Efficacy and side effects of mycophenolate mofetil therapy in children with steroid dependent nephrotic syndrome in a tertiary paediatric nephrology centre in Sri Lanka

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Abstract

Background: Mycophenolate mofetil (MMF) has been shown to be a well-tolerated drug which could maintain prolonged remission in patients with steroid dependent nephrotic syndrome (SDNS). MMF is known to have a steroid sparing effect.

Objectives: To determine the effect of MMF in reducing relapses in Sri Lankan children with SDNS and to ascertain the incidence of side effects of MMF in this population.

Method: Children between 1-18 years of age with SDNS who had been treated with MMF for 12 months or more at the paediatric nephrology unit, Teaching Hospital Peradeniya, were selected and reviewed retrospectively. Children who had previously received immunosuppressive therapy other than prednisolone, cyclophosphamide, cyclosporin A, tacrolimus and levamisole and those who were on MMF for indications other than idiopathic nephrotic syndrome were excluded. Children and parents were interviewed and their patient-held health records, including their 'nephrotic syndrome diary' were reviewed. Data were collected twice a week using pretested questionnaires, in the nephrotic syndrome clinic for a period of 8 weeks. Results were analysed using SPSS version 23.

Results: Thirty five children who met the selection criteria were included. Of them 26 (74.3%) were male and 09 (25.7%) were female. The median age was 9.7 years. Mean number of relapses in the year before starting MMF and the year after starting MMF were 3.5 and 1.8 respectively. The reduction in the relapse rate after being on MMF was significant (p=0.009). Child's age or gender did not impact the relapse rate (p>0.05). The most common side effect observed was cough (20%) and the least common ones were abdominal pain, dyspnoea and dizziness (3%).

Conclusions: In this study MMF reduced relapse rates of children with SDNS, despite some minor side effects.

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(Key words: Mycophenolate mofetil, relapses, side effects, childhood steroid dependent nephrotic syndrome)

Introduction

Nephrotic syndrome (NS) is the commonest glomerular disorder in children[1]. Histologically, minimal change disease (MCD) is found in about 80% of childhood NS[2]. Poor long term outcome is a feature of the less common histological variant known as focal segmental glomerulosclerosis (FSGS)[3]. Although corticosteroids are the first choice of treatment in NS with an initial response rate of nearly 90%, relapses will follow in around 60-90% of patients who initially respond well[4]. NS ultimately becomes frequently relapsing or steroid dependent in about 20% to 60% of patients, ultimately resulting in poor quality of life of patients and their families[4]. In addition, it complicates the treatment course for the clinician[4]. There are several second line treatment options in this group of patients, amongst which mycophenolate mofetil (MMF) is a relatively new medication[5].

In steroid sensitive NS (SSNS), irrespective of the treatment, more than 80% undergo spontaneous long term remission in later childhood[6]. However, until remission, there is a threat posed by the risk of sepsis, thrombosis, malnutrition, dyslipidaemia and hypovolaemia[7]. As such, a paediatrician should balance the benefits versus the toxicity of using steroids and immunosuppressive therapy for a benign condition such as MCD.

Corticosteroids are the first line treatment for NS[4]. Nonetheless, the majority of children will experience relapses after 8 weeks of oral corticosteroids, with more than 50% of them

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becoming steroid-dependent in order to maintain remission[8]. High-doses of prednisolone are associated with complications like hypertension, diabetes and behavioural disorders[9,10]. To alleviate adverse effects of steroid toxicity, steroid-sparing drugs like cyclophosphamide, cyclosporine A (CyA), levamisole (LEV) and tacrolimus are prescribed[5]. Though with good response rates, the severe side effects of the cytotoxic agent cyclophosphamide questions its safety in less severe cases[11]. CyA shows increasing relapse rates once treatment is stopped along with the harmful side effects along with the need to monitor blood CyA trough levels[12,13]. Though the immuno-modulating agent LEV has a very good side effect profile, it is less efficacious and is only effective in milder forms of the disease[14].

MMF is a well-tolerated drug which could maintain prolonged remission in patients with SDNS and frequently relapsing nephrotic syndrome (FRNS)[15,16]. Acting as a selective reversible inhibitor of inosine monophosphate dehydrogenase, MMF inhibits de novo synthesis of purines[17]. MMF has come up as an attractive alternative due to the better safety profile compared to cyclophosphamide and CyA while having a significant steroid sparing ability[18].

Most literature on the role of MMF in NS comes from the western world, and it is known that Asian children are more susceptible for NS than Caucasian children[19]. Due to the increase in prevalence of infections, especially upper and lower respiratory tract infections, in this part of the world, majority of Sri Lankan children with NS are steroid dependent and suffer from frequent relapses[20]. There is no published literature on the efficacy of MMF in the management of SDNS in Sri Lankan children.

Objectives

To determine the effect of MMF in reducing relapses in Sri Lankan children with SDNS and to ascertain the incidence of side effects of MMF in this population.

Method

This single-centre retrospective analytic study was conducted at the Paediatric Nephrology Unit, Teaching Hospital Peradeniya, Sri Lanka. The recruited population included children between ages 1-18 years with SDNS who had been treated with MMF for 12 months or more at the centre. Patients who had previously received immunosuppressive therapy other than prednisolone, cyclophosphamide, cyclosporin A, tacrolimus and levamisole and the ones who were on MMF for indications other than idiopathic NS (lupus nephritis, renal transplant recipients etc.) were excluded.

Child and parent were interviewed when they had their basic observations done by nursing staff before they saw their clinician. Each patient has a health record which they bring each clinic visit, and this document was reviewed for obtaining clinical data for the questionnaire. Quantitative data regarding number of relapses were obtained from the patient held 'nephrotic syndrome diary' which was reviewed alongside the patient held health record. At the clinic, parents were educated and trained to test and record urine protein excretion in this diary daily. Presence of 3+ proteinuria for three consecutive days was considered a relapse. The side effect profile was evaluated using any reported symptoms or documentation of physical examination at the time of data collection.

Ethical clearance for the study was obtained from the ethical review committee of the Sri Lanka College of Paediatricians (SLCP). Informed consent was obtained from all individual participants and/or parents where appropriate, prior to collecting data. The period of study was from December 2017 to January 2018. The data were analysed using SPSS version 23.

Results

Clinical data of 35 children between 4.25-18 years who fulfilled the inclusion criteria were analysed (median age= 10.0 years). Of them, 26 (74.3%) were male and 9 (25.7%) were female. The mean numbers of relapses within the year prior to starting MMF therapy and the year after starting MMF therapy were respectively 3.54 and 1.83 (Table 1).

A significant reduction in the relapse rate after being on MMF therapy for at least 12 months was observed (p=0.009). The steroid dose reduced significantly during the year after starting MMF therapy ($p<0.001$). The age or gender of the children did not have a significant impact on the relapse rate or steroid dose before and after starting MMF therapy ($p>0.5$).

Other immunosuppressive medications the patients had been on prior to MMF therapy were levamisole (22), cyclophosphamide (07), tacrolimus (04) and cyclosporine (13).

Table 1: ***Summary of the descriptive statistics of patient group (n=35)***

Characteristic	Value
Median age (years)	09.7
Gender Male Female	 26 (74.3%) 09 (25.7%)
Mean height (cm)	132.6
Mean weight (kg)	36.3
Mean number of months on MMF	19.9
Mean number of relapses prior to starting MMF therapy	3.54 (IQR = 2-5)
Mean number of relapses after starting MMF therapy	1.83 (IQR = 1-2)
Mean steroid dose prior to starting MMF therapy (mg/kg)	1.19 (IQR = 0.42-1.96)
Mean steroid dose after starting MMF therapy (mg/kg)	0.43 (IQR = 0.12-0.60)

IQR= interquartile range

Most common side effect was cough (20%) and the least common were abdominal pain, dyspnoea and dizziness (3%). The side effect profile of the patient group is shown in Table 2.

Table 2
Side effects encountered in patient group (n=35)

Side effect	*No. (%)*
Abdominal Pain	01 (03)
Diarrhoea/ Constipation	03 (09)
GI ulceration/bleeding	03 (09)
Tachycardia	02 (06)
Hypertension/ Hypotension	04 (11)
Cough	07 (20)
Dyspnoea	01 (03)
Insomnia	03 (09)
Tremor	04 (11)
Dizziness	01 (03)
Alopecia	05 (14)
Rash	01 (03)
Acne	03 (09)
Infections	04 (11)
Arthralgia	06 (17)

Discussion

Prednisolone was first prescribed for children with NS in 1956, when a study by Arneil reported four children (age 2-8 years), who responded to prednisolone at a daily dose of 60mg[21]. Although most children respond to steroid therapy, many will subsequently relapse[4]. Children with FRNS or SDNS need individualised treatment and are candidates for an array of immunosuppressive therapy[22]. However, due to the cytotoxicity and other side effects of such drugs, this ideal regimen should have a low side effect profile and be efficient at reducing relapses as well as steroid dependency.

Introduced as a steroid-sparing agent in 1967, different regimens of cyclophosphamide have been used to induce remission with different, but reasonable degrees of success[23-26]. Unfortunately, higher cumulative doses of cyclophosphamide are associated with adverse effects such as haemorrhagic cystitis, alopecia, nausea, gonadal toxicity and risk of future malignancies[11]. A more recent study on SDNS and FRNS patients concluded that only 20% of children on cyclophosphamide achieved long term remission[27].

CyA is now used in preference to cyclophosphamide especially in boys who need prolonged immunosuppression, due to the risk of gonadal toxicity[28]. However, unlike with cyclophosphamide, an increased rate of relapse of SDNS has been observed when CyA was discontinued[13]. Though CyA therapy for more than 5 years has achieved sustained remission in children with SDNS, the long-term dosage of CyA poses the risk of serious adverse effects such as nephrotoxicity and malignancy. The former requires regular monitoring of renal function, CyA trough blood levels and sometimes renal biopsies[29,30].

Levamisole is an immunomodulatory drug with minimal side effects and has shown to be more effective when combined with steroid therapy[31]. Reported side effects include vasculitis, neutropenia, and liver toxicity although there is evidence in existing literature to suggest that these side effects subsided upon discontinuation of levamisole[32,33]. On the contrary, levamisole may not be very suitable in severe cases of SDNS. Similarly, achieving remission using tacrolimus in SDNS has shown varying but not very significant degrees of success[8,34].

The use of MMF to reduce relapses in childhood NS was first reported in 1999[35]. Subsequent studies involving small groups of patients also reported reduced rates of relapses with MMF therapy[36,37]. Bagga *et al* in 2003 reported reduction in the rate of relapse in 19 children with SDNS. This study stated that there were no significant side effects. However, relapse frequency increased in more than half of the study population after discontinuation of MMF[38]. Percoraro et al also reported that 82% of

children achieving long-term remission in his study where 12 children with SDNS received MMF therapy for a period of 24 months[39].

More recent literature describes further the beneficial effects of MMF in children who previously received cytotoxic therapy[36]. In 2004, Gellerman et al published literature showing the efficacy of MMF in inducing and maintaining remission in 7 children who showed both steroid and CyA dependency. All patients already had signs of nephrotoxicity after long courses of CyA. Six of the 7 children remained in remission for the 25 months during which they received MMF. There were no reported adverse side effects or leucopenia[40]. A study by Ulinski *et al* also concludes that switching from CyA to MMF is safer for children with SDNS and SRNS in terms of disease control as well as side effects[18]. Children with SDNS remained in remission without proteinuria whereas both SRNS and SDNS patients showed a significant increase in GFR.

Our study revealed a statistically significant reduction in relapse rate in patients with SDNS treated with MMF when comparing the relapse frequencies in the year prior to and the year following commencement of MMF. Though one could argue that the natural history of the disease could have had a bearing on the reduction of this relapse frequency, we believe that a reduction of this magnitude could not be attributed to the natural history alone. MMF also proved to be a safe option with only a minimal side effect profile. Interestingly the significant gastrointestinal side effects that plague the transplant population were not seen in our patient. This could be due to the fact that the doses used were significantly lower.

This study revealed 'cough' as the most frequently reported side effect (20%) but it must be noted that given the high incidence of recurrent upper and lower respiratory tract infections in Sri Lankan children, it is likely that this is a significant confounder and more likely the cause of the reported incidence of cough, compared to being purely because of MMF. It must also be noted that these children were all steroid dependent therefore side effects such as gastrointestinal bleeds are also difficult to conclude as being solely due to MMF. Overall, there were no serious side effects reported solely from MMF therapy.

Conclusions

In this study MMF reduced relapse rates of children with SDNS, despite some minor side effects.

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