NEFROLOGÍA. Volumen 25. Número 4. 2005

Mycofenolate mofetil in high-risk IgA glomerulonephritis

M. A. Frutos, V. López, M. J. Alférez and P. Aranda
Servicio de Nefrología. Hospital Regional Universitario de Málaga.

SUMMARY

Mesangial IgA glomerulonephritis (MIgAGn) is the most common biopsied primary glomerulonephritis worldwide, with a poor long-term prognosis for renal function in over a third of all patients. No proven therapy currently exists for MIgAGn. Recent studies have suggested some benefit with mycophenolate mofetil (MMF), especially in hypertensive patients with kidney failure and proteinuria, though other studies have failed to corroborate these findings. We report eight adult patients with biopsy proven MIgAGn followed in a single hospital. They all received angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

Compassionate use of MMF was based on the presence of clinical and analytical data suggesting a high risk of short- to medium-term progression to chronic renal failure. MMF treatment was stopped after two and three months in two patients who had advanced renal failure at the start of therapy because of disease progression and greater fluid retention. Several months later they both required dialysis and kidney transplantation. The mean duration of MMF therapy in the other six patients was 15 (range: 10-18) months. The mean serum creatinine concentration fell from 1.82 ± 0.47 to 1.55 ± 0.41 mg/dl (p = 0.04). Protein loss in 24-hour urine collection fell from 1.95 ± 1.35 to 0.77 ± 0.58 g/day (p = 0.02).

These results in this low number of patients showed that treatment with MMF in high-riks patients with MIgAGn and early stage kidney failure generally stabilized the disease and reduced proteinuria. MMF was well tolerated and may be of some benefit in a subgroup of patients with MIgAGn and a poor prognosis.

Key words: ***Glomerulonephritis. Chronic Renal Failure. Proteinuria. Mycophenolate mofetil.***

MICOFENOLATO MOFERIL EN LA GLOMERULONEFRITIS IGA DE ALTO RIESGO

RESUMEN

La glomerulonefritis mesangial IgA (GMIgA) es la glomerulonefritis primitiva con mayor incidencia entre las actualmente biopsiadas y con un pronóstico sobre la

Correspondence: Dr. Miguel A. de Frutos Sanz
Servicio de Nefrología
Hospital Regional Universitario Carlos Haya
Avda. Carlos Haya, 82
29010 Málaga
E-mail: mangel.frutos.sspa@juntadeandalucia.es

función renal malo para algo más de un tercio de los pacientes. En la actualidad, no hay un tratamiento reconocido como de probada utilidad para la GMIgA. Estudios recientes han mostrado cierto beneficio en pacientes con GMIgA tratados con micofenolato mofetil (MMF) sobre todo en aquellos hipertensos con insuficiencia renal y proteinuria; sin embargo, otros autores no coinciden en su utilidad.

El presente estudio incluyó a ocho pacientes mayores de 18 años diagnosticados de GMIgA primitiva mediante biopsia renal y con amplio seguimiento en un único hospital. Todos recibían tratamiento con inhibidores de la enzima conversora de angiotensina I o bloqueantes receptores de angiotensina II. La decisión de administrar MMF como tratamiento compasivo se basó en la presencia de datos analíticos que sugerían la presencia de una forma potencialmente grave de GMIgA con elevado riesgo a corto-medio plazo de evolucionar a IRC.

Dos pacientes con insuficiencia renal avanzada al inicio del tratamiento con MMF lo recibieron tres y dos meses respectivamente y fue suspendido por ineficaz ante la progresión de la insuficiencia renal y mayores edemas. En los seis restantes, el tiempo medio de administración de MMF fue de 15 meses (10-18 meses). La concentración media de creatinina sérica (mg/dl) pasó de 1,82 ± 0,47 a 1,55 ± 0,41 (p = 0,04). Asimismo, se observó un descenso significativo de la pérdida de proteínas en orina de 24 horas (g/día) desde 1,95 ± 1,35 a 0,77 ± 0,58 (p = 0,02). Los resultados mostrados aquí permiten comentar que en algunas circunstancias el tratmiento con MMF a pacientes con GMIgA y estadios iniciales de insuficiencia renal, estabiliza la enfermedad y disminuye la proteinuria. Con la debida cautela al tratarse de un pequeño número de casos y de un estudio no controlado con placebo, se puede concluir que la administración de MMF a pacientes con GMIgA es bien tolerado y podría ser de utilidad en casos de GMIgA con alteraciones analíticas que presagiaran mal pronóstico.

Palabras clave: ***Glomerulonefritis IgA. IRC. Proteinuria. Micofenolato mofetil.***

INTRODUCTION

Mesangial IgA glomerulonephritis (MGIgA) is the most frequently biopsied primary glomerulonephritis in Spain. Of the whole renal biopsies collected in adults in the Spanish Glomerulonephritis Registry in 2003, 16.0% were MGIgA.[1] The onset and progression mechanisms of this disease have not been completely established and the IgA_1 deposition subtype at the mesangial level is the main evidence for renal disease.

The qualitative properties of polymeric IgA_1 have raised great interest among the pathogenic mechanisms of neuropathy, mainly focusing on the IgA_1 glycosilation pattern changes.[2] Besides, respiratory agents, gastrointestinal infections, and dietary antigens may initiate the onset of renal disease.[3] Currently, there is no useful proved curative treatment for MGIgA and the decision of choosing among several therapeutic options is not always based on scientific evidence.[4,5] A third of newly diagnosed MGIgA patients will have a poor prognosis and will develop renal failure two to three decades later.[6] In those cases that meet severity criteria, the decision to treat seems reasonable and it is necessary to keep away from the traditional nihilism that considers this condition as without treatment.

Some experiences[7-9] have shown some benefits in MGIgA patients treated with mycofenolate mofetil (MMF), especially in those with renal failure and proteinuria. However, other studies have not shown so convincing data.[10,11] The better current knowledge of MMF as a common treatment in multiple immunosuppressive regimens in transplanted patients and is good tolerability profile encourage its use in MGIgA cases with features that may foresee an accelerated course to renal failure.

The main goal of this study was to improve or stabilize renal function with regards to glomerular filtration and proteinuria.

PATIENTS AND METHODS

This was a prospective, open and non-controlled study, started on January of 2001. It includes 8 pa-

tients older than 18 years (5 M and 3 F), diagnosed with primary MGIgA by means of renal biopsy and with a prolonged follow-up at just one hospital. All patients previously received treatment with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonists (ARA-II).

Three patients have received previous immunosuppressive treatments: two with prednisone and cyclosporin, and one with prednisone and cyclophosphamide, with no overt results. The period between these immunosuppressive treatments and MMF administration was in all cases longer than 6 months. The decision to treating with MMF was based on the presence of analytical data that suggested a potentially severe form of MGIgA (renal failure with ClCr lower than 60 mL/min/1.73m^2 of body surface area, or the presence of proteinuria > 1 g/day in several consecutive samples), with a high risk for progressing to CRF in a short to intermediate term. MMF administration was done as a compassionate treatment according to the regulations in force and after signing the inform consent.

Seven patients presented arterial hypertension controlled with ACEIs (usually, lysinopril 10-40 mg/day) or ARA-II (usually, losartan 50-150 mg/day) during the whole time of MMF administration. In principle, MMF treatment ought to be maintained 12-18 months depending on the response and tolerability.

The primary outcomes of the study were progression of glomerular filtration and proteinuria. MMF was administered at a 1.5 g/day dose in patients weighing less than 65 kg and 2 g/day in those heavier. MMF blood levels were no quantified during the study. During the first 3 months, fortnightly leucocyte checks were done and patients were instructed to reduce or withdraw MMF in the presence of gastrointestinal side effects, fever, or potential infection. Every 3 months, a complete blood an 24-hour urine analysis was carried out, besides blood pressure measurement. Two patients with serious renal failure (grade 3) received MMF for 3 and 2 months each, having to be withdrawn because of renal failure progression and more extent edemas. These tow patients further required, 8 and 11 months later, respectively, hemodialysis treatment and renal transplantation. In the remaining six patients, treatment was well tolerated for periods varying from 10 to 18 months.

At the time of closing this study, two patients still receive MMF. The SPSS software was used for the statistical analysis of data. Values are expressed as means _ standard deviation (SD). According to data distribution, the Wilcoxon's test was used to compare paired data at the beginning and at the end of treatment.

RESULTS

The graphical progression of glomerular filtration, taken as the mean value from 24-hour urine collection and calculated by the Cockroft-Gault formula, is shown in Figure 1. Table I shows the details of the two patients that received MMF for less than 3 months. In these two patients, the decision to withdraw the treatment was based upon overt CRF progression with more extent edemas and greater proteinuria. Besides, one of them presented bouts of digestive intolerance.

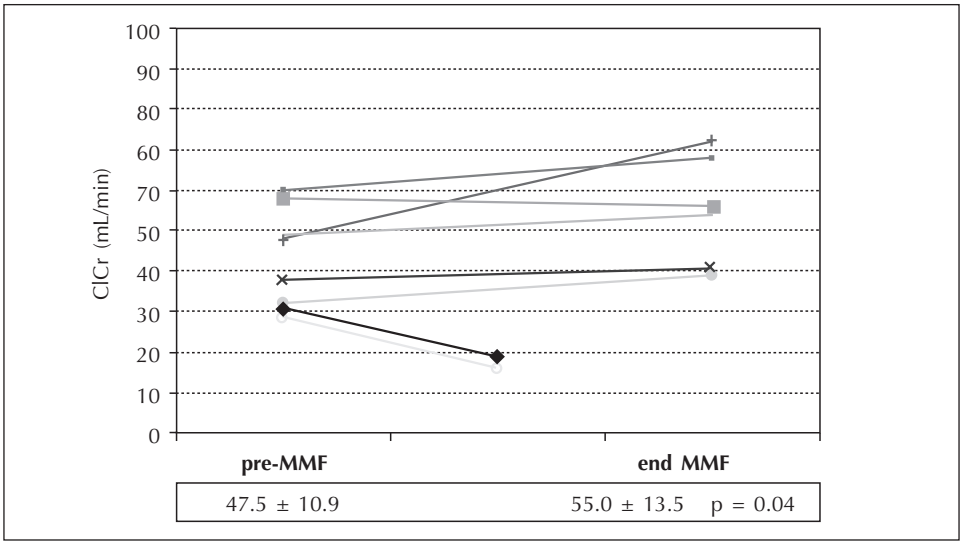

Fig. 1.—Creatinine clearance values (ClCr) expressed in mL/min at the begining and at the end of treatment with MMF.

Table I. Patients that did not complete MMF treatment

Patient	Age (years)	AHT	Disease duration (months)	Cr onset (mg/dL)	Cr end (mg/dL)	Proteinuria onset (g/day)	Proteinuria end (g/day)	Months of MMF treatment	Current state
#1	19	YES	90	2.8	3.6	2.0	2.8	3	RT
#2	52	YES	59	3.1	4.7	2.5	2.8	2	HD

The six remaining patients are pooled in table II. All received treatment without any detectable problem. No patient presented leucopoenia and just one had gastrointestinal discomfort with nausea and diarrhea that required postponement of medication for six days and restart at a 1.500 mg dose with good tolerance. In no case, there were infectious complications such as cytomegalovirus, herpes or bacterial.

Progression of serum creatinine and proteinuria is shown in Table II. Mean serum creatinine level (mg/dL) shifted from 1.82 ± 0.47 to 1.55 ± 0.41 ($p = 0.04$). Besides, a significant decrease in protein loss was observed in 24-hour urine (g/day), from 1.95 ± 1.35 to 0.77 ± 0.58 ($p = 0.02$).

There were no differences in other analyzed parameters at the beginning and at the end of the treatment period with MMF (immunoglobulins, complement fractions C3 and C4, hematocrit, hemoglobin, total leucocytes and platelets), except for serum albumin levels, which showed a significant increase, from 36.6 ± 1.2 to 39.5 ± 2.0 ($p = 0.04$).

Blood pressure was well controlled in all patients, and normotensive or hypertensive patients kept treatment with an ACEI or ARA-II drug for the whole period of MMF administration.

DISCUSSION

The results shown in the present study allow the interpretation that in some circumstances MMF treatment en patients with MGIgA and early stages of renal failure the disease stabilizes and proteinuria decreases.

Similar results had been reported in small series and with varying designs[8,9]. In most of them, MMF administration significantly reduced proteinuria at the same time that improved or stabilized glomerular filtration.

Based on the experience of the present work, two profiles are noticed depending on the degree of renal failure at the beginning of MMF treatment. Patients with stages 3 and 4 of renal failure are those in which treatment is useless, although in the present study they have not been able to maintain MMF treatment. In the two patients with advanced CRF, the latter progressed requiring dialysis. This progression is somewhat logical considering that most of the glomerular lesions will only regress if they are in initial stages with minimal or moderate fibrosis and with a low percentage of sclerosed glomeruli.

All patients but one were hypertensive and received antihypertensive treatment, which among others it included ACEI or ARA-II drugs. With one or several antihypertensive drugs, blood pressure values remained within normal ranges –low according to the most recent guidelines that seek not only proteinuria control but also a certain degree of renoprotection. Praga *et al.* observe a lesser worsening of renal function at 6-years follow-up in a group of MGIgA treated with enalapril[12]. Similar results have been reported by Nakao in a series of 131 patients with

Table II. Summary of features and results of patients treated with MMF

Patient	Age (years)	AHT	Disease duration (months)	Cr onset (mg/dL)	Cr end (mg/dL)	Proteinuria onset (g/day)	Proteinuria end (g/day)	Months of MMF (months)	Current state
#3	29	YES	72	1.4	1.4	2.1	0.5	18	END MMF
#4	31	YES	136	1.4	1.3	2.2	0.9	18	END MMF
#5	27	YES	59	2.3	2.2	2.4	1.6	16	END MMF
#6	59	YES	10	2.5	1.9	4.1	1.2	18	END MMF
#7	31	NO	10	1.7	1.1	0.4	0	10	MMF
#8	30	YES	120	1.6	1.4	0.6	0.4	12	MMF
Mean ± SD	34.5 ± 12.1		67.3 ± 52.3	1.82 ± 0.47	1.55 ± 0.41	1.95 ± 1.35	0.77 ± 0.58	15.3 ± 0.58	
p				0.04		0.02			

MGIgA treated with a combination of ACEI and ARA-II drugs,[13] so that the combination of these two drug types seems superior to the usefulness of each one of them separately.[14]

None of the patients of this series was submitted to tonsillectomy, a procedure recommended more enthusiastically by eastern groups.[15]

The recent work by Maes[11] on the usefulness of MMF in MGIgA is the most complete and well designed of all. His results after 3 years of consecutive treatment with MMF do not show significant effects on renal function or proteinuria. However, as the authors state, these results must be interpreted cautiously since patients were not previously treated with ACEI/ARA-II drugs, so that the study may be somewhat biased because the effects of MMF and ACEI/ARA-II, which are treatments that should never lack in any glomerulopathy with proteinuria,[16] could have coincided later. Besides, this study do not bring any conclusion on whether MMF administration at the initial stages of MGIgA may have favorable effects, as has been documented in experimental models.[17]

MMF treatment and the action of its active metabolite, mycofenolic acid, has allowed to show, in experimental models with acquired renal failure, that residual renal function was favorably affected in treated animals.[18] The mechanism of action in MGIgA is not clearly defined. Mycofenolic acid, MMF active metabolite, is able to block de novo synthesis of purines and monocytes and activated T and B lymphocytes proliferation. Besides, it has been proved that, at least in transplanted patients, it reduces adhesion molecules glycosilation and leucocytes migration to inflammation sites. Its immunosuppressive quality or reversible action by creating antibodies from activated B lymphocytes is a highly valued property of its mechanism of action. As relevant data that may have an application for its effect on MGIgA, we highlight that MMF administration has led to inhibition of proliferation and production of mesangial matrix induced by fetal calf serum or TGF-_.[19]

MGIgA recurrence following transplantation is a widely reported phenomenon.[20] Immunosuppressive regimens with MMF could slow progression of MGIgA recurrence[21] or even there have been reported cases of regression of IgA mesangial depositions in the donor kidney of transplanted patients treated with MMF.

The question of what type of MGIgA patients and at what time would MMF use be indicated is a difficult one to answer. The slow progression to CRF of patients with this diagnosis makes necessary multicenter studies that include a high number of patients in each cohort. For the time being, it is complicated to feel at early stages of MGIgA the cases with a poor prognosis before known factors such as severe AHT, proteinuria, decrease of GFR, or histological severity become evident.

Although tolerability to MMF has been good in this study, the risks that a prolonged immunosuppression may imply for these patients' future should not be concealed, and they should be taken into account at the time of the indication in order to be stated in the informed consent.

Measurement of serum MMF levels has not been considered useful for adjusting the dosing. Monitoring of immunosuppressive drugs in transplanted patients is an issue under revision, al least when transplantations have reached a stable state.[22] Choosing a 1500-2000 g/day dose was decided by previous studies and because it has been the one that has provided the best benefit and tolerability in renal transplantation.

Other treatments that have been shown useful in severe MGIgA include cortisone as a potent anti-inflammatory agent. The assessment of data shown bay Pozzi in MGIgA patients with proteinuria 1-3.5 g/day and serum creatinine lower than 1.5 mg/dL indicate some benefit at 5 years in renal function and proteinuria in the treated group.[23] In severe cases of patients with MGIgA and rapidly progressing renal failure, the combination of steroids and immunosuppressants such as cyclophosphamide has also shown a benefit.[24] Nevertheless, the adverse effects from high or prolonged steroid doses are risks to be taken into account.

Finally, favorable experiences of induction and maintenance regimens with MMF in lupus nephritis,[25,26] or in recurrences[27] as well as in other steroidal-dependent glomerulonephrites[28] and in experimental models of induced lupus nephritis[29] have been shown and the use of MMF is increasingly being introduced as an alternative therapy to consider both because of its favorable effects and its good tolerability profile.

As a conclusion, and with proper caution due to the low number of cases, MMF administration to patients with MGIgA is well tolerated and could be administered to patients with analytical changes that show a poor prognosis, while waiting for a larger experience with this regard.

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