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The Efficacy of Rabbit Anti-Thymocyte Globulin for Acute Kidney Transplant Rejection in Patients Using Calcineurin Inhibitor and Mycophenolate Mofetil-Based Immunosuppressive Therapy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Marieke van der Zwan
BE 2 Marian C. Clahsen-Van Groningen
CE 1 Joke I. Roodnat
B 1 Anne P. Bouvy
B 1 Casper L. Slachmuylders
E 1 Willem Weimar
E 1 Carla C. Baan
ACDE 1 Dennis A. Hesselink
ACDE 1 Marcia M.L. Kho

1 Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, University Medical Center Rotterdam, Rotterdam Transplant Group, Rotterdam, The Netherlands
2 Department of Pathology, Erasmus MC, University Medical Center Rotterdam, Rotterdam Transplant Group, Rotterdam, The Netherlands

Corresponding Author: Marieke van der Zwan, e-mail: m.vanderzwan@erasmusmc.nl
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Background: T cell depleting antibody therapy with rabbit anti-thymocyte globulin (rATG) is the treatment of choice for glucocorticoid-resistant acute kidney allograft rejection (AR) and is used as first-line therapy in severe AR. Almost all studies investigating the effectiveness of rATG for this indication were conducted at the time when cyclosporine A and azathioprine were the standard of care. Here, the long-term outcome of rATG for AR in patients using the current standard immunosuppressive therapy (i.e., tacrolimus and mycophenolate mofetil) is described.

Material/Methods: Between 2002 to 2012, 108 patients were treated with rATG for AR. Data on kidney function in the year following rATG and long-term outcomes were collected.

Results: Overall survival after rATG was comparable to overall survival of all kidney transplantation patients (P=0.10). Serum creatinine 1 year after rATG was 179 µmol/L (interquartile range (IQR) 136–234 µmol/L) and was comparable to baseline serum creatinine (P=0.22). Early AR showed better allograft survival than late AR (P=0.0007). In addition, 1 year after AR, serum creatinine was lower in early AR (157 mol/L; IQR 131–203) compared to late AR (216 mol/L; IQR 165–269; P<0.05). The Banff grade of rejection, kidney function at the moment of rejection, and reason for rATG (severe or glucocorticoid resistant AR) did not influence the allograft survival.

Conclusions: Treatment of AR with rATG is effective in patients using current standard immunosuppressive therapy, even in patients with poor allograft function. Early identification of AR followed by T cell depleting treatment leads to better allograft outcomes.

MeSH Keywords: **Antilymphocyte Serum • Calcineurin • Graft Rejection • Kidney Transplantation**

Abbreviations: **aABMR** – acute antibody-mediated rejection; **aTCMR** – acute T cell mediated rejection; **AR** – acute rejection; **ATG** – anti-thymocyte globulin; **C_0** – pre-dose concentrations; **CKD** – chronic kidney disease; **CKD-EPI** – Chronic Kidney Disease Epidemiology Collaboration; **CMV** – cytomegalovirus; **CsA** – cyclosporine A; **CI** – confidence interval; **DGF** – delayed graft function; **DSA** – donor-specific antibodies; **EBV** – Epstein-Barr virus; **eGFR** – estimated glomerular filtration rate; **HR** – hazard ratio; **IQR** – interquartile range; **MMF** – mycophenolate mofetil; **rATG** – rabbit anti-thymocyte globulin; **RR** – relative risk; **TAC** – tacrolimus

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Background

T cell depleting antibody therapy with rabbit anti-thymocyte globulin (rATG) is the treatment of choice for glucocorticoid-resistant or recurrent acute rejection (AR) [1]. In addition, many physicians use rATG as first-line therapy for severe acute T cell-mediated rejection (aTCMR, Banff grade IIA or higher) or as a component of treatment directed against acute antibody-mediated rejection (aABMR) [2].

The evidence of the efficacy of rATG therapy for AR dates from the era when azathioprine and cyclosporine A (CsA) were the standard of care. However, there is little evidence to guide the type of anti-rejection therapy in kidney transplant recipients treated with the current standard maintenance immunosuppressive therapy, consisting of tacrolimus (TAC) and mycophenolate mofetil (MMF) [3]. The advice on anti-rejection therapy in the KDIGO guideline [1] is based on a systematic review with meta-analysis [4], which was recently updated [5]. This review compared T cell depleting therapy (ATG, both horse and rabbit, anti-lymphocyte globulin and muromonab-CD3) to pulse glucocorticoids as treatment of the first episode of kidney transplant AR. ATG therapy showed less failure of reversal of AR compared with pulse glucocorticoids (relative risk (RR) 0.40; 95% confidence interval (CI) 0.22–0.74). Furthermore, allograft loss 18 months after AR was significantly less in the ATG group compared with patients treated with pulse glucocorticoids (RR 0.63, 95%CI 0.44–0.89) [5].

The studies included in this systematic review had a wide variation in definition of outcomes. Not all studies reported the immunization status of the patients, details about trial methodology were often incompletely reported, and most studies included only small numbers of patients [5]. Most importantly, because the studies were performed more than 2 decades ago, all patients received maintenance immunosuppressive treatment consisting of CsA and/or azathioprine. No patients received TAC plus MMF-based therapy.

The lack of data on the effectiveness of rATG in kidney transplantation patients using TAC plus MMF-based immunosuppressive therapy and the availability of several new options to treat aTCMR, such as anti-CD52 therapy (alemtuzumab) and anti-CD20 therapy [2,6,7], prompted us to analyze the results of rATG for AR after kidney transplantation at our center. The objectives of this study were to: 1) investigate the long-term outcomes (patient survival, allograft survival, and adverse events) and 2) characterize which patients were at greater risk for adverse outcomes after rATG therapy for AR. The outcomes presented here could serve as a basis for future studies that describe other anti-rejection therapies in patients treated with TAC and MMF.

Material and Methods

Study design and inclusion criteria

A retrospective analysis was conducted of all kidney transplant recipients who received rATG (Thymoglobulin®, Sanofi Genzyme, United States) because of AR between 2002 and 2012 in the Erasmus Medical Center. This specific period was chosen because from 2000 onwards, patients received TAC as the standard maintenance immunosuppression. After 2012, the anti-rejection protocol was changed and ever since patients have been treated with alemtuzumab in cases of glucocorticoid-resistant or severe aTCMR. According to Dutch law, the present study did not require formal approval of the local medical ethical review board [8]. All AR episodes were proven by biopsy except for one. In this case, no biopsy was performed. This case was included in all analyses except the analyses with the Banff classification. For the present study, all kidney allograft biopsies were revised by an experienced renal-pathologist (M.C.C-v.G) and categorized according to the Banff 2015 classification [9].

In the period 2002–2012, 1463 patients received a kidney transplantation at our center. Patients treated with rATG were identified by means of our kidney transplant registry and the electronic medication prescription system of our hospital pharmacy. Sixteen patients with blood group ABO-incompatible kidney transplantations who received rATG were excluded from the analysis.

Immunosuppressive protocol

The standard immunosuppressive regimen after 2009 included induction therapy with basiliximab (Simulect®, Novartis Pharma, Basel, Switzerland) 20 mg intravenously on days 0 and 4 after transplantation. Before 2009, induction therapy was not given in our center on a routine basis except to recipients of a deceased-after-circulatory-death donor kidney. The standard maintenance immunosuppressive regimen consisted of TAC (Prograf®, Astellas Pharma, Leiden, the Netherlands), MMF (Cellcept®, Roche Pharmaceuticals, Basel, Switzerland), and glucocorticoids.

Dosing of TAC was based on pre-dose concentrations (C_0). Target C_0 for tacrolimus were 10–15 µg/L (week 1–2), 8–12 µg/L (week 3–4), 5–10 µg/L (week 4–12), and 4–8 µg/L from month 4 onwards. MMF was started at 1000 mg twice daily. Before 2010, the dose of MMF was adjusted if the patient experienced side effects, like gastrointestinal complaints and leucopenia. From 2010, dosing of MMF was based on C_0, aiming for target C_0 of 1.5–3.0 mg/L. Glucocorticoids were given as an intravenous dose of 100 mg on days 0–3 and thereafter were started in a dose of 20 mg/day (days 4–20). Thereafter, glucocorticoids

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were tapered and completely withdrawn around month 4. Patients using other experimental immunosuppressive drugs as part of clinical studies were included in the current analysis.

Treatment of AR

Patients with AR were initially treated with intravenous methylprednisolone 1000 mg (Solu-Medrol®, Pfizer, New York, United States) daily for 3 consecutive days. Treatment with rATG was left at the discretion of the attending physician and was based on the effect of pulse glucocorticoids, severity of the AR (Banff category), previous transplant rejection, medical history, and patient immunization status. For a subgroup analysis, 2 reasons for rATG therapy were distinguished: 1) glucocorticoid-resistant and 2) severe AR. In glucocorticoid-resistant AR, patients were initially treated with pulse glucocorticoids. If the effect was not satisfactory, rATG therapy was administered subsequently. In patients with severe AR (based on Banff category and kidney function) rATG was given as first-line therapy or shortly after pulse glucocorticoids (without awaiting the full effect of glucocorticoids).

Rabbit ATG was administered in a high flow vein or central venous catheter as a single bolus (4 mg/kg [actual bodyweight, no maximum dose limit]) during 6 hours. The aim was an absolute whole blood CD3+ T cell count below 200×10^6/L for a duration of 2 weeks. If CD3+ T cell counts increased during this period, a repeat dose of rATG (4 mg/kg) was administered. Patients with an aABMR or a mixed type AR might be treated additionally with intravenous immunoglobulins, rituximab, or plasma-exchange, according to the KDIGO guideline and local protocol [1].

All patients received pre-medication prior to rATG administration: prednisolone 50 mg intravenously, 4 mg clemastine, and 1000 mg acetaminophen. For 3–6 months, patients received *Pneumocystis jirovecii* prophylaxis (sulfamethoxazole/trimethoprim) and cytomegalovirus (CMV) prophylaxis ([val]ganciclovir or CMV immunoglobulins).

Outcomes

The following data were collected: baseline characteristics, anti-rejection therapy, rejection type and severity according to the Banff 2015 classification [9], allograft function (serum creatinine and estimated glomerular filtration rate (eGFR; Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] [10] and proteinuria), allograft survival (censored for death), and serious adverse events. Baseline serum creatinine was defined as the lowest serum creatinine in the 3 months before AR. Baseline eGFR was defined as the highest eGFR in the 3 months before AR. Data on serum creatinine and eGFR were included in the analysis when the patient had a functioning allograft. The follow-up period for infection was from rATG administration until death, loss to follow-up, or re-transplantation. Malignancies and mortality were evaluated until last follow-up, which could be after a subsequent kidney transplantation. Allograft loss was defined as the need for dialysis or re-transplantation. In all patients who received a kidney transplant between 2002 and 2012 in our center, allograft survival and patient survival were analyzed and compared with that of patients suffering from AR and requiring rATG therapy. The hospital information system, NKR (Netherlands Cancer Registry, *https://www.cijfersoverkanker.nl/*), and NOTR (Netherlands Organ Transplant Registry, *https://www.transplantatiestichting.nl/*) were used for data retrieval regarding the occurrence of malignancies. Infections were considered serious if the infection necessitated hospitalization or occurred during hospital admission for another reason. Viral infections were recorded. BK viremia was tested on indication. Unexplained fever, chills, hypotension, rash, dyspnea, lymphadenopathy, arthralgia, or myalgia were considered serum sickness.

Statistical methods

Categorical variables are presented as number (percentage). Continuous variables are presented as mean with standard deviation for parametric variables or median with interquartile range (IQR) for non-parametric variables. For differences between paired samples, the paired 2-sample *t*-test or Wilcoxon signed rank test were used. For unpaired non-parametric continuous data, the Kruskal-Wallis test and Mann-Whitney U test were used. Allograft survival between groups was analyzed by means of Kaplan-Meier survival analysis. The influence of independent variables was analyzed with univariate Cox proportional hazard regression analysis. Because of the number of events (49 allograft losses), it was only possible to test a maximum number of variables mounting up to 5 degrees of freedom per analysis in the multivariate Cox proportional hazard regression analysis. The influence of the most significant variable was tested in the presence of all the other variables one by one in order of increasing *P* values. Variables were eliminated from the model by backward elimination. They were replaced by other variables so that at last all variables had been present in the model. A 2-sided *P* value <0.05 was considered statistically significant. For statistical analysis, GraphPad Prism, version 5 (San Diego, CA, USA) and SPSS version 21 (SPSS Inc., Chicago, IL, USA) were used.

Results

Patient demographics

A total of n=108 episodes of AR requiring rATG therapy were identified in 103 patients (Table 1). Five patients were diagnosed

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Table 1. Baseline characteristics of patients requiring rATG because of AR.

Characteristic		
Patients – no.	103	
Kidney transplantations– no.	107	
Recipient age – yr.	46	(35–56)
Donor age – yr.	54	(46–61)
Female sex – no. (%)	64	(62.1)
Cause of ESRD – no.		
DM/HTN/GN/PKD/reflux/other/unknown	23/10/18/16/17/16/3	
Ethnic distribution – no.		
Caucasian/Black/Asian/Arab/other	70/16/5/5/7	
Transplant number – no.		
1/2/3/4	76/25/5/1	
Preemptive kidney transplantation – no. (%)	25	(23.4)
Donor type – no.		
LR/LUR/DBD/DCD	35/47/15/10	
HLA mismatch		
HLA A: 0/1/2	21/60/23	
HLA B: 0/1/2	11/55/38	
HLA DR: 0/1/2	13/50/41	
PRA actual – no. (%)		
0–5%	81	(77.1)
6–83%	21	(20)
84–100%	3	(2.9)
PRA peak – no. (%)		
0–5%	62	(59)
6–83%	32	(30.5)
84–100%	11	(9.5)
CMV IgG serostatus recipient		
Positive/negative	75/31	
EBV IgG serostatus recipient		
Positive/negative	90/7	
Induction therapy – no.		
None	62	
Basiliximab/ATG/Daclizumab	33/10/2	
Maintenance immunosuppression – no. (%)		
TAC/MMF/glucocorticoids	58	(53.7)
TAC/MMF	20	(18.5)
TAC + other (non-MMF)	6	(5.6)
MMF + other (non-TAC)	20	(18.5)
Other combinations	4	(3.7)
rATG administration – no.	108	
DGF during rejection episode – no. (%)	19	(17.6)
Primary non-function – no. (%)	5	(4.6)
Time to rejection – days	24	(8–339)
Early rejection (<1 month) – no. (%)	56	(51.9)
Intermediate rejection (1–3 months) – no. (%)	8	(7.4)
Late rejection (>3 months) – no. (%)	44	(40.7)
Banff 2015 classification – no.*		
aTCMR		
aTCMR IA	6	
aTCMR IB	8	
aTCMR IIA	21	
aTCMR IIB	20	
aTCMR III	1	
ABMR		
a/aABMR	12	
c/aABMR	3	
Mixed aTCMR with a/aABMR		
aTCMR IA	1	
aTCMR IB	7	
aTCMR IIA	2	
aTCMR IIB	8	
Mixed aTCMR with c/aABMR		
aTCMRIIA	1	
C4d positive ABMR	18	
C4d negative ABMR	10	
No diagnosis after reclassification	18	
Anti-rejection therapy		
Methylprednisolone prior to rATG – no. (%)	93	(86.1)

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Table 1 continued. Baseline characteristics of patients requiring rATG because of AR.

Characteristic	
Cumulative dose of methylprednisolone, mg	
1000/2000/3000/6000	2/9/79/3
Cumulative dose of rATG per patient, mg	555(250–715)
Cumulative dose of rATG per patient, mg/kg	7.4
rATG number of gifts – no.	
1/2/3/4	30/62/15/1

Characteristic	
Necessity for additional anti-rejection therapy <3 months – no.	
Methylprednisolone	10
Intravenous immunoglobulins	6
Rituximab	3
Plasma exchange	3
Muromonab-CD3	1

Data are numbers (%) or median (interquartile range). Other kidney diseases included focal segmental glomerulosclerosis, hemolytic uremic syndrome, nephronophtisis, tuberous sclerosis or tubulo-interstitial nephritis. TAC + other regime contained combinations of TAC, glucocorticoids, sirolimus, everolimus, AEB071, or FTY720. MMF + other regime contained combinations of MMF, glucocorticoids, sirolimus, cyclosporine A, everolimus, or CP-690550. Other combinations existed of a combination of azathioprine, glucocorticoids, everolimus, cyclosporine A, AEB071, or FTY720. * Banff 2015 re-classification in 18 biopsies was not possible. Fifteen patients' biopsies were either missing from archives or there was insufficient material to allow for reclassification. In 3 patients, no histologic diagnosis of AR was made (although the clinical picture was strongly suspect for AR). ABMR – antibody mediated rejection; a/aABMR – acute/active antibody mediated rejection; aTCMR – acute T cell mediated rejection; c/aABMR – chronic/active antibody mediated rejection; CMV – cytomegalovirus; DBD – donation after brain death; DCD – donation after circulatory death; DGF – delayed graft function (need for dialysis in the first week after transplantation); DM – diabetes mellitus; EBV – Epstein-Barr virus; ESRD – end stage renal disease; GN – glomerulonephritis; HTN – hypertensive nephropathy; LR – living related; LUR – living unrelated; MMF – mycophenolate mofetil; PKD – polycystic kidney disease; PRA – panel reactive antibody; rATG – rabbit anti-thymocyte globulin; TAC – tacrolimus.

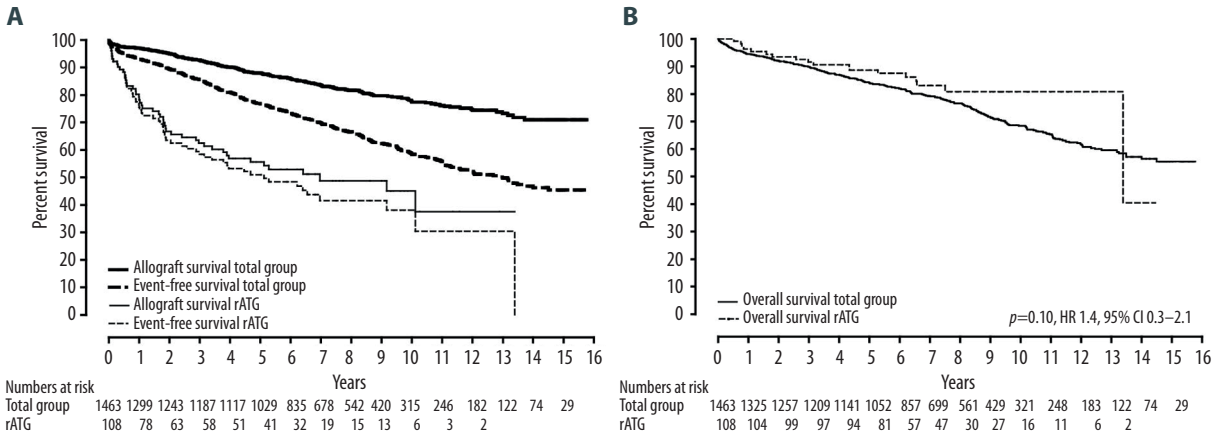

Figure 1. Event-free survival, overall survival and allograft survival curves of patients treated with rATG because of AR. (**A**) Event-free survival and allograft survival censored for death of patients treated with rATG for AR and all patients transplanted with a kidney and not treated with rATG between 2002 and 2012. Event-free survival is time from transplantation (in case of the total group of patients) or AR (in case of rATG treated patients) to death or allograft loss. Event-free survival of the total group of patients *versus* patients treated with rATG: *P*<0.0001, HR 3.9, 95%CI 2.6–5.8. Allograft survival of the total group *versus* patients treated with rATG; *P*<0.0001, HR 15.9, 95%CI 9.2–27.4. (**B**) Overall survival of all patients transplanted with a kidney between 2002 and 2012 and patients treated with rATG for AR; *P*=0.10, HR 1.4, 95%CI 0.3–2.1.

with a second episode of AR in the same kidney transplant, which also required rATG treatment. Most rejections were aTCMR (Table 1).

Forty-five patients received induction therapy (Table 1). At the time of AR, the majority of patients were treated with combination therapy consisting of TAC, MMF, with or without glucocorticoids (72.2%). Six patients (5.6%) used a TAC-based immunosuppressive regimen and 20 patients (18.5%) were treated with MMF-based immunosuppressive regimen (without TAC) at the time of rejection. TAC and glucocorticoid dosing was stable during the 2002–2012 study period. In contrast,

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Table 2. Results of the univariate cox proportional hazards analysis.

Variable (reference category)	Exp (B)	95% CI for Exp (B)	p-Value
Patient characteristics			
Recipient age at transplantation (per yr)	0.99	0.97–1.01	0.32
Recipient age at acute rejection (per yr)	0.99	0.97–1.01	0.47
Donor age (per yr)	0.99	0.97–1.02	0.54
Gender (female)	0.95	0.54–1.68	0.86
Race (Caucasian)	0.86	0.46–1.59	0.63
Transplant number (1)	0.84	0.45–1.57	0.59
PRA current (<6%)	1.13	0.58–2.20	0.73
PRA (per%)	1.00	0.99–1.01	1.00
Transplant characteristics			
Type donor (living donor)	1.36	0.69–2.68	0.37
HLA mismatch (per HLA mismatch)	0.94	0.78–1.14	0.54
Therapy characteristics			
Induction therapy (no)	0.90	0.50–1.63	0.74
Maintenance therapy (TAC+MMF)	0.70	0.38–1.27	0.23
Glucocorticoid maintenance (no)	0.40	0.22–0.72	<0.0001
Rejection characteristics			
Timing rejection (<1 month)			<0.0001
1–3 months	1.54	0.45–5.22	0.49
>3 months	3.64	1.97–6.72	<0.0001
Type rejection (aTCMR I)			0.55
CKD at time rejection (CKD 3b)			0.64
Reason rATG (GC resistant rejection)	0.88	0.50–1.54	0.65

Univariate analysis of the risk of allograft loss with hazard ratio (Exp(B), 95% confidence interval and p-value. Race is caucasian or non-caucasian. Transplant number is 1 or >1. PRA current is <6% or ≥6%. Type donor is living or postmortal. Maintenance therapy is TAC+MMF or TAC+other and MMF+other. Glucocorticoid use at the time of rejection. Type rejection is aTCMR I, aTCMR II+III, ABMR, or mixed. CDK at time rejection is CKD3b, CKD4, CKD5, or delayed graft function. Reason rATG is glucocorticoid (GC) resistant or severe rejection.

MMF dosing, was significantly lower in the 2010–2012 period compared with 2002–2006: 1000 mg (IQR 1000–2000 mg) versus 2000 mg (IQR 1250–2000 mg; *P*=0.04).

Efficacy

Allograft survival

Allograft survival and event-free survival (survival free from allograft loss or death) in rATG treated patients was significantly worse than in the total group of kidney transplant recipients without rATG treatment (*P*<0.0001, hazard ratio (HR) 3.9, 95%CI 2.6–5.8 and *P*<0.0001, HR 15.9, 95%CI 9.2–27.4, respectively; Figure 1A). In the year after rATG treatment, 28 patients (25.9%) experienced allograft loss, 5 of whom had primary non-functioning allografts (Figure 1A). In the full observation period (median 6.8 years, IQR 4.9–9.1) 49 patients lost their allograft. Median allograft survival of the total group was 7.0 years (Figure 1A).

In univariate Cox proportional hazard analysis, 2 variates had a significant influence on death-censored allograft survival: timing of AR and glucocorticoid use during AR (Table 2). Allograft survival was significantly better in the patients with early AR (<1 month)

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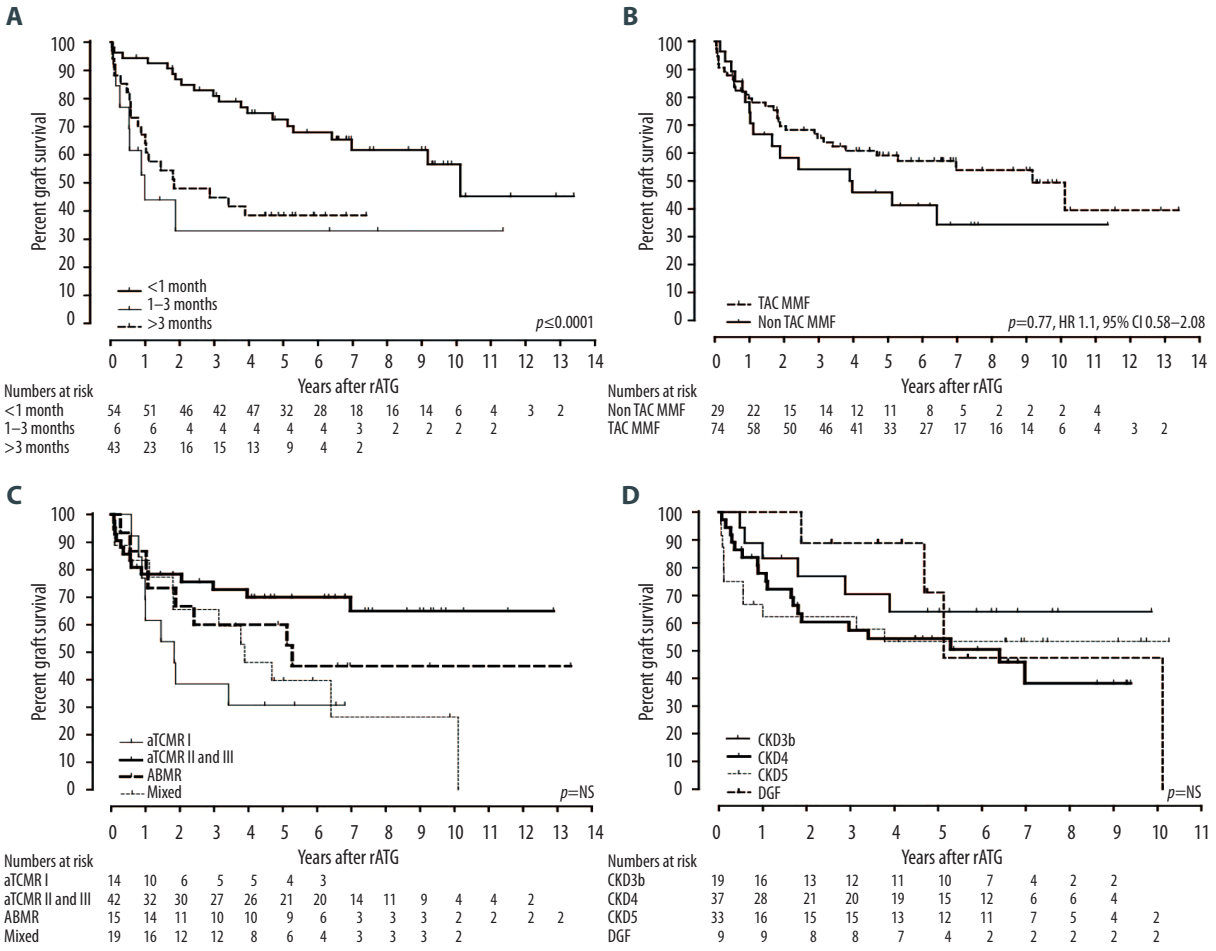

Figure 2. Allograft survival curves of different subgroups of patients treated with rATG for AR. (**A**) Death-censored allograft survival in early (<1 month after transplantation), intermediate (1–3 months) and late AR (>3 months). (**B**) Death-censored allograft survival of patients using the combination of maintenance immunosuppression TAC/MMF versus patients using other combinations of immunosuppression. (**C**) Death-censored allograft survival of patients after rATG therapy grouped by the categories of the Banff 2015 classification. aTCMR I – acute T cell mediated rejection grade IA+IB, aTCMR II and III – acute T cell mediated rejection grade II and III. ABMR – acute and chronic active antibody mediated rejection, mixed – patients with a mixed AR (aTCMR and aABMR). (**D**) Death-censored allograft survival grouped by chronic kidney disease (CKD) stage. CKD3b=30–45 mL/min, CKD4=15–30 mL/min, CKD5 ≤15 mL/min. DGF– delayed graft function (need for dialysis in the first week after transplantation); NS – not significant.

than in the patients with late AR (>3 months; *P*<0.0001, HR 3.64, 95%CI 1.97–6.72) (Table 2, Figure 2A). Allograft survival was not significantly different between intermediate AR (1–3 months after transplantation) and late AR (*P*=0.50; data not shown). Allograft survival was better in patients using glucocorticoids as part of the maintenance immunosuppressive therapy during AR (*P*<0.0001, HR 0.40, 95%CI 0.2–0.72; Table 2). Glucocorticoids were significantly more often used during AR in patients with early rejections (98%) compared to late rejections (42%; *P*<0.001).

Death-censored allograft survival of patients using TAC/MMF (± glucocorticoids) and patients using other combinations of immunosuppressive drugs was comparable (*P*=0.23, HR 0.70, 95%CI 0.38–1.27; Table 2, Figure 2B). Furthermore, no difference in allograft survival was seen between aTCMR grade I, aTCMR grade II+III, aABMR and mixed-type AR (Figure 2C; *P*=0.55; Table 2). Remarkably, death-censored allograft survival was comparable between all chronic kidney disease (CKD) stages (CKD 3b, CKD 4, CKD 5) and delayed graft function (DGF; Figure 2D, Table 2, *P*=0.64).

Sixty-two patients (57.4%) received rATG because of glucocorticoid-resistant AR, whereas 46 patients (42.6%) were treated with rATG because of severe AR. Death-censored allograft survival were comparable between the 2 groups (*P*=0.65, HR 0.88, 95%CI 0.50–1.54; Table 2, Supplementary Figure 1).

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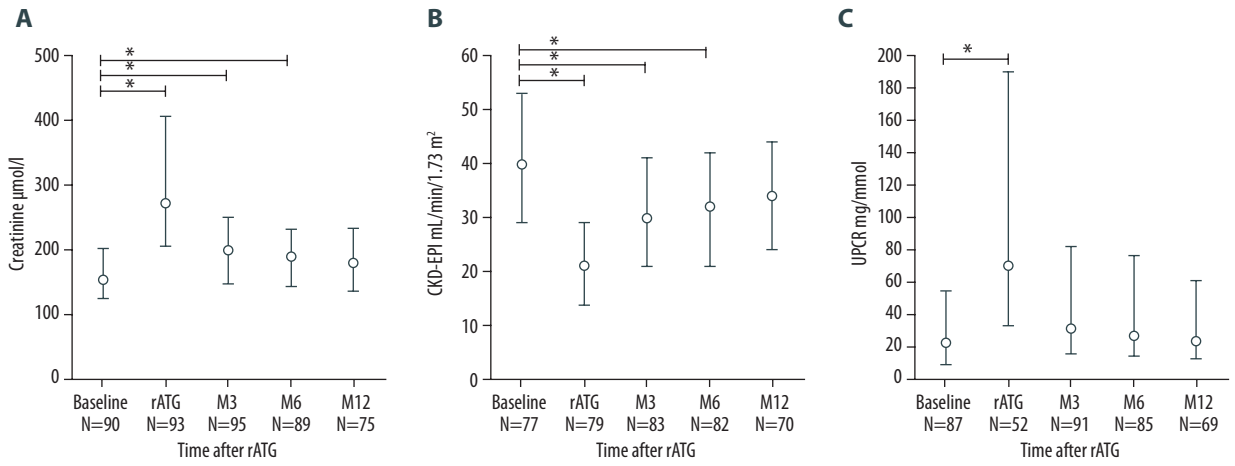

Figure 3. Serum creatinine (µmol/L), creatinine clearance (CKD-EPI, mL/min/1.73 m^2) and urine protein to creatinine ratio (UPCR) before and after AR and rATG therapy. Data are median and IQR. M3 – 3 months after rATG ±4 weeks. M6 – 6 months after rATG ±6 weeks. M12 – 12 months after rATG ±8 weeks. * Significantly different compared with baseline (P<0.05). N – number of patients with laboratory parameters at that specific time point.

In a multivariate analysis, the influence of timing of AR on allograft survival in the presence of each variable was tested. Apart from timing of AR, no other variables showed a significant influence on allograft survival. This means that the final result of the multivariate analysis was the same as that of the univariate analysis of the influence of timing of AR (Table 2).

Allograft function

Rabbit ATG efficacy was also reflected in kidney function. One year after rATG therapy, kidney function (median serum creatinine) in the patients without allograft loss in the first year was comparable to baseline kidney function (P=0.22; Figure 3). Twelve months after rATG, 33.9% of patients had a serum creatinine comparable to baseline level (±25%), 43.5% of patients showed an increase of serum creatinine of more than 25%, and 22.6% of patients showed a decrease in serum creatinine of more than 25% compared to baseline (data not shown). The urine protein/creatinine ratio (UPCR) was significantly higher at the moment of rejection compared to baseline level (P<0.001, Figure 3C). However, the UPCR had normalized to baseline level at 3 months after transplantation (Figure 3C).

Besides better allograft survival, the patients with early AR also had a significantly lower serum creatinine 12 months after AR compared to the patients with late AR (157 µmol/L [IQR 131–203] versus 216 µmol/L [IQR 165–269], respectively, P<0.05; Table 3). In patients with late AR, serum creatinine 12 months after AR did not return to baseline: 216 µmol/L versus 148 µmol/L, respectively (P<0.001; Table 3).

Serum creatinine was comparable between patients with various types of AR at baseline and at time of diagnosis (Table 3). Twelve months after rATG therapy, serum creatinine in patients with aTCMR grade I was significantly higher than in patients with aTCMR grade II and III: 248 µmol/L versus 144 µmol/L, respectively (P<0.05; Table 3) in the patients without allograft loss in the first year. Allograft function at 12 months was comparable between the other groups (Table 3). The interval between pulse glucocorticoids and rATG was significantly longer in patients with aTCMR grade I than in patients with aTCMR grade II and III: 31 days (IQR 23–92) versus 8 days (IQR 3–15; P<0.05).

In patients with glucocorticoid-resistant AR, serum creatinine after 12 months did not return to baseline (180 µmol/L versus 152 µmol/L, P=0.04) in the patients without allograft loss in the first year after rejection (Table 3). The interval between pulse glucocorticoids and rATG was significantly longer in patients with glucocorticoid-resistant AR than in patients with severe AR (15 days (IQR 5–27) versus 4 days (1–9); P=0.0003).

Serum creatinine in the patients with a functioning allograft 1 year after rATG was comparable between all CKD stages (CKD 3b, CKD 4, CKD 5) and DGF (Table 3). In the DGF group, all patients had a functioning allograft after 1 year and median serum creatinine was 170 µmol/L.

Complications

Adverse events and mortality

The overall survival of the patients treated with rATG for AR was similar to the overall survival of all patients who received

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Table 3. Serum creatinine of the subgroups.

Subgroups	Baseline		rATG		M12	
	Median (IQR)	Number	Median (IQR)	Number	Median (IQR)	Number
Banff classification						
aTCMR IA and IB	148 (208–299)	13	299 (229.5–382)[a]	13	248 (182–372)[b]	8
aTCMR IIA, IIB and III	165 (132–223)	39	270 (212–412)[a]	39	144 (132–190)	31
ABMR	153 (114–182)	11	224 (186–274)[a]	10	203 (140–320)	13
Mixed	143 (111–163)	19	211 (166–245)[a]	13	205 (140–239)	15
Reason for rATG therapy						
GC-resistant rejection	152 (111–176)	55	247 (198–367)[a]	55	180 (142–237)[a]	42
Severe rejection	163 (132–223)	35	285 (222–445)[a]	33	171 (129–223)	33
CKD stage						
CKD 3b	148 (116–162)	18	182 (165–200)[acd]	18	182 (131–208)	15
CKD 4	164 (124–207)	37	247 (224–276)[ad]	37	186 (140–252)[a]	25
CKD 5	157 (132–255)	19	428 (367–626)[a]	19	157 (122–203)	15
DGF	DGF	19	DGF	19	170 (137–212)	14
Timing of rejection						
<1 month	165 (141–220)[ef]	37	270 (223–420)[a]	37	157 (131–203)[f]	49
1–3 months	130 (98–152)	7	210 (193–412)[a]	7	182 (135–234)	4
>3 months	148 (109–174)	42	247 (200–340)[a]	40	216 (165–269)[a]	22

Data are median (interquartile range) and number of patients with available serum creatinine (µmol/l) at that specific time point. [a] Significantly different (p<0.05) compared with baseline; [b] Significantly different (p<0.05) compared with aTCMR II and III at M12; [c] Significantly different (p<0.05) compared with CKD4; [d] Significantly different (p<0.05) compared with CKD5; [e] Significantly different (p<0.05) compared with 1–3 months; [f] Significantly different (p<0.05) compared with >3 months. aTCMR I – acute T cell mediated rejection grade IA+IB; aTCMR II and III – acute T cell mediated rejection grade IIA, IIIB and III; ABMR – acute and chronic active antibody mediated rejection; Mixed – patients with a mixed rejection (aTCMR and aABMR); M12 – 12 months (±8 weeks) after rATG therapy; GC – Glucocorticoid-resistant.

a kidney transplantation between 2002 and 2012 in our center after exclusion of those treated with rATG (*P*=0.10, HR 1.4, 95%CI 0.3–2.1; Figure 1B).

Median length of hospital stay after rATG infusion was 15 days (IQR 13–19). Five patients (7.4%) were transferred to the intensive care unit because of hemodynamic instability (Table 4). None of these patients died during the intensive care unit stay. Six patients (5.6%) experienced serum sickness after rATG treatment and 1 patient had cytokine release syndrome.

A significant drop in hemoglobin, thrombocytes, and leukocytes was seen after rATG therapy (Supplementary Figure 2). T cells dropped from 0.54×10^9/L to a minimum of 0.01×10^9/L in the first week (*P*=0.01). After 4 weeks, T cell count was still significantly lower than before rATG therapy (0.11×10^9/L, *P*=0.001; data not shown).

Infections

A total of 124 serious infections were recorded in the first year following rATG therapy (median time after rATG 44 days, IQR 10–157). The most common infections were urinary tract infections and pneumonia (Table 4). In 4 out of 15 patients with pneumonia, *Pneumocystis jiroveci* was the causative pathogen. One patient died of *Pneumocystis jiroveci* pneumonia and 1 patient died of *Candida* sepsis 6 months after rATG therapy.

Median duration of follow-up for viral infections was 4.7 years (IQR 2–6.9). CMV reactivation occurred in 25% of

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Table 4. Adverse events.

Adverse events		
Patient death – no (%)	17	(16.5)
Time after rATG therapy – yr	3.1	(1–6.3)
Cause of death – no.		
Infectious		5
Carcinoma		2
Cardiovascular		3
Hepatic failure		1
Unknown		6
Length of stay – days	15	(13–19)
Serum sickness – no. (%)	6	(5.6)
Cytokine release syndrome – no. (%)	1	(0.9)
Fever* – no. (%)	42	(61.8)
Systolic blood pressure 90–100 mmHg* – no. (%)	6	(9)
Systolic blood pressure <90 mmHg* – no. (%)	7	(10.4)
Tachycardia >100/minute* – no. (%)	44	(69.8)
Interventions – no. (%)		
Transfer to ICU	5	(4.6)
Supplemental oxygen*	9	(13.4)
Volume resuscitation*	6	(9.0)
Diuretic administration*	3	(4.5)
Stop rATG infusion*	2	(3)
Infection in the first year after rATG – no.		124
Viral		19
Fungal		8
Bacterial		97
Blood		8
Urinary tract/urosepsis		51
Skin and soft tissue		9
Lung		15
Other/unknown		14
CMV infections		
CMV reactivation – no. (%)	27	(25)
CMV reactivation, time after rATG	32	(19–74)
Primary CMV infection – no. (%)	0	(0)
EBV infections		
EBV reactivation – no. (%)	4	(3.7)
EBV reactivation, time after rATG	22	(18–170)
Primary EBV infection – no. (%)	1	(0.9)
BK infections		
BK viremia – no. (%)	6	(5.6)
BK viremia, time after rATG	458	(322–844)
Malignancy		
Number		14
Time after rATG therapy – months	63	(45)
Age of patient at time malignancy – yr	56	(10)

Data are numbers (percentage), median (IQR), or mean (standard deviation). * Clinical data of the first 24 hours after rATG administration was retrieved from 67 patients. Fever was defined as temperature above 38.5°C. CMV – cytomegalovirus; EBV – Epstein-Barr virus. The types of malignancies were endometrial carcinoma, adenocarcinoma of the lung, non-seminoma testis, colon carcinoma, renal carcinoma, meningeoma, prostatic cancer, non-Hodgkin lymphoma and EBV related lymphoma. The EBV-related lymphoma was in an IgG seropositive patient and occurred fourteen months after treatment with rATG and was treated with irradiation.

patients (Table 4). One patient was diagnosed with CMV colitis and another with CMV retinitis. Four reactivations and 1 primo infection of Epstein-Barr virus (EBV) occurred (Table 4).

Malignancy

Median duration of follow-up for malignancies was 6.8 years (IQR 4.9–9.1). Twelve primary solid tumors occurred in 11 patients and 2 patients developed a lymphoma after a mean follow-up of 63 months (standard deviation 45; Table 4). In addition, 11 basal cell carcinomas and 4 squamous cell carcinomas were diagnosed in 6 patients after a median of 107 months (IQR 60–117).

Discussion

Rabbit ATG is a purified polyclonal immunoglobulin fraction obtained from the sera of rabbits immunized with human thymocytes [11]. Administration of rATG leads to a fast and profound

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depletion of T cells and to a lesser extent, B cells, which lasts for several months [11,12]. Rabbit ATG also modulates T cell activation by downregulation of molecules that control T cell activation [12]. Repopulation of lymphocytes occurs through homeostatic proliferation of CD4+ and CD8+ memory cells with a senescent and exhausted functional profile [13,14].

Here, the long-term outcomes and adverse events are described for the treatment of AR with rATG in patients using the current standard immunosuppressive therapy. In this cohort, overall 5-year patient survival after rATG treatment for AR was 89% and was similar to the overall survival of all kidney transplant patients transplanted in our center between 2002–2012 who did not receive treatment with rATG. In comparison, literature reported a 5-year patient survival (with and without AR) after deceased donor kidney transplantation and living donor kidney transplantation of 91.8% and 95.6%, respectively [15]. In a systematic review, ATG therapy for AR was not associated with increased mortality after 1 year compared to therapy with pulse glucocorticoids [5]. Our findings support the notion that survival is not affected by rATG in everyday clinical practice.

One year after rATG therapy, 78.2% of all patients had a functioning allograft and 5-year allograft survival was 55.6%. The allograft survival reported here is inferior to that described in 4 other studies where rATG was used as anti-rejection therapy. Two studies describing patients who received rATG as first-line anti-rejection therapy (cumulative dose of rATG 10.5–21 mg/kg) [16] and for glucocorticoid-resistant AR (cumulative dose of rATG 7.5 mg/kg) [17] showed 1-year allograft survival rates of 83% and 89%, respectively. Two other studies demonstrated 5-year allograft survival rates of 78% (cumulative dose rATG 40 mg/kg) [18] and 74% (cumulative dose of rATG not reported) [19] in patients treated with ATG as first-line treatment for AR. These studies are not entirely comparable to ours because in these studies, patients were mainly treated with azathioprine and CsA, and rATG was used as first-line therapy in 3 out of the 4 studies and the cumulative dose of rATG was not similar (being lower in the present study with a cumulative dose of 7.4 mg/kg). Because the efficacy of rATG is dose-dependent [20,21], the differences in the cumulative dose of rATG between the other studies and the present study could influence allograft survival. Given the favorable outcomes of these older studies, perhaps we should have used rATG sooner and in higher dose.

Various parameters of AR determined the risk for allograft loss and recovery of kidney function 1 year after rATG treatment, including timing, Banff grade of rejection, and the reason for rATG therapy (severe or glucocorticoid-resistant AR). Allograft survival and serum creatinine at 12 months were superior in patients with early AR versus late AR. This has also been described by others [22–25]. Late AR is different from early AR for 2 reasons. First, late AR occurs in patients who visit the outpatient clinic less frequently and with intervals of 1–4 months, likely leading to a delay in diagnosis. Second, a major proportion of late AR may have been related to non-adherence to immunosuppressive drugs. Furthermore, late AR is associated with the formation of *de novo* donor-anti-HLA antibodies and the development of aABMR for which no proven therapy exits [26–28].

Death-censored allograft survival was comparable for aTCMR I, aTCMR II+III, ABMR and mixed-type rejection. Surprisingly, kidney function after 12 months in patients with aTCMR grade II+III was superior to those with aTCMR grade I. Allograft survival rates according to Banff grade rejection have been described by others [29,30] and showed better allograft survival in patients with aTCMR I than in patients with aTCMR II and III. Our surprising finding may have resulted from a longer interval between pulse glucocorticoids and rATG in patients with aTCMR grade I. This may have been caused by reluctance of nephrologists to treat with rATG because of fear for complications. This delay may have resulted in more irreversible damage due to ongoing AR. Other possible explanations are that the attending physician did not intensify the maintenance immunosuppression after rATG treatment in the group with aTCMR grade I leading to ongoing and subclinical AR. Based on these results, we suggest treatment of patients with aTCMR grade I in whom kidney function does not improve after pulse glucocorticoids should be more aggressive and the administration of rATG should not be delayed for too long. The choice to prescribed rATG may be guided by a repeat kidney transplant biopsy. However, in this study, no data were collected of patients with aTCMR grade I treated with pulse glucocorticoids only, so we may have excluded the population with the most favorable prognosis.

The allograft survival of patients with ABMR is worse compared with patients experiencing TCMR [31]. In this study, no significant difference was seen in the allograft survival of patients with aTCMR or ABMR. A possible explanation for this surprising finding may be the fact that the number of patients with ABMR was small which may have resulted in limited statistical power to detect any difference in allograft survival.

Serum creatinine was significantly higher in patients with glucocorticoid-resistant AR compared to patients with severe AR. The interval between pulse glucocorticoids and rATG in patients with a glucocorticoid-resistant AR was 15 days. Possibly, kidney function may have been better if rATG had been given sooner. A multivariate prediction model, using intra-graft mRNA expression of immune and non-immune biomarkers designed to predict which patients will not respond to pulse glucocorticoid therapy may serve as a tool to guide the type of anti-rejection therapy [32].

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Despite the efficacy of rATG for AR, treatment with rATG is associated with considerable toxicity and morbidity. In this study, 5 patients were transferred to the intensive care unit and 6.5% of patients experienced serum sickness. Other studies described an incidence of serum sickness between 1.7% and 28% [17,33–36]. These infusion-related side-effects are the reason that certain patients cannot be treated with rATG (e.g., those with cardiac failure or fluid overload). Alternative treatment, such as alemtuzumab, is indicated in these patients [37,38]. Besides the infusion-related events, the rATG-treated patients experienced 124 serious infections in the first year after rATG treatment and 25% of patients suffered from CMV-related complications.

Although this was the largest cohort of patients treated with rATG for AR in the era of current standard immunosuppressive medicine, we realize that this study was heterogeneous and single-center. However, and unlike in clinical trials, this study illustrated the long-term outcomes in real life and not in highly selected subpopulations. We think this study provides more insight in the long-term outcomes of rATG therapy for AR in the modern era of immunosuppressive therapy. Future prospective studies should include a comparator and focus on the optimal dosing of rATG to better weigh the benefits and risks [3].

This study had limitations. Due to its retrospective character, not all patients treated with rATG may have been included. Since patients were identified by means of our institution's transplant database and the hospital pharmacy records; we believe not many patients were missed. Second, some clinical parameters could not be retrieved and data on long-term outcomes may have been missed if patients were admitted to other hospitals. Third, in the first period of the study, DSA (donor-specific antibodies) were not routinely tested in patients with AR in our hospital. Because of the incomplete data on the presence or absence of DSA, no meaningful analysis into the role of DSA could be performed. Fourth, follow-up biopsies after rATG therapy to evaluate for post-AR treatment changes, like ongoing inflammation or interstitial fibrosis, were not routinely performed. Finally, although all patients received the current gold standard immunosuppression (TAC plus MMF), subtle changes may have occurred over the study period. At the beginning of the 21st century, many of our patients received immunosuppression-minimizing treatment [39–41], whereas in the more recent era and with the recognition of aABMR as an important cause of allograft loss, we may have aimed for higher TAC exposure and have become more careful when considering glucocorticoid minimization. The median dose of MMF was lower in the period 2010–2012 compared with the period 2002–2006. Possibly, the introduction of therapeutic drug monitoring for mycophenolic acid in our clinic led to the difference in MMF dosing [42]. The retrospective design of the present study precluded a meaningful analysis of any such trend.

Conclusions

rATG is an effective anti-rejection treatment in patients using current standard immunosuppressive therapy, even in patients with poor allograft function. Treatment with rATG for AR does not seem to be associated with increased mortality although it is associated with considerable toxicity, especially CMV-related complications. Timing of rATG therapy is important. Early recognition of severe and/or glucocorticoid-resistant AR followed by aggressive treatment leads to better allograft function and allograft survival. When this window of opportunity is used, the benefits may outweigh the risks.

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Statement

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Conflicts of interest.

None.

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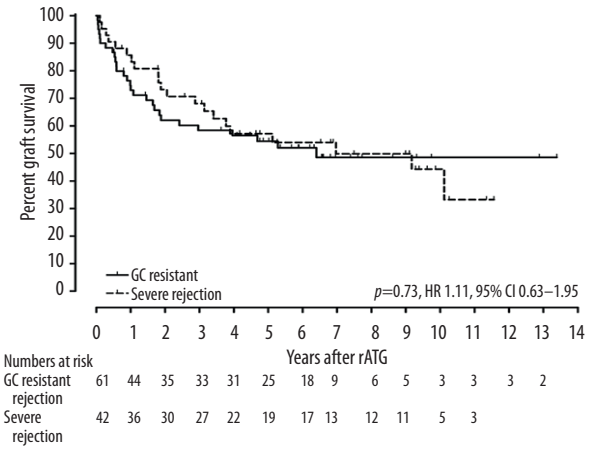
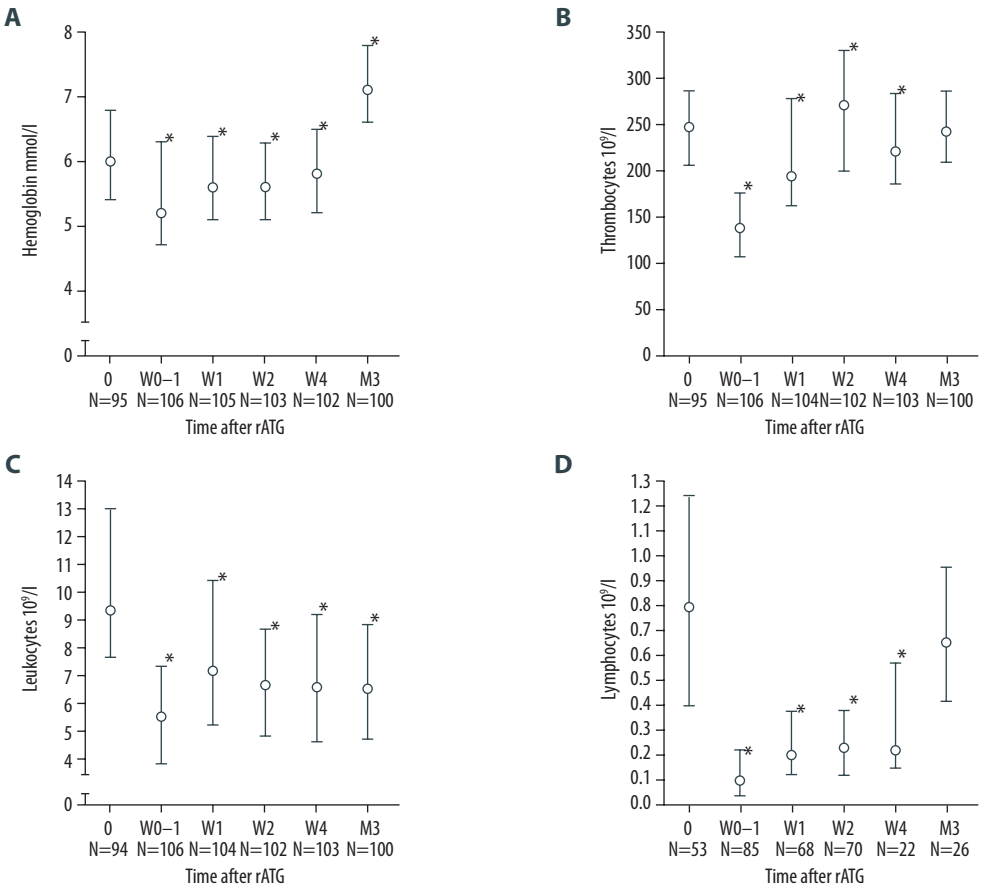
Supplementary Figures



Supplementary Figure 1. Death-censored allograft survival of glucocorticoid-resistant AR versus severe AR. GC – glucocorticoid.



Supplementary Figure 2. Laboratatory parameters of hemoglobin (**A**), thrombocytes (**B**), leukocytes (**C**), and lymphocytes (**D**). Data are median and interquartile range. 0 – the day of rATG; W0–1 – the lowest measured value in the first week after rATG; W1 – the value 1 week after ATG ±3 days; W2 – the value 2 weeks after ATG ±4 days; W4 – 4 weeks after ATG ±7 days; M3 – 3 months after rATG ±4 weeks. * Significant different compared with T=0 ($p<0.05$). N – number of patients with laboratory parameters at the specific time point.

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