RIC

ARTÍCULO ORIGINAL

# Basiliximab *vs.* limited-dose Daclizumab (2 mg/kg) administered in single or two separated doses in kidney transplantation†

Olynka Vega,* Guillermo Cárdenas,* Ricardo Correa-Rotter,* Josefina Alberú,** Luis E. Morales-Buenrostro*

* Department of Nephrology and Mineral Metabolism. ** Department of Transplantation, Division of Surgery.
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

**ABSTRACT**

**Introduction.** Addition of anti-IL2r monoclonal antibodies (chimeric or humanized) for induction therapy has reduced the frequency of acute rejection (AR). This study compares the impact of type and dosage of induction therapy on frequency of acute rejection and on renal function during the first year post-transplant. **Patients and methods.** Comparative retrospective study. Kidney transplant recipients (KTR) were divided in three groups according to induction therapy, as follows: (1) Basiliximab in two 20 mg doses, (2) Daclizumab 2 mg/kg in one dose, and (3) Daclizumab 2 mg/kg divided in two doses (1mg/kg each). Groups were paired for age, sex, number of shared haplotypes, and previous transplant history. Primary endpoints were AR episodes, time to first AR, graft loss, and death. Secondary endpoints were SCr (at 3, 6, 9 and 12 months), frequency and type of infection, and cost. **Results.** There were no baseline differences between groups. Twenty one patients were included in each group. The incidence of AR was similar: 14.2% in group 1, and 9.5% for groups 2 and 3. Two deaths were reported, one in group 1 and another in group 2. Mean SCr was similar between groups. Incidence of infection was 6, 5, and 7 in groups 1 to 3, respectively without a significant difference. The cost was higher in group 1 ($p < 0.001$). **Conclusion.** Low dose Daclizumab in one or two doses is equally effective and safe as basiliximab at 12-month follow-up, with inferior cost.

**Key words.** Induction therapy**.** Daclizumab. Basiliximab. Kidney transplantation.

***Comparación de Basiliximab vs. Daclizumab en dosis reducida (2 mg/kg) administrado en dosis única o en dos dosis en receptores de trasplante renal***

***RESUMEN***

***Introducción.*** *El uso de anticuerpos monoclonales anti-IL2r (quimérico o humanizado) como terapia de inducción, ha reducido la frecuencia de rechazos agudos. Este estudio compara el impacto del tipo y dosis de la terapia de inducción sobre la frecuencia de rechazos agudos y sobre la función renal durante el primer año postrasplante.* ***Pacientes y métodos.*** *Estudio retrospectivo y comparativo. Los pacientes receptores de trasplante renal fueron divididos en tres grupos de acuerdo con el uso de anticuerpos monoclonales anti-IL2r: (1) Basiliximab en dos dosis de 20mg, (2) Daclizumab 2 mg/kg en una dosis y (3) Daclizumab 2 mg/kg dividido en dos dosis (1 mg/kg cada una). Los grupos fueron pareados para edad, genero, número de haplotipos compartidos e historia de trasplantes previos. Los desenlaces primarios fueron: episodios de rechazo agudo, tiempo al primer rechazo agudo, pérdida del injerto y muerte del paciente. Los desenlaces secundarios fueron: creatinina sérica (a los 3, 6, 9 y 12 meses), frecuencia y tipo de infección, así como diferencia de costos.* ***Resultados.*** *Se incluyeron 21 pacientes en cada grupo y no hubo diferencias en las características basales entre los grupos. La incidencia de rechazos agudos fue similar: 14.2% en el grupo 1 y 9.5% para los grupos 2 y 3. Se reportaron 2 muertes, una en el grupo 1 y otra del grupo 2. Los promedios de las creatininas fueron similares entre los grupos. Los episodios de infección fueron similares: 6, 5 y 7 en los grupos 1 a 3, respectivamente. El costo fue mayor en el grupo 1 ($p < 0.001$).* ***Conclusión****. La dosis limitada de Daclizumab en una o dos dosis, es igualmente efectiva y segura que basiliximab a 12 meses de seguimiento, pero a un costo menor.*

***Palabras clave.*** *Terapia de inducción. Daclizumab. Basiliximab. Trasplante renal.*

† This study had no external support. The authors do not have a relationship with any company or commercial organization that makes products evaluated in this manuscript.

## INTRODUCTION

During the last decade induction therapy using monoclonal antibodies against the alpha chain of the interleukin-2 receptor (IL2r or CD25) has proved highly successful in reducing the frequency of AR in KTR with low to moderate risk. Actually it is known that regulatory T cells constitutively express CD25+, but this therapy was originally developed focusing on specific antigen-activated T cells that express alpha chains. Monoclonal antibodies bind with high affinity and specificity to this chain, thus inhibit the expansion of donor antigen-activated T lymphocyte clone and reduce the risk of AR. Recent studies demonstrated that using anti-IL2r monoclonal antibodies as induction therapy do not affect the regulatory T cells.[1,2.]

Products of genetic engineering, anti-IL2r monoclonal antibodies can be found in a chimeric (basiliximab, Simulect®) or humanized form (daclizumab, Zenapax®). Both agents have shown equivalent safety and minimal toxicity when added to calcineurin inhibitor based immunotherapy.[3] Previous studies adding anti-IL2r to cyclosporine-based regimens demonstrate a 49% decrease in AR during the first six months after transplant without increasing infectious complications.[4]

A 20 mg dose of Basiliximab is recommended on the day of surgery and on the 4$^{th}$ postoperative day.[5] Five 1 mg/kg doses of daclizumab beginning the day of surgery are recommended every 1-2 weeks.[6] Pharmacodynamic and pharmacokinetic studies show that this dose saturates 100% of T cell IL2r at a daclizumab concentration of 4 $\mu$g/mL for at least 3 months. This achieves optimum maintenance therapy even for grafts with delayed function. This dose maintains serum concentration between 1-5 $\mu$g/mL.[7] Its principal disadvantage is a higher cost compared to 2 doses of basiliximab. Initial studies involving daclizumab included corticosteroid with either cyclosporine A or azathioprine. Since then, more potent immunosuppressants have been developed for maintenance therapy and consequently lower doses have been investigated for induction therapy. Recent studies suggest daclizumab levels above 1 $\mu$g/mL are associated with 95% lymphocyte IL2r saturation. This concentration can be achieved with lower doses (2 mg/kg in one or divided in two doses).[8] Previous studies at our institution showed that lower doses (2 mg/kg in one or two doses) of daclizumab decreased the incidence of AR from 28 to 10% without increasing the incidence of infections or cancer during the first year post-transplant (not published).The present study compares the incidence of AR, first year graft function and cost of three induction alternatives: two 20 mg doses of basiliximab, limited-dose daclizumab in one and two doses.

## PATIENTS AND METHODS

We completed a comparative study within a retrospective cohort. We evaluated KTR (live o deceased donor) from December 1999 to January 2005 who received induction immunosuppression with anti-IL2r monoclonal antibodies. Three groups of KTR were formed according to the induction therapy administered: 1) two 20 mg doses of basiliximab, applied during surgery and 7 days post-transplant, 2) one 2 mg/kg dose of daclizumab during surgery, and 3) two 1 mg/kg doses of Daclizumab, during surgery and 7 days post-transplant. We had 21 patients that used Basiliximab, then, 21 patients from groups 2 and 3 were paired for age, sex, number of haplotypes shared and previous transplant history.

Primary endpoints were AR, graft and patient survival at one year. Secondary endpoints were serum creatinine (SCr) at 3, 6, 9, and 12 month follow-up, cost, hospital admissions, and infectious complications (number and type).

For univariate analysis, one-way ANOVA with Bonferroni Post Hoc test was used to evaluate continuous variables and chi-square for categorical variables. Multivariate analysis with logistic regression was employed to identify risk factors for AR. A value of $p < 0.05$ was considered statistically significant.

## RESULTS

During the mentioned time frame, 21 patients received basiliximab, 46 received daclizumab in one dose, and 49 received daclizumab in two doses. When paired for similar age, sex, haplotypes shared, and previous transplant history, 21 patients were included in each group (Table 1).

The cyclosporine and tacrolimus trough whole-blood concentrations are depicted in the figure 1. At 6, 9 and 12 months group 1 shows higher cyclosporine levels, however, these levels remain within therapeutic limits. There were no differences in the other drugs during follow-up.

### Primaryendpoints

Group 1 presented three AR (14.2%) while group 2 and 3 presented two in each (9.5%), without statistical significance, $p = 0.852$. Two patients from

Table 1. Clinical Characteristic per group.

| Variables | Group 1 n = 21 | Group 2 n = 21 | Group 3 n = 21 | P |
|---|---|---|---|---|
| Recipient age (years) | 35.5 ± 13 | 36.5 ± 13 | 37.4 ± 10 | 0.87 |
| Male sex n (%) | 13 (61.9) | 14 (66.6) | 14 (66.6) | 1.0 |
| No shared haplotype n (%) | 11 (52.3) | 9 (42.8) | 12 (57.4) | 0.61 |
| Donor age (years) | 36 ± 15 | 37 ± 13 | 40 ± 4 | 0.69 |
| Male Donor n (%) | 11 (52.3) | 11 (52.3) | 10 (47.6) | 0.86 |
| First transplant n (%) | 18 (85.7) | 18 (85.7) | 18 (85.7) | 1.0 |
| Living donor | 16 (76.2) | 20 (95.2) | 15 (71.4) | 0.12 |
| Immunosuppressive regimen * | | | | |
| CAP | 11 | 4 | 16 | 0.002 |
| TAP | 6 | 5 | 2 | 0.284 |
| CMP | 4 | 5 | 2 | 0.678 |
| TMP | 0 | 7 | 1 | 0.002 |
| Renal Failure Cause | | | | |
| Diabetes | 4 (19.0) | 2 (9.5) | 1 (4.8) | 0.33 |
| Glomerulopathy | 3 (14.3) | 4 (19.0) | 1 (4.8) | 0.37 |
| Unknown | 7 (33.3) | 12 (57.1) | 12 (57.1) | 0 20 |
| Other | 7 (33.3) | 3 (14.3) | 7 (33.3) | 0 28 |

* C: cyclosporine. T: tacrolimus. A: azathioprine. M: mycophenolate mofetil. P: prednisone.

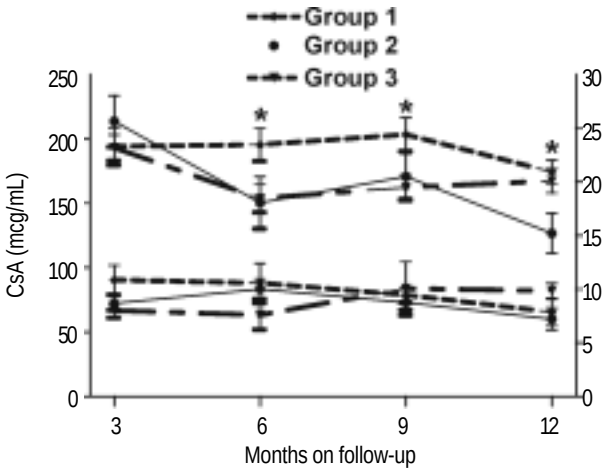


*Figure 1. Cyclosporine A (CsA) and Tacrolimus (TAC) levels during follow-up by group. Levels expressed in mean ± standard error. * p < 0.05.*

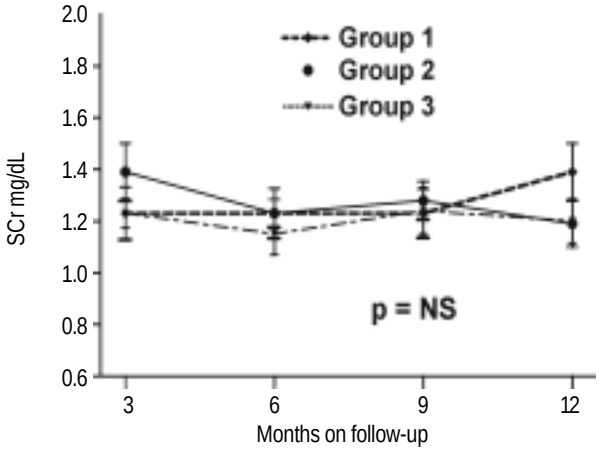


*Figure 2. SCr level per group at 3, 6, 9, and 12 month follow-up. SCr expressed in mean ± standard error. NS = Not significant.*

group 1 developed AR by month 2 both of them type I A (Banff classification), and one patient by month 3 type II A. One patient from group 2 presented AR type I A in the first month and another patient presented AR type II A at month 11. From group 3, one patient presented AR type I B in the first month and another AR type I A in the second month. All AR episodes were successfully treated with 3 doses of methylprednisolone (12 mg/kg).

Two deaths occurred by the first year. A patient from group 1 presented a fatal massive heart attack and another patient from group 3 presented cytomegalovirus pneumonitis (high-risk patient). The latter also lost the kidney graft to acute tubular necrosis due to severe cytomegalovirus infection and accounts for the only graft loss in the study population.

Although tacrolimus predominated in group 2, univariate and multivariate analysis failed to show association between AR and type of immunosuppressive drug or combination of drugs.

SCr (at 3, 6, 9, and 12 months) didn't vary significantly between groups (Figure 2). Groups 1 to 3

Table 2. Type of infection per group.

| Infection | Group 1 | Group 2 | Group 3 |
|---|---|---|---|
| Systemic Cytomegalovirus Infection | 0 | 0 | 3* |
| Urinary tract infection | 5 | 2 | 7 |
| Pneumonia | 2 | 0 | 1 |
| Gastroenteritis | 2 | 1 | 1 |
| Soft tissue infection | 2 | 2 | 0 |
| Nervous system infection | 1 | 0 | 0 |
| Other | 2 | 1 | 1 |

* Two of the three patients were high risk (positive donor, negative receptor) and one was intermediate risk.

presented 6, 6, and 9 infections, respectively, showing no statistical significance. Table 2 shows type of infection.

Although it didn't reach statistical significance, group 3 had more hospital admissions (in relation to AR, infection and parathyroidectomy). There were five, two, and seven in the group 1 to 3, respectively.

Cost analysis was based on commercial prices (US Dollars), during September 2006, in Mexico. Time at which 2 basiliximab 20 mg vials (dose required per patient) cost 3,575 USD, resulting in a whole group cost of 75,085 USD (2,478,290 pesos). On the other hand, one daclizumab 25 mg vial costs 568 USD. When patient's pre-transplant weight is factored in, group 2 had a total cost of 63,025 USD (2,098,992 pesos), averaging 2,725 USD per patient; and group 3 had a total cost of 57,915 USD (1,992,793 pesos), averaging 2,758 USD per patient. Cost analysis between group 1 and group 2 and between group 1 and 3, showed a statistical difference favoring groups 2 and 3, $p < 0.001$. No statistical difference was observed between group 2 and 3. Worth mention, group 2 had a higher average pre-transplant weight when compared to group 3, 65 kg *vs.* 60 kg.

## DISCUSSION

The current study demonstrates low dose daclizumab (in one or two doses) to be as effective and safe as basiliximab at a standard dosage, when considering AR events during the first year. Previous studies at our Institution are consistent with these findings, as are other studies that analyze limited-dose daclizumab in kidney, liver,[9] and heart[10] transplant recipients.

Vincenti, *et al.* studied pharmacokinetics and pharmacodynamics of daclizumab when administered as one 2 mg/kg dose (day 0) *vs.* one 2 mg/kg dose on day 0 and another 1 mg/kg dose on day 14 after transplantation. Patients receiving one dose had daclizumab blood serum levels $>1\mu$g/mL during $43 \pm 7$ days. Compared to $45 \pm 13$ days after the second dose (60 days total) for patients receiving two doses.[8] These levels saturated lymphocyte IL2r during 42 and 70 days when administered in one and two doses, respectively. In contrast, traditional dosage of daclizumab (five 1 mg/kg doses) provided lymphocyte IL2r saturation for 120 days.[11] This, however, did not impact the incidence of AR nor graft function when compared to low dose daclizumab. More potent drugs, like mycophenolate mofetil and tacrolimus used in low dose daclizumab trials were theorized to have played an important role in the relative success of such trials.

Maintenance therapy was predominantly tacrolimus and mycophenolate mofetil in group 2 yet this didn't prove to modify the AR incidence in univariate nor multivariate analysis. Therefore we conclude that the safety and efficacy observed in this group isn't due to the difference in maintenance therapy. A study by Niemeyer[12] also reinforces such conclusion, which analyzed liver transplant recipients who received low dose daclizumab (one 1 mg/kg dose and a second 0.5 mg/kg dose on postoperative day 4) and cyclosporine A-based maintenance therapy. It showed low dose daclizumab to be safe and effective as induction therapy.

Another study in kidney transplant recipients by Pham, *et al.*[13] compared basiliximab (two 20 mg doses) to low dose daclizumab (two 1 mg/kg doses). It showed equal performance in safety and efficacy, yet daclizumab showed lower costs. This study used tacrolimus, mycophenolate mofetil, and prednisone as maintenance therapy.

The objective in administering one daclizumab dose on day 0 is to achieve higher saturation of IL2r in the first weeks after organ transplant, during which maintenance therapy is adjusted to attain optimum levels and some cases will require a delay in starting calcineurin inhibitors (acute tubular necrosis or delayed graft function).

From an operative point of view, one dose simplifies administration and in some cases spares a vial per patient with an obvious economic implication. The current study demonstrates a clear economic benefit favoring daclizumab, while no difference between daclizumab groups was noted, even though group 2 had higher average weight.

The aforementioned results suggest daclizumab (in one or two doses) is equally effective and safe when compared to standard basiliximab dosage. Possible limiting factors for the present study are small sample size and retrospective cohort without randomization. However, pairing between groups sought to diminish these limitations. Worthy of mention, our results are consistent with other studies, further supporting our conclusion. However, it is the responsibility of each center to analyze all the evidence before adopting changes in the induction therapy.

REFERENCES


1. Cibrik DM, Kaplan B, Meier-Kriesche HU. Role of anti-interleukin-2 receptor antibodies in kidney transplantation. *BioDrugs* 2001; 15: 655-66.
2. Vlad G, Ho EK, Vasilescu ER, et al. Anti-CD25 treatment and FOXP3-positive regulatory T cells in heart transplantation. *Transpl Immunol* 2007;18: 13-21.
3. Van Gelder T, Warle M, Ter Meulen RG. Anti-interleukin-2 receptor antibodies in transplantation: what is the basis for choice? *Drugs* 2004; 64: 1737-41.
4. Adu D, Cockwell P, Ives NJ, Shaw J, Wheatley K. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. *BMJ* 2003; *326*: 789-93.
5. Nashan B, Moore R, Amlot P, Schmidt AG, Abeywickrama K, Soulillou JP. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. *Lancet* 1997; 350: 1193-8.
6. Vincenti F, Lantz M, Birnbaum J, et al. A phase I trial of humanized anti-interleukin 2 receptor antibody in renal transplantation. *Transplantation* 1997; 63: 33-8.
7. Vincenti F. Daclizumab: novel biologic immunoprophylaxis for prevention of acute rejection in renal transplantation. *Transplant Proc 1999;* 31: 2206-7.
8. Vincenti F, Pace D, Birnbaum J, Lantz M. Pharmacokinetic and pharmacodynamic studies of one or two doses of daclizumab in renal transplantation. *Am J Transplant* 2003; 3: 50-52.
9. Yan LN, Wang W, Li B, et al. Single-dose daclizumab induction therapy in patients with liver transplantation. *World J Gastroenterol 2003;* 9: 1881-3.
10. Cuppoletti A, Perez-Villa F, Vallejos I, Roig E. Experience with single-dose daclizumab in the prevention of acute rejection in heart transplantation. *Transplant Proc* 2005; 37: 4036-8.
11. Nashan B, Light S, Hardie IR, Lin A, Johnson JR. Reduction of acute renal allograft rejection by daclizumab. Daclizumab Double Therapy Study Group. *Transplantation* 1999; 67: 110-5.
12. Niemeyer G, Koch M, Light S, Kuse ER, Nashan B. Long-term safety, tolerability and efficacy of daclizumab (Zenapax) in a two-dose regimen in liver transplant recipients. *Am J Transplant* 2002; 2: 454-60.
13. Pham K, Kraft K, Thielke J, et al. Limited-dose Daclizumab versus Basiliximab: a comparison of cost and efficacy in preventing acute rejection. *Transplant Proc* 2005; 37: 899-902.



*Correspondence and reprint request:*

**Luis E. Morales-Buenrostro, MD**
Department of Nephrology and Mineral Metabolism
Instituto Nacional de Ciencias Médicas y Nutrición
Salvador Zubirán
Vasco de Quiroga # 15,
Col. Sección XVI, Tlalpan.
14080 Mexico City.
Tel.: (52-55) 5487-0900 Ext. 2524
Fax: (52-55) 5655-0382.
E-mail: luis_buenrostro@yahoo.com



*Recibido el 30 de mayo de 2007.*
*Aceptado el 14 de marzo de 2008.*