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CASE REPORT

Increasing access to kidney transplantation for sensitized recipient through three-way kidney paired donation with desensitization: The first Indian report

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Abstract

The combination of kidney paired donation (KPD) with desensitization represents a promising method of increasing the rate of living donor kidney transplantation (LDKT) in immunologically challenging patients. Patients who are difficult to match and desensitize due to strong donor specific antibody are may be transplanted by a combination of desensitization and KPD protocol with more immunologically favorable donor. We present our experience of combination of desensitization protocol with three-way KPD which contributed to successful LDKT in highly sensitized end stage renal disease patient. All recipients were discharged with normal and stable allograft function at 24 mo follow up. We believe that this is first report from India where three-way KPD

exchange was performed with the combination of KPD and desensitization. The combination of desensitization protocol with KPD improves access and outcomes of LDKT.

Key words: Kidney failure; Chronic; Desensitization; Immunologic; Kidney transplantation; Blood group incompatibility; Living donors; Tissue and organ procurement

Core tip: The combination of desensitization protocol with kidney paired donation (KPD) improves access and outcomes of living donor kidney transplantation, minimizing the limitation of either desensitization protocol or KPD alone. This is useful for sensitized patients who are both difficult to match and desensitize due to panel reactive antigens and strong donor specific antibody.

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INTRODUCTION

Living donor kidney transplantation (LDKT) is the optimal modality with the best long term outcome for end stage renal disease (ESRD) patients. There have been multiple efforts to expand the number of transplants for highly sensitized patients with living donors. Patients who are both difficult to match due to panel reactive antigens and difficult to desensitize due to strong donor specific antibody (DSA) are most likely to be transplanted by a combination of desensitization and kidney paired donation (KPD) with immunologically more suitable donor in KPD database[1-9]. The combination of KPD and desensitization avoids the high cost and complications of desensitization therapies alone for ABO-incompatible and HLA-incompatible-LDKT. We present our experience of combination of desensitization protocol with three-way KPD which contributed to successful LDKT in highly sensitized ESRD patient.

CASE REPORT

A 26-year-old man, diagnosed with ESRD due to chronic glomerulonephritis who was on regular hemodialysis since last 18 mo, presented to our transplant center for LDKT with his wife as potential healthy willing kidney donor.

Immunological tests [flow cytometry crossmatch (FCM), an anti-human, globulin-enhanced, complement-dependent cytotoxicity lymphocytotoxicity *cross matches* (*AHG-CDC*-LCM) and luminex DSA (LAB Screen, One Lambda, Inc, Canoga Park, CA, United States)], were performed in the recipients.

Table 1 gives demographic and HLA data of the 3 donor recipient pairs. Table 2 shows immunologic data in patient 1 and our cost of immune monitoring and desensitization therapy. Immunological tests were strongly positive: AHG-CDC 80% (acceptable < 20%) and T-cell FCM 212 (acceptable < 50%) median channel shift (MCS) and B-cell FCM 504 (acceptable < 100) MCS with 5 DSA above 5000 MFI. The patient was highly sensitized with his wife as kidney donor, and was therefore enrolled in our single center KPD registry. AHG-CDC, FCM and DSA were positive with all the potential KPD donors (more than 30) in our single center database. The patient was explained about the combination of desensitization protocol with KPD. Patent underwent desensitization with KPD donor 2 with best suitable immunological tests after written informed consent. Patients were consented and risks/benefits about possible failure of the desensitization protocol were explained.

In an attempt to undergo LDKT with his KPD donor he was started desensitization therapy[8] which consisted of four sessions of plasmapheresis (PP) + low-dose intravenous immunoglobulin (10 g/d) + bortezomib (1.3 mg/m$^{2)}$ and methyl prednisolone 125 mg on days 1, 4, 8, 11 He was also started with daily tacrolimus (0.05 mg/kg) and mycophenolate sodium 360 mg twice a day. AHG-CDC, FCM and DSA were performed before and after desensitization therapy.

The strength of DSA improved during the desensitization protocol. However, immunological profile remained unacceptable for KT with his wife even after desensitization protocol who had 6 DSA > 5000 MFI before desensitization (Table 2). DSA titer reduced marginally; however, AHG-CDC was unacceptable. The Immunological profile of patient 1 turned out acceptable for transplantation with KPD donor 2 after desensitization protocol who had only 2 DSA > 5000 MFI before desensitization (Table 2). Patients 2 and 3 had negative immunological tests with their intended KPD donors 3 and 1, respectively. The simultaneous three-way KPD transplantation was performed on same day (6th May 2014).

Induction immunosuppression in all the 3 recipients consisted of 2 mg/kg single dose rabbit-anti-thymocyte globulin (Sanofi Genzyme) with methylprednisolone 500 mg for 3 d. Maintenance immunosuppressive regimen consisted of prednisolone, tacrolimus, and mycophenolate. All the recipients had normal allograft function at time of hospital discharge and at 24 mo follow-up (Table 3). The patients were monitored by weekly DSA in the first month, and thereafter, monthly DSA, CMV DNA, and BKVDNA by polymerase chain reaction up to 6 mo. These were negative. All patients had stable allograft function without proteinuria at 24 mo post-transplant. Table 3 shows pre-transplantation, surgical

Table 1 Demographic and HLA data

	Age/gender	Blood group	Weight (kg)	HLA													
				A		B		Bw		Cw		DR B1		DRB3,4,5		DQ B1	
Patient 1	26/male	A+	37	3	32	40	-	6	-	3	15	4	10	53	-	5	8
Donor 1	25/female/wife	A+	65	3	24	40	58	4	6	3	12	17	11	52	-	2	7
Patient 2	51/male	B+	60	2	-	40	-	6	-	15	-	10	-	-	-	5	-
Donor 2	45/female/wife	A+		2	26	8	40	6	-	7	15	10	17	52	-	5	2
Patient 3	52/male	A+	52	2	3	44	56	4	6	4	7	7	14	52	53	2	5
Donor 3	45/female/wife	B+	70	2	31	40	55	6	-	1	15	13	15	51	52	6	-

Three-way KPD exchange: Patient 1, 2 and 3 received kidney from donor 2, 3, 1 respectively; KPD: Kidney paired donation.

Table 2 Immunologic data in patient 1 and our cost of immune monitoring and desensitization therapy

Patient 1	Before desensitization	After desensitization
With wife donor		
DSA (MFI)	A24-4924, B58-9767, DR11-13112, DR17-13598, DQ7-13194, DQ2-14751	A24-1000, B58-7055, DR11-4296, DR17-1925, DQ7-11838, DQ2-2410
AHG-CDC LCM (%)	80	20
T FCM (MCS)	212	Negative
B-FCM (MCS)	504	328
With KPD donor		
DSA (MFI)	B8, 6830: DR 17, 14751: DQ2, 13112	B8, 2400: DR 17, 1925: DQ2, 2410
AHG-CDC (%)	20	17
T-FCM (MCS)	88	Negative
B-FCM (MCS)	335	190
The cost of immune monitoring and desensitization therapy (USD)		
AHG-CDC LCM		20
T and B FCM		100
DSA (Luminexx, qualitative)		40
DSA (Luminexx, quantitative)		425
HLA (class 1 and 2)		200
Plasmapheresis		300
Bortezomib (Baximib, Ranbaxy) 2 mg		60
IVIg (Plasmaglob, Plasmagen) 5 gm		125
Rabbit anti-human thymocyte immunoglobulin (Thymoglobulin, Genzyme-Sanofi) 25 mg		200
Valganciclovir (Cymgal, Biocon) 450 mg		3
Methyl prednisolone (Solumedrol, Pfizer) 125 mg		4

DSA: Donor specific antibody; AHG-CDC-LCM: An anti-human, globulin-enhanced, complement-dependent cytotoxicity lymphocytotoxicity cross matches; FCM: Flow cross match; MCS: Median channel shift; MFI: Mean fluorescent intensity; KPD: Kidney paired donation.

data and outcome in three-way exchange.

DISCUSSION

ABO blood-type and HLA tissue incompatibility can be barriers to a successful LDKT. The reasons for rejecting healthy willing living kidney donor are ABO blood group incompatibility (35%) and sensitization (30%). Deceased donor KT in India is in initial stages and difficult to expand immediately despite various measures. Healthcare reimbursement is available only for few patients. The majority of the poor patients take medical treatment in Government hospitals with highly subsidized care[10].

Approximate Cost of LDKT in non-sensitized EDRD patient is USD 5000 in our hospital. The cost of immune monitoring and desensitization therapy is shown in Table 2. All children < 18 years, all patients below poverty line and farmers get free treatment in our hospital. Table 2 showed the cost of immune monitoring and desensitization therapy in our center.

In case of sensitized patient, we can match DSA of patient with HLA reports of patients and intended donor and if no DSA then we can proceed for actual LCM and FCM. In other way if HLA reports are not available then we can do only LCM if it is acceptable then FCM and if FCM is also acceptable then DSA and HLA testing. In our case, we initiated with KPD due to high DSA, cost and risks of desensitization. KPD is more benefited in easy to match pair like non-O patient and difficult to desensitize pair like high immunologic risk, high titer DSA. Desensitization is more beneficial in difficult to match pair (AB donor, highly sensitize) or easy to desensitize pair (low immunologic risk, low titer DSA). PRA indicate ability to match and DSA indicate ability to desensitize. The patients with high PRA and high DSA are less likely to be transplanted by single form of therapy with either desensitization or KPD and therefore require the combination of desensitization with immunologically more suitable donor in KPD database[1].

Table 3 Pre-transplantation and surgical data and outcome

	Patient 1	Patient 2	Patient 3
Cause of ESRD	Chronic glomerulonephritis	Hypertension	Hypertension
Dialysis duration (mo)	24	6	6
KPD waiting time (mo)	6	2	2
Warm ischemia time (s)	120	157	180
Cold ischemia time (min)	90	67	30
Anastomosis time (min)	22	23	25
Intra-operative urine output (mL)	800	1500	700
Laparoscopic donor nephrectomy	Yes	Yes	Yes
Rejection/ complications	No	No	No
Creatinine at discharge (mg/dL)	1	0.9	0.8
Creatinine at 24 mo (mg/dL)	1.4	0.8	0.8

ESRD: End stage renal disease; KPD: Kidney paired donation.

The outcome from desensitization is good with low starting DSA. ABO-incompatible paired kidney exchange for failed desensitization is the new strategy for highly sensitized patients. This strategy is more useful when anti blood group antibody titers are low[9]. For highly sensitized patients with a high-strength DSA, KPD can facilitate a safer, less expensive and more successful transplantation[10-12]. In most cases KPD can provide the best transplant solution for a patient with an incompatible donor, however not all phenotypes will benefit from KPD.

In our center, our protocol for sensitized patients in LDKT[12] is as follows: (1) KPD transplantation should be considered as first choice; (2) AHG-CDC negative with total T and or B cell FCM < 300 MCS and DSA < 5000 MFI receive KT with thymoglobulin and intravenous Immunoglobulin without PP with high risk consent; (3) AHG-CDC negative with total T and B cell FCM > 300 MCS and/or DSA > 5000 MFI receive pre-transplant desensitization; and (4) AHG-CDC positive patients should be considered for desensitization if they have < 3 DSA and only one DSA > 5000 MFI.

The matching success of sensitized patient in hybrid modality increases with the size of donor pool. Therefore, large national or even international registries may be needed to increase success rate and outcome[7]. Many centers accept the presence of low-strength DSA in LDKT for highly sensitized patients undergoing desensitization[11]. The impact of low-strength DSA on allograft outcome is not clear[11-15]. In our center the DSA < 3000 MFI is acceptable before LDKT. The participation of compatible pairs in KPD can increase LDKT for highly sensitized patients. The compatible pairs can get better HLA matched donor or younger donor without delay in transplant surgery for 3-6 mo[8,13,16].

Five highly sensitized patients successfully received KT after desensitization in combination with KPD[14]. They reported that early registration in KPD, use of combination of KPD with desensitization protocols, and accepting low-strength DSA can expand the LDKT options in highly sensitized patients. Finally, the creation of a novel "Global kidney Exchange Program" may increase the opportunity of LDKT for sensitized and O group patients. This could be an important step in achieving reduced costs, increases access and improved quality of match[17].

The combination of desensitization protocol with KPD improves access and outcomes of LDKT in highly sensitized ESRD patients, minimizing the limitation of single form of therapy alone. We believe that this is the first report from India where three-way KPD exchange is performed with the combination of KPD with desensitization.

COMMENTS

Case characteristics

End stage renal disease (ESRD) patients who are difficult to match and desensitize due to strong donor specific antibody (DSA) may be transplanted by a combination of desensitization protocol and kidney paired donation (KPD).

Clinical diagnosis

The authors report their experience of highly sensitized patients who underwent desensitization in combination with three-way KPD and successfully received living donor kidney transplantation (LDKT).

Differential diagnosis

Highly sensitized ESRD patients can underwent LDKT with desensitization protocol or KPD or combination of both.

Laboratory diagnosis

Lymphocytotoxicity cross matches, flow cytometry crossmatch and DSA are useful in immunological evaluation of highly sensitized ESRD patients.

Treatment

Plasmapheresis, bortezomib and immunoglobulin are useful in desensitization therapy.

Related reports

All patients had stable kidney allograft function without proteinuria at 24 mo post-transplant.

Term explanation

KPD: Kidney paired donation; LDKT: Living donor kidney transplantation; DSA: Donor specific antibody.

Experiences and lessons

The authors believe that this is the first report from India where three-way KPD exchange is performed with the combination of KPD with desensitization.

Peer-review

The paper of Kute *et al* shows an clinical case which offers interesting points of discussion about the combination of kidney patient donation with desensitization. The paper is well written.

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