorithms on matching probabilities and outcomes. Our results may provide a valuable basis for future strategies to further increase transplant rates and may encourage the implementation of larger international programs in and outside of Europe.

Patients and methods

Study population

A retrospective review report was performed on a cohort of 222 LD transplant candidates and their ABO- and/or HLA-incompatible intended LD, who were referred to the Prague (Institute of Clinical and Experimental Medicine) and Vienna transplant units (Medical University of Vienna) between January 2011 and March 2019. One hundred and ninety recipients entered the Czech and Austrian KPD registries, with a total of 81 KPD transplantations performed through donor exchanges. Demographics and baseline characteristics are provided in Table 1. All transplants were performed in compliance with the principles of the Declaration of Istanbul.

KPD program design

The Prague and Vienna transplant units coordinated the Czech and Austrian KPD programs, respectively. The Austrian program included also incompatible pairs from other countries, such as Germany (Hannover: $n = 3$, Köln: $n = 2$, Erlangen: $n = 1$, Heidelberg: $n = 1$, Berlin: $n = 1$), Slovenia (Ljubljana: $n = 1$), and the Ukraine (Kiev: $n = 1$). The two programs, which were both initiated in 2011, were merged in 2015, after a planning period of one year (several meetings between involved teams to discuss all relevant surgical, logistic, and ethical aspects, including possible concerns regarding an expected marginal increase in cold ischemia times, and to define a harmonized bi-national matching algorithm to maximize the number of possible KPD transplants).

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Table 1. Incompatible living donor transplant candidates - Baseline characteristics and immunological data

Parameters	All incompatible patients (*n* = 222)	Prague, Czech Republic (*n* = 141)	Vienna, Austria (*n* = 81)	*P* value
Primary option				
KPD referral	190 (85.6)	135 (95.7)	55 (67.9)	≤0.001
Direct ABO-incompatible transplantation	32 (12.4)	6 (4.3)	26 (32.1)	≤0.001
Recipient characteristics				
Female sex, *n* (%)	81 (36.5)	54 (38.3)	27 (33.3)	0.46
Recipient age at referral, years, median (IQR)	47.7 (37.9–57.1)	45.4 (36.8–55)	53.6 (41.1–60.5)	0.001
Dialysis vintage at referral, months, median (IQR)	1.5 (0–17.1)	1.7 (0–19.8)	1 (0–14.9)	0.47
CDC panel reactivity in sensitized recipients, median (IQR)	0 (0–34.5)	13.5 (0–44.75)	0 (0–11.5)	0.001
Previous kidney transplant, *n* (%)				
No previous kidney transplant	162 (73)	110 (78)	52 (64.2)	0.1
1 previous kidney transplant	44 (19.8)	22 (15.6)	22 (27.2)	
2 previous kidney transplants	12 (5.4)	8 (5.7)	4 (4.9)	
3 previous kidney transplants	3 (1.4)	1 (0.7)	2 (2.5)	
4 previous kidney transplants	1 (0.5)	0 (0.0)	1 (1.2)	
Recipient blood group, *n* (%)				
O	95 (42.8)	49 (34.8)	46 (56.8)	0.009
A	64 (28.8)	44 (31.2)	20 (24.7)	
B	54 (24.3)	40 (28.4)	14 (17.3)	
AB	9 (4.1)	8 (5.7)	1 (1.2)	
Characteristics of the directed donor				
Number of incompatible donors	232	143	89	
Living-unrelated donor, *n* (%)	152 (65.5)	87 (60.8)	65 (73.0)	0.057
Female sex, n (%)	147 (63.4)	89 (62.2)	58 (65.2)	0.65
Donor age at referral, years, median (IQR)	49.2 (40.3–57.6)	46.1 (37.8–55.3)	53.2 (46.7–59.5)	≤0.001
Donor blood group, *n* (%)				
O	38 (16.4)	20 (14.0)	18 (20.2)	
A	100 (43.1)	54 (37.8)	46 (51.7)	0.024
B	61 (26.3)	44 (30.8)	17 (19.1)	
AB	33 (14.2)	25 (17.5)	8 (9)	
Characteristics of registered combinations				
Number of incompatible combinations	232	143	89	
Type of incompatibility, *n* (%)				
HLA antibody-incompatible only	56 (24.1)	30 (21.0)	26 (29.2)	0.15
ABO-incompatible only	135 (58.2)	102 (71.3)	33 (37.1)	<0.001
HLA- plus ABO-incompatible	39 (16.8)	11 (7.7)	28 (31.5)	<0.001
Repeated mismatch	2 (0.9)	0 (0)	2 (2.2)	0.072

CDC, complement-dependent cytotoxicity; IQR, interquartile range; KPD, kidney paired donation.

Inclusion criteria for KPD were as follows: informed consent of donor and recipient, HLA antibody incompatibility (preformed DSA and/or a positive crossmatch considered to preclude transplantation without recipient desensitization), ABO incompatibility, or, in selected cases, a repeated HLA mismatch considered to confer an increased risk of rejection. Desensitization for HLA antibody-incompatible LD transplantation was not considered as a primary treatment option, and sensitized recipients were primarily offered registration for KPD. Nonsensitized ABO-incompatible recipients (all combinations including incompatible blood type A2 donors) were either listed for KPD (Czech program: transplantation with the directed donor only after one or two negative matching cycles) or, with the exception of recipients with excessive ABO antibody titers, subjected to ABO-incompatible transplantation as the primary option (Austria). All KPD-listed patients were in parallel listed for deceased donor (DD) transplantation.

In the Czech program, which from the beginning allowed for multi-way exchanges, matching was initially based on crossmatch test results. Virtual crossmatch-based computer matching – primarily based on HLA-A, HLA-B, HLA-DR typing results (additional HLA-C, HLA-DQ and HLA-DP typing according to individual HLA antibody profiles) – was introduced in 2013 and, two years later adopted for bi-national KPD [mean fluorescence intensity (MFI) threshold set at 1000 for HLA class I and 2000 for HLA class II antibodies]. Before 2015, the Czech program allowed for compromises in terms of immunological risk, including desensitization for a positive pretransplant flow crossmatch and/or preformed DSA. Since its implementation, the Austrian registry employed a virtual crossmatch approach using an MFI threshold for acceptable DSA set at 2000 [17]. Before merging the programs, HLA antibody-compatible 2- and 3-way exchanges were calculated on the basis of HLA typing in all relevant loci (HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ, and HLA-DP), employing the Australian national organ matching system [9]. KPD transplants across preformed DSA were not allowed, with one exception (low-level preformed DSA and ABO incompatibility) – a sensitized recipient with a limited estimated lifetime and an expected long DD waiting time [18]. In the initial phase of the combined program, centers were allowed to perform additional local match runs, but since 2017, all match runs were performed within the bi-national algorithm.

Donor nephrectomies were performed via hand-assisted retroperitoneoscopic approach (Prague) [19] or fully laparoscopic approach (Vienna). To minimize the risk of donor withdrawal, the Austrian program mandated simultaneous exchange. In contrast, the Czech program permitted also nonsimultaneous exchanges. In both countries, exchanges were performed anonymously. While being informed that KPD donors were carefully evaluated fulfilling all predefined medical criteria for donation, including an adjusted measured GFR above 80 ml/min, the recipients did not get any detailed personal or medical information, such as donor sex, age, or medical history. In order to keep anonymity for simultaneous transplants, involved operation theaters were strictly separated, and postoperative care involved separate wards. Both KPD programs included the option of bridge donor-linked segments of nonsimultaneous extended altruistic donor (NEAD) chains. For international KPD, kidneys were shipped via ground transport, with documented cold ischemia times between 258 and 365 min (median: 322 min).

Recipient desensitization

In both centers, all types of ABO-incompatible transplantation (blood types A1 or A2 to B or O; B to A or O) were performed using protocols based on antigen-specific immunoadsorption, with or without rituximab induction or low dose intravenous immunoglobulin (IVIG) [20]. In Prague, recipient desensitization for DSA-positive KPD transplantation included a course of plasmapheresis, together with IVIG and rituximab in the month before scheduled transplantation, and antithymocyte globulin (ATG) for induction. In a single Vienna case, a KPD transplant was performed across low-level DSA (and a major ABO barrier) using combined treatment with semi-selective and ABO antigen-specific immunoadsorption, together with ATG induction [18]. Baseline immunosuppression consisted of tacrolimus, mycophenolic acid, and steroids in all recipients subjected to desensitization.

Statistical analysis

Continuous variables were expressed either as median and interquartile range (IQR). Categorical variables were given as absolute and relative frequencies. For comparison of continuous data, Mann–Whitney *U*-test was used. Kaplan–Meier analysis was applied for calculation of graft and patient survival, using log-rank tests for comparisons between groups. A two-sided P-value < 0.05 was considered statistically significant. For analysis, SPSS Statistics 25 (IBM Corporation, Armonk, NY, USA) was used.

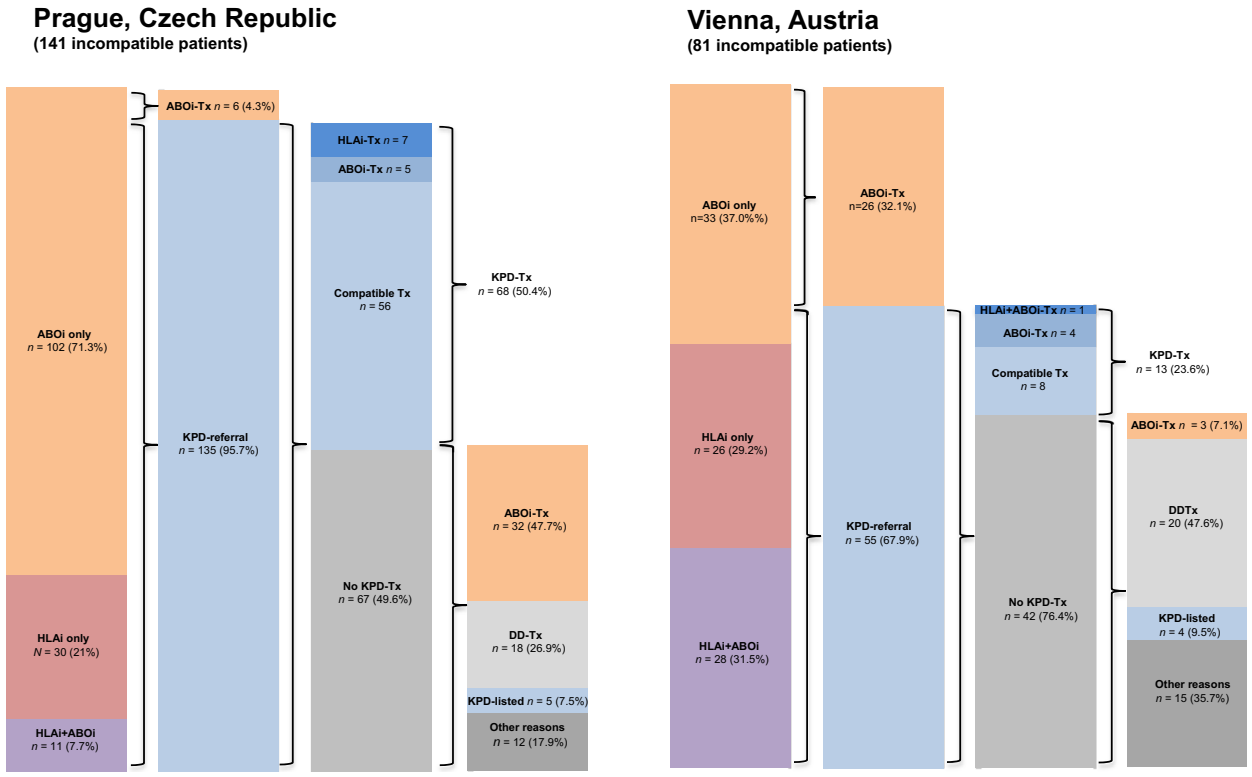

Figure 1 Patient flow. The disposition of recipients with a willing but incompatible donor is illustrated for transplant units in Prague and Vienna, respectively. ABOi, ABO-incompatible; HLAi, HLA-incompatible; DD, deceased donor; KPD, kidney paired donation; Tx, transplantation.

Results

Baseline data and demographics

Figure 1 illustrates the disposition of recipients referred to incompatible transplant programs between January 2011 and March 2019. The overall study population consisted of 222 LD transplant candidates who, together with their intended incompatible donors, were registered at the transplant units in Prague (n = 141; one intended incompatible donor: n = 139, two donors: n = 2) and Vienna (n = 81; one donor: n = 75, two donors: n = 4, three donors: n = 2), respectively. Baseline characteristics are shown in Table 1. The majority of recipients were male (63.5%), and the majority of donors were female (63.4%). Twenty-seven percent had a history of prior transplantation. The median recipient age at referral was 48 years, the donor age 49 years. The dialysis vintage at referral was in median 1.5 months. The majority of intended donors (65.5%) were living-unrelated. Baseline characteristics were not significantly different between the two units, with the exception of a younger recipient and donor age, and higher levels of cytotoxic panel reactivity in Prague (Table 1).

As shown in Table 1, the type of incompatibility was unevenly distributed between the two centers. ABO incompatibility without detectable DSA was more prevalent in Prague (71.3% vs. 37.1% in Vienna; $P < 0.001$), while in Vienna, this was the case for combined ABO- plus HLA antibody incompatibility (31.5% vs. 7.7% in Prague; $P < 0.001$). Moreover, there was a trend toward more HLA-incompatible (and ABO-compatible) combinations in Vienna (29.2% vs. 21.0% in Prague; $P = 0.15$). Blood group distributions were different between donors and recipients, with blood type O being more frequent among recipients and blood type A among donors. There were significant differences between the two programs, with blood type O being more prevalent in Vienna (Table 1).

One hundred ninety of the 222 recipients (and their intended donors) participated in the two national KPD registries as the primary option (baseline characteristics, see Table S1), with a significant higher proportion in the Czech (95.7%) than in the Austrian registry (67.9%) (Table 1, Fig. 1). In Vienna, the majority of ABO-incompatible (DSA-negative) recipients were transplanted with the directed donor (26 of 31 recipients with one or more ABO-incompatible intended donors), while in Prague, this was the case for only 6 of 100 such recipients (Table 1, Fig. 1).

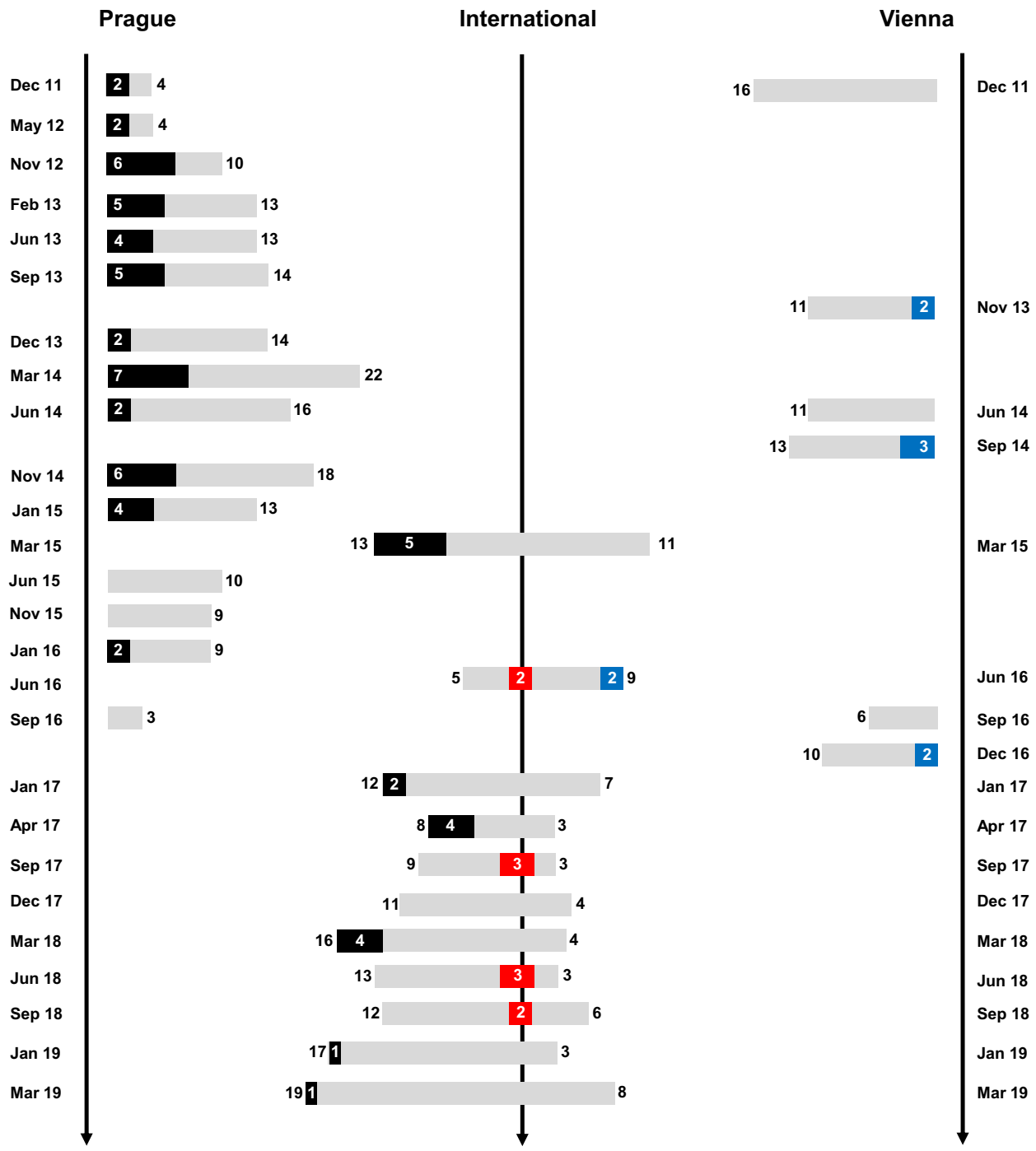

Figure 2 Match cycles before and after merging the Czech and Austrian KPD programs. National and international match runs are shown for the period between 2011 and March 2019. The number of included recipients and successful transplants [national transplants: black (Prague) or blue (Vienna) bars; cross-border exchanges: red bars] are shown for each individual run.

Match cycles and KPD transplant rates

KPD activity over time is illustrated in Fig. 2. In the period between 2011 (initiation of the Czech and Austrian national programs) and 2015 (implementation of bi-national KPD), the Czech KPD program conducted a total of 11 match runs, with a median of 13 (IQR: 10–16) pairs included. Each run yielded successful loops (four 2-way, two 4-way, three 5-way, two 6-way loops, and one 7-way loop) resulting in 45 KPD transplantations. During the same period, only 4 runs were conducted in Austria, with a median of 12 (11–15) pairs

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included per run. Two runs resulted in successful loops yielding 5 transplantations (one 2-way and one 3-way exchange).

After merging the programs in 2015, 11 international runs [median of 18 (14–20) pairs per run] and, in addition, 6 local runs (Czech program: $n = 4$, Austrian program: $n = 2$) were carried out. Ten international (seven 2-way loops, one 3-way, and one 4-way loop; two segments of a NEAD chain) and two local runs (two 2-way loops) yielded successful KPD loops resulting in 33 transplantations (Czech program: $n = 25$; Austrian program: $n = 8$). Eight of these transplants were performed in the context of cross-border kidney exchanges, five via a NEAD chain (Fig. 2).

Analyzing single-center match runs, we found three times higher rates of patients identified for transplantation in the Czech than in the Austrian program [30.8% (12.5–38.5%) vs. 9.1% (0–20.8%); $P = 0.054$]. For international match runs ($n = 11$), transplant rates were in median 18.8% (5–25%).

As of March 2019, 81 of the 190 recipients referred to KPD (42.6%) received a transplant through a suitable match. KPD transplant rates were thereby unevenly distributed between the two programs, with the Czech algorithm yielding 68 (50.4%) as compared to only 13 KPD transplants (23.6%) in Austria ($P = 0.001$) (Fig. 1, Table 2). Accordingly, the vintage between KPD referral and transplantation was by far shorter in the Czech than in the Austrian program (median: 4.9 vs. 16.3 months; $P < 0.001$) (Table 3). The proportion of transplantations in the context of international exchanges was about three times higher in the Austrian (30.8%) than in the Czech program (5.9%, $P = 0.028$) (Table 3).

As shown in Fig. 1, among KPD-listed patients who did not receive a KPD transplant during follow-up, 35 (18.4%) underwent direct ABO-incompatible transplantation after unsuccessful runs, with a by far higher rate in the Czech than in the Austrian program (23.7% vs. 5.5%). Thirty-eight registered patients (20.0%) received an allograft from a DD, more frequently in the Austrian (36.4%) than in the Czech program (13.3%). At the end of follow-up, nine patients were still actively listed for KPD to participate in future runs (Table 2).

Table 2. Clinical procedures for KPD-registered patients

Parameters	All KPD referrals ($n = 190$)	Czech program ($n = 135$)	Austrian program ($n = 55$)	*P* value
KPD transplants, *n* (%)	81 (42.6)	68 (50.4)	13 (23.6)	0.001
Preemptive transplantation, *n*	19	18	1	
No transplantation within the KPD program				
Direct ABO-incompatible transplantation, *n* (%)	35 (18.4)	32 (23.7)	3 (5.5)	0.003
Preemptive transplantation, *n*	15	15	0	
LD transplantation with other donor (outside KPD), *n* (%)	3 (1.6)	2 (1.5)	1 (1.8)	0.87
Preemptive transplantation, *n*	3	2	1	
DD transplantation, *n* (%)	38 (20.0)	18 (13.3)	20 (36.4)	≤0.001
Preemptive transplantation, *n*	1	0	1	
Still actively listed for KPD, *n* (%)	9 (4.7)	5 (3.7)	4 (7.3)	0.294
Withdrawal of consent for KPD, *n* (%)	12 (6.3)	4 (3.0)	8 (14.5)	0.003
Medical contraindication for transplantation, *n* (%)	9 (4.7)	6 (4.4)	3 (5.5)	0.77
Death while waiting for transplantation, *n* (%)	2 (1.1)	0 (0.0)	2 (3.6)	0.083
Loss of follow-up, *n* (%)	1 (0.5)	0 (0.0)	1 (1.8)	0.29

KPD, kidney paired donation.

KPD transplantations

Baseline data of the 81 KPD transplants are shown in Table 3. The proportion of ABO-incompatible KPD transplants was higher in the Austrian (39%) than in the Czech program (7%). In Prague, seven patients were

Table 3. KPD transplants - Baseline demographics and clinical characteristics

Parameters	All KPD transplants (*n* = 81)	Czech program (*n* = 68)	Austrian program (*n* = 13)	*P* value
Match runs				
Chain length, median (IQR)	4 (2–5)	4.5 (2–6)	2 (2–3)	0.002
Closed loops, *n* (%)				
2-way	10	7	3	
3-way	1	0	1	
4-way	4	4	0	
5-way	3	3	0	
6-way	2	2	0	
7-way	2	2	0	
NEAD chain	1	1	1	
International exchange, *n* (%)	8 (9.9)	4 (5.9)	4 (30.8)	0.02
KPD transplant characteristics				
Preemptive Tx, *n* (%)	19 (23.5)	18 (26.5)	1 (7.7)	0.14
Months between dialysis initiation and Tx, median (IQR)	9.6 (0.1–21.3)	5.7 (0–21.2)	17.6 (12.8–21.2)	0.043
Months between KPD referral and Tx, median (IQR)	5.7 (2.6–10.2)	4.9 (2–7.4)	16.3 (8–25.7)	<0.001
Recipient female sex, *n* (%)	34 (42.0)	27 (39.7)	7 (53.8)	0.34
Recipient age at transplantation, years, median (IQR)	46.6 (38.2–56.1)	45.5 (38.1–55.8)	53.6 (40–63)	0.26
Previous kidney transplant, *n* (%)				
No previous kidney transplant	62 (76.5)	54 (79.4)	8 (61.5)	0.35
1 previous kidney transplant	16 (19.8)	12 (17.6)	4 (30.8)	
2 previous kidney transplants	2 (2.5)	1 (1.5)	1 (7.7)	
3 previous kidney transplants	1 (1.2)	1 (1.5)	0 (0.0)	
Donor age at Tx, years, median (IQR)	46.7 (37.3–55.2)	45.2 (37.3–55.2)	50.4 (39.2–60.6)	0.22
Donor female sex, *n* (%)	45 (45.5)	41 (60.3)	4 (30.8)	0.05
HLA mismatch in HLA-A, HLA-B and HLA-DR, median (IQR)	4 (4–5)	4 (4–5)	5 (4–5)	0.30
Desensitization, *n* (%)	17 (21.0)	12 (17.6)	5 (38.5)	0.091
Preformed DSA, *n* (%)	8 (9.9)	7 (10.3)	1 (7.7)	0.77
MFI, median (IQR)	2000 (1519–3515)	1700 (1500–3664)	2300	0.83
ABO-incompatible transplantation, *n* (%)	10 (12.3)	5 (7.4%)	5 (38.5%)	0.002
Recipient blood group, *n* (%)				
O	24 (29.6)	19 (27.9)	5 (38.5)	0.65
A	28 (34.6)	24 (35.3)	4 (30.8)	
B	23 (28.4)	19 (27.9)	4 (30.8)	
AB	6 (7.4)	6 (8.8)	0(0.0)	

DSA, donor-specific antibody; IQR, interquartile range; KPD, kidney paired donation; MFI, mean fluorescence intensity; NEAD chain, nonsimultaneous extended altruistic donor chain.

Table 4. Allograft outcomes in patients subjected to KPD transplantation

Parameters*	All KPD transplants (n = 81)	Czech program (n = 68)	Austrian program (n = 13)	P value
Observation time (months), median (IQR)	53 (25–67)	54 (25–67)	32 (21–53)	0.067
Serum creatinine (mg/dl), median (IQR)				
1 year	1.35 (1.11–1.58)	1.35 (1.13–1.62)	1.20 (0.80–1.39)	0.062
3 years	1.30 (0.98–1.55)	1.32 (1.03–1.60)	1.16 (0.86–1.24)	0.07
eGFR, ml/min per 1.73 m^2, median (IQR)				
1 year	57.60 (49.6–72.0)	57.6 (49.2–68.4)	70.2 (53.3–82.2)	0.16
3 years	58.8 (49.2–70.7)	57 (48.6–67.8)	76.4 (69.7–87.9)	0.014
Biopsy proven rejection, n, (%)				
Banff Borderline	23 (28.4)	21 (30.9)	2 (15.4)	0.26
TCMR Banff I or II	15 (18.5)	14 (20.6)	1 (7.7)	0.27
ABMR	9 (11.1)	9 (13.2)	0 (0)	0.16
Overall graft survival, months, %				
12 months	96	95	100	0.37
36 months	95	94	100	0.37

IQR, interquartile range; KPD, kidney paired donation.

*3-year follow-up data were available for 61 and 5 recipients transplanted within the Czech and Austrian programs, respectively.

Figure 3 Graft survival after KPD transplantation. For comparison of overall graft survival rates in Prague (Czech Republic, Cz) and Vienna (Austria, A) log-rank test was used.

transplanted across the barrier of preformed DSA [MFI: 2000 (median; range: 1200–11 000), HLA class I: n = 3; HLA class II: n = 4]. There was only one recipient in Vienna, who was transplanted across low-level HLA class II DSA (MFI: 2300; and a major ABO barrier) (Table 3). Nineteen KPD transplantations (23.5%) were performed preemptively, 18 within the Czech and one within the Austrian program, respectively. Outcome results are shown in Table 4 and Fig. 3. During follow-up, two deaths and three graft losses were recorded, the latter including two cases of early antibody-mediated rejection (ABMR; mixed phenotype in a case of medication nonadherence) and one graft loss due to an early vascular complication. Overall 1- and 3-year graft survival was 96% and 95%, respectively, with no significant differences between the two programs (Fig. 3). Median serum creatinine at 12 and 36 months was 1.35 mg/dl and 1.30 mg/dL, respectively [median estimated glomerular filtration rate (eGFR) 57.6 and 58.8 ml/min per 1.73 m^2]. After 3 years, a small but significant difference in eGFR was observed between the Czech and Austrian programs. Overall, 15 patients were diagnosed with T-cell-mediated rejection and nine with ABMR. Four ABMR episodes occurred after desensitization for preformed DSA (MFI between 1500 and 11 000) and/or flow crossmatch positivity (Table 4).

Discussion

The present report on two small single-center KPD programs from two European countries that have been merged in an effort to increase match probabilities and facilitate transplant rates illustrates the feasibility of implementing a systematic program of trans-national LD kidney exchange. From its inception in 2015, the Czech-Austrian joint program has facilitated 33 KPD transplants, eight of them in the context of international exchanges. Our cooperation, which has led to the first cross-border LD kidney exchange in Europe [18], may be a starting point for the set-up of new larger-scale trans-national initiatives. So far, only few examples of cross-border shipping of KPD kidneys have been reported, one exchange between the United States and Canada [21], and, another between Spain and Italy [22].

The primary rationale behind merging our small programs was to increase KPD pool size, a critical determinant of match probability [4,5,13]. Indeed, in our single-center KPD programs, the average proportion of recipients identified for potential transplant was low, especially for Austria, where national runs yielded median match rates below 10%, less than a third of those reported for the Czech registry. After merging the programs, which led to a median pool size of 18 pairs included per run, the average proportion of recipients identified for transplant was about 20%, which is still by far lower than that reported for larger multicenter programs. The suboptimal performance of our bi-national program is in line with earlier published simulations, such as one performed with real data in the UK [13]. These simulations demonstrated consistently low match rates for a pool size below 20, a marked increase between 20 and 50 pairs, and an average proportion of patients identified for transplant of 38% for a pool size of 50 pairs [13]. These data strongly encourage the establishment of a multi-national KPD registry to maximize match rates and KPD activity, for example, in the context of the European ENCKEP project [14]. As detailed in recent review of the current status of KPD in Europe, several near neighbor countries, such as Switzerland, Italy, Poland, or Slovakia are performing kidney exchanges or have implemented systematic national (and even international) KPD programs. As currently discussed within the ENCKEP project [14], increasing international cooperation between involved countries, including those who have not yet started their own program (e.g., Hungary), would help enlarge donor pools and maximize match rates.

A particularly low KPD match and transplant rate in Austria (only 13 transplants, as compared to 68 transplantations in the Czech KPD program) may relate to a smaller number of pairs included and, before 2015, a by far lower frequency of matching cycles (four runs over a period of 4 years). However, there may also be other influencing factors, such as center differences regarding inclusion of ABO- and/or HLA-incompatible combinations and differences regarding pool composition. In the Czech program, ABO-incompatible pairs were offered to join the KPD registry as a primary option, in an effort to improve transplant opportunities also for registered HLA sensitized recipients [23,24]. In the Austrian program, however, most ABO-incompatible recipients underwent transplantation following anti-blood group antibody removal with their directed donor, and therefore pools mainly consisted of sensitized difficult-to-match patients. The Austrian program may have had a benefit from merging the programs, which led to the inclusion of more ABO-incompatible pairs. At the same time, the overall number of KPD transplants in Prague decreased, apparently due to the inclusion of a higher proportion of sensitized recipients in combined match runs. In addition, blood group distributions – 43% of the KPD-listed recipients, but only 16% of their intended donors, had blood type O – may have contributed to a low match potential [25]. Interestingly, distributions of blood groups in registered incompatible combinations varied significantly between our two centers, with blood group O being more frequent in Vienna, both at a recipient and donor level.

During the study period, desensitization was not used as a primary option for LD transplant candidates with high DSA levels against their intended donors. This policy was based on the results of previous studies that have demonstrated inferior transplant survival rates, especially in patients with a high strength of preformed DSA [1,2]. Since its implementation, the Austrian KPD program was based on a strict virtual crossmatch-based algorithm precluding preformed DSA above a defined threshold (MFI 2000), and there was only one exception, a broadly sensitized elderly recipient who, in the context of a cross-border two-way exchange, was desensitized for a preformed low-level DSA and ABO incompatibility [18]. Before merging the programs, the Czech algorithm, however, allowed for KPD transplantation across DSA levels and/or positive B cell flow crossmatches that were judged to be associated with acceptable risks. This strategy was earlier shown to be an

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effective approach to facilitate transplantation in highly sensitized difficult-to-desensitize recipients [23,26]. Nevertheless, considerable rejection rates led to a policy change, and MFI thresholds for acceptable DSA were set at 1000 MFI for HLA class I and 2000 for HLA class II antibodies, with recipient desensitization preserved only for exceptional cases. In both programs, systematic desensitization programs in the context of DD transplantation was established, in Vienna based on a protocol of peri-transplant immunoadsorption [27]. This may have facilitated DD transplantation in a considerable proportion of sensitized KPD-listed patients (36% in Vienna) as a viable alternative option.

For our KPD transplants, favorable clinical outcomes were recorded, with 96% and 95% overall graft survival rates at 12 and 36 months, respectively. Notably, after 3 years we found a significant difference in kidney function between KPD transplants in Prague and Vienna. We are aware that a small sample size (only five recipients have completed their 3-year follow-up in the Austrian program) may impede the interpretation of data, but one may speculate that a higher proportion of male donors among KPD recipients in Vienna has partly contributed to the observed differences in kidney function [28].

One may argue that restricting chain length to 2- and 3-way exchanges in Austria may have contributed to a low match potential. The Prague algorithm allowed for multi-way chains (one loop included seven pairs), which was possible because simultaneous transplantation within KPD loops was not considered a prerequisite. Nonsimultaneous transplantations, however, embody a small risk of a donor deciding against donation, once the intended recipient had received his KPD transplant [29]. Earlier studies have suggested that increasing the length of closed loops may to some extent increase the number of matched pairs, even though the overall benefit of including multi-way exchanges may be rather small [30,31]. A major benefit, however, may come from the inclusion of NEAD chains [32], and recently, the success of an altruistic donor-triggered chain, which included exchanges between the United States and Canada, was reported [21]. In our joint program, two of our combined match runs yielded bridging-donor-linked segments of an altruistic donor-triggered chain, to our best knowledge, the first international NEAD chain reported in Europe.

Overall, four joint match cycles resulted in eight transplantations, all of them via cross-border kidney exchanges. In median, cold ischemia times were 5 h and 22 min, and there was no case of delayed graft function. This was in line with previous studies indicating that prolonged cold ischemia times through organ shipping do not impair allograft function in the short- and long-term [33–35].

In conclusion, our results suggest a benefit from merging KPD programs between small countries. However, in our small bi-national KPD scheme, the average pool size still remained below 20 pairs, which resulted in match rates below 20%. Our results are in strong support of extending our project to include other international partner units. Inclusion of ABO-incompatible donor/recipient pairs may thereby further enhance program success. Our preliminary experience of a bi-national KPD program may provide a useful basis for the set-up of multi-national trans-border exchanges as a viable opportunity to promote LD transplantation.

Authorship

OV, SK, F, and GAB: involved in the conception and design, as well as data collection, analysis, and interpretation. All authors helped with data collection and/or interpretation of results, and participated in drafting. All authors provided intellectual content of critical importance to the work described and approved the final version to be published.m

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Conflict of interest

The authors declare no financial conflict of interest in relation to the reported work. The results presented in this paper have not been published previously in whole or part, except in abstract format.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patients referred to KPD as primary option - Baseline characteristics and immunological data.

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