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Daclizumab Versus Rabbit Antithymocyte Globulin in High-Risk Renal Transplants: Five-Year Follow-up of a Randomized Study

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We previously reported a randomized controlled trial in which 227 *de novo* deceased-donor kidney transplant recipients were randomized to rabbit antithymocyte (rATG, Thymoglobulin) or daclizumab if they were considered to be at high immunological risk, defined as high panel reactive antibodies (PRA), loss of a first kidney graft through rejection within 2 years of transplantation, or third or fourth transplantation. Patients treated with rATG had lower incidences of biopsy-proven acute rejection (BPAR) and steroid-resistant rejection at 1 year. Patients were followed to 5 years posttransplant in an observational study; findings are described here. Treatment with rATG was associated with a lower rate of BPAR at 5 years (14.2% vs. 26.0% with daclizumab; $p = 0.035$). Only one rATG-treated patient (0.9%) and one daclizumab-treated patient (1.0%) developed BPAR after 1 year. Five-year graft and patient survival rates, and renal function, were similar between the two groups. Overall graft survival at 5 years was significantly higher in patients without BPAR (81.0% vs. 54.8%; $p < 0.001$). In conclusion, rATG is superior to daclizumab for the prevention of BPAR among high-immunological-risk renal transplant recipients. Overall graft survival at 5 years was approximately 70% with either induction therapy, which compares favorably to low-risk cohorts.

Abbreviations: AR, acute rejection; ATG, antithymocyte globulin; BPAR, biopsy-proven acute rejection; CDC, complement dependent cytotoxicity; CI, confidence interval; GFR, glomerular filtration rate; HLA, human leukocyte antigen; HR, hazard ratio; IL-2Ra, IL-2 receptor-antagonizing monoclonal antibodies; MDRD, Modification of Diet in Renal Disease; MMF, mycophenolate mofetil; OR, odds ratio; PRA, panel reactive antibodies; PTLD, posttransplant lymphoproliferative disorder; SD, standard deviation

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Introduction

Acute rejection after kidney transplantation is a major cause of allograft dysfunction and can lead to rapid loss of graft function despite anti-rejection therapy. Even when kidney function initially recovers, acute rejection is associated with an increased risk of long-term graft failure (1). Acute rejection is, accordingly, a well-established surrogate endpoint for long-term outcomes. High-quality evidence has shown that induction therapy with a biological agent lowers the risk of acute rejection, and it is therefore widely administered as part of the early immunosuppressive regimen (2,3). In recipients at low immunological risk (i.e. patients with no previous exposure to human leukocyte antigens [HLA]) either lymphocyte-depleting polyclonal

antithymocyte globulin (ATG) or non-depleting IL-2 receptor monoclonal antibodies (IL-2Ra) are equally effective in preventing acute rejection (3). For patients at high risk for delayed graft function and/or acute rejection, however, ATG is superior to IL-2Ra for the prevention of biopsy-proven acute rejection (BPAR) in the first year after kidney transplantation (4,5).

In the TAXI study (4), we randomly assigned 227 high-immunologic risk patients prior to kidney transplantation from a deceased donor to either rabbit ATG (rATG) or daclizumab if they met one of the following risk factors: current panel reactive antibodies (PRA) >30%; peak PRA >50%; loss of a first kidney graft from rejection within 2 years of transplantation; or two or three previous grafts. Compared with the daclizumab group, patients treated with rATG had a lower incidence of both BPAR (15.0% vs. 27.2%; $p = 0.016$) and steroid-resistant rejection (2.7% vs. 14.9%; $p = 0.002$) at 1 year. Rates of graft and patient survival were also similar between the two groups (4). Graft and patient survival are the most important clinical endpoints but require clinical studies with long follow-up and very large sample sizes to detect any differences between treatment regimens and are therefore rare in kidney transplantation. A recent meta-analysis of randomized controlled trials (5–9) that provided outcomes data to at least 5 years posttransplant found no differences between treatment with IL-2Ra and ATG (3) but the limited patient numbers meant that the analysis lacked statistical power to detect relatively small differences in graft or patient survival. Furthermore, the vast majority of included patients were at low immunological risk. Since the advantages of rATG in preventing acute rejection are focused on highly immunized recipients, the long-term effect may be different in this subgroup.

After completion of the TAXI trial, patients were followed to 5 years posttransplant in an observational study. We report these 5-year results here.

Materials and Methods

Study design

The objective of this observational follow-up study was to compare the efficacy and safety of rATG and daclizumab in patients at high risk of acute rejection to 5 years posttransplant.

This investigator-driven study was undertaken at 16 French and three Belgian centers and was approved by the institutional review board at each site in Belgium and by the Comité de Protection des Personnes dans la Recherche Biomédicale in France. The design, data collection, analysis and writing were performed by the investigators. Written informed consent was obtained from all patients. The study was registered at the Cochrane Renal Group database (CRG020600038). The core TAXI study was a 1-year, prospective, randomized trial. Patients were assigned to receive either rATG or daclizumab before transplantation, according to a 1:1 central randomization procedure. Stratification was performed for patients with current PRA >80%. Each patient also received maintenance therapy comprising tacrolimus, mycophenolate mofetil (MMF) and steroids. After ending the randomized study at 1 year posttransplantation, patients were followed in an observational manner.

Inclusion and exclusion criteria

Adult renal transplant recipients (18–70 years) assigned to receive a single kidney graft from a deceased donor were eligible for the study if one or more of the

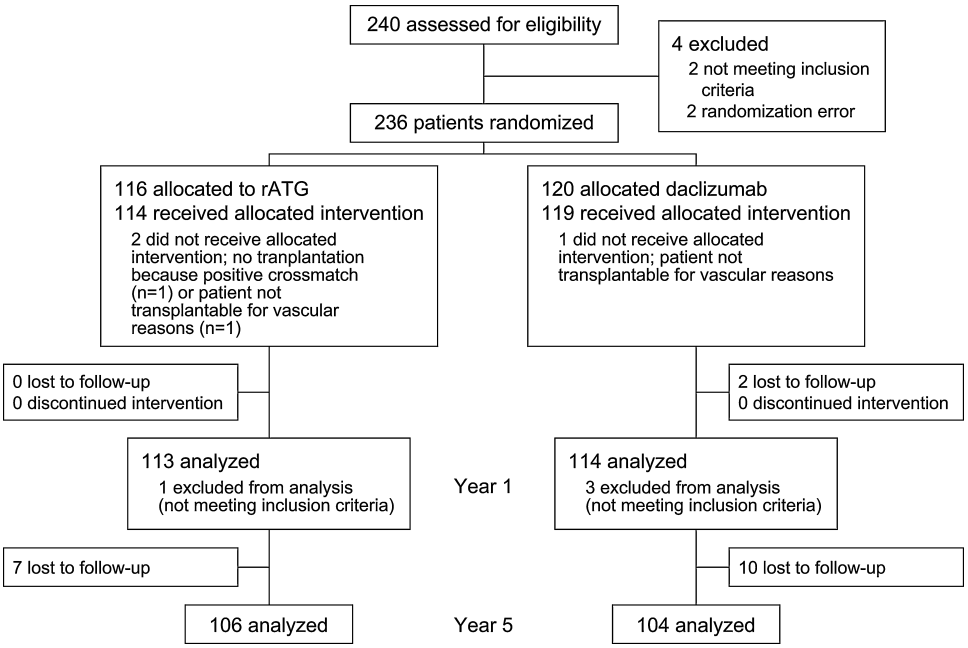

Figure 1: Patient disposition.

following risk factors were present: (i) a current anti-HLA PRA ≥30% (assessed by complement dependent cytotoxicity [CDC] test), (ii) peak PRA ≥50% (assessed by CDC test), (iii) patients scheduled for a second transplantation after losing a first graft due to rejection within 2 years posttransplant, or (iv) a third or fourth kidney graft, irrespective of HLA sensitization.

The main exclusion criteria were receipt of a multiorgan or a previous non-renal transplant or transplantation from a donor after cardiac death. Transplantations were performed only if the cytotoxic dependent cross-match from serum sampled on the day of transplantation was negative. Any additional cross-matching techniques and HLA matching selection policy were undertaken according to center practice.

Immunosuppression and concomitant medications

rATG (Thymoglobulin®, Genzyme, Cambridge, MA) was administered daily between day 0 and day 7 at a dose of 1.25 mg/kg/day. Five injections of daclizumab (Zenapax®, Roche, Basel, Switzerland) were administered at a dose of 1 mg/kg on days 0, 14, 28, 42 and 56. Methylprednisolone was administered on days 0 (500 mg intravenously) and 1 (250 mg intravenously), followed by oral doses of 16 mg/day during days 2–15, 12 mg/day during days 16–30, 10 mg/day during days 31–60, 8 mg/day during days 61–90, and then 0.1 mg/kg up to 1 year. MMF (CellCept®, Roche, Basel, Switzerland) was administered at a dose of 2 g/day during months 1 and 2 and could subsequently be reduced to 1.5 g/day during month 3 and 1 g/day thereafter according to individual center practice. In the daclizumab group, tacrolimus (Prograf®, Astellas, Tokyo, Japan) was initiated at a dose of 0.2 mg/kg before transplantation. In the rATG group, tacrolimus was initiated on day 2 and delayed until up to day 5 if there was no spontaneous decrease in serum creatinine. Target tacrolimus trough levels were 10–15 ng/mL for the first 3 months posttransplant and then 8–12 ng/mL up to 1 year.

Study endpoints

The primary endpoint of the core TAXI study was the proportion of patients with BPAR by 1 year posttransplant. Rejection severity was scored

Table 1: Baseline characteristics of organ recipients and donors

	rATG (n = 106)	Daclizumab (n = 104)	p-value
Male, n (%)	48 (45.3)	58 (54.7)	0.50
Age at transplantation, years	44.9 ± 10.3	47.3 ± 9.0	0.08
Cause of ESRD, n (%)			0.79
Glomerulonephritis	49 (46.2)	43 (41.3)	
Uropathy	10 (9.4)	14 (13.5)	
Autosomal dominant polycystic kidney disease	10 (9.4)	10 (9.6)	
Diabetes	3 (2.8)	1 (1.0)	
Other	22 (20.8)	21 (20.2)	
Unknown	12 (11.3)	15 (14.4)	
Number of HLA mismatches			
HLA A	0.9 ± 0.8	0.9 ± 0.7	0.66
HLA B	1.1 ± 0.8	1.2 ± 0.8	0.48
HLA DR	0.9 ± 0.8	0.9 ± 0.8	0.84
First graft, n (%)	30 (28.3)	32 (30.8)	*
Current PRA, %	35 ± 32	37 ± 33	0.82
Peak PRA, %	77 ± 20	78 ± 21	0.79
Second graft, n (%)	55 (51.9)	52 (50.0)	*
Current PRA, %	35 ± 28	40 ± 31	0.39
Peak PRA, %	69 ± 23	75 ± 18	0.14
Third or fourth graft, n (%)	21 (19.8)	20 (19.2)	*
Current PRA, %	26 ± 32	29 ± 31	0.74
Peak PRA, %	60 ± 32	67 ± 22	0.40
All patients			
Current PRA, %	33 ± 30	37 ± 32	0.38
Peak PRA, %	69 ± 25	75 ± 20	0.10
Cold ischemia time, hours	24.1 ± 8.1	22.4 ± 6.4	0.12
Donor			
Male, n (%)	70 (66.0)	60 (57.7)	0.21
Age, years	43.9 ± 13.9	44.1 ± 13.8	0.95
Death from stroke, n (%)	51 (48.1)	42 (40.4)	0.26
Cytomegalovirus serologic status, n (%)			0.64
D + R +	36 (34.0)	41 (39.4)	
D + R-	16 (15.1)	12 (11.5)	
D-R +	41 (38.7)	36 (34.6)	
D-R-	12 (11.3)	15 (14.4)	

Continuous variables are shown as mean ± SD.
rATG, rabbit antithymocyte globulin; ESRD, end-stage renal disease; HLA, human leukocyte antigen; PRA, panel reactive antibodies; SD, standard deviation.
*Number of patients receiving a first versus second versus third or fourth graft: p = 0.9.

Table 2: Graft function, blood pressure, and immunosuppressive therapy in patients with a functioning graft at year 5 posttransplant (n = 146)

	rATG (n = 73)	Daclizumab (n = 73)	p-value
eGFR (MDRD), ml/min/1.73m^2 (n = 142)	48.9 ± 19.0	53.0 ± 19.3	0.21
Proteinuria	n = 44[1]	n = 43[1]	
>0.5 g/L (n = 20) or >0.5 g/24 h (n = 67)	7 (15.9%)	16 (37.2%)	**0.030**
Blood pressure			
Number of antihypertensive drugs (n = 111)	1.6 ± 1.1	1.8 ± 1.0	0.56
Systolic blood pressure, mmHg (n = 121)	134 ± 17	137 ± 14	0.83
Diastolic blood pressure (mmHg) (n = 120)	78 ± 10	80 ± 10	0.15
Immunosuppressive therapy	n = 62[1]	n = 65[1]	
Tacrolimus, n (%)	53 (85.5%)	64 (98.5%)	**0.008**
Mean (median) tacrolimus trough level, ng/mL	6.8 (6.6)	7.3 (7.2)	0.45
Cyclosporine, n (%)	6 (9.7%)	0 (0%)	**0.012**
Sirolimus, n (%)	4 (6.4%)	3 (4.6%)	0.71
MMF, n (%)	54 (87.1%)	47 (72.3%)	**0.048**
Mean (median) MMF dose (mg/day)	1107 (1000)	1227 (1000)	0.42
Azathioprine, n (%)	1 (1.6%)	3 (4.6%)	0.61
Steroids, n (%)	49 (79.0%)	49 (75.4%)	0.62
Mean (median) prednisone dose (mg/day)	5.8 (5.0)	6.0 (5.0)	0.96
Number of immunosuppressive drugs			0.13
Triple therapy	43 (69.3%)	40 (61.5%)	
Dual therapy	19 (30.6%)	21 (32.3%)	
Monotherapy	0 (0%)	4 (6.2%)	

Significant p-values are shown in bold.
Continuous variables are shown as mean ± SD.
rATG, rabbit antithymocyte globulin; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; MMF, mycophenolate mofetil; SD, standard deviation.
[1]Number of patients with available data.

according to the Banff 1997 criteria (10). Borderline changes suspicious for acute rejection (mild tubulitis) were categorized as BPAR if the patient was treated for acute rejection. All patients were followed until death or until year 5 after transplantation regardless of graft loss.

Endpoints for this 5-year follow-up study were:

- Proportion of patients with BPAR to year 5 posttransplant;
- Patient and graft survival at year 5;
- Causes and risk factors for graft loss;
- Renal function at year 5, evaluated by serum creatinine levels and estimated glomerular filtration rate (eGFR) according to the abbreviated Modified Diet in Renal Disease (MDRD) formula;
- Proteinuria and blood pressure at year 5; and
- Immunosuppressive therapy at year 5.

Statistical analysis

All study endpoints were analyzed according to the intention-to-treat (ITT) principle. Categorical data were compared with the use of Pearson's Chi-squared test, and continuous variables were compared with the use of

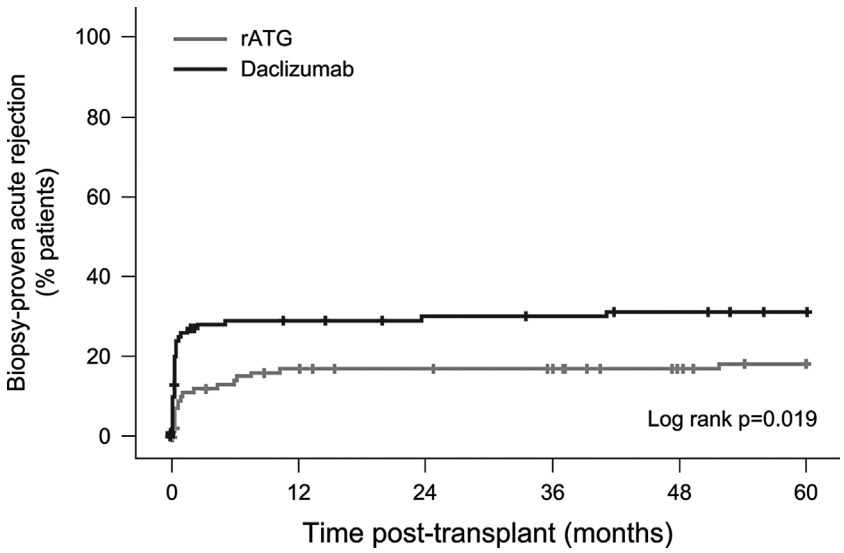

Figure 2: Probability of BPAR (Kaplan–Meier analysis).

the t test or Mann–Whitney U test, as appropriate. Survival free of BPAR rejection, death-censored graft loss or death was calculated by Kaplan–Meier analysis and compared between groups using the log-rank test. A p-value of less than 0.05 was considered statistically significant. Cox regression analysis was used to test the relationship between independent (nominal or continuous) covariates and a dependent nominal variable. Covariates were limited to those with $p < 0.05$ in the univariate analysis to avoid overfitting of the model.

Results

Patient characteristics and demographics

In total, 240 patients were assessed at 19 sites in France and Belgium during the period from May 2001 to November 2005, of whom 227 entered the trial (Figure 1). By year 5, 17 patients were lost to follow-up such that 210 patients (92.5%; 106 rATG, 104 daclizumab) could be analyzed. The groups were well balanced with respect to demographics and baseline characteristics (Table 1). Patients were broadly sensitized against HLA antigens, as reflected by a mean current PRA of 35% and a peak PRA of 72%. Approximately 40% of patients had a peak PRA above 80%. Sixty-two patients (29.5%) were receiving a first graft, 107 (51.0%) a second graft, 38 (18.1%) a third graft and three (1.4%) a fourth graft. Fifteen patients (7.1%) had a current PRA <30% and a peak PRA <50% but were still considered at high immunological risk because eight were recipients of a third graft and seven were recipients of a second graft after rejection of the previous graft within the first 2 years. At 12 months, mean MMF dose was 1.3 g/day, mean methylprednisolone dose was 7 mg/day and mean tacrolimus trough level was 8.8 ng/mL. At 5 years, the majority of patients were still receiving MMF, methylprednisolone and tacrolimus (Table 2).

Efficacy endpoints

By year 5, BPAR had occurred in 15 rATG patients (14.2%) and 27 daclizumab patients (26.0%) ($p = 0.035$, odds ratio [OR] 0.47, 95% confidence interval [CI] 0.22–0.95) (Figure 2, Table 3). Only one patient in the rATG group and one patient in the daclizumab group developed BPAR after 1 year of transplantation.

Five-year overall graft survival in the rATG and daclizumab groups was 68.9% and 70.2%, respectively ($p = 0.84$, OR 1.1 [95% CI 0.59–1.92]). The rate of death-censored graft survival was 76.4% and 75.0%, respectively ($p = 0.81$, OR

Table 3: Efficacy endpoints at 1 and 5 years after transplantation

	1 year				5 years					
					rATG (n = 106)		Daclizumab (n = 104)			
	rATG (n = 106)	Daclizumab (n = 104)	OR (95% CI)	p-value	Total at 5 years	1–5 years	Total at 5 years	1–5 years	OR (95% CI)	p-value
Biopsy-proven acute rejection (BPAR)	14 (13.2%)	26 (25.0%)	0.46 (0.22–0.93)	0.032	15 (14.2%)	+1	27 (26.0%)	+1	0.47 (0.22–0.95)	0.035
Graft loss	15 (14.2%)	15 (14.4%)	0.98 (0.45–2.12)	0.96	33 (31.1%)	+18	31 (29.8%)	+16	1.1 (0.59–1.92)	0.84
From death with functioning graft	3 (2.8%)	3 (2.9%)			8 (7.5%)	+ 5	5 (4.8%)	+2		
From acute rejection	5 (4.7%)	4 (3.8%)			5 (4.7%) (+0)	+0	5 (4.8%)	+1		
From chronic rejection, allograft glomerulonephritis	0 (0%)	1 (1.0%)			6 (5.7%)	+6	7 (6.7%)	+6		
From chronic allograft nephropathy without signs of rejection	0 (0%)	0 (0%)			5 (4.7%)	+5	5 (4.8%)	+5		
From recurrence of initial kidney disease	1 (1.0%)	0 (0%)			2 (1.9%)	+1	1 (1.0%)	+1		
From technical causes	3 (2.8%)	2 (1.9%)			3 (2.8%)	+0	2 (1.9%)	+0		
From other causes	1 (1.0%)	3 (2.9%)			2 (1.9%)	+1	4 (3.8%)	+1		
From unknown causes	2 (1.9%)	2 (1.9%)			2 (1.9%)	+0	2 (1.9%)	+0		
Death	4 (3.8%)	3 (2.9%)	1.32 (0.29–6.05)	0.72	9 (8.5%)	+5	8 (7.7%)	+5	1.1 (0.41–3.01)	0.83
From cardiovascular cause	0 (0%)	0 (0%)			2 (1.9%)	+2	2 (1.9%)	+2		
From infectious cause	1 (1.0%)	2 (1.9%)			1 (1.0%)	+0	3 (2.9%)	+1		
From cancer	1 (1.0%)	0 (0%)			2 (1.9%)	+1	0 (0%)	+0		
From posttransplant lymphoproliferative disease	0 (0%)	0 (0%)			0 (0%)	+0	1 (1.0%)	+1		
From other cause	0 (0%)	1 (1.0%)			1 (1.0%)	+1	1 (1.0%)	+0		
From unknown cause	2 (1.9%)	0 (0%)			3 (2.8%)	+1	1 (1.0%)	+1		

CI, confidence interval; OR, odds ratio; rATG, rabbit antithymocyte globulin.

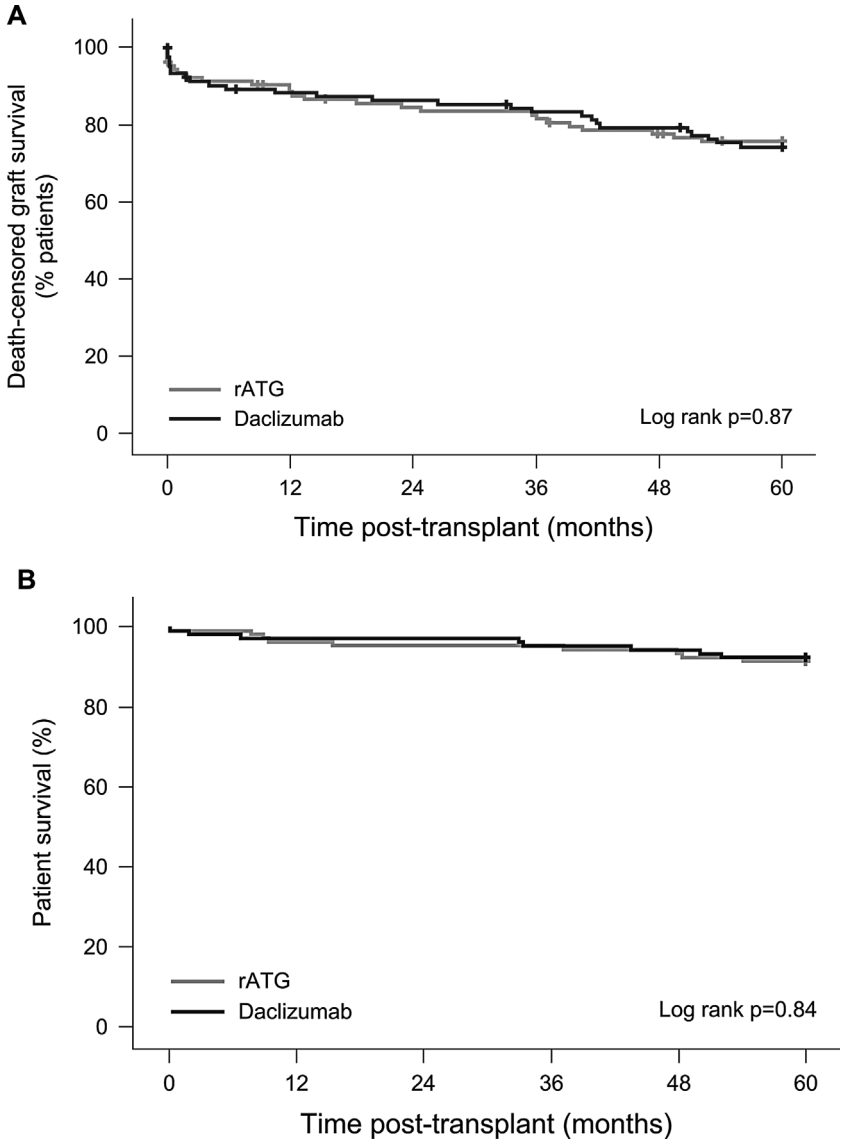

Figure 3: (A) Probability of freedom from death-censored graft loss; (B) probability of survival (Kaplan–Meier analyses).

0.93 [95% CI 0.49–1.74]), and the rate of patient survival was 91.5% and 92.3%, respectively ($p = 0.83$, OR 1.1 [95% CI 0.41–3.01]) (Figure 3, Table 3). There were no apparent differences in the reasons for graft loss or death between the two groups (Table 3).

One hundred and forty-six patients had a functioning graft at year 5, among whom serum creatinine level at year 5 was available in 142 cases. In these patients, serum creatinine (mean ± SD) at year 5 was 1.6 ± 0.7 mg/dl in the rATG group versus 1.5 ± 0.6 in the daclizumab group. eGFR (mean ± SD, MDRD) was similar in the two groups (Table 2). Proteinuria data at year 5, available for 87/146 patients, showed a significantly higher proportion of patients with proteinuria >0.5 g/L or >0.5 g/24 h in the daclizumab group (37.2% vs. 15.9% in the rATG group; $p = 0.030$). At year 5, systolic blood pressure, diastolic blood pressure and the number of different antihypertensive drugs taken daily was similar in both groups (Table 2).

To determine whether BPAR exerted a negative impact on graft survival, a *post hoc* analysis was performed based on the total study cohort to compare patients with BPAR ($n = 42$) with those who remained rejection-free ($n = 168$). Death-censored graft survival at 5 years was 54.8% in patients who had experienced BPAR versus 81.0% among rejection-free patients, ($p < 0.001$) (Figure 4). Other risk factors for graft loss at 5 years on univariate analysis included older donor age ($p = 0.010$), third or fourth graft versus first graft ($p = 0.010$), a higher number of HLA mismatches ($p = 0.027$) and the occurrence of delayed graft function ($p = 0.006$). Multivariate analysis confirmed that donor age,

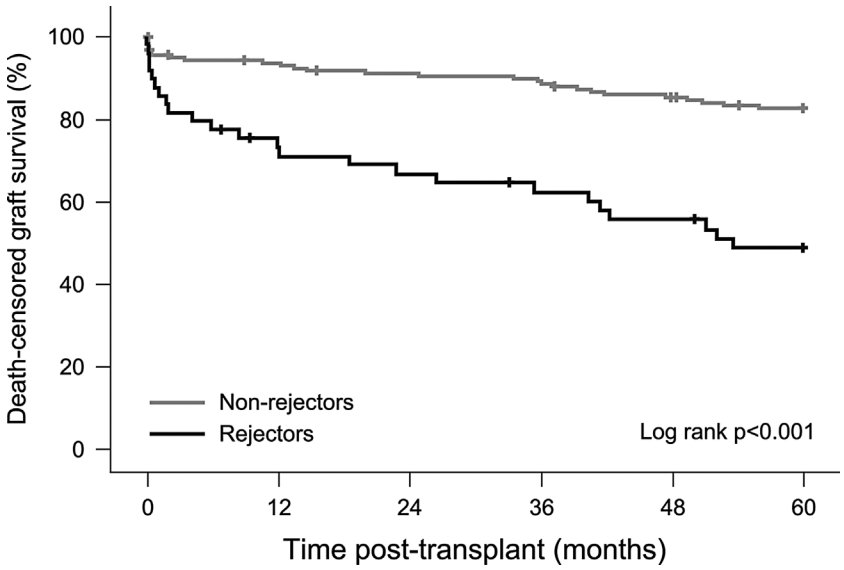

Figure 4: Probability of death-censored graft loss according to presence or absence of BPAR (Kaplan–Meier analysis).

third or fourth grafts and the number of HLA mismatches were independent risk factors for graft loss (Table 4).

Discussion

To date, the TAXI trial is the only large randomized study to compare induction with rATG or IL-2Ra specifically in highly immunized kidney transplant recipients. This follow-up study provides the largest prospectively-collected dataset so far on long-term graft survival in this selected population. The particularly high immunological risk of this cohort is confirmed by the mean peak and current PRA levels of 72% and 35%, respectively, with almost three-quarters of patients receiving a second, third or fourth graft. Furthermore, we should keep in mind that at the time that patients were enrolled in the study, highly sensitive immunoassay monitoring to detect HLA antibodies (e.g. flow cytometry, Luminex, or ELISA) was not performed. It is therefore likely that a proportion of these highly immunized patients were transplanted with donor-specific antibodies.

The most remarkable finding is that despite a difficult clinical course in the first year after transplant with a high frequency of BPAR, especially in the daclizumab group, long-term outcomes in these high-risk patients were not markedly dissimilar from those in lower-risk recipients. Firstly, BPAR was rare after the first year posttransplant. Thus, surprisingly, this immunosuppression regimen was adequate in these high-risk patients with only good compliance to a standard maintenance regimen even though no systematic biopsies were performed and there was no monitoring of HLA antibodies. Secondly, overall 5-year graft survival was approximately 70%. Although this is lower than 5-year graft survival rates reported recently for first transplants from deceased donors in Europe (78% (11)), it is comparable—and even higher—than 5-year graft survival following a first transplant from a deceased donor in white Americans (71%) and African Americans (63%) (12). Our findings also show that the number of HLA mismatches remains an important risk factor for graft loss in highly immunized patients.

The incidence of BPAR remained significantly lower with rATG induction than daclizumab induction at 5 years posttransplant, consistent with results at 1 year (4). There was no significant difference in 5-year graft survival, but the study was not powered to detect such a difference. A *post-hoc* analysis showed that 5-year graft survival was significantly lower in patients who experienced BPAR. A recent systematic review showed that the occurrence of acute rejection is associated with an increased risk of graft loss across a broad range of patients at different levels of immunological risk and receiving various concomitant immunosuppressive regimens (1). It is therefore likely that acute rejection is also an important surrogate endpoint for graft survival for patients at high immunological risk. Proteinuria is another well-documented risk factor for graft loss (13). Since the incidence of proteinuria >0.5 g/day was significantly higher in the daclizumab subgroup, this may suggest a worse long-term prognosis in daclizumab-treated patients. Larger study populations and longer follow-up (>5 years) may be required to identify any difference in graft survival using rATG versus daclizumab induction.

However, even discounting a possible benefit for graft survival, reducing the number and severity of acute rejection episodes by using rATG as compared to IL-2Ra induction lowers the risks, costs and psychological stress inherent to acute rejection episodes. Managing acute rejection typically requires a kidney biopsy, hospitalization and additional immunosuppressive therapy such as high-dose corticosteroids or, in cases of steroid-resistant and/or

Table 4: Risk factors for graft loss[1]

	Graft survival[1] (n = 146)	Graft loss[1] (n = 51)	Univariate analysis		Multivariate analysis[2]	
			HR (95% CI)	p	HR (95% CI)	p
Induction therapy[3]						
ATG	50%	49%	0.99 (0.75–1.30)	0.95		
Daclizumab	50%	51%				
Recipient age (mean ± SD)	45.8 ± 9.9	46.5 ± 9.5	1.01 (0.98–1.04)[4]	0.59		
Male recipient, %	45.9%	52.9%	1.30 (0.75–2.26)	0.35		
Donor age, years	42.2 ± 14.5	48.5 ± 11.0	1.03 (1.01–1.05)[4]	**0.010**	1.03 (1.01–1.05)[4]	**0.015**
Male donor, %	65.8%	51%	0.60 (0.34–1.03)	0.065		
Cold ischemia time, hours	23.3 ± 7.3	22.8 ± 7.7	0.99 (0.96–1.03)[5]	0.73		
Graft number[6]			Overall:	**0.037**	Overall:	0.056
First graft	35%	18%				
Second graft	49%	53%	1.95 (0.92–4.14)	0.083	1.64 (0.77–3.50)	0.078
Third or fourth graft	16%	29%	2.95 (1.29–6.75)	**0.010**	2.22 (0.96–5.14)	**0.017**
Current PRA[7]						
≤ 30%	51%	48%				
> 30%	49%	52%	1.08 (0.62–1.89)	0.78		
Peak PRA[8]						
≤ 50%	17%	22%				
> 50%	83%	78%	0.79 (0.40–1.54)	0.49		
Primary nephropathy			Overall:	0.70		
Glomerulonephritis	42.5%	45%				
Uropathy	12%	12%				
Autosomal dominant polycystic kidney disease	12%	4%				
Diabetes	2%	2%				
Other	18.5%	25%				
Unknown	13%	12%				
HLA mismatches (0–6)	2.8 ± 1.5	3.3 ± 1.5	1.23 (1.02–1.47)[9]	**0.027**	1.23 (1.02–1.48)[9]	**0.029**
Delayed graft function	32.2%	52.0%	2.17 (1.25–3.78)	**0.006**	1.68 (0.95–2.98)	0.073

Continuous variables are shown as mean ± SD. Significant p-values are shown in bold.
CI, confidence interval; HLA, human leukocyte antigen; HR, hazard ratio; PRA, panel reactive antibodies.
[1]Excluding patients who died with a functioning graft.
[2]Cox regression analysis.
[3]Reference: daclizumab.
[4]Unit change for HR: 1 year.
[5]Unit change for HR: 1 hour.
[6]Reference: first graft.
[7]Reference: Current PRA ≤30%.
[8]Reference: Peak PRA ≤50%.
[9]Unit change for HR: per mismatch.

antibody-mediated rejection, the use of rATG, intravenous immunoglobulin, plasma exchange, eculizumab or anti-CD20 antibodies (2). In a prospective randomized pilot trial comparing rATG or daclizumab induction therapy in 22 immunologically high-risk kidney recipients, Kim et al (14) showed that the costs for hospitalization per day at 2 years posttransplant was approximately five times higher in the daclizumab group, resulting in an average cost-difference of more than 10 000 USD per patient. Popat et al (15) also showed that following kidney transplantation from a donor after cardiac death the use of rATG versus IL-2Ra induction resulted in significant cost savings (for example due to less frequent BPAR, shorter bed stays and fewer clinic visits in the first years after transplantation).

In some respects, our study can be compared to the trial by Brennan and colleagues, who performed a prospective randomized trial with rATG versus IL-2Ra induction in patients at high risk for delayed graft function and/or acute rejection (5,16). In contrast to our study, only 10% of patients enrolled in that trial were retransplants and peak and current PRA values were 14% and 6%, respectively. The study was carried out in centers throughout both Europe and the US (compared to only France and Belgium in our trial), and donor and recipient age was higher, with a longer cold ischemia time. Despite these differences, however, the results of Brennan et al closely mirrored our findings. During the first year, acute rejection rates were lower in the rATG group (15.6% vs. 25.5% with IL-2Ra

induction, $p = 0.02$) and after the first year, acute rejection became rare in both arms (<5%). As in our study, they found no difference in 5-year graft or patient survival rates (69% vs. 63% [$p = 0.63$] and 76% vs. 80% [$p = 0.59$] respectively), based on the subgroup of US patients.

With regard to safety, rATG has historically been associated with an increased risk of infection or malignancy compared to IL-2Ra (3). However, we did not observe any difference in 5-year patient survival, nor any suggestion of increased mortality from infection or malignancy in the rATG arm. In addition, although the risk of posttransplant lymphoproliferative disorder (PTLD) was reported to reach 1% in patients receiving rATG at 3 years after transplantation during the mid-1980s to early 2000s (17) (a significantly higher proportion than in patients given IL-2Ra induction), only one patient in the current study died of posttransplant lymphoma within 5 years, in the daclizumab induction group. Our findings are also in line with those of Brennan et al, which showed a lower incidence of treated cytomegalovirus infection in the rATG group and no significant differences in malignancy or PTLD (16). One reason for the similar rates of infectious complications or malignancy with rATG or IL-2Ra therapy in these high-risk patients may lie in the higher rate of acute rejection and steroid-resistant acute rejection in the daclizumab group. These patients received additional antirejection immunosuppression, lowering the difference in overall immunosuppressive intensity between the two arms. Given the apparent positive balance of benefits versus harm, the results of this study support the current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which suggest using rATG rather than IL-2Ra induction in highly immunized patients (2).

Alemtuzumab is a monoclonal antibody which, like rATG, strongly depletes T-lymphocytes in humans. It has been shown to reduce BPAR compared to IL-2Ra induction, but not compared to ATG (18). This has been established in patients with 'low' and 'intermediately high' immunological risk (18,19). Graft and patient survival appear to be similar with either alemtuzumab or rATG. Data on infection or malignancy risks in alemtuzumab-treated patients remain limited (18). Even if alemtuzumab and ATG were equivalent in high-risk patients, which is as yet untested in a head-to-head comparison, it is not commercially available in Europe due to legal and administrative reasons.

There are several notable limitations to our study. Firstly, the observational design of the follow-up study inherently implies that uncontrolled treatment modifications could occur, limiting the power of the statistical comparisons. Secondly, since 17 patients (7.5% of the original study population) were lost to follow-up at 5 years, preferential selection of patients with better outcomes cannot be ruled out.

Today, the approach to managing highly immunized patients has broadened. There is growing experience with desensitization protocols, paired-kidney donation and new pharmacological options such as eculizumab (20). Technical advances in antibody characterization using sensitive bead immunoassays and the C1q assay can help to guide therapeutic strategies. However, these newer therapeutic and diagnostic tools are often complex and expensive, and their optimal clinical use has not yet been defined. Recent studies have focused primarily on HLA-incompatible transplantation, but the definition of humoral incompatibility remains subjective: apart from ''clear-cut'' CDC-positive cross-match, studies often include CDC cross-match negative subjects with a positive cross-match based on flow cytometry or solid-based immunoassays (20,21). As mentioned above, it is likely that a proportion of patients in this study had (CDC-negative) donor-specific antibodies at the time of transplantation or developed them afterwards. Nevertheless, this study indicates that with only rATG or IL-2Ra induction and tacrolimus-based triple maintenance therapy, long-term outcomes in highly immunized patients are not markedly dissimilar from those of their lower-risk counterparts. When investigating newer therapeutic strategies in high-immunological risk patients, including CDC-negative HLA incompatible transplant recipients, a treatmen t protocol similar to that used here and incorporating rATG induction should be considered the ''standard'' comparator.

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Disclosure

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