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Research Paper

Daclizumab prevents acute renal allograft rejection: 1 year analysis

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Abstract

Objective: To investigate the clinical effect of Daclizumab on preventing acute rejection in renal transplant recipients. **Methods:** 71 patients were randomly divided into two groups: Daclizumab group (n =26) and control group (n = 45). Baseline regimen of mycophenolate mofetil (MMF), cyclosporin (CsA), methylprednisolone (MPD) and prednisone (Pred) were administered to all patients. The treatment of Daclizumab was based on baseline regimen. The Daclizumab group received Daclizumab twice before and after renal transplant. The occurrence of post-transplantation acute rejection, renal function and T lymphocyte subtypes were sequentially monitored; meanwhile adverse events, infection episode, and patient and graft survival were observed. All of patients received a follow-up of 12 months at least. **Results:** The occurrence of acute rejection in Daclizumab group in 1, 3, 6 and 12 months after renal transplantation was 7.7%, 19.2%, 23.1% and 30.8%, respectively, while it was 15.6%, 28.9%, 35.6% and 46.7% in the control group. There was significant difference between the two group ($P < 0.05$). There was no difference in infection episodes and adverse events between the Daclizumab group and control group. One year patient survival was 92.3% in Daclizumab group, 91.1 % in control group ($P > 0.05$), compared with graft survival of 96.2 % and 93.3 % for Daclizumab and control group, respectively ($P > 0.05$). The renal function in Daclizumab group in 1, 6 and 12 months after renal transplantation was better than that in control group ($P < 0.05$). The CD3+ and CD4+ subtypes decreased in both two groups after operation but no significant difference ($P > 0.05$). **Conclusion:** Daclizumab combined with MMF, CsA, MPD and Pred therapeutic regimen was effective to reduce the occurrence of acute rejection in renal transplant recipients and have no influence on T lymphocyte subtypes.

Keywords: acute coronary syndrome; matrix metalloproteinase-9; soluble intercellular adhesion molecule-1; C-reactive protein; white blood cell count

INTRODUCTION

Daclizumab is a genetically engineered human immunoglobulin G monoclonal antibody specific for the interleukin-2 (IL-2) receptor. It is composed of 90% human IgG sequences and 10% murine IgG sequences, similar to human IgG. It has advantages over murine antibodies to the IL-2 receptor, including improved effector function, a low potential for immunogenicity. It binds specifically to the α subunit (Tac/CD 25) of IL-2 receptor on T cells and achieves immunosuppression by competitive antagoism of IL-2 induced T cell proliferation, a critical pathway in the cellular immune response involved in allograt rejection [1,19,23]. The available data indicated that daclizumb could reduce acute rejection in organ transplant recipients. Patient survival at 1 year after transplantation was found significantly higher than before[2,11]. We therefore investigated the clinical effect of Daclizumab in preventing acute rejection in renal transplant recipients.

MATERIALS AND METHODS

Patients

71 patients were transplanted between January 2002 to December 2004. All of patients receiving their first cadaver renal transplant were eligible to participate in studies. 26 patients (M/F 22/4; age 32 ± 5years) received Daclizumab and 45 patients

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(M/F 36/9; aged 34 ± 11 years) were as control group. The two groups were matched with age, sex, cause of end-stage renal disease; presence of panel reactive anti-histocompatibility leakocyte antigen (HLA) antibodies, with no difference in donor characteristic with respect to warm ischemic time (< 10 min), cold ischemic time (< 8 h), and number of HLA mismatch. All of patients were followed up to 1 year.

Immunosuppressive treatment

Baseline regimen of mycophenolate mofetil (MMF), cyclosporin (CsA), methylprednisolone (MPD) and prednisone (Pred) were administered to all patients. MMF was given at a dose of 2 g/d. CsA was started at an initial oral dose of 4.5 mg (kg·d) twice a day and continued at the necessary dose to maintain blood levels within accepted therapeutic limits [3]. MPD 750 mg was administered by intravenous infusion during the operation, followed by 750 mg on d 1, 750 mg on d 2, 500 mg on d 3, 250 mg on d 4, switched to oral Pred 20 mg/d. The treatment of Daclizumab (Daclizumab made by Hoffmann-La Roche Ltd) was based on the baseline regimen. The first dosage of Daclizumab 1 mg(kg·d) was administered within 24 hrs prior to operation. Daclizumab was administered by intraverous infusion over 15 min. This was diluted to 50 mL of 0.9 % sodium chloride injection before injection. The second same dosage was administered in day 14(after operatio).

Monitoring

Diagnosis and treatment of acute rejection

Acute rejection was proven by clinical signs, symptoms, examination of renal function, and renal biopsy. The final diagnosis depended on histological confirmation by Banff classification 97 [4]. First line treatment of acute rejection was methylprednisolone for 3-5 days, depending on condition. Baseline immunosuppression was continued unchanged. Second line therapy for steroid-resistant rejection consisted of monoclonal antibody anti CD3 10-14 days, or ATG/ALG for 7-10 days without other immunosuppressive treatment.

Detection of T lymphocyte subtypes

Peripheral blood $CD3^+$, $CD4^+$, $CD8^+$ positive cells percentage were examined by flow cytometry, respectively.

Detection of renal allograft function

Serum creatinine and BUN was monitored once a day in first week, then twice a week in second to sixth week, after six weeks, once a week.

Adverse events

The examination of blood and urine function of the liver and kidney, and concentration of CsA were monitored every week within 1 month once every month thereafter. The adverse reactions data (which included gastrointestinal disorder, allergic reaction, and cytokine release syndrome) were collected up to 3 months. The occurrences of any malignancies were recorded to 1 year.

Infection episodes

In order to prevent cytomegalovirus(CMV) infection, all of the patients were treated with intravenous ganciclovir 250 mg from d 14 to d 28 after transplantation. The makers of CMV were monitored every 2 wk within 1 month after operation. The occurrences of pulmonary and urinary infection were recorded and examination of culture of bacteria and fungus was routinely tested.

Patient and graft survival of 1 year

Patients and graft survival were followed up to 1 year.

Statistical Analysis

The data was expressed as mean±SD, and test of significance adopted t-test and chi-square criterion interclass. $P < 0.05$ was considered to be statistically significant.

RESULTS

Acute rejection

The occurrence of biopsy-proven acute rejection in Daclizumab group in 1,3,6 and 12 months after renal transplantation was 7.7% ,19.2% ,23.1% and 30.8% , while it was 15.6% ,28.9% ,35.6% and 46.7% in the control group. There was a significant difference between the two groups($P < 0.05$, ***Tab 1***).

Tab 1 **The comparison of acute rejection episodes at 12 months between two groups** (n ,%)

Post-transplantation time	Daclizumab group (n = 26)	Control group (n = 45)
within1 month	2(7.7%)*	7(15.6%)
within 3 month	5(19.2%)*	13(28.9%)
within 6 month	6(23.1%)*	16(35.6%)
within 12 month	8(30.8%)*	21(46.7)

*$P < 0.05$, All cases with acute rejection were confirmed by biopsy at the standard Banff 97

T lymphocyte subtypes

All of the expression of CD3+ and CD4+ were decreased in two groups after transplant, but there was no significance difference between groups($P > 0.05$);

However, there was significant difference in comparing the expression of $CD3^+$ and $CD4^+$ before operation to 3 months post operation in each group ($P < 0.01$), and no difference in expression of CD8+ in situation above. The data was shown as follow(***Tab 2***)

Renal allograft function

The serum creatinine and BUN level one week post transplant showed no significant difference in the two groups; but renal function in the Daclizumab group (1, 6 and 12 months after renal transplantation) was better than that in the control group (P< 0.05, ***Tab 3***).

Tab 2 **The comparison of percentage of T lymphocyte subtypes between Daclizumab group and control group**

($\bar{x} \pm s$)

	Daclizumab group			Control group		
	CD3+	CD4+	CD8+	CD3+	CD4+	CD8+
Pre-operation	65.7 ± 9.3	38.6 ± 6.2	22.5 ± 4.9	65.4 ± 9.1	39.1 ± 6.3	22.3 ± 4.6
Post-operation						
1 w	60.5 ± 8.9	34.4 ± 5.7	22.6 ± 4.8	63.6 ± 6.1	36.3 ± 6.1	22.0 ± 4.5
2 w	52.3 ± 7.5	28.9 ± 5.1	21.4 ± 4.2	54.7 ± 7.2	30.2 ± 5.3	21.4 ± 4.3
1 mon	51.5 ± 7.2	27.7 ± 4.8	20.3 ± 4.0	53.6 ± 7.3	30.6 ± 5.2	21.2 ± 4.0
3 mon	50.7 ± 6.9#	26.6 ± 4.3#	20.1 ± 3.6	53.2 ± 7.2#	29.4 ± 4.9#	20.6 ± 3.8

Note: Compared with pre-operation, #$P < 0.01$

Tab 3 **The comparison of renal function between Daclizumab and control group** ($\bar{x} \pm s$)

Post-operation time	SCr(umol/L)		BUN(mmol/L)	
	Daclizumab	Control	Daclizumab	Control
1 w	136.2 ± 45.8	139.1 ± 46.6	6.3 ± 3.7	7.5 ± 3.7
2 w	115.9 ± 37.3	127.0 ± 40.8	6.0 ± 2.4	7.3 ± 3.2
1 mon	99.4 ± 34.2*	130.7 ± 41.2	5.9 ± 2.3#	7.5 ± 3.6
3 mon	103.9 ± 37.5	118.4 ± 38.5	6.8 ± 2.6	7.0 ± 3.1
6 mon	109.7 ± 42.6*	142.7 ± 50.3	7.1 ± 3.0*	10.4 ± 4.5
12 mon	131.7 ± 46.3#	161.2 ± 54.9	7.4 ± 3.2*	11.8 ± 4.6

Note: Compared with control, #$P > 0.05$; *$P < 0.05$

Adverse events

Administration of Daclizumab was not associated with an allergic reaction or cytokine release syndrome. The incidence of all adverse events including leucocytopenia (4% for Daclizumab *vs.* 8% for control group, $P > 0.05$), liver lesion (7% for Daclizumab *vs.* 10 % for control group, $P > 0.05$) and gastrointestinal disturbance (14% for Daclizumab vs. 18 % for control group, $P > 0.05$) was similar in the Daclizumab and control group. There were not any malignanc(reactions?) in the two groups within 1 year.

Infections

There was no significant difference between the groups for the percentage of patients with CMV pulmonary infections and urinary infections ($P > 0.05$). The fatality rate of infections seems to be higher in control recipients than that in Daclizumab group, but the difference did not reach statistical significance ($P > 0.05$, ***Tab 4***).

Patient and graft survival

The patient and graft survival up to 1year were recorded. Patient survival was higher with daclizumb 92.3 % (24/ 26) as compared with the control group 91.1% (41/45), but there was no significant difference ($P > 0.05$). Graft survival at 1 year was with Daclizumab 96.2%(25/26) compared with the control group 93.3%(42/45)($P > 0.05$).

Tab 4 **The comparison of the infections rate at 12 mon between two groups** (n,%)

Items	Daclizumab group (n = 26)	Control group (n = 45)
Total number of patients with infections	10(38.5%)	16(35.6%)
Total number of patients with CMV pulmonary infections	8(30.8%)	13(28.9%)
Patients with CMV pulmonary infections at 3 mon	6(23.1%)	10(22.2%)
Patients with CMV infections during 4-12 mon	2(7.7%)	3(6.7%)
Total number of patients with urinary infections	2(7.7%)	3(6.7%)
Total number of death with infections at 12 mon	2(7.6%)	4(8.8%)

$P > 0.05$, compared with control group using χ^2-test

DISCUSSION

As acute rejection is still a major problem in renal transplantation and is one of the important causes of chronic graft dysfunction and subsequent graft loss, the search for more effective, specific and well tolerated immunosuppressive agents remains a major goal in renal transplantation.

Daclizumab, (a new humanized monoclonal antibody) was recently introduced as induction therapy in renal transplants to reduce acute rejection episodes [5,6,12,13]. Daclizumab is a genetically engineered human IgG1 monoclonal antibody that binds specifically to the subunit Tac/CD25 of the interleukin-2 (IL-2) receptor on the surface of activated lymphocytes. The exact mechanism(s) by which Daclizumab exerts an immunosuppressive effect remains unclear; however, it is most likely that the saturation of IL-2 receptor and subsequent competitive antagonism of IL-2-dependent T cell proliferation, account in a large measure for its action [7,14]. One of the main advantages of this new monoclonal antibody is that it does not appear to increase the incidence of adverse events when added to standard cyclosporine-based therapy [5,6,18]. And it is indicated that 5 dosages could maintain a sufficient immunosuppressive effect lasting 6 months after transplantation[5]. The most critical period of acute rejection occurrence is the first 3 months. The treatment of 2 dosages of Daclizumab was also effective to reduce the incidence of acute rejection in the recipients of delayed graft function [8, 9,15, 22]. Our studies showed that 2 dosages of Daclizumab can effectively release the incidence of acute rejection. The occurrence of acute rejection in Daclizumab group in 1,3,6 and 12 months(7.7%,19.2%,23.1% and 30.8%) after renal transplantation was significantly lower than that of the control group (15.6%,28.9%,35.6% and 46.7%). So, Daclizumab was effective in the prevention of acute rejection in renal transplant recipients.

Data available indicated that Daclizumab was well tolerated with a low potential for immunogenicity [11-14,16,17,20,24,25]. In our research, Daclizumab has no direct relationship with allergic reaction and cytokine release syndrome. The rate of adverse events including leucocytopenia, liver lesion and gastrointestinal disorder did not increase. It indicted that clinical application of Daclizumab humanised monoclonal antibody should be safer and with fewer adverse reactions.

It must be noted that two patients, a serious mixture infection occurred in their lungs within 3 months, in the Daclizumab group. Both of them died of acute respiratory distress syndrome (ARDS). Patient/allograft survival in daclizumb group however was higher than that in control group, but there was no significant difference ($P > 0.05$), this result showed no difference from data available [8,11,18,21]. In our research, the number of Daclizumab treated patients, was less than that in control group owing financial constraints. The differences between the numbers of two groups were likely to have influenced results. The effects of Daclizumab on long term graft and patient survival require further investigation. It will be most likely be settled by both a longer follow-up and a larger number of patients studied.

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