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DIAGNOSTIC VALUE OF ANTI-HLA ANTIBODY MONITORING IN THE DIAGNOSIS OF IMMUNOLOGICAL COMPLICATIONS FOLLOWING KIDNEY TRANSPLANTATION

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Introduction. Despite improvements in immunosuppressive therapy procedures, immunological complications continue to be a major cause of kidney graft loss. The level of pre-existing and *de novo* synthesized anti-HLA antibodies (AB) has shown high significance in modern diagnosis of graft rejection and assessment of the efficacy of anti-crisis therapy. **Objective:** to analyze the frequency and specificity of pre-existing and *de novo* synthesized (including donor-specific), anti-HLA antibodies, to assess their impact on acute rejection crisis and kidney transplant (KT) outcomes in the early postoperative period. **Materials and methods.** We retrospectively analyzed the treatment outcomes of 637 patients, who received a deceased-donor kidney transplant at Sklifosovsky Research Institute of Emergency Care from 2020 to 2022. Pre-existing and *de novo* synthesized anti-HLA AB, including donor-specific antibodies (DSA), were determined and their impact on the incidence of acute rejection crisis (ARC) in the early postoperative period and on kidney graft function was assessed. **Results.** In non-sensitized patients, the ARC rate was 10.7% (n = 58), primary initial graft function was noted in 354 patients (65.6%), and satisfactory function at discharge was observed in 377 patients (70%). Pre-existing anti-HLA AB was detected in 97 recipients (15.2%); ARC developed in 14 recipients (14.4%) from this group, 51 (52.6%) patients had primary initial function, and 62 (63.9%) exhibited satisfactory function at discharge. *De novo* anti-HLA AB synthesis after transplantation was noted in 70 (11%) patients, ARC in 10 of them (16.7%), 38 (54.3%) had primary function, and 43 (61.4%) had satisfactory function at discharge. DSA synthesis was detected in 10 patients, ARC was diagnosed in 5 (50%) of them, primary initial function and satisfactory function at discharge were noted in 3 (30%) recipients. **Conclusions.** The presence of pre-existing and/or *de novo* anti-HLA AB synthesis after KT under rationally selected immunosuppressive therapy did not statistically significantly affect the early outcomes of graft function. However, DSA synthesis statistically significantly increased the incidence of acute rejection, kidney graft dysfunction and increased the time of recovery of nitrogen excretory function.

Keywords: anti-HLA antibodies, pre-existing anti-HLA antibodies, de novo anti-HLA antibodies, donor-specific anti-HLA antibodies, acute kidney graft rejection.

INTRODUCTION

According to the registry of the Russian Dialysis Society, as of 2020, 60,547 patients with chronic kidney disease stage 5 (stage 5 CKD) had received renal replacement therapy (RRT) in the Russian Federation. This translates into a rate of 414.2 people per million population. RRT dialysis therapy was administered to 50,563 patients (83.5% of all RRT patients); hemodialysis patients made up over 78% of the RRT population, while peritoneal dialysis was received by 4.3% of patients [1]. In 2022, 1,562 kidney transplants were performed in Russia, a 12.9% increase (+178 kidney transplants) over 2021 [2]. Kidney transplantation (KT) is the most desired modality of RRT – it not only increases the life expectancy of patients but also improves their quality of life and offers the best possible medical and social rehabilitation [3–5].

Despite advancements in immunosuppressive therapy protocols, immunological complications remain one of the leading causes of kidney graft loss [6]. About 5–10% of recipients return to RRT within the first year after KT due to graft dysfunction [7].

Renal graft survival is largely determined by the major histocompatibility complex genes and the leukocyte antigens they encode [8]. It is known that the incompatibility of human leucocyte antigens (HLA) in the donor-recipient pair when there is insufficient pro-

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phylactic anti-crisis therapy causes an immune response against the graft, ultimately leading to its destruction. Determination of the level of pre-existing and *de novo* synthesized anti-HLA antibodies (ABs) is of high importance in the diagnosis of graft rejection and evaluation of the effectiveness of anti-rejection therapy. Numerous studies claim that anti-HLA ABs are found in more than 30% of the population and they are formed after blood transfusion, pregnancy or previous transplantation [9, 10].

Donor-specific antibodies can also be formed *de novo*, increasing the risk of antibody-mediated acute and chronic graft rejection and worsening the prognosis of renal allograft (RA) survival [11]. One of the main causes of RA endothelial activation is the binding of circulating anti-HLA donor-specific antibodies (DSAs) to endothelial cells, which contributes to the process of antibody-mediated rejection (AMR). Anti-HLA DSAs are also associated with increased risk of RA rejection and loss [12, 13]. According to various sources, acute AMR occurs in 7% of patients but can be as high as 50% in patients with HLA-incompatible grafts [14].

Currently used immunosuppressants have extremely potent, rejection-blocking effects; however, none of them are antigen-specific [15]. Careful immunological screening before and after transplantation is of paramount importance to minimize the risk of AMR in order to preserve and ensure maximum efficiency of RA function. Currently, many studies have been published on the role of pre-existing and *de novo* synthesized anti-HLA ABs in acute rejection crisis (ARC) after KT, but no such analysis has been performed in our country, which is why we carried out this study.

Objective: to analyze the frequency and specificity of pre-existing and *de novo* synthesized (including donor-specific), anti-HLA ABs, to assess their impact on ARC and KT outcomes in the early postoperative period.

MATERIALS AND METHODS

At the kidney and pancreas transplantation department of Sklifosovsky Research Institute of Emergency Care, 637 single-group deceased-donor kidney transplants were performed in the period from 2020 to 2022.

Inclusion and exclusion criteria

Inclusion criteria: technically successful deceased-donor KT, assessed pre-existing anti-HLA ABs levels (so-called "zero point").

Exclusion criteria: combined transplantation with other solid organs (kidney + liver, kidney + pancreas), living related KT, technically unsuccessful operations (intraoperative graft removal); no "zero point" for anti-HLA ABs.

Recipients

The study group comprised 388 men (60.9%) and 249 women (39.1%), with a median age of 43 [35–53] years. Prior to transplantation, 566 patients (88.8%) received RRT: 434 (68.1%) via hemodialysis, 132 (20.7%) via peritoneal dialysis; 220 (34.5%) recipients had blood group 0 (I), 248 (38.9%) had blood group A (II), 127 (20%) had blood group B (III) and 42 (6.6%) had blood group AB (IV).

Immunological compatibility/incompatibility

The median number of matches (compatibility) for HLA antigens in the donor-recipient pair for class I was 1 [0; 1] antigen (25 [0; 25]%); for class II was 1 [0; 1] antigen (50 [0; 50]%), and the median overall compatibility was 2 [1; 2] antigens (33.3 [16.7; 33.3]%). The median number of class I mismatches, respectively, was 3 [3; 4] antigens (75 [75; 100]%), the median number of class II mismatches was 1 [1; 2] antigen (50 [50; 100]%), and the median total incompatibility by HLA antigens in the donor-recipient pair was 4 [4; 5] antigens (66.7 [66.7; 83.3]%).

Kidney transplant features

Most patients (n = 565, 88.7%) had primary KT, 67 (10.5%) had second transplantation, and 7 (0.8%) had third transplantation.

Immunosuppressive therapy features

In the postoperative period, patients received triple-medication baseline immunosuppressive therapy (IST): tacrolimus was administered as a calcineurin inhibitor in 559 recipients (87.7%) and cyclosporine in 78 (12.3%). As the second component of IST, 612 recipients (96%) received mycophenolate, 19 recipients (3%) were given mTOR inhibitors (everolimus), and 6 patients (1%) were administered azathioprine. Monoclonal antibodies (basiliximab) were used as induction IST in 531 patients (83.3%) and polyclonal antibodies in 66 patients (10.4%), of which 58 patients (9.1%) received antithymocyte immunoglobulin (rabbit) and 8 recipients (1.3%) received antithymocyte equine immunoglobulin. In 40 patients (6.3%), mono- or polyclonal antibodies were not included in the induction IST.

Determination of pre-existing and *de novo* synthesized anti-HLA antibodies

When all patients were placed on the waiting list, anti-HLA class I and class II ABs were determined in venous blood. The study was performed on the Luminex platform, using LABScreen (ONE LAMBDA, USA) and LIFECODES Lifescreen Deluxe (IMMUCOR, USA) kits. With MFI (mean fluorescence intensity) of less than 500 units, anti-HLA ABs were considered negative. *De novo* anti-HLA ABs were defined as anti-HLA ABs that appeared after transplantation or when the level of

pre-existing anti-HLA ABs increased after transplantation by more than 10% of the baseline MFI. *De novo* anti-HLA ABs synthesized in the post-transplant period but not detected in the control study were classified as "transient". *De novo* anti-HLA ABs synthesized after transplantation and detected in the control study were classified as "persistent".

Determination of donor-specific antibodies

The patient's venous blood was tested for HLA antibodies on the Luminex platform using LIFECODES LSA Class I and LIFECODES LSA Class II reagents (IMMUCOR, USA). The anti-HLA ABs specificities detected in the recipient were compared with the donor's HLA typing data – the so-called "virtual cross-match". The match between the identified recipient's ABs and the donor's major histocompatibility complex antigens was considered as the presence of DSAs in the recipient.

Diagnosis of acute rejection

In the presence of one or a combination of several symptoms listed below – decreased diuresis, pain in the kidney graft area, subfebrile body temperature without an infection source, excessive increase in nitrogenous waste (serum creatinine and blood urea) after ruling out other causes of graft dysfunction, changes in ultrasound images over time (appearance of graft edema signs, deterioration of blood supply characteristics), and an increase in the level of *de novo* anti-HLA ABs on the background of or without a decrease in the anti-HLA ABs level. A diagnosis of rejection was made based on a combination of clinical and morphological signs.

Patient allocation into groups

To evaluate the impact of pre-existing and *de novo* synthesized anti-HLA ABs on the incidence of ARC and KT outcomes, patients were divided into the following groups: I_{sens-} and II_{sens+} and $I_{de\ novo-}$ $II_{de\ novo+}$, respectively. In addition, patients were categorized into I_{DSA-} and II_{DSA+} groups based on the presence/absence of DSA. These groups did not differ statistically significantly in terms of the main characteristics (age, sex, body mass index, RRT type and duration, blood group ($p > 0.05$).

Statistical processing methods

Statistical analysis was performed using the programs StatTech v. 2.8.8 (StatTech LLC, Russia) and IBM SPSS Statistics v 24 (IBM, USA). Quantitative parameters were evaluated for conformity to normal distribution using the Shapiro–Wilk test. Quantitative data were described using median and lower and upper quartiles. Categorical data were described using absolute values and percentages. The two groups were compared by quantitative indicator having normal distribution, provided the variance was equal, using Student's t test. The Mann–Whitney U test was used to compare two groups based on a quantitative indicator whose distribution deviated from normal. Patient and graft survival were calculated using the Kaplan–Meier estimate. The 95% confidence interval limits were computed to assess the significance of the odds ratio. Differences were considered statistically significant at $p < 0.05$.

RESULTS

Follow-up periods

Anti-HLA AB levels were monitored during the post-KT in-hospital period, with a median hospital stay of 19 [15–27] days.

Pre-existing anti-HLA antibodies

Pre-existing anti-HLA ABs were detected in 97 recipients (15.2%), including 36 patients after the second transplant surgery and 3 patients after the third. Anti-HLA class I ABs were noted in 68 patients (10.7%), their levels ranged from 505 to 14,444 MFI, with a median level of 1,332 [657–4,093] MFI; anti-HLA class II ABs were noted in 61 patients, their levels ranged from 503 to 14,116 MFI, with a median level of 1,724 [794–7550] MFI; 32 patients had elevated levels of pre-existing HLA class I and class II anti-HLA ABs. During the entire post-transplant follow-up period, no synthesis of anti-HLA ABs was observed in 38 initially sensitized patients.

De novo synthesized anti-HLA antibodies

In the early post-transplant period, *de novo* synthesis of anti-HLA ABs was noted in 70 patients (11%), 37 of whom were not sensitized before surgery. Synthesis of "persistent" ABs was noted in 56 recipients, and "transient" ABs in 14 patients. In 33 patients, *de novo* anti-HLA class I ABs were detected, their levels varied from 504 to 14,729 MFI, with a median level of 2,259 [744–7,672] MFI; *de novo* anti-HLA class II ABs were detected in 58 patients, their levels ranged from 506 to 17,115 MFI, with a median level of 2,983 [917–9,699] MFI; both class I and class II *de novo* anti-HLA ABs were detected in 21 patients. Their detection time ranged from 7 to 46 days; median detection time was 9 [7–13] days.

Donor-specific antibodies

Following identification and comparison with donor antigens, DSAs were detected in 10 recipients: against class I antigens in 2 patients, against class II in 3 patients, and against both classes in 5 patients.

Comparative characteristics of ARC and kidney transplantation outcomes in the study groups are presented in Tables 1, 2, and 3.

Anti-crisis therapy

Seventy-two recipients had ARC at the hospital stage, with 14 of them having been sensitized prior to transplantation, and 10 recipients had *de novo* synthesis of anti-HLA antibodies. Pulse glucocorticoid therapy was

administered to 70 patients as a part of anticrisis therapy: it was used as a part of combined anticrisis therapy in 17 of them, and as monotherapy in 53 patients; its course dose varied from 500 to 1,500 mg, the median was 1000 [1000–1250] mg. Twelve patients had polyclonal antibody infusions as part of a combined anti-crisis therapy, while only two recipients received them as monotherapy; the median number of infusions was 10 [7–10] and the median course dose was 475 [425–3,250] mg. Plasmapheresis was used as part of a combination anti-crisis therapy in the vast majority of cases (n = 12) and as monotherapy in just one recipient. The median number of plasmapheresis sessions was 3.5 [3–4].

DISCUSSION

KT remains the best modality for RRT, providing the longest possible life expectancy, better quality of life and higher socio-medical rehabilitation. The big problem of modern world transplantation is the mismatch between the need and the possibility of providing transplant care for patients with stage 5 CKD. In addition, acute rejection is still widely common in the early post-transplant period, which significantly lowers kidney graft survival. For this reason, many transplantologists recognize the paramount need to advance techniques for diagnosing and treating immunological complications following KT. The importance of identifying pre-existing and *de novo* synthesized anti-HLA ABs, including donor-specific

Table 1

Comparative characteristics of transplant outcomes in $I_{sens–}$ and II_{sens+} groups

Parameter	$I_{sens–}$ (n = 540)	II_{sens+} (n = 97)	P
Immunological complications			
Acute rejection crisis (n (%))	58 (10.7)	14 (14.4)	0.29
Time of rejection onset* (days)	10 [6.17]	8 [4.11]	0.35
Methylprednisolone pulse therapy (n (%))	55 (95)	13 (93)	0.35
Polyclonal antibodies (n (%))	12 (20.7)	2 (14.3)	0.92
Plasma exchange (n (%))	8 (13.8)	5 (35.7)	0.02**
Outcomes			
Primary/delayed function (n (%))	354 (65.6) / 186 (34.4)	51 (52.6) / 46 (47.4)	0.01**
Time to normalization of azotemia (days)	8 [5.13]	9 [4.15]	0.45
Satisfactory KA function at discharge (n (%))	377 (70)	62 (64)	0.31
KA dysfunction (n (%))	142 (26.2)	25 (25.8)	0.96
Non-functioning KA (n (%)) – In-hospital removal of KA (n (%)) – Continuation of RRT at discharge (n (%))	16 (3) 5 (0.9) 11 (2)	8 (8.4) 1 (1) 7 (7.2)	0.01** 0.9 0.004**
In-hospital mortality (n (%))	5 (0.9)	2 (2)	0.32

Note: KA, kidney allograft; RRT, renal replacement therapy. * = Me [25%; 75%]; ** = statistically significant difference (p > 0.05).

Table 2

Comparative characteristics of transplant outcomes in $I_{de\ novo–}$ and $II_{de\ novo+}$ groups

Parameter	$I_{de\ novo–}$ (n = 567)	$II_{de\ novo+}$ (n = 70)	P
Immunological complications			
Acute rejection crisis (n (%))	62 (11)	10 (16.7)	0.43
Time of rejection onset* (days)	10 [7.19]	7 [6; 13]	0.32
Methylprednisolone pulse therapy (n (%))	60 (96.7)	8 (80)	0.83
Polyclonal antibodies (n (%))	10 (16.1)	4 (40)	0.03**
Plasma exchange (n (%))	6 (9.7)	6 (60)	<0.001**
Outcomes			
Primary/delayed function (n (%))	366 (64.6) / 201 (35.4)	38 (54.3) / 32 (45.7)	0.09
Satisfactory KA function at discharge (n (%))	395 (70.4)	42 (60.9)	0.1
Time to normalization of azotemia (days)	8 [5.14]	9 [5.15]	0.28
KA dysfunction at discharge (n (%))	150 (26.7)	21 (30.4)	0.51
Non-functioning KA (n (%)) – In-hospital removal of KA (n (%)) – Continuation of dialysis at discharge (n (%))	16 (2.9) 5 (0.9) 11 (2)	6 (8.7) 1 (1.5) 5 (7.2)	0.01** 0.65 <0.01**
In-hospital mortality (n (%))	6 (1)	1 (1.4)	0.78

Note: KA, kidney allograft.

Table 3

Comparative characteristics of transplant outcomes in I_{DSA-} and II_{DSA+} groups

Parameter	I_{DSA-} (n = 627)	II_{DSA+} (n = 10)	P
Immunological complications			
Acute rejection crisis (n (%))	67 (10.7)	5 (50)	<0.001**
Time of rejection onset* (days)	9 [6.17]	14 [9; 32]	0.27
Methylprednisolone pulse therapy (n (%))	64 (95.5)	4 (80)	0.003**
Polyclonal antibodies (n (%))	14 (21)	0 (0)	0.63
Plasma exchange (n (%))	11 (16.4)	2 (40)	<0.001**
Outcomes			
Primary/delayed function (n (%))	402 (64.1) / 225 (35.9)	3 (30) / 7 (70)	0.03**
Time to normalization of azotemia (days)	8 [5.13]	14.5 [8.21]	0.1
Satisfactory KA function at discharge (n (%))	435 (69.4)	3 (30)	0.006**
KA dysfunction at discharge (n (%))	163 (26)	6 (60)	0.02**
Non-functioning KA (n (%)) – In-hospital removal of KA (n (%)) – Continuation of dialysis at discharge (n (%))	22 (3.5) 6 (1) 16 (2.6)	1 (10) 0 (0) 1 (10)	0.28 0.75 0.15
In-hospital mortality (n (%))	7 (1.1)	0	0.74

Note: KA, kidney allograft.

ABs, in patients undergoing KT has been reported in other countries, but there have been remarkably few of these studies conducted in our country.

According to international experts, over 25% of patients undergoing KT may have elevated levels of pre-existing anti-HLA ABs [16–18]. The donor specificity levels of these ABs are often clinically significant. Our investigation found that 97 recipients (15.2%) of the study group had pre-existing anti-HLA ABs. The sensitized patients had statistically significantly higher frequency of delayed initial KT function compared to patients without pre-existing anti-HLA ABs (47.4% and 34.4%, respectively; p = 0.01). Notably, patients with and without pre-existing anti-HLA antibodies did not differ statistically significantly in terms of ARC frequency and period (14.4% and 10.7%, p = 0.29; 8 [4.11] days and 10 [6.17] days, p = 0.35, respectively). This is probably due to the more frequent use of polyclonal antibodies as part of induction IST in the sensitized patient group. In-hospital kidney graft survival was statistically significantly lower in patients with pre-existing anti-HLA ABs (91.6% and 97%, respectively, p = 0.01), with the incidence of hospital RA removal not significantly different (1% *vs.* 0.9%, p = 0.9), and the incidence of non-functioning RA with patient discharge to continue RRT was significantly higher in II_{sens+} patients (7.2% *vs.* 2% (p = 0.004). In-hospital recipient survival was statistically significantly independent of the presence/absence of pre-existing anti-HLA ABs (98% and 99.1%, respectively, p = 0.32).

Jung et al. reported that the *de novo* synthesized anti-HLA AB rate was 15.5%. Most researchers agree that *de novo* synthesized anti-HLA ABs can dramatically raise the probability of delayed renal graft function, acute rejection crisis, and decreased renal graft survival without reducing recipient survival [19]. Seventy recipients (11%) had *de novo* synthesis of anti-HLA ABs. At the same time, 34% of patients with prior sensitization had *de novo* formation of anti-HLA ABs, compared to 7.4% in the I_{sens-} group (p < 0.001). Moreover, our investigation found that *de novo* antibody formation did not statistically significantly increase the frequency of ARC (16.7% and 11.1% (p = 0.43). Patients in the $I_{de\ novo-}$ and $II_{de\ novo+}$ groups did not significantly vary in terms of incidence of primary/delayed initial RA function. Despite the anti-crisis therapy provided, which, in the $II_{de\ novo+}$ group, significantly more frequently included polyclonal anti-HLA ABs (40% *vs.* 16%, p = 0.03) and plasmapheresis sessions (60% *vs.* 10%, p < 0.001), in-hospital RA survival in this group was statistically significantly lower (91.3% *vs.* 97.1%, p = 0.01). In-hospital survival was statistically significantly lower in patients discharged with a non-functioning graft to continue RRT (7.2% *vs.* 2%, p < 0.01). In-hospital recipient survival was not statistically significantly different between the groups with and without *de novo* synthesis of anti-HLA ABs (98.6% versus 99%, respectively, p = 0.78).

Some researchers estimate that the frequency of donor-specific anti-HLA AB synthesis could reach 10%, while others estimate that it could be as high as 20%. Current theories suggest that DSA increases the incidence of acute rejection and renal graft loss by a statistically significant amount [19, 20]. In our study, the relatively low incidence of *de novo* DSA synthesis (1.6%) was due to the fact that patients awaiting repeat KT were carefully selected for the organ, taking into account immunological compatibility/incompatibility by HLA antigens in the donor-recipient pair, including identification. In addition, induction immunosuppressive therapy by polyclonal antithymocyte ABs was performed for 4–7 days, as well as individual selection of baseline immunosuppressive therapy. Synthesis of donor-specific anti-HLA ABs statistically significantly increased

the frequency of delayed initial graft function (70% *vs.* 35.9%, p = 0.03), acute rejection crisis (50% *vs.* 10.7%, p < 0.001), graft dysfunction at the time of discharge (60% *vs.* 26%, p = 0.02), and it decreased the frequency of satisfactory RA function at recipient discharge (30% *vs.* 69.4%, p = 0.006). Meanwhile, in-hospital survival of RA (90% *vs.* 96.5%, p = 0.28) and recipients (100% *vs.* 98.9%, p = 0.74) were not statistically significantly different between the groups.

CONCLUSION

Identifying patients with increased immunological risk before KT is carried out helps in the rational selection of a donor, the administration of immunosuppressive therapy and, ultimately, the improvement of KT outcomes. Thorough immunological screening for donor-specific ABs and organ organ selection require special consideration.

The authors declare no conflict of interest.

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