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Efficacy and safety of combined cyclosporin A and mycophenolate mofetil therapy in patients with cyclosporin-resistant focal segmental glomerulosclerosis

A. Segarra Medrano[1], J. Vila Presas[1], L. Pou Clavé[2], J. Majó Masferrer[3], J. Camps Domenech[1]

[1] Nephrology Department. Vall d'Hebron Hospital. Barcelona, Spain
[2] Biochemistry Department. Vall d'Hebron Hospital. Barcelona, Spain
[3] Anatomical Pathology Department. Vall d'Hebron Hospital. Barcelona, Spain

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ABSTRACT

Introduction: The combination of cyclosporin A (CsA) and mycophenolate mofetil (MMF) has a synergistic immunosuppressive effect and, as a result, it may induce remission of nephrotic syndrome in patients with steroid- and CsA-resistant focal segmental glomerulosclerosis (FSGS). **Objective:** To analyse the efficacy and safety of the combined CsA and MMF treatment in patients with cyclosporin A-resistant FSGS. **Patients and methods:** Twenty-seven patients with CsA-resistant FSGS were treated for 12 months with CsA (4mg/kg/day) combined with MMF (2g/day). The overall follow-up lasted for 5 years. The proportion of patients with remission of proteinuria and the evolution of kidney function after 5 years were used to measure the outcome. **Results:** At the end of the treatment period, no patients were in complete remission and 4 patients (14.8%) had reduced proteinuria to values <3.5g/day. These patients had significantly lower baseline proteinuria (5.62±2.19 compared to 8.1±2.96g/day, P=.042), significantly lower GFR (-0.08 compared to -0.69±0.38; P=.003) and higher baseline kidney function (99.6±12.9 compared to 85.05±15.5ml/min; P=.003). Sixteen out of the 27 patients (59.2%) had progressive or stage 5 kidney disease at the end of the follow-up period. Adverse gastrointestinal effects were observed in 33.3% of the patients and acute transitory nephrotoxicity in 14.8%. The dosage and/or number of anti-hypertensive drugs had to be increased in 22.2% of patients during the 12 months of treatment. **Conclusions:** Twelve months of combined CsA and MMF therapy does not significantly alter the evolution of kidney function in patients with cyclosporin-resistant FSGS, although it may induce partial reductions in proteinuria.

Keywords: Cyclosporin A. Mycophenolate mofetil. Focal and segmental glomeruloesclerosis. Cyclosporine resistance.

Eficacia y seguridad del tratamiento combinado con ciclosporina A y micofenolato de mofetilo en enfermos con glomeruloesclerosis segmentaria y focal ciclosporina-resistente

RESUMEN

Introducción: *La asociación de ciclosporina A (CsA) y micofenolato mofetil (MMF) tiene un efecto inmunosupresor sinérgico y, en consecuencia, podría inducir una remisión del síndrome nefrótico en enfermos con glomeruloesclerosis segmentaria y focal resistente a esteroides y a CsA.* ***Objetivo:*** *Analizar la eficacia y el perfil de seguridad de la asociación CsA y MMF en enfermos con GSF resistente a ciclosporina A.* ***Pacientes y método:*** *27 enfermos con GSF resistente a CsA recibieron tratamiento con CsA (4 mg/kg/día) asociada a MMF (2 g/día) durante 12 meses. El seguimiento total fue de 5 años. Como medida de resultado, se consideró la proporción de enfermos con remisión de la proteinuria y la evolución de la función renal a los 5 años.* ***Resultados:*** *Al finalizar el período de tratamiento, ningún paciente presentó remisión completa; 4 pacientes (14,8%) presentaron reducción de proteinuria a valores <3,5 g/día. Estos enfermos presentaban proteinuria basal (5,62 ± 2,19 frente a 8,1 ±*

Correspondence: Alfonso Segarra Medrano
Servicio de Nefrología.
Hospital Vall d'Hebron.
Vall d'Hebron, 119-129. 08036 Barcelona. Spain.
alsegarr@gmail.com
alsegarr@vhebron.net

2,96 g/día; p = 0,042) y pendientes de FG (–0,08 ± 0,12 frente a –0,69 ± 0,38; p = 0,003) significativamente inferiores y mayor función renal basal (99,6 ± 12,9 frente a 85,05 ± 15,5 ml/min; p = 0,003). Dieciséis de los 27 enfermos (59,2%) presentaron una enfermedad renal progresiva o estadio V al final del período de seguimiento. Se apreciaron efectos adversos gastrointestinales en el 33,3% de los enfermos y nefrotoxicidad aguda transitoria en el 14,8%. El 22,2% de los enfermos precisó un incremento en la dosis y/o número de hipotensores durante los 12 meses de tratamiento. ***Conclusiones:*** *En enfermos con GSF resistente a ciclosporina, el tratamiento con asociación de CsA y MMF durante 12 meses, aunque puede inducir reducciones parciales de la proteinuria, no modifica significativamente el curso evolutivo de la función renal.*

Palabras clave: *Ciclosporina. Micofenolato de mofetil. Glomeruloesclerosis focal y segmentaria. Resistencia a ciclosporina.*

INTRODUCTION

Current available evidence shows that for patients with focal segmental glomerulosclerosis (FSGS) who have steroid-resistant nephrotic syndrome, treatment with cyclosporine A (CsA) can improve the long-term prognosis for renal function. However, despite initial reports that up to 75% of patients may have full or partial remission of proteinuria, more than 50% of steroid-resistant cases also develop resistance to treatment with cyclosporine and, in the long term, suffer progressive kidney disease. For these cases, apart from hypertension control and angiotensin II blockers, there is no treatment with proven efficacy that would modify the clinical course of the disease.[1-4]

In recent years, there have been various observational studies analysing the efficacy and safety of mycophenolate mofetil (MMF), in monotherapy and in combination with steroids, in the treatment of idiopathic FSGS, with conflicting response rates that are generally low.[5-13] Studies carried out in organ transplantation show that the combination of MMF and CsA has an additive or synergistic immunosuppressive effect.[14,15] This effect could be useful in treating patients with FSGS who show resistance to steroids and/or CsA. However, the efficacy of this combination in FSGS has only been described in a single observational study in steroid-resistant patients who also received other immunosuppressants.[16]

The aim of this pilot study was to analyse the potential efficacy and safety of CsA and MMF therapy in a group of patients with primary CsA-resistant FSGS.

PATIENTS AND METHODS

Design

Observational study with prospective follow-up.

Patients

Between 1996 and 2004, 27 patients who met the following criteria were included in the study:

1. Histological diagnosis of FSGS (all biopsies were analysed by the same pathologists).
2. Exclusion of secondary aetiologies including: renal mass reduction, morbid obesity, HIV-related nephropathy, heroin or cocaine use, analgesic treatment, vesicoureteral reflux and obstructive sleep apnoea.
3. Previous resistance to a treatment cycle of six months with steroids and a treatment cycle of six months with CsA, defined as persistent proteinuria >3.5g/day.
4. Glomerular filtration rate >60ml/min/1.73m^2.
5. No other therapy with immunosuppressive or non-steroidal anti-inflammatory drugs in the six months prior to inclusion.
6. No family history of chronic kidney disease or renal replacement therapy.
7. Absence of contraindications for treatment with MMF.
8. Provided written informed consent.

Studies prior to inclusion

After verifying resistance to steroids and CsA, all patients were followed for at least six months before being included in the study. During this period, they were only prescribed a low-sodium diet (5g/day) and treatment with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB). The dosage of these drugs was adjusted to achieve blood pressure readings under 140/80. If necessary, amlodipine and/or furosemide treatment was included. None of the patients were treated with combined ACEi/ARB or with aldosterone antagonists. In case of hypercholesterolaemia, statins were prescribed to achieve LDL cholesterol levels under 120 mg/dl.

Treatment protocol

After inclusion in the study and throughout the follow-up, ACEi and ARB doses were kept constant. All patients received treatment with CsA at an initial dose of 4mg/kg/day, which was later adjusted to maintain trough levels between 150 and 200ng/ml (12h post-dose in total blood). The MMF dose was 2000mg/day in all cases.

After 12 months of treatment, patients with persistent proteinuria >3.5g/day were considered resistant. The study proceeded with the withdrawal of both drugs. If there was evidence of full or partial remission of proteinuria, the treatment could be continued for another 12 months. At the end of this period, the dose was reduced by 25% each month until full withdrawal had been achieved.

Anatomopathological analysis of renal biopsies

All biopsies were stained with haematoxylin-eosin, PAS and Masson's trichrome for morphological analysis. Immunofluorescence studies were performed with antibodies against IgA, IgG, IgM, C3, fibrinogen and light chains. In each biopsy, the percentage of glomeruli with total or segmental sclerosis was calculated. The extent of interstitial fibrosis was measured using quantitative morphometry, in 5μm sections stained with Masson's trichrome, using an Olympus WCUE-2 autoanalyser.

Operational definitions

Proteinuria was considered to be in the nephrotic range for readings >3.5g/day. Nephrotic syndrome was defined as proteinuria >3.5g/day combined with hypoalbuminaemia <3.5g/dl. Complete remission: proteinuria <0.3g/day in two consecutive tests. Partial remission: proteinuria <3.5g/day and >0.3g/day. Arterial hypertension: Systolic blood pressure (SBP) >140mm Hg or diastolic blood pressure (DBP) >90mm Hg. Chronic renal failure: GFR<60ml/min calculated by endogenous creatinine clearance. Chronic renal failure (Stage 5): GFR<15ml/min. Acute cyclosporine renal toxicity: >30% increase in serum creatinine reversible after 25% reduction in CsA dose.

Clinical follow-up and monitoring

After inclusion in the study, patients were monitored on an outpatient basis each month for the first six months, every two months until the end of the first year and every four months during the remaining follow-up period until 60 months had been completed or renal replacement therapy was initiated. At each follow-up visit, SBP and DBP were measured. A general biochemical examination was performed that included serum creatinine, liver function, electrolytes, endogenous creatinine clearance, glycaemia, CsA level and 24-hour proteinuria. Glomerular filtration was calculated using endogenous creatinine clearance. Urinary protein excretion was quantified in 24-hour urine samples.

If there was evidence of a greater than 30% increase in creatinine, the CsA dose was reduced by 25% and another renal function check was performed seven days later. For those cases where gastrointestinal symptoms appeared after initiating MMF therapy, the total dose was reduced by 50% for one week. The dose was subsequently increased progressively until the maximum tolerated dose was reached. MMF therapy was suspended for cases of persistent gastrointestinal symptoms, onset of leukopaenia or fever.

Outcome variables

The primary outcome variable was the number of patients with total or partial remission of proteinuria after 12 months of treatment. The secondary variables were the number of patients with proteinuria reduced to non-nephrotic levels, the presence of progressive kidney disease or the need for renal replacement therapy during follow-up and the identification of independent predictors of the evolution of the glomerular filtration slope.

Statistical analysis

The results are expressed as the mean±1 SD. Changes in urinary protein excretion and GFR throughout treatment were analysed using an analysis of variance for repeated measures after a logarithmic transformation of both variables. The GFR slope was used as a criterion for loss of renal function. It was estimated by including at least 10 GFR measurements, and a linear progression model was assumed. A simple linear regression analysis was performed using the logarithm of the glomerular filtration slope up to the end of follow-up or the start of the renal replacement therapy as the dependent variable. To analyse independent predictors of the glomerular filtration evolution, with the variables that had a significant association in the univariate analysis, a stepwise multiple regression model was created. All values with $P<.05$ were considered significant.

The study met the provisions set forth in the Declaration of Helsinki and was approved by the hospital ethics committee. The treatment was authorised by the Spanish ministry of health with the provision for compassionate use in all patients.

RESULTS

Baseline characteristics

Clinical and biochemical variables

Table 1 shows the main characteristics of the sample of 27 patients studied.

Table 1. Baseline clinical, biochemical and histological characteristics

	No.=27
	Mean (SD)
Age	45.8 ± 9.9
Sex (% men)	63
Time	32.9 ± 8.5
GFR	87.6 ± 16.5
GF slope	–0.63 ± 0.9
Albumin	2.4 ± 1.1
Proteinuria	7.7 ± 3.9
SBP	120.8 ± 4.6
DBP	70.9 ± 9.6
Total no. glomeruli per biopsy	14 ± 6
Interstitial fibrosis (%)	28.4 ± 19.2
Overall glomerular sclerosis (%)	16 ± 9.5
Segmental glomerular sclerosis (%)	45 ± 12
Immunofluorescence	
- IgM	16 (49)
- C3	4 (15)
- IgM + C3	4 (15)
- Negative	3 (7.5)

Time since renal biopsy (months); GFR: glomerular filtration rate (ml/mn/1.73m^2); GF slope: prior to inclusion in (ml/min/month); albumin (g/dl); proteinuria (g/24h); SBP: systolic blood pressure (mm Hg); DBP: diastolic blood pressure (mm Hg).

Anatomopathological data

According to the morphological pattern, all patients had predominantly peripheral FSGS lesions (classic form, NOS). None of the patients had collapsing glomerulonephritis. Immunofluorescence showed focal IgM deposits in 16 patients, C3 in four cases, IgM and C3 in four, and a lack of deposits in three patients. A significant correlation was observed between GFR and the number of glomeruli with total sclerosis (r=0.48; *P*<.01) and the extent of interstitial fibrotic lesions (r=0.52; *P*<.01).

Response to treatment

After the treatment period was over, none of the patients had full remission. There were no significant changes in proteinuria in 23 patients. Four patients (14.8%) had a decrease in proteinuria to below 3.5g/day (partial remission). These four patients had baseline proteinuria (5.62±2.19 versus 8.1±2.96g/day; *P*=.042) and significantly lower GFR slopes prior to inclusion in the study (–0.08±0.12 versus –0.69±0.38; *P*=.003) and greater baseline renal function (99.6±12.9 versus 85.05±15.5ml/min/1.73 m^2; *P*=.003) than patients without changes in urinary protein excretion. Treatment with CsA and MMF in these four patients was maintained for an average of 17.6 months (maximum: 24 months, minimum: 17 months). After drug withdrawal, proteinuria was kept at levels lower than 3.5g/day in three patients throughout the follow-up. In the fourth patient, it increased to levels of 5.5g/day, but a new pattern of immunosuppressive treatment was not indicated.

During the five years of follow-up, patient GFR suffered a significant decline (mean absolute decline: –32.5±13.77ml/min/1.73 m^2; *P*=.0001; average slope: –0.54±0.19ml/min/month; *P*=.001). Sixteen out of the 27 patients (59.2%) met the criteria for progressive renal failure or stage 5 CKD at the end of follow-up. Regarding patients with no evidence of significant loss of renal function, these 16 patients had significantly lower baseline levels of GFR (70.3±7.39 versus 97±10.3ml/min/1.73 m^2; *P*=.001), greater baseline proteinuria (10.56±3.2 versus 6.1±2.42g/day; *P*=.006), evidence of a faster drop in renal function during the follow-up prior to inclusion in the study (–1.3±0.8 versus –0.19±0.41ml/min/month; *P*=.002) and greater proteinuria during the follow-up after treatment with CsA and MMF (7.2±3.1 versus 4.1±1.93g/day; *P*=.033). The slope of glomerular filtration loss in the four patients with partial remission was significantly lower than in the patients who did not respond (–0.073±0.19 versus –0.71±0.29; *P*=.002). However, none of the four patients showed a significant difference between the slopes prior to and after the treatment period. In the entire sample, there were no significant differences between the slope of GFR loss prior to inclusion and that observed during the five years of follow-up after treatment with CsA and MMF (–0.63±0.9ml/min/month versus –0.54±0.19ml/min/month; *P*=NS). The only variables associated with the glomerular filtration slope throughout the follow-up period in the multivariate analysis were initial glomerular filtration (*P*=.041) and mean proteinuria during the follow-up (*P*=.037).

Side effects

All patients completed the 12-month treatment period. Gastrointestinal side effects appeared in 33.3% of the patients. In all cases, the symptoms were mild and disappeared when the MMF dose was reduced. In none of the cases was it necessary to withdraw treatment. Transient acute renal toxicity was observed in 14.8% of the patients. Three patients (11.1%) had gingival hyperplasia. Some 22.2% of the patients required an increase in the dose and/or number of anti-hypertensive drugs during the 12 months of treatment with CsA and MMF (Table 3 shows the anti-hypertensive treatment used throughout the follow-up period). None of the patients had episodes of fever or leukopaenia.

DISCUSSION

This study was established with the aim of analysing the potential efficacy and safety of the CsA and MMF treatment in patients with steroid- and CsA-resistant FSGS. When it was designed, the clinical usefulness of CsA in the treatment of FSGS had been adequately shown in randomised clinical trials,[1-3] but there was no data on the potential efficacy of MMF. The decision to combine both drugs was based exclusively on the possible additive immunosuppressive effect described in organ transplantation.[14,15]

The observed results indicate that for patients with resistance to glucocorticoids and CsA, treatment with CsA and MMF for 12 months does not induce total remission of proteinuria. Throughout the follow-up period, however, a moderate but significant reduction in proteinuria was observed in four patients. Considering the relationship observed between mean proteinuria and the glomerular filtration slope during the follow-up, treatment with CsA and MMF would be expected to have a beneficial effect in the preservation of renal function in patients who had a greater reduction in proteinuria. However, none of the four cases showed significant differences between the pre- and post-treatment slopes of glomerular filtration loss. The improved evolution of this small subgroup of patients is associated with the course of the disease prior to inclusion in the study, but not with the effect of the treatment. A reasonable explanation for this would be that since patients with greater reductions in baseline proteinuria also showed significantly lower levels of proteinuria, better renal function and lower slope of glomerular filtration loss, they may have suffered from a histologically indistinguishable form of FSGS with slower more benign evolution. Both the percentage and the type of response observed in our patients was lower than those reported in the only study published to date that examines the effect of combining MMF with calcineurin inhibitors in patients with FSGS.[16] This is probably because that study included patients with resistance to glucocorticoids, while our study included patients with resistance to glucocorticoids and CsA. Moreover, the data observed in our cohort of patients in terms of proteinuria reduction are at the lower limit of the interval described in observational studies that analyse the potential efficacy of MMF in FSGS adults (in monotherapy or combined with steroids).[5-13] Overall, the available information does not suggest that the combination of CsA and MMF has a relevant role in inducing remission in patients with multiple resistance.

Table 2. Evolution of proteinuria and renal function throughout follow-up

Baseline GFR	88.6 ± 16.5
GFR 12 months	87 ± 14
GFR 60 months	56.4 ± 13.9[c]
Baseline proteinuria	7.74 ± 3.9
Proteinuria 12 months	6.03 ± 4.1
Proteinuria 60 months	4.26 ± 2.02[b]
Baseline albumin	2.4 ± 0.8
Albumin 12 months	2.5 ± 0.7
Albumin 60 months	3.6 ± 0.46[a]
Baseline SBP	120.8 ± 4.6
SBP 12 months	128 ± 5.2
SBP 60 months	129.7 ± 7.3
Baseline DBP	70.9 ± 9.6
DBP 12 months	74.3 ± 7.32
DBP 60 months	71.56 ± 7.04
Baseline UNa	134 ± 79
UNa 12 months	176 ± 101
UNa 60 months	128 ± 93
Renal function at 60 months (%)	
- Non-RRT progressive kidney failure RRT	10 (37)
- RRT	6 (22.2)
- Total patients with CRF progression	16 (59.2)

GFR glomerular filtration (ml/min/1.73m^2); albumin: serum albumin (g/dl); proteinuria: g/24H; SBP: systolic blood pressure (mm Hg); diastolic blood pressure (mm Hg); UNa: urine sodium excretion (mEq/24h); RRT: renal replacement therapy.
[a]P<.05; [b]P < .01; [c]P<.0001.

Although this is not a controlled study, the likelihood of progression to chronic renal failure and renal replacement therapy observed in the whole sample of patients after five years of follow-up does not differ from that described in most series of symptomatically treated patients with resistance to CsA.[3,4,17-19] This would also be an argument against a possible beneficial effect of the combination of CsA and MMF for long-term preservation of renal function.

All patients included had proteinuria in the nephrotic range and hypoalbuminaemia and were carefully studied to rule out secondary aetiologies. However, we are not able to definitively reject that some of them present with forms of FSGS that can not be modified using immunosuppressive treatment. In this regard, it should be noted that a genetic study was not performed in any of the cases, and therefore it is possible that some of the patients who were classified as having idiopathic forms actually suffered sporadic mutations of the podocyte proteins. This limitation is common to all studies performed to date that analyse the effectiveness of various immunosuppressants in FSGS patients. However, given the low reported prevalence of these types of mutations in FSGS adults with no family history of the disease, it is unlikely that this is the main reason for the observed lack of response to immunosuppressive treatment.

The treatment was well tolerated but was not without side effects. The most significant was the high incidence of gastrointestinal symptoms, which were mild and did not require withdrawal of either of the two drugs.

In conclusion, the data from this pilot study show that for CsA-resistant FSGS patients, treatment combination of CsA and MMF for 12 months does not significantly modify the evolution of renal function, although it may induce partial reductions in proteinuria in some patients.

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