Alemtuzumab induction in kidney transplant recipients

Authors

Edison Luiz Mandia Sampaio[1]
Tainá Veras de Sandes Freitas[1]
Nelson Zocoler Galante[1]
Sung In Park[1]
Kelly Miyuki Harada[1]
Filipe Augusto Bettencourt Haolla[1]
Claudia Rosso Felipe[1]
Paul Henri Clesca Troconis[1]
Marcello Fabiano de Franco[2]
Hélio Tedesco Silva Júnior[1]
José Osmar Medina Pestana[1]

[1]Hospital do Rim e Hipertensão, Nephrology Discipline, Medicine Department, Universidade Federal de São Paulo
[2]Department of Pathology, Transplante Renal e Nefropatologia, Universidade Federal de São Paulo

Hospital do Rim e Hipertensão, Discipline of Nephrology, Department of Medicine, Universidade Federal de São Paulo.

Submitted on: 09/17/2009
Accepted on: 12/25/2009

Corresponding author:
Hélio Tedesco Silva Jr.
Rua Borges Lagoa 960, 11ºandar - Vila Clementino, São Paulo, SP, Brazil
CEP: 04038-002
E-mail: heliotedesco@hrim.com.br

We declare no conflict of interest.

Abstract

Introduction: Induction therapy has been used in sensitized patients, re-transplants, and in patients who have high risk to delayed graft function (DGF) after renal transplantation. **Methods:** Retrospective study with aim to compare transplant endpoints between recipients of deceased donors which have received induction with alemtuzumab (n = 9) *versus* thymoglobulin (n = 18). Patients were matched for age, duration of dialysis treatment and cold ischemia time. **Results:** There were no differences at demographic characteristics. All patients received kidney grafts from deceased donors and 67% of these donors met the expanded criteria. The incidence of DFG was similar in alemtuzumab and thymoglobulin groups, 55% and 56%. At 12 months, rates of rejection free survival (67% *versus* 89%, p = 0,13), graft survival (62,5% *versus* 76,6%; p = 0,73), graft with death censored (62,5% *versus* 76,6%; p = 0,82) and patient survival (83,3% *versus* 81,2%; p = 0,63) were similar between the two groups. Viral infections and renal function were similar between groups. At the end of the first month, alemtuzumab patients displayed a fewer lymphocyte number (135 ± 78 *versus* 263 ± 112 N/mm^3, p < 0,05) followed by a more rapid recovery after 3 months (day 90: 683 ± 367 *versus* 282 ± 72 N/mm^3; p < 0,05). Cost associated with alemtuzumab and thymoglobulin inductions therapies were R$ 1,388.00 and R$ 7,398.00. **Conclusion:** In this cohort of patients, alemtuzumab induction showed efficacy and safety comparable to thymoglobulin but with significant cost reduction.

Keywords: kidney transplantation, immunosuppressive agents, monoclonial antibodies.

[J Bras Nefrol 2010;32(1):89-97]

Introduction

Administration of biological agents that cause lymphocyte depletion in peripheral blood and lymphoid tissues is one strategy of induction, in addition to the use of monoclonal anti-interleukin-2 (IL-2) receptor antibodies. That strategy is indicated after renal transplantation to reduce the incidence and severity of acute rejection episodes, mainly in patients traditionally classified as at high immune risk, such as highly sensitized patients, retransplanted patients, and pediatric or Afro-American recipients.[1,2,3] This therapeutic strategy has also been more frequently used in patients whose grafts fail to show immediate renal function, enabling a delay in starting calcineurin inhibitors, and, consequently, a faster recovery of renal function.[4,5,6] Finally, those biological agents have allowed the use of immunosuppressive regimens with or without reduced doses of corticosteroids or calcineurin inhibitors in some subgroups of patients.[7,8,9] The confirmed efficacy and possible combination with several immunosuppressive regimens are the main reasons for the recent increase in induction use, especially in transplant centers in the United States. However, the benefits of that strategy are somehow minimized by its high cost and higher morbidity and mortality observed after renal transplantation. Higher incidences of infections (mainly cytomegalovirus and polyomavirus) and neoplasias (especially lymphoproliferative disease) have already been reported in several clinical studies and retrospective analyses of data bases.[10]

Thymoglobulin (Thymoglobuline®) is a immunosuppressive agent composed of polyclonal antibodies directed against a

large variety of T and B cell antigens, antigens of the major histocompatibility complex (MHC), NK cells, adhesion molecules, and chemokine receptors.[11,12] The mechanism of action results predominantly from the rapid, intense and prolonged depletion of T lymphocytes in peripheral blood and lymphoid tissues. That pharmacodynamic effect occurs in a dose-dependent way through mechanisms involving antibody-mediated cytotoxicity, cell-mediated cytotoxicity, and apoptosis, limiting tissue migration during organ reperfusion or acute rejection episodes.[13,14] In some studies, the use of thymoglobulin has been associated with a lower incidence and duration of delayed graft function[4], lower incidence of acute rejection, and better graft survival.[14] However, thymoglobulin has been approved and registered only for the treatment of acute rejection. Thus, its dosage and length of treatment in induction strategies have not been systematically tested, still requiring better characterization. Currently, the total of 6 mg/kg is often used, in a single dose, usually before transplantation, or fractioned doses between the first and fifth postoperative days.

Alemtuzumab (Campath®) is a humanized monoclonal antibody directed against CD-52 antigen, whose biological function is still unknown. The CD-52 antigen is widely expressed in all lymphocyte lineages (except for plasma cells), macrophages, monocytes, and eosinophils. Alemtuzumab causes rapid and deep depletion of T and B cells in peripheral blood, but monocytes, macrophages, and memory T cells are relatively more resistant to its pharmacodynamic effect.[15] Although alemtuzumab has been approved only for the treatment of lymphoid neoplasias, it has been used, due to its mechanism of action, after renal transplantation and autoimmune diseases, such as rheumatoid arthritis, vasculites, and multiple sclerosis.[16,17] Similarly to thymoglobulin, the administration dosage of alemtuzumab is varied, and doses of 20 to 30 mg, in single or fractioned infusion, in the perioperative period are the most commonly used.

Alemtuzumab was tested in renal transplantation for the first time in 1998, and showed a relative efficacy in the prophylaxis of rejection when administered in association with low doses of cyclosporine.[18] In subsequent studies, the isolated use of alemtuzumab caused cortico-sensitive acute rejection episodes in all recipients, which resulted in banning its use as an immune-tolerance inducing agent.[19] Later, alemtuzumab was used as induction therapy in association with several immunosuppressive regimens. When combined with sirolimus (SRL), the incidence of acute rejection episodes was 27.6%, and some of those episodes had a humoral component, requiring specific treatment.[20] The use of alemtuzumab and maintenance of immunosuppression with calcineurin inhibitors and mycophenolate mofetil (MMF), with no corticosteroid, has resulted in reducing the incidence of acute rejection to 9.1%.[21] This was probably due to the fact that memory T cells, more resistant to depletion and to the action of corticosteroids and SRL, are sensitive to calcineurin inhibitors, particularly tacrolimus (TAC).[22]

This study aimed at assessing the efficacy and safety of the use of alemtuzumab in an initial series of renal transplanted patients.

Material And Methods

Patients

This study assessed nine patients who received induction therapy with alemtuzumab between May 22 and August 20, 2007.

Study design

Alemtuzumab induction therapy was used in the following patients: (i) recipients of organs from expanded-criteria deceased donors; (ii) recipients of organs with cold ischemia time longer than 24 hours; (iii) sensitized recipients (panel reactive antibodies greater than 50%); (iv) patients undergoing second transplantation.

For comparison analysis, 18 patients who had received thymoglobulin between November 1, 2005, and April 9, 2006, were selected. Their use indications met the same criteria described for alemtuzumab. The following variables were used for pairing: (i) recipient's age; (ii) dialysis time; (iii) cold ischemia time. The analysis was retrospective with data from at least one-year follow-up for all patients. Efficacy and safety were assessed prior to transplantation on days 7, 14, and 30, and after transplantation on months 3, 6, and 12.

Definitions

Expanded-criteria deceased donor was defined as a donor over the age of 60 years or aged from 50 to 59 years with at least two of the following conditions: systemic arterial hypertension, creatinine higher than 1.5 mg/dL, and cerebro-vascular accident as cause of death.[23]

Renal graft loss was defined as the need for dialysis for more than 30 consecutive days or a new transplantation. Delayed graft function (DGF) was defined as the need for dialysis in the first seven days

after transplantation. Patients were classified as lost to follow-up when definitively transferred to be followed up at another center without coming back for at least one visit every six months.

Acute rejection episodes were diagnosed based on acute graft failure and classified as biopsy-proven acute rejection (BPAR) in case of histological confirmation.

Patients with no dialysis access and clearly identified in the transplant program of the State Health Secretariat were prioritized recipients for transplantation.

Post-transplantation diabetes mellitus (PTDM) was defined as the need for initiating treatment with oral hypoglycemic agents or insulin.

Immunosuppression induction therapy

Alemtuzumab (Campath, Millenium Pharmaceutics®, Cambridge, USA, presentation: 30 mg/mL vial) was administered at the single dose of 30mg diluted in 200mL of saline solution, through intravenous infusion for 3 hours on the first postoperative day.

Thymoglobulin (Thymoglobuline, Genzyme®, New Jersey, USA, presentation: 25 mg vial) was administered at the dose of 1 mg/kg/day, diluted in 500mL of saline solution, through intravenous infusion for 6 to 8 hours. The daily administration of the drug was monitored by use of peripheral lymphocyte count as follows: the daily dose of the drug was suspended when the count was lower than 100 cells/mm^3; the daily dose of the drug was reduced when the count was between 100 and 150 cells/mm^3; the daily dose of the drug was maintained, when the count was between 150 and 250 cells/mm3; and the daily dose of the drug was increased, when the count was higher than 300 cells/mm3. The duration of treatment with thymoglobulin ranged from 1 to 12 days, depending on the patient's daily clinical assessment, mainly regarding the renal function recovery signs.

Maintenance immunosuppression

Tacrolimus was administered at the dose of 0.2-0.3 mg/kg/day divided into two equal daily doses, and monitored by use of blood residual concentration. Adjuvant therapy was individualized, and fixed doses of mycophenolate sodium (MPS, 1440 mg/day), mycophenolate mofetil (MMF, 2000 mg/day), or azathioprine (AZA, 1.5-2.0 mg/kg/day) were used. Prednisone was administered to all patients at the initial dose of 0.5 mg/kg/day (maximum of 30 mg/day), and progressively reduced to 0.2 mg/kg/day, reaching 10 mg/day 90 days after transplantation.

Prophylaxis

All patients received prophylactic treatment for pneumocystosis with sulfamethoxazole trimethoprim starting in the postoperative period and continuing until six months after renal transplantation.

Although the patients used anti-lymphocyte antibodies, no prophylaxis against cytomegalovirus infection was performed. The cytomegalovirus antigenemia test was monitored weekly, and from the time it became positive, patients received preventive treatment with gancyclovir.

Efficacy and safety parameters

The primary outcomes assessed were as follows: incidence of delayed graft function (DGF) and analysis of acute rejection-free graft and patient survivals by the end of 12 months after transplantation.

The secondary outcomes included the analysis of infectious episodes (number of patients with at least one infectious episode, infectious episodes per patient, hospitalization time, and diagnosis), incidences of PTDM and post-transplantation lymphoproliferative disorders (PTLP). Safety analyses also included hematologic assessments, fasting glycemia, and renal function evaluation, measured through serum creatinine and estimated creatinine clearance through the method proposed by Cockroft and Gault.[24]

Cost analysis of induction therapy

The numbers of alemtuzumab and thymoglobulin vials used in the immunosuppression protocol of each patient were accounted. The analysis was carried out with the unitary nominal value of each product (R$ 1,388.00 per one vial of 30 mg of alemtuzumab and R$ 425.45 per one vial of 25 mg of thymoglobulin) and the number of vials administered.

Statistical analysis

The categorical variables related to the demographic characteristics and incidences of DGF and infectious episodes, PTDM, and PTLP were compared between the two groups using the chi-square test or Fisher exact test, depending on the number of observations. Continuous noncategorical variables were compared by using independent Student t test. The acute rejection-free survival rate, and the graft and patient survivals were obtained by using the Kaplan-Meier method, and the groups were compared by using the log-rank test. The statistical significance level adopted was $p < 0.05$. The statistical analyses were performed with the SPSS software, version 7.5 (SPSS Inc., Chicago, IL, USA).

Results

Patients' profile

The demographic characteristics show that the groups were properly paired, because the recipients' age, dialysis time, and cold ischemia time were similar (Table 1).

The population studied was composed exclusively of transplant recipients from deceased donors, with a mean age of 47 ± 9 years, a long dialysis time (67.9 ± 38.0 months), and high percentage of sensitized recipients. No differences were observed in HLA compatibility, degree of sensitization, and number of previous transplants in the groups studied. In 55% of the recipients, the most recent determination of the percentage of panel reactive antibodies was over 20%. The mean age of donors was elevated (59±9 years), and 66% of them were classified as expanded criteria donors. Cold ischemia time exceeded 24 hours in 67% of the patients. Eleven (40.7%) recipients did not receive calcineurin inhibitors in the initial immunosuppressive regimen (Table 1).

Immunosuppression

The nine patients received alemtuzumab induction at the fixed dose of 30 mg on the first postoperative day. The 18 patients of the thymoglobulin group received individualized treatment regimens ranging from one to 12 days, and with total doses ranging from 75mg to 725mg. Compared with the patients who received thymoglobulin, those receiving alemtuzumab showed initially a greater reduction in lymphocyte count in peripheral blood (day 14: 172±129 vs. 390±195 N/mm3, p<0.05; day 30: 135±78 vs. 263±112 N/mm3, p<0.05). However, between the third and 12th month after transplantation, a faster recovery was observed in that count (day 90: 683±367 vs. 282±72 N/mm3, p< 0.05; day 180: 842±500 vs. 439±234 N/mm3, p< 0.05; day 360: 1269±806 vs. 690±444 N/mm3, p< 0.05) in patients receiving alemtuzumab (Figure 1).

Tacrolimus doses were lower in the alemtuzumab group on days 14, 30, 90, and 180, but the concentrations of that drug were similar in both groups. No difference was observed between groups regarding the mycophenolate doses. The prednisone doses were also lower in the alemtuzumab group on days 14, 30, and 90 (Table 2).

Efficacy analysis

The incidences of DGF were similar in the alemtuzumab and thymoglobulin groups (55% vs. 56%). Although BPAR-free survival was 17.6% greater in the group receiving thymoglobulin, that difference did not reach statistical significance. All BPAR episodes were treated with methylprednisolone. Graft survival (62.5% vs. 66.7%), patient survival (83.3% vs. 81.2%), and death-censored graft survival (62.5% vs. 76.6%) were also similar. One death caused by infection was observed in each treatment group (Table 3).

Safety analysis

The proportion of patients with at least one infectious episode was higher, but not statistically significant, in patients receiving alemtuzumab as compared with those receiving thymoglobulin (89% vs. 56%, p=0.193). The number of episodes of bacterial pulmonary infection was statistically greater in the alemtuzumab group (p=0.029), while the incidence of other infections, including the viral ones (CMV and herpes), was similar in both groups.

The incidence of PTDM was similar in the groups, although fasting glycemia on month 12 was higher in the thymoglobulin group (76.0 ± 5.2 mg/dL vs 99.5 ± 12.2 mg/dL, p<0.05). No PTLP was observed in the patients studied. The mean creatinine levels (1.5 ± 0.6 mg/dL vs. 2.1 ± 1.4 mg/dL) and creatinine clearance (61.6 ± 18.2 mL/min and 52.7 ± 26.1 mL/min) were similar in both groups at the end of the first post-transplant year. The thymoglobulin group recipients showed lower hemoglobin concentrations on days 7 (10.3±2.0 vs. 8.5±1.6 mg/dL; p< 0.05) and 14 (10.2 ± 2.5 vs. 9.0 ± 1.2 mg/dL; p< 0.05) after transplantation (Table 4).

Cost analysis

The cost of the treatment with alemtuzumab was R$ 1,388.00 per patient. The mean cost of treatment

Figure 1. Lymphocyte count in peripheral blood during the 12 months following renal transplantation in the alemtuzumab and thymoglobulin groups (* p < 0.05).

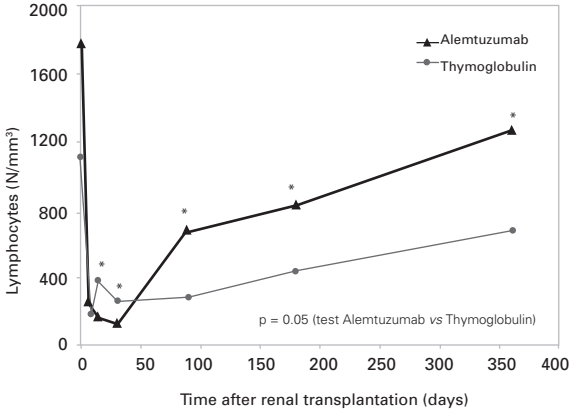

Tabela 1 Demographic characteristics

Grupo		Alemtuzumab	Thymoglobulin	p value
n		9	18	-
Sex (male/female)		6/3	11/7	1.000
Age (years)		45.4 ± 7.8	47.9 ± 9.7	0.510
Ethnicity (white/mixed/black)		7/2/0	9/6/3	0.321
Body mass index - BMI (kg/m^2)		23.5 ± 5.0	25.1 ± 3.2	0.322
Type of dialysis (hemodialysis/peritoneal)		8/1	17/1	1.000
Dialysis time (months)		70.7 ± 31.7	65.1 ± 41.5	0.725
		[18 - 120]	[17 - 180]	
HLA incompatibilities		2.1 ± 0.9	3.1 ± 1.6	0.107
		[1 - 4]	[0 - 6]	
Panel reactive antibodies (%)		14.2	22.5	0.541
		[0 - 89]	[0 - 86)]	
	≥ 20 %	2 (22.2)	6 (33.3)	0.551
	≥ 50 %	1 (11.1)	5 (27.3)	0.362
Retransplantation		2 (22.2)	2 (11.1)	0.582
Prioritized recipient		2 (22.2)	5 (28.0)	1.000
Donor's age (years)		61.8 ± 7.6	57.7 ± 9.8	0.282
Donor's sex (male/female)		6/3	9/9	0.683
Standard-criteria deceased donor		04 (44.4)	04 (22.2)	0.375
Extended-criteria deceased donor		05 (55.6)	14 (77.8)	
Cold ischemia time (hours)		26.1 ± 5.9	25.3 ± 4.6	0.710
		[17 - 35]	[20 - 37]	
	≥ 24 hours	6 (66.7)	11 (61.1)	0.778
	≥ 30 hours	3 (33.3)	2 (11.1)	0.161
Initial immunosuppression				
Tacrolimus/mycophenolate/prednisone		04 (44.4)	12 (66.7)	0.471
Mycophenolate/prednisone		05 (55.6)	04 (22.2)	
Azathioprine/prednisone		-	02 (11.1)	

with thymoglobulin was R$ 7,398.00, ranging from R$ 1,276.35 to R$ 12,338.05, depending on the number of doses received per each patient.

Discussion

This study population characterizes well the current scenario of renal transplantation. The growing disproportion between the number of donors and recipients determines the increase in waiting time for transplantation (dialysis time) and in sensitized patients waiting for transplantation, resulting in an increasing number of transplantations from expanded-criteria donors. There is no definition about the ideal immunosuppressive regimen for such clinical situations, which partially accounts for the diversity of immunosuppressive strategies already tested. In addition, the major outcomes of renal transplantation are significantly lower in that population.

The incidence of DGF was high probably due to the characteristics of the transplantations performed, and was not influenced by the induction therapy used.[25] The overall incidence of BPAR (18.5%) was relatively greater when compared with the incidence of rejection observed in patients with no DGF, usually ranging from 10% to 12%.[26] Patients undergoing alemtuzumab induction showed a higher incidence of acute rejection (33.3% vs. 11.1%) and graft loss (33.3% vs. 22.2%) as compared with those receiving thymoglobulin, probably due to shorter duration of its pharmacodynamic effect, here analyzed through the reduction in lymphocyte count in peripheral blood. All acute rejection episodes occurred after the second month of transplantation, coinciding

with the phase of return to normal lymphocyte count in peripheral blood. This has already been reported in a retrospective study with 14,362 recipients, whose acute rejection incidence at the end of the first year of transplantation was greater in the group of patients receiving alemtuzumab induction as compared with that receiving thymoglobulin (19.2% vs. 10.2%; p< 0.001).[27] Prospective studies have also compared the use of induction therapies with thymoglobulin or alemtuzumab in renal transplant recipients receiving TAC, TAC and MMF, or SRL. [20,21,28] Acute rejection incidences were 18%, 23%, and 28%, respectively.

Tabela 2 Doses and blood concentrations of immunosuppressive drugs during the 12 months following renal transplantation.

Days	Tacrolimus dose (mg/day)		Tacrolimus (ng/mL)		Mycophenolate dose (mg/day)		Prednisone dose (mg/day)	
	Alemtuzumab	Thymoglobulin	Alemtuzumab	Thymoglobulin	Alemtuzumab	Thymoglobulin	Alemtuzumab	Thymoglobulin
7	11.5 ± 4.4	14.7 ± 1.8	11.5 ± 3.1	14.2 ± 8.2	1,840.0 ± 379.5	1,440.0 ± 0.0	30.0 ± 0.0	30.0 ± 0.0
14	9.5 ± 1.0	16.3 ± 3.5 *	10.2 ± 2.2	13.3 ± 5.4	1,360.0 ± 240.0	1,329.0 ± 270.4	22.8 ± 5.7	30.0 ± 0.0 *
30	6.0 ± 1.6	14.3 ± 4.6 *	9.0 ± 1.0	11.0 ± 5.0	1,120.0 ± 379.5	1,290.0 ± 276.5	13.9 ± 7.3	25.3 ± 4.8 *
90	4.4 ± 3.3	9.8 ± 4.7 *	5.9 ± 2.6	9.1 ± 3.8	855.0 ± 267.8	1,160.0 ± 300.0	9.7 ± 7.9	15.8 ± 4.2 *
180	3.2 ± 1.1	8.3 ± 4.5 *	6.7 ± 3.8	6.9 ± 2.1	990.0 ± 372.6	1,188.0 ± 296.4	9.2 ± 4.7	11.9 ± 4.1
360	3.3 ± 1.2	7.0 ± 4.3	6.1 ± 3.8	6.5 ± 1.8	1,080.0 ± 415.7	945.0 ± 329.8	7.0 ± 2.7	8.8± 1.7

* p < 0.05 Alemtuzumab *vs.* Thymoglobulin.

Table 3 Efficacy parameters 12 months after renal transplantation

Group	Alemtuzumab (n = 9)	Thymoglobulin (n = 18)	p value
Delayed graft function	5 (55 %)	10 (56 %)	1.00
BPAR-free survival	67.0 %	84.6 %	0.26
Severity (BANFF)			
IA	1	0	
IB	1	0	
IIA	1	1	
IIB	0	0	
III	0	1	
Graft survival	62.5 %	66.7 %	0.82
Cause of graft loss			
"de novo" glomerulonephritis	1	0	
Suspension of immunosuppression	2	1	
Vascular thrombosis	0	2	
Primary dysfunction	0	1	
Patient's survival	83.3 %	81.2 %	0.63
Cause of death			
IInfection	1	1	
Subarachnoid hemorrhage	0	1	
Pulmonary thromboembolism	0	1	
Death-censored graft survival	62.5 %	76.6 %	0.73
Loss to follow-up	1 (11%)	0 (0%)	-

BPAR: biopsy-proven acute rejection

Table 4 Safety parameters 12 months after renal transplantation.

Parameter	Alemtuzumab (n = 9)	Thymoglobulin (n = 18)	p Value
Infection	8 (89%)	10 (56%)	0.193
Urinary tract	3 (33%)	3 (17%)	0.628
Cytomegalovirus	2 (22%)	7 (39%)	0.667
Pneumonia	3 (33%)	0	**0.029**
Herpes simplex or zoster	2 (22%)	2 (11%)	0.582
Tuberculosis	1 (11%)	0	0.333
Post-transplantation *diabetes mellitus*	2 (22%)	4 (22%)	1.000
Glycemia (mg/dL)	76.0 ± 5.2	99.5 ± 12.2	**0.009**
Renal function			
Creatinine (mg/dL)	1.54 ± 0.60	2.17 ± 1.41	0.358
Creatinine clearance (mL/min)	61.6 ± 18.2	52.7 ± 26.1	0.503
Hematology			
Hemoglobin (mg/dL)	13.9 ± 1.9	13.5 ± 2.0	0.680
Hematocrit (%)	41.3 ± 6.2	41.7 ± 5.3	0.896
White blood cells (N/mm^3)	6920 ± 2224	6733 ± 1848	0.860
Platelets (10^3 N/mm^3)	217.6 ± 40.6	172.7 ± 42.4	0.062

Despite the high proportion of organs from extended-criteria donors and acute rejection incidence, patients receiving alemtuzumab achieved renal function on average 8.9 mL/min higher than that observed in patients receiving thymoglobulin (61.6 vs. 52.7 mL/min). When attributing the value of 10 mL/min for patients who lost their grafts and carrying the last renal function value to those who died before completing the first year of transplantation, the results were also similar (44.0±28.6 vs. 40.0±28.6 mL/min, p=0.735). The occurrence of PTDM was similar in both groups (22%) and comparable to that of protocols with no induction therapy. Mean glycemia was more elevated in patients receiving thymoglobulin. Considering all factors involved in that observation, the greatest doses and concentrations of TAC and the greatest doses of prednisone used in patients receiving thymoglobulin can have been determinant.

Our study also suggests that patients receiving alemtuzumab have a greater incidence of infection as compared with those receiving thymoglobulin (89% vs. 56%).[28,13] Bacterial pneumonia was more frequent in the alemtuzumab group (33% vs 0%, p<0.029), as also reported in the study by Vathsala *et al*s. [28] Cytomegalovirus infection was equally present in both groups (22% vs. 39%, p= ns), but with a higher incidence than that reported in another series (6.5% vs. 3.3%)[29], possibly due to the non systematic use of prophylaxis at our center. The prophylactic treatment has been associated with reduced incidences of CMV infection in other series using induction therapy with alemtuzumab (5%)[28] or thymoglobulin (10.4%).[13] No lymphoproliferative disease occurred during follow-up.

The cost was an evident difference between the induction therapy regimens, as reported by other authors.[30] Although expenditures with new hospitalizations, other drugs, and treatment of complications have not been considered, the cost of using thymoglobulin was, on average, five times greater than that of using alemtuzumab (R$ 1,388.00 vs. R$ 7,398.10).

Due to the intrinsic limitations of the study (retrospective nature and reduced sample size), no conclusive and sound information could be extracted from that analysis. The lack of statistical significance in comparing the outcomes selected could have resulted from the reduced sample size (beta error). However, alemtuzumab or thymoglobulin induction in the population

studied has determined apparently unsatisfactory efficacy and safety. Theoretically, a higher dose of alemtuzumab (40 mg in a single dose or two doses of 20 mg) could increase efficacy in preventing acute rejection. However, the diversity of immunosuppressive regimens using alemtuzumab as induction therapy in several centers and the possibility of jeopardizing the safety of treatment made more sound conclusions impossible. In addition to the high incidence of acute rejection, three grafts were lost after immunosuppression suspension during severe infectious episodes, and two recipients died due to infection.

Immunosuppressive regimens with or without induction therapy with monoclonal antibodies directed to interleukin-2 receptor produce results considered to be adequate in most renal transplant recipients. However, the ideal immunosuppressive regimen for sensitized recipients and recipients from organs of extended-criteria donors, who represent an increasing part of the transplantations annually performed, has not yet been identified. Induction therapy, using antibody preparations that cause lymphocyte depletion, is believed to be necessary in such clinical situations. In this exploratory study, alemtuzumab, despite its significantly reduced cost, apparently did not show efficacy and safety comparable to those of thymoglobulin.

References

1. Thibaudin D, Alamartine E, de Filippis JP, Diab N, Laurent B, Berthoux F. Advantage of antithymocyte globulin induction in sensitized kidney recipients: a randomized prospective study comparing induction with and without antithymocyte globulin. Nephrol Dial Transplant 1998; 13(3):711-5.
2. Ettenger RB, Rosenthal JT, Marik JL *et al.* Improved cadaveric renal transplant outcome in children. Pediatr Nephrol 1991; 5(1):137-42.
3. Gaston RS, Hudson SL, Deierhoi MH *et al.* Improved survival of primary cadaveric renal allografts in blacks with quadruple immunosupression. Transplantation 1992; 53(1):103-109.
4. Benvenisty AI, Cohen D, Stegall MD, Hardy MA. Improved results using OKT3 as induction immunosuppression in renal allograft recipients with delayed graft function. Transplantation 1990; 49(2):321-7.
5. Lange H, Müller TF, Ebel H *et al.* Immediate and long-term results of ATG induction therapy for DGF compared to conventional therapy for immediate graft function. Transpl Int 1999; 12(1):2-9.
6. Szczech LA, Berlin JA, Feldman HI. The effect of antilymphocyte induction therapy on renal allograft survival. A meta-analysis of individual patient-level data. Ann Intern Med 1998; 128(10):817-26.
7. Vincenti F, Monaco A, Grinyo J, Kinnkhabwala M, Roza A. Multicenter randomized prospective trial of steroid withdrawal in renal transplant recipients receiving basiliximab, cyclosporine microemulsion and mycophenolate mofetil. Am J Transplant2003; 3(3):306-11.
8. ter Meulen CG, van Riemsdijk I, Hené RJ *et al.* Steroid withdrawal at 3 days after renal transplantation with anti-IL receptor alpha therapy: a prospective, randomized, multicenter study. Am J Transplant 2004; 4(5):803-10.
9. Kuypers DR, Evenepoel P, Maes B, Coosemans W, Pirenne J, Vanrenterghem Y. The use of an anti-CD25 monoclonal antibody and mycophenolate mofetil enables the use of a low-dose tacrolimus and early withdrawal of steroids in renal transplant recipients. Clin Transplant 2003; 17(3):234-41.
10. Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, Hanto DW. Association of the type of induction immunosuppression with posttransplant lymphoproliferative disorder, graft survival, and patient survival after primary kidney transplantation. Transplantation 2003; 76(9):1289-93.
11. Mueller TF. Mechanisms of action of thymoglobulin. Transplantation 2007; 84:S5-S10.
12. Bonnefoy-Berard N, Vincent C, Revillard JP. Antibodies against functional leukocyte surface molecules in polyclonal antilymphocyte and antithymocyte globulins. Transplantation 1991; 51:669.
13. Brennan DC, Flavin K, Lowell JA *et al.* A randomized, double-blinded comparison of Thymoglobulin versus Atgam for induction immunosuppressive therapy in adult renal transplant recipients. Transplantation 1999; 67:1011-18.
14. Malinow L, Walker J, Klassen D *et al.* Antilymphocyte induction immunosuppression in the post-Minnesota anti-lymphocyte globulin era: incidence of renal dysfunction and delayed graft function. A single center experience. Clin Transplant 1996; 10:237-42.
15. Zand MS. Therapeutic antibody agents for B-cell immunomodulation in renal transplantation. Transplantation 2007; 84 (Suppl11):S11-S19.
16. Bindon CI, Hale G, Waldmann H. Importance of antigen specificity for complement-mediated lysis by monoclonal antibodies. Eur J Immunol 1988; 18: 1507-14.
17. Hale G, Dyer MJ, Clark MR *et al.* Remission induction in non-Hodgkin lymphoma with reshaped human monoclonal antibody CAMPATH-1H. Lancet 1988; 2: 1394-9.
18. Calne R, Friend P, Moffatt S *et al.* Prope tolerance, perioperative campath 1H, and low-dose cyclosporin monotherapy in renal allograft recipients. Lancet 1998; 351:1701-2.
19. Kirk AD, Hale DA, Mannon RB *et al.* Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). Transplantation 2003; 76:120-9.
20. Knechtle SJ, Pirsch JD, H Fechner J Jr *et al.* Campath-1H induction plus rapamycin monotherapy for renal transplantation: results of a pilot study. Am J Transplant 2003; 3:722-30.
21. Ciancio G, Burke GW, Gaynor JJ *et al.* A randomized trial of thymoglobulin vs. alemtuzumab (with lower dose maintenance immunosuppression) vs. daclizumab in renal transplantation at 24 months of follow-up. Clin Transplant 2008; 22: 200-10.

22. Margreiter R, Klempnauer J, Neuhaus P, Muehlbacher F, Boesmueller C, Calne RY. Alemtuzumab (Campath-1H) and tacrolimus monotherapy after renal transplantation: results of a prospective randomized trial. Am J Transplant 2008; 8:1480-5.
Expanded criteria donor kidney policy. Disponível na internet no site: http://www.unos.org/
23. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31-41.
24. Goggins WC, Pascual MA, Powelson JA *et al.* A prospective, randomized, clinical trial of intraoperative versus postoperative Thymoglobulin in adult cadaveric renal transplant recipients. Transplantation 2003;76(5):798-802.
25. Ekberg H, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, ELITE-Symphony Study. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007; 357(25):2562-75.
26. Huang E, Cho YW, Hayashi R, Bunnapradist S. Alemtuzumab Induction in Deceased Donor Kidney Transplantation. Transplantation 2007; 84:821-8.
27. Thomas PG, Woodside KJ, Lappin JA, Vaidya S, Rajaraman S, Gugliuzza KK. Alemtuzumab (Campath 1H) induction with tacrolimus monotherapy is safe for high immunological risk renal transplantation. Transplantation. 2007; 83:1509-12.
28. Vathsala A, Ona ET, Tan SY *et al.* Randomized trial of Alemtuzumab for prevention of graft rejection and preservation of renal function after kidney transplantation. Transplantation 2005; 80:765-74.
29. Calne RY. Prope tolerance: the future of organ transplantation from the laboratory to the clinic. Transplantation 2004; 77:930-2.
30. Farney A, Sundberg A, Moore P *et al.* A randomized trial of alemtuzumab vs. anti-thymocyte globulin induction in renal and pancreas transplantation. Clin Transplant. 2008; 22:41-9.