



Efficacy of Anti-Interleukin-2 Receptor Antibody (Daclizumab) in Reducing the Incidence of Acute Rejection After Renal Transplantation

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ABSTRACT

Background: Acute rejection remains a major problem in renal transplantation and represents one of the most important causes of chronic allograft dysfunction and late graft loss. Daclizumab is a genetically engineered human IgG1 monoclonal antibody that binds specifically to the α chain of the interleukin-2 receptor, and may thus reduce the risk of rejection after renal transplantation.

Objectives: The aim of this study was to examine the effect of daclizumab induction therapy combined with a triple immunosuppressive protocol including prednisolone, cyclosporine microemulsion (CsA), and mycophenolate mofetil (MMF), in reducing the incidence of acute rejection in recipients of living unrelated donor kidneys.

Patients and Methods: In this historical cohort study, 43 adult recipients of their first kidney allograft received daclizumab (three 1 mg/kg doses administered every 2 weeks) with triple immunosuppressive therapy (steroids, CsA, and MMF). This group was compared to 43 first-time graft recipients who received maintenance triple immunosuppressive therapy comprising steroids, CsA, and MMF. The end point was the incidence of biopsy-confirmed acute rejection within 6 months after transplantation.

Results: At 6 months, 5 (11.6%) of the patients in the daclizumab group had biopsy-proven rejections, as compared to 14 (32.5%) in the control group ($P = 0.017$). The sex and the age of recipients had no impact on the incidence of acute rejection episodes in the two groups.

Conclusions: Adding interleukin-2 receptor antibody (daclizumab) to maintenance triple immunosuppressive therapy (prednisolone, CsA, and MMF) reduces the incidence of acute rejection episodes at 6 months in first-time transplant recipients of living unrelated donor.

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► Implication for health policy/practice/research/medical education:

Acute rejection is one of the most important causes of chronic allograft dysfunction and late graft loss. Several studies showed that interleukin2 receptor antibody (daclizumab) can reduce acute rejection episodes in the high risk kidney transplant recipients and The aim of this study is to determine the effect of daclizumab induction therapy in reducing the incidence of acute rejection in low risk living unrelated donor first kidney recipients.

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1. Background

The survival of renal allograft transplantation, which is the treatment of choice for patients suffering from end-stage renal disease, has increased in recent decades

(1). This is primarily attributable to the development of new immunosuppressive drugs (1). One of the important predictors of allograft survival is the incidence of acute rejection (AR) during the first 3–6 months postoperatively (1, 2). The more frequently AR occurs, the higher the possibility that early renal allograft dysfunction will occur subsequently (2). Previously, this problem affected 20%–50% of transplantations and caused renal allograft loss in 5%–10% of the patients (3). Despite recent advances, AR episodes represent important challenges during the postoperative care of kidney transplant recipients (3).

2. Objectives

Several studies have shown that interleukin 2 receptor antibody (daclizumab) can reduce acute rejection episodes in high-risk kidney transplant recipients. In the current study, we proposed to evaluate the efficacy of daclizumab in low-risk first-time transplant recipients of living unrelated donor kidneys.

3. Patients and Methods

In this historical cohort study, 86 patients who underwent their first live renal transplantation were examined in the early period after transplantation. This survey was carried out between 2004 and 2008 in Taleghani Hospital, Tehran. All participants gave verbal informed consent following an explanation of the procedures involved in the study. Consent to perform the study was obtained from our hospital ethics committee.

The baseline maintenance immunosuppressive therapy protocol including prednisolone, cyclosporine microemulsion (CsA = 5 mg/kg/d), and mycophenolate mofetil (MMF = 2 g/d) was administered to all patients. Subjects were divided into two groups of the same size. The case group had 27 men and 16 women and the control group had 25 men and 18 women. Patients in the case group received 1 mg/kg daclizumab (Zenapax; Roche, Basel, Switzerland) every 2 weeks for three doses in addition to the baseline maintenance therapy. The two groups were matched with age, sex of donors and recipients, the cause of end-stage renal disease, and the cytomegalovirus and Epstein-bar virus serologic status of donors and recipients. All patients were followed for 6 months. Exclusion criteria included age less than 18 years, HIV, hepatitis B infection, or active and significant infectious conditions. In addition, participants were excluded if they were receiving therapy with other immunosuppressive regimens. In patients presenting with renal dysfunction, we initially ruled out other causes such as renal artery stenosis, viral and other infectious diseases, cyclosporine overdose, or urinary tract obstruction. Acute rejection was diagnosed based on clinical signs and symptoms, physical examination, and histological confirmation from a renal biopsy by an expert pathologist. The results of histological studies were positive based on the presence of acute tubulitis or vasculitis. Finally, the data were analyzed using the chi-square test. Results were considered statistically sig-

nificant if the *P*-value was <0.05.

4. Results

There were 27 men and 16 women in the case group (daclizumab), with a mean age of 35.9 ± 8.1 years. The mean age in the control group, comprising 25 men and 18 women was 35.7 ± 8.2 years. We found that AR, as defined by the histological analysis of a biopsy sample, occurred in 19 (22%) patients during the 6-month postoperative period. Five (11.62%) of these patients were in the daclizumab group (2 women and 3 men) and the remaining 14 (32.5%) were in the control group (5 women and 9 men) (Figure 1). There was a statistically significant difference between the groups (*P* = 0.017). According to the current study, age and gender did not affect the incidence of AR.

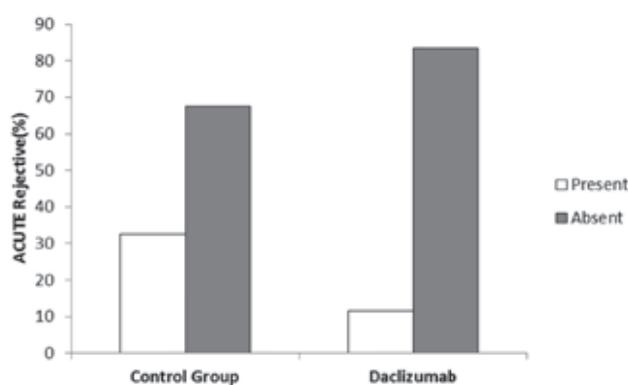


Figure 1. The Incidence (percentage) of Acute Rejection in the Control and Daclizumab Groups Within 6 Months After Transplantation.

5. Discussion

Renal allograft transplantation is the treatment of choice for patients with ESRD. Episodes of acute rejection are an important predictor of renal function and graft loss in renal allograft recipients. Recently, because of exact and detailed preoperative laboratory assessments and newer immunosuppressive drugs, the incidence of AR has decreased. Even though appropriate treatments help the management of the patients with AR, it should be remembered that this problem may decrease allograft survival by 50% (2, 4). Daclizumab is a recombinant humanized immunoglobulin G1 subclass monoclonal antibody that specifically blocks the α subunit (CD 25) of interleukin-2 (IL-2) receptor, which is expressed on the surface of activated lymphocytes (5–8).

The use of antibody induction after kidney transplantation has increased from 25% to 63% in the past decade. The induction agent used in approximately half of the patients is IL-2RA, i.e., basiliximab or daclizumab (9). Several studies have demonstrated the benefits of daclizumab in high-risk renal allograft transplantation from deceased donors or in kidney recipients with positive WBC cross-match (2, 8–11). In the current study, we showed that daclizumab is effective in reducing the incidence of acute rejection in first-time kidney transplant recipients from

unrelated live donors, if administered together with baseline maintenance immunosuppressive therapy, including prednisolone, cyclosporine microemulsion, and mycophenolate mofetil as an induction therapy. Bumgardner *et al.* (12) found that daclizumab decreases the incidence of biopsy-proven AR at 1 year post-transplantation, and Ekberg *et al.* (13), Meier-Kriesche *et al.* (14), Millan *et al.* (15), and Morris *et al.* (16) obtained similar results in their studies. Kandus (17) showed that basiliximab or daclizumab combined with triple therapy was an efficient and safe immunosuppressive strategy, which was demonstrated by the low incidence of acute rejections, excellent graft function, high survival rates, and an acceptable adverse event profile in adult recipients within the first year after renal transplantation with kidneys from deceased donors.

Daclizumab combined with triple immunosuppressive therapy, including steroids, CsA, and MMF, reduces the incidence of AR in low-risk firsttime recipients of transplanted kidneys from unrelated living donors. Further studies are needed to evaluate the overall benefits of these new strategies on the long-term survival of patients and allografts.

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References

1. Danovitch GM. *Handbook of kidney transplantation*. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2009.
2. Almond PS, Matas A, Gillingham K, Dunn DL, Payne WD, Gores P, *et al.* Risk factors for chronic rejection in renal allograft recipients. *Transplantation*. 1993;**55**(4):752-6; discussion 6-7.
3. Lindholm A, Ohlman S, Albrechtsen D, Tufveson G, Persson H, Persson NH. The impact of acute rejection episodes on long-term graft function and outcome in 1347 primary renal transplants treated by 3 cyclosporine regimens. *Transplantation*. 1993;**56**(2):307-15.
4. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med*. 2000;**342**(9):605-12.
5. Abou-Jaoude MM, Ghantous I, Almawi WY. Comparison of daclizumab, an interleukin 2 receptor antibody, to anti-thymocyte globulin-Fresenius induction therapy in kidney transplantation. *Mol Immunol*. 2003;**39**(17-18):1083-8.
6. Ekberg H, Backman L, Tufveson G, Tyden G. Zenapax (daclizumab) reduces the incidence of acute rejection episodes and improves patient survival following renal transplantation. No 14874 and No 14393 Zenapax Study Groups. *Transplant Proc*. 1999;**31**(1-2):267-8.
7. Poorrezaghali F, Einollahi B, Firoozan A, Nafar M, Yadegari H, Moghaddam SM, *et al.* Effect of daclizumab (zenapax) on prevention of acute rejection of renal transplantation. *Transplant Proc*. 2003;**35**(7):2735-6.
8. 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**(1):110-5.
9. Sageshima J, Ciancio G, Chen L, Burke GW, 3rd. Anti-interleukin-2 receptor antibodies-basiliximab and daclizumab-for the prevention of acute rejection in renal transplantation. *Biologics*. 2009;**3**:319-36.
10. Kahan BD, Rajagopalan PR, Hall M. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. United States Simulect Renal Study Group. *Transplantation*. 1999;**67**(2):276-84.
11. Kandus A, Grego K, Bren AF. Prevention of early acute rejection with daclizumab and triple immunosuppression in cadaveric renal allograft recipients. *Ther Apher Dial*. 2005;**9**(3):262-4.
12. Bumgardner GL, Ramos E, Lin A, Vincenti F. Daclizumab (humanized anti-IL2Ralpha mAb) prophylaxis for prevention of acute rejection in renal transplant recipients with delayed graft function. *Transplantation*. 2001;**72**(4):642-7.
13. Ekberg H, Persson NH, Kallen R, Gul-Baykurt N. Two doses of daclizumab in conjunction with low-dose cyclosporine, mycophenolate mofetil and steroids resulted in a low incidence of acute rejection after renal transplantation. *Scand J Immunol*. 2003;**58**(6):670-7.
14. Meier-Kriesche HU, Kaza H, Palekar SS, Friedman GS, Mulgaonkar SP, Ojo AO, *et al.* The effect of Daclizumab in a high-risk renal transplant population. *Clin Transplant*. 2000;**14**(5):509-13.
15. Millan M, Pavlakis M, Alfrey E, Salvatierra O, Dafoe D, Scandling J. A Two Dose Regimen of Daclizumab (Zenapax) in High-Risk Renal Transplant Recipients. *Transplantation*. 1999;**67**(7):S84.
16. Morris JA, Hanson JE, Steffen BJ, Chu AH, Chi-Burris KS, Gotz VP, *et al.* Daclizumab is associated with decreased rejection and improved patient survival in renal transplant recipients. *Clin Transplant*. 2005;**19**(3):340-5.
17. Kandus A, Arnol M, Omahen K, Oblak M, Vidan-Jeras B, Kmetec A, *et al.* Basiliximab versus daclizumab combined with triple immunosuppression in deceased donor renal transplantation: a prospective, randomized study. *Transplantation*. 2010;**89**(8):1022-7.