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Mycophenolate mofetil in IgA nephropathy: Results of a 3-year prospective placebo-controlled randomized study

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Background. Because humoral immunity is believed to play a pivotal role in the pathogenesis of IgA nephropathy (IgAN), a prospective placebo-controlled randomized study was started in patients with IgAN using mycophenolate mofetil (MMF).

Methods. A total of 34 patients with IgAN were treated with salt intake restriction, angiotensin-converting enzyme (ACE) inhibition and MMF 2 g per day ($N = 21$) or placebo ($N = 13$). After 36 months of follow-up clinical, biochemical, and radiologic data were analyzed using linear mixed models for longitudinal data and Kaplan-Meier survival analysis.

Results. Therapy had to be stopped prematurely in five patients. Two patients (MMF group) evolved to end-stage renal disease (ESRD). There was no difference between groups in the percentage of patients with a decrease of 25% or more in the inulin clearance or with a serum creatinine increase of 50% or more over 3 years. There was also no significant difference between groups in annualized rate of change of serum creatinine, computed by linear regression analysis. No significant difference was noted between groups for inulin clearance, serum creatinine, proteinuria, blood pressure, or other parameters of renal function. Hemoglobin and C-reactive protein were significantly lower in the MMF group compared with the placebo group. As a function of time, a significant decline in both groups was noted of proteinuria, parenchymal thickness of the kidneys and C3d.

Conclusion. In patients with IgAN at risk for progressive disease, no beneficial effect of 3-year treatment with MMF 2 g per day could be demonstrated on renal function/outcome or proteinuria. However, larger randomized studies are needed to confirm or reject these results.

IgA nephropathy (IgAN) is the most common glomerulopathy in the world. The pathogenesis of the disease is not fully understood [1]. While humoral immunity is believed to play a pivotal role, characterized by the predominant mesangial IgA_1 deposition, also secondary inflammatory processes may be important in the progression of renal injury [2, 3]. Immune-mediated glomerulopathies like IgAN can be considered as resulting from inappropriate activation of the immune response, followed by an inflammatory reaction, and leading to progressive destruction of nephrons with ultimately renal fibrosis. Renal failure develops in up to 30% of patients after 20 to 30 years [4–6]. Risk factors for unfavorable prognosis have been defined, but to date no curative treatment for IgAN is available [7–9]. Because strategies aimed at stopping immune-mediated processes have failed to cure IgAN until now, therapies have been based largely at reducing hemodynamic stress by lowering blood pressure and proteinuria via the angiotensin II suppression, to retard progression of renal disease.

Recently, mycophenolate mofetil (MMF) was suggested to be a promising therapeutic agent in the treatment of IgAN [10, 11]. Mycophenolic acid (MPA), released from MMF by tissue and systemic esterase activity, is a potent, reversible, and noncompetitive inhibitor of inosine 5′-monophosphate dehydrogenase, a key enzyme for de novo purine synthesis and for the glycosylation of adhesion molecules in T and B lymphocytes [12–15]. As such, MPA selectively inhibits the proliferation of T and B lymphocytes, the production of antibodies, the generation of cytotoxic T cells and the recruitment of leukocytes to sites of inflammation. Results from large-scale clinical trials in renal transplantation demonstrated that MMF is a highly effective immunosuppressive drug with an acceptable safety profile [16–18]. MMF has become one of the standard immunosuppressive agents in many transplant centers and has been successfully used in short-term pilot studies to treat immune-mediated glomerulopathies and systemic immune disorders [10, 11, 19–22]. There is, however, also growing experimental evidence that the anti-inflammatory properties of MMF may, by attenuating glomerular and interstitial injury, be beneficial in

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the treatment of progressive nephropathies [23–25]. At present, no unequivocal clinical data supporting this hypothesis are available.

The effect of MMF in addition to angiotensin-converting enzyme (ACE) inhibition—the reference renoprotective treatment—combined with other strategies (rigorous blood pressure control, sodium restriction, nondihydropyridine calcium blockade) that interfere with progressive proteinuric nephropathies has never been studied in humans. The aim of this single-center, prospective, placebo-controlled randomized study was to evaluate the effect of MMF 2 g per day versus placebo, in addition to standard renoprotective treatment, during a 3-year period on the progression of renal disease in patients with IgAN with prognostic unfavorable features, but judged not to be treated with corticosteroids and/or cytotoxic agents.

METHODS

Study design

The study was a single-center, prospective, placebo-controlled, randomized comparison of treatment with MMF 2 g/day versus placebo for 3 years. The diagnosis of IgAN was based on histologic assessment of renal biopsy tissue stained with hematoxylin and eosin, periodic acid-Schiff (PAS) and methenamine silver for light microscopy and staining with C1q, C3, IgG, IgA, and IgM for immunohistology, showing pre- or codominant mesangial deposition of IgA. The study protocol was approved by the Ethics Committee of the University of Leuven and all patients gave written informed consent.

Patient selection

The inclusion criteria consisted of (*1*) age 18 years and older, (*2*) written informed consent, and (*3*) renal biopsy proven IgAN within 5 years, in conjunction with a decreased renal function at diagnosis [as defined by an inulin clearance >20 but <70 mL/min/1.73 m^2 body surface area (BSA)] and/or proteinuria >1 g/day/1.73 m^2 BSA and/or arterial hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic or currently being treated for hypertension) and/or histologic unfavorable criteria (grades II to IV defined by Churg and Sobin [26] and/or glomerular capillary wall IgA deposits).

Exclusion criteria were rapidly progressive IgAN (IgAN with rapid decline in renal function characterized histologically by necrotizing capillaritis and crescent formation) necessitating the use of other immunosuppressive drugs, other renal diseases and systemic diseases [systemic lupus erythematosus (SLE), Goodpasture syndrome, vasculitis], the intake of other immunosuppressive drugs or any study drug during the last 6 months, pregnancy, lactation or women with child-bearing potential using no effective contraceptives, malignancy, active central nervous/hepatic/metabolic/cardiovascular/gastrointestinal diseases, psychiatric antecedents, ongoing or latent infections, leukopenia (<3000/mm^3) or thrombocytopenia (<75.000/mm^3) or a contraindication for the use of ACE inhibitors.

The screening phase consisted of a complete medical history, clinical examination, electrocardiogram, ultrasound of the abdomen, blood [serum creatinine, urea, sodium, potassium, chloride, bicarbonate, calcium, phosphate, protein content and electrophoresis, fasting glucose, bilirubin, aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), alkaline phosphatase, lactatedehydrogenase, gamma-glutamyltransferase, uric acid, complet and formula, partial thromboplastin time (PTT), IgG/A/M, C-reactive protein, Rheuma Factor, complement (CH50, C3, C3d, and C4), antinuclear factor, antineutrophilic cytoplasmic antibodies (ANCAs), circulating immune complexes, and hepatitis B and C serology] and urine (urine sediment, creatinine clearance, 24-hour proteinuria, and salt excretion) analysis and evaluation of the renal biopsy.

Patient treatment and monitoring

Eligible patients were randomized (2:1; MMF:placebo) and treated with restriction of salt intake (aimed at < 5 g NaCl/day), ACE inhibitors (aimed blood pressure 125/75 mm Hg) and either MMF (Cellcept®) (Hoffmann-LaRoche, Basel, Switzerland) 1 g twice a day or placebo (identical lactose-containing capsules) twice a day. Clinical examination, blood (routine biochemistry, serum IgA/G/M, and serum complement) and urine (urine sediment, measured creatinine clearance, 24-hour proteinuria, and salt excretion) analysis was performed at 1, 2, and 3 months, and every 3 months thereafter; MPA predose level, ultrasound of the kidneys, and inulin clearance was performed every 12 months after randomization.

The following guidelines with regard to the MMF therapy were followed. At every visit, the patients were clinically examined and judged on tolerance and adverse effects (especially infections). In infectious complications, MMF was to be discontinued until resolution of symptoms. In case of gastrointestinal intolerance of MMF, the dose of MMF was to be reduced (from 1 g twice a day to 0.5 g twice a day; and if persistent from 0.5 g twice a day to 0.25 g twice a day). If dose reduction was not sufficient to resolve the symptoms, MMF was to be stopped. In case of leukopenia <3000 white blood cells/mm^3 and/or thrombocytopenia <75,000/mm^3, the dose of MMF was to be reduced to 0.5 g twice a day. In case of leukopenia <2000 white blood cells/mm^3 and/or thrombocytopenia <50,000/mm^3, MMF was to be discontinued for at least 2 weeks. After disappearance of the gastrointestinal

symptoms or restoration of the cell counts, MMF could be reintroduced starting at a dose of 0.5 g twice a day.

As far as blood pressure was concerned, enalapril (Renitec®; Merck, Sharp & Dohme, Whitehouse Station, NJ, USA) was used as first line treatment and doses were increased until blood pressure was <130/80 mm Hg. If supplementary antihypertensive drugs were needed, titration was done using the nondihydropyridine calcium antagonist verapamil (Lodixal®) (Knoll AG, Ludwigshafen, Germany), followed by other. Restriction of salt intake was instructed and monitored using 24-hour NaCl excretion.

Study end points

The primary end point of the study was the loss of renal function, defined as a decrease of 25% or more in the inulin clearance during the 3-year treatment period. Secondary end points were the cumulative percentage of patients that were free of death, development of end-stage renal disease (ESRD) (defined as chronic repetitive dialysis or renal transplantation) or discontinuation of therapy due to adverse events or noncompliance, the cumulative percentage of patients that were free of death, development of ESRD, and the cumulative percentage of patients whose serum creatinine increased by 50% or more over 3 years. Other variables monitored included changes in blood pressure, the estimated annualized within-patient slope in serum creatinine, serum urea, albumin, C-reactive protein, peripheral blood counts, immunoglobulins and complement factors, 24-hour creatinine clearance, 24-hour proteinuria, 24-hour renal sodium excretion, the number of red blood cells per high power field and the percentage of dysmorphic red blood cells in the urine, bipolar diameter (mean of left and right) and parenchymal thickness of the kidneys (mean of left and right upper pole, interpolar region and lower pole), and MPA predose levels. The treatment code was broken for patients reaching ESRD, death, or premature stop of the study due to serious adverse events or patient's decisions.

Statistical analyses

Continuous variables were summarized as means and SD or SEM. Univariate baseline comparisons between the two groups were done using the Wilcoxon rank sum test (SAS, PROC NPAR1WAY) or chi-square test (SAS, PROC FREQ) [27]. The cumulative percentage of patients with a decrease of 25% or more in the inulin clearance, the cumulative percentage of patients that were free of death, development of ESRD (or discontinuation of therapy) and the cumulative percentage of patients whose serum creatinine increased by 50% or more in both groups was calculated by Kaplan-Meier survival analysis (SAS, PROC LIFETEST) [27]. The annualized slope in serum creatinine was calculated using linear regression analysis in each patient; the Wilcoxon rank sum test was then used to compare the distributions of the slopes in both groups. The clinical, biochemical, and radiologic variables monitored at regular intervals over a period of 36 months were compared in the two groups using linear mixed models for longitudinal data (SAS, PROC MIXED) [27, 28].

RESULTS

Between October 1997 and December 1999, 49 patients with IgAN were screened for this study. Thirty-four met the criteria for eligibility and were willing to enter the study. Twenty-one were assigned to receive MMF, and 13 to receive placebo. The baseline clinical and laboratory characteristics of the patients in both groups were similar. At the time of randomisation, the age was 39 ± 11 years in the MMF group versus 43 ± 15 years in the placebo group ($P = 0.37$). There were no differences in gender (76% versus 62% male; $P = 0.29$), race (90% versus 92% Caucasian; $P = 0.45$), number of hypertensive patients (86% versus 85%; $P = 0.73$), or time elapsed from renal biopsy to randomization (3.4 ± 1.7 years versus 3.7 ± 2.1 years; $P = 0.19$). And there were also no significant differences in baseline data of systolic ($P = 0.40$) and diastolic ($P = 0.94$) blood pressure, renal function [inulin clearance ($P = 0.57$), serum creatinine ($P = 0.65$), 24-hour proteinuria ($P = 0.17$)] or 24-hour urinary NaCl excretion ($P = 0.25$).

Outcome

In the follow-up of the 34 patients who entered the trial, one patient in the placebo group died due to metastasized rectal carcinoma, and two patients in the MMF group evolved to ESRD. Therapy was stopped prematurely in another four patients due to adverse events (one subject in each group) or emigration (MMF group, two subjects).

Nine patients (seven in the MMF group and two in the placebo group) reached the primary end point of the study, a decrease of 25% or more in the inulin clearance at 36 months. The respective Kaplan-Meier estimates were 33% and 15% (log-rank $P = 0.3357$; Wilcoxon $P = 0.3650$) (Fig. 1A). Survival free of ESRD, adverse events leading to discontinuation of treatment or refusal to continue therapy was also similar in both groups (76% versus 85%) (log-rank $P = 0.6555$; Wilcoxon $P = 0.7420$) (Fig. 1B). Also survival free of ESRD was similar in both groups (89% versus 92%) (log-rank $P = 0.8179$; Wilcoxon $P = 0.8388$). There was also no difference in the cumulative percentage of patients whose serum creatinine increased by 50% or more in both groups (14% versus 0%) (log-rank $P = 0.1560$; Wilcoxon $P = 0.1605$) (Fig. 1C).

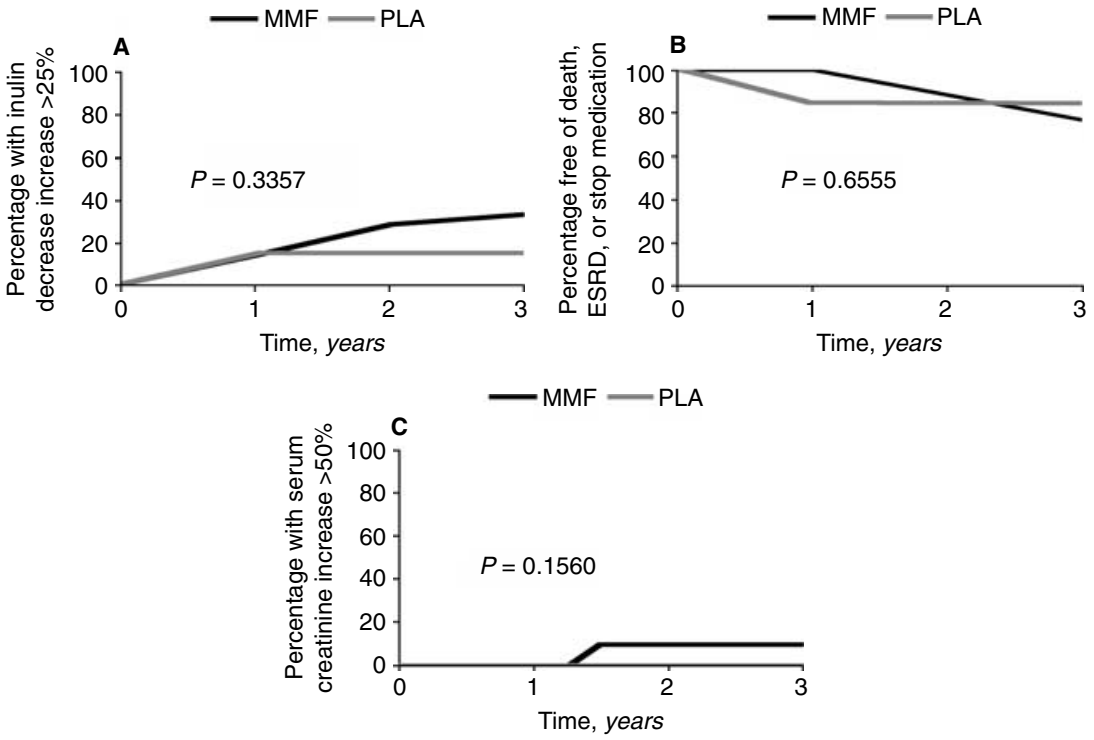

Fig. 1. Cumulative percentage of patients with IgA nephropathy (IgAN) treated with mycophenolate (MMF) or placebo (PLA). (*A*) Patients whose inulin clearance decreased by 25% or more. (*B*) Patients who were free of death, development of end-stage renal disease (ESRD), or premature discontinuation of therapy. (*C*) Patients whose serum creatinine increased by 50% or more during the 3-year treatment period.

Changes in renal function and morphology and management of hypertension

Renal function was maintained equally in both patient groups, as indicated by evolution of inulin clearance, serum creatinine, and by the median annual changes in serum creatinine concentration (Fig. 2) (Table 1). The annualized median change in serum creatinine was 0.11 mg/dL per year in the MMF group and 0.05 mg/dL per year in the placebo group ($P = 0.5007$).

A small but significant decline in proteinuria was noted in both groups as a function of time; differences between groups were absent. There was also no difference in the cumulative percentage of patients whose proteinuria decreased or increased by 50% or more or in the percentage of patients with proteinuria more than 1 g or 3 g per day over time. No differences were noted within or between groups in number of urinary red blood cells per high power field or in the percentage of dysmorphic urinary red blood cells.

Although the bipolar diameter of the kidneys remained unchanged over the treatment period of 3 years, a significant decline in parenchymal thickness could be noted in both groups as a function of time; the differences between groups, however, were not significant (Fig. 3) (Table 1).

Both systolic and diastolic blood pressures were similar in both groups and did not change significantly during the treatment period (Table 1). Nine patients (27%), six in the MMF group and three in the placebo group, were already on enalapril before enrollment in the study. All but one patient were treated with enalapril and also received other antihypertensive drugs, including calcium antagonists (verapamil) [14 (eight MMF/six placebo)], adrenergic antagonists (eight), centrally acting alpha$_2$-adrenergic agonists (one), and diuretic agents (six). Two patients (one in both groups) developed symptomatic hypotension to enalapril, for which enalapril had to be stopped; no other adverse effects to antihypertensive treatment was noted. The dose of enalapril was twice as high in the MMF group (19 ± 12 mg/day) compared with the placebo group (11 ± 7 mg/day) ($P = 0.0484$). Renal sodium chloride excretion initially dropped in both groups due to dietary restrictions, but then again rose from month 6 on in both groups.

Changes in biochemistry

A small but significant increase over 3 years was noted in hemoglobin (or hematocrit/red cell count) in the placebo group that was absent in the MMF group. There was also a small but consistent difference between groups in C-reactive protein. In both groups, complement factor C3 slightly but significantly increased. This was associated with a significant decrease in C3d. No other significant differences in biochemistry were present.

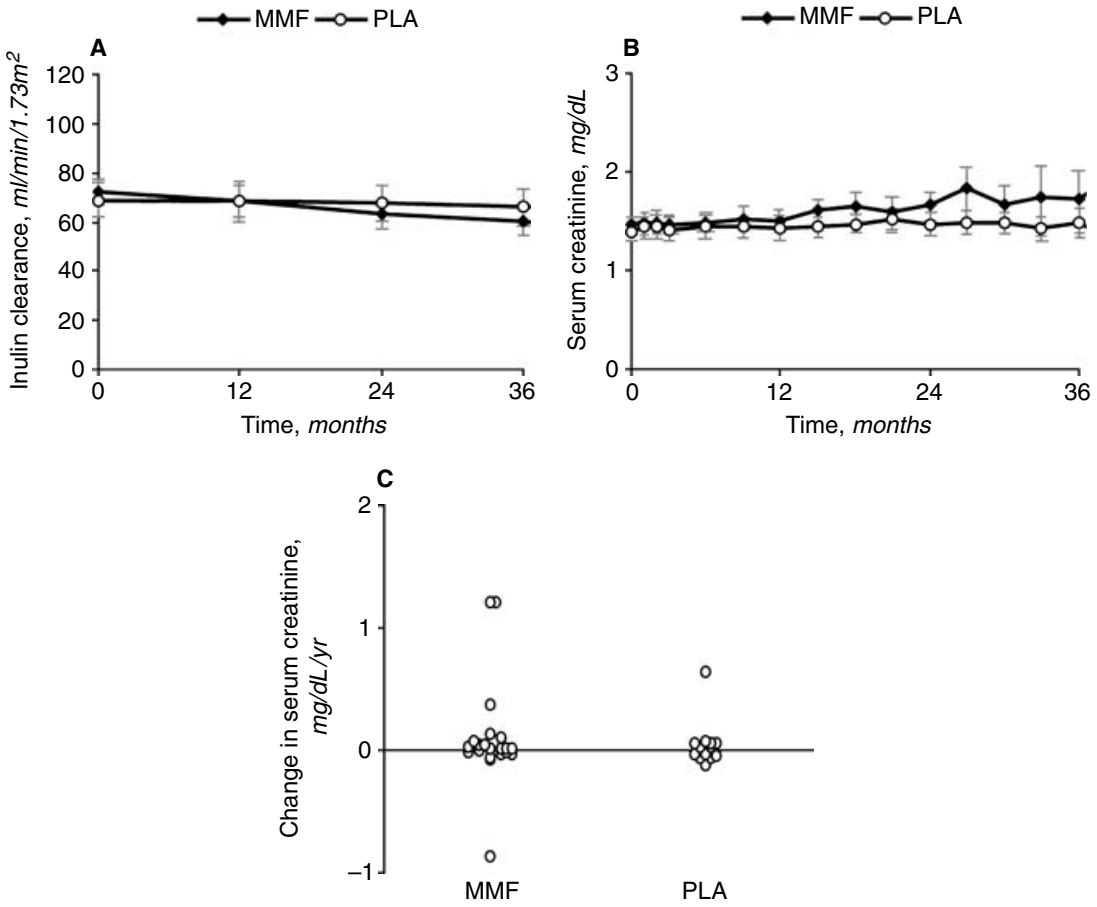

Fig. 2. Inulin clearance (*A*) (mean ± SEM), serum creatinine (*B*) (mean ± SEM) and annualized rate of change in serum creatinine (*C*) in patients with IgA nephropathy (IgAN) treated with mycophenolate mofetil (MMF) or placebo (PLA).

Table 1. Renal function and morphology, and blood pressure: Comparison of results from baseline to 36 months of therapy in patients with IgA nephropathy (IgAN) treated with mycophenolate mofetil (MMF) or placebo during the 3-year treatment period (mean ± SEM)

	MMF		Placebo		Linear mixed model	*P* value
	Month 0	Month 36	Month 0	Month 36	Treatment effect	Time effect
Inulin clearance *mL/min/1.73 m²*	73 ± 5	60 ± 7	69 ± 7	67 ± 7	0.33	0.95
Serum creatinine *mg/dL*	1.46 ± 0.08	1.72 ± 0.35	1,39 ± 0,10	1.48 ± 0.16	0.12	0.97
Serum urea *mg/dL*	47 ± 4	53 ± 11	47 ± 5	48 ± 6	0.23	0.92
Bipolar diameter *cm*	10.5 ± 0.9	10.7 ± 0.8	10.5 ± 1.1	10.2 ± 1.1	0.20	0.94
Parenchymal thickness *mm*	15.8 ± 0.7	14.6 ± 0.5	16.7 ± 0.6	13.9 ± 0.6	0.92	0.0013
Proteinuria *g/day*	1.9 ± 0.3	1.6 ± 0.6	1.3 ± 0.4	1.0 ± 0.6	0.97	0.0001
Systolic blood pressure *mm Hg*	122 ± 4	125 ± 3	134 ± 8	124 ± 8	0.12	0.72
Diastolic blood pressure *mm Hg*	80 ± 3	74 ± 2	80 ± 3	71 ± 5	0.27	0.75
Renal sodium excretion *g/day*	8.6 ± 0.8	7.8 ± 0.7	6.7 ± 0.9	7.6 ± 1.5	0.95	0.0089
Number of urinary red blood cells/high power field	149 ± 51	51 ± 25	111 ± 33	29 ± 18	0.15	0.55
Dysmorphic urinary red blood cells %	64 ± 6	66 ± 9	73 ± 6	40 ± 8	0.28	0.82

Compliance with treatment and adverse reactions

As a measure of compliance, MPA predose levels were dosed every year in the MMF-treated group. Nondetectable predose levels were absent in all patients at any time. As shown in Figure 4, a mean predose level of 3.5 mg/L was measured after 1 year of treatment, followed by a slight nonsignificant increase over time ($P =$ 0.7489). Reactivation of pulmonary tuberculosis in a patient of Indian origin 4 months after study entry required the discontinuation of MMF treatment; a good response to antimycobacterial therapy (isoniazid, rifampicin, and ethambutol) was obtained. Two patients developed gastrointestinal complaints (nausea and epigastric pain) for which the dose of MMF was reduced; a transient dose

Table 2. Biochemistry: comparison of results from baseline to 36 months of therapy in patients with IgA nephropathy (IgAN) treated with mycophenolate mofetil (MMF) or placebo during the 3-year treatment period (mean ± SEM)

	MMF		Placebo		Linear mixed model Treatment effect	*P* value Time effect
	Month 0	Month 36	Month 0	Month 36		
Hematocrit %	43 ± 1	43 ± 2	39 ± 1	42 ± 1	0.0069	0.98
Hemoglobin *g/dL*	14.4 ± 0.3	14.1 ± 0.6	13.0 ± 0.5	13.9 ± 0.6	0.0056	0.99
Red blood cell count 10^{12}/*L*	4.81 ± 0.12	4.88 ± 0.21	4.23 ± 0.17	4.53 ± 0.20	<0.0001	0.99
White blood cell count 10^{9}/*L*	7.3 ± 0.6	6.7 ± 0.5	6.4 ± 0.4	6.7 ± 0.5	0.72	0.94
Lymphocyte count %	28 ± 2	25 ± 3	27 ± 2	26 ± 2	0.68	0.99
Platelet count 10^{9}/*L*	263 ± 16	265 ± 25	279 ± 9	254 ± 17	0.07	0.17
C-reactive protein *mg/L*	4.1 ± 0.7	3.5 ± 0.5	4.8 ± 0.7	5.1 ± 0.7	0.0001	0.79
IgA *g/L*	3.2 ± 0.2	2.6 ± 0.3	3.0 ± 0.2	2.8 ± 0.3	0.41	0.89
IgG *g/L*	9.6 ± 0.6	9.6 ± 1.0	9.8 ± 0.8	9.3 ± 0.7	0.52	0.99
IgM *g/L*	1.1 ± 0.1	0.7 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.42	0.98
Albumin g/L	40.5 ± 0.9	38.7 ± 1.0	39.5 ± 1.3	39.2 ± 1.0	0.85	0.30
C3 *g/L*	1.05 ± 0.04	1.06 ± 0.09	1.07 ± 0.04	1.15 ± 0.12	0.48	0.01
C3d %	2.4 ± 0.2	1.7 ± 0.2	2.1 ± 0.3	1.4 ± 0.1	0.23	0.0004
C4 *g/L*	0.25 ± 0.02	0.23 ± 0.03	0.25 ± 0.02	0.25 ± 0.04	0.96	0.52
CH50 *U/mL*	514 ± 25	526 ± 22	508 ± 36	517 ± 35	0.86	0.56

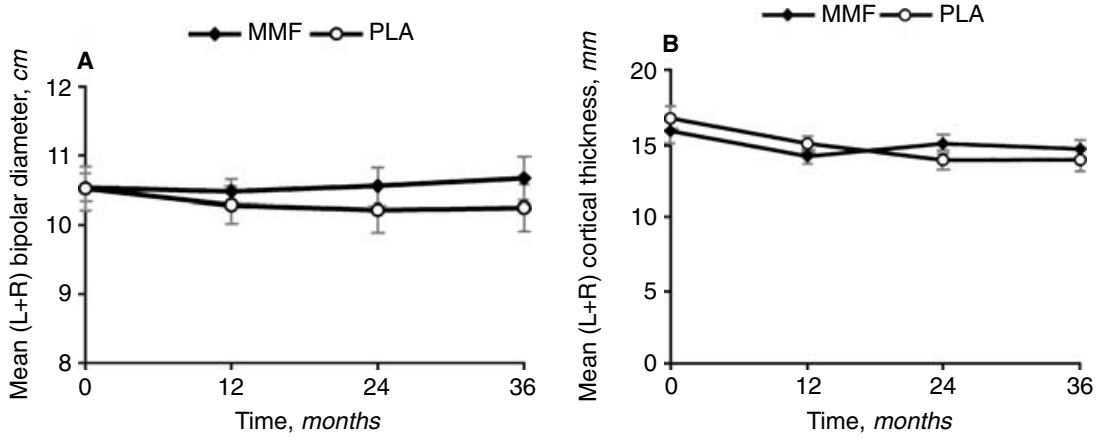

Fig. 3. Bipolar diameter (mean of left and right kidney) (*A*) and parenchymal thickness (mean of left and right upper pole, interpolar region and lower pole) (*B*) (mean ± SEM) in patients with IgA nephropathy (IgAN) treated with mycophenolate mofetil (MMF) or placebo (PLA).

reduction was required in one patient with a temporary leukopenia. The mean dose of MMF was 1.85 ± 0.45 g/day.

In the placebo group, one patient became pregnant 6 months after inclusion in the study after stopping oral contraceptives; the pregnancy evolved uneventfully. Another female developed rectal carcinoma 12 months after study entry and died of disseminated disease 2 months later. No adverse effects were noted in the placebo group.

DISCUSSION

This prospective, placebo-controlled randomized study failed to show an additive effect of MMF 2 g/day versus placebo added to salt intake restriction and ACE inhibitors during a 3-year period on the progression of renal disease in patients with IgAN with prognostic unfavorable features. This is in contrast with the beneficial effects of MMF reported in other immune-mediated nephropathies and anecdotic reports in IgAN (10, 11, 19–22). Several factors have to be taken into account.

First, the number of patients included was small because of the single-center design; on the other hand, it allowed to evaluate some markers of renal disease and therapy accurately (inulin clearance, immunology, ultrasound of the kidneys by one radiologist, and dosing of MPA). Moreover, in order to maximize the number of patients treated with MMF, a 2:1 randomization has been performed. However, the conclusions have to interpreted with caution since the study is statistically not powered to unequivocally prove differences or equivalence between the two groups. Therefore, large multicenter trials are warranted in the future to confirm or reject these results.

Second, patient selection may have influenced the outcome of the study. Patients judged to be treated with corticosteroids and/or cytotoxic agents [(*1*) rapidly progressive IgAN and (*2*) patients with mild histopathologic changes, proteinuria >3 g/day and preserved renal function (creatinine clearance >70 mL/min)] [6] were

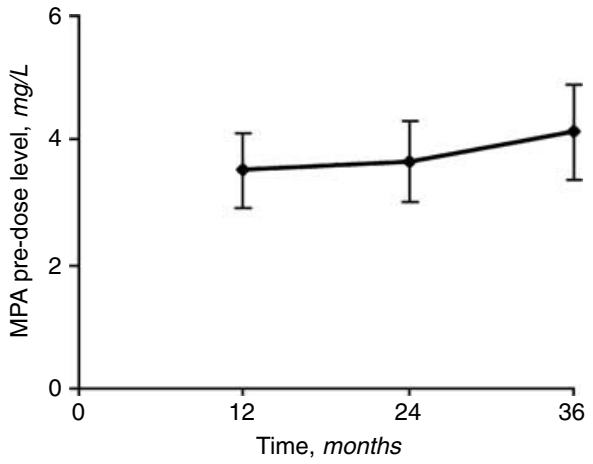

Fig. 4. Mycophenolic acid (MPA) predose level (mean ± SEM) in patients with IgA nephropathy (IgAN) treated with mycophenolate mofetil (MMF).

excluded; whether an additional beneficial effect of MMF in these groups can be obtained is not addressed in this study. Because experimental data showed that effective renal protection by MMF in some nephropathies occurred if it was instituted early in the course of the disease [29–31], only patients with IgAN without severe renal insufficiency were studied. Nevertheless, risk factors for progression (hypertension, proteinuria, decreased renal function, and histologic criteria) had to be present. As a result, the annualized rate of change in serum creatinine was comparable with other studies in IgAN with moderate renal disease and slightly lower compared with some studies in severe IgAN [32, 33]. In 27% of patients, enalapril was already started before enrollment in the study, albeit with an equal distribution in the two groups. And no differences in evolution of renal function or proteinuria have been observed between patients with and without ACE inhibition at the time of enrollment. The dose of enalapril was twice as high in the MMF-group compared with the placebo group, as a result of dosing according to blood pressure control and tolerance. Because no influence of MMF on blood pressure has ever been reported in humans, this might indirectly indicate a more severe disease or more rapid progression in patients on MMF treatment. However, no markers at baseline or during follow-up pointed at significant differences in severity or progression of IgAN (renal function or morphometry, proteinuria, blood pressure, or salt intake).

In this subset of patients with IgAN (that probably represents the major part of patients with progressive IgAN) administration of MMF 2 g/day during a 3-year period of time offered no benefit over the standard therapy of salt restriction, angiotensin II suppression and frequent follow-up (compliance) as far as (renal) outcome or proteinuria is concerned. None of the immunologic parameters measured suggested a positive influence of MMF on inappropriate activation of the immune response (immunoglobulin A/G/M, complement factors). On the other hand, patients in the MMF group displayed a significantly lower C-reactive protein, compatible with the anti-inflammatory properties of MMF. While these anti-inflammatory properties of MMF exerted effective renal protection (agonistic with ACE inhibition) in the early course of both immune and nonimmune nephropathies in experimental models [23, 29–31], this resulted not in clinically measurable benefits in humans with IgAN on standard therapy. The small but significant decline of proteinuria, parenchymal thickness, and C3d with associated increase of total C3 in both groups are suggestive for anti-inflammatory actions of the standard therapy based on the consideration to ameliorate hemodynamic stress or immune injury.

Although the safety profile of MMF is favorable and only minor adverse effects were noted in this study, the risks of prolonged immunosuppression by MMF [lymphoma, cytomegalovirus (CMV) disease] without clinical benefits made us stop the study after 3 years. Whether the decreasing hemoglobin level is due to the administration of MMF or the higher doses of ACE inhibitor in this group is not known. And, whether higher doses of MMF are able to slow progressive disease in this subset of patients with IgAN is not answered by this study. However, the measured MPA predose levels were within the ranges accepted as safe and effective to prevent allograft rejection, albeit in dual or triple immunotherapy. The slight but not significant increase of MPA predose levels are in agreement with the observations in organ transplantation of a gradual increase of exposure to MPA with time [34]. Because of the interindividual variability of exposure, increasing the dose to 3 g MMF per day would probably give rise to more (serious) adverse effects. Therefore, future studies with MMF in immune disorders should use MPA levels to monitor adequate individual exposure rather than fixed doses.

CONCLUSION

In patients with IgAN with moderate risk for progressive disease, no beneficial effect of three years treatment with MMF 2 g/day could be demonstrated on renal outcome/function or proteinuria. However, larger multicenter studies are warranted to confirm or reject these findings.

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