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Review Article

Mycophenolate Mofetil as a Steroid-Sparing Agent in Childhood Nephrotic Syndrome: A Real-World Experience from A Middle-Income Country

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Abstract

Background: Children with nephrotic syndrome often develop frequently relapsing or steroid-dependent disease, resulting in prolonged exposure to corticosteroids that leads to significant health and psychosocial burdens. This study evaluates the real-world effectiveness of Mycophenolate Mofetil (MMF) as a steroid-sparing agent in treating childhood nephrotic syndrome. **Methods:** This prospective observational cohort study was conducted in Malaysia, involving 29 children aged 2-18 years with frequently relapsing or steroid-dependent nephrotic syndrome. MMF was administered as a second-line steroid-sparing agent, and patients were followed for 12 months. Demographic data, treatment history, clinical outcomes, and side effects were collected. The primary outcome was the annualized relapse rate (ARR) before and after MMF initiation. **Results**: Of the 29 patients, 75.9% were steroid-dependent. The median ARR decreased significantly from 4.31 to 1.72 episodes per patient-year ($p = 0.001$), with 87.2% of patients showing sustained remission or improved relapse rates. Growth parameters improved, significantly increasing height z-scores ($p < 0.001$). Side effects were mostly gastrointestinal (17.2%), including nausea and diarrhea, which were manageable in most cases. No patients developed leucopenia and no hospital admissions for serious infections. **Conclusion:** MMF demonstrated a favorable safety profile and effectively reduced relapse rates in children with frequently relapsing or steroid-dependent nephrotic syndrome. Given its steroid-sparing potential, MMF may offer a viable treatment option with potential health-economic benefits, though further research in larger, controlled cohorts is needed to confirm these findings.

Keywords: Mycophenolate Mofetil; Steroid-Sensitive Nephrotic Syndrome; Steroid-Sparing Therapy

Introduction

The presence of proteinuria, hypoalbuminemia, and oedema characterises nephrotic syndrome. By far, this is one of the most common glomerular diseases in children. The disease is steroid-responsive in ≥ 90% of cases [1]. (Table 1) Despite response to corticosteroids, up to 60% of patients with steroid-sensitive nephrotic syndrome develop a frequently relapsing course or steroid dependence that significantly impacts the patient's health, psychosocial adaptation and quality of life [2]. It is now evident from extensive observational data in children that long-term use of corticosteroids is associated with numerous adverse effects [3]. Mitigating the effects of glucocorticoids is important as such effects continue to affect their health even as they reach adulthood. The KDIGO Guideline for Glomerulonephritis in 2020 advocates for the use of steroid-sparing agents in children with frequently relapsing nephrotic who develop serious corticosteroid-related adverse effects and for all children with steroid-dependent

nephrotic syndrome, rather than no treatment or continuation with corticosteroid treatment alone [4].

Characteristics	At baseline n=29	At 12 months	Difference	95%Confidence interval of difference	p
Gender Male Female	 18 11				
Age (years)	8.6 ± 3.30				
Disease vintage (years)	3.5 [2.01,5.19]				
Disease phenotype: -Frequent relapser non-steroid-dependent -Frequent relapser steroid-dependent	 7(24.1%) 22(75.9%)				
Prior steroid-sparing agent used: -Levamisole -Cyclophosphamide -Both of the above	 10 (34.5%) 7(24.2%) 12 (41.3%)				
Children with: One steroid toxic features* Two or more steroid-toxic features*	 21(72.0%) 8(28.0%)				
Weight Z-score	-0.6 ± 1.61	-0.2 ± 1.67	-0.4	[-0.74, -0.05]	0.026
Height Z-score	-1.4 ± 1.19	-0.3 ± 1.31	-1.1	[-1.33, -0.81]	<0.001
BMI Z-score	0.2 ± 1.69	-0.1 ± 1.64	0.3	[-0.17, 0.7]	0.215

Table 1: Demographic characteristics of the study population at baseline and after 12 months of MMF.

Mycophenolate mofetil (MMF) is a prodrug that is metabolized to mycophenolic acid. It selectively inhibits inosine monophosphate dehydrogenase, an important enzyme in the de novo purine synthesis pathway [5]. This leads to the suppression of T and B lymphocyte proliferation, making MMF an effective immunosuppressant. Ever since its approval for use in 1995, several small-sized observational studies on MMF in the early 2000s demonstrated the potentials of MMF on nephrotic syndrome [6-8]. Contrary to cyclosporine A (CSA) which has been widely used for similar indications among children, MMF has no known nephrotoxic side effects. Hence, there is continuous interest in exploring more evidence in support of its use as a steroid-sparing agent in childhood nephrotic syndrome.

This study aims to evaluate the effectiveness of MMF as a steroid-sparing agent in treating childhood nephrotic syndrome based on real-world experience.

Methodology

This prospective observational cohort study was conducted at participating tertiary care hospitals in Malaysia. The study was approved by the Ethics Committee and consent was taken from parent or legal caregiver. A convenience sampling method was applied. The study population consisted of children aged 2 to 18 years with a diagnosis of frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome, who were treated with MMF between January 2022 and December 2024.

Patients included in the study received MMF as a second-line steroid-sparing agent and followed up for 12 months. They were in remission at the time of entry into the study. Exclusion criteria were patients who demonstrated steroid resistance, pre-existing cytopenia (i.e. anaemia (Hb less than 9g/dL)) or leucopenia (total white count < 3.0 x 109/L) and reduced glomerular filtration rate < 90 ml/min/1.73m2.

Dose of MMF given was in the range of 1000 to 1400mg/m2/day in two divided doses (not more than 1 gm twice a day) [9]. If patients develop side effects (leucopenia, anaemia, severe diarrhoea or serious infection), the MMF dose will be decreased by 250 mg aliquot. Adjustment of MMF dosing was not governed by mycophenolate trough level monitoring. Patients with persistent side effects will be considered for cessation of treatment. Demographic data, clinical characteristics, treatment history, and outcomes were collected from electronic medical records. Parents/caregivers consented to the study.

Statistical Analysis

Baseline characteristic parameters such as demographic data (i.e. age, gender, height, weight, and primary disease), comorbidities and laboratory investigations will be tabulated. They will be expressed as z scores wherever possible since the paediatric cohort may come in various sizes.

Categorical variables will be described as percentages. Continuous variables will be described as either mean ± standard deviation with the respective 95% Confidence Interval (95%CI) or median (first quartile, third quartile) whenever appropriate. Normality testing will be applied using both the Shapiro-Wilk and Kolmogorov-Smirnov tests. Comparisons between groups will be performed with either one-way analysis of variance (ANOVA) or Kruskal-Wallis H Test followed by Dunn's procedure. A p-value of < 0.05 is considered significant for all the above circumstances. All statistical analysis will be performed using the SPSS software, version 23.0 (SPSS Inc. Chicago, IL, USA) and DATA tab: Online Statistic Calculator (2024) [10].

Results

A total of 29 patients with childhood nephrotic syndrome were included in the analysis (Table 1). All tests indicate that the data follows a normal distribution. All patients were frequently relapsing. Most of them (n=22, 75.9%) were steroid-dependent, while the remaining (n=7, 24.1%) were otherwise. Approximately half of the cohort (41.3%) received both Cyclophosphamide and Levamisole as sparing-agent while the remaining half (58.7%) received either one of the two. Children in our cohort experienced significant adverse effects from prolonged steroid use; 28% reported more than 1 side effect. Growth failure is a prevalent issue among the children (48%). (Figure 1) All except 4 children received 12 months of MMF. The latter dropped out of the study as they had to be switched to a different steroid-sparing agent.

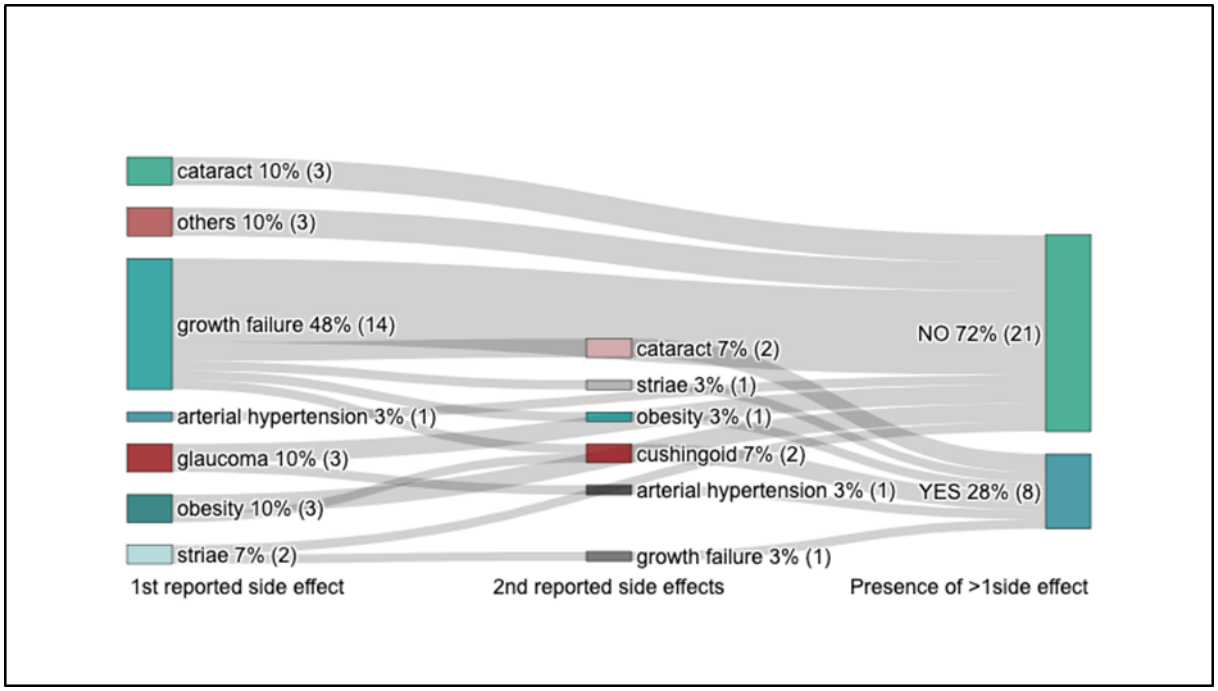

Figure 1: Reported steroid-related side effects upon entry to the study.

Thirteen out of the 29 patients (44.8%) remained in sustained remission for 12 months while on MMF. Eleven (37.9%) improved their relapse rate while 5 (17.2%) did not experience any improvement with MMF. Four children required hospital admissions (7 episodes of hospitalisation) while on MMF for oedema control during their relapses. The cohort's Annualised relapse rate (ARR) generally reduced to 1.72 episodes per patient-year from 4.31 episodes per patient-year. (Figure 2). A Wilcoxon Test indicated that this difference was statistically significant, W = 41.5, p = 0.001. The effect size r is 0.63. With r = 0.63, there is a large effect.

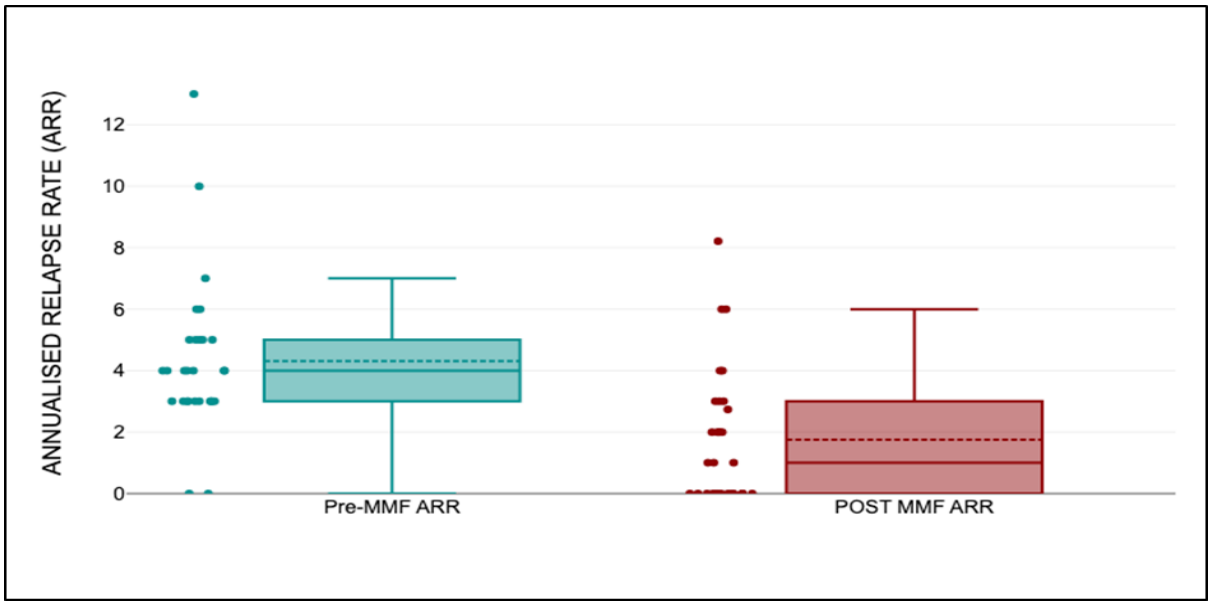

Figure 2: Comparison between pre and post-MMF ARR.

Five out of 29 patients experienced gastrointestinal upset (ie nausea, diarrhoea). One patient developed serious diarrhoea and MMF had to be stopped. Two patients reported concurrently increased hair loss while on MMF. Additionally, we did not observe any new onset leucopenia during the study period and none of the children was admitted to the hospital for serious infection.

Discussion

The relapsing-remitting nature of nephrotic syndrome presents a significant challenge, particularly when the disease becomes frequently relapsing. The disease imposes a substantial burden on both patients and their caregivers. Additionally, children often experience complications related to treatment, primarily due to the prolonged use of corticosteroids [11].

Our cohort includes 29 children who, despite being treated with levamisole, cyclophosphamide, or a combination of both, continue to experience active relapsing disease. It is evident that approximately half (52.0%) of the children experienced growth failure due to prolonged corticosteroid use, and a quarter (28.0%) suffered from multiple steroid-related adverse effects. A significant proportion of patients (82.7%) showed improved disease control with MMF, and nearly half of the patients maintained sustained remission. The marked reduction in the annual relapse rate (ARR) and the significant improvement in height z-scores following the initiation of MMF further underscore its potential to reduce reliance on steroids while effectively managing the disease.

There are always concerns about the potential side effects versus the benefits when using any immunosuppressants. Cyclosporin A has been widely recognised as an effective steroid-sparing agent in childhood nephrotic syndrome. Nevertheless, concerns remain regarding its cosmetic effects (e.g., hirsutism and gingival hypertrophy) and the potential nephrotoxicity that could lead to interstitial fibrosis.

MMF on the other hand, commonly causes gastrointestinal side effects and it could potentially lead to leucopenia [12-14]. A fifth of the patients (5 out of 29, 17.2%) experienced nausea and diarrhoea, which is a known side effect of MMF. These symptoms were manageable for most patients, but one patient had to discontinue MMF due to the severity of the diarrhoea. Following the cessation of the drug, diarrhoea resolved completely, and the patient was closely monitored throughout the process. Interventions such as timing the medication with meals and adjusting the MMF dose helped manage the symptoms in the remaining 4 patients. MMF-related leucopenia was not observed in our cohort. Though uncommon, mycophenolate mofetil (MMF)-associated alopecia has been reported in the literature [15]. Additionally, the absence of drug-related interstitial fibrosis with MMF further supports its potential as a promising treatment, particularly when compared to cyclosporine A, which has been associated with such adverse effects. Interestingly, in our cohort, we observed two patients who experienced increased hair loss during the study period. The dose of MMF was lowered for both patients, and this adjustment effectively mitigated the hair loss.

From a health economics perspective, mycophenolate mofetil (MMF) offers the advantage of being a potentially more cost-effective treatment strategy when compared to cyclosporine A, with a lower unit cost in our country. Given the benefits observed in our cohort, including manageable side effects for most patients, MMF could offer an attractive option for cost-conscious healthcare systems.

One of the key limitations of this study is its relatively small sample size, which may limit the generalizability of our findings. As the study only collected data for up to 12 months, it does not provide insights into the long-term outcomes of patients who discontinued MMF after achieving sustained remission. Therefore, the effects of stopping treatment beyond the 12 months remain unclear. Our study also may not capture the full spectrum of potential side effects or outcomes that could occur in a larger, more diverse cohort. As this study represents real-world data, there may be inherent biases in treatment adherence and data collection.

Conclusion

In this study, Mycophenolate mofetil (MMF) demonstrated an acceptable therapeutic potential with a favourable safety profile. Further research, ideally in larger and more controlled cohorts, is needed to confirm these findings. Overall, MMF could be a viable option as a steroid-sparing agent in childhood nephrotic syndrome, offering both clinical and potential health-economic advantages.

Conflict of Interest

None

Acknowledgement

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Research Registration

This study is registered with the National Medical Research Registry (NMRR-20-3182-57832).

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