Prophylactic Effect of Mycophenolate Mofetil on Early Outcomes of Living Donor Kidney Transplantation

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Introduction. Living donor transplantation allows a priori scheduling and the recipient can receive immunosuppressive prophylaxis several days before surgery, which is preoperative induction therapy with oral agents. We evaluated the impact of preoperative mycophenolate mofetil on the outcomes of living donor kidney transplantations.

Materials and Methods. In a randomized controlled trial was from November 2008 to November 2010, 99 patients receiving their first living donor kidney transplantation were divided into the mycophenolate mofetil (500 mg) and placebo groups, and received 2 tablets per day for 5 days before transplantation.

Results. Forty-nine patients received mycophenolate mofetil and 48 received placebo. The mean serum creatinine on discharge day and hospitalization period were significantly less with mycophenolate mofetil compared to placebo (1.62 ± 1.00 mg/dL versus 1.22 ± 0.24 mg/dL, $P = 0.03$ and 20.8 ± 11.2 days versus 13.5 ± 4.4 days, $P < .001$, respectively). No delayed graft function was observed. Slow graft function was 2-fold higher in the placebo group (14.6% versus 8.2%, $P = .32$). Acute rejection was seen in 12.2% of the patients with mycophenolate mofetil and in 29.2% of the controls ($P = .04$). Serum creatinine levels at discharge were significantly lower in the mycophenolate mofetil group compared with that in the placebo group ($P = .03$).

Conclusions. Prophylactic administration of mycophenolate mofetil before living donor kidney transplantation reduced hospitalization period, improved early graft function, and decreased the risk of acute rejection in the first month posttransplant.

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INTRODUCTION

The enhancement of kidney allograft survival has been an important goal of researchers and clinicians in an attempt to increase life expectancy and reduce rejection, hospitalization, and costs of transplantation. Acute rejection (AR) occurs in about 15% of the kidney allografts.[1] Since most complications and mortalities happen within the first year of transplantation,[2] nephrologists pay special attention to the follow-up care and appropriate immunosuppressive protocols in the first months after transplantation in order to increase graft survival. In this regard, several methods have been suggested, including administration of various immunosuppressive drugs, antibodies, and immunoglobulins that are often applied in deceased donor kidney recipients, albeit associated with high costs and some complications.[3]

Factors affecting prognosis and allograft survival are delayed graft function (DGF), defined as requirement of dialysis in the first week after transplantation; slow graft function (SGF), a serum creatinine level greater than 3 mg/dL on day 5 after transplantation; and AR.[4,5] In various studies, the incidence of DGF has been reported to be 5% to 40% in deceased donor kidney transplants compared to zero to 5% in living donor kidney transplants.[6] On the other hand, 1-year survival of living donor kidney transplants is about 15% more than that of deceased kidney transplants, which is probably due to the lack of ischemic damage.[3,4,7] In a study performed in Iran, DGF was reported to be 7.7% in living donor kidney transplants.[5]

Various factors, including prolonged cold and warm ischemia time, high donor serum creatinine level at the time of transplantation, blood pressure, gender and age of donor and recipient, recipient race, human leukocyte antigen mismatch, previous transplantation, duration of dialysis before transplantation, and preparation protocol of graft before anastomosis, can affect the outcome of transplantation and influence development of DGF or SGF in the early weeks.[5,8] Some measures have been proposed to reduce DGF, such as appropriate matching of donor and recipient; improvement of initial graft preparation, like preservation by hypothermic machine perfusion, shortening the ischemia time, and accurate care of brain-death donors; and intra-operative administration of antithymocyte globulin, which are often used in deceased donor kidney transplantation.[5,8-10]

While organ transplantation, particularly kidney transplantation, has technical and immunological improvements in the last 3 decades, no suitable method is yet provided for the prevention of DGF or SGF.[6] However, several efforts, such as delayed prescription of calcineurin inhibitors and injection of antithymocyte globulin or interleukin-2 receptor inhibitors were successful to some extent in reducing the incidence of rejection.

Since living donor transplantation allows a previous planning and scheduling, we are able to prepare the recipient with immunosuppressive drugs as prophylaxis several days before the surgery (preoperative induction therapy with oral agents). Mycophenolate mofetil (MMF) is an antiproliferative agent used in most immunosuppressive protocols whose benefits and advantages have been proved in various studies.[11-14] Dalal and colleagues reviewed 87 articles and confirmed the superiority of MMF over other immunosuppressants such as azathioprine.[11] In this study, we aimed to evaluate the impact of preoperative MMF administration on the programmed living donor kidney transplantations, and also to evaluate its efficacy as a method to reduce DGF and AR to improve early outcomes of this type of transplantation.

MATERIALS AND METHODS

Patients

This randomized controlled trial was conducted from November 2008 to November 2010 on 99 patients receiving living donor kidney allograft in Imam Reza Hospital of Kermanshah University of Medical Sciences, in Kermanshah, Iran. The inclusion criteria were an age of at least 15 years old, living donor source, negative panel reactive antibodies, and the first planned transplantation. Candidates with cancer, acquired immune deficiency syndrome, hepatitis, and pregnancy were excluded. Furthermore, kidney transplant recipients who received immunoglobulins or monoclonal antibodies (antithymocyte globulin or interleukin-2 antagonists) within the perioperative period and those with significant postoperative complications such as arterial thrombosis and leucopenia were excluded from the study. The study protocol was approved by the ethics committee of Kermanshah University of Medical Sciences.

Intervention

Similar packages each containing 20 tablets of MMF, 500 mg (CellCept, Roche, Basel, Switzerland), and placebo were prepared and numbered using a table of random numbers for administration in each arm of the study. The research team and the patients were blinded to the package contents. The participants received 2 tablets, twice daily, for 5 days before the operation. The commonly reported adverse effects, including nausea, vomiting, diarrhea, abdominal pain, and rarely, leucopenia or thrombocytopenia were recorded, if any. The following data were collected on the transplantation day: donor and recipient's age and gender, donor-recipient relationship, recipient's weight, duration of dialysis before transplantation, serum creatinine level, and anastomosis time (from

clamping of donor's artery during nephrectomy to removal of the clamp from the recipient's artery after anastomosis). All donor nephrectomies were done through an open intercostal incision.

Outcomes and Follow-up

All of the patients were treated with a standard immunosuppressive protocol that included prednisolone, MMF, and cyclosporine and serum creatinine level was recorded on days 2, 5, and 7, as well as the discharge day. Delayed graft function was recorded if the recipient needed dialysis within the first week after the surgery. A creatinine level equal to or more than 3 mg/dL on the 5th day after transplantation was considered as SGF. Also, SGF was documented if serum creatinine decreased to less than 30% of its pretransplant value on the 2nd postoperative day, without the need of dialysis in the first week.

The patients were followed for 1 month. Acute rejection was defined clinically when an unexplained elevation of serum creatinine (allograft dysfunction) responded to antirejection therapy and confirmed with technetium Tc 99m diethylene triamine pentacetic acid renal scintigraphy. Patients with AR received antirejection therapy and those with SGF were treated conservatively.

Statistical Analyses

The data were processed with the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). The independent sample *t* test was used to compare continuous variables with normal distributions, and the Kruskal-Wallis test and the Mann-Whitney U test were applied for comparisons of continuous variable with skewed distributions. Categorical variables were compared with the Pearson chi-square and the Fisher exact tests. A *P* value less than .05 was considered significant.

RESULTS

During the study, 1 patient experienced renal arterial thrombosis postoperatively and 1 lost her kidney allograft in the next several days probably due to hyperacute rejection. Both of these patients were excluded from the study. Thus, 97 kidney transplant recipients were included in the analyses (49 patients in the MMF group and 48 controls). The donor and recipient profiles and their correlation with the intervention (administration of MMF or placebo 5 days before transplantation) are depicted in the Table. No considerable adverse effects were observed.

The mean serum creatinine levels on days 5

Characteristics of Donors, Recipients, and Kidney Transplant By Intervention*

Characteristics	MMF (n = 49)	Placebo (n = 48)	Risk Difference (95% Confidence Interval)	*P*
Donor				
Age, y	27.8 ± 5.5	27.6 ± 6.0	-0.347 (-2.64 to 1.95)	.76
Male gender	42 (85.7)	32 (66.7)	-0.209 (-0.46 to 0.05)	.03
Related	3 (6.1)	1 (2.1)	-0.306 (-0.82 to 0.21)	.62
Recipient				
Age, y	41.9 ± 12.6	39.2 ± 13.9	-2.918 (-8.24 to 2.40)	.28
Male gender	37 (75.5)	25 (52.1)	-0.169 (-0.39 to 0.05)	.02
Weight, kg	62.23 ± 13.54	59.8 ± 12.8	-1.604 (-7.24 to 4.03)	.57
Dialysis duration, mo	14.6 ± 13.8	14.1 ± 7.9	-0.442 (-6.27 to 5.38)	.43
Pretransplant creatinine, mg/dL	7.06 ± 2.39	6.76 ± 2.14	-0.251 (-1.16 to 0.66)	.58
Follow-up				
Anastumosis time, min	51.94 ± 11.86	49.77 ± 10.21	-2.165 (-6.67 to 2.34)	.42
Serum creatinine, mg/dL				
Day 2	2.01 ± 1.05	1.97 ± 0.98	-0.141 (-0.59 to 0.31)	.54
Day 5	1.69 ± 0.65	1.95 ± 1.36	0.345 (-0.118 to 0.808)	.14
Day 7	1.59 ± 0.61	1.77 ± 1.03	0.255 (-0.117 to 0.627)	.18
At discharge	1.22 ± 0.25	1.62 ± 1.00	0.400 (0.11 to 0.69)	.03
Hospital stay, d	13.53 ± 4.42	20.76 ± 11.21	7.224 (3.81 to 10.64)	< .001
Acute rejection	6 (12.2)	14 (29.2)	1.082 (0.025 to 2.139)	.04
Slow graft function	4 (8.2)	7 (14.6)	...	.32

*Values in parentheses are percents. MMF indicates mycophenolate mofetil. Ellipsis indicates not analyzed.

and 7 after transplantation were lower in the MMF group than those in the placebo group, but the differences were not significant ($P = .14$ and $P = .18$, respectively). The mean serum creatinine on the discharge day and duration of hospital stay in the MMF group were significantly less than those in the placebo group ($P = .03$ and $P < .001$, respectively). In the first week after transplantation, only 1 excluded participant who was in the placebo group required dialysis and lost her kidney allograft on the following days. Thus, none of the included participants had DGF. There were 4 patients in the MMF group (8.2%) and 7 in the placebo group (14.6%) who experienced SGF ($P = .32$). Finally, AR was reported in 20.6% of the participants; 6 patients in the MMF group (12.2%) and 14 in the placebo group (29.2%) in the placebo group ($P = .04$). Acute rejection significantly correlated only with recipient's weight ($P = .048$).

The mean serum creatinine level on days 2, 5, and 7 after transplantation and on the discharge day significantly correlated with AR ($P = .006$, $P = .001$, $P < .001$, and $P < .001$, respectively). Furthermore, SGF had a significant relationship with AR ($P < .001$).

Slow graft function significantly correlated with recipient's weight ($P = .03$). Serum creatinine concentration on all days 2, 5, and 7 after transplantation and on the discharge day correlated significantly with SGF ($P < .001$ for all measurements). When the alternative definition of SGF was considered (a decrease in serum creatinine less than 30% of the pretransplantation level in 48 hours postoperatively), these relationships remained significant.

DISCUSSION

Despite numerous developments in kidney transplantation and the advent of drugs and protocols that improves graft outcomes, there is still no certain cure for DGF after transplantation.[6] Some studies have achieved several successes such as lack of early reception of calcineurin inhibitors and perioperative use of antithymocyte globulin and interleukin-2 receptor inhibitors that are often applied for sensitized or deceased donor kidney allograft recipients with high costs.[10,15,16]

Since living donor transplantation allows a previous planning and schedule, we are able to prepare the recipient with immunosuppressive prophylaxis several days before transplant surgery (preoperative induction therapy with oral agents). Some centers applied this method for living donor kidney transplants in their immunosuppressive protocols.[17-19] Considering that the main source of donation supply is living donor in Iran, the study sample was selected from living donor transplantations, and since the role of MMF has proven in large studies in reducing AR, DGF, and SGF,[20-22] we selected this drug to be administered 5 days before transplantation as outpatient, evaluating its preoperative effects on kidney allograft function and hospitalization length. Rudich and coworkers used cyclosporine as preoperative induction therapy for 5 days which showed no beneficial effect on improving the outcome of transplantation compared to the control group. Discharge and follow-up serum creatinine levels were higher in the cyclosporine group. Early administration of cyclosporine is deemed not suitable because of its nephrotoxicity.[19] Hence, we speculated that MMF is preferred for immunosuppressive prophylaxis.[11]

In our study, serum creatinine at discharge and hospitalization length were significantly less than those in the control group ($P = .03$ and $P < .001$, respectively), and acute rejection rate was lower ($P = .04$). The shorter hospitalization was noticeable in the MMF group because of its potential indication of reducing costs. The use of MMF in posttransplant immunosuppressive protocol has some advantages such as a decrease in acute rejection episodes (reduction from 32% to 14%),[23] lower serum creatinine in short term,[24] better overall graft survival (when compared with sirolimus),[13] reducing proliferation of T cells and activity of inosine monophosphate dehydrogenase, and decrease in CD25 and CD71.[25] In addition, MMF was effective as a rescue therapy for AR as compared with azathioprine and high-dose steroid and also in reducing the episodes of later rejections and graft loss because of AR.[11]

Wolters and colleagues used MMF and prednisolone 5 days before transplantation and reported 17.2% AR and 1% DGF.[18] Guirado and associates administered MMF 48 hours before transplantation; AR and DGF were 18.0% and zero, respectively.[17] In our study, these values were 12.2% and zero for the MMF group, respectively, and were 29.2% and zero with placebo, respectively. Thus, prophylactic administration of MMF could reduce acute renal allograft rejection. Among the

97 patients, no one required dialysis in the first week after transplantation, and therefore, we could not assess risk factor of DGF; however, since DGF risk factors are the same as those for SGF,[26] and graft outcomes in DGF and SGF are similar,[27] our the results obtained in the study of SGF can also be generalized to DGF. A variety of definitions are available for SGF. We utilized 2 commonly used definitions, which were similar in terms of their relationship with measured covariates.

It seems that decreasing of serum creatinine less than 30% of pretransplant level in 48 hours postoperatively is a more accurate definition for SGF, because firstly serum creatinine in patients before surgery is very different, and it gradually decreases perioperatively; thus, it could be a fraction of preoperative serum creatinine. Secondly, in the first days after the surgery, serum creatinine could rise again due to AR or other causes. Zeraati and colleagues defined SGF as a serum creatinine less than 2.5 mg/dL at day 7 after transplantation and reported SGF and DGF rates of 10% and 5% in living unrelated kidney transplants, respectively.[28] Based on different definition, we found SGF in 12.9% of the living unrelated kidney transplants at day 7, in 11.8% at day 5, and 4.3% at day 2. As mentioned, these differences could be due to the further rising of serum creatinine at later days because of AR or other causes, leading to a bias. Nonetheless, SGF at days 2 and 5 were less frequent in the MMF group than in the placebo group, but the differences were not significant (2.0% versus 6.2% and 8.2% versus 14.6%, respectively).

Although donor and recipient's age and gender and duration of dialysis before transplantation were considered as risk factors for SGF, DGF, and AR in most studies,[3-6] we failed to find considerable correlation between. Anastomosis time was not associated with SGF and AR, either. This can be due to the concurrent donor nephrectomy and kidney transplantation and the short duration of ischemia time (50.91 ± 11.087 minutes). This time correlated with recipient's age and duration of dialysis before transplantation, which could help the planning of surgery.

In this study, of 11 patients who experienced SGF, 4.1% were in the MMF and 7.2% in the placebo group. Ten patients had AR too, and thus, SGF had a strong relationship with AR. Of 4 patients with SGF in the MMF group, 3 (75%) were involved in AR episode ($P = .004$), and in the placebo group, all of those with SGF experienced AR ($P < .001$). We specualted that if SGF and DGF are reduced, AR rate will be reduced, too.

In our study, long-term outcomes and survival rate were not evaluated. Therefore, further investigation of immunosuppression before transplantation is necessary to assess its long term effects on graft outcomes. Another limitation was that AR was not biopsy-proven in all of the cases. Finally, MMF was not compared with other induction therapy agents, and we cannot make any recommendation on the immunosuppressive medications appropriate for pretransplant induction therapy.

CONCLUSIONS

We conclude that the prophylactic administration of oral MMF several days before living donor kidney transplantation may improve kidney allograft function by decreasing the risk of SGF and AR early after transplantation. Also, this strategy can reduce hospitalization period and its related costs during the first posttransplant month. Therefore, preventive administration of MMF for at least 5 days prior to the surgery seems reasonable. Further studies are warranted to confirm these findings.

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CONFLICT OF INTEREST

None declared.

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