Mycophenolate mofetil in children with steroid-dependent and/or frequently relapsing nephrotic syndrome

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BACKGROUND: Mycophenolate mofetil (MMF) has emerged as a new agent for treatment of a variety of glomerular diseases. This study examines the safety and efficacy of MMF in treating pediatric patients with steroid-dependent (SD) and/or frequently relapsing (FR) nephrotic syndrome (NS).

METHODS: We retrospectively reviewed the medical records of 18 patients with SDNS and/or FRNS treated with MMF for at least 3 months. MMF was used in 11 patients with SDNS (n=10) and FRNS (n=1), including 7 males and 4 females.

RESULTS: Mean age at time of diagnosis of NS was 3.3 years (range, 1.1-8.5 years), and at the start of MMF 5.9 years (range, 2.9-10 years). Seven patients had a renal biopsy prior to starting MMF; all had mesangial proliferative glomerulonephritis. Mean follow-up after starting MMF was 12.2 months (range, 4-24 months). Mean MMF dose was 948 mg/m^2/day (range, 500-1087 mg/m^2/day). MMF resulted in improvement in 9 of 11 patients, with 8 patients weaned off steroids completely, with a reduction in the mean relapse rate from 4.7 relapses/patient/year (range, 2.4-6) before MMF to 1.05 relapses/patient/year (range, 0-4.5) after MMF therapy (P=0.0001). The relative risk for relapse before MMF was 4.7 (P=0.0002). None of the patients had significant adverse events or intolerance to MMF therapy.

CONCLUSION: We conclude that MMF is a safe and effective option for treatment of children with SDNS and/or FRNS.

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Approved for publication June 2005

Ann Saudi Med 2005;25(5):380-384

Corticosteroids are the first line of therapy in children with nephrotic syndrome. The response rate after appropriate treatment of the initial episode of illness reaches 85% to 90%,[1,2] but more than 90% of nephrotic children develop a relapse at some point and about 50% of those become steroid-dependent or frequent relapsers.[1,2] However, the side effects of steroid therapy limit their long-term usage. Second-line agents, such as cyclophosphamide (CYC) and cyclosporine (CSA) have proven to be effective in treatment of patients with SD or FR-NS,[3] but their toxic side effects limit chronic use or repeated courses of therapy. Mycophenolate mofetil (MMF), an immunosuppressive drug that inhibits both B- and T-cells, is used primarily for rejection prophylaxis in renal transplant recipients.[4] Because of its potent immunosuppressive action, MMF has emerged as a new agent for treatment of a variety of glomerular diseases such as lupus nephritis,[5-7] focal segmental glomerulosclerosis and treatment-resistant NS[8-12] and membranous nephropathy[13,14] with variable rates of success. The major advantages of MMF over other agents are the lack of nephrotoxicity compared to CSA, the absence of steroid adverse effects, and relatively

mild and reversible gastrointestinal and hematological side effects, properties which, if efficacy is proven, make MMF an attractive choice in patients who require long-term therapy.

Patients and Methods

We retrospectively reviewed the charts of pediatric patients under the age of 14 years (the pediatric age limit at our hospital) with the diagnosis of nephrotic syndrome who were treated with MMF. Eighteen patients who received therapy with MMF were identified. A total of 7 patients were excluded because they did not complete 3 months of therapy (3 patients), had incomplete data (2 patients), or had steroid-resistant nephrotic syndrome (2 patients). All remaining 11 patients fulfilled the criteria for SD (10 patients) or FR (1 patient) NS,[1,2] with 5 patients satisfying criteria for both categories. For the initial episode of illness, treatment consisted of prednisone 60 mg/m^2/day in a single daily dose for 4 to 6 weeks, followed by prednisone 40 mg/m^2/day on alternate days for 4 to 6 weeks. Treatment of relapse consisted of prednisone 60 mg/m^2/day in a single daily dose until the urine dipstick (*Multistix* 10 SG, Bayer AG, Leverkusen, Germany) for protein was negative or trace for 3 consecutive days, then prednisone 40 mg/m^2/day on alternate days tapered gradually over 3 to 6 months. Relapse definition parameters used in our clinical practice were the presence of proteinuria of 3+ or more on the urine dipstick on at least 3 consecutive days and/or the presence of clinical signs of relapse. The primary outcome measure was the average number of documented relapses per patient before (up to 2 years) and after (up to last follow-up) treatment with MMF, adjusted per year of follow-up. Other data collected and analyzed included renal function as measured by serum creatinine and hematological data obtained during scheduled clinic visits.

For statistical analysis of data, Microsoft Excel was used to calculate means. The paired t test was used to calculate *P* values. Relative risk values were calculated using *SAS* software program.

Results

Mean age at diagnosis of NS was 3.3 years (range, 1.1-8.5 years). The mean age at the start of MMF therapy was 5.9 years (range, 2.9-10 years). Seven of 11 patients had a renal biopsy at some point prior to starting MMF. All 7 biopsies were adequate and were examined by light microscopy, immunofluorescence, and electron microscopy. Second-line therapy failed in 4 patients (levamisole [LEV] in 1, CYC in 2, and LEV, CYC and CSA in 1) prior to starting MMF. Mean follow-up after starting MMF was 12.2 months (range, 4-24 months). Mean MMF dose was 948 (range, 500-1087) mg/m^2/day in 2 divided doses (8 patients) or 3 divided doses (3 patients).

Individual patient responses and clinical courses are summarized in Table 1. Nine of the 11 patients (82%) had a good response to treatment, with a reduction in the number of relapses, with 8 (73%) completely weaned off steroids. The mean time off steroids was 8.2 months (range, 4-15 months). Only 2 patients (18%) did not benefit from therapy and continued to be steroid-dependent. Both had mesangial proliferative glomerulonephritis without evidence of focal and segmental glomerulosclerosis on renal biopsy. One of these 2 patients had focal mesangial IgM deposits (patient 9), and was switched to CYC with good response, while the second patient continued to be steroid-dependent after further treatment with CYC (patient 3). Patient 3 had no relapses during the initial 12-month period after starting MMF, and was off steroids for 6 months, but had frequent relapses and steroid dependency afterwards; therefore, MMF was stopped after an additional 6 month period with no response. Patient 2 was initially treated for 6 months with no relapses, and was weaned off steroids. However, he relapsed 3 months after stopping MMF, and was restarted on it. He continued to be in remission 11 months later (a total follow up of 20 months with 1 relapse). Patient 11 was a late responder to prednisone, and relapsed twice when he was switched to alternate-day therapy. He was in remission at last follow-up 4 months after starting MMF, and was only on a small dose of alternate-day prednisone.

The mean number of relapses was significantly reduced from 4.9 (range, 2-6) to 1.05 (range, 0-4.5) relapses/patient/year with MMF treatment (P=0.0001). The relative risk for relapse before use of MMF was significantly higher by 4.7 fold (P=0.0002). Before MMF therapy, 10 patients (91%) had an average of 3 or more relapses per year, while after treatment only 2 patients (18%) had an average of 3 or more relapses per year, 6 patients (55%) had no relapses, 2 patients (18%) had only 1 relapse per year, and 2 patients (18%) had an average of 2 to 3 relapses per year.

There was no change in hematological parameters or serum creatinine before and after treatment. Only 2 patients had mild gastrointestinal side effects, and 1 patient developed herpetic stomatitis while on

Table 1. Individual patient characteristics and outcome

Patient	Age (years) at diagnosis of NS	Age (years) at start of MMF	Category SD/FR	Biopsy	Other treatment before MMF	Time on MMF (months)	Time off Prednisone (months)	Average # of relapses/ year before MMF	Average # of relapses/ year after MMF
1	2.3	4.5	SD+FR	No	LEV	8	4	4	0
2	2.5	5	SD	No	None	20	15	4	0.7
3	2.7	7	SD	MesPGN	None	18	Still on	5	3.3
4	8.5	10	SD+FR	MesPGN	None	12	6	5	2
5	2	9	SD	No	None	24	12	4.7	0
6	1.1	2.9	FR	MesPGN	None	12	6	5	0
7	2.7	5	SD+FR	MesPGN	LEV+CYC+CSA	12	9	2.4	0
8	3	5.5	SD+FR	MesPGN	CYC	12	8	6	1
9	2.8	4	SD+FR	MesPGN+IgM	None	8	0	4	4.5 (3 in 8 mos)
10	3.3	9	SD	No	None	4	2	6	0
11	2.5	2.9	SD	MesPGN	None	4	on 5 mg QOD	6 (2 in 4 mos)	0

SD=steroid-dependent, FR=frequent relapser, MesPGN=mesangial proliferative glomerulonephritis, LEV=levamisole, CYC=cyclphosphamide, CSA=cyclosporine, MMF=mycophenolate mofetil, QOD=every other day

MMF and the drug was stopped only briefly. None of the patients had intolerance to MMF.

Discussion

Children with steroid-dependent and frequently relapsing nephrotic not only suffer from the disease, but also have to bear the side effects of the various therapies. The side effects are often more unbearable than the disease itself, and can affect the physical and psychological well-being of these children. Corticosteroids have a well-recognized and broad toxicity profile, especially when used in repeated courses to treat relapses or when used for long periods of time. Chemotherapeutic agents such as cyclophosphamide and chlorambucil have well-established efficacy in these settings. However, in our practice, we face significant resistance from families when these are offered as alternative therapies despite reassurance of the high efficacy and relative safety associated with the use of these agents. Additionally, repeated courses of therapy, where toxic cumulative doses are likely to be exceeded, are generally not recommended. CSA, while very effective in this subgroup of patients, has significant nephrotoxicty and cosmetic side effects.[15-20] In addition, CSA dependence is a well-recognized feature in a significant proportion of these patients, with tendency for relapse after stopping the drug.[21,22] Therefore, we among others, tend to use CSA only when all other therapies have failed.

In this uncontrolled, retrospective, single-center study, MMF-treated patients had a significant reduction in the number of relapses from a mean of 4.7 to a mean of 1 relapse/patient/year (P=0.0001), and in the majority of patients, steroids were completely and successfully withdrawn indicating that MMF may play a role in alleviating steroid dependence. Furthermore, there was an almost 5-fold reduction in the relative risk of relapse in MMF-treated patients (P=0.0002), despite the small number of patients in our study. Our observations are consistent with those of Barletta et al.[11] In their series of 14 patients, 4 patients were steroid-dependent, all previously treated with CYC, and there was a trend for reduction in the number of relapses in the year on MMF therapy compared with the year before MMF, from a mean of 4.25±0.63 relapses to a mean of 1.75±0.48 relapses. However, due to the small number of patients, the difference did not reach statistical significance (P=0.06). Interestingly, using MMF in CSA-dependent patients, the authors also reported a reduction in the relapse rate in 8 of 10 other patients (5 were steroid-resistant, and 5 were steroid-dependent), with 5 patients weaned off steroids and CSA completely within 1 to 2 years of starting MMF therapy. For the 14 patients combined, there was a significant reduction in the mean number of relapses from 2.85±0.4 in the year preceding MMF therapy to a mean of 1.07±0.3 relapses (P<0.01). Although our results are mostly consistent with those of Barletta et al, our

patients represent a more homogenous group, which allows for better interpretation of the results. Our data is also in keeping with data reported by Bagga et al.[23] The authors reported a significant reduction in the mean relapse rate in children with steroid-dependent nephrotic syndrome, from 6.6 (95% confidence interval, 5.4-7.7) to 2 (95% CI, 1.2-2.7) episodes/year with MMF therapy for 12 months (P<0.0001). The majority of their patients (73.7%) had at least a 50% reduction in relapse frequency. In that prospective, uncontrolled trial of 19 patients with SDNS who were previously treated with long-term steroids (19 patients), LEV (16 patients) and CYC (15 patients), they were also able to demonstrate the steroid-sparing effect of MMF, with a reduction in the mean prednisolone dose from 0.7 mg/kg/day (95% CI, 0.6-0.8) to 0.3 mg/kg/day (95% CI, 0.2-0.4) (P<0.0001). We were unable to calculate the steroid dose accurately in our patients, but in 8 of 9 patients who responded favorably to MMF, steroids were completely withdrawn, and in 1 patient (patient 11) the dose was reduced to 5 mg (0.25 mg/kg/dose) of prednisone every other day at the last follow up 4 months after starting MMF therapy, compared with the lowest dose of 20 mg every other day (1 mg/kg/dose), which was associated with relapse on two successive occasions of steroid tapering trials before MMF therapy. Another observation by Bagga et al[23] was the high rate of relapse (68.4%) after stopping MMF, with recurrence of steroid dependence. We have observed two relapses in 2 patients within 4 months of stopping MMF (patients 2 and 8). In these 2 patients MMF was restarted and they had no further relapses. These 2 patients were among the earliest patients treated with MMF, and their relapses after stopping MMF may have influenced the decision to extend duration of therapy to more than 6 months in the remaining patients. The question of whether MMF-treated patients develop drug dependence, as is the case with CSA, could not be answered in our study, although data from the study by Bagga et al suggests that may be the case. Similar to the results by Bagga et al, in a prospective multi-center clinical trial of MMF in FR nephrotic children, Hogg et al recently reported the benefit of using of MMF in children with FRNS. However, they also reported a 71% relapse rate (17 of 24 patients) after stopping MMF therapy,[24] suggesting that longer duration of therapy may be required to maintain a state of remission.

In addition to alleviating steroid dependence, recent reports indicate a potential role for MMF in decreasing CSA dependence as well. Gellermann et al[25] used MMF in 7 children with steroid-resistant nephrotic syndrome receiving CSA therapy with evidence of CSA nephrotoxicity. In 5 of 6 patients with minimal change disease, CSA was discontinued, resulting in normalization of glomerular filtration rate and effective renal plasma flow after discontinuation of CSA. Furthermore, all 5 patients remained relapse-free after stopping CSA. In one patient with focal and segmental glomerulosclerosis, MMF successfully induced remission in a treatment resistant relapse episode, with subsequent reduction in CSA dose and trough levels, resulting in improvement in serum creatinine and sustained remission up to 28 months after starting MMF and low-dose CSA.

As expected, in our study the renal function as measured by serum creatinine was not affected. Gastrointestinal, and infectious side effects normally reported with the use of MMF in renal transplant patients[26,27] were only minor and observed in 3 patients, 2 had occasional and mild abdominal pain that resolved spontaneously, and 1 had herpetic stomatitis. Hematological adverse effects were not observed in any of our patients.

In summary, our study suggests that MMF is safe and effective in treating children with SDNS or FRNS. The major advantages of MMF are the ability to withdraw or reduce steroids and alleviate steroid dependence. MMF has relatively mild side effects compared with other agents, most importantly, the lack of nephrotoxicity, and as a few studies suggest, the ability to decrease the CSA requirement and/or dependence. Based on the findings from our study, which are also supported by other studies, we propose that MMF may be considered as an alternative, and perhaps as the first alternative after steroids, in the treatment of nephrotic patients with SDNS or FRNS. Further confirmation of these results, however, is still required through large, controlled, randomized clinical trials. The optimal dosing regimen and length of therapy, and the need for therapeutic drug monitoring in these patients are issues that still need further study and clarification.

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