

Two-dose basiliximab compared with two-dose daclizumab in renal transplantation: a clinical study

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Abstract: Background: Addition of the interleukin-2 receptor (IL-2R) antagonists basiliximab or daclizumab to a calcineurin inhibitor-based regimen significantly reduces risk of acute rejection with a tolerability profile similar to a placebo. Use of a truncated two-dose regimen of daclizumab has been reported, but till date, there has been no controlled study of two-dose daclizumab vs. two-dose basiliximab.

Methods: Deceased-donor renal transplant recipients were randomized to basiliximab (20 mg on days 0 and 4) or daclizumab (50 mg on days 1 and 14) with cyclosporine, mycophenolate mofetil and corticosteroids. Flow cytometry was used to calculate the proportion of CD25⁺ T cells in peripheral blood.

Results: Thirty patients were randomized to basiliximab and 28 to daclizumab. There was one patient death in each group, with no other graft losses. By six months, the incidence of biopsy-proven acute rejection was 0% with basiliximab vs. 21.4% with daclizumab ($p < 0.05$). Three patients in the daclizumab group required OKT3 for steroid-resistant rejection. There were no between-group differences in the incidence of infection. The proportion of CD25⁺ T cells declined markedly during the first two wk in both groups, but was significantly lower in the basiliximab group during weeks six to eight. **Conclusion:** Two doses of basiliximab are more effective than two 1 mg/kg doses of daclizumab in preventing acute rejection in *de novo* renal transplant patients receiving cyclosporine, mycophenolate mofetil and corticosteroid maintenance therapy. In patients receiving relatively low-level immunosuppression in order to minimize toxicity, basiliximab may be preferable to a truncated daclizumab regimen.

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Acute rejection is one of the strongest predictors of long-term graft survival following renal transplantation (1, 2). Rejection occurring during the first year after renal transplant almost halves projected graft half-life (3). Since 1995, rates of acute rejection have fallen dramatically; in the United States, for example, the incidence of acute rejection during the first six months post-transplant has declined from over 40% in 1995 to around 15% in 2000 (4). Part of this improvement results from increased use of induction therapy with the introduction of more selective induction agents, particularly the interleukin-2 receptor antagonists (IL-2RA) basiliximab and daclizumab.

These are now widely used in many transplant centers (4, 5), either routinely or for high-risk individuals. Addition of an IL-2RA to a variety of calcineurin inhibitor-based immunosuppressive regimens reduces acute rejection by 30–50% (6, 7), and a large-scale analysis of data from the United Network for Organ Sharing (UNOS) has reported that graft survival improved by 17% ($p = 0.002$) with addition of IL-2RA induction compared with no induction (8). The favourable side effect profile of IL-2RA, including the apparent lack of any increased risk of cytomegalovirus (CMV) infection or malignancy (8), is a notable advantage.

Basiliximab and daclizumab are monoclonal antibodies (IgG_{1k}) produced by recombinant DNA technology. They bind with and block the IL-2R α -chain, also known as CD25 antigen, on the surface of activated T lymphocytes. This competitively inhibits the binding of serum IL-2 to CD25, thereby inhibiting the proliferation of activated T cells and subsequent release of cytokines. Administration of IL-2RA induction also leads to down-regulation of IL-2R expression, which in turn alters circulating lymphocyte distribution. Basiliximab is a chimeric antibody, i.e. composed of the variable domains of the original mouse monoclonal antibody and the constant regions of human immunoglobulin. Daclizumab is a humanized antibody, comprising only the hypervariable region of the mouse antibody with the remainder being human. Basiliximab has a higher affinity for CD25, and its license states two fixed doses of 20 mg for adults, one given on the day of transplant and one on day four after transplant (9). The license for daclizumab stipulates five weight-adjusted doses (1 mg/kg) given on the day of transplant and four times subsequently at 14 d apart (10). Using these dosage schedules, the CD25 subunit is saturated for approximately five to eight wk after transplantation with basiliximab (9) and 120 d with daclizumab (10) in adults.

There is a scarcity of data comparing clinical outcomes with basiliximab and daclizumab. The only directly comparative trial reported in the literature is a study in which 23 renal transplant recipients were alternately given either two 20 mg doses of basiliximab or five doses of daclizumab (1 mg/kg/d) (11). The incidence of acute rejection was low and similar with either agent, and there was no difference in tolerability. Indirect comparative data from two meta-analyses also indicate that the incidence of acute rejection is similar with basiliximab or daclizumab therapy (6, 7). The overwhelming majority of clinical data relating to daclizumab is based on the recommended regimen of five doses over an eight wk period. Several authors, however, have reported their experience using a truncated two-dose daclizumab regimen in kidney (12, 13), kidney-pancreas (14), liver (15–17) and cardiac (18) transplantation, to avoid the practical difficulties associated with administering a five-dose course over an eight wk period. To our knowledge, however, no trial has compared the use of the recommended two doses of basiliximab vs. two doses of daclizumab. Here we report the efficacy and safety results of a prospective, open-label trial in which renal transplant patients were randomized to two doses of either basiliximab or daclizumab in combination

with cyclosporine (CsA), mycophenolate mofetil (MMF) and prednisolone.

Patients and methods

Patients receiving a first renal transplant from a deceased donor were randomized to treatment with two doses of either basiliximab or daclizumab. Basiliximab was administered at a dose of 20 mg by intravenous infusion two h before surgery and on day four after transplantation. Daclizumab 50 mg was administered intravenously approximately 24 h before surgery and 14 d after transplantation. All patients received CsA, MMF and corticosteroids. CsA was initiated at a dose of 6 mg/kg/d and tapered to 4–5 mg/kg/d by three months and 3–4 mg/kg/d thereafter, based on CsA trough levels. The initial dose of MMF was 0.5 g t.i.d., reduced to 0.5 mg b.i.d. within one month. Prednisolone was commenced at 30 mg/d, reduced to 20 mg/d by 3 wk and 10–15 mg/d at six months. Acute rejection was confirmed by biopsy and graded according to Banff criteria (19). Rejection was treated with intravenous pulsed methylprednisolone at 500 mg/d for three d. Steroid-resistant cases were treated with a five d course of OKT3.

Incidence of biopsy-proven acute rejection (BPAR), patient and graft survival was assessed at six months; survival rates were also recorded at 12 months.

A Beckman Coulter flow cytometer was used to obtain a count of CD25⁺ T cells in peripheral blood on day 0, and thereafter weekly for the first eight wk after transplantation.

Data are expressed as mean \pm standard deviation. CD25⁺ counts between treatment groups were compared using the χ^2 test. The *t*-test was used for other between-group comparisons.

Results

A total of 58 patients were randomized to treatment with basiliximab (*n* = 30) or daclizumab (*n* = 28). There were no significant differences between the groups in terms of demographics or baseline characteristics (Table 1). No significant differences were observed in the mean time to graft function or mean dose of steroids between the two treatment groups.

One patient in each group died by month 12. One death was due to heart failure on day 71 (basiliximab group) and the other resulted from a lung infection on day 102 (daclizumab group). All other patients had functioning grafts at the end of one yr. During the first six months post-transplant, there were no rejection episodes in the basiliximab

Table 1. Patient demographics and baseline characteristics

	Basiliximab (n = 30)	Daclizumab (n = 28)
Age (y)	40.3 ± 3.5	41.0 ± 2.8
Gender	19 (63%) 11 (37%)	18 (64%) 10 (36%)
Male		
Female		
Recipient weight (kg)	51.7 ± 2.1	52.0 ± 1.3
HLA mismatch	2.8 ± 1.1	2.8 ± 1.3
PRA status (%)	4.3 ± 1.2	4.1 ± 1.5
Type of dialysis (HD/CD)	25/10	26/9
Duration of dialysis (months)	7.2 ± 2.5	6.9 ± 3.1
Warm ischaemia time (min)	7.0 ± 2.0	7.2 ± 1.8
Cold ischaemia time (h)	6.0 ± 2.1	6.7 ± 1.2

Continuous variables are shown as mean values ± SD

group whereas six patients in the daclizumab group experienced seven episodes of BPAR (0% vs. 21.4%, $p < 0.05$). Single episodes of BPAR occurred on days 23, 29, 35, 43, 48 post-transplant in five daclizumab-treated patients; in the sixth patient, two episodes occurred on days seven and 44. One episode was Grade I, the remaining six were Grade II (Fig. 1). All cases of BPAR were treated with pulsed methylprednisolone, which led to graft function recovery in three patients. In the other three patients, BPAR was reversed with OKT3 treatment.

Four cases of infection were reported by the end of month six. There were three cases of bacterial infection and one case of CMV infection in each treatment group. During months 6–12, bacterial infection occurred in two patients in each group and CMV was reported in one basiliximab-treated and two daclizumab-treated patients. No patient experienced symptoms of cytokine release syndrome and no cases of post-transplant lymphoproliferative disorder or malignancy were observed.

The proportion of CD25⁺ T cells in peripheral blood declined markedly during the first two wk post-transplant in both groups and remained suppressed at week five (Fig. 2). During weeks six

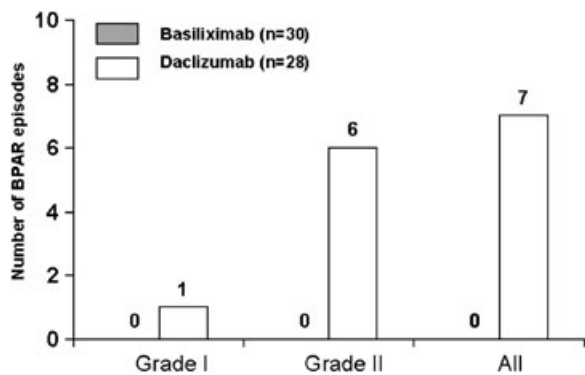


Fig. 1. Biopsy-proven acute rejection (BPAR) episodes to month six post-transplant.

to eight post-transplant, the proportion of T cells that were CD25⁺ was significantly lower in basiliximab-treated patients ($p < 0.05$). At week eight, CD25⁺ T cells had returned to baseline levels in the daclizumab group but remained suppressed with basiliximab. The mean CD25⁺ count in peripheral blood in patients who experienced acute rejection was $12.3 \pm 1.4\%$.

Discussion

The results of this randomized trial indicate that two doses of daclizumab are less efficacious than two dose of basiliximab in renal transplant patients receiving CsA, MMF and corticosteroids. Patients receiving basiliximab experienced no acute rejection during the first six months post-transplant, while approximately a fifth of patients in the daclizumab cohort had a rejection episode. Although all episodes of acute rejection in the daclizumab group were resolved following anti-rejection intervention with recovery of graft function, occurrence of acute rejection is associated with impaired long-term graft survival in at least a proportion of the patients (4). Adverse events, including bacterial CMV infection, were similar between groups and, both agents demonstrated a highly favourable tolerability profile, as has been widely reported in other studies.

Consistent with these clinical findings, flow cytometry evidence indicated that recovery of activated CD25⁺ T cells is significantly more rapid with two-dose daclizumab than two-dose basiliximab using our dosing regimen. Three of the seven rejection episodes occurred during wk six to eight, a period during which the proportion of CD25⁺ T cells was significantly higher in the daclizumab group.

The majority of studies reporting the use of a two-dose daclizumab regimen have had no comparator arm (13, 15–18). Only two other trials have compared the efficacy of a two-dose regimen vs. the licensed five-dose regimen, one in simultaneous kidney–pancreas transplants (14) and the other in kidney transplants (12), each of which concluded that the truncated regimen was as effective as the licensed five-dose schedule. These trials each used a 2 mg/kg daclizumab dose of daclizumab in the two-dose regimen (total dose 4 mg/kg) vs. a 1 mg/kg dose in the standard five-dose regimen (total dose 5 mg/kg) (12, 14). One pharmacodynamic study in renal transplant patients has suggested that 3 mg/kg daclizumab over a period of 14 d can saturate the IL-2R for eight wk (20); therefore, it could be anticipated that a two-dose regimen using 4 mg/kg daclizumab in total would

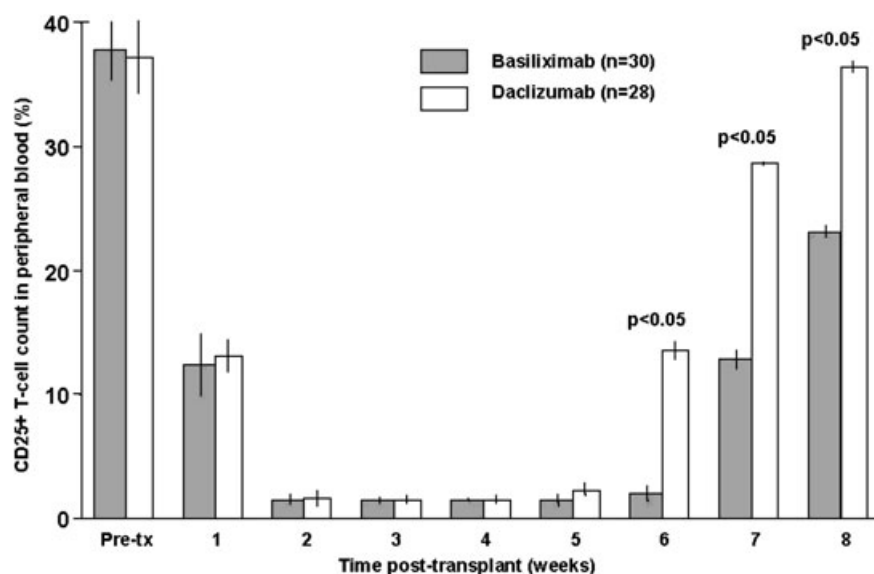


Fig. 2. CD25⁺ T cell count in peripheral blood (%).

achieve bioequivalence with a five-dose daclizumab regimen delivering 5 mg/kg in total.

In our study, we used a dose of 50 mg daclizumab administered twice; with a mean body weight of approximately 50 kg, this was broadly equivalent to 2 mg/kg daclizumab in total. We also selected a maintenance immunosuppression regimen that reflected the standard or low immunologic risk status of our patients, including a relatively low dose of MMF (1 g/d) so as to minimize risk of toxicity related to over-immunosuppression. When given in combination with two doses of basiliximab, this regimen entirely avoided acute rejection for the critical first six months post-transplant, indicating that immunosuppression was adequate. Our results demonstrate that daclizumab dosing > 2 mg/kg would be necessary to achieve a similarly effective level of protection against rejection.

In conclusion, a two-dose regimen of basiliximab is more effective than two-dose daclizumab (2 mg/kg in total) in preventing acute rejection in *de novo* renal transplant patients receiving CsA, MMF and corticosteroid maintenance therapy. In patients receiving relatively low-level immunosuppression in order to minimize toxicity, basiliximab may be preferable to a truncated daclizumab regimen. Extended follow-up is necessary to confirm whether the clinical differences reported here translate to different graft outcomes in the long term.

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