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ORIGINAL ARTICLE

Discontinuation of mycophenolate mofetil from a tacrolimus-based triple regimen 2 months after renal transplantation: a comparative randomized multicentre study

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Summary

Previous clinical data suggested that with a tacrolimus-based regimen adjunctive immunosuppressives may be withdrawn after an initial treatment period. This study investigated the early discontinuation of mycophenolate mofetil (MMF) from a standard triple regimen. Patients were randomized either to receive a continued tacrolimus/MMF/steroids triple regimen (control group) or to reduce and then stop the MMF dose (MMF stop group). Both groups received identical daily tacrolimus and corticosteroid doses. The initial MMF dose was 1 g/day in both arms, but in the MMF stop group the dose was reduced to 0.5 g/day from week 7 to week 12 and then stopped. The intent-to-treat population consisted of 74 (control) and 78 (MMF stop) patients. MMF was tapered off as planned in 82.9% of the patients in the MMF stop arm. The 6-month incidence of biopsy-proven acute rejection was similar in both arms (21.6% control, 16.7% MMF stop). Graft loss occurred in 5.4% (control) and 3.8% (MMF stop) of the patients. MMF could be safely discontinued from a tacrolimus-based triple therapy early after transplantation without any rebound in efficacy during the 6-month follow-up period.

(Name of registry: ClinicalStudyResults.org, number: FG-02-CEE-01, date: 9 June 2006)

Introduction

The triple regimen of tacrolimus in combination with mycophenolate mofetil (MMF) and corticosteroids is one of the most widely used standard treatments following renal transplantation. The effective and safe combinations of tacrolimus and MMF have been evaluated in a European dose-ranging study comparing daily MMF doses of 1 and 2 g [1]. While the efficacy of both MMF doses was similar, MMF-related side effects increased with the 2-g dose. It was concluded that in a European setting the preferable combination with the best risk–benefit ratio was a combination of tacrolimus plus 1 g/day MMF.

The risk of an acute rejection is greatest in the first week after transplantation [2]. Therefore, during the early post-transplant period, appropriate full immunosuppressive coverage is crucial. However, any high immunosuppressive load invariably has untoward side effects. Therefore, currently, many clinical studies in transplantation focus on strategies to tailor and safely reduce the immunosuppressive therapy, aiming to minimize side effects and optimize the prospects for the patients' long-term survival.

A recent large, European trial (THOMAS study [3]) has shown that with a tacrolimus-based triple regimen, either adjunctive immunosuppressive medication, corticosteroids or MMF can be stopped after 3 months, without an increase of the overall acute rejection. The present study was designed to evaluate expected benefits and potential risks of an MMF dose reduction and subsequent discontinuation following 2 months of standard tacrolimus-based triple regimen.

Materials and methods

Study design

This prospective, open-label, randomized study was conducted in 14 centres in four European countries: Poland, Czech Republic, Hungary and Slovakia. Study period was from February 2003 to August 2004.

The study was conducted in accordance with the ethical principles formulated in the Declaration of Helsinki. The study protocol was reviewed and approved by the relevant ethics committees for each centre. All patients gave written informed consent before enrolment into the study.

Criteria for inclusion

Patients were eligible for enrolment into the study if they were at least 18 years of age, received a kidney transplant from an ABO compatible cadaveric or living donor and provided written informed consent.

Patients were excluded from participation if they had a high immunological risk (panel reactive antibody (PRA) grade of ≥50%), significant liver disease, a significant uncontrolled concomitant infection or severe diarrhoea, vomiting or peptic ulcer, required ongoing dosing with a systemic immunosuppressive for any reason other than kidney transplantation, had a history of malignancies (except of successfully treated metastatic basal or squamous cell carcinoma) or were allergic or intolerant to any component of the study medication. Patients receiving an organ from a nonheart-beating donor or with a cold ischaemia time of >40 h were also excluded.

Patients were free to withdraw at any time. The investigator could also terminate a patient's involvement if the patient's clinical condition warranted removal. Graft loss or failure, or retransplantation also led to withdrawal. Additional protocol defined reasons for withdrawal were suspension of tacrolimus for >7 days, suspension of MMF for >21 days, and administration of prohibited medication.

Randomization details

Each centre was provided with a unique sequence of patient numbers to be allocated to enrolled patients. When a patient was enrolled, he or she received the lowest patient number available on the centre's list. The corresponding sealed randomization envelope, generated and provided by the Data Operations Department of the local Contract Research Organisation, was opened, specifying the allocated treatment arm. Further patients were allocated the next consecutive number. The randomization was 1:1, stratified by centre. As this was an open-label study, no blinding was performed.

Immunosuppressive medication

Patients were randomized into one of the two following treatment arms: continued tacrolimus/MMF/steroids regimen (control group) or initial tacrolimus/MMF/steroids triple regimen with MMF reduction from week 7 to week 12 and subsequent MMF discontinuation (MMF stop group).

Administration of antibodies for induction treatment was not permitted by the study protocol. Dosing of tacrolimus and corticosteroids was identical in both arms. The initial daily oral tacrolimus dose was 0.2 mg/kg given in two doses (0.1 mg/kg twice daily), one preoperatively and one postoperatively. The first postoperative dose of 0.1 mg/kg was administered according to normal hospital routine. Subsequent oral tacrolimus doses were adjusted on the basis of clinical evidence of efficacy and occurrence of adverse events. The recommended whole blood

trough level ranges were 10–20 ng/ml for days 0–14 and 5–15 ng/ml for days 15–183. A perioperative bolus of 500-mg methylprednisolone (or equivalent) was administered intravenously followed by 125 mg on day 1. Subsequently, oral prednisolone (or equivalent) was given with daily doses of 20 mg on days 2–14, 15 mg on days 15–28, 10 mg on days 29–56 and 5 mg thereafter.

The daily MMF dose in the control arm was 1 g (500 mg twice daily) throughout the study period. In the MMF stop arm, the daily dose was 1 g until day 43, followed by a reduced dose of 0.5 g MMF per day (250 mg twice daily) until day 84. MMF was discontinued from day 85, depending on the following criteria: there was no rejection episode or a maximum of one steroid-sensitive rejection in the first 2 months post-transplantation, and the patient was free of rejection during month 3, and there were no other circumstances that would contraindicate an MMF stop.

Diagnosis, grading and treatment of acute rejection

All rejections had to be verified by biopsy and graded using the BANFF '97 classification [4]. First-line treatment for an acute rejection was corticosteroids according to local practice. Antibodies could be given as first-line treatment, according to local practice, when a biopsy indicated a severe vascular rejection (BANFF IIb or III). If the tacrolimus through level was below 10 ng/ml, an increase in tacrolimus dose was also to be considered as a response.

In case the rejection episode did not respond to corticosteroids, additional agents such as OKT3 or polyclonal antibodies could also be used. The addition of another adjunctive immunosuppressant resulted in patient withdrawal. Thus, patients with acute rejection refractory to antibody treatment or for whom the study maintenance immunosuppressive therapy was considered to be insufficient were to be withdrawn.

Criteria for evaluation

The primary endpoint of the study was the incidence of and time to first biopsy-proven acute rejection (BPAR) over the first 6 months post-transplantation. Secondary endpoints were: severity of BPARs within 6 months post-transplantation; incidence of and time to first corticosteroid-resistant acute rejection; renal function as assessed by measured serum creatinine concentration and by calculated creatinine clearance (Cockcroft–Gault formula). Patient and graft survivals were also to be followed up for patients who were prematurely withdrawn from the study. Graft loss was defined as need to return to long-term dialysis, retransplantation, graftectomy or death. Safety was assessed by spontaneous adverse events reporting, and monitoring of vital signs and routine laboratory parameters.

Statistical analysis

In general, descriptive statistics were calculated as *n*, mean, SD, median, minimum and maximum for continuous variables. For categorical variables, frequencies and, where appropriate, percentages were determined.

The intent-to-treat (ITT) analysis set included all randomized patients who received at least one dose of study drug.

The incidence of and time to the first BPAR within 6 months post-transplantation and first corticosteroid resistant acute rejection, were estimated using Kaplan–Meier survival procedures and analysed using the Wilcoxon (Gehan–Breslow) test and the log-rank test. The overall frequency of acute rejection episodes within 6 months post-transplantation was assessed using the chi-squared test.

Patient and graft survivals were assessed using Kaplan–Meier survival procedures. Treatment failure, defined as graft loss or premature discontinuation due to an adverse event, was also analysed using Kaplan–Meier methods. The difference between arms was assessed using the Wilcoxon (Gehan–Breslow) test and the log-rank test.

Differences between the groups in kidney function were assessed for completers at month 6 using the Mann–Whitney nonparametric or exact test, as applicable. Differences between day 7 and month 6 were assessed within a treatment group using the Wilcoxon signed-rank test for related samples.

Details of medical history, secondary diagnoses and adverse events reported during the study were coded using a Medical Dictionary for Regulatory Activities (MedDRA), version 6.0, prior to the statistical analyses. Incidences of adverse events were also summarized by body system and MedDRA-preferred term. Prior and concomitant medications were coded using the World Health Organisation-Drug Reference List.

A formal statistical sample size calculation was not performed. Sample size was based on considerations of resources such as number of participating centres and the time needed for patient enrolment. Statistical analysis was generally of descriptive nature; all tests should be interpreted accordingly and not in a confirmatory sense.

Results

Patients

A total of 155 patients were randomized into a treatment arm. Three patients did not receive a transplant. The ITT population comprised 152 patients, 74 patients in the

control group and 78 in the MMF stop group. Figure 1 summarizes the patient flow in the study. Demographics and baseline characteristics were balanced between both treatment arms (see Table 1), with the exception of the mean age being higher in the MMF stop group than in the control group ($P = 0.007$, Mann–Whitney test).

Most patients had end-stage renal failure as a consequence of chronic glomerulonephritis or uropathy. The mean cold ischaemia time of the kidney grafts was 14.8 h (range 0–33 h) in the control group and 16.0 (range–37) h in the MMF stop group. Mean total human leukocyte antigen (HLA) mismatch was 3.0 in the control group and 2.8 in the MMF stop group. Most patients received their first transplant; five (6.8%) and seven (9.0%) patients in the control group and the MMF stop group, respectively, had received one previous transplant.

The study was completed by 63 (85.1%) patients in the control group and 70 (89.7%) patients in the MMF stop group. Main reasons for premature withdrawals were suspension of either tacrolimus for >7 days or MMF for >21 days. There were no withdrawals of informed consent and no withdrawals due to noncompliance. Two (2.7%) patients in the control arm and four (5.1%) patients in the MMF stop arm prematurely discontinued the study due to the following adverse events: procedural complications (control 1, MMF stop 2), graft thrombosis (MMF

Table 1. Patient demographics and baseline characteristics.

	Control (N = 74)	MMF stop (N = 78)
Male, *n* (%)	47 (63.5)	40 (51.3)
Female, *n* (%)	27 (36.5)	38 (48.7)
Age (years), mean (range)	41.3 (20–67)	46.7 (22–72)*
Weight (kg), mean (range)	71.2 (41–108)	70.4 (47–116)
Viral status, *n* (%)†		
CMV positive	51 (71.8)	53 (74.6)
EBV positive	26 (65.0)	21 (52.5)
HBV positive	0	0
HCV positive	1 (1.4)	3 (4.0)
CMV mismatch, *n* (%) (recipient negative, donor positive)	10 (13.5)	11 (14.1)
Primary diagnosis, *n* (%)		
Glomerulonephritis	42 (56.8)	34 (46.2)
Uropathy (including chronic pyelonephritis)	11 (14.9)	14 (17.9)
Other	21 (28.4)	30 (38.5)

Intent-to-treat population; number of patients (%).
CMV, cytomegalovirus; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; MMF, mycophenolate mofetil.
Primary diagnosis 'other' includes: nephrosclerosis, polycystic disease, other hereditary nephropathy, diabetic nephropathy, unknown and other.
*$P = 0.007$, Mann–Whitney test.
†Number of evaluated patients (=denominator for percentage calculation) varies for each viral status assessment.

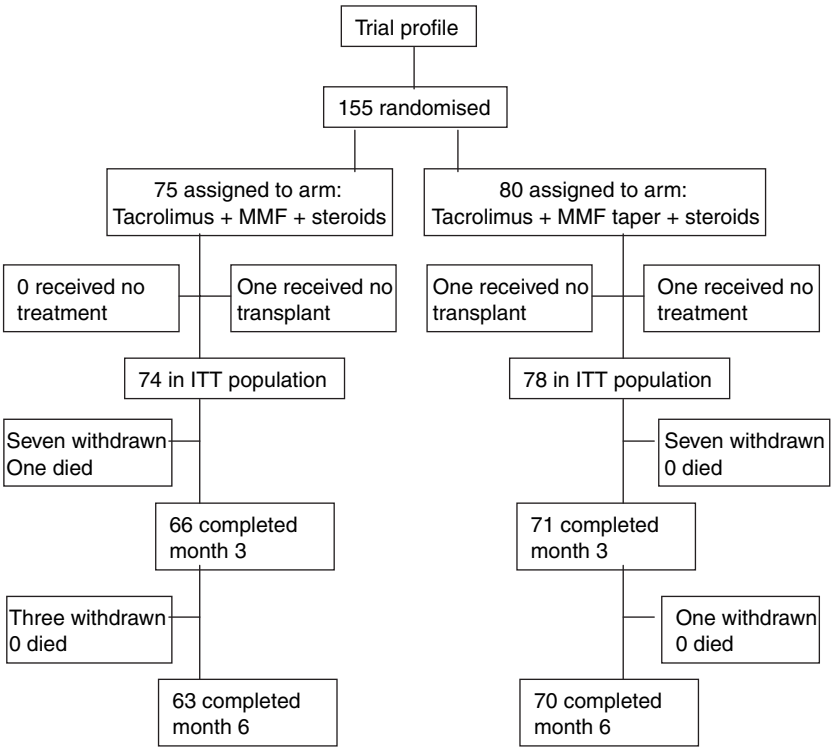

Figure 1 Disposition of patients.

stop 1), intra-abdominal haemorrhage (control 1) and renal artery thrombosis (MMF stop 1).

Immunosuppressive therapy

The daily doses of tacrolimus and corticosteroids abided by the protocol and were virtually identical in both treatment arms. Mean tacrolimus whole-blood trough levels were 13.9 ± 5.7 ng/ml in the control group and 13.4 ± 5.4 ng/ml in the MMF stop group at day 7, and decreased to 8.3 ± 3.1 ng/ml (control group) and 8.2 ± 2.7 ng/ml (MMF stop group) by day 183. The cumulative daily dose of corticosteroids in patients who completed the study until month 6 was 33.0 ± 7.6 g (control) and 33.4 ± 7.0 g (MMF stop).

Mycophenolate mofetil dosing was also similar in both treatment arms during the initial study period. In the majority of patients in the MMF stop arm, MMF was tapered and discontinued according to protocol; 12 (15.4%) patients in this group continued MMF therapy. The stated reasons were that in seven patients the protocol-defined MMF withdrawal criteria were not met (due to acute rejection episodes or adverse events), whereas in four patients MMF therapy was continued in error; in one patient, MMF was not tapered according to the protocol-defined time schedule but stopped later in the study. The mean cumulative daily MMF dose for completers from day 0 to end of study was 179.9 g (±34.2 g) in the control group and 35.7 g (±74.7 g) in the MMF stop group, $P < 0.0001$.

Almost all patients in the control group continued to receive MMF throughout the study. MMF was discontinued for more than 21 days in five (6.7%) patients: in four patients due to adverse events and in one patient due to an organizational mistake.

The majority of patients in both groups were receiving their randomized immunosuppressive regimen at study end: for the study completers in the control group, 61/63 (96.8%) patients received a triple regimen and 2/63 (3.2%) received a tacrolimus/corticosteroids dual regimen; in the MMF stop group, 58/70 (82.9%) patients received a tacrolimus/corticosteroids dual regimen and 12/70 (17.1%) patients received a tacrolimus/MMF/corticosteroids triple regimen.

Efficacy

The estimated rate (Kaplan–Meier method) of patients free from BPAR within 6 months post-transplantation was similar in both treatment arms (control: 76.8% and MMF stop: 82.5%; $P = 0.865$, Gehan–Breslow test; $P = 0.871$, log-rank test). The incidence of BPAR was 21.6% (16/74 patients) in the control group and 16.7% (13/78 patients) in the MMF stop group. Most rejections responded to corticosteroid therapy. The biopsy gradings of acute rejections gave similar results in both treatment arms; there was no severe acute rejection in either group (see Table 2).

Most acute rejections occurred in the first month after transplantation. There were eight (10.3%) patients in the control arm and three (3.8%) patients in the MMF stop arm with acute rejection in the time period from month 2 to 6, when MMF was tapered and discontinued in the MMF stop arm.

Dialysis at any time during the study was reported in 24 (32.4%) patients in the control group and 29 (37.2%) patients in the MMF stop group; the mean (±SD) number of days on dialysis was 9.7 (±7.5) and 9.1 (±9.1), respectively. Dialysis was mainly needed during the first week after surgery. Long-term dialysis, defined as longer than 2 weeks, was reported in eight (10.8%) patients in the control group and seven (9.0%) patients in the MMF stop group.

Overall, grafts were lost in four (5.4%) patients in the control group and three (3.8%) patients in the MMF stop group. Three patients in both groups received a never functioning graft. The estimated 6-month graft survival rate (Kaplan–Meier method) was 94.1% in the control group and 96.0% in the MMF stop group ($P = 0.479$, Gehan–Breslow test; $P = 0.501$, log-rank test).

Renal function was comparably good in both treatment arms. Median serum creatinine improved after transplantation and was below 2 mg/dl in both groups after 2 weeks, and continued to improve in both arms. Median creatinine in study completers was 1.49 mg/dl in the control group and 1.41 mg/dl in the MMF stop group at study end (see Fig. 2).

Mean creatinine clearance, as calculated for the day 7 visit and the month 6 visit, improved from 35.4 (±22.6)

Table 2. Efficacy results, incidence of acute rejection and severity grading.

	Control group (N = 74), *n* (%)	MMF stop group (N = 78), *n* (%)
Incidence of BPAR		
Total	16 (21.6)	13 (16.7)
Steroid-resistant BPAR	3 (4.1)	6 (7.7)
Severity grading of acute rejections (BANFF' 97)*		
Mild	10 (13.5)	8 (10.3)
Moderate	9 (12.2)	5 (6.4)
Severe	0	0

n = ITT patients (who received at least one dose of study drug).
BPAR, biopsy proven acute rejection; MMF, mycophenolate mofetil; ITT, intent-to-treat.
*Worst histological grade of biopsy recorded for each patient.

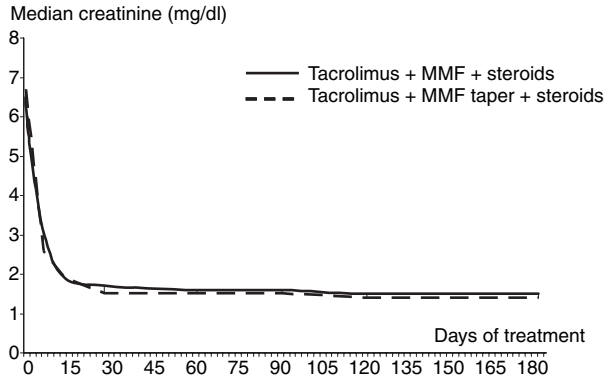

Figure 2 Serum creatinine over time.

to 90.4 ml/min (±36.1 ml/min) in the control group, and from 35.3 (±22.7) to 78.2 ml/min (±27.9 ml/min) in the MMF stop group.

Safety

One patient in the control group died of myocardial infarction on day 26 of the study. This 51-year-old man had been recorded with coronary heart disease at study entry. The estimated 6-month patient survival rate (Kaplan–Meier method) was 98.5% in the control group and 100% in the MMF stop group.

Overall, a total of 447 adverse events were reported in 71 (95.9%) patients in the control group, compared with 385 adverse events in 71 (91.0%) patients in the MMF stop group. The most frequent adverse events were urinary tract infection and procedural complications (see Table 3). Anaemia, cytomegalovirus (CMV) infection, leucopenia and diabetes mellitus occurred with higher incidences in the control group than in the MMF stop group, although the differences between the treatment groups were not statistically significant. The differences between the groups were most evident when adverse events were analysed for the time period from month 2 to 6, when MMF was tapered and discontinued in the MMF stop arm.

A medical history of diabetes mellitus at study entry was reported for six (8.1%) patients in the control group and nine (11.5%) patients in the MMF stop group. New-onset long-term (>30 days) insulin therapy in patients without pre-existing glucose metabolism disorder was reported for 10/58 (17.2%) patients in the control group and 7/69 (10.1%) patients in the MMF stop group. New-onset insulin therapy was ongoing at study completion or premature withdrawal in 7/58 (12.1%) and 8/69 (11.6%), respectively.

No malignancy occurred during the study period. The treatment arms were comparable with regard to the incidence of neurological and gastrointestinal disorders, and the administration of concurrent antihyperlipidaemic and antihypertensive medication. There were also no relevant differences between the treatment arms in mean clinical laboratory parameters or vital signs.

Table 3. Most frequent* adverse events, regardless of relationship to study medication.

	Control group (N = 74)	MMF stop group (N = 78)
MedDRA-preferred term	Patients, *n* (%)	Patients, *n* (%)
Urinary tract infection	26 (35.2)	24 (30.8)
Procedural complications of transplanted kidney	20 (27.1)	22 (28.3)
Anaemia	20 (27.1)	15 (19.3)
CMV infection	17 (23.0)	10 (12.9)
Blood alkaline phosphatase increased	13 (17.6)	11 (14.2)
Diabetes mellitus	15 (20.3)	8 (10.3)
Hypercholesterolaemia	12 (16.3)	11 (14.2)
Hyperkalaemia	11 (14.9)	10 (12.9)
Leucopenia	11 (14.9)	8 (10.3)
Serum creatinine increased	7 (9.5)	11 (14.2)
Diarrhoea	7 (9.5)	8 (10.3)
Hyperglycaemia	8 (10.9)	6 (7.7)
Haematoma	9 (12.2)	4 (5.2)
Incidence of selected adverse events during months 2–6		
Urinary tract infection	16 (21.7)	12 (15.4)
Anaemia	6 (8.2)	1 (1.3)
CMV infection	16 (21.7)	9 (11.6)
Diabetes mellitus	11 (14.9)	2 (2.6)
Leucopenia	10 (13.6)	5 (6.5)
Diarrhoea	3 (4.1)	3 (3.9)

CMV, cytomegalovirus; MMF, mycophenolate mofetil; MedDRA, Medical Dictionary for Regulatory Activities.
*Incidence rate of at least 10% of patients in either treatment arm (*P*-values for all comparisons between the groups = not significant).

Discussion

The focus of clinical research in transplantation changes increasingly from short- to long-term outcome. As mortality and morbidity of renal graft recipients are greatly affected by the side effects of their immunosuppressive medication, the effort is to optimize and minimize the maintenance regimens.

In this respect, mainly steroid-sparing strategies have been investigated in recent clinical transplantation studies. It could be demonstrated that maintenance corticosteroids can be safely withdrawn after 3 months (COSTAMP study [5]) or even avoided (ATLAS and CARMEN studies [6,7]) with tacrolimus-based regimens, leading immediately to an improved cardiovascular risk profile, which in turn is hoped to have a beneficial effect on patients' long-term survival.

The present observations suggest that early MMF withdrawal could be another therapeutic option to decrease the overall exposure to immunosuppressive medication. With only two patients in the MMF stop arm experiencing a BPAR after month 2, there was no sign of a rebound in graft rejection when MMF was tapered and discontinued. Moreover, mean kidney function remained comparably good in both arms throughout the 6-month study period, implying there was also no increase in subclinical rejection upon MMF taper. The low incidence of acute rejection and the sustained low creatinine levels after month 2 indicate that there was still sufficient immunosuppressive coverage to protect the graft after the discontinuation of MMF.

The study protocol was generally well adhered to, with only six patients deviating from their randomized immunosuppressive regimen. The study protocol allowed MMF withdrawal only in patients who had no ongoing acute rejection and a history of not more than one steroid-sensitive acute rejection during the first 2 months. More than 80% of the patients fulfilled these criteria, showing that the triple regimen of tacrolimus, MMF and corticosteroids is very effective in preventing rejection in the early post-transplant period. Thereafter, the dual regimen of tacrolimus (mean trough levels at month 6 were approximately 8 ng/ml) and low-dose corticosteroids provides adequate prevention of acute graft rejection for the time following the initial high-risk period. This applies at least for the typical European setting of this study, with all study patients being of Caucasian race and receiving well-matched grafts.

Our findings support previous reports that adjunctive MMF medication can be safely reduced and stopped after an initial period of tacrolimus-based triple therapy. A large immunosuppression minimization study (THOMAS study [3]) with a tacrolimus-based triple regimen showed that either adjunctive medication, MMF or steroids can be discontinued 3 months after surgery without any significant increase in acute rejection. Both experimental arms showed the expected benefits; stop of corticosteroids significantly improved the serum cholesterol, while MMF stop significantly reduced the incidences of leucopenia and serious CMV infection at 6 months. The incidences of anaemia and diarrhoea were lower in the MMF stop group than in the steroid stop group, although without statistical significance.

Also in the present study, withdrawal of MMF led to a reduction of the adverse events that are typically associated with the use of MMF [8–10], namely haematological side effects, urinary tract infection and CMV infection, although there were no statistically significant differences between the treatment groups. In contrast to the results of the THOMAS study, the incidence of diarrhoea was similarly low in both groups.

The reported incidences of post-transplant diabetes mellitus (PTDM) in other recent studies with a tacrolimus/MMF/corticosteroids triple regimen were approximately 5% when new-onset long-term insulin use was the criterion for PTDM [3,6,7] and 11% relying on spontaneous reports of glucose metabolism disorders [5]. We found no satisfactory explanation for the higher frequency of spontaneous diabetes mellitus reports in the present study, or for the higher incidence in the control group compared with the MMF stop group. There are reports indicating a possible relation between CMV infection and new-onset PTDM in renal transplantation; the data and potential pathogenic mechanisms were discussed in a recent editorial [11]. Thus, in the present study, the higher incidence of CMV infection, which is a well-known side effect of MMF therapy, might have contributed to the higher incidence of PTDM in the control group. However, in accordance with the established MMF side-effect profile that has not been reported to be in association with glucose metabolism disorders [8–10], the proportion of patients with ongoing new-onset insulin use was similar (approximately 12%) in both groups at study end or premature withdrawal.

The efficacy of MMF in the prevention of acute rejection after transplantation is well established. Through a variety of mechanisms, such as inhibition of smooth muscle and fibroblast proliferation and inhibition of nitric oxide synthase, MMF may also contribute to improved graft survival [12]. However, although analyses of registry data have shown that MMF may also protect against long-term deterioration of renal function and chronic allograft nephropathy, to date there is no clinical data clearly demonstrating a long-term benefit in renal transplantation [13]. Therefore, although MMF is generally well tolerated, due to its propensity to cause gastrointestinal and haematological disorders, to increase infectious complications and also because of the high costs of MMF therapy, the necessity of its long-term use has been under investigation in some other recent studies. There were also clinical trials using a cyclosporin-based immunosuppression which showed that elective MMF withdrawal was possible in stable patients after 6 months [14] or 1 year [15].

The promising results of the present 6-month study do not allow making conclusions on the long-term effects of early MMF stop. However, the recently published follow-up data of the above-mentioned THOMAS study [16] did not reveal any late drawbacks of the controlled early minimization of adjunctive immunosuppression, with unimpaired high patient and graft survival rates and stable renal function after 3 years.

In conclusion, early MMF dose reduction and subsequent discontinuation were safe in this population of

low-risk renal transplant recipients after an initial period of triple therapy. There was no rebound in acute rejection during the 6-month follow-up period and mean kidney function remained good. The immediate advantage of the reduced immunosuppressive load was a decrease in MMF-related adverse effects, which translates in a better quality of life for the patient and thus may also contribute to achieve a better long-term compliance. Finally, although quantification was not in the scope of this study, early MMF withdrawal in stable patients will obviously lead to reduced costs of immunosuppressive therapy, which eventually will benefit the stretched health budgets in many countries. Thus, minimization strategies in post-transplant immunosuppression are becoming increasingly relevant and may become frequent practice in managing transplant recipients, but all possible cost benefits will eventually have to be carefully weighed against any potential negative effects on patient and graft survivals.

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Conflict of interest

The study was sponsored by Astellas Pharma GmbH (former Fujisawa GmbH).

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