BMC Nephrology

RESEARCH Open Access

Efficacy and safety of oral cyclophosphamide versus mycophenolate mofetil in childhood nephrotic syndrome: an open-label comparative study

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Abstract

Introduction There is a scarcity of research comparing the efficacy of cyclophosphamide and mycophenolate mofetil in childhood nephrotic syndrome. The aim was to evaluate the efficacy and safety of oral cyclophosphamide (CYC) and mycophenolate mofetil (MMF) in children with steroid-sensitive nephrotic syndrome in terms of the proportion of children who have been off steroids for at least 6 months without proteinuria (responders).

Methods This open-label retrospective-prospective comparative study was conducted in a pediatric nephrology clinic of a referral center for children between 1 and 18 years of age with FR/SD nephrotic syndrome. Group A consisted of patients who received oral cyclophosphamide (100, 25% female) at a dose of 2–2.5 mg/kg once daily for a period of 8–12 weeks. Group B consisted of patients who received oral mycophenolate mofetil ($n=61$, 18% female) (dose: 800–1200 mg/m2) for at least 12 months. Responders were defined as children who were off steroids for at least 6 months along with absence of proteinuria.

Results In the CYC group, 50% of the patients were responders, whereas 54% of the patients in the MMF group were responders ($p=0.614$). The time to first relapse with CYC was 7 months (IQR 5.25–11) compared to 7 months (IQR 3.5–12) with MMF ($p=0.092$). The relapse rate in the CYC group was 1.77 relapses per patient-year compared to 1.295 relapses per patient-year in the MMF group. The difference in relapse rate was significant (-0.474; 95% CI, 0.09 to 0.86 relapses/person-year) (p value = 0.009). Multivariate analysis revealed that an age of less than 5 years at the start of treatment was a significant factor for a better response to MMF (p value = 0.039, OR = 2.988, CI -1.055-8.468).

Conclusions The efficacy of MMF was similar to that of CYC in terms of response (6 months without steroids) in children with FR/SD nephrotic syndrome. MMF showed a favorable response in terms of the frequency of relapse and treatment failure.

Registration of the study with Clinical Trials Registry of India (http://ctri.nic.in;CTRI/2021/06/034421) (Dt: 28/06/2021).

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Keywords Mycophenolate mofetil, Oral cyclophosphamide, Nephrotic syndrome in children, Steroid sensitive

Introduction

Nephrotic syndrome (NS) is the most common glomerular disease in children, with 85–90% of patients responding to steroids. [1] The treatment of relapsing NS is a major challenge. Long-term use of high-dose steroids has been associated with steroid toxicity and impaired quality of life. [2]

Steroid-sparing drugs such as cyclophosphamide (CYC) or mycophenolate mofetil (MMF) can minimize the risk of relapse in patients with relapsing nephrotic syndrome. [3–6] There is a scarcity of research comparing the efficacy of cyclophosphamide and mycophenolate mofetil for children with frequently relapsing / steroid dependent nephrotic syndrome (FRNS/SDNS). This comparative cohort study was conducted in children with frequently relapsing steroid-dependent nephrotic syndrome treated with 12 months of MMF or a single course of oral cyclophosphamide. Their efficacy was assessed regarding the proportion of children who had been off steroids for at least 6 months and remained in clinical remission with absence of proteinuria (responders).

Methods

Study design: This was an open-label retrospective-prospective comparative study.

Study duration: two years, from June 2021 to July 2023 (prospective cohort).

Setting and location of the study: Pediatric Nephrology Clinic, Dayanand Medical College and Hospital, Ludhiana, Punjab, India.

Population: Patients with frequently relapsing/steroid-dependent nephrotic syndrome attending the Pediatric Nephrology Clinic were included in the study.

Participants: Group A (retrospective cohort) included patients who received oral cyclophosphamide ($n=100$) (from 2007 to 2019). The cumulative dose of CYC was kept at less than 168 mg/kg to avoid toxicity at dosages of 2–2.5 mg/kg once daily for 10–12 weeks. - already published data from our center [7]. Our treatment protocol was in accordance with the 2008 guidelines on childhood nephrotic syndrome from the Indian Society of Pediatric Nephrology [8], which state that levamisole may be an appropriate initial option for patients who have frequent relapses or steroid dependence before using CYP or MMF. Parents were provided with all available treatment alternatives, and many parents chose CYP treatment over other steroid-sparing treatments due to the shorter therapy duration and lower cost.

Therapy was initiated once patients were in remission with prednisolone 2 mg/kg daily (maximum 60 mg/day) until urine albumin was nil/trace for 3 consecutive days. In the CYC group, prednisolone was administered at a dose of 1.5 mg/kg on alternate days for 4 weeks, 1 mg/kg for the next 4 weeks, and 0.5 mg/kg for 4 weeks, after which the treatment was stopped. Group B (prospective cohort) included patients who received oral mycophenolate mofetil ($n=61$) taken consecutively over the study period at a dosage of 800–1200 mg/m^2 in two divided doses for at least 12 months. All children classified as steroid-dependent with a threshold ≥1 mg/kg on alternate days or frequent relapse not responsive to levamisole were enrolled and initiated with MMF after providing informed consent. As the majority of patients were steroid dependent, a mean dose of MMF of 1000 mg/m^2 was prescribed. In younger children, where there was difficulty swallowing MMF tablets, a suspension was used. Therapy was initiated once patients were in remission with full-dose prednisolone (as above). In the MMF group, patients were then weaned off prednisolone via the same protocol as CYC, and the treatment was stopped. Care was taken to ensure that no child was included in both cohort group.

The exclusion criteria for patients were as follows: congenital and infantile nephrotic syndrome; nephrotic syndrome due to secondary causes (including systemic lupus erythematosus, Henoch Schonlein purpura, IgA nephropathy, etc.); eGFR according to the Schwartz equation (<60 ml/min per 1.73 m^2); and prior therapy with MMF, cyclosporine, tacrolimus, or cyclophosphamide in the past 6 months. Five patients receiving MMF therapy were not included: 2 patients who withdrew consent and 3 patients who received CYC retrospectively (CYC cohort).

Definitions Definitions of steroid-sensitive nephrotic syndrome, frequent relapses, and steroid-dependent NS were used according to published guidelines on steroid-sensitive nephrotic syndrome [1, 9].

Relapse was defined as a urine albumin concentration ≥3+ (urine PCR >2 mg/mg) for 3 consecutive first morning samples and previous remission. Relapses linked to outcomes such as severe infections, thrombosis, or hypovolemia necessitating hospitalization were classified as complicated relapses. [9]

Patients were classified as either responders or nonresponders based on their status. Responders were defined as children off steroids for at least 6 months and remained in clinical remission with absence of proteinuria within a 12-month study period of starting treatment with MMF or oral cyclophosphamide. Treatment failure was defined as frequent relapse (≥3) or a change in patient status to a steroid-resistant state within the 12-month study period.

[10] The time to first relapse was defined as the duration from the initiation of the cyclophosphamide/MMF course until the first relapse.

Data collection: Clinical parameters such as age, sex, hypertension at onset, hematuria (gross or microscopic), age of disease onset, and prior medications received were entered into a preformed proforma. The classification of NS (FR/SD), frequency of relapses, steroid-dependent dose (mg/kg/day) before starting medication, and duration of nephrotic syndrome before treatment initiation were recorded. Adverse effects such as gastritis, increased transaminase levels, leucopenia, hemorrhagic cystitis, alopecia, and minor or major infections (those requiring hospitalization) that occurred during the one-year period were noted.

Follow-up monitoring: Urine dipstick albumin was monitored daily until remission, then twice weekly, and during episodes of fever, infection, or edema. Patients were prospectively followed up, initially every month and then every 2 months for 1 year. The physical parameters included growth parameters, blood pressure, and features of relapse, infection, and side effects of medication. Every visit included a complete blood cell count as well as renal function tests, electrolytes, albumin, cholesterol, transaminases, and blood glucose. An ophthalmological examination was conducted for subcapsular cataracts at six and twelve months.

For relapse, prednisolone was given daily at a dose of 2 mg/kg to induce remission (urine albumin negative or trace for 3 days), followed by 1.5 mg/kg every other day for 4 weeks, and the treatment was stopped.

Clinical indices such as time to first relapse, relapse-free survival, frequency of relapses, reduction in steroid-dependent dose, and steroid-free duration were documented.

Outcome: The primary outcome was the proportion of children off steroids for at least 6 months (responders) after 12 months of the study period. The secondary outcomes were the time to first relapse, the number of relapses within 12 months, the reduction in the steroid-dependent dose, the proportion of patients who experienced treatment failure, and the frequency of side effects in each group. In this study, STROBE reporting guidelines were used for reporting observational studies. [11]

The study was approved by the Institutional Ethics Committee Board of Dayanand Medical College and Hospital, Ludhiana, Punjab, India. The study was registered on 28/06/2021 at the Clinical Trials Registry of India (http://ctri.nic.in; CTRI/2021/06/034421). Written informed consent was obtained from the caretakers of all patients, and assent was obtained for children older than 7 years.

Sample size calculation: According to previous studies, the rate of response (off steroids and in remission for at least 6 months) to oral CYC reached 50%, i.e., 0.5 [7]. The use of a steroid-sparing agent was considered superior if a 25% better response rate was achieved in terms of the proportion of responders. To achieve a 25% improvement in the response rate, the sample size was calculated to achieve 80% power and a 95% confidence interval. Fifty-five subjects in each group were included. With 10% dropouts, the minimum sample size required in each group was 60.

Statistical methods

The results are expressed as medians (IQRs) or means ± SDs and percentages. Categorical data were compared using the chi-square or Fisher exact test. To calculate relapse-free survival, Kaplan–Meier analysis was performed, with the time of the first relapse from the initiation of the CYC course or MMF therapy serving as the endpoint. Univariate analysis was performed using probable variables affecting medication response, such as age of onset of NS, sex, prior levamisole use, indication of medication (FR/SD), prior steroid maintenance dose, age of start of medication, and duration of illness before start of medication. Multivariate logistic analysis was conducted to evaluate factors that showed significance in univariate analysis, balancing the effect of a higher prior steroid maintenance dose and a greater proportion of FR patients in the CYC group. A P value less than 0.05 was considered significant. Data calculations were performed using SPSS version 21.

Results

Baseline demographic data

In the present study, one hundred patients (75% boys) with steroid-sensitive nephrotic syndrome received oral cyclophosphamide, and sixty-one patients received mycophenolate mofetil (82% boys). The patients in both groups were similar in terms of age of onset of nephrotic syndrome, duration of nephrotic syndrome, and age of start of medication. Of the 100 children on CYC, 81% were steroid dependent, while 95% of the 61 patients in the MMF group were steroid dependent. The maintenance steroid dose at study entry was 1.2 mg/kg/day (IQR 0.8–1.4) in the CYC group compared to 1 mg/kg/day (IQR 0.98–1) in the MMF group ($p=0.004$). Cyclophosphamide was dispensed at a cumulative dose of 154 mg/kg (IQR 149–160), while the MMF dose was 973 mg/m2 (IQR 953–1021). (Table 1)

The response rate in the groups

In the CYC group, 50% and 54% of the patients in the MMF group were responders (those who were not treated with steroids for a minimum of 6 months and without proteinuria, respectively) ($p=0.614$). The time to first relapse from initiation of CYC was 7 months (IQR

Table 1 Demographic variables of children receiving oral cyclophosphamide (CYC) and mycophenolate mofetil (MMF)

Demographic data	*CYC (n = 100)*		*MMF(n = 61)*		*p-value*
	Median	**IQR**	**Median**	**IQR**	
Age at onset of nephrotic syndrome, years	3.00	2-5.2	2.50	2.5–3.24	0.089
Age at start of CYC/ MMF, yr	5.70	3.7–7.9	5.00	5-5.51	0.102
Duration of NS before starting medication, years	1.90	1.3-3.275	1.70	1.7–2.40	0.205
Frequency of relapses/yr (Before)	4.00	4–4	4.00	3.92-4	**0.96**
Steroid maintenance dose(Before) (mg/kg/day)	1.20	0.845–1.45	1.00	0.98-1	0.004*
Dosage of medication$	154.00	149–160	973.50	953.06–973.5	
Demographic data#	*CYC (n = 100)*		*MMF(n = 61)*		*p-value*
	Number	*Percentage*	*Number*	*Percentage*	
Sex-Male, n (%)	75	75.0 (%)	50	82.0 (%)	0.336
Hypertension at onset, n (%)	7	7.0 (%)	3	4.9 (%)	0.595
Steroids only, n (%)	59	59.0 (%)	38	62.3 (%)	0.839
Prior Levomisole, n (%)	38	38.0 (%)	23	37.7 (%)	0.97
Prior MMF, n (%)	3	3 (%)	0	0 (%)	0.17
FRNS, n (%)	19	19.0 (%)	3	4.9 (%)	0.016*
SDNS, n (%)	81	81.0 (%)	58	95.1 (%)	0.016*
Renal Biopsy Findings					
MCD, n (%)	12	12 (%)	3	4.9 (%)	0.104
FSGS, n (%)	4	4.0 (%)	1	1.6 (%)	
Mes proliferative GN, n (%)	0	0.0 (%)	2	3.3 (%)	

SDNS steroid-dependent nephrotic syndrome, FRNS frequently relapsing nephrotic syndrome

$ Median cumulative CYC dose mg/kg and median daily MMF dose/m^2;

Subheadings of median and IQR apply only to continuous variables

Proportion data and percentages mentioned separately in the sub-table

*p value < 0.05 is significant

5.25–11) in comparison to 7 months (IQR 3.5–12) in the MMF group ($p=0.092$).

Incidence relapse rates

There were 177 relapses in the 100 patients who received CYC in one year (relapse rate: 1.77 relapses per patient-year), compared to 79 relapses in the 61 patients who received MMF (relapse rate: 1.295 relapses per patient-year). The difference in the incidence of relapse was 0.474 (95% CI, 0.088 to 0.861 relapses per patient-year), which was statistically significant (p value = 0.009).

After CYC therapy, the steroid dose decreased from 1.2 (IQR 0.8–1.5) to 0.8 (IQR 0.42–1) mg/kg/day ($P<0.001$). However, in the MMF group, the steroid dose decreased from 1.0 (IQR 0.98–1) to 0.7 (IQR 0.30–1.28) mg/kg/day ($P<0.001$). The reduction in the dependent dose between the groups was not significant.

According to the Kaplan–Meier curve, the relapse-free survival rate at 12 months in the CYC group was 35% (95% CI: 24–42%), whereas it was 38% (95% CI: 27–52%) in the MMF group ($p=0.729$). (Fig. 1)

We also compared the relapse-free survival time between the two age groups. In the less than 5-year-old age group, relapse-free survival at 12 months in the CYC group ($n=53$) and the MMF group ($n=43$) was 24% and 37%, respectively (p value = 0.6). At more than 5 years, the relapse-free survival times at 12 months in the CYC group ($n=47$) and the MMF group ($n=18$) were 47% and 39%, respectively (p value = 0.336). (Fig. 2)

Logistic regression analysis

According to the univariate analysis, young age at medication initiation (age ≤ 5 years) significantly affected the response rate. Of the responders in the MMF group, 72.2% were in the ≤ 5 years age group, whereas in the CYC group, 58% of the patients were in the > 5 years age group ($P=0.007$). With regard to the steroid maintenance dose, 87.1% of the responders in the MMF group had a steroid maintenance dose < 1 mg/kg/day, while 64.9% of the patients in the CYC group had a steroid maintenance dose > 1 mg/kg/day ($p=0.001$). The age of onset of NS had some influence on the response rate. Among the responders, 54.5% of the patients in the MMF group had an age of onset ≤ 3 years, whereas 66% of the patients in the CYC group had an age of onset > 3 years ($p=0.064$). Regarding the type of nephrotic syndrome (FR/SD), although there was a significant difference between the two groups, there were only 3 patients with FRNS in the MMF group. (Table 2)

Multivariate logistic regression analysis revealed that children aged less than 5 years at the start of treatment had a nearly 3-fold greater response to MMF therapy than to CYC therapy (OR = 2.988, CI -1.055-8.468) (p value = 0.039). CYC therapy was associated with a

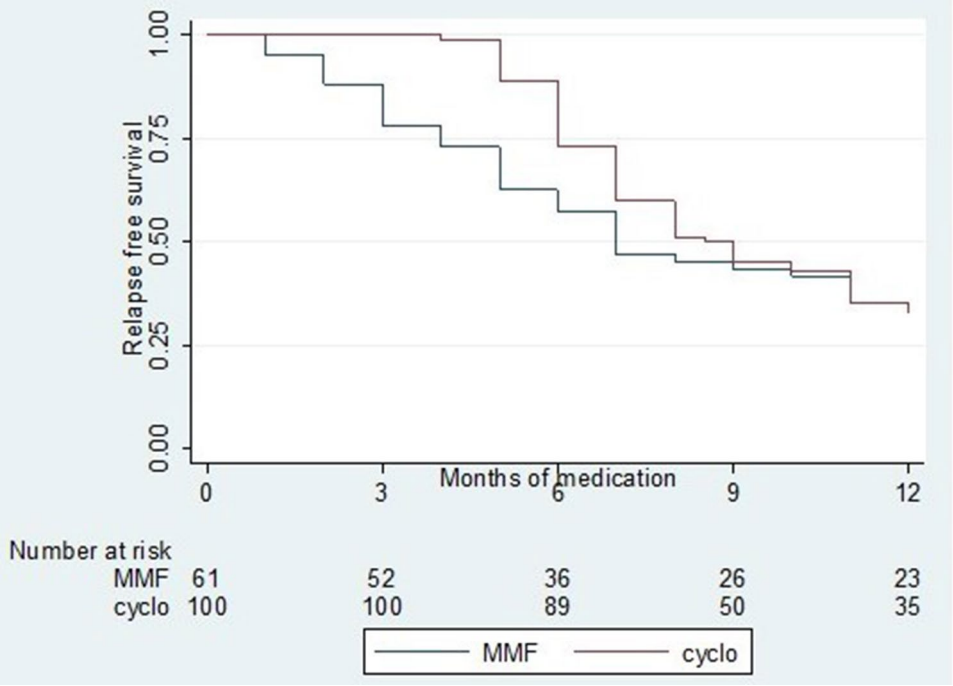

Fig. 1 Relapse-free survival according to steroid-sparing agent (Kaplan–Meier analysis)

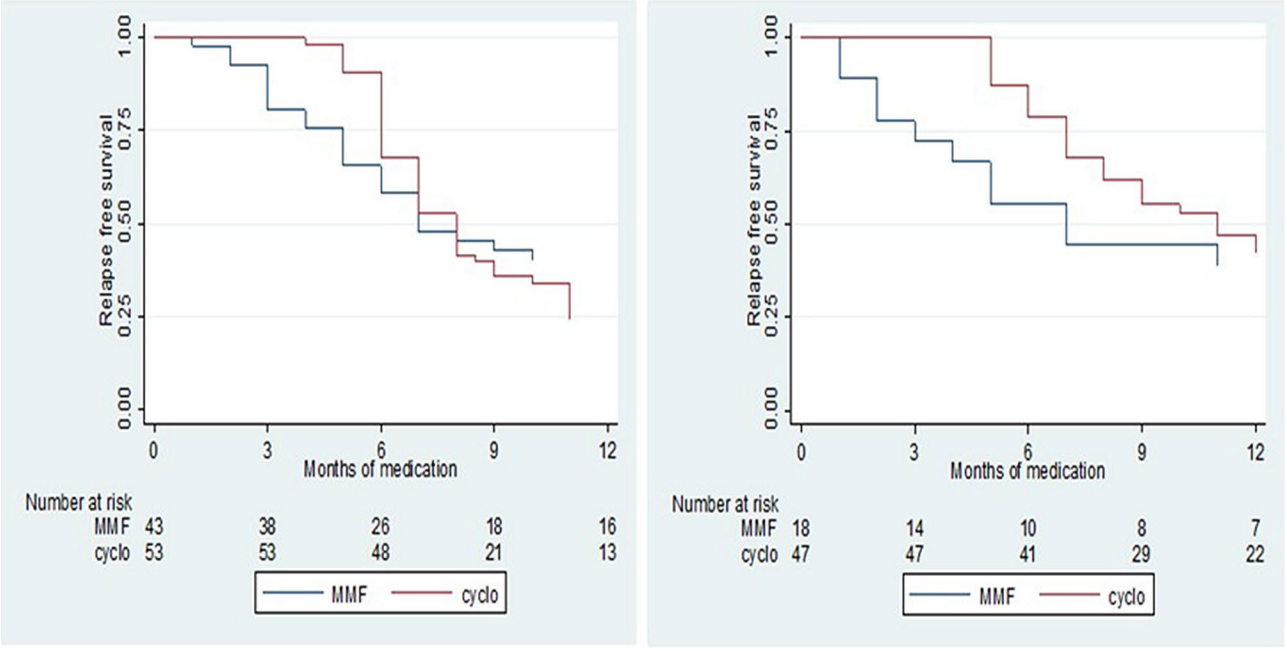

Fig. 2 Relapse-free survival in less than 5 years age and more than 5 years group according to steroid-sparing agent

significantly better response in patients with a prior steroid maintenance dose>1 mg/kg/day (OR=12.517, CI -3.331-47.036) (p value=0.001) (Table 3).

Patient status after one year

51% of patients in the CYC group experienced treatment failure [(frequent relapses (≥3)] compared to 20% in the MMF group (p=0.001). (Fig. 3) No patient in either group shifted to a steroid-resistant state. After one year of the study period, in the CYC group, 49% of patients improved (no relapse in 35%, infrequent relapse in 14%), whereas 80% of patients improved in the MMF group (no relapse in 38%, infrequent relapses in 42%) and did not require alternative medicines.

Table 2 Factors affecting response to oral cyclophosphamide and mycophenolate in children with nephrotic syndrome (univariate regression analysis)

Univariate Variables		*Responder Group*				*p-value*
		CYC (n = 100)		*MMF (n = 61)*		
Age of onset of NS, yrs (%)	≤ 3 years	17	34.0%	18	54.5%	0.064
	> 3 years	33	66.0%	15	45.5%	
Sex, n (%)	F	13	26.0%	9	27.3%	0.898
	M	37	74.0%	24	72.7%	
Prior Levomisole, n (%)	N	31	62.0%	20	60.6%	0.898
	Y	19	38.0%	13	39.4%	
Indication of Medication, n (%)	FRNS	13	26.0%	1	3.0%	0.006*
	SDNS	37	74.0%	32	97.0%	
Steroid maintenance dose Before, n (%)	< 1 mg/kg/day	13	35.1%	27	87.1%	0.001*
	> 1 mg/kg/day	24	64.9%	4	12.9%	
Age of start of medication, n (%)	≤ 5 years	21	42.0%	24	72.7%	0.007*
	> 5 years	29	58.0%	9	27.3%	
Duration of illness n(%)	≤ 2 years	34	68.0%	25	75.8%	0.472
	> 2 years	16	32.0%	8	24.2%	

*p value < 0.05 is significant

Table 3 Factors affecting response to oral cyclophosphamide and mycophenolate in children with nephrotic syndrome (multivariate regression analysis)

Multivariate variables	***p*-value**	**OR**	**95% C.I.**	
			Lower	**Upper**
Age of onset of NS	0.246	1.839	0.657	5.146
Age of start of medication	0.039*	2.988	1.055	8.468
Prior Steroid maintenance dose (mg/kg/day)	0.001*	12.517	3.331	47.036
Indication of medication (FR/SD)	0.022*	12.377	1.441	106.327

OR odds ratio, CI confidence interval *p value < 0.05 is significant

Safety profile

In this study, MMF was shown to have a better safety profile, with fewer patients experiencing adverse effects (9%) than CYC (25%) patients. (p=0.001). The most common side effect in CYC patients was leukopenia (TLC ≤ 4000 cells/cumm), which was observed in 23% of patients, led to temporary interruption of therapy and was reversible in all patients. One patient each on CYC developed hemorrhagic cystitis and UTI. Two patients on MMF had gastrointestinal symptoms, while no patient developed leukopenia. Two patients on MMF developed UTIs, and one patient developed an uncomplicated varicella zoster infection. (Table 4) All 161 children had normal renal function at the time of the last follow-up.

Discussion

This study was undertaken to compare the effectiveness and safety of MMF and oral CYC therapy in Indian children with steroid-sensitive nephrotic syndrome. Although the proportions of responders (those who did not respond to steroids for a minimum of 6 months along with absence of proteinuria) in the CYC group were 50% vs. 54% in the MMF group (p=0.614), there was a significantly lower number of relapses, with the use of MMF suggesting better treatment efficacy.

Age of initiation significantly affected the response rate to medications. Among the responders, 72.2% of the patients in the MMF group were in the ≤5 years age group, whereas 58% of the patients in the CYC group were in the >5 years age group (P=0.007). CYC therapy was associated with a significantly better response in patients with a prior steroid maintenance dose > 1 mg/kg/day (p value = 0.001).

Cyclophosphamide is an alkylating agent (type 2 nitrogen mustard) and one of the first steroid-sparing drugs used for the management of steroid-responsive NS. [12] Side effects caused by CYC include susceptibility to infections, bone marrow suppression, hemorrhagic cystitis, alopecia, gonadal toxicity, and teratogenicity. These conditions are infrequently observed, except for leucopenia. [13, 14] For these reasons, the use of CYC has been decreasing, particularly in developed countries, where MMF is now preferred over oral CYC.

MMF acts by inhibiting inosine monophosphate dehydrogenase, thereby affecting DNA synthesis and lymphocytic proliferation. [12] MMF in children with SSNS has a satisfactory safety profile and has gastrointestinal side effects in 3–11% of patients [15]. In a few patients who are not tolerant of MMF, it can be replaced with enteric-coated sodium mycophenolate, which is often tolerated better. For this reason, many pediatric nephrologists prefer to prescribe MMF if therapy is necessary for prolonged periods.

No other study has previously compared MMF with CYC in patients with FR/SD nephrotic syndrome.

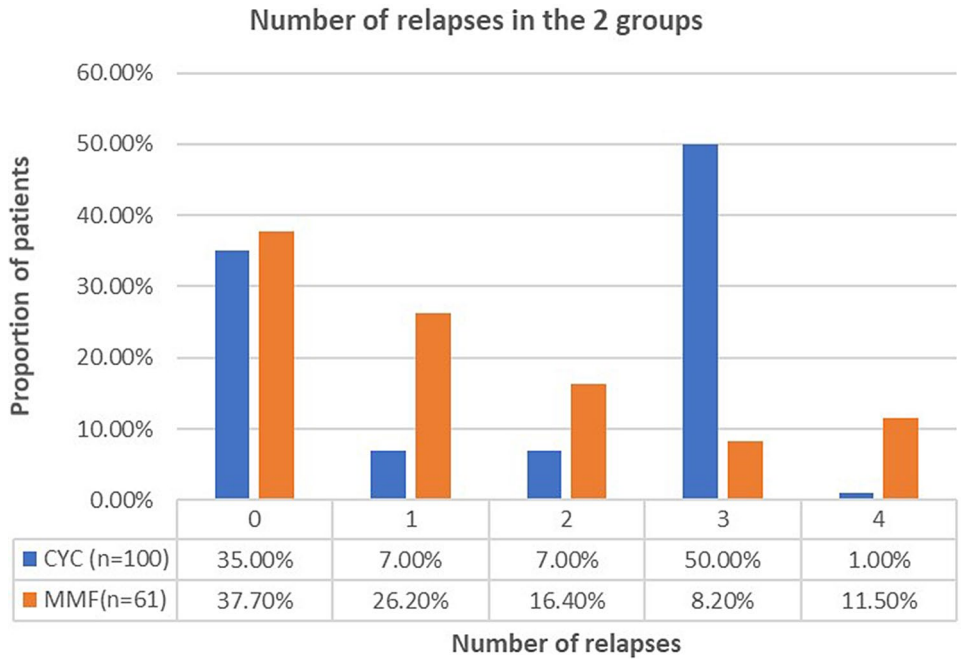

Fig. 3 Number of relapses over one year in both groups

Table 4 Adverse effects of medications (oral cyclophosphamide and mycophenolate mofetil)

Adverse effects	*CYC (n = 100)*		*MMF(n = 61)*	
	Number	**Percentage**	**Number**	**Percentage**
Leukopenia (TLC ≤ 4000 cells/cumm),	23	23%	0	0
Hemorrhagic cystitis	1	1%	0	0
UTI	1	1%	2	3%
Gastrointestinal symptoms	0	0	2	3%
Varicella Zoster	0	0	1	1.5%
Tinea Cruris	0	0	1	1.5%
Total	25	25%	5	9%

Although the proportions of children off steroids for 6 months (responders) in the two groups were similar, the difference in the incidence of relapse was statistically significant (-0.474 relapses/person-year) in favor of MMF.

Pharmacokinetic studies confirmed the value of therapeutic drug monitoring during MMF therapy. It was noted that subjects with low exposure (AUC < 50 µg·h/ml) had more relapses/year (1.4 relapses), in contrast to 0.27 relapses with high exposure (AUC > 50 µg·h/ml; $P < 0.05$). High-exposure MMF had an efficacy similar to CsA therapy. [16, 17]

Our previous study on CYC by Sandhu et al. highlighted that the treatment of children younger than 5 years with CYC should be avoided because it does not improve clinical outcomes and puts them at an unreasonable risk. [7] Since CYC is less effective in children younger than 5 years and has more gonadal toxicity during adolescence, the CYC treatment response is optimal in children aged 6 to 12 years. [12, 13] The current study showed that patients in the less than 5-year-old age group who received MMF had a significantly better response rate than those in the younger than 5-year-old age group who received CYC, suggesting that MMF is a better alternative for this age group.

While the CYC dosage is typically calculated based on body weight (mg/kg), the study showed suboptimal effectiveness in children under 5 years of age. This could be due to discrepancies in dosage calculations for children under 30 kg, where body surface area (BSA) might be a more appropriate metric and could influence treatment efficacy in younger children. Although there was a considerable difference in cumulative dosage depending on BSA in different age groups, our prior study on CYC by Jasjeet et al. revealed that this difference did not alter responsiveness to CYP. [7] Vester et al., however, demonstrated a significant association between sustained remission and a cumulative dosage per BSA of more or less than 5040 mg/m2 (45% vs. 11%, $p < 0.01$). For optimal results, younger children might require dosage calculations based on the BSA [18].

MMF and oral cyclophosphamide in steroid-sensitive nephrotic syndrome patients have not been compared in any previous study. The strengths of this study included its relatively large sample size and low attrition rate.

An important limitation of this study was its open-label nonrandomized design and comparison of two

different cohorts treated with two steroid-sparing agents; one cohort was retrospective. The two populations were not matched for sample size, dose of steroids, or type of nephrotic syndrome. The sample sizes of the two cohorts were not the same. The baseline steroid maintenance dose was greater in the CYC group, suggesting that the CYC group had more difficult cases, which may impact the response to treatment. One-fifth of the patients in the CYC group were of frequent relapsing compared to MMF group, the majority of whom experienced steroid-dependent disease. We could not monitor blood levels of mycophenolic acid because of its nonavailability. Although we used a uniform average dose of MMF (1000 mg/$m^{2)}$ in most patients, this dose is lower than the standard dose of MMF used for SDNS (1200 mg/$m^{2)}$. The efficacy of MMF treatment could have improved if therapy was guided by therapeutic C0/AUC plasma levels and higher doses of MMF were used.

The results of this study showed that MMF treatment was similar to CYC in children with relapsing nephrotic syndrome in terms of the responder rate (off steroid for 6 months or more). MMF therapy was associated with a favorable response in terms of the frequency of relapses, treatment failure, and safety profile. MMF therapy had a threefoldfold greater effect on less than 5-year-old children than CYC therapy. CYC is currently rarely used in children in developed countries due to its toxicity concerns despite its good efficacy.

This could be one of the first cohort studies between the two steroid-sparing agents in a developing country, looking at their safety and efficacy and helping in the selection of steroid-sparing agents in patients with frequent relapses or steroid-dependent nephrotic syndrome in different age groups.

Survival curve showing time to relapse from initiation of medications. Relapse events occurred within 12 months from treatment initiation. Blue line depicts patients receiving MMF and red line depicts patients receiving CYC.

(Overall relapse-free survival with CYP vs. MMF at 12 months was 35% vs. 38% ($p=0.729$).

Time to relapse from initiation of medications. Relapse events occurred within 12 months from treatment initiation. Blue line depicts patients receiving MMF and red line depicts patients receiving CYC. Left graph depicts age at medication ≤ 5 years and right graph depicts age at medication > 5 years.

In the less than 5-year-old age group, relapse-free survival at 12 months in the CYC group ($n=53$) vs. MMF group ($n=43$) was 24% vs. 37%, respectively (p-value = 0.6).

In more than 5 years, relapse-free survival time at 12 months in the CYC group ($n=47$) vs. the MMF group ($n=18$) was 47% vs. 39%, respectively (p-value = 0.336).

Blue bar depicts patients receiving CYC and orange bar depicts patients receiving MMF. #Numbers 0,1,2,3,4 in the X axis indicate the number of relapses.

Abbreviations

CYC	Oral cyclophosphamide
MMF	Mycophenolate mofetil (MMF)
FRNS	Frequent relapsing nephrotic syndrome
SDNS	Steroid dependent nephrotic syndrome
IQR	Interquartile range
OR	Odds ratio
CI	Confidence interval
CTRI	Clinical Trials Registry of India
NS	Nephrotic syndrome
eGFR	Estimated Glomerular Filtration Rate
urine PCR	Urine protein creatinine ratio
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SPSS	Statistical Package for the Social Sciences
TLC	Total Leukocyte Count
UTI	Urinary tract infection
DNA	Deoxyribonucleic acid
AUC	Area Under the Curve
CsA	Cyclosporin A
BSA	Body surface area

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03739-z.

Supplementary Material 1

Acknowledgements

The authors acknowledge all of the parents of children with nephrotic syndrome around the world for their patience and perseverance who are constantly involved in the management of children with nephrotic syndrome.

Author contributions

NG, DB: recruited the subjects, collected the data, carried out a literature review, and prepared the initial draft of the manuscript; PAP, SB, SK: contributed to manuscript writing; GSD: conceived and designed the study, analyzed the data, and finalized the manuscript. All authors have approved the manuscript submitted.

Funding

No funding was required and not taken in this study.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee Board of Dayanand Medical College and Hospital, Ludhiana, Punjab, India. The study was registered at the Clinical Trials Registry of India (http://ctri.nic.in; CTRI/2021/06/034421 [Registered on: 28/06/2021]. Written informed consent was obtained from the caretakers of all patients, and assent was obtained for children older than 7 years. Parent information sheet containing background information, safety of the study and possible benefit were provided prior to obtaining consent. The investigators ensured that the subjects' anonymity is maintained. On the case report forms or other documents, participants will not be identified by their names, but by their assigned identification number.

Consent for publication

Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 9 April 2024 / Accepted: 30 August 2024
Published online: 09 September 2024

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