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The Efficacy and Safety of Mycophenolate Mofetil Combined With Low-Dosage Tacrolimus and Corticosteroid Regimen in Renal Transplant Recipients in China

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ABSTRACT

Objectives: Investigation into the efficacy and safety of mycophenolate mofetil combined with low-dosage tacrolimus and corticosteroid regimen in renal transplant recipients in China.

Methods: A total of 210 patients having received a single-organ renal allograft were randomized into a standard-dosage tacrolimus group (n=104) and a low-dosage tacrolimus group(n=106). Individual patients were treated for 12 months. The primary efficacy endpoints were the biopsy chronic allograft damage index (CADI) already confirmed and the glomerular filtration rate (GFR) for 12 months after transplantation.

Results: The vast majority of patients were administrated with a sufficient dosage of mycophenolate mofetil (1.5 g/d or above) in these two groups of treatment. The average trough level of tacrolimus was significantly lower in the low-dosage tacrolimus group than in the standard-dosage tacrolimus group, i.e. respectively, 10.6±2.7 ng/ml versus 12.8±2.5 ng/ml, during the post-transplantation in the first three months. As for the standard-dosage group and low-dosage tacrolimus group, the mean biopsy CADI already confirmed was 1.82 and 2.13 respectively (p=0.0813), the mean GFR was 77.08 ml/min and 80.12 ml/min (p=0.7949), the acute rejection rate was 2.6% and 5.2% (p=0.6812), and patient and graft survival was 100% and 99.1% (p=1.0000).

Conclusions: The use of sufficient dosage of mycophenolate mofetil can reduce the dosage of tacrolimus, and effectively reduce the incidence of acute rejection post-transplantation, while increasing the rate of patient and graft survival.

KEYWORDS Renal transplantation; Mycophenolate mofetil; Tacrolimus; Low-dosage; Standard-dosage; Efficacy

1 Introduction

With the continuous development and extensive application of novel potent immunosuppressant, the incidence of acute renal allograft rejection is significantly reduced and the short-term survival of patient and renal allograft has been significantly enhanced. However, the immunosuppressant-related toxicities, including chronic nephrotoxicity, hypertension, hyperlipidemia and new-onset diabetes, do not result in significantly-improved long-term survival of patient and renal allograft, and there is 3-5% of the graft lost each year [1]. As shown by a research into the survival follow-up of renal transplant recipients for more than 25 years, cardiovascular diseases, including hypertension, hyperlipidemia and diabetes, are the main reasons for the death of renal transplant recipients (40%) [2]. Therefore, optimization of immunosuppressant regimen, seeking to give full play to the maximization of immunosuppressant to prevent rejection, reducing the adverse reactions caused by immunosuppressant to the minimum and delaying the occurrence of chronic allograft dysfunction, is an important condition for increasing the long-term survival of renal allograft, which has become the focus of research in the field of kidney transplantation. As shown by Symphony research [3], sufficient dosage of mycophenolate mofetil (MMF) combined with low-dosage tacrolimus and corticosteroid may be the ideal treatment regimen for renal transplant recipients. Due to its low renal toxicity, fewer adverse reactions and stronger immune inhibition effects on this regimen are becoming more common in clinical practice. In order to clarify the efficacy and safety of mycophenolate mofetil (Cellcept®, Shanghai Roche Pharmaceutical Co., Ltd.) combined with low-dosage tacrolimus and corticosteroid, including the incidence of acute rejection, graft survival, adverse reactions and tolerability, as well as renal protection, six-research centers had conducted the research into the comparison of efficacy and safety between MMF combined with low-dosage tacrolimus and corticosteroid and MMF combined with standard-dosage tacrolimus and corticosteroid in renal transplant patients from September 2009 to February 2013.

2 Materials and Methods

2.1 Subjects: There were 210 consecutive adult first renal transplant recipients from allogeneic living donors in six units in China and these subjects were recipients who accept single-organ allograft. Donor male 129,female 81,donor age 34.2±12.1(42-57) years. Inclusion criteria: I. The study was approved by the Committee of Ethics. All patients gave their written consent; II. 18 to 75-year-old males or females; III. Single-organ renal transplant recipients; IV. Pregnancy test of reproductive women was negative, as they should take reliable contraceptive measures. All patients gave their written consent. Exclusion criteria: I. In any form of drug abuse, patients with mental diseases or other patients with understanding disorders in the requirements of this study according to the researchers; II. Patients with severe digestive tract diseases which may affect their oral drug absorption; III. Patients with severe infections, or HIV demonstrated by evidence, or those wih chronic active hepatitis; IV.Patients with active gastric ulcer; V. Patients with malignant tumor, except those with cured skin in situ cancer; VI. Severe anemia (hemoglobin: less than 6g/dl), severe leukopenia (leukocytes: less than 2500/mm3), and severe thrombocytopenia (platelets: less than 100,000/mm3); VII. PRA > 50% and cold ischemia time of over 30 hours; VIII. Patients who participated in other clinical studies within 30 days before taking part in the study.

2.2 Study design: This is a randomized, open, multicenter, and paralleled study for comparison. All recipients received the therapy of daclizumab induction (a single dose 1 mg/kg of ideal body weight and intravenous infusion. Zenapax®, Hoffman-La Roche, Nutley, NJ) two hours before operation. All patients who met the inclusion/exclusion criteria were randomly divided by the research centers: the standard-dosage tacrolimus group (MMF, standard-dosage tacrolimus and corticosteroids) and the low-dosage tacrolimus group (MMF, low-dosage tacrolimus and corticosteroids) were in proportion of 1 to 1, and received treatment of twelve months. The dosage of MMF was 0.75-1g, twice a day. The dosage of tacrolimus is as follows: standard-dosage tacrolimus group: standard-dosage was orally administrated twice a day, the target plasma trough concentration in the first three months after enrollment reached 10-12ng/ml and maintained at 8-10ng/ml after three months; Low-dosage tacrolimus group: the initial dosage was twice a day by oral administration, the target plasma trough concentration in the first two months reached 8-10ng/ml and 3-7ng/ml in the third month, and 3-5ng/ml after three months. Corticosteroid was used according to the actual situation of each research center. The first dosage of MMF and tacrolimus must be given before transplantation or within 24 hours after transplantation, but recommended to being given within six hours before transplantation.

All demographic data and baseline characteristics in the standard-dosage and low-dosage tacrolimus groups were balanced and comparable (Table 1, Table 2).The average warm ischemia time was 4.44 minutes and the mean cold ischemia time was 7.17 hours during the renal transplant operation.

2.3 Observation indicators: The primary efficacy indicators included chronic allograft damage index proved by kidney biopsy in the 12th month after renal transplantation (CADI) and the rate of glomerular filtration was calculated based on the serum creatinine concentration by Cockcroft-Gaul formula [5]. The secondary indicators included the incidence of acute rejection, graft loss or death in 6 months and 12 months after renal transplantation, the incidence of treatment failure in 12 months after renal transplantation (defined as using other immunosuppressants for maintenance treatment beyond the immunosuppressant specified by the regimen in this treatment group, or the withdrawal of the immunosuppressant specified by the regimen for more than 14 days continuously or more than accumulative 30 days, or graft loss or death), and the survival rate of patients and grafts in six months and 12 months after renal transplantation, etc. The safety indicators included leukopenia, neutropenia and anemia; cardiovascular disease; mellitus of new-onset post-transplantation diabetes; new-onset hypertension; new-onset hyperlipidemia; clinical assessments (vital signs, laboratory tests, adverse events, opportunistic infection, malignant tumors and death); and the incidence of cystic lymphangioma required intervention in the first six months after transplantation.

Diagnosis and treatment of acute rejection episodes: Acute rejection episodes were routinely diagnosed by using percutaneous transplant biopsy specimens which were scored according to the Banff classification [6]. The first line of therapy for Banff grade rejection episodes was 500-mg bolus doses of methylprednisolone.

2.3 Statistical processing: A statistical analysis was made of SAS 9.1 software. The primary efficacy indicators were analyzed by using covariance analysis (ANCOVA) model with the treatment group, the research center and the interaction of the treatment group and the research center as fixed factors. The secondary efficacy indicators (acute rejection, incidence of graft loss or death, treatment failure rate, survival rate of patients and grafts) were compared between groups by using Fisher's exact test, and the time from transplantation to the first occurrence of acute rejection was evaluated between groups by using Log-rank test. The safety index was mainly demonstrated by a descriptive summary.

3 Results

3.1 General clinical data: In this study, 210 patients were randomly enrolled from six-transplant centers, 104 cases in the standard-dosage tacrolimus group and 106 cases in the low-dosage tacrolimus group, with the average age being 38.8 years, ranging from 17 to 64 years old. 147 patients (70.0%) were males. In terms of end-stage renal disease history, the mean disease duration was 4.31 years (ranging from 1 to 28.0 years).

3.2 Conditions for using drugs: In this study, the majority of patients used sufficient amount of MMF. In the standard-dosage tacrolimus group and in the low-dosage tacrolimus group, the ratios of the MMF daily dose were at baseline, i.e. 2 weeks, 4 weeks, 13 weeks, 26 weeks, 39 weeks and 52 weeks after transplantation being 1.5g and more than 1.5g were no different(Fig.1,P>0.05). At baseline, in the standard-dosage tacrolimus group, 20.2% of patients were administrated with the MMF dosage of more than or being equal to 2.0 g/day, and 20.8% of patients were administrated in the low-dosage tacrolimus group (P>0.05). At baseline, in the standard-dosage tacrolimus group, 20.2% of patients were administrated with the MMF dosage of more than or being equal to 2.0 g/day, and 20.8% of patients were administrated in the low-dosage tacrolimus group (P>0.05).

The average trough level of tacrolimus was significantly lower in the low-dosage tacrolimus group than in the standard-dosage tacrolimus group, 10.6±2.7 ng/ml versus 12.8±2.5 ng/ml respectively, during posttransplantation in the first three months. In the low-dosage tacrolimus group, the average trough level of tacrolimus in the first two months reached 9.1± 2.3 ng/ml and 6.9± 1.9 ng/ml in the third month, and it was reduced to 4.5±1.1 ng/ml after three months. In the low-dosage tacrolimus group, 100% achieved the intended target level in the first two months, 99.1% in the third month, and 98.1% from the fourth month to the twelfth month. In the standard-dosage tacrolimus group, 100% achieved the prescribed target level in one month, 99% from the third month, and 99% from the fourth month to the twelfth month.

The average dosage of corticosteroids was at baseline, i.e. 2 weeks, 4 weeks, 13 weeks, 26 weeks, 39 weeks and 52 weeks after transplantation in the standard-dosage tacrolimus group and in the low-dosage tacrolimus group (Fig.2,P>0.05).

3.3 Clinical efficacy evaluations: The average CADI score of renal pathological changes in the 12th month after renal transplantation was 1.97 points, of which the average CADI score in the standard-dosage tacrolimus group was 1.82

points and the average CADI score in the low-dosage tacrolimus group was 2.13 points. The difference between these two groups was not statistically significant (p=0.0813).

The average glomerular filtration rate in the 12th month after renal transplantation was 78.56 mL/min, of which the average glomerular filtration rate in the standard-dosage tacrolimus group was 77.08 ml/min and the average glomerular filtration rate in the low-dosage tacrolimus group was 80.12 ml/min. The difference between these two groups was not statistically significant (p=0.7949). The glomerular filtration rates at each time point after renal transplantation in these two groups were similar, and the average glomerular filtration rate reached about 70 ml/min at the second week after renal transplantation and showed a gradually increasing trend over time.

The incidence of acute rejection within 6 months and 12 months after renal transplantation was only 3.9%, and the incidence in the standard-dosage and low-dosage groups was 2.6% and 5.2% respectively. The difference between these two groups was not statistically significant (p=0.6812).

There was no graft loss occurring within 6 months and 12 months after renal transplantation. There was no death within 6 months after transplantation. Within 12 months after renal transplantation, one case died in the low-dose group. The survival rate of patients and grafts was 99.5%, of which the patient survival rate in the standard-dosage and low-dosage groups was 100% and 99.1% respectively. The difference between these two groups was not statistically significant (p=1.0000). 17 patients (8.1%) experienced treatment failures within 12 months after renal transplantation, of which 10 cases failed in the standard-dosage tacrolimus group (9.6%) and 7 cases failed in the low-dosage tacrolimus group (6.6%). The difference between these two groups was not statistically significant (p=0.4586). Among these failed patients, one case died, 16 patients used other immunosuppressants for maintenance treatment beyond the regimen specified in this treatment group, of which 8 cases used cyclosporine, 6 cases used mizoribine, one case used leflunomide and one case used mycophenolate sodium enteric coated tablets.

3.4 Safety evaluation: In this study, only 8.6% of patients (8.7% in the standard-dosage tacrolimus group and 8.7% in the low-dosage tacrolimus group) had leukopenia, 4.8% of patients (4.8% in the standard-dosage tacrolimus group and 4.7% in the low-dosage tacrolimus group) had diarrhea, 2.4% of patients (2.9% in the standard-dosage tacrolimus group and 1.9% in the low-dosage tacrolimus group) had new-onset diabetes, 3.3% of patients (2.9% in the standard-dosage tacrolimus group and 3.8% in the low-dosage tacrolimus group) had new-onset hyperlipemia, 3.8% of patients (3.8% in the standard-dosage tacrolimus group and 3.8% in the low-dosage tacrolimus group) had infections, 0.5% of patients (none in the standard-dosage tacrolimus group and 0.9% in the low-dosage tacrolimus group) had opportunistic infections All patients had no anemia, neutropenia, new-onset vascular disease, new-onset hypertension, new-onset malignant tumors and cystic lymphoma in need of intervention in the first six months after transplantation.

In this study, the incidence of treatment-related adverse effects was 34.8% (31.7% in the standard-dosage tacrolimus group and 37.7% in the low-dosage tacrolimus group), and the most common treatment-related adverse effects included increased glutamic-pyruvic transaminase (10.5%), decreased white blood cell count (8.6%) and diarrhea (5.7%). The majority of treatment-related adverse effects were mild or moderate. 6 subjects (2.9%) (1 case in the standard-dosage tacrolimus group (1.0%) and 5 cases in the low-dosage tacrolimus group (4.7%)) were reported with serious adverse effects, including 1 case of cardiovascular accident, 1 case of renal allograft rupture, 2 cases of acute renal transplant rejection, 1 case of renal graft ureteral obstruction and 1 case of cytomegalovirus infection, of which 3 cases of serious adverse effects were considered as being related to the drugs tested by the researchers, including 2 cases of acute renal transplant rejection and 1 case of cytomegalovirus infection. One subject in the low-dosage tacrolimus group died of unexpected cardiovascular serious adverse effect. In this study, the clinical lab-tests and vital signs had no change with clinically significant meaning.

4 Discussion

As the most extensively-used calcineurin inhibitor [7,8,9,10], tacrolimus has a good effect on the prevention of post-operation acute rejection, but a number of serious adverse reactions in clinical practice limit its clinical application. One of the most significant clinical consequences is nephrotoxicity, showing significantly higher serum creatinine, tubular damage, glomerular mesangial proliferation and glomerular mesangial matrix increase [11]. In addition, the common adverse reactions of tacrolimus include hypertension, hyperlipemia, new-onset diabetes, as well as neurotoxicity [12]. The synergistic effect of these adverse reactions and nephrotoxicity affects the long-term effects of renal transplantation. As shown by studies, the occurrence of tacrolimus nephrotoxicity is closely related to the dosage of its application [13]. Reducing the dosage of tacrolimus to control the blood concentration within a certain range can effectively reduce the occurrence of nephrotoxicity [14]. At the same time, reducing the dosage of tacrolimus can also significantly reduce the incidence of adverse effects, such as hypertension, hyperlipemia, new-onset diabetes and neurotoxicity [15]. Therefore, in recent years in clinical practice, how to reduce the dosage of tacrolimus has become an important issue that influences the long-term survival rate after renal transplantation for ensuring the immunosuppressive intensity.

Compared with calcineurin inhibitors, mycophenolate mofetil serves to improve renal function after transplantation [15], without increasing the risks of hypertension, high cholesterol, diabetes and cardiovascular disease. In clinical practice, mycophenolate mofetil combined with calcineurin inhibitors and corticosteroids can effectively prevent the acute rejection in renal transplant patients and enhance the survival rates of patients and grafts. As confirmed by one year follow-up data of the mycophenolate mofetil study group for renal transplantation patients in U.S., the European mycophenolate mofetil cooperative group and mycophenolate mofetil study group of three continents for renal transplantation patients [17,18,19], sufficient amount of mycophenolate mofetil (2g/day or 3g/day) can reduce nearly 50% of graft loss caused by acute rejection. Therefore, as a safe and efficient immunosuppressant, mycophenolate mofetil has become the basis of immunosuppressive drugs, and its sufficient quantity provides favorable conditions for reducing the calcineurin inhibitor. TRANCEPT study [16] evaluated the effectiveness of conversion treatment by using sufficient quantity of MMF instead of other immunosuppressive agents. As shown by the results of interim analysis, for patients whose treatment had been converted to mycophenolate mofetil because of renal allograft dysfunction, 38 % of patients reduced the dosage of calcineurin inhibitors and some patients completely stopped using the calcineurin inhibitors. For these patients, the GFR was obviously enhanced, and the incidence of acute rejection and severe adverse reactions was very low, i.e. only 2.4% and 5.0%.

So far, this study is a randomized and controlled study of mycophenolate mofetil combined with low-dosage tacrolimus and corticosteroids with the largest domestic sample size. The initial design is to compare the efficacy and safe of mycophenolate mofetil combined with standard-dosage tacrolimus and corticosteroids and mycophenolate mofetil combined with low-dosage tacrolimus

and corticosteroids in renal transplant patients, but in the course of this study, the use of low-dosage tacrolimus has currently become a trend and has been extensively accepted by the researchers, so the tacrolimus dosage actually used by researchers is very low and the standard dosage has reached the level of low-dosage, also resulting in the fact that the final efficacy and safety in the standard-dosage and low-dosage groups are all very similar. The actual blood concentrations in the standard-dosage and low-dosage groups are within the scope of the low-dosage tacrolimus, so the efficacy and safety of the two groups actually reflect the efficacy and safety of mycophenolate mofetil combined with low-dosage tacrolimus and corticosteroids.

In this study, the mycophenolate mofetil dosage of most patients was 1.5 g/day or more than 1.5 g/day, and sufficient dosage of mycophenolate mofetil combined with low-dosage tacrolimus and corticosteroids showed strong immunosuppressive effects on renal transplant patients, the incidence of acute rejection was 3.9% and the survival rates of patient and graft was as high as 99.5%. The use of sufficient dosage of mycophenolate mofetil reduced the dosage of tacrolimus, thus effectively reducing the tacrolimus-induced renal toxicity and improving the renal function. The average glomerular filtration rate was gradually increased over time after renal transplantation, reaching 78.56 ml/min after 12 months and showed a growing trend, and the incidences of the adverse reactions, such as tacrolimus-induced hypertension, hyperlipidemia and new onset diabetes, were also significantly reduced. Only 2.4% and 3.3% of patients had diabetes and hyperlipidemia respectively, and there was no new-onset hypertension taking place. The incidences of some mycophenolate mofetil-related adverse reactions was also very low among Chinese patients, of which the incidence of diarrhea was 4.8%, the incidence of reduced white blood cell count was 8.6%. 0.5% of patients had opportunistic infections and there was no anemia, new-onset malignant tumors and cystic lymphoma in need of intervention in the first six months after transplantation. The safety and tolerability were good. Symphony study [3] also fully confirmed the advantages of using low-dosage tacrolimus regimen in the efficacy and safety on the basis of sufficient dosage of MMF and reduced usage of tacrolimus, where the average glomerular filtration rate within 12 months after renal transplantation was 65.4 ml/min, the incidence of acute rejection was 12.3%, the organ survival rate was 94.2%, and the patient survival rate was 97.2%.

5 Conclusions

Mycophenolate mofetil is a safe and efficient immunosuppressant. In the renal transplantation immunosuppressive therapy regimen combined with tacrolimus and corticosteroids, using sufficient dosage of mycophenolate mofetil can reduce the dosage of tacrolimus, thus successfully reducing the incidence of acute rejection that maintains a strong immune inhibition, significantly reducing the tacrolimus-induced nephrotoxicity and adverse reactions, such as hypertension, hyperlipidemia, and new-onset diabetes, to achieve the balance between efficacy and toxicity. The emergence of MMF has changed the original model of renal transplantation immunosuppressive therapy and reduced the dosage of calcineurin inhibitors represented by tacrolimus. With the wide use of reduction regimen of calcineurin inhibitor represented by tacrolimus, the advantages of mycophenolate mofetil marked by high efficacy and safety have more efficiently consolidated the basic position of mycophenolate mofetil in the renal transplant immune suppression combined regimen.

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Table 1 Comparison of the general information (measurement data) of the patients in the standard-dosage tacrolimus group and low-dosage tacrolimus group (x±s)

	Low-dosage tacrolimus group (n=106)	Standard-dosage tacrolimus group (n=104)
Age (years)	38.8±12.0	38.8±11.0
Dialysis time (mons)	15±6	14±6
Cold ischemia time (h)	7.7±2.2	7.6±2.4
CDC (%)	5.0±1.3	5.1±1.1
PRA-I (%)	3.6±1.4	3.6±1.2
PRA-II (%)	4.3±0.9	4.2±0.9
Fasting blood-glucose (mmol/L)	4.6±1.3	4.8±1.2
Glycosylated hemoglobin (%)	4.3±1.1	4.4±1.2
Serum albumin (g/L)	36.1±8.2	36.3±8.2
Serum total cholesterol (mmol/L)	5.6±1.3	5.7±1.4
Serum triacylglycerol (mmol/L)	1.43±0.15	1.53±0.38
HDL-c (mmol/L)	1.3±0.4	1.4±0.4
LDL-c (mmol/L)	4.0±1.0	4.1±1.0

Two groups of balanced than baseline measurement data

Table 2 Comparison of the general information (count data) of the patients in the standard-dosage tacrolimus group and low-dosage tacrolimus group (n/%)

		Low-dosage tacrolimus group (n=106)	Standard-dosage tacrolimus group (n=104)
Gender	Male	74/69.8	73/70.2
	Female	32/30.2	31/29.8
Hemodialysis		98/92.5	96/92.3
Peritonealdialysis		8/7.5	8/7.7
CYP3A5 genotype	*1/*1	4/3.8	3/2.9
	*1/*3	35/33.0	34/32.7
	*3/*3	67/63.2	67/64.4

Two groups of balanced than baseline measurement data

Figure 1. The ratios of the MMF daily dose were at baseline, i.e. 2 weeks, 4 weeks, 13 weeks, 26 weeks, 39 weeks and 52 weeks after transplantation being 1.5g/day and more than 1.5gday both the groups

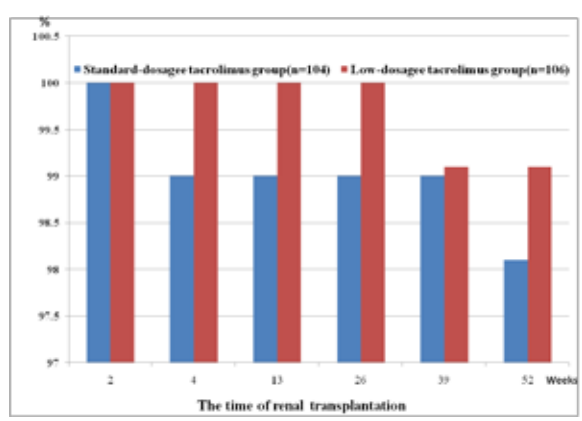
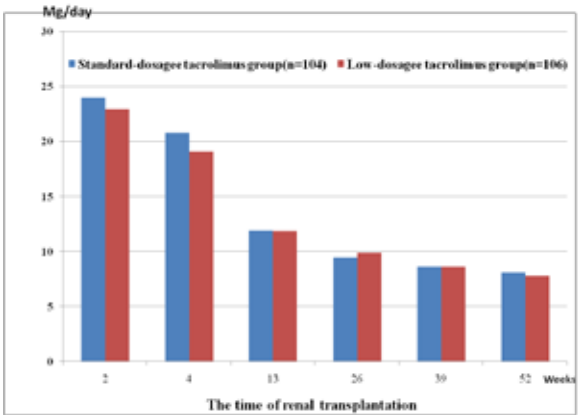


Figure 2. The average dosage of corticosteroids both the groups



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