Effect of induction therapy in kidney transplantation in sensitive patients: analysis of risks and benefits

Efeito da terapia de indução em pacientes sensibilizados: análise dos riscos e benefícios

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Submitted on: 04/07/2015.
Approved on: 10/03/2015.

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DOI: 10.5935/0101-2800.20160013

Abstract

Introduction: Sensitization is associated with worse clinical outcomes after kidney transplantation (KT), including increased incidence of delayed graft function, acute rejection (AR) and graft loss. **Objectives:** To evaluate 1-year efficacy and safety outcomes in sensitized KT recipients receiving anti-thymocyte globulin (ATG) induction and compare them to non-sensitized patients. **Methods:** Deceased donors KT recipients transplanted between January 1998 and December 2009 were divided into 5 groups: control group 1 - n = 89, PRA negative, without induction therapy; control group 2 - n = 94, PRA negative, basiliximab induction; control group 3 - n = 81, PRA negative, ATG induction; test group 4 - n = 64, PRA 1-49%, ATG induction; test group 5 - n = 118, PRA ≥ 50%, ATG induction. **Results:** There was no difference in the incidence of AR among patients sensitized and non-sensitized, except for group 1, with highest incidence of AR (20.2%, p = 0.006 *vs.* Group 4 and p = 0.001 *vs.* group 5). Sensitized patients induced with ATG had higher incidence of citomegalovirus infection when compared with group 2 (26.6% and 14.4% *vs.* 2.1%). There were no differences in graft and patient survivals. In multivariable analysis, PRA > 50% and ATG induction were not associated with graft loss, death or death-censored graft loss. **Conclusion:** Sensitized patients induced with ATG presented similar or lower incidence of AR when compared with non-sensitized patients not induced. Besides, these patients had similar safety profile and graft and patient survivals at 1 year.

Keywords: graft rejection; immunosuppression; kidney transplantation; survival.

Resumo

Introdução: A sensibilização está associada a piores desfechos clínicos após o transplante renal (TxR), incluindo maior incidência de função tardia, rejeição aguda e perda do enxerto. **Objetivos:** Avaliar os desfechos de eficácia e segurança de 1 ano de receptores de TxR com doador falecido sensibilizados induzidos com globulina antitimócito (ATG) e compará-las aos de pacientes não sensibilizados. **Métodos:** Receptores de TxR com doador falecido entre janeiro de 1998 e dezembro de 2009 foram divididos em 5 grupos: grupo controle 1 - n = 89, PRA negativo, sem indução; grupo controle 2 - n = 94, PRA negativo, indução com basiliximabe; grupo controle 3 - n = 81, PRA negativo, indução com ATG; grupo teste 4 - n = 64, PRA 1-49%, indução com ATG; grupo teste 5 - n = 118, PRA ≥ 50%, indução com ATG. **Resultados:** Não houve diferença na incidência de rejeição entre pacientes sensibilizados e não sensibilizados, exceto pelo grupo 1, que apresentou a maior incidência de rejeição aguda comprovada por biópsia (20,2%, p = 0,006 *vs.* grupo 4 e p = 0,001 *vs.* grupo 5). Os pacientes sensibilizados induzidos com ATG apresentaram maior incidência de infecção por citomegalovírus quando comparados aos pacientes do grupo 2 (26,6% e 14,4% *vs.* 2,1%). Não houve diferença nas sobrevidas do enxerto e do paciente. Na análise multivariada, PRA > 50% e uso de ATG não foram associados à perda, perda com óbito censorado ou óbito. **Conclusão:** Os pacientes sensibilizados induzidos com ATG apresentaram incidência de rejeição semelhante ou inferior à de pacientes não sensibilizados não induzidos. Estes pacientes apresentaram sobrevidas do enxerto e do paciente semelhantes em 1 ano e comparável perfil de segurança.

Palavras-chave: quimioterapia de indução; rejeição de enxerto; sobrevivência; transplante de rim.

Introduction

The term sensitization as regards the development of specific IgG antibodies to HLA *(Human Leukocyte Antigens),* usually related to previous pregnancies, transfusions or previous transplants.[1] The anti-HLA antibodies can negatively impact renal graft foster the development of hyperacute rejection, acute and chronic.[1,2] Despite being a well-known phenomenon, there is no consensus on the definition of awareness on how best monitoring and the optimal management of sensitized patients on the waiting list.

In the context of transplantation, the antibody reactivity panel (PRA) is the tool used to investigate the presence of anti-HLA antibodies in the recipient's serum. Regardless of the technique used, there is no consensus about the ideal cutoff of PRA for risk definition. Evidence points to the presence of specific anti-donor HLA antibodies (DSA) is lighter than the impact value of PRA in these transplant outcomes and should ideally be identified in the presence of a positive PRA.[3] In addition, it is possible that sensitization *per se,* regardless of the presence of DSA, is associated with worse long-term survival.[4,5]

Because of the increased risk of acute rejection, high efficiency systems are generally used in sensitized patients, including induction therapy with anti-thymocyte globulin (ATG).[6,7]

Although renal transplantation is the treatment of choice for patients with end-stage renal disease, we questioned about the benefit of this treatment modality in sensitized patients without the use of sophisticated methodologies for detection of antibodies. The objective of this study was to evaluate the outcomes of kidney transplantation with deceased donor in sensitized recipients without the prior identification of the presence of DSA, and compare them with the outcomes of non-sensitized patients.

Methods

Population

This retrospective cohort study included adult patients undergoing kidney transplantation with deceased donor from January 1998 to December 2009 at a single center. The inclusion of cases began by selecting patients with PRA above 50% during the period described above, which received induction therapy with ATG (group 5, n = 118). The following patients were selected PRA between 1 and 49% receiving ATG induction therapy (Group 4, n = 64); The other groups were selected from the pairing by age and maintenance immunosuppressive regimen, as follows: Group 1: patients with negative PRA and who did not receive induction therapy (n = 89); Group 2: patients with negative PRA and receiving basiliximab induction therapy (n = 94); Group 3: patients with negative PRA and received induction therapy with ATG (n = 81). Thus, the sample consisted of 446 patients stratified into two test groups (groups 4 and 5) and 3 control groups (groups 1, 2, and 3) who were followed for 1 year.

Patients younger than 18 years were excluded; those who received other agents for induction therapy than those specified above; transplant recipients with living donor; and multiple organ patients with DSA fluorescence intensity transplant recipients (MFI) above 1500.

Data were collected retrospectively by analyzing the multidisciplinary records. This study was approved by the local Ethics Committee.

Definitions

Those proven acute rejection on biopsy were considered (RACB), according to the classification of Banff in 1997, including *borderline* infiltrates.[8] Infections were defined as those that led to the need for hospital readmission, independent of time following transplantation. Renal function was measured using the calculated creatinine clearance by Cockroft-Gault formula.

To conduct the PRA, we used the cytotoxic techniques complement dependent (CDC) from 1998 to July 2001; *Enzyme Linked Immunosorbent Assay* (ELISA) from July 2001 to March 2006; and the PRA calculated by Luminex® methodology from March 2006. The value of PRA used was the highest value identified in the historical sera of patients analyzed (PRA peak).

Outcomes

The primary endpoint of the study was to evaluate patient survival and graft at 1 year in sensitized patients induced with ATG compared to patients not sensitized. Secondary objectives were to evaluate the incidence of acute rejection, the incidence of viral and bacterial infections, and renal function in these groups.

Analysis statistics

Categorical variables were expressed as frequencies and proportions and compared using the Chi-square or Fisher test. Parametric numeric variables were presented as mean and standard deviation and the groups were compared using ANOVA with Tukey test for *post hoc* analysis. The nonparametric data were expressed as median and interquartile range and the groups were compared using Kruskal-Wallis test. The cumulative survival was evaluated by Kaplan-Meier method and the groups were compared using the Log-rank test. For risk assessment of graft loss, death and graft loss with censorado death were conducted univariate analysis and variables with $p < 0.05$ were selected for proportional hazards Cox analysis. Statistical analysis was performed using the *Statistic* program *Package for Social Science* v. 20.0 (SPSS Inc., Chicago, IL, USA) and assumed to be statistically significant when the p value was less than 0.05.

Results

Demography

The population consisted mainly of adults (46.4 ± 11.2 years), women (52.9%), whites (53.4%), patients with chronic kidney disease of undetermined etiology (39%), with median time on dialysis for 60 months, and 11.5% were retransplantation. Donors were predominantly young adults (median age 45 years) who died of cerebrovascular disease (63.5%) and 11.7% expanded criteria donors (ECD). The mean duration of cold ischemia was 24.2 ± 7.4 hours. Most receivers (86.8%) received initial immunosuppressive regimen as the combination of tacrolimus, prednisone and mycophenolate. The groups formed by sensitized patients (groups 4 and 5) had a higher percentage of women and retransplantation. Detailed information about the demographics of the population tested is available in Table 1.

Efficiency

The incidence of delayed graft function (FTE) of the sample was 67% and, except for a higher incidence in group 3 (80.2%), there was no difference between the other groups. The incidence of RACB was 8.1% and there was no difference between the test 4:05 and controls groups 2 and 3. However, group 1 had a higher incidence of RACB compared to test groups (20.2%). When considering all the episodes of rejection within the period of one year, there was no difference between groups, except for the most serious failures in group 1 compared to group 5 ($p = 0.032$). When compared to group 4, group 1 patients had renal function higher than the end of 1 year follow-up (58.8 ± 21.8 *vs.* 44.9 ± 19.1mL/min, $p = 0.028$) (Table 2).

Graft survival in groups 4 and 5 was 82.8% and 81.3%, respectively. Graft survival with censorado death was 88.8% and 90.5% in groups 4 and 5 and patient survival was 92% in group 4 and 90.9% in group 5. There was no difference between groups Test 4 and 5 when they were compared to the other groups (Figures 1, 2 and 3). The main cause of graft loss at 1 year was acute rejection (57.6%) and the main cause of death was infection (58.9%) and there was no difference between groups.

Safety

The major infectious cause of hospitalization was re-infection with cytomegalovirus (CMV) (16.1%), followed by urinary tract infection (11.7%). Patients in group 4 had a higher incidence of CMV infection when compared to group 5 patients (26.6% *vs.* 14.4%, $p = 0.045$). The group 2 patients had a lower incidence of CMV infection (2.1%) compared to group 4 ($p < 0.001$) and 5 ($p = 0.002$). There was no difference between groups 1 and 3 in relation to the test groups. There was no difference in the incidence of urinary infection between groups 4 and 5 (15.6% in group 4 and group 5 in 10.2%, $p = 0.28$), however was lower in group 2 (4.3%) compared to group 4 (15.6%, $p = 0.014$). Groups 1 and 3 showed no differences from the test groups. There were also differences in the incidence of bronchopneumonia in need of re-hospitalization among patients in groups 4 and 5, with the highest incidence in the first (7.8% *vs.* 1.7%, $p = 0.040$). The group 1 was also higher proportion of episodes bronchopneumonia the group 5 (11.2% *vs.* 1.7%, $p = 0.004$). In the other groups there were no differences in the groups 4 and 5. There was no difference between the test against other infections (10.9% in group 4 and 4.2% in group 5, $p = 0.08$) and when these were compared to group 3 (7.4%). However, the group 1 had more episodes (14.6%) compared to group 5 (4.2%), $p = 0.009$. Group 2 had a lower incidence of other infections (2.1%) compared to group 4 (10.9%, $p = 0.019$) (Table 3).

Table 1 Demographic characteristics of the population evaluated

	Total (n = 446)	Group 1 (n = 89)	Group 2 (n = 94)	Group 3 (n = 81)	Group 4 (n = 64)	Group 5 (n = 118)	*p* value
Age, mean ± SD (years)	46.4 ± 11.2	46.0 ± 10.1	48.4 ± 10.5	46.7 ± 13.1	47.9 ± 10.9	44.1 ± 11.1	0.059
Male, n (%)	210 (47.1)	47 (52.8)	66 (70.2)	44 (54.3)	25 (39.1)	28 (23.7)	< 0.001
Caucasians, n (%)	238 (53.4)	49 (55.1)	46 (48.9)	54 (66.7)	26 (40.6)	63 (53.4)	0.009
Cause of CKD, n (%)							
Indeterminate	117 (39.0)	37 (41.6)	40 (42.6)	34 (42.0)	20 (31.2)	43 (36.4)	0.214
HAS	68 (15.2)	12 (13.5)	10 (10.6)	12 (14.8)	13 (20.3)	21 (17.8)	
GNC	63 (14.1)	16 (18.0)	13 (13.8)	10 (12.3)	5 (7.8)	19 (16.1)	
Diabetes	59 (13.2)	11 (12.4)	19 (20.2)	12 (14.8)	9 (14.1)	8 (6.8)	
Others	82 (18.4)	6 (6.7)	7 (7.4)	5 (6.2)	5 (7.8)	9 (7.6)	
Time on dialysis, median (interquartile range) (months)	60 (32-88)	72 (39-84)	54 (28-84)	48 (31-85)	60 (37-84)	60 (36-107)	0.213
Retransplantation, n (%)	17 (11.5)	0 (0.0)	1 (1.1)	2 (2.5)	3 (4.7)	11 (9.3)	0.003
Donor age, median (interquartile range) (years)	45 (34-54)	37.0 (24.5-44.5)	49.5 (39.2-55.0)	52.0 (41.5-59.0)	46 (32.2-54.0)	43.5 (34.0-52.0)	< 0.001
Donor with cerebrovascular death, n (%)	283 (63.5)	41 (46.1)	65 (69.1)	59 (72.8)	42 (65.6)	76 (64.4)	0.016
DCE, n (%)	52 (11.7)	3 (3.4)	0 (0.0)	36 (38.3)	2 (3.1)	11 (9.3)	< 0.001
CMV serology							
D+/R+	220 (49.3)	33 (37.1)	53 (56.4)	34 (42)	36 (56.3)	64 (54.2)	0.004
D+/R-	12 (2.7)	2 (2.2)	5 (5.3)	2 (2.5)	2 (3.1)	1 (0.8)	
D-/R+	39 (9)	5 (5.6)	14 (14.9)	5 (6.2)	5 (7.8)	10 (8.5)	
Ddes/R+	167 (37)	45 (50.6)	22 (23.4)	39 (48.1)	19 (29.7)	42 (35.6)	
Ddes/R-	8 (1.7)	4 (4.5)	0 (0)	1 (1.2)	2 (3.1)	1 (0.8)	
TIF, mean ± SD (hours)	24.2 ± 7.48	18.9 ± 7.3	26 ± 6.8	28.5 ± 8.6	26.9 ± 7.6	23.5 ± 6.0	< 0.001
ISS maintenance, n (%)							
CSA/AZA/PRED	26 (5.8)	23 (25.8)	0 (0.0)	0 (0.0)	2 (3.1)	1 (0.8)	< 0.001
CSA/MPA/PRED	9 (2.0)	2 (2.2)	0 (0.0)	7 (8.6)	0 (0.0)	0 (0.0)	
TAC/AZA/PRED	15 (3.4)	3 (3.4)	1 (1.1)	6 (7.4)	2 (3.1)	3 (2.4)	
TAC/MPA/PRED	387 (86.8)	61 (68.6)	93 (98.9)	65 (80.2)	57 (89.1)	111 (94)	
OTHERS	9 (2.0)	0 (0.0)	0 (0.0)	1 (1.2)	2 (3.1)	2 (1.7)	

DP: Standard deviation; CKD: Chronic kidney disease; HAS: Hypertension high blood pressure; GNC: Chronic glomerulonephritis; D: Donor; R: Receiver; DDEs: Donor with unknown serology; CMV: Cytomegalovirus; ISS: Immunosuppression; CSA: Cyclosporine; AZA: Azathioprine; PRED: Prednisone; TAC: Tacrolimus; MPA: Mycophenolate; DCE: Expanded criteria donor; TIF: Cold ischemia time.

Multivariate analysis

In multivariate analysis, neither the PRA, nor with ATG induction therapy were associated with risk of loss, graft loss with censorado death and death. No variable was statistically significant in the risk identification for graft loss. Above 14 days transplant of hospitalization (HR 2.03 95% CI 1.10 -3.74, p = 0.023) and acute rejection (HR 2.27 95% CI 1.18 to 4.38, p = 0.014) were independent risk factors for graft loss with censorado death. Age over 47 years (HR 2.09 95% CI 1.17 to 3.72, p = 0.012) and time on dialysis over 60 months (HR 1.81 95% CI 1.05 to 3.13, p = 0.032) were risk factors for death.

Discussion

In this retrospective cohort study, the patient and graft survival of renal transplant recipients sensitized induced with ATG were similar to those of non-sensitized patients by the end of 1 year follow up. The incidence of acute rejection in these patients was similar to that of low immunological risk patients induced with basiliximab and ATG or lower than

Table 2 Significant clinical outcome following transplantation

	Total (n = 446)	Group 1 (n = 89)	Group 2 (n = 94)	Group 3 (n = 81)	Group 4 (n = 64)	Group 5 (n = 118)
Incidence FTE, n (%)	299 (67.0)	48 (53.9)	69 (73.4)	65 (80.2)	42 (65.6)	75 (63.5)
P value vs. group 4		0.147	0.294	0.047	reference	0.781
P value vs. group 5		0.163	0.127	0.011	0.781	reference
Incidence of the first episode RACB, n (%)	36 (8.1)	18 (20.2)	7 (7.4)	2 (2.5)	3 (4.7)	6 (5.1)
P value vs. group 4		0.006	0.484	0.467	reference	0.906
P value vs. group 5		0.001	0.476	0.356	0.906	reference
Episodes of RACB	49	23	10	4	5	7
Banff Classification n (%)						
Borderline	10 (20)	2 (9)	1 (10)	1 (25)	1 (20)	5 (72)
IA	13 (26.5)	6 (26)	4 (40)	2 (50)	0 (0)	1 (14)
IB	8 (16.3)	3 (13)	1 (10)	1 (25)	3 (60)	0 (0)
IIA	13 (26.5)	9 (39)	3 (30)	0 (0)	0 (0)	1 (14)
IIB	4 (8.1)	2 (9)	1 (10)	0 (0)	1 (20)	0 (0)
III	1 (2.0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Creatinine clearance at 1 year (ml/min), mean ± DP	55.4 ± 20.0	58.8 ± 21.8	57.3 ± 18.7	53.9 ± 14.9	44.9 ± 19.1	57.2 ± 20.2
P value vs. group 4		0.028	0.208	0.424	reference	0.145
P value vs. group 5		0.997	1.000	0.964	0.145	reference

FTE: Delayed graft function; RACB: Acute cellular rejection proven by biopsy; DP: Standard deviation.

Figure 1. Kaplan- Meier survival curve of the graft at 1 year.

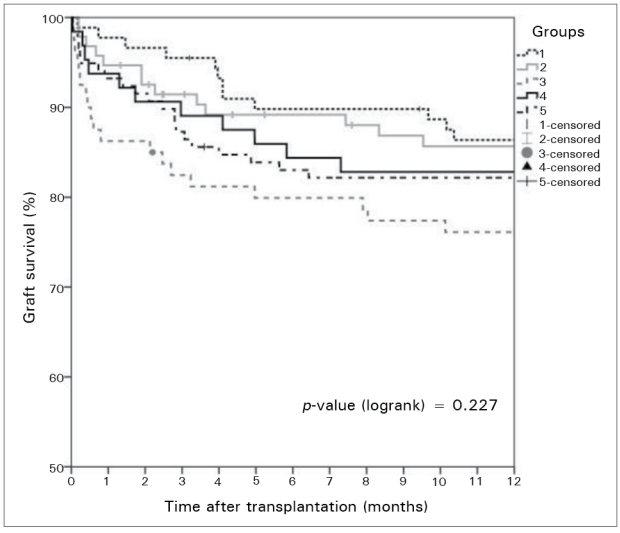
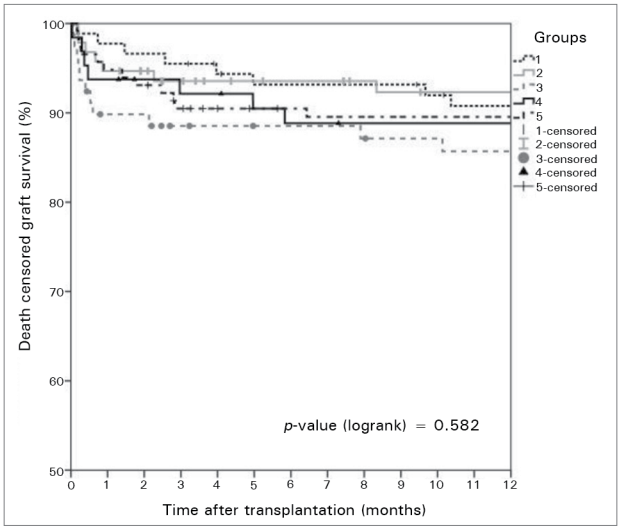


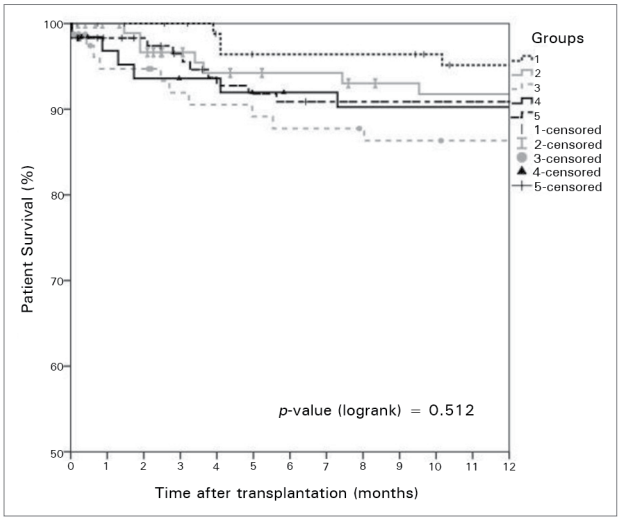
Figure 2. Kaplan- Meier survival curve of the graft with death censorado.



the low immunological risk patients who did not receive induction therapy. In addition, there was no difference in renal function at the end of one year and the induction therapy was not associated with higher incidence of infections.

Preliminary evidence demonstrated the superiority of the ATG as induction therapy in immune high risk patients, compared to treatment with induction of anti-interleukin 2 receptor antibodies (anti-IL2R) or not using this therapy.[7] However, few studies have explored the efficacy of induction therapy with ATG in high-risk patients, compared with low-risk patients not induced. Taber *et al.*[9] showed results similar to those found in our cohort in a retrospective study including 311 kidney transplant recipients of a single American center. In this study, patients induced with ATG, predominantly transplant recipients with deceased donor, sensitized, retransplantation and

Figure 3. Kaplan- Meier survival curve of patients at 1 year.



greater incidence of FTE, they had a lower incidence of acute rejection. Graft survival at 3 years was similar to that of patients induced with anti-IL2R antibodies or those who did not receive induction. This population consisted predominantly of transplant recipients with living donors, not sensitized, first transplant recipients, and reduced incidence of FTE. In the multivariate analysis, receive induction with ATG was independently associated with a lower risk of acute rejection (RR 0.302, 95% CI 0.15 to 0.61, $p < 0.001$).

Previous studies have shown that people who benefit most from induction therapy with ATG patients are sensitized.[10] However, in our cohort, the benefit of induction therapy in reducing the incidence of acute rejection was also seen in patients at low immunological risk, many of them transplant recipients at high risk for FTE. The benefit of induction therapy with ATG in this situation has already been explored in previous studies.[11]

Importantly, the characterization of the immune risk is a very controversial topic in literature. Clinical studies using various criteria, including PRA, number of HLA incompatibilities, donor characteristics, cold ischemia time and the presence of specific antibodies against donor. However, there is no clear definition of the value of the PRA the definition of this risk, nor the impact of clinical outcomes, especially today, in the PRA was calculated.[2,12,13] A better correlation between antibodies and outcomes have been described in studies evaluating the presence of specific preformed antibodies against the donor.[3]

Importantly, due to the retrospective nature of the study, the groups are heterogeneous in terms of demographic characteristics and as the period in which the transplant was performed. The first group was mostly made up of transplants performed until 2005; were patients at low immunological risk, with low percentage of DCE and although the pairings of the groups consider the initial immunosuppressive regimen, this group had a significant percentage of receivers in use of cyclosporine and azathioprine compared to the other groups. Group 2 consisted of transplant recipients predominantly carried out after 2005;were low immunological risk recipients who received standard criteria donor kidneys. Group 3 was formed predominantly by transplant recipients made after 2001; were low-risk immune receptors, with a

Table 3 Infection leading to re-hospitalization after transplantation

	Total (n = 446)	Group 1 (n = 89)	Group 2 (n = 94)	Group 3 (n = 81)	Group 4 (n = 64)	Group 5 (n = 118)
CMV, n (%)	72 (16.1)	20 (22.5)	2 (2.1)	16 (19.8)	17 (26.6)	17 (14.4)
P value vs. group 4		0.560	<0.001	0.332	reference	0.045
P value vs. group 5		0.134	0.002	0.319	0.045	reference
BCP, n (%)	25 (5.6)	10 (11.2)	4 (4.3)	4 (4.9)	5 (7.8)	2 (1.7)
P value vs. group 4		0.482	0.344	0.476	reference	0.040
P value vs. group 5		0.004	0.264	0.189	0.040	reference
ITU, n (%)	52 (11.7)	15 (16.9)	4 (4.3)	11 (13.6)	10 (15.6)	12 (10.2)
P value vs. group4		0.839	0.014	0.728	reference	0.281
P value vs. group 5		0.157	0.105	0.460	0.281	reference
Outras, n (%)	33 (7.4)	13 (14.6)	2 (2.1)	6 (7.4)	7 (10.9)	5 (4.2)
P value vs. group 4		0.507	0.019	0.460	reference	0.082
P value vs. group 5		0.009	0.393	0.336	0.082	reference

CMV: Cytomegalovirus; BCP: Bronchopneumonia; ITU: Urinary tract infection.

lower percentage of blacks receptors when compared to the other groups; and a high percentage of DCE. Groups 4 and 5 are very similar in demographics and differ by PRA and induction therapy used. In order to identify the effect of sensitization and induction therapy with ATG in this population with different characteristics, we performed a multivariate analysis. In this analysis, the value of PRA and with ATG induction therapy were not associated with risk of graft loss, death or loss to censorado death.

Our data demonstrated that the incidence of CMV infection was most induced in all groups compared to the ATG induced basixilimabe group. In contrast, this incidence was similar when patients were induced with ATG compared to low risk patients not induced (group 1). This finding should be explained by the higher incidence of acute rejection in group 1, including serious rejections leading to increased need for treatments with steroids in high doses and ATG. There is no consensus in the literature on the impact of induction therapy with ATG in the development of CMV infection. However, it is noteworthy that most of the available studies evaluated the incidence of events CMV as a secondary endpoint or *post-hoc* analysis and that it is heterogeneous studies on the dose used, maintenance immunosuppression, incidence of rejection, *serostatus* pre -transplant and used prevention strategy (prophylaxis or preemptive treatment).[7,14-17] In analysis of the Spanish *network* database *Spanish of Infection in Transplantation* (RESITRA), the use of induction therapy with depleting antibodies was an independent risk factor for the development of CMV disease (OR 2.14; 95% CI 1.1 -4.4 $p = 0.04$).[18]

Our study has some limitations that should be mentioned: it is a retrospective cohort therefore consisting of groups with different demographic populations. Furthermore, groups were formed by transplant patients at different ages, which can be influenced by medical practice changes occurred over the years. The short follow-up precludes conclusions about the later outcomes. There was carried out the research C4D in graft dysfunction by biopsies in all episodes of rejection, however important to stress that the review of medical records do not identify any patient who has received treatment of acute antibody-mediated rejection. Finally, our patients were assessed for PRA by different technologies, depending on the availability of these technologies, and the interpretation of PRA change depending on the measurement method.

In conclusion, the survival of the graft and patient and renal function at 1 year in sensitized patients induced with ATG were similar to those of low-risk patients induced with basiliximab, ATG or not induced. The ATG induction therapy was associated with reduced incidence of acute rejection, and is safe for the development of infection, comparable to the group formed by non-sensitized patients not induced.

Acknowledgements

On the Coordination of Higher Education Personnel (CAPES) for their support in developing this study.

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