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MULTICENTER STUDY

The impact of different induction immunosuppression protocol on patient survival, graft survival and acute graft rejection after kidney transplantation

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ABSTRACT

OBJECTIVES: The aim of the study was to stratify the immunological risk based on the presence of risk factors using different induction immunosuppressive protocols.

BACKGROUND: The path to successful kidney transplantation reflects the accuracy of immunological risk assessment and choice of correct induction and maintenance of immunosuppression to avoid acute kidney rejection.

METHODS: We performed a multicentre prospective analysis consisting of patients after kidney transplantation with a 12-month follow-up.

RESULTS: In total, 152 kidney transplant recipients were included, of whom 100 were males (66.4 %). We divided patients according to the induction immunosuppression as follows: no induction (n = 19), induction with basiliximab (n = 60), and induction with ATG cumulative dose 3.5 mg/kg (n = 42) and 6 mg/kg (n = 31). In our study, we demonstrated a shorter survival of patients without induction immunosuppression. In the basiliximab group, the duration of dialysis ≥ 3 years (p = 0.0191), cold ischaemia time ≥ 1,020 minutes or expected delayed graft function (p < 0.0001) are independent risk factors for graft loss (p = 0.0097).

CONCLUSIONS: Risk of no induction immunosuppression significantly exceeds the risks associated with its administration and is desirable even in patients at low immunological risk. Induction immunosuppression should be tailored individually and thus differ from patient to patient *(Tab. 6, Fig. 1, Ref. 15)*. Text in PDF *www.elis.sk*

KEY WORDS: kidney transplantation, induction immunosuppression, graft survival, patient survival, acute kidney rejection.

List of abbreviations: ATG – anti-thymocytary globulin, BPAR – biopsy proven acute rejection, CIT – cold ischemia time, CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration, dnDSA – *de novo* donor-specific antibodies, ECD – extended-criteria donor, eGFR – estimated glomerular filtration rate, ESKD – end-stage kidney disease, HLA – human leukocyte antigen, IS – immunosuppression, KDIGO – Kidney Disease: Improving Global Outcomes, KRT – kidney replacement therapy, KT – kidney transplantation, KTR – kidney transplant recipients, MMF – mycophenolate mofetil, MPA – mycophenolic acid, PRA – panel reactive antibodies, WL – waiting list

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Introduction

The path to successful kidney transplantation (KT) as the most effective method of kidney replacement therapy (KRT) in terms of patient survival and occurrence of complications mainly reflects the necessary development of immunosuppressive treatment (IS). During the previous decades, a number of drugs have been developed in order to find the optimal equilibrium in preventing acute graft rejection. Nowadays, an emphasis is laid also on long-term survival of the patient and graft. On the other hand, potent IS treatment leads to the occurrence of many complications, predominantly to the development of opportunistic infections and neoplasms (1).

The choice of inducing immunosuppressive therapy is variable and depends on many factors, namely attributes of the donor, recipient, immunological factors (HLA compatibility, re-transplantation, etc.). In the context of the above, it is important to adequately evaluate (according to the immunological risk) whether the induction immunosuppressive therapy is necessary and, if so, which type to choose and at what dose. In Transplant Centers in Slovakia, we use anti-thymocyte globulin (ATG) and a monoclonal

Tab. 1. Immunological risk stratification.

Immunological factors	Points	
	YES	NO
Compatibility index ≥ 18	2	0
PRA (actual or maximal)		
20–50	3	0
50 and more	6	0
Re-transplantation	6	0
Duration of dialysis ≥ 3 years or positive crossmatch history (1 or both)	3	0
Non-immunological factors		
CIT ≥ 18 hours	3	0
ECD (according to UNOS criteria)	3	0

PRA – panel reactive antibodies, DGF – delayed graft function; CIT – cold ischemia time; ECD – extended criteria donor

antibody against the receptor for interleukin-2 (IL-2R) – basiliximab. The aim of the present multicenter study was to stratify the immunological risk of kidney transplant recipients (KTR) based on the presence of risk factors using different induction immunosuppressive protocols (no induction IS, basiliximab, ATG at a cumulative dose of 3.5 mg/kg and 6 mg/kg) and its effect on patient and graft survival and incidence of acute kidney rejection.

Materials and methods

The study is a multicentre prospective analysis which consisted of patients after KT in transplant centers in Martin, Košice and Bratislava, Slovakia from 1st January 2019 to 31st December 2019. Induction immunosuppression was selected based on the sum of points assigned to individual immunological and non-immunological risk factors. Immunological and non-immunological factors and points given for their presence are shown in Table 1.

In low immunological risk patients with sum of points ≤ 5 points, no induction IS or induction with basiliximab was chosen, and it was administered 20 mg intravenously on day 0 and 4 days after KT. In moderate immunological risk (6 points for non-immunological factors only), anti-thymocyte globulin cumulative dose of 3.5 mg/kg was given. In patients with high immunological risk, a cumulative dose of 6 mg of anti-thymocyte globulin was administered as an induction IS. Induction IS protocol in all patients included pulses of 500 mg methylprednisolone given on day 0 (shortly before KT) and on day 1 after KT. Maintenance IS treatment consisted of a combination of tacrolimus, mycophenolic acid (MPA) and corticosteroids (usually prednisolone). Tacrolimus was administered per orally with an initial daily dose of 0.2 mg/kg of patient's weight adjusted based on through levels to target 10–15 ng/ml 3 months after KT, 6–10 ng/ml 3 to 6 months after KT and thence 3–6 ng/ml. Starting oral dose of natrium-mycophenolate was 720 mg twice a day or mycophenolate mofetil (MMF) 1 g twice a day (1 g of MMF equivalent to 720 mg mycophenolate sodium). Initial daily dose of prednisolone was 20 mg weaning on 15 mg a day 2 weeks after KT, 10 mg daily 1 month after KT, 7.5 mg/day 4 months after KT to the minimal maintenance dose of 5 mg/day starting 1 year after KT. Patients underwent regular check-ups at the Transplant and Nephrology Outpatient Clinic at regular intervals.

The collected baseline information included recipient and donor age at time of KT, gender of recipient and donor, type of donor – standard donor criteria (SCD), living donor and expanded criteria donor defined as a donor older than 60 years, or donor over age of 50 years with at least two of the parameters as follows: serum creatinine level > 133 μmol/l, history of arterial hypertension or cause of death from cerebrovascular accident. Information about recipients included duration of dialysis in months, time on waiting list, duration of cold ischemia, degree of transplantation (primary, secondary or tertiary KT), panel reactive antibodies, number of mismatches (A, B and DR antigens) and presence of delayed graft function defined as a need for dialysis 7 days after KT.

We monitored the maintenance of immunosuppression – presence of tacrolimus, MPA and corticosteroids, incidence and time of acute humoral or cellular rejection after KT. Acute graft rejection was diagnosed by needle biopsy (biopsy proven acute rejection – BPAR) according to the 2019 Banff criteria and by *de novo* donor-specific antibodies (dnDSA) detection using the Luminex method. We monitored serum levels of creatinine and we estimated glomerular filtration rate (using the CKD-EPI creatinine equation in ml/s) 3, 6 and 12 months after KT. We monitored dnDSA regularly or when graft function deteriorated. We performed protocolar kidney graft biopsy 3 months after KT.

We used a certified statistical program, namely MedCalc version 13.1.2 (MedCalc Software VAT registration number BE 0809 344,640, Member of International Association of Statistical Computing, Ostend, Belgium). Categorical variables were presented as counts and weighted percentages. Comparisons of continuous variables between groups were performed using parametric (*t*-test) or non-parametric (Mann-Whitney) tests; associations between categorical variables were analysed using the χ^2 test and Fisher's

Tab. 2. The basic characteristics of the donors and recipients.

Characteristics of donors	Number of patients, n=152
Age (years)	47.7±14.8
Gender – male (%)	61.8
ECD (%)	30.9
Living donor (%)	10.5
Characteristics of recipients	
Age at time of transplantation (%)	49.6±13.7
Gender – male (%)	66.4
Duration of dialysis (months)	35±31, median 22
Time on waiting list (days)	800±485, median 230
CIT (minutes)	870±390
Secondary transplantation (%)	11.8
Tertiary transplantation (%)	0.7
PRA (%)	13.5±7.8, median 2
Mismatch A	1.2±0.6
Mismatch B	1.3±0.6
Mismatch DR	1.1±0.7
Basiliximab induction (%)	39.5
ATG induction (cumulative dose 3.5 mg/kg) (%)	27
ATG induction (cumulative dose 6 mg/kg) (%)	20.4
Delayed graft function (%)	20.4

ECD – expanded criteria donor; WL – waiting list; CIT – cold ischemia time; PRA – panel reactive antibodies; ATG – anti-thymocyte globulin

exact test, as appropriate. A p value < 0.05 was considered to be statistically significant.

Ethical approval: All the procedures involving human participants have been approved according to the ethical standards of the institutional ethical committee (University Hospital Martin), including the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent for included participants was checked and approved by University Hospital's ethical committee and all signed informed consents have been archived for at least 20 years after research completion. The clinical and research activities being reported are consistent with the principles of the Declaration of Istanbul, as outlined in the Declaration of Istanbul on organ trafficking and transplant tourism.

Results

During the study period, 152 kidney transplant recipients were included, of whom 100 were males (66.4 %). Basic characteristics of the donors and recipients are shown in Table 2.

We divided patients according to induction of IS used: no induction (n = 19), induction with basiliximab (n = 60), induction with ATG at a cumulative dose of 3.5 mg/kg (n = 42) and induction with ATG at a cumulative dose of 6mg/kg (n = 31). The basic characteristic according to the type of induction immunosuppression is shown in Table 3.

By using Kaplan–Meier survival probability, we found a statistically significant difference in patient survival between no induction and other induction immunosuppressive treatment (p = 0.0097) (Fig. 1).

We compared basiliximab group and ATG 3.5 mg/kg group. We found statistical difference in donors´ age (43.9 ± 14.7 years vs 51.2 ± 17.3 years; p = 0.0239), ECD (18.3 % vs 45.2 %; p = 0.0035), duration of dialysis (18.4 ± 14.5 vs 36.3 ± 34.9 months; p < 0.0001), time on waiting list (315 ± 251 vs 761 ± 594 days; p = 0.0006), CIT (713 ± 390 vs 876 ± 357 minutes; p = 0.0064), number of secondary KT (0 % vs 11.9 %; p = 0.0064), PRA (3.3 % vs 10.0%; p = 0.0010), B group mismatches (1.2 ± 1.6 vs 1.5 ± 1.6; p = 0.0146), incidence of ACR (33.3 vs 14.2 %; p = 0.0301), time of acute kidney rejection diagnosis (3.3 ± 2.2 vs 7.4 ± 4.3; p < 0.0001), eGFR (CKD-EPI) 1st month after KT (0.96 ± 0.3 vs 0.7.6 ± 0.4 ml/s; p = 0.0048) (Tab. 4). Table 5 shows the distribution of the group of patients according to the number of points.

Tab. 3. Basic characteristics according to type of induction immunosuppression.

	no induction n=19	basiliximab n=60	ATG (3.5 mg/kg) n=42	ATG (6 mg/kg) n=31
	Donors‘ characteristics			
Age (years)	50.5±9.8	43.9±14.7	51.2±17.3	48.6±12.5
Gender – male (%)	57.9	68.3	57.1	58.1
ECD (%)	31.6	18.3	45.2	35.5
Living donor (%)	0	13.3	7.1	12.9
	Recipients‘ characteristics			
Age at time of transplantation (%)	55.2±10.9	47.3±14.5	52.7±14.6	46.6±10.6
Gender – male (%)	68.4	65	66.7	67.7
Duration of dialysis (months)	30.3±18.8	18.4±14.5	36.3±34.9	55.5±49.3
Time on waiting list (days)	363±313	315±251	761±594	1357±898
CIT (minutes)	753±316	713±390	876±357	955±424
Secondary transplantation (%)	0	0	11.9	41.9
Tertiary transplantation (%)	0	0	0	3.2
PRA (%)	5.8 (median 2.5)	3.3 (median 1)	10.3 (median 16)	8.9 (median 14)
Mismatch A	1.2±0.4	1.2±0.7	1.4±0.6	0.8±0.6
Mismatch B	1.2±0.6	1.2±0.6	1.5±0.6	1.2±0.5
Mismatch DR	1.1±0.7	1.1±0.6	1±0.8	1.1±0.6
	Graft function			
Delayed graft function (%)	10,5	16.7	19	35.5
ACR (%)	42	33.3	14,2	12.9
AHR (%)	0	1.7	7.1	6.5
ACR + AHR (%)	0	6.7	0	3.2
acute rejection – time of diagnosis (weeks after Tx)	7.8±3.4	3.3±2.2	7.4±4.3	1.7±1.3
Creatinine M1 (μmol/l)	136±34	146±70	163±73	140±57
eGFR CKD-EPI M1 (ml/s)	0.84±0.3	0.96±0.3	0.76±0.4	0.94±0.3
Creatinine M3 (μmol/l)	125±30	146±76	141±50	137±53
eGFR CKD-EPI M3 (ml/s)	0.92±0.3	0.82±0.3	0.88±0.3	0.91±0.3
Creatinine M6 (μmol/l)	113±28	141±58	144±52	130±51
eGFR CKD-EPI M6 (ml/s)	1±0.3	0.82±0.3	0.81±0.3	1±0.4
Creatinine M12 (μmol/l)	120±31	133±64	147±77	130±58
eGFR CKD-EPI M12 (ml/s)	0.9±0.3	0.98±0.4	0.84±0.3	1±0.4

ATG – anti-thymocyte globulin; ECD – expanded criteria donor; WL – waiting list; CIT – cold ischemia time; PRA – panel reactive antibodies; ACR – acute cellular rejection; AHR – acute humoral rejection; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; M – months after transplantation; Tx – transplantation

By using logistic regression, we identified independent risk factors for BPAR, graft and patient survival in observed groups based on induction IS.

In the basiliximab group, the duration of dialysis ≥ 3 years (p = 0.0191), CIT ≥ 1,020 minutes or expected DGF (p < 0.0001) are independent risk factors for graft loss (Tab. 6).

In either of ATG groups (cumulative dose of 3.5 mg/kg or 6 mg/kg) we did not confirm any of immunological and non-immunological factors as a risk factor for BPAR.

Based on identification of the dialysis duration ≥ 3 years, CIT ≥ 1,080 minutes, expected DGF as a risk factor for graft loss in basiliximab group, by using multivariate analysis, none of the risk factors (donor's age and gender, ECD, recipient's age and gender, time on WL, CIT, PRA, number of HLA mismatches, DGF, BPAR) was confirmed as a risk factor for graft loss.

Tab. 4. Comparison of the basiliximab and ATG cumulative dose 3.5 mg/kg groups.

	Basiliximab n=60	ATG (3.5 mg/kg) n=42	p
	Donors' characteristics		
Age (years)	43.9±14.7	51.2±17.3	0.0239
Gender – male (%)	68.3	57.1	0.2494
ECD (%)	18.3	45.2	0.0035
Living donor (%)	13.3	7.1	0.3221
	Recipients' characteristics		
Age at time of transplantation (%)	47.3±14.5	52.7±14.6	0.0679
Gender – male (%)	65	66.7	0.8594
Duration of dialysis (months)	18.4±14.5	36.3±34.9	0.0006
Time on waiting list (days)	315±251	761±594	<0.0001
CIT (minutes)	713±390	876±357	0.0340
Secondary transplantation (%)	0	11.9	0.0064
Tertiary transplantation (%)	0	0	–
PRA (%)	3.3 (median 1)	10.3 (median 16)	0.0010
Mismatch A	1.2±0.7	1.4±0.6	0.1357
Mismatch B	1.2±0.6	1.5±0.6	0.0146
Mismatch DR	1.1±0.6	1±0.8	0.4724
	Graft function		
Delayed graft function (%)	16.7	19	0.7654
ACR (%)	33.3	14.2	0.0301
AHR (%)	1.7	7.1	0.1689
ACR + AHR (%)	6.7	0	0.0885
Acute rejection – time of diagnosis (weeks after Tx)	3.3±2.2	7.4±4.3	<0.0001
Creatinine M1 (μmol/l)	146±70	163±73	0.2384
eGFR CKD-EPI M1 (ml/s)	0.96±0.3	0.76±0.4	0.0048
Creatinine M3 (μmol/l)	146±76	141±50	0.7097
eGFR CKD-EPI M3 (ml/s)	0.82±0.3	0.88±0.3	0.3226
Creatinine M6 (μmol/l)	141±58	144±52	0.7892
eGFR CKD-EPI M6 (ml/s)	0.82±0.3	0.81±0.3	0.8687
Creatinine M12 (μmol/l)	133±64	147±77	0.3200
eGFR CKD-EPI M12 (ml/s)	0.98±0.4	0.84±0.3	0.0577

ATG – anti-thymocyte globulin; ECD – expanded criteria donor; WL – waiting list; CIT – cold ischemia time; PRA – panel reactive antibodies; ACR – acute cellular rejection; AHR – acute humoral rejection; eGFR – estimated glomerular filtration rate; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; M – months after transplantation; Tx – transplantation

Discussion

Over a decade, KT has represented the most effective mean of KRT mainly because of the development of a wide range of IS leading to an increase in the patient and graft survival. Based on the immunological risk, induction IS should be chosen carefully to evaluate maximum benefit on one side and

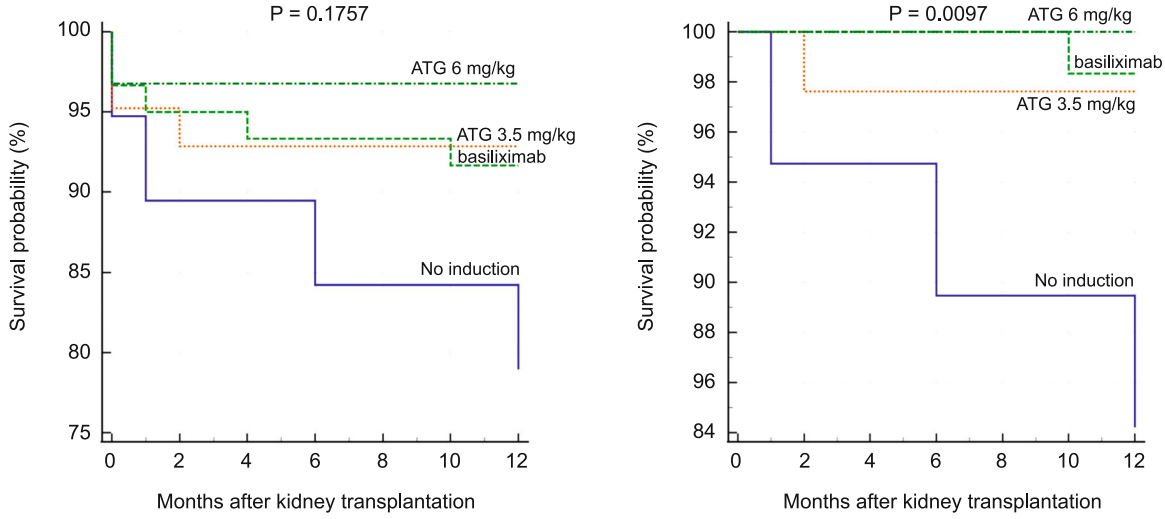

Fig. 1. Kaplan–Meier survival curves: A – graft survival, B – patient survival.

minimal harm on the other. A proportion of 80 % of KTR in USA receive induction IS treatment (2). In our study, 87.5 % of KTR received induction IS therapy. According to the available literature, the induction IS is not required in HLA-identical donors and in elderly KTR, as elderly patients generally have a lower risk of BPAR and a higher risk of infectious and malignant complications, but the risk of graft loss is higher in elderly as compared to younger KTR, which is in contrast to a study conducted at the Transplant Center in Martin where we did not find significant differences in the incidence of infections in patients older than 60 years (3, 4). In our study, we confirmed a significantly worse patient survival in a group with no induction as compared to patients with induction IS ($p = 0.0097$).

In case of moderate-to-higher immunological risk, the choice of induction IS treatment is the use of basiliximab or ATG. ATG is used in patients at high immunological risk, namely with HLA incompatibility, young patients, patients with donor-specific antibodies, high titer reactive antibody (PRA) panel, AB0 incompatible kidney transplants, recipients with delayed graft function and patients with cold ischemia time (CIT) > 24 hours, and retransplantation (5). The most commonly used cumulative dose is 1.5 mg/kg body weight up to 6 mg/kg body weight. Along with hematological complications (leukopenia, thrombocytopenia, anemia), the main side effects include the 'first-dose syndrome' (fever, chills, nausea, vomiting, dyspnea, headache) (6). Basiliximab is a chimeric monoclonal antibody directed to the alpha chain of interleukin-2 receptor preventing its activation (7). Basiliximab should be used in KTR with standard immunological risk (adult KTR without HLA sensitization, first KT from non-identical HLA donor). In our study, in ATG group at a cumulative dose of 3.5 mg/kg, we noticed several differences as compared to the basiliximab group, namely older kidney donors, increased number of ECD, longer duration of KTR dialysis, longer time on waiting list, longer CIT, increased number of secondary KT, higher PRA, and more B group mismatches. Based on these differences, we would expect a higher incidence of acute kidney rejection in the ATG group, but we noticed a higher incidence of ACR and earlier diagnosis of acute kidney rejection. We also found lower eGFR (CKD-EPI) 1st month after KT in ATG group as compared to the basiliximab group, which can be explained by a higher proportion of risk factors for DGF (ECD, length of dialysis, CIT, etc.) and also by minimizing intrinsic nephrotoxic side effect of calcineurin inhibitors by basiliximab. The differences in eGFR between comparison groups are not seen 6 and 12 months after KT.

Based on the presence of immunological and non-immunological factors and chosen induction immunosuppressive treatment, we found in the basiliximab group that HD duration ≥ 36 months, and CIT ≥ 18 hours were independent risk factor for graft loss. The view of the effect of CIT on graft loss is controversial; some studies claim that CIT has no effect on graft survival, others that CIT is a major factor in graft loss after KT through pathophysiological pathways inducing ischemia reperfusion injuries (8, 9). Salahudeen et al demonstrated CIT ≥ 30 hours to worsen graft survival; Opelz et al described CIT ≥ 18 hours to be not associated with an increased risk of graft failure (10, 11). Some studies explained CIT as a risk factor when adjusting for the occurrence of graft loss through DGF and/or acute graft rejection (12). In our study, there was an increased incidence of acute cellular rejection in the basiliximab group, but a decreased incidence of DGF. The 2009 KDIGO guidelines for the care of kidney transplant patient recommends basiliximab be the first-line induction therapy (1B), but lymphocyte-depleting agents (ATG) should be used in patients at high immunological risk. However, among risk factors mentioned above, there is CIT > 24 hours. Based on the results of our study, CIT ≥ 18 hours should be considered as a risk factor and crucial for choosing ATG as an induction IS. Our finding is confirmed by a study which claims that each additional hour of CIT significantly increases the risk of graft failure following KT (13).

Several studies demonstrated increased time on dialysis prior to KT to negatively predict short-term allograft outcomes (14). As mentioned above, CIT can be a risk fac-

Tab. 5. Distribution of patients by points for immunological and non-immunological factors.

Immunological factors	Basiliximab n=60	ATG (3.5 mg/kg) n=42	ATG (6 mg/kg) n=31
Compatibility index ≥ 18 (2 points) (%)	16.7	35.7	19.4
PRA 20–50% (3 points) (%)	1.7	7.1	6.5
PRA ≥ 50% (6 points) (%)	0	4.8	3.2
Re-transplantation (6 points) (%)	0	11.9	45.2
Duration of dialysis ≥ 3 years (3 points) (%)	6.7	47.6	61.3
Non-immunological factors			
CIT ≥ 1080 min, expected DGF (3 points) (%)	25	57.1	64.5
ECD (3 points) (%)	18.3	45.2	35.5

ATG – anti-thymocyte globulin; PRA – panel reactive antibodies; CIT – cold ischemia time; ECD – expanded criteria donor

Tab. 6. Univariant analysis (logistic regression) in basiliximab group.

Basiliximab Immunological factors	Outcome: rejection OR (95% CI)	p	Outcome: graft loss OR (95% CI)	p	Outcome: death OR (95% CI)	p
Compatibility index ≥ 18 (%)	0.56 (0.13–2.43)	0.4438	0.39 (0.02–7.63)	0.5420	1.11 (0.04–24.90)	0.9456
PRA 20–50% (%)	2.45 (0.14–40.92)	0.5307	2.79 (0.10–75.9)	0.5419	7.80 (0.24–24.33)	0.2421
Duration of dialysis ≥ 3 years (%)	2.52 (0.33–18.98)	0.3691	2.34 (1.54–12.7)	0.0191	2.60 (0.10–6.27)	0.5564
Non-immunological factors						
CIT ≥ 1080 min, expected DGF (%)	2.52 (0.80–7.96)	0.1131	4.90 (1.52–9.15)	<0.0001	0.75 (0.03–16.54)	0.8583
ECD (%)	3.47 (0.95–12.7)	0.0598	1.10 (0.11–10.43)	0.9338	1.01 (0.04–22.66)	0.9913

PRA – panel reactive antibodies; CIT – cold ischemia time; ECD – expanded criteria donor

tor for graft survival through DGF. ECD is also a risk factor for DGF and was mostly present in the 3.5 mg/kg ATG group (45.2 %), then in the 6 mg/kg ATG group (35.5 %) and was last in the basiliximab group (18.3 %). It is important to say that in 2009 KDIGO guidelines for KTR, the immunological risk assessment does not include the duration of dialysis regarding the type of dialysis modality. While pre-emptive KT would appear superior over traditional KT, it is unclear whether it is due to an absence of the negative effect associated with dialysis, or absence of a large number of co-morbidities and longer duration of ESKD (15). In our study, neither HLA compatibility index ≥ 18, nor PRA 20–50 % represented risk factors for graft loss, death of patient or acute graft survival in all groups.

In the next step, we analyzed patients with basiliximab induction IS and dialysis duration ≥ 36 months, and did not find the presence of independent risk factors involved in graft loss. Identical results were obtained in the basiliximab group with CIT ≥ 1,080 minutes. CIT ≥ 1,080 minutes and HD duration ≥ 3 years were not risk factors for graft loss in the ATG group (in either of cumulative doses). In the 3.5 mg/kg ATG group, there were 47.6 % of patients dialyzed ≥ 3 years, and 57.1 % of patients with CIT > 18 hours; in the 6 mg/kg ATG group, 61.3 % of patients were dialyzed ≥ 3 years while 64.5 % of patients had CIT ≥ 1,080 minutes. Yet, it did not represent an independent risk factor for graft loss. Based on the obtained data, we will re-evaluate the weight of points for individual immunological and non-immunological risk factors in all transplantation centers with the modification of the induction immunosuppressive protocol. It follows that patients with dialysis duration ≥ 3 years and CIT ≥ 18 hours should have ATG included in induction IS.

Conclusion

Induction immunosuppressive therapy plays an important role in the kidney transplantation process. To minimize the incidence of acute graft rejection, graft loss, and maximize patient survival, it is necessary to stratify the patient's immunological risk. This can be achieved only by using conventional immunological factors (duration of dialysis) alongside with non-immunological factors (CIT) with increased regard to duration (18 hours vs 24 hours). Induction IS treatment should be tailored individually and thus differ from patient to patient; the risk of no induction IS significantly exceeds the risks associated with its administration and is desirable even in patients with low immunological risk.

References

1. Bauer AC, Manfro R, Franco RF. Immunosuppression in Kidney Transplantation: State of the Art and Current Protocols. Curr Pharm Design 2020; 26 (28): 3440–3450.

2. Hart A, Smith JM, Skeans MA et al. OPTN/SRTR 2016 annual data report: kidney. Am J Transplant 2018; 18 (1): 18–113.

3. Peeters LEJ, Andrews LM, Hesselink DA, de Winter BCM, van Gelder T. Personalized immunosuppression in elderly renal transplant recipients. Pharmacol Res 2018; 130: 303–307.

4. Vnučák M, Graňák K, Skálová P, Laca Ľ, Mokáň M, Dedinská I. Effect of mycophenolic acid and tacrolimus on the incidence of infectious complications after kidney transplantation. International Immunopharmacology 2021. DOI: https://doi.org/10.1016/j.intimp.2021.107908.

5. Hill P, Cross NB, Barnett AN, Palmer SC, Webster AC. Polyclonal and monoclonal antibodies for induction therapy in kidney transplant recipients. Cochrane Database Syst Rev 2017; 2017 (7): CD004759.

6. Hertig A, Zuckermann A. Rabbit antithymocyte globulin induction and risk of post-transplant lymphoproliferative disease in adult and pediatric solid organ transplantation: An update. Transpl Immunol 2015; 32 (3): 179–187.

7. Kahan BD, Rajagopalan PR, Hall M. United States Simulect Renal Study Group. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. Transplantation 1999; 67 (2): 276–284.

8. Mikhalski D, Wissing KM, Ghisdal L et al. Cold ischemia is a major determinant of acute rejection and renal graft survival in the modern era of immunosuppression. Transplantation 2008; 85: S3–S9.

9. Summers DM, Johnson RJ, Hudson A et al. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. Lancet 2013; 381: 727–734.

10. Salahudeen AK, Haider N, May W. Cold ischemia and the reduced long-term survival of cadaveric renal allografts. Kidney Int 2004; 65: 713–718.

11. Opelz G, Döhler B. Multicenter analysis of kidney preservation. Transplantation 2007; 83: 247–253.

12. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009; 9 (Suppl 3): S1–S155.

13. Debout A, Foucher Y, Trébern-Launay K et al. Each additional hour of cold ischemia time significantly increases the risk of graft failure and mortality following renal transplantation. Kidney Int 2015; 87 (2): 343–349.

14. van Biesen W, Veys N, Vanholder R, Lameire N. The impact of the pre-transplant renal replacement modality on outcome after cadaveric kidney transplantation: the ghent experience. Contrib Nephrol 2006; 150: 254–258.

15. Mange KC, Joffe MM, Feldman HI. Dialysis prior to living donor kidney transplantation and rates of acute rejection. Nephrol Dial Transplant 2003; 18: 172–177.

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