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MONOCENTRIC ANALYSE

Imunological aspects of kidney retransplantation

Igor GALA[1], Tatiana BALTESOVA[1], Stefan HULIK[2], Rastislav KALANIN[2], David ADANDEDJAN[2], Jana KATUCHOVA[2], Luboslav BENA[1], Jan BREZA Jr[3]

1st Department of Surgery, L. Pasteur University Hospital, Kosice, Slovakia.
rastislav.kalanin@upjs.sk

ABSTRACT
The number of patients on the waiting list for a kidney retransplant has increased. Patients who are candidates for a second kidney transplant often have higher levels of PRA (Panel of Reactive Antibodies). The previous failed kidney transplant is one of the main factors that leads to the production of antibodies against human leukocyte antigens – HLA. The consequences of sensitisation are a long waiting time for repeated kidney transplantation and a negative effect on graft survival after retransplantation.
The aim of our analysis was to evaluate the immunological parameters of patients undergoing renal retransplantation at the Kosice Transplant Centre, their influence on graft function, the occurrence of rejection episodes and to analyse the sensitisation status of recipients on the waiting list for renal retransplantation at the Kosice Transplant Centre.
We retrospectively analysed 46 adult patients who underwent secondary renal transplantation. In the group of retransplanted patients, we found a higher immunological risk and PRA values ($p<0.001$) and a higher need for induction therapy to reduce the lymphocyte count ($p<0.001$). Retransplant patients with DGF were 48% more likely to experience acute rejection.
In the context of the published literature, we have observed increased sensitisation in retransplanted patients, which is a major challenge to overcome the immunological barrier in transplantation medicine *(Tab. 4, Fig. 1, Ref. 24)*. Text in PDF www.elis.sk
KEY WORDS: retransplantation, sensitisation, panel of reactive antibodies.

Introduction

Kidney transplantation is currently the „gold standard" treatment for end-stage chronic kidney disease (CKD), significantly improving patient survival and quality of life compared to dialysis. Kidney retransplantation has become the standard therapy for patients who have previously undergone kidney transplantation after a previous transplanted kidney has failed. The success rate of retransplantation is comparable to that of primary transplantation, although there is a higher risk of non-immunological and immunological complications (1). Long-term graft survival is still limited and, despite a wide range of immunosuppressive drugs, the average graft survival is around 10 years. These patients need a new transplant after the previous one has failed (2). In the Eurotransplant region, retransplants account for approximately 14% of all deceased donor kidney transplants (3).

Factors that influence the outcome of retransplantation include:

- Outcome of first transplantation (longer survival of first graft and higher glomerular filtration rate correlate with better survival of subsequent retransplantation) (3),
- Waiting time for retransplantation (longer time on dialysis has a negative impact on retransplantation outcomes) (4),
- Delayed onset of graft function (DGF – Delayed Graft Function, defined as the need for supportive dialysis in the first 7 days after retransplantation),
- Recurrence of underlying disease or de novo glomerulonephritis,
- Chronic graft injury due to immunological and non-immunological factors (5) ,
- Immunological factors (number of HLA mismatches and PRA – panel-reactive antibody level, hyperimmunisation of recipients) (6),
- Increase in morbidity associated with chronic kidney disease (7),
- Expanded Criteria Donor – ECD (worse graft survival outcomes are experienced by ECD donors compared to non-ECD donors) (8).

The primary goal of retransplantation in hyperimmunised candidates is to find a donor with the fewest HLA mismatches. While hyperacute rejection is rare in a desensitised individual, the rate of acute humoral rejection is higher (9). Retransplanted patients are at a high risk of acute rejection. This risk ranges from 33–69%, according to the literature. Acute antibody-mediated rejections (ABMR) account for approximately 2/3 of all rejections

[1]Department of Transplantation, L. Pasteur University Hospital, Kosice, Slovakia, [2]1st Department of Surgery, L. Pasteur University Hospital and Faculty of Medicine at Univerisity of Pavol Jozef Šafarik, Kosice, Slovakia, and [3]Department of Pediatric Urology, Faculty of Medicine, Comenius University and National Institute of Children's Diseases, Bratislava, Slovakia

Address for correspondence: Rastislav Kalanin, MD, PhD, MBA,1st Department of Surgery, L. Pasteur University Hospital, Trieda SNP 1, SK-040 01 Kosice, Slovakia.

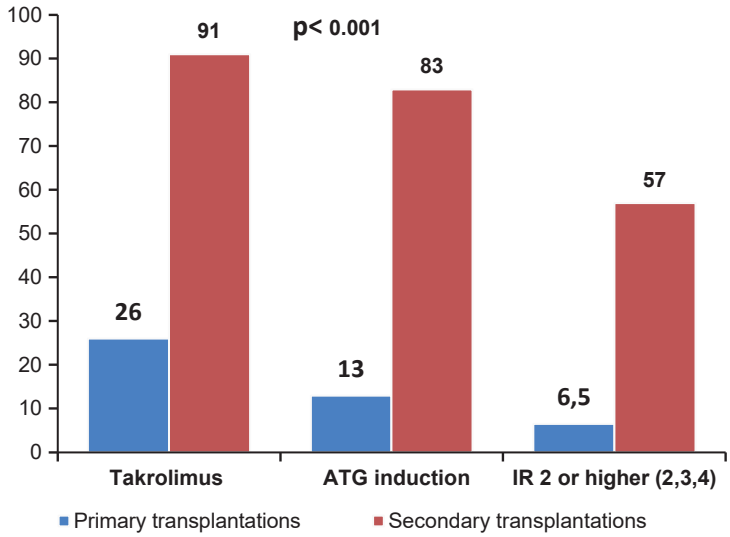

Fig. 1. Selected clinical and immunological parameters.

and are the primary cause of graft loss in the early post-transplant period. T-cell mediated rejection (TCMR) may also cause graft damage, but to a lesser extent. To prevent acute ABMR after renal retransplantation, it is important to strictly select donors based on immunological factors. Additionally, pre-transplantation desensitization therapy and induction immunosuppressive therapy should be administered using either depleting or non-depleting antibodies (2).

Hyperimmunization or sensitization can occur due to exposure to HLA antigens during pregnancy, after receiving erythrocyte transfusions, or after previous transplantations (10).

In addition to the above characteristics, the transplantation expert group (COMMIT group) has identified additional risk factors for patients with a ‚higher immunological risk' status. These include:

- Sensitization from previous blood transfusions, pregnancies and transplants,
- HLA mismatch (partially complete mismatch at the DR locus),
- PRA >0%,
- Presence of preformed DSAs,
- Younger age at the time of retransplantation,
- Adolescents have a higher risk of nonadherence in the use of immunosuppression,
- Black race,
- Previous graft loss due to immunologic causes (11).

Patients and methods

Patient data were collected from the Transplant Registry of the Košice Transplant Centre. By 30.8.2019, 1134 kidney transplants had been performed. So far, we have performed (n=79, i.e. 7%) retransplantations at the Košice Transplant Centre, most of which were secondary retransplantations (n=67, i.e. 6%). We included 46 adult patients who underwent secondary kidney retransplantation at the L. Pasteur University Hospital in Košice between November 1988 and August 2019 and who fulfilled the inclusion criteria. Inclusion criterion was successful secondary retransplantation in an adult at our transplant centre. Exclusion criteria were: non-functioning graft after retransplantation, paediatric population (age under 18 years), primary transplantation in another transplant centre and death of the patient. The clinical characteristics of the cohort are shown in Table 1. The representation of males and females was approximately equal (54% vs 46%). The majority of patients were on tacrolimus (91%). The polyclonal depleting antibody antithymocyte globulin was used for induction in 83% of patients, the monoclonal antibody rituximab was administered in the remaining patients due to high immunological risk and the presence of DSA, and in one patient the protocol was extended by the addition of plasmapheresis. The study design was retrospective.

The following variables were used for analysis: sex, PRA act %, PRA max %, Δ PRA, immunological risk, compatibility index, ATG (antithymocyte globulin) induction, graft function (DGF, SGF, IGF), presence of rejection, creatinine at hospital discharge, incidence of acute rejection, donor age and donor type. Delayed graft function (DGF) was defined as the use of dialysis in the first week after transplantation. All episodes of acute rejection were confirmed by biopsy.

All patients underwent retransplantation with a negative pre-transplant cytotoxic T and B cross-match. Initial clinical and laboratory assessments were performed on the day of admission. Anti-lymphocyte antibody (ALPA) testing, i.e. the „sensitisation rate" expressed as a percentage of the PRA, was performed in each waiting list patient prior to retransplantation using lymphocytes from peripheral venous blood.

Statistical analysis

Data are expressed as mean and standard deviation or median (25th and 75th percentiles) for continuous variables and as number (percentage) for categorical variables.

We used the chi-squared test or Fisher's exact test to compare the frequencies of categorical variables between groups. We tested predictors of acute graft rejection in a multivariate logistic model. To compare continuous variables between groups, we used parametric and non-parametric tests, both paired tests when comparing first and second kidney transplantation in identical recipients (paired Student's t-test, Wilcoxon test) and unpaired tests when comparing groups according to the incidence of acute rejection, immunological sensitisation, etc. (Student's t-test, Mann–Whitney test). The level of statistical significance was set at 0.05. SPSS Statistics 17.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Hyperimmunised individuals have an increased risk of graft loss due to rejection and subsequent graft failure. In our study, we analysed immunological aspects in secondary retransplanted patients and compared them with primary transplant recipients,

which was the primary objective. Men and women were equally represented in both groups. In the retransplanted group, Tacrolimus (n=42; 91%) was predominantly used as maintenance immunosuppression according to international recommendations, whereas in the primary transplant group, Cyclosporine (n=34; 74%; p<0.001) was used. The depleting polyclonal antibody ATG was used significantly more often in the secondary transplant group than in the other group (83% vs 13%; p<0.001). Analysing immunological variables, we identified higher sensitisation rates in retransplant recipients according to the degree of immunological risk (i.e. anti-lymphocyte antibody levels) as well as the median current and historical PRA. Both immunological units were statistically significantly higher in this group compared to the control group (p<0.001). The rate of HLA mismatch (ABDR mismatch) was similar in both groups. We also observed no significant difference in the incidence of acute rejection, although the incidence of acute rejection was numerically higher in sensitised retransplanted patients. Among the non-immunological parameters, we assessed graft function by creatinine levels at hospital discharge, and both serum creatinine (p=0.003) and median creatinine (p=0.012) were statistically lower in the retransplanted group. The cause of the lower creatinine may be multifactorial, such as the use of tacrolimus in maintenance immunosuppression, ATG induction, lower incidence of DGF and others. The incidence of delayed graft function was lower in the secondary transplant group. Individual clinical and immunological characteristics are shown in Table 2.

We used parametric testing to analyse risk factors for acute rejection in a group of secondary retransplant recipients. 45% of patients had acute biopsy-proven rejection. Retransplanted patients with acute rejection had numerically higher Δ PRA, number of HLA mismatches and immunological risk according to ALPL values. The acute rejection group had a higher incidence of DGF compared to the control group (52% vs 24%; p=0.047).

In a univariate logistic regression model where the dependent variable was acute rejection (AR) of the retransplanted kidney, we observed that DGF (OR 3.48; 95% CI 0.99–12.22; p=0.049) was a risk factor for acute rejection in this immunologically high-risk group of patients.

Tab. 1. Initial clinical and immunological characteristics of the patient population.

Initial clinical and immunological characteristics of the patient population	
	Secondary transplantation
Number of patients (n)	46
women n, (%)	21 (46 %)
Cyclosporine n, (%)	4 (9 %)
Tacrolimus n, (%)	42 (91 %)
DGF n, (%)	17 (37 %)
creatinine (μmol/l)	159±63
creatinine (μmol/l) (median, 25th a 75th percentile)	149 [113;200]
ATG induction n, (%)	38 (83 %)
Acute rejection n, (%)	21 (46 %)
Imunological risk	1.87±0.91
Imunological risk (median, 25th a 75th percentile)	2 [1;3]
IR 2 or higher (2,3,4)	26 (57 %)
Compatibility index	10.4±5.5
Compatibility index (median, 25th a 75th percentile)	12 [7;13]
PRA act. % (median, 25th a 75th percentile)	1 [0;3]
PRA max. % (median, 25 a 75 percentile)	23 [10;53]

Discusion

The aim of our analysis was to identify immunological aspects of retransplanted patients and compare them with primary transplanted patients. The retransplanted group had a higher rate of sensitisation. We identified statistically significant immunological factors that contributed to this sensitisation: the ALPL titer, expressed as immunological risk and divided into four groups according to the percentage of PRA, and the median historical and current PRA (p<0.001).

Benkö et al. found a high rate of high PRA levels in tertiary and subsequent retransplant recipients, resulting in a high incidence of biopsy-proven acute rejection (BPAR). The high incidence of acute rejection is explained by hyperimmunisation, which was present in up to 30% of patients in this study. These results are comparable to the literature, where the rate of BPAR after retransplantation ranges from 28 to 45% and correlates with worse graft survival (12).

An increase in peak PRA of more than 50% between the first and second transplantation in about 20% of recipients has also been confirmed in the work of Australian authors (13).

Tab. 2. Initial clinical and immunological characteristics of the recipients.

Initial clinical and immunological characteristics of the recipients			
	Primary trnsplantation	**Secondary transplantation**	**p**
n	46	46	
women n, (%)	21 (46 %)	21 (46 %)	1.0
Cyclosporine n, (%)	34 (74 %)	4 (9 %)	
Tacrolimus n, (%)	12 (26 %)	42 (91 %)	**<0.001**
DGF n, (%)	24 (52 %)	17 (37 %)	0.142
creatinine (μmol/l)	215±101	159±63	**0.003**
creatinine (μmol/l) (median, 25th a 75th percentile)	174 [144;246]	149 [113;200]	**0.012**
ATG induction n, (%)	6 (13 %)	38 (83 %)	**<0.001**
Acute rejection n, (%)	14 (30 %)	21 (46 %)	0.133
Immunological risk	1.07±0.25	1.87±0.91	**<0.001**
Immunological risk (median, 25th a 75th percentile)	1 [1;1]	2 [1;3]	**<0.001**
IR 2 or higher (2,3,4)	3 (6.5 %)	26 (57 %)	**<0.001**
Compatibility index	11.7±5.8	10.4±5.5	0.236
Compatibility index (median, 25th a 75th percentile)	13 [9;13]	12 [7;13]	0.207
PRA act. % (median, 25th a 75th percentile)	0 [0;2]	1 [0;3]	**<0.001**
PRA max. % (median, 25th a 75th percentile)	0 [0;10]	23 [10;53]	**<0.001**

Tab. 3. Risk factors for acute rejection in secondary retransplanted patients.

Risk factors for acute rejection in secondary retransplanted patients			
	Acute rejection		
	no	yes	p
Number (n)	**25**	**21**	
ΔPRA max.>10%	18 (72 %)	16 (76 %)	0.747
ATG induction	22 (88 %)	16 (76 %)	0.293
Compatibility index	9.4±4.6	11.5±6.3	0.185
DGF	6 (24 %)	11 (52 %)	**0.047**
Female sex	13 (52 %)	8 (38 %)	0.346
Immunological risk	1.80±0.96	1.95±0.87	0.577
Immunological risk 2,3,4 vs 1	12 (48 %)	14 (67 %)	0.203
Cyclosporine	1 (4 %)	3 (14 %)	
tacrolimus	24 (96 %)	18 (86 %)	0.318
Serum creatinine, umol/L	140±53	182±67	**0.023**

Candidates for kidney transplantation have higher levels of panel reactive antibodies (PRA) due to allo-sensitisation from previous organ transplantation. In addition, pregnancy and blood transfusions can also contribute to hypersensitisation.

A retrospective study by Akgul and colleagues evaluated different sensitisation patterns in wait-listed candidates and their impact on PRA profiles. Of the 906 candidates, 32.8% were PRA positive. The risk of developing anti-HLA class I antibodies was higher in pregnant patients (p<0.001), while the risk of developing anti-HLA class II antibodies was significantly higher in waitlist candidates who had previously undergone organ transplantation (p<0.001). Using multiple regression analysis, the authors found that the prevalence of PRA positivity was significantly higher in female candidates who were pregnant, odds ratio 1.003 (95% CI, 0.441–2.281; p=0.031) compared with previous transplant or transfusion (14).

A similar trend of HLA antibody formation after previous pregnancy and transplantation has been published by Portuguese authors (15). In a retrospective study by Huyn et al, transplantation had the strongest immunising effect, especially for HLA class II antigens. Candidates for retransplantation had a statistically significantly higher PRA positivity rate than those awaiting primary kidney transplantation (80.2% vs 41.1%; p<0.001). Similarly, retransplant candidates had a significantly higher antibody intensity compared to primary transplant recipients (MFI 14164 vs 5456; p<0.001) as assessed by LUMINEX (16).

Tab. 4. Risk factors for acute rejection in secondary retransplanted patients.

Risk factors for acute rejection in secondary retransplanted patients			
	OR	95% CI	p
ΔPRA max.> 10%	1.24	0.33–4.70	0.747
ATG induction	0.44	0.09–2.10	0.3
Compatibility index	1.08	0.96–1.21	0.189
DGF	3.48	0.99–12.22	**0.049**
Female sex	0.57	0.18–1.85	0.347
Immunological risk	1.21	0.63–2.30	0.568

Several other studies have shown that poorer HLA matching at first transplantation is associated with higher PRA at retransplantation (17, 18).

In this study, we also looked at the incidence of acute rejection in sensitised retransplanted patients. We found a numerically higher incidence of acute rejection episodes, but the difference between the retransplanted group and the primotransplanted group was not statistically significant. The reason for this phenomenon may be due to the more „aggressive“ immunosuppressive therapy and the extension of the immunosuppressive protocol to include ATG in the retransplanted group.

In a retrospective study, Heaphy et al. found that recipients treated for AR within one year of their primary transplant were 26% more likely to be treated for AR within one year of their retransplant (OR adj. 1.26; 95% CI 1.07–1.48; p=0.0053) (19).

The incidence of AR as an immunological complication in retransplant recipients compared to primary transplant recipients (11.54% vs 10%) was not statistically different, even in the Asian population, which is consistent with our findings (20).

In a further subanalysis, we also evaluated the presence of DGF, which may be associated with increased graft immunogenicity. Retransplanted patients who had experienced acute rejection had a significantly higher incidence of DGF (p=0.047), which was also reflected in worse graft function as measured by serum creatinine (182±67 umol/L). A statistically significant (p=0.023) worsening of creatinemia was observed in the retransplant recipients who did not undergo AR compared to the group of retransplant recipients who did undergo AR. In the logistic regression model, we found that DGF was an independent risk factor for the development of AR in the retransplanted group. In other words, retransplanted patients with DGF were 48% more likely to develop AR (p=0.049). When evaluating individual variables in the secondary retransplanted patients stratified by sex, we found that the male population had a higher prevalence of DGF compared to females (60% vs 10%; p<0.001) and, analogously, they had worse graft function as assessed by serum creatinine, which was statistically significant (p<0.001). Again, the prevalence of AR was numerically higher in the male group but did not reach statistical significance.

In their study, Khalil et al found a significantly higher incidence of DGF in retransplanted patients (28% vs 25%; p=0.007). Among other immunological variables, DGF contributes to poorer graft survival (7).

In a monocentric study, Kim et al. found a non-significant prevalence of DGF (27.2%) and AR (36.4%) in tertiary retransplanted patients (21).

The future of transplantation immunology lies in epitope matching, as it has been shown that antibodies are not produced against the entire HLA molecule, but only against a specific epitope on the HLA molecule. Assessing epitopes prior to minimising immunosuppression may be a more effective tool to identify patients at highest risk of allosensitisation (22).

A better understanding of the immunogenicity and structural characteristics of HLA epitopes will lead clinicians to integrate epitope matching as an important parameter for donor selection in hyperimmunised individuals for kidney retransplantation (23).

In transplant nephrology, there is a need to better understand HLA epitopes and interpret the pattern of HLA antibody cross-reactivity into clinical practice (24).

Conclusion

This article provides an overview of the immunological problems in renal retransplantation. Patient and graft survival is worse after second kidney transplantation than after first kidney transplantation. Patients considered for retransplantation are highly immunised due to the development of HLA-specific antibodies to pre-transplant antigens.

PRA testing is a routine screening measure to assess the degree of sensitisation in a potential retransplant recipient due to previous exposure to HLA antigens, whether from previous blood transfusions, pregnancies or solid organ transplants. Any candidate for retransplantation is at high immunological risk and should be treated with lymphocyte-depleting induction therapy. Solid organ transplantation is more immunogenic than pregnancy or transfusion, especially for HLA class II antigens.

Despite the shortage of organ donors, retransplantation outcomes are acceptable among the transplant community.

Graft damage due to rejection and reduced access to retransplantation for highly sensitised patients are two major challenges facing the transplant community.

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