Research Article

J Ped. Nephrology 2018;6(1)
http://journals.sbmu.ac.ir/jpn

Mycophenolate Mofetil versus Cyclosporine in Children with Frequent Relapse Nephrotic Syndrome

How to Cite This Article: Rahman A, Muinuddin G, Rahman H, et al. Mycophenolate Mofetil versus Cyclosporine in Children with Frequent Relapse Nephrotic Syndrome. J Ped. Nephrology 2018;6(1).

Md. Azizur Rahman,*
Golam Muinuddin,
Md. Habibur Rahman,
Ranjit Ranjan Roy,
Afroza Begum,
Syed Saimul Huque,
Tahmina Jesmin

Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

*** Corresponding Author**
Dr. Md. Azizur Rahman, MBBS, MD
Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
Email: aziz44_rmc@yahoo.com
Tel: +8801711789689

Introduction: Children with frequently relapsing nephrotic syndrome (FRNS) usually develop adverse effects of prednisolone and attempts to induce long-term remission in such patients have varying degrees of success.
Materials and Methods: We conducted a randomized clinical trial in a tertiary care level hospital to compare the efficacy and safety of a 1-year treatment course with mycophenolate mofetil (MMF) and cyclosporine (CsA) in 60 pediatric patients with FR-SSNS. We assessed the relapse frequency as the primary end-point and evaluated the clinical and laboratory profile after 3 and 6 months of treatment.
Results: The mean number of relapses was 1.50 ± 1.44 in the MMF and 0.72 ± 1.30 in the CsA group at 6 months (p=0.045). Diarrhea was statistically significant in the MMF group. Hypertrichosis and hypertension were statistically significant in the CsA group. There was no significant difference in the Hb level, lipid profile, and eGFR between the two groups.
Conclusions: The results of the study showed MMF is inferior to CsA in preventing relapse in patients with FRNS. It is also less nephrotoxic.

Keywords: Cyclosporine; Frequently relapsing; Mycophenolate mofetil; Nephrotic syndrome; Child.

Received: Mar-2018
Revised: Mar-2018
Accepted: Mar-2018

Running Title: Mycophenolate Mofetil versus Cyclosporine in Nephrotic Syndrome

Introduction

The most common form of childhood idiopathic nephrotic syndrome is minimal change nephrotic syndrome [1]. The majority (92%) of these patients respond to corticosteroids. However, 70% of the children with nephrotic syndrome experience a relapsing course. Approximately 30% develop more than one relapse with or without steroid dependency [2].

Although corticosteroids are the mainstay of therapy in patients with minimal change disease, repeated use results in severe side effects. Therefore, other therapeutic options are needed to prevent steroid toxicity [3].

A short course of cyclophosphamide leads to prolonged remission (25-60%) of children with FRNS [3]. The patients who do not respond to cyclophosphamide can achieve prolonged remission with cyclosporine (CsA), but long-term use may have result in CsA nephrotoxicity [2]. Several uncontrolled studies suggest a positive effect of the new immunosuppressive drug mycophenolate mofetil (MMF) in FRNS [4]. Both MMF [5] and CsA [6] have some racial differences in the outcome. To the best of our knowledge, no randomized controlled study has been done in children in Bangladesh.

We performed a randomized clinical trial to compare the efficacy and safety of these two drugs.

Materials and Methods

We studied the efficacy and safety of MMF in patients with FR-SSNS in comparison with CsA in a prospective randomized trial in a tertiary center. The protocol was approved by the university institutional review board. Informed consent was obtained from parents. The study period was between December 2014 and December 2015.

Inclusion and exclusion criteria

Children (<18 years) with FRNS with or without steroid dependency were asked to participate in the study. Inclusion criteria were a glomerular filtration rate (GFR) >80 ml/min per 1.73 m^2. Patients with severe leucopenia (leucocyte count <4000/cumm), severe anemia (hemoglobin <7 g/dl), or active infections or malignancy, those using levamisole or cyclophosphamide, and subjects allergic to MMF or CsA were excluded from the study.

Patient Characteristics:

Sixty patients were included in the study. The patients were divided into two groups: Group A (MMF group) and Group B (cyclosporine group). Treatment allocation was done according to a simple randomization method, using lottery. Each group had 30 patients. Seven patients were excluded, six from group A (lost to follow up, n=6,) and one from group B (lost to follow up, n=1). The final analysis was done in 53 patients.

Study medication

Both drugs were administered after excluding infection (urine R/M/E and culture & sensitivity, complete blood count, HBsAg, Montoux test, and chest X-ray) with prednisolone therapy at a dose of 60mg/m^2/day.

Group A patients were treated with MMF 1200 mg/m^2 per day in two divided doses (maximum dose 1 g twice daily before meals) for 12 months. In the case of severe leucopenia, severe anemia, or diarrhea, the dose was decreased by 25%. If side effects persisted for 48 hours, the dose was then reduced by an additional 25% of the initial dose. Dose adjustment was not based on mycophenolate trough levels.

Group B patients were treated with CsA 3–5 mg/kg per day in two divided doses for 12 months. The trough level of cyclosporine was measured by microparticle enzyme immunoassay (MEIA) after clinical remission and at three months. The dose was adjusted aiming at trough levels of 50–150 µg/L to prevent nephrotoxicity. All patients in group B underwent renal biopsy before starting CsA to assess the baseline renal histology as there may be cyclosporine induced nephrotoxicity.

Prednisolone was administered in both groups at a dose of 60 mg/m^2/day up to reach protein free urine for 3 consecutive days, followed by 40 mg/m^2 every alternate day for 4 weeks. Then, the dose was gradually tapered by 5mg every two weeks and stopped within 6 months.

Relapse was detected through testing the bedside urine for albumin and confirmed by dipstick.

During treatment, relapse was treated by daily prednisolone at a dose of 60 mg/m^2/day up to protein free for 3 consecutive days, followed by 40 mg/m^2 every alternate day for 4 weeks. Then, the dose was gradually tapered by 5mg every two weeks and stopped within 6 months.

The duration of the study was 12 months.

Follow-up

The hospital outcome (time to urinary remission, any adverse effect of the therapy, i.e. infection, HTN, and GIT upset, and length of hospital stay) of the patients was recorded. The patients were followed up 3 monthly for two times at 3rd month & 6th month and in each follow up visit, the patients were evaluated by number of relapses, duration of remission and any adverse effect of therapy. To assess clinical adverse effects, blood pressure, height, and weight were recorded, and eGFR was calculated using the Schwartz formula. Complete blood count, serum creatinine, serum electrolytes, serum cholesterol, serum albumin, serum magnesium, and random blood sugar were used to detect hematological and biochemical adverse effect in each follow up visit.

eGFR was calculated using the Schwartz formula [eGFR(ml/min/1.73m^2) = k × height(cm) /serum creatinine (mg/dl)]), where k is 0.45 for 2-7 year-old children, 0.55 for 7-11 year-old boys and girls, and 0.7 for 12-16 year-old boys [7].

Statistical Analysis

Data are reported as mean±SD. Continuous and categorical variables were compared using the student's unpaired t-test and chi-square test, respectively. P-values less than 0.05 were considered significant. SPSS version 22 was applied for all analyses.

Results

The characteristics of the patient and pathologic findings are shown in Tables 1 and 2. Of 60 randomized patients with FRNS who were

enrolled in the study, seven were excluded due to loss to follow up (Figure. 1). The remaining 53 children were evaluated.

Table I. Characteristics of patients at the beginning of the study (n=53)

Characteristic	Group		p value
	Group A n (%)	Group B n (%)	
Patients (n)	24	29	
Age (year) [mean ± SD]	8.99 ± 4.10	7.69 ± 4.05	0.252
Male [n (%)]	15 (62.5)	15 (51.7)	0.431
Female [n (%)]	9 (37.5)	14 (48.3)	
Age of first onset (year) [mean ± SD]	5.09 ± 2.84	4.00 ± 2.59	0.153
Duration of disease (year) [mean ± SD]	4.05 ± 3.25	4.33 ± 3.21	0.777
Number of relapses (per year before study) **[mean ± SD]**	4.21 ± 0.67	3.94 ± 1.57	0.440
Steroid dependent [n (%)]	9 (37.5)	16 (55.2)	0.200
Alternative drug used 3 months before study*			
-Levamisole [n (%)]	7 (29.2)	8 (27.6)	0.899
-Cyclophosphamide [n (%)]	6 (25.0)	12 (41.4)	0.210

Unpaired t test was done to measure the level of significance
*Chi-square test was done to measure the level of significance in case of alternative drug used 3 months before study.

Table 2. Biopsy findings of group B patients (n=29)

Histology	Number of patients
Minimal change disease (MCD)	15
Mesangial proliferative glomerulonephritis (MesPGN)	12
Nonspecific findings	02

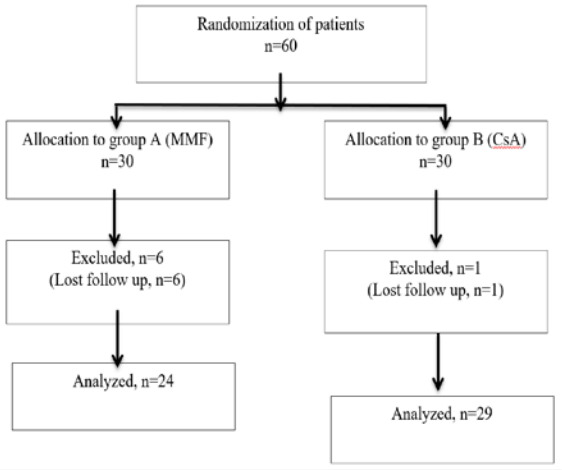

Figure 1. Flow chart of study comparing MMF and CsA

Efficacy:
Efficacy was determined by the time required for urinary remission, number of relapses during 6 months of treatment, and the mean steroid dose.
The Relapse rate was higher in the MMF group (1.50 ± 1.44) as compared to the CsA group (0.72 ± 1.30) (p= 0.045). The mean prednisolone dose during the study period was not significantly different between the two groups (Table 3).

Table 3. Efficacy of drugs according to number of relapses at 6 months

Relapse	Group		P value
	Group A n (%)	Group B n (%)	
0	8 (33.3)	20 (69.1)	
1	5 (20.8)	3 (10.3)	
2	6 (25.0)	3 (10.3)	
3	1 (4.2)	0 (0.0)	
4	4 (16.7)	3 (10.3)	
Total	**24 (100.0)**	**29 (100.0)**	
Mean ± SD	**1.50 ± 1.44**	**0.72 ± 1.30**	**0.045***

Unpaired t test was done to measure the level of significance.

Time to urinary remission was 12.20 ± 4.80 days in group A and 11.58 ± 5.77 days in group B (p= 0.676). The mean hospital-stay was17.83 ± 8.37 days in group A and 21.62 ± 11.43 days in group B (p= 0.183).

There was no significant difference in time to remission and hospital stay between the two groups (Table 4).

Table 4. Comparison of time to remission, hospital stay, and drug dose between two groups

	Group		p value
	Group A (Mean ± SD)	Group B (Mean ± SD)	
Time to urinary remission (days)	12.20 ± 4.80	11.58 ± 5.77	0.676
Hospital stay (days)	17.83 ± 8.37	21.62 ± 11.43	0.183
Prednisolone dose (mg/kg/day)	0.55 ± 0.27	0.53 ± 0.24	0.737
MMF Dose (mg/m^2/day)	777.33 ± 167.50		
Cyclosporine dose (mg/kg/day)		3.90 ± 0.63	

Unpaired t test was done to measure the level of significance

Adverse effect:

Clinical:

Diarrhea was seen in 4 patients at 3 months and at 6 months follow-up in group A while no patient in group B suffered from diarrhea. There was a significant difference in diarrhea between the two groups. GIT upset was seen in 2 patients at 3 months and in 1 patient at 6 months in group A but none of the patients in group B developed GIT upset. Hypertrichosis was seen in 5 patients at 3 months and 6 months follow-up in group A while it was seen in 16 patients at 3 months and in 18 patients at 6 months in group B. Gum hypertrophy was seen in 3 patients at 3 months and in 5 patients at 6 months in group B but none of the patients in group A had gum hypertrophy. Hypertension was seen in 1 patient in the MMF group at 3 months and 6 months follow-ups while it was detected in 5 patients at 3 months and in 11 pat5ients at 6 months in the CsA group (Table 5).

Laboratory:

The laboratory findings of the patients at baseline, 3 months, and 6 months follow-up are presented in Table 6. There was no significant difference in serum creatinine, serum Mg, serum cholesterol, RBS, SGPT, and eGFR between the two groups and within each group at baseline, 3 months, and 6 months, but serum potassium was significantly high in group B at 6 months. Hb was significantly low in both groups at 6 months compared to baseline; it was also significantly lower in group B as compared to group A at 6 months. Serum albumin and serum calcium were significantly high in both groups at 6 months when compared to baseline.

Table V. Comparison of adverse effects between two drugs.

Complications	Group		p value
	Group A (Mean ± SD)	Group B (Mean ± SD)	
Diarrhea			
• At 3 months	4 (16.7)	0 (0.0)	0.036#
• At 6 months	4 (16.7)	0 (0.0)	0.036#
GIT upset			
• At 3 months	2 (8.3)	0 (0.0)	0.200#
• At 6 months	1 (4.3)	0 (0.0)	0.442#
Hypertrichosis			
• At 3 months	5 (20.8)	16 (55.2)	0.011##
• At 6 months	5 (20.8)	18 (62.1)	0.003##
Gum hypertrophy			
• At 3 months	0 (0.0)	3 (10.3)	0.242#
• At 6 months	0 (0.0)	5 (17.2)	0.056#
Tremor			
• At 3 months	0 (0.0)	0 (0.0)	
• At 6 months	0 (0.0)	1 (3.4)	1.000#
HTN			
• At 3 months	1 (4.2)	5 (17.2)	0.204#
• At 6 months	1 (4.2)	11 (37.9)	0.007#

##Chi-square test was done to measure the level of significance

Fisher's Exact test was done to measure the level of significance

Table 6. Comparison of clinical and laboratory findings between two groups

Clinical & Laboratory parameter	Drug	Baseline 0 Months (a)	3 Months (b)	6 Months (c)	P Value a vs c
Systolic BP (mmHg)	MMF	99.16 ± 12.82	97.9 ± 10.62	99.16 ± 10.59	1.000
	CsA	101.72 ± 12.83	100.86 ± 8.24	105.34 ± 13.22	0.157
Diastolic BP (mmHg)	MMF	66.87 ± 9.53	65.00 ± 5.89	66.25 ± 7.10	0.709
	CsA	65.68 ± 8.63	67.93 ± 7.73	71.20 ± 8.82	0.007
Height (cm)	MMF	123.33±20.53	124.41±19.70	124.66±19.45	0.004
	CsA	114.79±23.10	116.41±22.01	116.89±21.83	0.003
Weight (kg)	MMF	31.83±15.47	31.58±15.32	31.75±15.31	0.831
	CsA	25.81±11.89	26.34±11.94	26.89±11.99	0.003
Hb (gm/dl)	MMF	12.73 ± 1.18	11.69 ± 1.23	12.07 ± 1.01	<0.001
	CsA	12.36 ± 0.94	11.36 ± 1.06	11.14 ± 1.78	0.002
S. Creatinine (mg/dl)	MMF	0.54 ± 0.22	0.58 ± 0.20	0.58 ± 0.16	0.095
	CsA	0.52 ± 0.18	0.58 ± 0.27	0.58 ± 0.21	0.104
S. Albumin (gm/L)	MMF	10.10±8.19	25.07 ± 7.54	24.17 ± 5.78	<0.001
	CsA	10.66±8.18	26.07 ± 6.28	25.74 ± 7.00	<0.001
S. Calcium (mg/dl)	MMF	7.42 ± 0.66	8.32 ± 0.58	8.60 ± 0.59	<0.001
	CsA	7.46 ± 0.80	8.18 ± 1.08	8.94 ± 0.64	<0.001
S. Potassium (mmol/L)	MMF	3.87 ± 0.59	3.97 ± 0.46	3.95 ± 0.39	0.581
	CsA	4.01 ± 0.55	4.11 ± 0.46	4.24 ± 0.41	0.056
S. Mg (mg/dl)	MMF	1.89 ± 0.14	1.86 ± 0.09	1.88 ± 0.09	1.000
	CsA	1.86 ± 0.12	1.85 ± 0.10	1.86 ± 0.09	0.648
S. Cholesterol (mg/dl)	MMF	340.73 ± 154.62	270.58 ± 69.38	279.16 ± 65.82	0.088
	CsA	295.46 ± 67.33	269.65 ± 66.31	255.55 ± 62.19	0.009
SGPT (mg/dl)	MMF	35.00 ± 8.79	36.20 ± 10.44	36.95 ± 8.62	0.490
	CsA	34.82 ± 12.21	32.93 ± 10.47	35.39 ± 9.52	0.866
RBS (mmol/L)	MMF	6.00 ± 1.20	6.28 ± 1.00	6.31 ± 1.01	0.363
	CsA	6.15 ± 1.15	5.80 ± 1.23	5.87 ± 0.97	0.217
eGFR (ml/min/1.73m²)	MMF	124.38 ± 41.93	126.29 ± 46.17	122.55 ± 36.73	0.330
	CsA	113.67 ± 33.93	116.82 ± 43.48	113.01 ± 45.30	0.869

Discussion

Treatment of frequently relapsing nephrotic syndrome with steroids results in undesirable side effects, and switching to other medications is then essential to prevent relapse. As an alternative therapy, MMF and CsA may be used. To date, no study has evaluated the difference in efficacy between MMF and cyclosporine in Bangladeshi children. Therefore, we performed this randomized study to compare the efficacy of MMF and cyclosporine.

The side-effect profile of MMF in our patients was more favorable than that of CsA.

Hypertension was significantly more frequent in the CsA group. This finding is similar to to the results of a previous study [2]. Patients that receive cyclosporine may develop hypertension because it activates the sympathetic nervous system and increases ET-1 secretion [8]. As expected, similar to previous studies, hypertrichosis, gingival hypertrophy, and tremor were more frequent in patients treated with CsA [2, 9], whereas diarrhea was more common in the MMF group. Diarrhea and GIT symptoms like abdominal pain and vomiting are well-known adverse effects of MMF [9].

The results of hematological parameters revealed that patients in the MMF group had a significantly higher hemoglobin level at 6 months than those in the CsA group. This finding is in contrast to studies reporting a negative effect of MMF on erythropoiesis

in renal transplant recipients [10,11]. However, none of our patients developed anemia, nor did any of them suffer from significant leucopenia or lymphopenia.

Our data suggest that CsA is more effective in preventing relapses than MMF. The relapse rate was significantly higher in the MMF group; this finding is similar to the results of a study by Dorresteijn et al. (2008), although the difference in the relapse rate was not significant in their study while the rate was much higher in the MMF group [2].

There was no significant difference in time to urinary remission and the mean hospital stay between the two groups. There are no previous data about the days required for urinary remission after starting MMF or CsA and there is no hospital-based study of the days required for recovery.

We used the MEIA method for therapeutic drug monitoring of CsA but we could not monitor the drug level of MMF as it is not available in our country.

Conclusions

The results suggest that cyclosporine is more effective in preventing relapses while mycophenolate mofetil has fewer adverse effects than cyclosporine.

Acknowledgement

None declared

Conflict of Interest

None declared

Financial Support

None declared

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