Combination of a Low Dose of Daclizumab and Standard Regimen for Prevention of Rejection in Men and Women Receiving a Kidney Transplant

Seyed Mojtaba Sohrevardi,[1] Jalal Azmandian,[2] Zahra Shafii,[3] Faramarz Fazeli,[4] Abbas Etminan,[2] Sara Azizi Shoul[5]

[1]Department of Clinical Pharmacy, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[2]Physiology Research Center and Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[3]Department of Internal Medicine, Shahroud University of Medical Sciences, Shahroud, Iran
[4]Department of Urology, Zahedan University of Medical Sciences, Zahedan, Iran
[5]Kerman University of Medical Sciences, Kerman, Iran

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Introduction. This study aimed to investigate the effectiveness of low-dose daclizumab for prevention of acute kidney allograft rejection and to evaluate differences between men and women receiving living donor transplants.

Materials and Methods. This randomized controlled trial was performed on 120 living donor kidney transplant recipients. Participants in the case group received a low dose of daclizumab (1 mg/kg) before and 14 days after transplantation in addition to their standard immunosuppressant regimen. Participants in the control group received the standard treatment protocol only. Acute rejection episodes and graft survival were compared between the two groups. Additionally, graft survival of women and men was compared separately between the two groups.

Results. Acute rejection was significantly less frequent in the daclizumab group than in the controls (6.7% versus 18.3%; P = .048). The 6-month survival rates were 95% (95% CI, 92% to 98%) in the daclizumab group and 85% (95% CI, 81% to 89%) in the control group (P = .03). The 6-month graft survival rates of the women were 97% (95% CI, 95% to 99%) in the daclizumab group and 74% (95% CI, 65% to 83%) in the control group (P = .02). However, the difference in graft survival rates was not significant among the men.

Conclusions. The use of induction therapy with two doses of daclizumab reduces the incidence of acute rejection and improves graft survival of living donor kidney transplant reciepients. This study showe that these effects are prominent among the female recipients.

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INTRODUCTION

End-stage renal disease is one of the growing health problems in the world, for which various treatments have been developed.[1] Kidney transplantation is the treatment of choice, which has been available in Iran from years ago. The kidney transplant patients need multiple immunosuppressive drugs to prevent transplant rejection. There are various combinations of these drugs in different treatment protocols and each has its own advantages and disadvantages.[2] Recent studies have tried to find immunosuppressive drugs with more effects and fewer side effects. Among recently proposed drugs is daclizumab, which

is a monoclonal antibody against interleukin-2. Its conventional dose is 1 mg/kg as intravenous infusion for 5 doses, which is administered initially during the 24 hours before transplantation (day zero), and then every 14 days.[3,4] Daclizumab has no interaction with other medications in transplant patients. Its reported complications including gastrointestinal side effects are not significant.

Like other immunosuppressants, daclizumab can increase the risk of opportunistic infections and lead to anaphylactic reactions.[3,4] In various centers in Iran and in the world, this drug is added to the standard treatment protocol of transplant patients to investigate rate of allograft rejections,[5-12] which have led to various results. In some studies, daclizumab has been associated with reduced risk of rejection.[5,9-11] While in some others, no significant difference was observed in the rejection rates as compared to the conventional regimens.[6,8,12] These differences may be due to small sample size in some of these studies. Moreover, donor source and racial differences in the study populations must also be considered.[13]

The studies in Iran on the effects of daclizumab on kidney transplantation are all conducted using the standard doses of the drug. Considering that administration of low-doses of the drug compared with the standard dose can be cost saving and that the studies conducted in Iran have used the standard dose (ie, 5 doses),[12,14] this study aimed to investigate the effect of adding 2 doses of daclizumab on the day zero and 14 after kidney transplantation from living donors in comparison with the standard regimen (mycophenolate mofetil, corticosteroids and cyclosporine). Gender differences in kidney transplantation have been largely ignored.[15] There are a few sex-specific studies on immunosuppresants in transplant patients.[16] Therefore our comparisons included the evaluation of daclizumab efficacy based on patients' sex.

MATERIALS AND METHODS

Patients admitted to Afzalipour Hospital, in Kerman, Iran, for receiving a living donor kidney transplant were enrolled the study. The patients were excluded in case of sensitivity to daclizumab, any other limitations to administration of all doses of daclizumab, and existence of a history of a previous kidney transplant. This study was approved by the Ethics Committee of Kerman University of Medical Sciences (code number, 88.166) and registered as a clinical trial at Iranian Registry of Clinical Trials (registry number, IRCT138802021836N1). The participants provided written informed consent after being explained in detail the study protocol and risks and benefits of participants.

Simple random sampling was used to assign the participants into the case and control groups. Based on the current literature[17] and considering $\alpha = 0.05$ and $\beta = 20$, a sample size of 50 participants in each group were required. We included 60 patients in each group to ensure enough number of patients would complete the study. In the case (daclizumab) group, 60 patients received low-dose daclizumab (1 mg/kg) on day 0 and day 14 of transplantation (Zenapax, Hoffmann-La Roche, Basel, Switzerland), in addition to their standard treatment protocol, which consisted of cyclosporine (5 mg/kg to 8 mg/kg, and then an adjusted dose based on serum level), prednisolone (1 mg/kg and then slow decreasing), and mycophenolate mofetil (2 g/d). The control group patients received the standard treatment protocol only. The research team was blinded to the treatment protocols of the participants.

The patients were followed up for 6 months and compared in terms of allograft rejection based on the suggestive clinical symptoms such as serum creatinine, ultrasonography, and biopsy of the transplant kidney, if necessary. The two groups were also compared for side effects of the immunosuppressive drugs, particularly infectious complications. The data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, Ill, USA). Proportion (%; 95% confidence interval [CI]) of rejections in each group was separately calculated and compared using the chi-square test. The log-rank test was used for survival comparisons between men and women. A *P* value less than .05 was considered significant.

RESULTS

A total of 120 patients were included the study, and 60 patients were allocated to the intervention group and received daclizumab and standard immunosuppressive regimen, while the rest of the patients were enrolled as the control group and received only the standard regimen. There were 29 (48.3%) women in the daclizumab group and

Characteristics of Kidney Transplant Recipients

Characteristic	Kidney Transplant Recipients	
	Daclizumab Group	Control Group
Mean age, y	36.1 ± 13.3	34.7 ± 13.5
Sex (%)		
Male	31 (51.7)	35 (58.4)
Female	29 (48.3)	25 (41.6)

25 (41.6%) women in the control group (Table).

Allograft rejection occurred in 4 patients (6.7%; 95% CI, 5.5% to 7.9%) in the daclizumab group and 11 patients (18.3%; 95% CI, 9.7% to 26.9%) in the control group (P = .048). The 6-month survival rates were 95% (95% CI, 92% to 98%) in the daclizumab group and 85% (95% CI, 81% to 89%) in the control group (P = .03). In each of the groups, 5 patients developed unusual infectious complications requiring hospitalization and other complications only developed in 1 patient in the control group.

The 6-month graft survival rates of the women were 97% (95% CI, 95% to 99%) in the daclizumab group and 74% (95% CI, 65% to 83%) in the control group (P = .02). However, the difference in graft survival rates was not significant among the men (P = .75); graft survival was 94% (95% CI, 90% to 98%) versus 92% (95% CI, 88% to 96%) in the daclizumab and control groups, respectively.

DISCUSSION

Preventing acute rejection has been one of the most important problems in the treatment of transplant patients. Daclizumab is a human monoclonal antibody that is administered in 5 doses of 1mg/kg. Considering that one of the limitations in prescribing daclizumab is its high cost, we administered it in 2 doses in our clinical trial and demonstrated that it reduced rejection rate and also 6-month graft survival in the women.

In one study the efficacy of daclizumab was investigated in combination with an antilymphocyte globulin drug in preventing transplant rejection in immunologically high-risk kidney transplant recipients. It was revealed in this study that daclizumab in comparison with the antilymphocyte globulin drug only resulted in improved graft survival and less complications.[14] More similarly to our study, Ekberg and colleagues, in a study on 43 recipients of cadaveric kidney transplant, evaluated the effect of adding 2 doses of daclizumab on days zero and 14 after kidney transplantation to the triple-drug regimen of mycophenolate mofetil, corticosteroids, and low-dose cyclosporine. This study demonstrated a reduction and delay in acute rejection of kidney graft and increased survival rate.[13] The findings are even promising with lower doses; in a study by Ji and colleagues in China, the effect of adding one dose of daclizumab (1 mg/kg) to the standard triple-drug regimen of 58 kidney transplant patients was assessed and the findings of this study confirmed the positive effect of this extra dose in preventing acute rejection.[9]

Zhu and coworkers showed that 5 half-doses of daclizumab (0.5 mg/kg) reduced the risk of acute rejection in patients with appropriate kidney function after surgery; however, it was not beneficial in patients with delayed recovery of kidney function after surgery.[18] Jain and colleagues found that 2 doses of daclizumab reduced acute rejection. They studied pediatrics kidney rejection and concluded that this regimen was effective in rejection prevention and did not increase the side effects.[19]

In some other studies, the efficacy of low doses Daclizumab is compared with other antirejection drugs. In a study by conducted Pham and coworkers, the effect of low-dose daclizumab was compared with basiliximab; it was found that administration of two doses of daclizumab is as much effective as basiliximab in preventing acute rejection.[20] In another study by Vega and associates these two drugs were also compared for effectiveness. The results of this study also indicated that administration of two doses daclizumab is comparable with basiliximab in reducing rejection rates, while its cost was significantly less.[21]

There are few study about gender differences in immunosuppresant drugs in transplant patients. The study which was done by Aros and colleagues in 2005 showed no gender-associated differences of cyclosporine pharmacolinetics in stable kidney transplant patients treated with diltiazem.[16] Considering that the aforementioned studies have been conducted on the recipients of cadaveric kidney transplantation and there is no previous study in Iran applying low dose of daclizumab and gender differences in daclizumab effectiveness, the present study is a unique one of its kind that supports the effectiveness of daclizumab and

shows the highest benefit fro the women receiving a kidney transplant.

CONCLUSIONS

Based on this study, induction therapy with 1 mg/kg daclizumab on the day of transplantation surgery and two weeks later results in reduced rejection rates without increased risk of serious infections, and this reduction is more prominent in the women. Although this study showed that treatment with lower doses of daclizumab can be used as a safe drug for reducing acute kidney rejection, it is suggested to conduct further studies with more patients and longer follow-up duration. Moreover, comparing a low dose of this drug with the standard dose provides us with more information about the safety of recommending low doses of the drug instead of the standard dose. Finally, according to these results, gender-associated differences should be an important consideration in patients treated with low dose of daclizumab; however, more studies seem to be necessary for a solid conclusion.

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CONFLICT OF INTEREST

None declared.

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Correspondence to:
Jalal Azmandian, MD
Physiology Research Center and Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
E-mail: j_Azmandian@yahoo.com

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