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The Effect of Panel Reactive Antibody Results on Graft Functions of Patients with Chronic Kidney Failure

Panel Reaktif Antikor Sonuçlarının Kronik Böbrek Yetmezliği Olan Hastaların Greft Fonksiyonu Üzerindeki Etkisi

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ABSTRACT

Objectives: This study aims to evaluate panel reactive antibody (PRA) results of patients with chronic kidney failure (CKF) and to obtain information about pre-transplantation PRA results and graft function of transplanted patients.

Patients and methods: We evaluated PRA results of 2,517 patients (1,428 males, 1,089 females; mean age 49.9±14.7; range 2 to 82 years) with CKF on the waiting list and 304 transplanted patients (178 males, 126 females; mean age 41.1±11.4; range 9 to 71 years). Of the PRA tests, 85% and 15% were performed by Luminex and flow cytometric methods, respectively. The final post-transplantation serum creatinine levels and transplantation ages of the patients were recorded. We also assessed glomerular filtration ratio (GFR) for graft functions of transplanted patients.

Results: Of the PRA positive patients (40.52%) on the waiting list, 12.55% were class I PRA positive (group 1), 8.78% were class II PRA positive (group 2), and 19.19% were both class I and II PRA positive (group 3). Of the patients, 59.48% were PRA negative (group 4). Pre-transplantation negative PRA results (group 4) were significantly higher among patients who were transplanted from related donor (78.09%) than patients with cadaveric transplantation (48.88%) and patients on the waiting list (59.48%) ($p<0.05$). Glomerular filtration ratios (GFRs) were higher among patients who were transplanted from related donor for all PRA groups. Of transplanted patients, although GFR values of the patients who had acute rejection episode (ARE) were higher than those without ARE, there was no statistically significant difference in between.

Conclusion: Regularized pre-transplantation PRA tests and cautious evaluation of their results constitute great importance to prevent ARE and increase graft survival in Turkey, which is a country with already low organ donation ratios.

Keywords: Chronic kidney failure; graft function; panel reactive antibody.

ÖZ

Amaç: Bu çalışmanın amacı kronik böbrek yetmezliği (KBY) olan hastaların panel reaktif antikor (PRA) sonuçlarının değerlendirilmesi ve nakil öncesi PRA sonuçları ile nakil yapılan hastaların greft fonksiyonu hakkında bilgi edinildi.

Hastalar ve yöntemler: Bekleme listesindeki KBY olan 2.517 hastanın (1.428 erkek, 1.089 kadın; ort. yaş 49.9±14.7 yıl; dağılım 2-82 yıl) ve nakil yapılan 304 hastanın (178 erkek, 126 kadın; ort. yaş 41.1±11.4 yıl; dağılım 9-71 yıl) PRA sonuçları değerlendirildi. Panel reaktif antikor testlerinin %85 ve %15'i sırasıyla Luminex ve akım sitometri yöntemleriyle yapıldı. Hastaların nakil sonrası son serum kreatinin düzeyleri ve nakil yaşları kaydedildi. Ayrıca, nakil olan hastaların greft fonksiyonları için glomerüler filtrasyon hızı (GFH) incelendi.

Bulgular: Bekleme listesindeki PRA pozitif hastaların (%40.52) %12.55'i sınıf I PRA pozitif (grup 1), %8.78'i sınıf II PRA pozitif (grup 2) ve %19.19'u hem sınıf I hem sınıf II PRA pozitif (grup 3) idi. Hastaların %59.48'i PRA negatif (grup 4) idi. Nakil öncesi negatif PRA sonuçları (grup 4) canlı vericiden nakil yapılan hastalarda (%78.09) kadavradan nakil yapılan (%48.88) ve bekleme listesinde olan hastalardan (%59.48) anlamlı şekilde daha yüksekti ($p<0.05$). Glomerüler filtrasyon hızları tüm PRA grupları için canlı vericiden nakil olan hastalarda daha yüksekti. Nakil yapılan hastalarda akut rejeksiyon atağı (ARA) olanların GFR değerleri ARA'sı olmayanlardan daha yüksek olsa da aralarında istatistiksel olarak anlamlı farklılık yoktu.

Sonuç: Halihazırda organ bağışı oranlarının düşük olduğu bir ülke olan Türkiye'de ARE'yi önlemek ve greft sağkalımını artırmak için düzenli uygulanan nakil öncesi PRA testleri ve bunların sonuçlarının dikkatle değerlendirilmesi büyük önem taşımaktadır.

Anahtar sözcükler: Kronik böbrek yetmezliği; greft fonksiyonu; panel reaktif antikor.

Renal transplantation has by now become an option for treating a significant proportion of patients with terminal chronic renal disease. Early sensitization due to blood transfusion, pregnancy or organ transplantation may lead to sustained production of non-self anti-human leukocyte antigen (HLA) antibodies.[1,2] The significance of HLA antigen-specific antibodies (panel reactive antibodies; PRA) in kidney transplantation has been recognized for decades.[3-6]

The number of patients with high PRA on the waiting list increases due to the limited number of compatible donors, and this is of increasing concern for many transplant centers.[7] In order to increase the transplantation chance of hypersensitive patients, there are various approaches containing intravenous immunoglobulin, plasmapheresis, acceptable mismatch tests, HLA matchmaker program, and tests with single antigen beads.[8]

Glomerular filtration rate (GFR) is the most useful indicator of renal function; although age, sex, and ethnicity may also affect its value. The National Kidney Foundation recommends estimating GFR using creatinine-based equations such as the Modification of Diet in Renal Disease (MDRD) study equation.[9,10]

In this study, we aimed to evaluate the PRA results of patients with chronic kidney failure (CKF) and to obtain information about pre-transplantation PRA results and graft function of transplanted patients.

PATIENTS AND METHODS

The study included 2,517 patients (1,428 males, 1,089 females; mean age 49.9±14.7; range 2 to 82 years) on the waiting list with CKF who were tested for PRA by our Tissue Typing Laboratory in Tepecik Teaching and Research Hospital (TRH) between January 2008 and June 2014. In addition, we also evaluated the association between pre-transplantation PRA results and GFRs of 304 transplanted patients (178 males, 126 females; mean age 41.1±11.4; range 9 to 71 years). Our laboratory provides immunological support to related-donor and cadaveric transplantations at three teaching and research hospitals, plus other hospitals in Aegean region of Turkey. The final post-transplantation serum creatinine levels and transplantation ages of the patients were recorded. Glomerular filtration rates of transplanted patients were calculated using MDRD formula using their last creatinine. The patients with CKF on the waiting list are tested for PRA regularly at least twice a year. The PRA results used in this study were the highest PRA levels reported in the hospital records. Of the PRA tests, 85% and 15% were performed by Luminex and flow cytometric methods, respectively. All patients (both those on the waiting list and transplanted patients) were divided into four groups according to their sensitizations: class I PRA positive patients as group 1, class II PRA positive patients as group 2, class I and II PRA positive patients as group 3, and PRA negative patients as group 4. The study was approved by the Committee on Medical Ethics of the Tepecik Teaching and Research Hospital. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

The Lifecodes LifeScreen Deluxe Kit (Immucor Gamma, USA) was used during the Luminex PRA test. After the PRA plate was moisturized, 40 µL wash buffer, 12.5 µL patient/control sera and 5 µL HLA class I/II beads were added to the wells. The plate was incubated at room temperature for 30 minutes in the dark, and after this incubation the wells were washed three times with buffer. Next, conjugate was prepared in the appropriate concentration and added to the wells. After incubation at room temperature for 30 minutes in the dark, 150 µL wash buffer was also added. Finally, the plate was gently mixed and analyzed by the Quick-Type program in Luminex/Life-Match instrument. >1000 mean fluorescent index (MFI) values were accepted as positive.

Flow PRA test was performed using the FlowPRA Detection Kit (MDSS GmbH, Hannover, Germany). Five micro liter class I and II beads were added to the patient and control tubes and 20 µL sera were added to the beads. The tubes were gently mixed and incubated at room temperature for 30 minutes. After incubation, the samples were washed with 1X Wash Buffer (Gibco, Paisley, UK) twice and a second antibody was added to the tubes, which were then gently mixed and incubated at room temperature for 30 minutes in the dark. After incubation, the samples were washed with 1X Wash Buffer (Gibco, Paisley, UK) twice, and then analyzed by FACSCalibur Flow Cytometer (Becton, Dickinson, and Company, NJ, USA). When compared to negative control, fluorescent values >3% were accepted as positive.

Statistical analysis

Panel reactive antibody-positive rates between the groups were compared using the Student's t test. In a one-way analysis of variance, multiple mean value comparisons using Tukey's multiple comparison tests were performed. Descriptive and frequency analyses were performed by using an IBM SPSS version 20.0 software for Windows (IBM Corporation, Armonk, NY., USA). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

Of the PRA positive patients (40.52%, n=1020) on the waiting list, 12.55% were class I PRA positive (group 1, n=316), 8.78% were class II PRA positive (group 2, n=221),

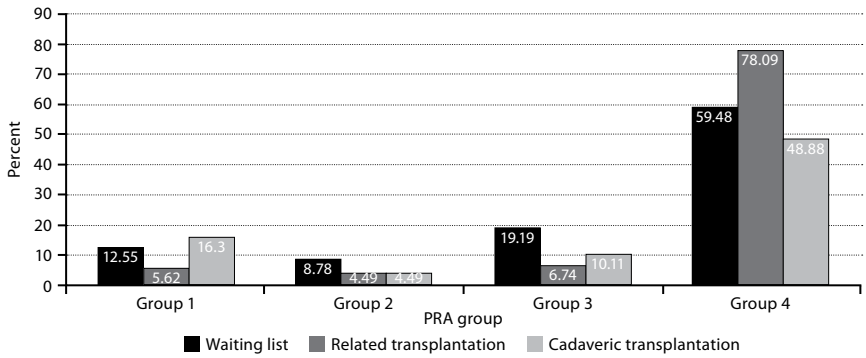

Figure 1. Ratios of panel reactive antibody groups. PRA: Panel reactive antibodies.

and 19.19% were both class I and II PRA positive (group 3, n=483); while 59.48% of the patients were PRA negative (group 4, n=1497) (Figure 1). A total of 169 patients had related-donor, while 135 patients had cadaveric kidney transplantation (Table 1).

An assessment of the pre-transplantation PRA results of the transplanted patients revealed that 5.62% (n=10) of the patients with related-donor kidney transplantation were in group 1, 4.49% (n=8) were in group 2, 6.74% (n=12) were in group 3, and 78.09% (n=139) were in group 4 (Figure 1). Of patients with cadaveric kidney transplantation, 16.30% (n=22) were in group 1, 4.49% (n=8) were in group 2, 10.11% (n=18) were in group 3, and 48.88% (n=87) were in group 4 (Figure 1).

Pre-transplantation negative PRA ratio (78.09%) (group 4) was significantly higher among patients with related-donor transplantation than patients with cadaveric transplantation and patients on the waiting list ($p<0.05$). The ratios of patients with related-donor transplantation in group 1 and 3 were 5.62% and 6.74%, respectively. These values were significantly lower than patients on the waiting list and those with cadaveric transplantation ($p<0.05$).

The patients with positive PRA (group 1, 2, and 3) were divided into three groups according to their PRA ratios (<10%, 10-85%, and >85%) as shown in Tables 2 and 3.

Mean GFRs of transplanted patients according to PRA groups are given in Table 4. Mean GFRs were higher in patients with related-donor transplantation; however, the results were not statistically significant ($p>0.05$).

Of the patients, 19.40% had acute rejection episodes (AREs). Mean GFRs according to ARE and PRA groups are shown in Table 5.

DISCUSSION

The transplantation probability of a patient with CDF in terms of immunology is referred to as the 'transplantability index'. Briefly, this term explains the probability of getting one negative result from the patient with 80% positive PRA who has been crossmatched with

TABLE 1

Demographic features of patients according to transplantation type

	Cadaveric transplantation		Related transplantation		
	%	Mean±SD	%	Mean±SD	*p*
Recipient sex					NS*
Male	57.2		59.6		
Female	42.8		40.4		
Recipients age		42.3±11.1		38.4±11.7	<0.05
Donor sex					<0.05
Male	73.8		44.3		
Female	26.2		55.7		
Donor age		39.1±17.8		50.0±13.9	
Acute rejection episode	23.5		20.0		
Alloimmunization	52.0		57.6		NS
Dialyze time (month)		79.8±57.3		24.5±34.0	<0.05
Followed up post-tx period (month)		35.8±23.3		36.2±24.1	NS

SD: Standard deviation; * NS: Not significant; Post-tx: Post-transplantation.

TABLE 2

Evaluation of panel reactive antibody results of groups 1 and 2 according to their panel reactive antibody ratios

	Group 1								Group 2							
	<10		10-85		>85		*Total*		<10		10-85		>85		*Total*	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Waiting list	54	17.1	211	66.8	51	16.1	316	100.0	33	14.9	160	72.4	28	12.7	221	100.0
Related transplantation	1	10.0	8	80.0	1	10.0	10	100.0	0	0	6	75.0	2	25.0	8	100.0
Cadaveric transplantation	2	9.1	17	77.3	3	13.6	22	100.0	0	0	5	62.5	3	27.5	8	100.0

five different donors.[11] In other words, the crossmatch results are estimated according to PRA results.[12]

One in every three of the patients in United Network for Organ Sharing (UNOS) waiting list is sensitive to HLAs. Our study demonstrated that 40.52% of the patients were sensitive to HLAs. We considered that our results, which are higher than UNOS data, might be due to excessive levels of pregnancy and blood transfusion in our country.

In this study, we evaluated the relationship between transplanted patients and their pre-transplantation PRA results. Pre-transplantation negative PRA ratio in related-donor transplantation group was significantly higher than the waiting list patients and the cadaveric transplantation group. The PRA positivity in group 1 and 3 was significantly lower in the related-donor transplantation group than the other patients. Furthermore, the waiting duration for transplantation of the patients with related-donor transplantation was shorter than the patients with cadaveric transplantation. Thus, the sensitization probability of the latter patients increased. Patients who applied to our laboratory for related-donor transplantation may be registered on the waiting list mandatorily because of a positive crossmatch. However, this does not mean that each of the PRA positive patients has an equal chance for transplantation. Having a full-match sibling increases the transplantation chance of patients in related-donor transplantations. In cadaveric transplantations, patients with a frequent HLA haplotype have a higher chance for transplantation than those patients with rare haplotypes. When we compared the PRA ratios of PRA positive patients on the waiting list and transplanted patients, we observed that the numbers of patients on the waiting list and transplanted patients were high in the PRA range of 10% to 85% (group 1, 2, and 3). We considered that this may be due to the wide range of PRA ratios that we selected for dividing the patients into groups.

A criterion for CKF diagnostic thresholds for GFR is less than 60 mL/minute per 1.73 m^2.[13] Graft functions of transplanted patients were evaluated according to their last GFR. The lower level of GFR values among patients who were transplanted from a deceased donor may be explained by a longer cold ischemia time and lower patient-donor compatibility than transplantations from a related-donor, respectively. Related-donor renal transplantation has more successful outcomes than deceased-donor transplantation and this has been reported on a number of occasions in the literature,

TABLE 3

Evaluation of panel reactive antibody results of group 3 according to their panel reactive antibody ratios

Class I	Class II	Waiting list		Related tx		Cadaveric tx		Class II	Class I	Waiting list		Related tx		Cadaveric tx	
%	%	(n=483)	%	(n=12)	%	(n=18)	%	%	%	(n=483)	%	(n=12)	%	(n=18)	%
	<10	11	2.3	1	8.3	0	0.0		<10	11	2.3	1	8.3	0	0.0
<10	10-85	20	4.1	–	0.0	1	5.6	<10	10-85	18	3.7	1	8.3	2	11.1
	>85	6	1.2	–	0.0	–	0.0		>85	6	1.2	–	0.0	–	0.0
Total	37		1		1			Total	35		2		2		
	<10	18	3.7	1	8.3	2	11.1		<10	20	4.1	–	0.0	1	5.6
10-85	10-85	186	38.5	7	58.3	11	61.1	10-85	10-85	186	38.5	7	58.3	11	61.1
	>85	44	9.1	2	16.7	–	0.0		>85	115	23.8	1	8.3	2	11.1
Total	248		10		13			Total	321		8		14		
	<10	6	1.2	–	0.0	–	0.0		<10	6	1.2	–	0.0	–	0.0
>85	10-85	115	23.8	1	8.3	2	11.1	>85	10-85	44	9.1	2	16.7	–	0.0
	>85	77	15.9	–	0.0	2	11.1		–	77	15.9	0	0.0	2	11.1
Total		198		1		4			Total	127		2		2	

Tx: Transplantation.

TABLE 4

The analysis of graft functions by glomerular filtration rate according to panel reactive antibody groups

	Group 1	Group 2	Group 3	Group 4
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
GFR* (mL/min/1.73 m^2)				
Cadaveric transplantation	51.6±30.2	53.1±35.6	50.3±22.1	56.7±27.2
Related transplantation	67.6±14.2	58.3±33.1	49.9±24.8	64.5±18.2

SD: Standard deviation; * GFR: Glomerular filtration ratio by modification of diet in renal disease= 175 * (Serum creatinine mg/dL)-1.154 * (age)-0.203 * (0.742 if female) * (1.210 if African American).

TABLE 5

Mean glomerular filtration rates (mL/minute/1.73m^2) according to rejection episode and panel reactive antibody groups

Acute rejection episode	Group 1		Group 2		Group 3		Group 4		*Total*	
	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD	n	Mean±SD
Negative	24	61.6±23.3	14	66.0±31.3	29	53.1±21.3	178	60.6±25.1	245	60.3±24.9
Positive	8	47.0±32.7	4	22.2±9.6	10	43.8±26.6	37	53.6±24.0	59	47.8±26.3
p		>0.05		<0.05		>0.05		>0.05		<0.05

SD: Standard deviation.

especially in studies with large sample sizes. In a recent study, Opelz et al.[14] concluded that the longest kidney graft survival occurred with identical twins, followed by kidney grafts from haplo-identical living donors. The worst survival rate was observed with deceased donors used for renal transplantation.

An individual assessment of the results revealed that although there was no statistically significant relationship, the highest GFR was observed in group 4 among post-transplantation final GFR values. When we compared GFR values of patients who were performed related-donor transplantation, we detected that GFR values were higher in group 1 than group 4 (Table 4). We considered that the smaller number and lower ages of patients in group 1 may have affected the high results of GFR.

Glomerular filtration rate is usually accepted as the most useful indicator of kidney function. A number of previous studies have investigated the effect of ageing on GFR among healthy individuals and found that GFR decreased with advancing age.[15,16] In Table 5, GFR results of PRA groups were compared according to AREs among all transplanted patients. It was found that GFRs of patients without ARE were higher than patients with ARE in all groups. However, the difference was statistically significant in only group 2 ($p<0.05$). When all of the patients were evaluated according to their ARE (without PRA groups), the mean GFR was lower in patients with ARE than that of patients without ARE ($p<0.05$). A number of studies have assessed the prevalence of PRA and the clinical significance of these antibodies in acute allograft rejection.[17,18] It has been reported that post-transplantation ARE is also a risk factor for the development of chronic rejection.[5,19]

In conclusion, ARE is one of the most important factors affecting graft survival and is affected by a number of factors such as HLA mismatches, immunosuppression, infection, donor and patient ages, and donor resource. Regularized pre-transplantation PRA tests and cautious evaluation of their results constitute great importance to prevent ARE and increase graft survival in Turkey, which is a country with already low organ donation ratios.

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