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Original Article

Efficacy and safety of 'rescue therapy' with mycophenolate mofetil in resistant primary glomerulonephritis—A multicenter study*

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Abstract

Background. Studies of mycophenolate mofetil (MMF) in primary glomerulonephritis have varied in their inclusion criteria, regimen and follow-up compromising assessments of efficacy and optimal dose.

Method. This multicentre study analysed the safety and efficacy of MMF monotherapy in a large cohort with primary glomerulonephritis that was resistant to other conventional therapies. A total of 98 patients with biopsy-proven primary glomerulonephritis resistant to other drugs received MMF monotherapy for 1 year. Primary outcome measures were urinary protein excretion and the number of patients with complete or partial remission of proteinuria. Secondary analyses were time to remission and changes in the slope of creatinine clearance.

Results. Fifty-four percent of the patients achieved either complete or partial remission of proteinuria with no significant differences between glomerulonephritis types. Median (range) dose of MMF was 2 g/day (1.5–2 g/day) Mean (SD) treatment time to remission was 141.5 (±61.1) days with no significant differences between glomerulonephritis types. Serum albumin increased ($P < 0.01$), whereas proteinuria ($P < 0.01$) serum LDL-cholesterol ($P < 0.01$) and mean blood pressure ($P < 0.05$) decreased post-treatment. No significant changes were observed in glomerular filtration rate (GFR), serum creatinine or slopes of GFR. The reduction of urinary protein excretion was significantly higher in patients with basal nephrotic proteinuria and preserved renal function; it did not arise from an increased dose of angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, since, among responders, mean blood pressure significantly decreased and the number of antihypertensive drugs could be reduced.

Conclusions. MMF monotherapy causes a moderate decrease in proteinuria in >50% of the patients who do not have other treatment options. The response to therapy is largely influenced by a preserved renal function and requires sustained MMF treatment.

Keywords: mycophenolate mofetil; primary glomerulonephritis; resistant glomerulonephritis

Introduction

Primary glomerular diseases are the leading cause of end-stage renal failure in young patients [1]. General measures, which include salt restriction, blood pressure control and angiotensin-converting enzyme inhibitors (ACEIs), often retard but do not prevent disease progression. Glucocorticoids and classic immunosuppressive drugs, which target the underlying immune-mediated pathogenesis, can induce sustained remission and improve long-term outcomes. However, serious toxicity, high rates of inadequate clinical response and frequent relapses following discontinuation limit the utility of these drugs in clinical practice [2].

Consequently, there is a pressing need for new treatments for primary glomerular diseases. Advances in transplant immunosuppressants have provided drugs that could benefit chronic glomerulonephritis, which include calcineurin inhibitors (such as ciclosporin A) and mycophenolate mofetil (MMF). Large clinical trials have proved that ciclosporin A induces sustained remission in a significant proportion of patients with idiopathic focal segmental glomerulosclerosis (FSGS) or membranous nephropathy,

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(MN) [3–5]. However, the long-term use of ciclosporin A is limited by chronic nephrotoxicity [3–5].

The first clinical reports suggesting that MMF might be effective in glomerulonephritis emerged in the late 1990s [6,7]. Since then, however, only four randomized studies have been published in patients with IgA nephropathy (IgAN), with conflicting results [8–11]. Most studies assessing MMF in primary glomerulonephritis included a small number of patients and varied especially in the inclusion criteria, doses and follow-up [12–23]. Therefore, for the role of MMF in the management of primary glomerulonephritis is uncertain. In particular, for the group of patients that would benefit from MMF, the optimum doses and the minimum treatment period remain unclear.

This multicentre study aimed to analyse the efficacy and safety of MMF as monotherapy in patients with different types of primary glomerulonephritis whose disease was not controlled by treatments suggested by evidence-based guidelines [3,24]. The study was limited to 12 months to assess short-term efficacy data, minimum treatment period, potential predictors of outcome and response rates in each type of disease.

Materials and methods

A total of 98 patients with primary glomerulonephritis were recruited from eight Spanish hospitals between 1999 and 2002. Follow-up ended in May 2004.

Patients fulfilled the following inclusion criteria:

- Diagnosis by renal biopsy of mesangial proliferative IgAN, IgM glomerulonephritis (IgMN), FSGS, MN or membranoproliferative glomerulonephritis (MPGN) with no secondary glomerulonephritis.
- Glomerular filtration rate (GFR) >30 ml/min and <80 ml/min measured by endogenous creatinine clearance (CrC).
- No contraindications to MMF, such as pregnancy, infection, peptic ulcers, malignancy or leucopenia.
- No use of immunosuppressant or non-steroidal anti-inflammatory drugs 6 months before inclusion.
- Resistance to treatments recommended in evidence-based guidelines [3].
- IgAN: proteinuria >2.5 g/day after at least a 6-month treatment with steroids and ACEI.
- FSGS and MN: proteinuria >3.5 g/day after a 6-month treatment with steroids, ciclosporin A (5 mg/kg/day) and ACEI.
- MPGN type 1: proteinuria >3.5 g/day after a 12-month treatment with ACEI.
- IgMN: proteinuria >3.5 g/day after at least a 6-month treatment with steroids.

The study conformed to the Declaration of Helsinki. All patients gave written, informed consent and each centre's ethics committee approved the study. The Spanish Ministry of Health authorized the treatment with MMF.

Six months before study entry, all patients started a low-salt diet and treatment with ACEI or angiotensin II receptor antagonists (AIIRA). After taking these measures, we only enrolled in the study those patients in whom the urinary protein excretion was higher than the cut-off values defined in the inclusion criteria.

No patients received concurrent treatment with both ACEI and AIIRA agents or with aldosterone receptor antagonists.

After study admission, patients remained on a low-salt diet and received treatment with either ACEI or AIIRA during the whole follow-up.

We prescribed both ACEI and AIIRA for non-hypertensive patients at fixed doses (enapril 20 mg/day, losartan 50 mg/day), which were not changed during the whole follow-up. Whenever possible, hypertensive patients received fixed doses of ACEI and AIIRA. However, clinicians could increase the doses to control blood pressure adequately. If it was considered necessary, other anti-hypertensive drugs were added to achieve a mean blood pressure [diastolic + 1/3 (systolic − diastolic)] ≤90 mmHg.

Clinicians were free to treat hyperlipidaemia with statins according to their usual practice, but a target level for LDL-cholesterol was not defined.

The dose of MMF depended on renal function. Patients with CrC ≥ 60 ml/min received a dose of 2.0 g/day and those with CrC < 60 ml/min, 1.5 g/day. The treatment lasted for 12 months. Patients with evidence of CR or PR had MMF tapered at a rate of 500 mg every 4 weeks until either treatment discontinuation or relapse. Relapse was defined as an increase in urinary protein excretion >1 g/day in IgAN and >3.5 g/day in the other groups, confirmed in two consecutive analyses. If proteinuria recurred during dose reduction, MMF doses were increased to the previous dose that sustained remission. Relapses of proteinuria upon discontinuation were treated according to the preceding regimen.

Outcome measures

The primary outcome measures were urinary protein excretion after a 12-month treatment and the number of patients with complete remission (CR) of proteinuria (PR) (defined as PR < 0.3 g/day in two consecutive measurements within 3 months) or partial remission of PR defined for IgAN as PR ≥ 0.3 and ≤1 g/day; for the other groups as PR > 0.3 g/day and <3.5 g/day). Secondary measures included time to achieve CR or PR, the evolution of the slopes of GFR over 12 months, and the relationship between mycophenolic acid (MPA) levels and clinical outcome.

Follow-up and safety assessment

During the first 3 months patients were followed every month and then at 3-month intervals. Patients who achieved remission and discontinued treatment were examined every month for 6 months for signs of relapse. At each follow-up visit clinical status, blood pressure, serum creatinine, 24 h CrC, electrolytes, lipids, liver function, glycaemia and 24 h urinary protein excretion were recorded. The total plasma levels of MPA, the active metabolite of MMF, were measured at 12 h post-dosing (trough) in 52 patients by the EMIT MPA assay using a COBAS MIRA PLUS analyzer (Roche Laboratories). MPA levels were only determined in a sample of 52 patients, as not all participating centres were able to perform this measurement.

Table 1. Baseline characteristics of the study population

	Primary glomerular disease					All patients
	IgAN	MN	FSGS	MPGN	IgMN	
n	25	21	22	15	15	98
Sex (M/F)	19/6	12/9	15/7	10/5	4/11	70/28
Mean age (SD; years)	37 (11.7)	51.8 (12.6)	39 (14)	38.2 (9.6)	39.5 (11.3)	41.6 (12.4)
Time (SD) from biopsy to study entry (years)	3 (0.39)	2.7 (0.53)	3.5 (1.8)	4.3 (1.5)*	4.02 (1.1)*	3.17 (0.9)
Serum creatinine (SD; mg/dl)	2 (0.48)	1.9 (0.26)	1.6 (0.5)	2.12 (0.12)	1.48 (0.2)	1.96 (0.7)
GFR (SD; ml/min)	52.3 (11.5)	58.2 (10)	67.1 (6.3)*	54.5 (2.7)	65 (7.39)*	56 (12.6)
Slope GFR (SD; ml/min/month)	−0.82 (0.35)	−0.69 (0.48)	−0.92 (0.42)	−0.48 (0.13)	−0.3 (0.3)	−0.74 (0.35)
Number (%) of patients with GFR <60 ml/min	15 (60)	11 (52.3)	10 (45.4)	15 (100)	2 (13.3)	56 (57.1)
Mean serum albumin (SD; g/dl)	3.7 (0.6)**	2.9 (0.6)	2.7 (0.4)	2.87 (0.49)	2.57 (0.38)	2.5 (0.7)
Mean (SD) urinary protein excretion (g/day)	2.74 (1.3)*	7.96 (4.1)	7.2 (3.2)	6.05 (1.9)	4.9 (1.34)	5.63 (3.2)
Number (%) of patients with urinary protein excretion >3.5 g/day	4 (16)**	21 (100)	22 (100)	15 (100)	15 (100)	72 (73.4)
Mean (SD) blood pressure (mmHg)	90.8 (3.3)	91.0 (6.0)	87.0 (4.7)	94.0 (5.6)	89.0 (2.1)	88.0 (6.3)
Number (%) of patients with high blood pressure	18 (72)	13 (61.9)	12 (54.5)	15 (100)	3 (20)	55 (56.1)

GFR, glomerular filtration rate; Slope GFR, slope of GFR over time before study entry.
*$P < 0.05$,**$P < 0.01$ when compared with the rest of groups.

Each febrile episode was systematically assessed. Septic complications were defined as the presence of a source of infection with known bacteriology. Sepsis was defined by more than one of the following: fever, tachycardia, tachypnea or hyperventilation, leucocytes >12 000 cells/mm^3 or <3000 cells/mm^3, or the presence of >10% immature neutrophils. Pulmonary infection was diagnosed following clinical and radiographic confirmation and isolation of pathogens in sputum or bronchoalveolar lavage. Urinary tract infection was diagnosed when clinical symptoms of bacteriuria were present. Infectious causes of every episode of diarrhoea were ruled out by bacteriological tests.

In the patients who developed gastrointestinal side effects, the total daily dose of MMF was decreased 50% for 2 weeks and then increased to the recommended dose. MMF was discontinued in cases of leucopenia ($<3500 \times 10^9$ cells) or acute febrile episodes. After any dose reduction or interruption, MMF was reinstated in increments until the recommended dose was achieved—MMF was withdrawn if gastrointestinal symptoms persisted after 4 weeks on a lower dose, or when patients developed severe infectious complications.

Statistical analysis

Safety was analysed in the entire cohort. Efficacy was analysed for each type of glomerulonephritis by using an intention-to-treat protocol. The efficacy analysis included that all the patients be treated with MMF for more than 1 month. Patients who discontinued MMF before the end of follow-up were considered treatment failures.

Results are given as the mean ± SD for normally distributed variables or the median and the interquartile range (IQR 25–75%) for variables with non-normal distribution. The chi-squared or Fisher's exact tests were used to compare proportions and Student's *t*-test to compare normal quantitative variables or Mann–Whitney U-test for non-normal variables.The Bonferroni correction was applied to account for multiple observations. Correlation analyses were done using Pearson's correlation coefficient.

Slopes of GFR over time were determined by a single regression analysis using at least five values obtained before study entry, assuming a linear model of progression of renal failure. Slopes of GFR and proteinuria showed non-normal distributions. Therefore, the differences in renal function and proteinuria over time within groups were analysed by a repeated measure analysis of variance after logarithmic transformation. A *P*-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 10.0 software.

Results

Baseline characteristics

Table 1 summarizes baseline characteristics for the 98 recruited patients according to the nature of the primary glomerular disease. Baseline values were broadly similar across the primary disease groups. However, the time lapse between the renal biopsy and the MMF therapy was significantly longer in the IgMN and MPGN groups ($P < 0.05$ in both cases), GFR was significantly higher in those with FSGS and IgMN compared with the other groups ($P < 0.05$). Similarly, serum albumin was significantly higher ($P < 0.01$) and urinary protein significantly lower ($P < 0.05$) in the IgAN group compared with the other groups. Significantly fewer ($P < 0.01$) patients in this group had also a urinary protein excretion of >3.5 g/day compared with the other groups.

Mean slope of GFR before study entry was −0.74 ml/min/month (SD: ±0.35, median: −0.67, range: −2 to 0.41), 19.3% of the patients showed evidence of progressive renal failure. Fifty-six percent of the patients had hypertension at study entry. Statins were taken by 73% of the patients (doses were not changed during follow-up).

Patients had received a wide variety of therapies for the treatment of the primary glomerular disease prior to study entry (Table 2).

Table 2. Prior therapies

Prior treatment	*n* (%)					
	Primary glomerular disease					
	IgA N (25)	MN (21)	FSGS (22)	MPGN (15)	IgMN (15)	All patients (98)
6-month trial of ciclosporin	2 (8)	16 (76.1)	22 (100)		5 (33)	45 (45.9)
6-month prednisone/chlorambucil trial		14 (67)				14 (14.2)
6-month trial of prednisone monotherapy	25 (100)		22 (100)	5 (33)	5 (33)	57 (58.1)
Cyclophosphamide			5 (23)	5 (33)		10 (10)
6-month trial of tacrolimus		5 (24)	4 (18)		3 (20)	12 (14)
Fish oil	2 (8)					2 (2)
Azathioprine	6 (24)	5 (24)				11 (11.2)
High-dose immunoglobulin	3 (12)	4 (19)				7 (7.1)
Antiplatelet drugs				9 (60)		9 (9.1)

The mean (SD) extent of interstitial fibrosis was 26.3% (18.2), of sclerosed glomeruli 15.2% (11.5), and of glomeruli with focal sclerosis 32% (20). No significant correlations emerged between GFR and the proportion of glomeruli with total sclerosis (*r*: 0.17, NS) or the amount of interstitial fibrosis (*r*: 0.11, NS).

Efficacy analysis

Overall, 89.7% of the patients completed a 12-month treatment. Table 3 summarizes the effects of treatment on proteinuria during follow-up, whereas Table 4 illustrates the time course for proteinuria after stratifying patients according to urinary protein excretion.

On the whole, 53 (54%) patients achieved CR or PR. Urinary protein excretion decreased significantly from 5.6 (±3.23) to 2.55 (±1.06) g/day ($P < 0.01$). The mean time to remission was 141.5 (SD ± 61.1, median: 120, range: 30–300, IQR 105–150) days. Time to response varied noticeably among the patients. More than 15% of the patients required treatment for >210 days.

GFR, GFR slope and creatinine levels did not change during follow-up. Serum albumin levels increased only in the patients who achieved CR or PR. These 'responders' showed a mean increase of 1.39 mg/dl ($P < 0.01$ *vs* non-responders). Serum LDL-cholesterol concentrations decreased significantly ($P < 0.01$) (Table 5) and were higher in non-responders than in responders ($P < 0.01$).

Table 4 summarizes antihypertensive treatment at study entry and during follow-up, according to the response to MMF. There were no differences in basal treatment among the groups. However, 23.07% of non-responders *vs* zero responders needed three or more drugs to control blood pressure. The proportion of patients controlled with ACEI or AIIRA monotherapy was also significantly higher in responders ($P = 0.033$).

We found no significant differences in the dose of either ACEI or AIIRA between those patients who achieved remission and those who did not—median (range) enalapril dose 20 mg (10–40 mg) in both groups, median (range) losartan dose 50 mg (25–100 mg).

The median dose of MMF was 2.0 g/day (range 1.5–2.0) with no significant differences among the different disease groups. MPA trough levels ranged from 2 to 8 μg/ml (median 2.8) during the first month of treatment, from 1.8 to 7.2 μg/ml (median 3.1) at 3 months, 1.9–9.2 μg/ml (median 3.6) at 6 months and 1.77–6.8 μg/ml (median 2.9) at 12 months. MPA trough levels were not correlated with remission of proteinuria (median 2.78 μg/ml, range 1.8–6.7) in patients with remission of proteinuria *vs* 3.01 μg/ml (1.7–9.2) ($P = 0.43$ in patients with no response), serum albumin ($P = 0.22$) or GFR ($P = 0.34$).

In the whole group, the probability of remission (complete or partial) was not associated with age ($P = 0.12$), gender ($P = 0.4$), type of glomerulonephritis ($P = 0.13$) or time from diagnosis ($P = 0.57$). In all the groups of glomerulonephritis, which include patients with and without renal failure, the proportion of patients achieving complete or partial remission was significantly higher for patients with GFR ≥ 60 ml/min (IgA: 30 *vs* 0%, MN: 80 *vs* 27.2%, $P = 0.044$, FSGS: 66.6 *vs* 40%, $P = 0.043$, IgMN: 53.8 *vs* 0). Moreover, quantitative reduction of proteinuria was significantly higher in patients with baseline GFR > 80 ml/min than in patients with basal GFR < 80 ml/min (−4.7 (±2.8) *vs* −2.03 (±1.1), $P < 0.05$). Patients with basal nephrotic proteinuria showed higher reduction of proteinuria than patients with basal non-nephrotic proteinuria [urinary protein loss reduction: −5.5 (±3.8) g/day *vs* −1.3 (±1.08); $P < 0.001$]. As the time lapse between kidney biopsy and study entry was long and varied widely among patients, the influence of histopathological data on response was not statistically analysed.

Relapses of proteinuria

During follow-up, an attempt to reduce the dose of MMF was made in 41 out of the 53 responder patients (77, 35%). Among them, 71 episodes of relapse were

Table 3. Proteinuria during the 12-month follow-up period

	n (%)					
	Primary glomerular disease					
	IgAN (25)	MN (21)	FSGS (22)	MPGN (15)	IgMN (15)	All patients (98)
Number (%) achieving complete remission	3 (12)	0	2 (9)	0	2 (13)	7 (7.1)
Number (%) achieving partial remission	12 (48)	11 (52)	10 (45)	7 (47)	6 (40)	46 (46.9)
Mean time to achieve CR or PR (SD; days)	131 (66)	155 (65)	150 (68)	123 (41)	133 (54.2)	141 (61)
Number (%) with proteinuria unchanged	10 (40)	10 (48)	10 (45)	8 (53)	7 (46)	45 (46)

	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Basal proteinuria (g/day)	2.74	0.4	2.8	2.4–3.1	7.96	2.1	8	4–10.3	7.2	3.2	6.05	4–8.6	6.05	1.9	6	4–7	4.9	1.34	4.5	4–5.3	5.6	3.23	5.5	3.5–8
Proteinuria at 3 months	1.97	1.37	1.7	1.3–2.4	4.73	2.11	4	3–6	5.9	2.45	5.22	3.8–4.7	5.4	1.0	4.9	3.1–4.3	3.99	0.57	3.9	3.1–4.2	3.4	1.8	4.5	2.1–4.8
Proteinuria at 6 months	1.40	1.17	1.27	0.4–1.8	3.95	1.5	3.9	2.3–5.6	3.49*	0.88	3.3	1.3–4.6	3.8	0.8	3.9	2.1–4.2	3.74*	0.66	3.6	2.1–3.9	3.35	1.3	3.1	1.7–4.1
Proteinuria at 12 months	1.25**	0.93	0.9	0.7–2.6	3.09*	1.47	3.33	2.1–6.5	3.02*	2.1	3.22	1.3–4.1	3.1*	1.3	3.8	1.6–4.1	3.34*	0.95	3.4	1.9–3.84	2.55**	1.06	2.7	1.3–3.6

*$P < 0.05$,**$P < 0.01$ when compared with basal value.

Table 4. Antihypertensive treatment during follow-up according to the response to MMF

	R $n=29$			NR $n=26$		
	Basal	6 m	12 m	Basal	6 m	12 m
ACEI or ARAIIRA monot	15 (51.7)	15 (51.7)	8 (62) +	14 (53.8)	9 (34.6)	8 (30.7)
ACEI or ARAIIRA + diur	10 (34.5)	10 (34.5)	11 (37.9)	9 (34.6)	12 (46.1)	12 (46.1)
3 or more drugs: ACEI or ARAIIRA + diur	4 (13.7)	4 (13.7)		3 (11.5)	5 (19.2)	6 (23.07)
+Calcium antg	2	2		1	3	2
+β-Bloc	1	1		1	1	2
+Calcium antg + β-bloc	1	1		1	1	2

R, responders; NR, non-responders; *n*, number of patients with high blood pressure in each group; ACEI or ARAIIRA, monotherapy with either angiotensin II converting enzyme inhibitors or angiotensin receptor antagonists; Diur, diuretics; Calcium antg, calcium antagonists; β-bloc, β blockers.
+proportion of patients controlled with ACEI or ARAII RA monotherapy at 12 months, significantly higher in responders $P=0.033$.

Table 5. Number and percentage of patients by urinary protein excretion category before and after treatment with MMF

Primary glomerular disease	Time of measurement	Urinary protein excretion (g/day)			
		<0.3	0.3–2.0	>2.0 to <3.5	>3.5
IgAN	Basal			21 (84)	4 (16)
	12 months	3 (12)	12 (48)	8 (32)	2 (8)
MN	Basal				21 (100)
	12 months		3 (14.2)	8 (38)	10 (47.6)
FSGS	Basal				22 (100)
	12 months	2 (9.1)	4 (18.1)	6 (27.2)	10 (45.4)
MPGN	Basal				15 (100)
	12 months		3 (20)	4 (26.6)	8 (53.3)
IgMN	Basal				15 (100)
	12 months	2 (13.3)	2 (13.3)	4 (26.6)	7 (46.6)

documented (1, 34 relapses/pac). Forty-one out of these patients suffered 1 relapse, 20 patients relapsed twice and 10 patients experienced three relapses. Most relapses [61/71 (85, 9%)] were observed after the MMF was reduced <1000 mg/day. Ten episodes were recorded after temporary MMF discontinuation.

Proteinuria was significantly reduced and sustained remission was achieved in all patients after restarting the treatment with MMF or increasing the dose to 1500 mg/day.

The median dose of MMF needed to sustain remission was 1.5 g/day (range 1.0–2.0 g/day). At the end of follow-up, MMF was withdrawn from all non-responders. Patients who achieved PR or CR continued on MMF treatment.

Adverse effects

The most frequent adverse effects were gastrointestinal symptoms (Table 7). All the diarrhoea episodes occurred during the first month of treatment; 91.6% of which were mild and improved after a temporary dose reduction. In eight (8.4%) patients, MMF was withdrawn because of persistent gastrointestinal symptoms after 4 weeks on the lower dose. We also discontinued the treatment in two other patients because of a perceived lack of efficacy after 3 and 4 months of therapy.

Two patients had an oral herpes simplex infection confirmed by culture and received acyclovir for 1 week. One patient with MPGN and nephrotic syndrome had thoracic herpes zoster, which resolved after acyclovir treatment. Two MN patients were admitted to hospital with bacterial pneumonia that resolved with antibiotics. Both were non-smokers with exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenza* or *Streptococcus pneumoniae*. Pneumonia episodes were not associated with leucopenia.

Adverse effects were not correlated with serum albumin levels ($P=0.12$), age ($P=0.34$), gender ($P=0.15$) or GFR ($P=0.09$). MPA trough levels were not significantly higher ($P=0.4$) in the 12 patients with either gastrointestinal or infectious complications than in the patients without side effects (median 2.45, range 1.8–6.0 μg/ml).

Discussion

This study differs from previous observational trials in two main points. First, this is an observational clinical trial analysing the efficacy and safety of MMF monotherapy in a large cohort of patients with resistant primary glomerulonephritis defined according to strict criteria. Secondly, our study is the only one in which patients are treated according to a standard protocol. On the whole, the treatment with MMF only induced complete remissions of proteinuria in a minority of patients. However, it improved urinary protein excretion in more than half of the patients whose disease could not be controlled by other immunosuppressant drugs and who showed persistent proteinuria, despite receiving ACEI or AIIRA and a low-salt diet. The reduction of urinary protein excretion was significantly higher in those patients with basal nephrotic proteinuria and preserved renal function; it did not arise from an increased dose

Table 6. Clinical and biochemical variables during the 12-month follow-up period

	Primary glomerular disease																			
	IgAN				MN				FSGS				MPGN				IgMN				All patients			
GFR (ml/min)																								
Basal	52.3 (11.6)				58.2 (10)				67.1 (6.3)				54.5 (12.7)				65 (7.39)				56 (12.6)			
3 months	51.6 (11.5)				57.76 (10.52)				65.2 (7.1)				52.3 (10.2)				64.9 (6.23)				55.3 (11.45)			
6 months	49.7 (13.3)				57.23 (11.02)				66.4 (9.03)				53.8 (12.7)				66.7 (5.14)				51.6 (13.17)			
12 months	49.2 (15.2)				56.19 (12)				63.1 (13.5)				52.3 (15.3)				67.1 (12.2)				49.08 (17.4)			
Slope GFR (ml/min/month)	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Pre-treatment	−0.82	0.35	−0.77	(−0.4) to (−1)	−0.69	0.48	−0.63	(−0.51) to (−0.91)	−0.92	0.4	−0.55	(−0.3) to (−0.9)	−0.48	0.13	−0.49	(−0.4) to (−0.6)	−0.3	0.3	−0.28	(−0.12) to (−0.66)	−0.74	0.35	−0.67	(−0.5) to (−1)
Post-treatment	−0.75	0.24	−0.43	(−0.1) to (−0.9)	−0.58	0.33	−0.59	(−0.40) to (−0.78)	−0.68	0.37	−0.40	(−0.31) to (−1.03)	−0.39	0.41	−0.45	(−0.3) to (−0.5)	−0.4	0.21	−0.38	(−0.1) to (−0.42)	−0.52	0.23	−0.6	(−0.1) to (−0.9)
Serum albumin (g/dl)																								
Basal	3.73 (0.6)				2.9 (0.6)				2.7 (0.4)				2.87 (0.49)				2.57 (0.38)				2.5 (0.7)			
12 months	3.98 (0.3)				4.07 (2.37)*				3.9 (0.97)**				3.78 (0.46)*				3.4 (0.60)*				3.8 (0.8)*			
LDL-C (mg/dl)																								
Basal	143 (50.7)				235 (66.3)				276 (65.3)				261 (68.5)				251 (74.6)				250 (63.27)			
12 months	128 (87.1)*				171 (70.45)*				194 (78.04)*				118 (40.2)**				124 (45.3)**				186.2 (76.4)*			
MBP (mm Hg)																								
Basal	90.8 (3.3)				91 (6)				87 (4.7)				94 (5.6)				89 (2.1)				88 (6.3)			
3 months	90 (2.9)				81.8 (5.4)				85 (2.3)				86.5 (4.3)				89 (4.7)				85.7 (5.0)			
6 months	88.3 (4.3)				81 (6.0)				81 (5.6)				83.5 (5.1)				87 (2.6)				82 (4.9)*			
12 months	81 (2.4)*				79.8 (7.1)*				79.5 (6)*				81.1 (6.5)*				87.6 (3.5)				82.3 (6.5)*			
Urinary Na excretion (mEq/24 h)																								
Basal	99 (43.2)				104 (50.1)				113.1 (68.5)				102 (32.6)				132 (78.3)				108.7 (49.4)			
6 months	101 (44.6)				97.6 (62.3)				106.5 (73.2)				116 (45.9)				121 (38.4)				106.8 (56.3)			
12 months	109 (66.7)				112 (38,76)				119 (54.1)				121.3 (55.2)				114.6 (47.3)				114.6 (47.8)			

*$P < 0.01$,**$P < 0.05$

Table 7. Adverse events observed in the study population during MMF treatment

Adverse event	*n*	%
Diarrhoea	25	25.5
Epigastralgia	7	7.1
Vomiting	6	6.1
Herpes simplex	2	2.04
Bacterial pneumonia	2	2.04
Herpes zoster	1	1.02
Otitis media	1	1.02

of ACEI or AIIRA, since among responders, mean blood pressure significantly decreased and the number of antihypertensive drugs could be reduced.

The relationship between MMF treatment and proteinuria reduction is further supported by the fact that, during the whole follow-up, attempts to reduce or discontinue the dose of MMF resulted, invariably, in one or more relapses of proteinuria, relapses which were responsive to MMF. Responders showed increases in serum albumin and decreases in serum LDL-cholesterol. The latter should, however, be interpreted with caution since most patients received concomitant statin therapy.

The efficacy of MMF was less marked in this trial than in previous observational case studies [12, 16, 19 and 21]. However, the present study used MMF as 'rescue' therapy i.e. all patients had been unsuccessfully treated with different immunosuppressants and more than half of them suffered from chronic renal failure.

The absence of significant changes in GFR may be due to the relatively short observation period, whereas the absence of a significant relationship between histopathological variables and the renal function could reflect the long-time lapse between the renal biopsy and study entry.

Besides anecdotal observations [6, 7, 12, 19], the efficacy of MMF in IgAN has previously been evaluated in four randomized studies with contradictory results. Chen *et al.* [9] compared MMF [1–1.5 g/day, $n = 62$) with steroid treatment ($n = 31$) as first-line therapy. MMF was superior to prednisone in decreasing proteinuria and protecting renal function. In contrast, Maes *et al.* [8] compared MMF (2.0 g/day, $n = 20$) with placebo ($n = 13$). No significant differences in proteinuria or renal function emerged after a 3-year follow-up. In the third study, Frisch *et al.* [10] found no benefit in high-risk patients who received MMF, and finally Tang *et al.* [11] found benefit of MMF *vs* conservative treatment. In our study, only the three patients with basal normal renal function achieved CR after MMF monotherapy, and patients with established renal failure showed no improvement in urinary protein excretion. This observation concurs with previous published data and suggests that MMF cannot modify the clinical course of IgAN, once renal fibrosis has developed.

MMF did not induce CR in patients with MN and was associated only to a mild reduction of proteinuria. The low rate of remission of nephrotic proteinuria in our patients is similar to that observed in previous studies [15, 16, 19 and 20] and suggests that MMF monotherapy is of limited efficacy to treat patients with resistant nephrotic membranous glomerulonephritis.

The efficacy of MMF in FSGS has been analysed in several studies, with differing results [12–14,16, 17–19,22]. Some studies recruited only patients with previous steroid and ciclosporin A resistance, whereas patients who were dependent, resistant or intolerant to ciclosporin were enrolled in other studies. Our series included patients with primary FSGS and proven resistance to steroids and ciclosporin A. MMF monotherapy induced CR in a minority of cases. In more than half of the patients, however, MMF reduced urinary protein excretion and improved the consequences of nephrotic proteinuria. These results are better than those described in the first case series of patients with resistant FSGS [13] and agree with response rates described in other studies [12–14,16,17–19,22]. They also show that certain patients with FSGS could benefit from MMF monotherapy.

Current guidelines for adults with nephrotic syndrome caused by primary MPGN recommend anti-platelet therapy [23], as it is resistant to all immunosuppressant drugs tested. However, our results indicate that MMF could improve nephrotic proteinuria in patients with MPGN, which agrees with recently published data [25].

Around 30% of the patients with nephrotic syndrome secondary to IgMN develop end-stage renal failure after 10 years. In these patients, proteinuria is often resistant to steroids and few studies have evaluated alternative immunosuppressants [26]. In spite of the fact that they are based on a small group, our results suggest that MMF could induce, at least a short-term improvement in the nephrotic syndrome in some patients.

Trough MPA levels varied widely and did not correlate with either efficacy or safety. These findings concur with previous data reported for transplant recipients [27–29]. They do not coincide, however, with recent studies in patients with autoimmune diseases that suggest measuring 12-h trough MPA to optimize individual immunosuppressive therapy [30]. In nephrotic patients, hypoalbuminaemia could, potentially, induce a significant increase in the percentage of free MPA for a given MMF dose. As a result, it has been suggested that the measurement of free MPA should replace the measurement of total plasma MPA [24]. Theoretically, higher free MPA concentrations caused by hypoalbuminaemia could be

associated with an increased incidence of toxicity in nephrotic patients. However, the incidence of adverse effects observed in our cohort was not higher than that reported in large studies of transplant recipients [31]. This proves that, at least within the dose range used in our patients MMF is safe even in the presence of hypoalbuminaemia. Nevertheless, monitoring free MPA may further increase the safety of MMF in patients with primary glomerulonephritis.

Given the alterations in MPA pharmacokinetics [32], dose reduction and close monitoring is recommended for patients with renal failure. Our decision to reduce the MMF dose to a maximum of 1.5 g/day for patients with GFR < 60 ml/min was arbitrary. The suitable dose of MMF for patients with renal failure should be accurately defined on the basis of pharmacokinetic studies.

In summary, our data does not allow us either to quantify definitively the efficacy of MMF in primary glomerulonephritis that is resistant to other conventional therapies or to establish solid treatment rules. They show, however, that, when MMF is prescribed as a 'rescue' treatment, it can cause a moderate reduction of proteinuria in more than half of the patients who do not have other treatment options. The response is significantly better in patients with nephrotic proteinuria and normal renal function, and requires sustained MMF treatment. In our experience, measuring 12 h-trough total MPA plasma level was not clinically helpful.

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