Induction Therapy With ATG Compared With Anti-IL2 Basiliximab in Low–Immunologic Risk Kidney Transplant Recipients

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ABSTRACT

Practically all kidney allograft recipients require immunosuppressive therapy to prevent rejection and loss of the allograft. The aim of this study was to determine the occurrence of biopsy-proven acute rejection in low–immunologic risk kidney transplant recipients according to the type of induction (basiliximab vs low-dose of rabbit antithymocyte globulin [rATG], 3.5 mg/kg).

Materials and Methods. A total of 125 patients after primary kidney transplant were included in the retrospective analysis with 6-month follow-up. The immunosuppression regimen included tacrolimus, mycophenolic acid, and corticoids.

Results. We did not find any significant difference in the occurrence of acute rejection or difference in the occurrence of infection complications. Patients in the rATG group had a significantly longer period of cold ischemia, more frequently received kidney transplants from expanded criteria donors, and had significantly more mismatches in HLA-DR. Delayed graft function (DGF) was identified as an independent risk factor for biopsy-proven acute rejection (hazard ratio, 3.4859; $P = .003$). There was comparable incidence of DGF between the 2 groups despite that there were several factors that are more commonly associated with DGF in the rATG group.

Conclusion. Patients with low immunologic risk and high risk of DGF benefit from the rATG induction in dose of 3.5 mg/kg without the increased risk of infection complications with the assumption of good graft function in long-term post-transplant period.

PRACTICALLY all kidney allograft recipients require immunosuppressive therapy to prevent rejection and loss of the allograft. The optimal regimen, including induction therapy, is not clear. A large number of controlled, randomized trials and meta-analyses indicate that induction therapy consisting of biologic antibodies plus

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Novelty Statement: The presented retrospective analysis compares 2 groups of patients (basiliximab vs low-dose rabbit antithymocyte globulin [rATG]) with low immunologic risk after the kidney transplant with 6-month follow-up. The aim of the analysis was to determine the occurrence of acute rejection within the monitored period and to identify risk factors for the development of acute rejection in this "nonrisk" group of patients. We found that the induction with rATG in a dose of 3.5 mg/kg is safe also for this group of patients, it does not represent any increased risk of infectious complications, and it is clearly beneficial for patients with high risk of delayed graft function. Our analysis even confirmed as much as 2 times higher probability of a good graft function 6 months after the transplant in patients with rATG in induction.

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conventional immunosuppressive agent therapy is superior to conventional agent therapy alone in reducing kidney allograft rejection and allograft failure [1–4].

Induction immunosuppressive protocols form the basis of care of a kidney transplant recipient, and every transplant center strives to create the most effective protocol with elimination of risks that induction brings with it. We know from available reviews of the literature that the use of induction improves both short-term and long-term results of transplants. However, use of induction has risks, especially the increased risk of infection complications or malignant diseases [5,6]. There are many diagnostic methods currently available that can determine immunologic risk of the recipient and thus significantly individualize the use of induction.

The induction therapy using T cell–depleting agents or nondepleting interleukin 2–receptor antagonist is commonly used in everyday practice for patients undergoing kidney transplant [7].

Basiliximab (Simulect) is a high affinity chimeric monoclonal antibody with murine variable and human constant regions directed against the interleukin 2 receptor alpha chain on T lymphocytes [8]. Expression of CD25 is specific for activated T cells; basiliximab selectively targets activated lymphocytes and does not affect resting cells [9]. Chimerization of the murine antibody by human immunoglobulin G1 is associated with reduced immunogenicity. Basiliximab has been widely used as an induction treatment in renal transplantation with a 2-dose regimen of 20 mg at days 0 and 4 [10].

Rabbit antithymocyte globulin (rATG) is used in the treatment of acute rejection in a dose of 1.5 mg/kg for 7 to 14 days. Induction doses have ranged from 1 to 6 mg/kg/dose over 1 to 10 days with a more typical regimen of 1.5 mg/kg for 3 to 5 days and a cumulative target of 4.5 to 10 mg/kg. In the United States, antibody induction is used in the majority ($> 70\%$) of kidney and almost 50% of thoracic organ transplants, and rATG is the most frequently used induction agent. High doses of rATG in induction can increase the risk of infections; on the other hand, the cumulative dose of < 3 mg/kg might not ensure the prevention of acute rejection development [11].

The aim of this study was to compare the group of patients according to the used induction (basiliximab vs low dose of rATG) regarding the occurrence of acute rejection within the monitored period of 6 months after patients with standard immunologic risk received transplants. Another aim was to identify risk factors for the development of acute rejection in this group of patients as well as to determine factors for good graft function 6 months after the transplant.

MATERIAL AND METHODS

The presented retrospective analysis with follow-up 6 months after the transplant consisted of a total number of 133 adult patients (white) after primary transplant of a kidney from a brain-dead donor, who underwent the transplant in the Martin Transplant Center from January 2012 to April 2018. Patients who underwent graftectomy or died of nonimmunologic cause within 7 days from transplant ($n = 4$) and patients who did not receive any induction ($n = 4$) were excluded from the study, whereby we created a group of 125 patients.

We determined following parameters of all patients included in the monitoring: age at the time of transplant, sex, donor type (expanded criteria donor [ECD], standard criteria donor), cold ischemia time (CIT), time in dialysis program, transplant waiting time, panel-reactive antibodies (PRAs) value, number of mismatches, presence of the delayed graft function (DGF)—defined as the need for at least 1 dialysis session in the first week after kidney transplant, presence of biopsy-proven acute rejection (BPAR) (acute cellular rejection, acute antibody-mediated rejection), and occurrence of infection. We divided the presence of virus diseases into symptomatic and asymptomatic infection. Asymptomatic infections included replication of cytomegalovirus (CMV) more than 1000 cop/mL without any clinical manifestations, replication of BK virus without proof of BK nephropathy in the biopsy or replication of Epstein Barr virus with the need of reduction of the standard immunosuppressive treatment (mycophenolate mofetil). The number of copies of individual viruses was standard determined by means of the polymerase chain reaction. Symptomatic virus infections included symptomatic CMV infection and BK nephropathy. Furthermore, we identified the presence of bacterial infection (determined by the necessity to administer antibiotic treatment, except for prophylaxis) and mycotic infection (necessity to administer antimycotic treatment, except for prophylaxis). We determined estimated glomerular filtration rate (eGFR) (according to Chronic Kidney Disease Epidemiology Collaboration) at the end of the monitored period.

Standard immunosuppression was identical in the whole group: tacrolimus (TAC) (Advagraf), mycophenolate sodium (Myfortic), and prednisone. Dosage and levels of TAC during the first 3 months

Table 1. Immunosuppressive Protocols I and II

	D0	D1	D2	D3-7	D8-14	D15-28	D29-3 mo
Methylprednisolone	500 mg IV	500 mg IV					
Prednisone			20 mg	20 mg	20 mg	15 mg	10 mg
Mycophenolate sodium	2 g/1440 mg	2 g/1440 mg	2 g/1440 mg	2 g/1440 mg	2 g/1440 mg	2 g/1440 mg	1.5g/1080 mg
Tacrolimus	0.2 mg/kg 1 × per d			levels 10-15 ng/mL			levels 8-12 ng/mL
Basiliximab - Protocol I			20 g before reperfusion and at D4				
rATG - Protocol II	1.5 mg/kg	1.0 mg/kg	1.0 mg/kg				

Abbreviations: IV, intravenously; rATG, rabbit antithymocyte globulin.

are shown in Table 1. Reduction of prednisone in the fourth month after the transplant continued to 7.5 mg/d and did not change until the end of the sixth month after the kidney transplant. The level of TAC was in the fourth to sixth month after the transplant was maintained in range of 7 to 10 ng/mL.

Induction immunosuppressive protocols using basiliximab (Simulect) or rATG (Thymoglobulin) are shown in Table 1.

Indications for the induction protocol with basiliximab were the following:

- dialyzing therapy < 5 years,
- PRA 0%,
- standard criteria donor,
- CIT ≤ 12 hours.

Indications for the induction protocol with rATG (3.5 mg/kg cumulatively) were the following:

- dialyzing therapy > 5 years,
- PRA 0%,
- expanded criteria donor,
- CIT > 12 hours (Table 1).

A donor with extended criteria means a donor per the definition of ECD codified in 2002: donors older than 60 years without comorbidities or donors older than 50 years with at least 2 comorbidities that include blood hypertension, death from cerebrovascular accident, or terminal serum creatinine levels > 1.5 mg/dL [12].

Dose of rATG was administered in the standard way with possible correction according to values of CD4 lymphocytes, but significant decrease of CD4 did not occur in any patient; therefore, it was not necessary to reduce or skip the dose. In cases of using the protocol with rATG we used standard pre-emptive prophylaxis with valganciclovir according to the eGFR for all patients during 6 weeks after the transplant.

Aforementioned induction protocols are used in the Martin Transplant Center, and they are not used as general guidelines.

We used a certified statistical program, MedCalc version 13.1.2. (MedCalc Software; International Association of Statistical Computing, Ostend, Belgium). Comparisons of continuous variables between groups were carried out using parametric (t test) or nonparametric (Mann-Whitney) tests; associations between categorical variables were analyzed using the χ^2 test and Fisher exact test, as appropriate. Cox proportional hazard model was used for multivariate analysis and Kaplan-Meier curves were used for survival analyses. We considered a P value $< .05$ to be statistically significant.

Ethical Approval

All procedures involving human participants have been approved according to the ethical standards of the institutional and/or national research committee, including the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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

A total of 125 patients with average age at the time of transplant of 46.4 (SD, 12.8) years was included in the monitoring; the group contained 98 men (71.2%). The group contained 38 patients who received induction with basiliximab and 87 patients who received induction with rATG. Basic characteristics are shown in Table 2.

Table 2. Characteristics of the Group – Baseline

	Basiliximab n = 38	rATG n = 87	*P* Value
Age at KT, mean (SD), y	43.2 (12.7)	47.7 (12.4)	.07
Sex, % men	63.2	74.7	.19
ECD donor, %	13.2	31	.04†
CIT, mean (SD), min	542 (306)	704 (367)	.02†
Dialysis program, mean (SD), mo	18 (17.3)	35.8 (35.6)	.004†
Waiting time for KT, mean (SD), d	219 (198)	896 (479)	< .001†
Mismatch HLA-A, mean (SD)	1.1 (0.7)	1.2 (0.6)	.42
Mismatch HLA-B, mean (SD)	1.2 (0.7)	1.3 (0.6)	.42
Mismatch HLA-DR, mean (SD)	0.7 (0.6)	1.1 (0.6)	< .001†
DGF, %*	13.2	12.6	.93
ACR, %	10.5	8	.16
AMR, %	10.5	11.5	.97
Asymptomatic virus infection, %	34.2	25.3	.31
Symptomatic virus infection, %	2.6	1.2	.57
Bacterial infection, %	15.8	20.7	.52
Mycotic infection, %	0	1.2	.499

Abbreviations: ACR, acute cellular rejection; AMR, acute antibody-mediated rejection; CIT, cold ischemia time; DGF, delayed graft function; ECD, expanded criteria donor; KT, kidney transplant; rATG, rabbit antithymocyte globulin.

*Need of dialysis treatment in the first week after KT.

†$P < .05$.

We found that patients in the rATG group underwent a transplant of a kidney from an ECD donor significantly more often, had significantly longer CIT, spent significantly longer time in a dialysis program, waited for transplant longer, and had significantly more HLA-DR mismatches. We did not find any significant difference in the occurrence of acute rejection and infection complications within the monitored period 6 months after the kidney transplant. We recorded symptomatic virus infection (CMV pneumonia) during the monitored period in the case of 1 patient in the basiliximab group and 1 biopsy-proven BK nephropathy with BK viremia and viruria in the case of a patient in the rATG group. We did not record any mycotic infection in the basiliximab group, and we identified mycotic infection (pneumonia) in 1 patient in the rATG group.

We did not find any significant difference in the occurrence of BPAR between monitored groups.

We determined independent risk factors for the development of BPAR by applying multivariate analysis. Of monitored parameters, only DGF was identified as an independent risk factor for the development of BPAR (Table 3). There was comparable incidence of DGF between the 2 groups despite that there were several factors that are more commonly associated with DGF in the rATG group.

Furthermore, we determined which of the monitored parameters influence good function of the graft determined by eGFR ≥ 60 mL/min (Chronic Kidney Disease Epidemiology Collaboration). We found that in the cases of basiliximab induction and a history of acute rejection independently reduce the chance of good graft function.On the other hand, in the case of rATG induction, the occurrence of good graft function increases by 2 times (Table 4).

Table 3. Cox Regression Hazard Model

Biopsy-Proven Acute Rejection	Hazard Ratio	95% CI	*P* Value
Age at KT ≥ 60 y	1.2150	0.4479-3.2958	.70
Sex, men	0.8100	0.3709-1.7691	.60
ECD donor	1.4661	0.6049-3.5536	.40
CIT > 720 min	0.5288	0.0688-4.0638	.54
Dialysis program > 60 mo	1.0997	0.3689-3.2786	.86
Waiting time for KT > 365 d	1.7031	0.7515-3.8595	.20
1 mismatch HLA-A	1.4159	0.6289-3.1877	.40
2 mismatches HLA-A	1.2050	0.5200-2.7922	.66
1 mismatch HLA-B	0.6642	0.2952-1.4947	.32
2 mismatches HLA-B	1.0825	0.5169-2.2670	.83
1 mismatch HLA-DR	1.4944	0.5472-4.0808	.43
2 mismatches HLA-DR	1.8864	0.5165-6.8890	.34
DGF*	3.4859	1.5211-7.9884	.003†
Basiliximab induction	1.2449	0.5687-2.7252	.58
rATG induction	0.6857	0.2940-1.5994	.38
Asymptomatic virus infection	1.3083	0.6079-2.8158	.49
Bacterial infection	0.9382	0.3657-2.4067	.89

Abbreviations: CIT, cold ischemia time; DGF, delayed graft function; ECD, expanded criteria donor; KT, kidney transplant; rATG, rabbit antithymocyte globulin.
*Need of dialysis treatment in the first week after KT.
†$P < .05$.

Table 4. Cox Regression Hazard Model

eGFR ≥ 60 mL/min (6 mo after KT)	Hazard Ratio	95% CI	*P* Value
Age at KT ≥ 60 y	0.5021	0.1204-2.0933	.34
Sex, men	1.6093	0.7193-3.6006	.25
ECD donor	0.7633	0.4209-1.3843	.37
CIT > 720 min	0.7310	0.4253-1.2565	.26
Dialysis program > 60 mo	1.2079	0.4491-3.2493	.71
Wait time for KT > 365 d	1.0006	0.4298-2.3295	> .99
1 mismatch HLA-A	0.7872	0.2627-2.3586	.67
2 mismatches HLA-A	0.5772	0.2742-1.2150	.15
1 mismatch HLA-B	1.2839	0.5109-3.2265	.60
2 mismatches HLA-B	1.2142	0.7288-2.0229	.46
1 mismatch HLA-DR	1.2461	0.7584-2.0474	.38
2 mismatches HLA-DR	0.6111	0.5138-1.4794	.87
DGF*	0.4374	0.1370-1.3962	.16
Induction: basiliximab/ daclizumab	0.5489	0.3318-0.9082	.02†
Induction: rATG	2.0532	1.2514-3.3688	.004†
Asymptomatic virus infection	1.7042	0.8010-3.6258	.17
Bacterial infection	0.8152	0.4656-1.4273	.51
Case history of acute rejection	0.3421	0.1358-0.8622	.02†

Abbreviations: CIT, cold ischemia time; DGF, delayed graft function; ECD, expanded criteria donor; eGFR, estimated glomerular filtration rate; KT, kidney transplant; rATG, rabbit antithymocyte globulin.
*Need of dialysis treatment in the first week after KT.
†$P < .05$.

Average value of eGFR 6 months after transplant was 46 (SD, 15) mL/min in the basiliximab group and 45.5 (SD, 11.8) mL/min in the rATG group ($P = .83$).

Figures 1 and 2 represent 6-month graft and patient survival, where we did not confirm any significant difference.

DISCUSSION

The Kidney Disease: Improving Global Outcomes guidelines recommend that T cell–depleting agents should be used only for kidney transplant recipients at high immunologic risk. Our analysis was performed on patients with standard immunologic risk using low doses of rATG with standard immunosuppressive regimen (TAC, mycophenolic acid, and steroid) [13]. We did not find difference in the occurrence of acute rejection between monitored groups (basiliximab vs rATG) despite the fact that parameters of donors (ECD) and recipients (duration of dialysis treatment, waiting time for transplant, CIT, HLA-DR mismatches) were significantly worse in the rATG group. That would presuppose higher occurrence of acute rejection in this group of patients. On the other hand, the immunologic risk was low in both groups (PRA = 0%, primary transplant, white).

Lee at al [14] compared (but in a very small group of patients, n = 46) 2 induction protocols (basiliximab vs 3 mg rATG cumulatively + standard immunosuppressive regimen: TAC, mycophenolic acid, and prednisone) in a group of donors with low immunologic risk. They confirmed that rATG significantly reduces the occurrence of acute rejection in the period of 6 months after kidney transplant in these patients (occurrence BPAR was 0% in rATG group vs 23.8% in basiliximab group; $P = .002$). Of possible infection complications, the authors monitored only the occurrence of CMV infection, which was more often recorded in the rATG group. We did not confirm in our analysis any significant difference in the occurrence of virus or bacterial infections [14]. Of other analyses and studies comparing the induction with basiliximab and rATG (3 mg/kg cumulatively), the ongoing (or recently completed) randomized multicentric TAILOR study of patients undergoing kidney transplant from a living donor [15] should be noted. In cases of kidney transplant from a living donor, factors supporting the development of DGF are eliminated.

We confirmed that the independent risk factor for the development of acute rejection in our group was DGF. Use of rATG in low doses, as it was used in our analysis, can therefore benefit patients with low immunologic risk but with other parameters (ECD, long CIT, long dialysis treatment) that increase the risk of DGF and in the end also the occurrence of acute rejection.

Delayed graft function is commonly considered a risk factor for acute rejection. Analysis by Wu et al of 645 patients confirmed significantly higher occurrence of BPAR in the group of patients with DGF compared with a

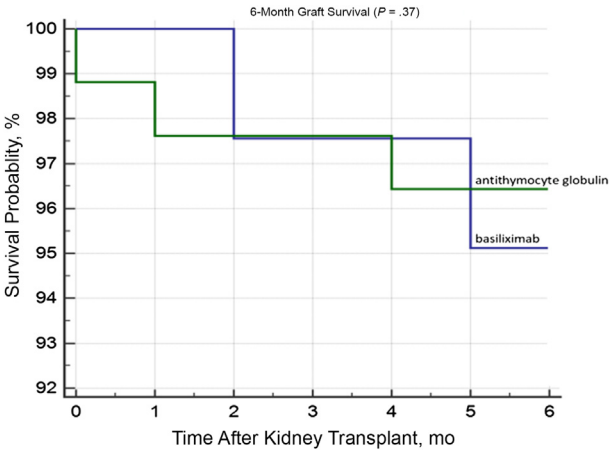

Fig 1. Six month graft survival.

non-DGF group. The adjusted relative hazard for BPAR in DGF (vs no DGF) was 1.55 (95% CI, 1.03-2.32) [16]. The effect of DGF on long-term results of transplants is described by the analysis on almost 30,000 patients. The DGF-associated risk of graft failure was greatest in the first post-transplant year and in patients with concomitant acute rejection (hazard ratio, 8.22; 95% CI, 4.76-14.21). In contrast, the DGF-associated risk of graft failure after the first post-transplant year in patients without acute rejection was far lower (hazard ratio, 1.15; 95% CI, 1.02-1.29) [17]. Results of this extensive analysis again confirm that patients with low immunologic risk but with a high risk of DGF development will benefit from the low-dose rATG induction.

In our analysis there was no significant difference in incidence of DGF between the 2 monitored groups.

Rabbit antithymocyte globulin has complex immunomodulatory effects that are relevant to DGF. In addition to rapid and deep T cell depletion, rATG inhibits leukocyte migration and adhesion; rATG experimental studies have demonstrated impaired ischemia-reperfusion injury-related tissue damage in reperfused tissues, consistent with histologic evidence from transplant recipients. Intraoperative rATG treatment can improve kidney transplant function and reduce the incidence of DGF [18].

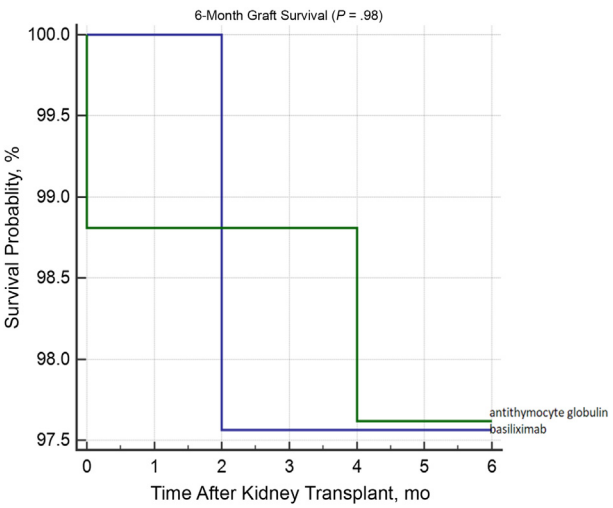

Fig 2. Six month patient survival.

We did not confirm in our analysis any significant difference in the graft and patient survival within the monitored period, but we did confirm that the acute rejection in case history significantly reduces the probability of good graft function 6 months after transplant, and induction with rATG increases this probability by as much as 2 times. There are several factors that affect the graft function, not only parameters of the recipient and post-transplant period, but also parameters of the donor. We did not record in our group of patients any significant difference between eGFR in the sixth month after transplant between the basiliximab group and rATG group. Based on our results, we assume that patients with low immunologic risk and high risk of DGF benefit from the rATG induction in a dose of 3.5 mg/kg without increased risk of infection complications with the assumption of good graft function in the long-term post-transplant period.

CONCLUSION

Patients with low immunologic risk and a high risk of DGF benefit from the rATG induction in a dose of 3.5 mg/kg without the increased risk of infection complications with the assumption of good graft function in the long-term post-transplant period.

We confirmed in our analysis that induction with low-dose rATG or patients with low immunologic risk is safe and effective from the perspective of development of the acute rejection in patients with high risk of DGF. According to our analysis, it can be assumed that ATG might reduce the incidence of DGF.

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