Original Article

Outcomes of Mycophenolate Mofetil vs. Intravenous Cyclophosphamide in Induction Therapy of Childhood-Onset Lupus Nephritis

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Background: Intravenous cyclophosphamide (IVCY) concomitant with corticosteroids demonstrated better outcomes in therapy of proliferative lupus nephritis albeit adverse effects may occur. Mycophenolate mofetil (MMF) is a newer oral medication for treating lupus nephritis.

Objective: To compare renal outcomes between IVCY and MMF in conjunction with corticosteroid for induction therapy of proliferative lupus nephritis.

Materials and Methods: The authors reviewed the medical records from four university hospitals of children who received prednisolone with either MMF or IVCY for induction therapy of proliferative lupus nephritis between 2005 and 2014 in the present retrospective cohort study.

Results: Twenty-eight and 85 patients were included in the MMF and IVCY group, respectively. The respective mean age at MMF and IVCY initiation was 12.36±2.87 and 11.84±3.04 years. Renal remission was not significantly different between the groups (p=0.690). Non-nephrotic range proteinuria (adjusted OR 2.93, 95% CI 1.23 to 6.94, p=0.015), and high initial GFR (adjusted OR 2.93, 95% CI 1.14 to 7.56, p=0.026) were significantly associated with achieving renal remission. Both infectious (82.1%) and non-infectious complications (96.9%) were more common in the IVCY group. Neither death nor end-stage renal disease (ESRD) occurred during the induction therapy.

Conclusion: There was no significant difference in renal remission whether children received MMF or IVCY for induction therapy of lupus nephritis; however, adverse events occurred less frequently in the MMF group.

Keywords: Children, Lupus nephritis, Systemic lupus erythematosus, Mycophenolate, Cyclophosphamide, Induction

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Lupus nephritis in childhood-onset systemic lupus erythematosus (SLE) is more frequent and severe than in adults. The severity of lupus nephritis is a significant prognostic factor in SLE patients, so the more effective the treatment of lupus nephritis the better the outcome[1]. Although systemic corticosteroid is essential for therapy of proliferative lupus nephritis, outcomes among these patients are significantly improved after administration of intravenous cyclophosphamide (IVCY) in conjunction with steroid treatment[2-7]. The two phases of IVCY therapy in proliferative lupus nephritis include induction and maintenance. Renal remission after a 6-month-course of induction phase is crucial for a favorable outcome.

Adverse events and infection from IVCY such as, alopecia, hemorrhagic cystitis, malignancy, gonadal failure may occur[6-8]. Mycophenolate mofetil (MMF)

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is a newer oral medication for treatment of lupus nephritis. It has fewer side effects but has variable outcomes in adults when compared with IVCY[9-19]. Moreover, not much research has been done in children.

In the present study, the authors compared renal remission after a six-month induction course between MMF and IVCY in therapy of childhood-onset proliferative lupus nephritis, and determined its associated factors and adverse events.

Materials and Methods

The medical records of children diagnosed SLE with proliferative lupus nephritis and treated with MMF or IVCY initiation between January 2005 and June 2014 from the four University Hospitals in Thailand, which are Srinagarind Hospital, Siriraj Hospital, King Chulalongkorn Memorial Hospital and Maharaj Nakorn Chiang Mai Hospital, were reviewed in the present retrospective cohort study.

The inclusion criteria were children who (a) received induction therapy with MMF or IVCY, (b) were under 18 at diagnosis and initiation of MMF or IVCY therapy, (c) fulfilled at least 4 of the 11 American College of Rheumatology (ACR) criteria for diagnosis of SLE[20], (d) had biopsy-proven lupus nephritis based on the World Health Organization (WHO) class III, IV, or mixed class IV and V before or during the induction therapy, and (e) had a urine protein and creatinine ratio of 1.0 mg/mg or greater at induction therapy initiation.

The exclusion criteria were patients who (a) had a glomerular filtration rate (GFR) of less than 30 ml/minute/1.73 m^2 persisting for at least three months, (b) required any dialysis modalities more than four weeks before the initiation of the induction therapy, (c) were treated with other immunosuppressive drugs except corticosteroids within six months prior to MMF or IVCY initiation, or (d) had no urine protein and creatinine collection either at the initiation or at completion of the induction therapy.

The present study was approved by the Ethics Committees of Khon Kaen University (HE571474), Mahidol University (Si279/2015), Chulalongkorn University (090/58) and Chiang Mai University (189/2558). The need for informed consent was waived.

Treatment

All patients received prednisolone and either MMF or IVCY for induction therapy. IVCY was given every month for six months at a dose of 0.5 to 1 g/m^2/dose in the IVCY group. In the MMF group, MMF was given orally twice a day at a dose of 800 to 1,200 mg/m^2/day for six months. Hydroxychloroquine and anti-hypertensive drugs were given to the patients based on the clinical judgement of the pediatric nephrologist.

Operational definitions

The primary outcome was a renal response after completion of a 6-month course of induction therapy of IVCY or MMF, defined as an ordinal outcome (i.e., complete, partial, or no remission), using urine protein and creatinine ratio (UPCR), and the estimated glomerular filtration rate (eGFR). Complete renal remission was defined as a UPCR of less than 0.5 mg/mg and a normal eGFR. Partial renal remission was defined as 50% or more UPCR reduction and a UPCR of less than 3.0 mg/mg, if the baseline UPCR was in the nephrotic range and the eGFR was stable or less than 20% worsening. "No remission" was defined as patients who (a) did not meet any criteria of remission, (b) needed rescue therapy with other treatment such as other immunosuppressive drugs or dialysis, or (c) died due to the disease or complications of treatment during the induction therapy. The estimated eGFR was calculated using the Schwartz's formula.

Sample size calculation

The formula for ordinal logistic regression with α=0.05, power 80% and two-tailed analysis was used for sample size calculation. The calculated sample size was 151 patients.

Statistical analysis

Renal remission was analyzed by using ordinal logistic regression adjusted for any clustering effect. Factors associated with renal remission were analyzed using univariate logistic regression analysis. All variables in the univariate logistic regression analysis were included in the final multivariate logistic regression analysis. The results were reported as the adjusted odds ratio. A p-value of less than 0.05 was considered to be statistically significant. Data were analyzed using Stata, version 10 (StataCorp LP, College Station, TX, USA). The potential bias in the present study included selection bias, missing data, and varied drug dosage adjustment in each center due to the retrospective study design. All data from any participant with missing values were deleted.

Results

Demographic data

One hundred thirteen patients were included in

Table 1. Demographic data of patients (n=113)

Data	MMF (n=28) Mean±SD	IVCY (n=85) Mean±SD	p-value
Age at diagnosis of SLE (years)	10.75±2.30	11.09±3.02	0.239
Age at initiation of induction (years)	12.36±2.87	11.84±3.04	0.505
Sex; n (%)			0.041*
Male	1 (3.6)	17 (20.0)	
Female	27 (96.4)	68 (80.0)	
Renal pathology; n (%)			0.079
Class III	8 (28.6)	11 (12.9)	
Class IV	20 (71.4)	74 (87.1)	
GFR at induction initiation (ml/minute/1.73 m^2)	92.14±28.41	87.66±34.70	0.574

MMF=mycophenolate mofetil; IVCY=intravenous cyclophosphamide; SD=standard deviation; SLE=systemic lupus erythematosus; GFR=glomerular filtration rate

* Statistical significance, p<0.05

Table 2. Renal remission after induction course completion

Drug	Renal remission; n (%)			Total
	No remission	Partial remission	Complete remission	
MMF	7 (25.0)	9 (32.1)	12 (42.9)	28
IVCY	19 (22.4)	26 (30.6)	40 (47.1)	85
Total	26 (23.0)	35 (31.0)	52 (46.0)	113

MMF=mycophenolate mofetil; IVCY=intravenous cyclophosphamide

the present study. Twenty-eight patients used MMF and 85 received IVCY for induction therapy. Males comprised more of the IVCY group (20.0%) than the MMF group (3.6%) (p=0.041). The respective mean age at diagnosis of SLE was 10.75±2.30 and 11.09±3.02 years in the MMF and IVCY group (p=0.239). The respective mean age for induction therapy initiation with MMF versus IVCY was 12.36±2.87 and 11.84±3.04 years (p=0.505). Lupus nephritis WHO class IV was primarily demonstrated from renal biopsy among patients of both the MMF (71.4%) and IVCY (87.1%) group (p=0.079). The respective mean initial GFR was 92.14±28.41 and 87.66±34.70 ml/minute/1.73 m^2 in the MMF and IVCY group, which was not significantly different, p=0.574 (Table 1).

Treatment data

The median prednisolone dosages (interquartile range, IQR) at induction initiation were 0.90 (0.52) and 1.25 (0.63) mg/kg/day in the MMF group and IVCY group, respectively. The median prednisolone dosages (IQR) at induction completion were 0.25 (0.26) and 0.38 (0.47) mg/kg/day in the MMF group and IVCY group, respectively. The median differences of prednisolone dosage reduction (IQR) between initiation and completion of induction were 0.49 (0.40) and 0.83 (0.69) mg/kg/day in the MMF group and IVCY group, respectively, which were significantly different between the two groups (95% CI 0.09 to 0.49, p=0.007). The mean dosage of MMF was 882.45±211.47 mg/m^2/day, and the mean dosage of IVCY was 626.25±129.29 mg/m^2/dose. Hydroxychloroquine was used in 14 of 28 patients (50.0%) in the MMF group, and in 57 of 85 patients (67.1%) in the IVCY group (p=0.105). Enalapril was administered in 21 of 28 patients (75.0%) in the MMF group, which was not significantly different from the 57 of 85 patients (67.1%) in the IVCY group (p=0.431).

Outcomes and adverse events

Complete and partial remission occurred in about three quarters of the patients on induction therapy whether it was MMF or IVCY. Renal remissions in both groups were not significantly different (OR 0.85, 95% CI 0.38 to 1.88, p=0.690) (Table 2).

In the univariate and multivariate logistic regression analyses, non-nephrotic range proteinuria (adjusted OR 2.93, 95% CI 1.23 to 6.94, p=0.015), and high initial GFR (adjusted OR 2.93, 95% CI 1.14 to 7.56, p=0.026) were significantly associated with achieving renal remission, while induction drugs, gender, hydroxychloroquine, and angiotensin-converting enzyme inhibitor usage were not significantly associated (Table 3, 4).

There were 56 infection episodes in 43 patients,

Table 3. Univariate analysis of factors associated with renal remission

Factors	Crude OR	95% CI	p-value
MMF	0.85	0.38 to 1.88	0.690
Female	1.39	0.54 to 3.52	0.487
High initial GFR	3.32	1.35 to 8.15	0.009*
Non-nephrotic ranged proteinuria	3.45	1.50 to 7.88	0.003*
HCQ usage	1.65	0.81 to 3.37	0.166
ACEI usage	1.04	0.49 to 2.17	0.915

OR=odds ratio; CI=confidence interval; MMF=mycophenolate mofetil; GFR=glomerular filtration rate; HCQ=hydroxychloroquine; ACEI=angiotensin-converting enzyme inhibitors

* Statistical significance, p<0.05

Table 4. Multivariate analysis of factors associated with renal remission

Factors	Adjusted OR	95% CI	p-value
MMF	0.73	0.30 to 1.74	0.478
Female	1.21	0.44 to 3.36	0.709
High initial GFR	2.93	1.14 to 7.56	0.026*
Non-nephrotic ranged proteinuria	2.93	1.23 to 6.94	0.015*
HCQ usage	1.35	0.63 to 2.89	0.432
ACEI usage	0.73	0.32 to 1.63	0.442

OR=odds ratio; CI=confidence interval; MMF=mycophenolate mofetil; GFR=glomerular filtration rate; HCQ=hydroxychloroquine; ACEI=angiotensin-converting enzyme inhibitors

* Statistical significance, p<0.05

mostly in the IVCY group (82.1%). Most of the episodes were caused by bacteria (62.5%). Pneumonia and cellulitis were the two most frequent infections in the IVCY group. The two most common infection in the MMF group were candidiasis and paronychia. Non-infectious complications were also more common in the IVCY group (96.9%). The three most common non-infectious complications were leucopenia, hemorrhagic cystitis, and alopecia. Neither diarrhea nor abdominal pain associated with induction medications occurred in the present study. Rescue therapy with pulse methylprednisolone was administered in eight cases in the IVCY group. The reasons for rescue therapy were worsening lupus nephritis in four cases, cerebral lupus in three cases, and cardiac involvement in one case. Neither death nor end-stage renal disease (ESRD) occurred during induction therapy in both groups.

Discussion

Although IVCY is effective in therapy of proliferative lupus nephritis for preserving renal function and reduction of ESRD, both infectious and non-infectious adverse events are of concern[2-8,21]. MMF is a non-competitive and selective inhibitor of inosine monophosphate dehydrogenase (IMPDH). It can inhibit T- and B-cell proliferation, as well as antibody production[22]. It has been proposed for use in treatment of SLE, as well as lupus nephritis[23,24]. Comparison between MMF and IVCY has been studied, but mostly in adults[9-19].

According to a meta-analysis studies of randomized controlled trials (RCT) on the treatment of proliferative lupus nephritis and a systematic review from Cochrane database, MMF was as effective as cyclophosphamide in achieving remission but was safer, in terms of less leucopenia, alopecia, and ovarian failure[7,17,19]. Two other meta-analyses showed the superiority of MMF for inducing renal remission, as evidenced by the development of fewer non-infectious adverse events compared with IVCY[16,18]. Most patients in those studies, however, were adults and few adolescents. There was only one RCT of MMF therapy for lupus nephritis in adolescents, but it was a subgroup analysis of a multinational RCT of SLE patients (age 12 to 75 years) with lupus nephritis[12]. Of the 24 adolescents in the current subgroup analysis, a respective 70% and 57% of the renal response rates were found in the MMF and IVCY induction treatment of lupus nephritis (p=0.53). The small sample size is likely undermined the statistical significance[25]. A retrospective cohort study in children demonstrated a higher remission rate in the MMF group (83%) compared with the IVCY group (57%) after six months of induction therapy[11]. Despite a larger sample size in the present study of childhood-onset SLE, renal remission was not statistically different between the MMF and IVCY groups, which is consistent with some previous meta-analyses[7,17]. Of note, in the IVCY group in the present study, there was a higher prednisolone dosage and pulse methylprednisolone usage for rescue therapy for both renal and non-renal purposes. However, the present study had some limitations due to the retrospective study design particularly in selection bias, incomplete data, varied drug dosage adjustment in each center, and small sample size.

The severity of proteinuria and initial renal function were associated with achieving renal remission in the induction course of treatment, thus, early initiation of adjunctive immunosuppressive agents with corticosteroid is important for inducing

renal remission in children with proliferative lupus nephritis.

Adverse events, including both infection and non-infection, were more common in the IVCY group as was found in other studies[7,10,16,18]. Unlike some previous studies, gastrointestinal symptoms such as diarrhea or abdominal pain, were not found in the present study[7,16].

Conclusion

In conclusion, renal remission was not significantly different between children receiving MMF and IVCY for induction therapy of childhood-onset lupus nephritis, however, adverse events seem to be less in the MMF group.

What is already known on this topic?

Renal remission is crucial for better outcome in therapy of lupus nephritis. The outcomes for induction treatment with the older drug (IVCY) compared with the newer one (MMF) are debated. Few studies comparing between those two drugs in childhood-onset lupus nephritis have been published.

What this study adds?

Renal remission of children with proliferative lupus nephritis after a 6-month-course of induction therapy with MMF was not different from IVCY, but adverse effects seems to be more frequent in the IVCY group.

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Conflicts of interest

The authors declare no conflict of interest.

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