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Elective withdrawal of mycophenolate mofetil in renal transplant recipients treated with mycophenolate mofetil, cyclosporine, and prednisone

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Abstract In a retrospective study we investigated the risk of acute rejection after the withdrawal of mycophenolate mofetil (MMF) in 39 adult patients treated with cyclosporine (CyA), prednisone, and MMF for at least 6 months following renal transplantation. After reaching a stable renal graft function, MMF was withdrawn and CyA and prednisone were continued. Preceding the withdrawal of MMF, four patients experienced an acute rejection. During a median follow-up of 38 months after discontinuing MMF, no acute rejection occurred. The mean serum creatinine level did not change during the first 6 months after withdrawal of MMF. We conclude that elective withdrawal of MMF in stable renal transplant recipients at 6 months after transplantation bears no important risk of an occurrence of acute rejection.

Keywords Mycophenolate mofetil · Kidney transplantation · Acute rejection

Abbreviations *AZA* Azathioprine · *CyA* Cyclosporin A · *MMF* Mycophenolate mofetil · *RTx* Renal transplantation

Introduction

The addition of mycophenolate mofetil (MMF) to the immunosuppressive treatment with cyclosporine (CyA) and prednisone results in an important reduction in the incidence of acute rejection during the first half-year after renal transplantation (RTx) [2, 5, 15, 16]. However, improvement in graft survival has not convincingly been demonstrated by continued treatment with MMF for 3 years after RTx [3, 11, 17]. The risks of over-immunosuppression with regard to an increased susceptibility to infections and malignancies are well known. Therefore, a reduction in the amount of immunosuppressive drug treatment seems desirable once stable engraftment of the kidney has been reached. Withdrawal of CyA or steroids from triple drug therapy consisting of CyA, azathioprine (AZA), and steroids has been associated with the occurrence of acute rejection episodes [8, 9], which might influence long-term outcome. Currently, no data exist concerning the risk of rejection after the discontinuation of MMF. The aim of our study was to investigate the risk of acute rejection after withdrawal of MMF in RTx patients who were initially treated with MMF in combination with CyA and prednisone.

Patients and methods

We performed a retrospective study including 39 adult patients who received a renal graft from a cadaveric or living donor at the University Hospitals of Nijmegen and Rotterdam (the Netherlands) between June 1994 and November 1998. All patients were treated with the combination of CyA, prednisone, and MMF for at least 6 months following transplantation, and all patients had a stable renal function. Twenty-one patients participated in a dose-finding study of MMF [5]. The MMF dose varied between 1000 and 4400 mg (median 2000 mg) in these patients. In 8 of these patients, treated in one participating center, MMF was stopped at 6 months after transplantation. In 13 of these 21 patients, treated in the other center, the decision to stop MMF treatment was arbitrarily made at a median time of 12 months after RTx (range 6–26 months). The remaining 18 of the 39 patients received a stan-

Table 1 Characteristics of patients for whom mycophenolate mofetil (*MMF*) was stopped after renal transplantation ($n = 39$). (*RTx* renal transplantation)

Sex (male/female)	15/24
Median age (years)	48 (18–67)
Mismatches on HLA-A and HLA-B ≤ 1/ ≥ 2	8/31
Mismatches on HLA-DR 0/1	17/22
Re-transplantation	5
Median time of withdrawal of MMF after RTx (months)	6 (6–26)
Patients with acute rejection before withdrawal of MMF	4
Median duration of follow up after stopping MMF (months)	38 (6–59)

dard dose of 2000 mg MMF. These patients also stopped receiving MMF at 6 months after transplantation, which was our standard protocol for patients who did not participate in a clinical trial requiring the continuation of this drug. Beside the MMF dose and duration, the immunosuppressive therapy and other basic characteristics were similar in patients treated with MMF for 6 months and in patients with whom MMF was discontinued at a later time, so we decided to analyze these patients as one group. For 23 patients we decided to stop treatment with MMF at once, and for the remaining 16 patients the MMF dose was tapered to zero over several weeks. CyA (target trough level 100–300 ng/ml) and prednisone (0.10–0.15 mg/kg) were continued. For 17 patients we decided to increase the prednisone dose slightly to 0.15 mg/kg per day, which was the standard dose in one of the participating centers. The CyA dose and target level were not changed. The analysis was restricted to patients with a duration of follow-up of more than 6 months after the stopping of MMF.

Acute rejection was defined as a rise in serum creatinine levels in combination with the histologic evidence of acute rejection, which necessitated the use of antirejection treatment. Serum creatinine levels, hemoglobin levels, leukocyte counts, and thrombocyte counts were assessed at baseline (2 months before and on the day of stopping or reducing MMF), and at 2 and 6 months after the withdrawal of MMF.

Results are presented as median and range or as mean and standard deviation. Comparison of the numerical data between baseline and follow-up was performed using the Wilcoxon's signed rank test. For correlation analysis, a Spearman rank test was used. A P value of less than 0.05 was considered statistically significant.

Results

The baseline characteristics of the 39 patients are shown in Table 1. Four patients had experienced an acute rejection during the first 6 months after RTx while receiving triple therapy. Three of these patients were treated with 1 g methylprednisolone i.v. on 3 consecutive days, and one patient with anti-T-cell therapy. MMF was withdrawn more than 5 months after antirejection treatment for these patients. For two of these patients, the prednisone dose was subsequently increased from 0.12 mg/kg per day to 0.15 mg/kg per day.

The median duration of follow-up after withdrawal of MMF was 38 months. During this period none of the patients experienced an acute rejection. There was no change in serum creatinine level or in proteinuria during the first half-year after withdrawal of MMF (Table 2). Leukocyte counts increased significantly after discontinuing MMF. The same was true for hemoglobin levels, although a stable situation had not been reached at the time of MMF withdrawal. During the first 2 months after stopping MMF, the median increase in body weight was 1.0 kg (range –3.9 to + 8.0 kg; $P < 0.01$). There was no correlation between the MMF dose and the increase in body weight, or between the increase in body weight and the increase in prednisone dose, after the discontinuation of MMF. The weight-adjusted MMF dose correlated weakly with the increase in leukocyte counts after the withdrawal of MMF ($r = 0.3$, $P < 0.05$).

Discussion

From this retrospective study we conclude that elective withdrawal of MMF bears no important risk of an occurrence of acute rejection in stable renal transplant patients. None of the patients in our study group experienced an acute rejection after stopping MMF. It is important to recognize that these patients had a stable renal graft function at 6 months or more after transplantation and, as such, form a selected population. Only 10% of the patients had an acute rejection before the withdrawal of MMF, while the incidence of acute rejection

Table 2 Clinical and laboratory parameters at baseline (–2 months and T0) and 2 and 6 months after stopping mycophenolate mofetil, respectively

	–2 months	T0	+ 2 months	+ 6 months
CyA trough level (ng/ml)	167 (96–360)	171 (95–360)	162 (59–290)	170 (86–330)
Prednisone dose (mg/kg)	0.12 (0.09–0.2)	0.12 (0.09–0.2)	0.14 (0.09–0.2)	0.13 (0.08–0.2)
Creatinine (μmol/l)	119 ± 32	118 ± 32	116 ± 30	120 ± 34
Proteinuria > 0.5 g/l (n)	4	3	1	1
Hemoglobin (mmol/l)	7.8 ± 1.1*	8.1 ± 1.1	8.5 ± 1.0*	8.5 ± 1.1*
Leukocytes (× 10^9/l)	7.7 ± 2.1	7.7 ± 2.3	8.8 ± 1.5*	9.2 ± 1.8*
Thrombocytes (× 10^9/l)	240 ± 63	232 ± 62	229 ± 61	244 ± 61

*$P < 0.01$ vs T0

in our hospital was approximately 25% for all patients treated with MMF, CyA, and prednisone. In comparable cohorts of patients treated with the combination of MMF, CyA, and prednisone, the incidence of acute rejection varied between 17% and 20% [2, 5, 15, 16]. Thus, the low rejection incidence in our study population might be explained by selection due to exclusion of patients with unstable renal graft function. On the other hand, a previous rejection episode in a patient with a stable renal function was no reason to continue MMF in our hospitals.

The best procedure for the withdrawal of MMF is not clear from our data. The MMF dose was tapered to zero with a concomitant increase in prednisone dose to 0.15 mg/kg body weight in approximately 40% of the study group. The relevance of these measures is probably minor because rejections did not occur in the rest of our study group either. Our data do not allow firm conclusions concerning the risk of late chronic rejection after the withdrawal of MMF. However, during at least half a year after the withdrawal of MMF, renal function remained stable and there was no increase in proteinuria.

Body weight increased slightly after the withdrawal of MMF, while it had been stable during 2 months before. The use of MMF is associated with gastrointestinal complaints, and the weight gain might reflect increased appetite after the discontinuation of MMF. Hemoglobin level and leukocyte counts increased slightly after stopping MMF. This seems to reflect some bone marrow suppression induced by MMF. Notably, the hemoglobin level already increased during the baseline period, so other factors aside from the withdrawal of MMF may play a role. Adverse effects of MMF may be related to higher trough levels of mycophenolic acid, the active metabolite of MMF [1, 14], although other data indicated a dose relationship between MMF dose and the occurrence of side effects [5]. The limited variation in MMF dose (69% of our patients received a standard dose of 2 g per day) reduced the possibility to detect a relationship between MMF dose and the severity of side effects. Nevertheless, a weak correlation was found between the MMF dose and the increase in leukocyte count after stopping MMF.

MMF is a very valuable drug for reducing the incidence of acute rejection in the first period after RTx. After this period, the risk of acute rejection is considerably lower, possibly due to a certain degree of immunologic adaptation to the renal graft [10]. The additional benefit of MMF in preventing acute and chronic rejections once the host immune response to the graft has adequately been suppressed has not been demonstrated. On the other hand, the risks of over-immunosuppression are well known. Over-immunosuppression has been related with an increased risk of (opportunistic) infections and the development of malignancies [13]. MMF in particular seems to increase the incidence of symptomatic cytomegalovirus infections [12], and has been related with human herpes 8 virus infections and, consequently, Kaposi's sarcoma [7]. The risk of development of other malignancies during long-term treatment with MMF is not known at this moment. A reduction in the amount of maintenance immunosuppression is desirable as long as it does not negatively influence the long-term outcome. At the time of this study, no data concerning the risks of withdrawal of CyA or prednisone from triple therapy consisting of CyA, prednisone, and MMF were available. However, withdrawal of CyA or prednisone from triple drug therapy consisting of CyA, prednisone, and AZA has been associated with an increased incidence of acute rejection episodes [8, 9] which might negatively influence long-term renal graft survival. Withdrawal of AZA from this triple drug regimen at more than 6 months after RTx is associated with a low incidence of acute rejection (0–5%) [4, 6]. We therefore chose to withdraw MMF and to continue CyA and prednisone in our stable patients, which appeared to be a safe procedure with no acute rejection episodes at all.

In conclusion, these data suggest that treatment with MMF can safely be stopped for renal transplant patients with a stable graft function at 6 months or more after RTx.

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