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The Mycophenolate Mofetil Therapy in Corticoresistent Idiopathic Focal Segmental Glomerulosclerosis

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Abstract

The Focal Segmental Glomerulosclerosis (FSGS) is one of the most frequent glomerular nephropathies affecting both children and adults. The aim of this study is the evaluation of the effects of Mycophenolate Mofetil (MMF) in Nephrotic Syndrome (NS) with biopsy proven Focal Segmental Glomerulosclerosis (FSGS) resistant to other therapies. We treated 20 patients, of which 12 males, with a median age of 39 years (ranging between 18 and 62 years), with Nephrotic Syndrome, all being resistant to or relapsing on steroid and immunosuppressive therapy. They were treated with MMF (1-2 g/day) and Methylprednisolone 0.5 mg/kg at alternate days for an average period of ten months (ranging between 3 and 13 months). Two patients discontinued treatment after three and five months respectively, for gastric intolerance. Another patient discontinued MMF after six months due to deterioration of kidney function. No significant differences were observed between pretreatment values and at the end of the treatment for plasma creatinine, Glomerular Filtration Rate (GFR), while the excretion rate of urinary proteins was significantly reduced from 7.68 ± 3.54 to 3.20 ± 2.92 g/day, ($p<0.001$). After MMF we observed a complete remission in two patients (10%), an incomplete remission in three patients (15%), a partial remission in six patients (30%), no response in eight patients (40%) and a worsening of kidney function in one patient (5%). It was concluded that in resistant Nephrotic Syndrome by FSGS, MMF can favor stable remission, preserving renal function and hence being considered as an alternative therapy to calcineurin inhibitors, but with lower toxicity.

Keywords: Glomerulosclerosis, Idiopathic Focal Segment, Hypoalbuminuria.

Abbreviations: FSGS-Focal Segmental Glomerulosclerosis, MMF-Mycophenolate Mofetil, NS-Nephrotic Syndrome, GFR-Glomerular Filtration Rate, CR-Complete Remission, IR-Incomplete Remission, PR-Partial Remission.

Introduction

The Focal Segmental Glomerulosclerosis (FSGS) is one of the most frequent glomerular nephropathies affecting both children and adults. It may be idiopathic or secondary to such causes known as the reduced nephron mass, obesity, viral infection or drugs and toxins. The morphological/histological pattern recognized on kidney biopsy is characterized by sclerotic (fibrotic) lesions in glomeruli that are focal (less than 50% of all glomeruli affected on light microscopy) and segmental (less than 50% of the glomerular tuft affected). This pathological pattern has been further classified by the Columbia group according to specific pathological light microscopic findings (tip lesion, cellular, collapsing, perihilar and not otherwise specified). Podocyte injury is the earliest morphological feature of FSGS, which has led to the current paradigm that classic FSGS is primarily a podocyte disorder, at least initially. The causes of podocyte damage can either be genetic or related to circulating permeability factors. The prognosis of FSGS is predicted by the severity and persistence of proteinuria, with 60% of patients with persistent nephrotic-range proteinuria progressing to end-stage renal disease within 5-10 years. Achievement of a remission, whether complete or partial, is associated with a good outcome [1-6].

At present, corticosteroids are the standard first-line approach in patients with idiopathic FSGS. Cytotoxic agents and cyclosporin A constitute a good therapeutic option for steroid-dependent patients or frequent relapsers. During the last years, the use of Mycophenolate Mofetil (MMF) has been proposed in the Nephrotic Syndrome by FSGS together with steroids with varying results, but with the advantage of a lower toxicity compared with other immunosuppressants. The aim of this work is to report our experience with the therapy of MMF in a group of idiopathic FSGS with Nephrotic Syndrome who have been previously treated with steroids and immunosuppressive and who had not responded to treatment showing a resistant or relapsing nephrotic syndrome [7-10].

Patients and Methods

There were examined twenty patients with a histological diagnosis of Focal and Segmental Glomerulosclerosis having a resistant or relapsing nephrotic syndrome. The nephrotic syndrome was defined by a proteinuria>3 g/day, hypoalbuminuria<3g/dl and oedema. The median age was 39 years ranging between 18 and 62 years old, in which 12

were males? All patients had a nephrotic syndrome at onset and were treated with various therapies and through different periods and dosages: six patients with steroids alone (two with bolus of 500 mg x 3 days and then steroids per os, four with steroids per os), eight patients with steroids + cyclophosphamide, five patients with steroids + cyclosporine and one patient steroids + azathioprine. All patients were examined on an outpatient basis generally every 3 months with a clinical examination and control of the main tests (plasma creatinine, 24-h urinary protein excretion rate, hemochrome, plasma glucose, serum total protein, cholesterol and transaminase). The Glomerular Filtrate (GFR) was calculated using the CKD-EPI formula.

In addition, all patients were recommended to follow a low-salt diet and used other medications such as antihypertensives, statins, calcium supplements and vitamin D3. All patients (after the prolonged therapeutic regimes previously reported), which still presented the clinical and laboratory picture of nephrotic syndrome where put on a regime with Mycophenolate (Cell Cept) 1 g/day for a month and then, if well tolerated, the dose was increased to 2 g/day with a first step at 6 months. If the Nephrotic Syndrome was in complete remission MMF was suspended. Otherwise, it was continued for up to 12 months with follow-up of the patients. In two cases with a creatinine level greater than 2 mg/dl and a glomerular filtrate less than 50 ml/min it was used a dose of Mycophenolate of 1g/day.

In all patients, therapy with Methylprednisolone 0.5 mg/kg every other day, Ramipril, Calcium and vitamin D3 was used. The clinical response was definied as a Complete Remission (CR) if the rate of urinary protein excretion was <0.3 g/day, an Incomplete Remission (IR) if the rate of urinary protein excretion was between 0.3 and 1 g/day, Partial Remission (PR) if the rate of urinary protein excretion was between 1 and 3 g/day, No Remission (NR) if the urinary protein excretion remained >3 g/day, worsening (W) if there was an increase in plasma creatinine of at least 50 % over the baseline value.

The results were expressed as means ± SD. Student's t test was used for statistical comparison of the means.

Statistical Analysis

The statistical analysis was performed with SPSS, (Statistical Package for Social Sciences Inc., Chicago, IL, USA), version 19.0. Results were expressed as mean ± SD. Data were compared between groups by t test.

Results

Patient data before and after treatment with MMF and duration of therapy are presented in **table 1**. Before starting MMF, the median plasma cretonne was 1.22 ± 0.44 mg/dl with an average Glomerular Filtrate Rate (GFR) of 78.1 ± 21.9 ml/min. In two patients the values of creatinine were higher than 2 mg/dl (2.1 and 2.2 mg/dl) and GFR was <50 ml/min (40 and 39 ml/min). The 24 hours urinary protein excretion was 7.68 ± 3.54 g/day and the serum total proteins was 5.03 ± 0.38 g/dl. Eight patients had hypertension treated with ACE-inhibitors or ARB. Two patients discontinued treatment after 3 and 5 months respectively, for gastric intolerance.

Another patient discontinued MMF after 6 months due to deteroration of kidney function (plasma creatinine was raised from 2.1 mg/dl to 8.1 mg/dl).No significant differences were observed between pretreatment values and end of treatment values for plasma creatinine (p=0.56), GFR (p=0.44) while the excretion rate of urinary proteins was significantly reduced from 7.68 ± 3.54 to 3.20 ± 2.92 g/day, (p<0.001). After MMF we observed a complete remission in two patients (10%), an incomplete remission in three patients (15%), a partial remission in six patients (30%), no response in eight patients (40%) and a worsening in one patient (5%).

Age	Before MMF			Duration MMF	After MMF			Clinical Results
years	Creat mg/dl	GFR ml/min	U prot g/day	months	Creat mg/dl	GFR ml/min	U prot g/day	
40	1,4	66	6,4	9	1,4	64	0,17	CR
51	1,3	78	6,7	12	1,8	68	5,8	NR
48	2,1	40	7,4	6	8,1	9.5	2,2	W
50	1,6	58	4,5	3	1,8	47	3,8	NR
62	0,8	88	7,3	5	0,8	86	5,2	NR
59	2,2	39	5,8	7	2,6	30	12	NR
26	1,3	81	6,4	11	1,2	83	0,9	IR
24	1,9	60	5,3	12	1,5	64	1,8	PR
20	1,1	94	6,1	10	1,0	96	0,8	IR
26	0,8	110	10,2	10	0,9	105	1,1	PR
33	1,5	69	10,5	12	1,2	75	1,8	PR
40	0,8	105	4,1	11	0,9	106	2,1	PR
18	0,7	120	6,6	12	1,1	84	6,0	NR
24	1,0	104	3,3	12	0,9	108	1,1	PR
60	1,1	54	4,8	12	1,2	50	2,1	PR
54	1.1	78	7.5	12	1	80	6	NR
37	0.8	82	14.4	12	0.9	78	0.2	CR
32	0.9	78	8.8	12	1	75	6.6	NR
48	1.2	74	18	12	1.1	74	0.8	IR
29	0.8	84	9.5	13	0.9	82	4.4	NR
39,05	1.22	78,1	7.68	10.2	1.56	76.7	3.2	Mean
14,14	0,44	21,9	3.54	2.8	1.52	26.1	2.9	± SD

Table 1: Clinical data of the patients before and after MMF therapy (CR-Complete Remission, IR-Incomplete Remission, PR-Partial Remission, NR-No Remission, W-Worse).

Discussion

The initial treatment of primary FSGS usually involves corticosteroids. In observational and uncontrolled trials, prolonged prednisone therapy (mean 9 months) in adults resulted in complete and partial remission rates in the 25-33% of patients. Improved outcome was suggested with long-term high-dose pulse corticosteroid therapy in conjunction with cytotoxic agents compared with historic controls. These studies suggest that long-term corticosteroid therapy may improve the partial and complete remission rate in patients with FSGS and resistance to a

standard short course of corticosteroids. Randomized clinical trials have shown the Cyclosporine (CSA) coupled with low-dose prednisone can increase the rate of partial and complete remission, but this therapy suffers the causing of high relapse rate following discontinuation of CSA and presents the risk of frequent side effects, including nephrotoxicity. If the authors agree to use steroids as initial treatment, there is a great variety in their dosages and duration and then in the choice of drugs for the treatment of resistant or recurrent forms [11-17]. In the last few years numerous authors have studied the effects of MMF on FSGS [7-10]. The MMF is an immunosuppressant which acts by inhibiting the purine synthesis by a selective, non-competitive and reversible inhibition of inosine monophosphate dehydrogenase which is the rate-limiting enzyme in the de novo biosynthesis of guanosine nucleotides. MMF strongly inhibits both T-and B lymphocyte proliferation.

Moreover, MMF is also capable of inhibiting the proliferation of non-immune cells as smooth muscle cells, renal tubular cells and mesangial cells and prevents the appearance of Heymann Nephritis. In the animal studies, MMF reduces the expression of nitric oxide synthase at the cortical level by decreasing glomerulosclerosis and glomerular crescent formation, increasing the expression of nephrine and podocin in diabetic rats, inhibits abnormal renal cell growth by regulating cell cycle or apoptosis related genes, ameliorates renal lesions in immune-mediated disease, but was also effective in non-immune-mediated renal damage in the rat remnant-kidney model [18-23]. Initially it has been used in the prevention of acute and chronic allograft rejection since the mid-1990s. MMF showed beneficial effects in the treatment of calcineurin inhibitor toxicity through reduction of immune - and non-immune-mediated renal damage.

Nevertheless, it is well tolerated and has proven to be a relatively safe drug causing only minor bone marrow suppression. In addition, there is a growing body of evidence pointing to therapeutic applications of MMF in the prevention of fibrosis. These observations prompted several investigators to study the effects of MMF in human renal diseases. It was noted that the MMF significantly reduced proteinuria in minimal-change disease, especially in the steroid-resistant nephrotic syndrome of children. In adults MMF has been used in various nephropathies: in the lupus nephritis, where favorable results have been reported to maintain remission of the disease, while in other nephropathies as the membranous nephropathy, the IgA nephropathy, the membranoproliferative glomerulonephritis, ANCA-associated vasculitis and FSGS, the results were very variable and even more controversial [24-38]. In this work, there were examined twenty adult patients with a biopsy-proven diagnosis of primitive Focal Segmental Glomelosclerosis who had a Nephrotic Syndrome being treated with various therapies whithout positive outcome.

Regardless of therapeutical regime applied, a clinical and laboratory picture of Nephrotic Syndrome was still present in all of them. Afterwards, therapy with MMF associated with Methylprednisolone was started and continued for 3-13 months (on average 10.2 ± 2.8 months). At the end of MMF therapy we observed a remission in eleven patients, two of which with complete remission and nine with incomplete or partial remission. In eight patients, the Nephrotic Syndrome remained unchanged, two of which suspended early therapy for side effects, while in one case the therapy was suspended due to the worsening of renal function. In total we have observed a remission in eleven patients (55%) and this can be considered a good outcome, considering that these patients did not respond to previous therapies. After treatment, the mean urinary protein excretion significantly decreased compared with baseline, while plasma creatinine and the glomerular filtrate did not show significant variations. In our view this is an important result, as remission either complete or partial, is the critical factor for predicting renal survival in nephrotic syndrome due to primary FSGS with 5-year renal survival of about 90% [7]. In addition, the results remain stable also at the end of follow up.

Furthermore, the MMF was generally well tolerated and only in 2 cases appeared to have gastric intolerance and no alteration of hepatic enzymes were observed. One patient had a deteroration of kidney function during the regime and started hemodialysis treatment. The results of this study, despite the relatively low number of patients, can have a clinical impact, considering the high remission rate and the good side effect profile observed with MMF regime in the treatment of Nephrotic Syndrome due to FSGS resistant to other drugs. These results confirm what was reported by other authors [39,40]. Hence, we may conclude that in the treatment of resistant Nephrotic Syndrome due to FSGS, MMF represents a therapeutic alternative with favorable effects and most importantly with reduced side effects, in comparison to Calcineurin inhibitors such as Cyclosporine, which however has a high renal toxicity [41,37]. Our contribution is limited by the lack of casistic and it is retrospective study, but the results are encouraging and we believe that it deserves to be taken into consideration and to be confirmed by further larger studies comparing the MMF with other drugs recommended by the literature.

Conclusion

Our results give an additional confirmation for the benefits of MMF regime in FSGS. Hence, we may conclude that in the treatment of resistant Nephrotic Syndrome due to FSGS, MMF represents a therapeutic alternative with favorable effects and most importantly with reduced side effects, in comparison to Calcineurin inhibitors such as Cyclosporine, which however has a high renal toxicity.

Ethical Approval

This study was in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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