IJKD KIDNEY DISEASES

Mycophenolate Mofetil for Treatment of Idiopathic Nephrotic Syndrome in Children

Azar Nickavar,[1] Amir Ebrahim Safarzadeh,[1] Kambiz Sotoudeh,[2] Hasan Otukesh,[1] Nakisa Hooman[1]

[1]Aliasghar Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2]School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Keywords. steroid-resistant idiopathic nephrotic syndrome, recurrence, mycophenolate mofetil, child

Introduction. Management of frequently relapsing steroid-responsive or steroid-resistant idiopathic nephrotic syndrome (NS) in children has been a clinical challenge for pediatric nephrologists. In addition, adverse effects of long-term corticosteroids and cyclosporine administration emerge seeking a safe and effective treatment. The purpose of this study was to evaluate the safety and efficacy of mycophenolate mofetil (MMF) in these patients.

Materials and Methods. This study reviewed the outcomes of children with frequently relapsing or steroid-resistant idiopathic NS who were treated with MMF.

Results. A total of 36 patients (23 boys and 13 girls) were included. Their mean age at the time of diagnosis of NS was 61.94 ± 43.9 months. Of the children, 91.6% of those who had frequent relapses and 8.3% of those with steroid-resistant NS responded to MMF significantly ($P < .001$), with no significant association between age and gender with response to MMF. The treatment was well tolerated with no significant complications.

Conclusions. In children with frequently relapsing NS, MMF was a safe and useful drug for maintaining remission, while it was of low value in children with steroid-resistant NS.

IJKD 2012;6:346-9
www.ijkd.org

Original Paper

INTRODUCTION

Idiopathic nephrotic syndrome (NS) constitutes 72% to 85% of all NS cases among children.[1] About 90% of children with the first episode of minimal change idiopathic NS achieve remission by corticosteroid treatment. About 70% to 80% of these children experience relapse and 30% develop frequent relapses and become steroid dependent.[2,3] Frequently relapsing steroid-responsive NS is a clinical dilemma with the risks of steroid toxicity and complications of NS such as infection, thrombosis, and acute kidney failure.[4,5] Efficacy of drugs such as levamisole or cyclophosphamide has been limited, and cyclosporine nephrotoxicity with the recurrence risk after its discontinuation indicates the need for alternative treatment.

Mycophenolate mofetil (MMF) has been suggested to be a useful adjunctive in the treatment of "difficult" NS.[5] Mycophenolate mofetil is the inhibitor of inosine monophosphate dehydrogenase, an enzyme required for purine synthesis pathway,[2] inhibits the proliferation of B and T lymphocytes, suppresses antibody formation, prevents glycosylation of adhesion molecules and intercellular adhesion to endothelial cells,[3,6] inhibits mesangial cell proliferation and nitric oxide synthase, and induces apoptosis of activated T cells.[7] Mycophenolate mofetil has been reported to be an effective drug for maintaining remission and preventing relapse in frequently relapsing NS (FRNS) with a moderate efficacy in steroid-resistant NS (SRNS).[2,8-10] It has been considered

as an alternative drug in cyclosporine-dependent and cyclosporine-resistant patients, as well as in those with cyclosporine nephrotoxicity, without renal, hemodynamic, metabolic, and cosmetic complications. It has been effective both alone or in combination with low-dose steroid treatment.[1,6,7,11]

In this study we evaluated the therapeutic effects of MMF in children with FRNS and idiopathic SRNS.

MATERIALS AND METHODS

This retrospective study was performed on the medical charts of children admitted to Aliasghar Children's Hospital, in Tehran, Iran. This study was performed on children admitted in Ali Asghar children's hospital, Tehran, Iran. The inclusion criteria were a diagnosis of frequently relapsing and steroid-resistant biopsy-proven idiopathic NS treated with MMF. The exclusion criteria were low complement level, leukopenia, anemia, and acute infection. Three types of idiopathic NS, including minimal change disease (MCD), diffuse mesangial proliferation (DMP), and focal segmental glomerulosclerosis (FSGS) were diagnosed through kidney biopsy. The FRNS was defined as 2 or more relapses within 6 months of initial response, and the SRNS was defined as persistent proteinuria after 4 to 8 weeks of daily steroids or 4 weeks of daily steroids followed by 3 alternate-day methylprednisolone pulse therapy. Remission was implied as nil to trace urine dipstick protein in 3 consecutive days and maintenance as persistent remission during the period of study by checking urine protein every 2 months.

Prednisone and alternative drugs such as levamisole, cyclophosphamide, and cyclosporine had been administered previously, with multiple relapses or resistance. Mycophenolate mofetil was started at the initial dose of 1200 mg/m^2/d, following corticosteroid remission in children with frequent relapses or combined to low-dose steroid in SRNS. The through level of MMF was not checked in responsive patients. Treatment outcome was defined as maintaining remission for at least 12 to 24 months.

Statistical analyses were performed by the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). The chi-square test, Fisher exact test, and independent *t* test were used to compare the two groups. A *P* value less than .05 was considered significant.

RESULTS

Of more than 800 patients with NS, 36 (23 boys and 13 girls) were treated with MMF. The mean age at the time of diagnosis of NS was 61.94 ± 43.9 months (range, 12 to 156 months). Eleven of these children (30.6%) had MCD, 13 (36.1%) had DMP, and 12 (33.3%) had FSGS. Twelve patients (33.3%) were categorized as steroid responsive with frequent relapses and the remaining 24 (66.7%) as steroid resistant (Table 1). Frequent relapses were more common in DMP.

Eleven of 12 patients (91.6%) in the FRNS group and 2 of 24 (8.3%) in the SRNS group responded to MMF ($P < .001$; Table 2). Mycophenolate mofetil was more effective in the treatment of DMP, followed by MCD and FSGS (Table 1). No significant association was found between the age and gender of patients with response to MMF (Table 2). Mycophenolate mofetil was well tolerated and there were no serious

Table 1. Characteristics of Patients by Kidney Pathologic Findings*

Characteristics	Pathologic Diagnosis		
	MCD	DMP	FSGS
Number of patients (%)	11 (30.6)	13 (36.1)	12 (33.3)
Gender (%)			
Male	9 (81.8)	7 (53.8)	7 (58.3)
Female	2 (18.2)	6 (46.2)	5 (41.7)
Mean age, mo	33.1 ± 31.1	54.0 ± 37.4	96.8 ± 38.7
Response to steroid (%)	4 (36.4)	7 (53.8)	1 (8.3)
Response to MMF (%)	4 (36.5)	7 (53.8)	2 (16.7)

*MCD indicates minimal change disease; DMP, diffuse mesangial proliferation; FSGS, focal segmental glomerulosclerosis; and MMF indicates mycophenolate mofetil.

Table 2. Characteristics of Patients by Response to Mycophenolate Mofetil*

Parameters	Response to MMF		*P*
	Yes	No	
Mean age, mo	60.9 ± 44.5	62.5 ± 44.6	.92
Gender (%)			
Male	9 (69.2)	14 (60.9)	
Female	4 (30.8)	9 (39.1)	.73
Pathology (%)			
Minimal change disease	4 (30.8)	7 (30.4)	
Diffuse mesangial proliferation	7 (53.8)	6 (26.1)	
Focal segmental glomerulosclerosis	2 (15.4)	10 (43.5)	.15
Response to steroid (%)			
Resistance	2 (15.4)	22 (95.7)	
Frequent relapses	11 (84.6)	1 (4.3)	< .001

*MMF indicates mycophenolate mofetil.

complications, such as leukopenia and infection. Gasterointestinal symptoms occurred in 1 patient, which were improved by dose reduction.

DISCUSSION

Depending on the immune dysregulation, various drugs such as corticosteroids, levamisole, cyclophosphamide, cyclosporine, and recently MMF, tacrolimus, and rituximab have been introduced for the treatment of idiopathic NS with different results.[1,9] Mycophenolate mofetil has been reported an effective treatment in maintaining remission and reducing relapse rate in NS, with steroid-sparing effect and minimal complication in some of the previous studies.[6,11,12] In addition, MMF was an effective drug for inducing and maintaining remission in children with FRNS in our study.

Barletta and colleagues reported a significant decline in the frequency and severity of relapse rate in cyclosporine-dependent patients on MMF. In addition, a slight increase in cyclosporine dose was required for the achievement of remission in these patients. Relapse rate decreased nonsignificantly in steroid-dependent patients, and 2 patients with SRNS had repeated relapses on MMF treatment.[5] In the study by Novak and coworkers, 21 patients with steroid-dependent NS were treated with MMF for about 1 year. Relapse declined in 40% of their patients (from 0.8 to 0.47 times per month). There was no significant adverse effect, except mild gastrointestinal symptoms.[3] Mycophenolate mofetil was suggested an effective adjunctive treatment in steroid-dependent NS with steroid-sparing effects.[3] In the study by Hogg and colleagues, relapse rate declined from 1 per 2 months to 1 per 14.7 months in patients with FRNS on MMF treatment for at least 6 months. Remission was stable in 75% of 32 patients during the treatment period and persisted in 12 patients for at least 6 months after its discontinuation. Therefore, MMF was considered an effective treatment for maintaining remission in FRNS.[10] Mendizabal and coworkers reported decreased relapse rate and steroid dosage in 21 patients with steroid-dependent NS; 47% experienced an immediate relapse after drug withdrawal. Only 1 patient with SRNS achieved complete remission. Similar to cyclosporine, MMF was considered a useful drug for maintaining remission in steroid-dependent N.[13] Afzal and colleagues reported the efficacy of MMF in 42 patients with steroid-dependent NS treated with levamisole and cyclophosphamide previously. Seventy-six percent of patients had 50% or more reduction in relapse rate and 21% remained in remission with no significant complication. The authors concluded that MMF was an effective drug in steroid-dependent NS, reduced steroid dose, and supported for longer than 12 months administration.[9] A switch from cyclosporine to MMF was performed for patients with steroid-dependent NS by Ulinski and coworkers.[7] They reported that MMF was an effective and safe drug for maintaining remission, improving kidney function, and reducing steroid dose. There was no significant change in the residual proteinuria in SRNS.[7]

In a randomized controlled trial to compare the efficacy of MMF and cyclosporine in treating frequent relapse MCD, 7 of 12 in the MMF group and 11 of 12 in cyclosporine group maintained in remission during the period of study, with a higher relapse rate in the MMF group. Probably because of a low sample size, MMF failed to prove superiority over cyclosporine, and cyclosporine was suggested a suitable drug in children with frequently relapsing MCD. However, MMF was well tolerated with mild adverse reactions and better effect on kidney function.[2] Relapse rate declined in patients with steroid-sensitive frequently relapsing MCD with sustained remission, even with cyclophosphamide failure.[4] In a study by Okada and colleagues on 11 patients with cyclosporine-refractory FRNS, MMF induced remission in 10 patients without a significant complication. Remission remained in 7 patients for 1 year. Complete remission occurred in 1 patient with cyclosporine-resistant SRNS. The authors suggested MMF administration in cyclosporine-resistant FRNS and SRNS.[14]

Mycophenolate mofetil had a beneficial effect of reducing proteinuria and steroid withdrawal in 7 patients with SRNS.[15] It was an effective drug for reducing proteinuria and treating SRNS in children less than 2 years, with mild and transient leukopenia and gasterointestinal symptoms.[8] In accordance with the most studies, MMF was a safe and well-tolerated drug for maintaining remission in Iranian children with FRNS, compared to those with SRNS. In addition, no significant complication occurred during MMF treatment, similar to the previous reports of rare MMF complications.

CONCLUSIONS

Mycophenolate mofetil had a significant potential for maintaining remission in children with FRNS compared to SRNS, with no significant adverse effects.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Azar Nickavar, MD
Division of Pediatric Nephrology, Aliasghar Children's Hospital, Tehran University of Medical Sciences, Tehran, Iran
E-mail: anickavar@yahoo.com

Received December 2011
Revised May 2012
Accepted May 2012