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Original Research Article

A clinical study of mycophenolate mofetil combined with low-dose steroids in the management of pediatric systemic lupus erythematosus

Qiming Pang, Bangtao Li, Bo Ding, Shuo Gu, Jiaoyang Li, Suli Zhang*
Hainan Women and Children's Medical Center, Haikou, China

For correspondence:* ***Email:* *69704936@qq.com;* ***Tel:*** *86018678186209*

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Abstract

Purpose: *To investigate the efficacy and safety of mycophenolate mofetil (MMF) combined with low-dose steroids in the treatment of pediatric systemic lupus erythematosus (pSLE).*
Methods: *A total of 76 children were diagnosed and admitted with SLE, lupus nephritis (LN) and type IV diffuse proliferative glomerulonephritis at Hainan Women and Children's Medical Center, Haikou, China from March 2017 to December 2018, had their clinical data analyzed retrospectively. Among them, 38 children received methylprednisolone pulse combined with MMF and intermittent oral low-dose glucocorticoids (GC), labelled MMF group, while the remaining 38 children, which served as control group, were treated with oral GC and transitional reduction. Pertinent biochemical parameters were evaluated*
Results: *Compared with control group, MMF group showed a notably lower level of erythrocyte sedimentation rate (ESR), a higher level of complement C3, lower level of serum creatinine (Scr) and 24-h urine protein level 6 months after treatment ($p < 0.05$). Albumin level was higher in MMF group at 6 months and 12 months after treatment than in the control group. Compared to control group, the SLEDAI score in MMF group was significantly lower at 6 months and 12 months after treatment ($p < 0.05$). Body mass index, triglyceride, fasting blood glucose and intraocular pressure levels in the MMF group were significantly lower than those in the control group ($p < 0.05$). Post-treatment, peripheral blood $CD3^+$ and $CD4^+$ T lymphocytes, $CD4^+/CD8^+$ ratio and NK cell levels in the two groups were significantly increased, while $CD8^+$ T lymphocyte level declined.*
Conclusion: *MMF combined with low-dose methylprednisolone controls symptoms early and mitigates renal injury in the treatment of pSLE. It is also safe, and effectively regulates the patient's cellular immune function.*

Keywords: *Mycophenolate mofetil, Methylprednisolone, Proliferative glomerulonephritis, Lupus nephritis, Systemic lupus erythematosus, SLEDAI score*

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INTRODUCTION

Systemic lupus erythematosus (SLE) ranks second on the list of systemic connective tissue diseases which affect children, with the incidence rate on the increase every year. Compared to adults, pediatric SLE (pSLE) is characterized by a more acute onset, and a rapid progression and involvement of multiple organs and systems, which threatens patients' lives [1,2], and lupus

nephritis (LN) is an important factor which affects the prognosis [3]. At present, glucocorticoids (GC) remain the first choice for treating SLE, and it also serves as the main medicine used to treat more than 90% of patients with pSLE [4]. Long-term oral GC combined with immunosuppressants is widely used to treat SLE, which is of significance to the improvement of the long-term prognosis [5]. However, in the treatment of pSLE, there is no GC-based application standard yet, so different pediatric rheumatology centers employ different therapeutic schemes; thus, long-term, high-dose oral GC may cause obvious adverse reactions [6].

Mycophenolate mofetil (MMF) is an immunosuppressant which is used in anti-rejection therapy after organ transplantation [7]. In 1998, MMF was first adopted by Briggs *et al* in the treatment of glomerular diseases, and its efficacy was well established [8]. MMF has a unique advantage in the treatment of vasculitis and kidney diseases. Moreover, with good tolerance, it has little adverse reaction on liver and kidneys, and hardly any inhibitory effect on the bone marrow. Thus, great progress has been made in the treatment of kidney diseases in children [9,10]. The purpose of the present study was to investigate the efficacy and safety of methylprednisolone pulse, combined with MMF and intermittent oral low-dose GC in the management of pSLE.

METHODS

Subjects

A total of 76 children were admitted with SLE, LN and type IV diffuse proliferative glomerulonephritis, and diagnosed by pathology from March 2017 to December 2018, were selected as research subjects. Among them, 38 patients which were administered with methylprednisolone pulse combined with MMF, and intermittently oral low-dose GC made up the MMF group, while the other 38 patients which were treated with oral GC and transitional reduction made up the control group. Inclusion criteria: a) patients aged 7 - 16 years old; b) those who received treatment for the first time; and c) those without contraindications to GC. Exclusion criteria: a) patients with severe heart, liver or kidney diseases; b) those with various infections, especially tuberculosis or fungal infections, lupus crisis, or neuropsychiatric SLE; and c) those with drug allergies. Baseline information between the two groups of patients showed no statistical difference (Table 1, $p > 0.05$). The study was conducted in line with the Declaration of Helsinki. This study was approved by the Ethics Committee of Hainan Women and Children's Medical Center (17-HN-340AC-02). Signed written informed consents were obtained from the guardians.

Table 1: Baseline demographic and clinical characteristics of the studied children

Parameter	MMF group (n=38)	Control group (n=38)	*P*-value
Age	10.57±1.95	11.17±1.89	0.177
Gender (*male/female*)	7/31	4/34	0.516
Course of disease (months)	1.13±0.76	1.04±0.58	0.564
SLEDAI score (points)	15.22±3.71	15.88±4.43	0.484
Activity of disease			0.714
Mild	11 (28.9%)	14 (36.8%)	
Moderate	19 (50.0%)	18 (47.4%)	
Severe	8 (21.1%)	6 (15.8%)	

Treatment methods

The MMF group was treated with methylprednisolone pulse therapy (20 mg/kg/day, max dose: 1,000 mg/day), three days every week initially at an interval of 4 days between courses, for 3 consecutive courses. Thereafter, the therapy was administered for three days every week, at an interval of 2 - 3 weeks for 3 consecutive courses, and then gradually extended to three days every week at an interval of 4 weeks, giving a total of 6 - 9 times of pulse therapy, depending on the patient's condition, for a total period of 3 - 6 months. During the intervals, oral prednisone acetate was administered (7.5 - 10.0 mg/d), while cyclophosphamide (CTX) was given at the same time, once every two weeks.

When the cumulative dosage reached 120 - 140 mg/kg, CTX was replaced with oral MMF (30 - 50 mg/kg/day, twice daily, orally). Oral hydroxychloroquine (HCQ) was also routinely given (5 - 7 mg/kg/day, twice daily, orally).

Control group was treated with methylprednisolone pulse for 3 days, at an interval of 4 days between courses, for 2 courses. Subsequently, oral GC and transitional reduction were adopted. MDP and CTX were given at the same time, once every two weeks. When the cumulative dosage reached 120 - 140 mg/kg, CTX was stopped and substituted with routine oral HCQ (5 - 7 mg/kg/day, twice daily, orally).

Evaluation of indicators

The score of SLE Disease Activity Index (SLEDAI), erythrocyte sedimentation rate (ESR), complementary C3 and C4 levels, serum albumin and serum creatinine (Scr) were determined prior to treatment, and at 1, 6 and 12 months after treatment; 24-h urine protein levels were also obtained.

Clinical efficacy of the treatments given to the two groups of children was evaluated. Complete remission was defined as the disappearance of clinical symptoms and attainment of normal indicators 6 months after treatment. The treatment was effective if SLEDAI score dropped by more than two-thirds 6 months after treatment, the clinical symptoms and indicators significantly declined, and the patient's condition was stabilized after medication. Effective treatment was taken as decline in SLEDAI score between 1/3 and 2/3, and reduction in clinical symptoms and indicators 6 months after treatment. Ineffective treatment meant that clinical symptoms were slightly relieved after treatment, and the patient's condition was unstable, and the symptoms of SLE were evident. Clinical effectiveness (CE) was calculated as in Eq 1.

$$CE\ (\%) = \{(R + E)/T\}100 \quad \ldots\ldots\ldots\ldots\ldots (1)$$

where R, E and T are the no. of complete remission cases, no. of markedly effective case, and total no. of cases, respectively. The body mass index (BMI), fasting blood glucose (FBG), triglyceride (TG) and intraocular pressure (IOP) levels were determined before treatment, and at 1, 6 and 12 months after treatment. Adverse reactions in the children were recorded, including infections, acute pancreatitis, gastrointestinal bleeding and perforation, nervous system dysfunction (convulsions, mental changes and behavioral abnormalities) and arrhythmia. Flow cytometry was utilized to determine T lymphocyte subsets, $CD4^+/CD8^+$ ratio and changes in NK cell between the two groups of patients before treatment and 6 months after treatment.

Statistical analysis

SPSS statistical analysis software (version 26.0) was adopted for statistical analysis. Measurement data are expressed as mean ± standard deviation (SD). Differences between the two groups were analyzed using t Student's t-test. Enumeration data were expressed as percentage (%), and analyzed using chi-square test or Fisher's exact probability test. $P < 0.05$ indicate significant difference.

RESULTS

Efficacy indicators and inflammatory factors

Prior to treatment, there were no statistically significant differences in ESR, peripheral blood white blood cell count, complementary C3 and C4 levels, albumin, Scr, 24 h urine protein quantity and SLEDAI score between the two groups of patients ($p > 0.05$). Peripheral blood white blood cell count in the MMF group was higher compared with that in control group at 6 months and 12 months after treatment ($p = 0.013$, $p = 0.030$). MMF group showed a lower level of ESR ($p < 0.001$) and a remarkably higher level of complementary C3 ($p = 0.003$) compared to those in the control group.

Post-treatment, complementary C4 level was not statistically significant between MMF and control groups ($p > 0.05$). The albumin level in MMF group was higher compared to the control group at 6 months and 12 months after treatment ($p = 0.014$, $p = 0.009$). MMF group had a lower level of Scr ($p = 0.031$) as well as a lower level of 24-h urine protein level ($p < 0.001$) at 6 months after treatment compared with the control group. The SLEDAI score in MMF group was significantly lower than that in the control group 6 and 12 months after treatment ($p < 0.001$, $p = 0.012$). No significant differences were found for all the foregoing indicators between the two groups for the rest of the study period ($p > 0.05$, Table 2 and Table 3). In addition, clinical effectiveness was 89.5 % (34/38) in MMF group and 78.9 % (30/38) in the control group, and no marked differences were found between the two groups ($p = 0.175$) (Table 4).

Comparison of safety-related indicators between the two groups of children

Prior to treatment, there were no statistically significant differences in BMI, TG, FBG, and IOP levels between the two groups ($p > 0.05$). The MMF group exhibited a significantly lower level of BMI [21.04 ± 2.69 kg/m^2 *vs.* 24.73 ± 3.63 kg/m^2, $p = 0.019$], TG [(1.44 ± 0.61) mmol/L *vs.* 2.24 ± 0.59 mmol/L, $p = 0.009$], FBG [(4.53 ± 0.60) mmol/L *vs.* 4.99 ± 0.79 mmol/L, $p = 0.041$ and IOP [R/L = (16.35 ± 4.14/17.06 ± 4.21) mmHg *vs.* (18.45 ± 3.52/18.96 ± 4.10) mmHg, $p = 0.012$, $p = 0.039$] compared to the control group, and there were no statistically significant differences in the above indicators between the two groups in the rest of the time period of this study ($p > 0.05$) (Table 5).

Table 2: Comparison of renal function indices and inflammatory factors in SLE children in the two study groups

Parameter	MMT group (n=38)	Control group (n=38)	*P*-value
WBC ($\times 10^9$/L)			
Preoperative	1.24±0.15	1.29±0.13	0.125
1 month postoperative	3.84±0.58	3.62±0.47	0.073
6 months postoperative	4.83±0.59	4.11±0.55	0.013
12 months postoperative	5.29±0.63	4.74±0.60	0.030
ESR (mm/h)			
Preoperative	34.69±3.78	33.60±3.28	0.184
1 month postoperative	17.50±6.53	18.83±5.22	0.143
6 months postoperative	8.56±3.77	11.68±3.73	0.001
12 months postoperative	8.33±3.84	9.94±3.48	0.059
C3 (g/L)			
Preoperative	0.30±0.12	0.34±0.09	0.205
1 month postoperative	0.74±0.41	0.63±0.36	0.145
6 months postoperative	1.21±0.45	0.89±0.33	0.003
12 months postoperative	1.27±0.44	1.04±0.39	0.099
C4 (g/L)			
Preoperative	0.09±0.04	0.11±0.05	0.369
1 month postoperative	0.19±0.09	0.18±0.08	0.550
6 months postoperative	0.27±0.07	0.23±0.06	0.228
12 months postoperative	0.33±0.08	0.28±0.07	0.297
Albumin (g/L)			
Preoperative	18.12±1.55	17.86±1.61	0.476
1 month postoperative	23.21±1.94	22.39±1.86	0.064
6 months postoperative	25.89±1.99	23.44±1.74	0.014
12 months postoperative	28.67±2.52	25.74±2.07	0.009

Table 3: Comparison of renal function indices and inflammatory factors of SLE children in the two study groups (*contd.*)

Parameter	MMT group (n=38)	Control group (n=38)	*P*-value
Scr (μmol/L)			
Preoperative	148.78±14.51	150.65±16.06	0.596
1 month postoperative	121.82±11.11	125.25±10.79	0.176
6 months postoperative	109.18±12.08	115.73±12.93	0.031
12 months postoperative	106.99±10.59	111.55±11.39	0.057
24 h urine protein quantitation (g/24 h)			
Preoperative	3.15±1.64	3.30±1.46	0.675
1 month postoperative	1.19±0.91	0.98±0.79	0.286
6 months postoperative	0.28±0.09	0.40±0.12	0.001
12 months postoperative	0.18±0.08	0.21±0.10	0.153
SLEDAI score (points)			
Preoperative	15.22±3.71	15.88±4.43	0.484
1 month postoperative	7.90±5.54	9.34±4.70	0.226
6 months postoperative	2.36±1.31	4.57±2.68	0.001
12 months postoperative	1.81±1.07	2.45±1.10	0.012

Table 4: Comparison of clinical effectiveness of treatments in SLE children

Parameter	MMF group (n=38)	Control group (n=38)	*P*-value
Complete remission	16 (42.1%)	14 (36.8%)	
Markedly effective	13 (34.2%)	10 (26.3%)	
Effective	5 (13.2%)	6 (15.8%)	
Non-effective	4 (10.5%)	8 (21.1%)	
Overall effectiveness	34 (89.5%)	30 (78.9%)	0.175

Table 5: Comparison of safety-related indicators of children in the two groups

Parameter	MMT group n=38	Control group n=38	*P*-value
BMI (kg/m^2)			
Preoperative	18.27±3.35	18.89±3.17	0.410
1 month postoperative	17.61±3.09	18.11±3.73	0.527
6 months postoperative	20.33±3.52	22.02±3.57	0.083
12 months postoperative	21.04±2.69	24.73±3.63	0.019
Triglyceride (mmol/L)			
Preoperative	2.36±0.75	2.12±0.72	0.159
1 month postoperative	1.59±0.64	1.79±0.70	0.188
6 months postoperative	1.66±0.87	1.98±0.76	0.070
12 months postoperative	1.44±0.61	2.24±0.59	0.009
FBG (mmol/L)			
Preoperative	4.90±0.52	4.65±0.77	0.252
1 month postoperative	4.57±0.46	4.84±0.85	0.164
6 months postoperative	4.49±0.48	4.89±0.37	0.101
12 months postoperative	4.53±0.60	4.99±0.79	0.041
IOP (R/L, mmHg)			
Preoperative	16.13±4.56/17.10±3.86	16.48±4.76/17.38±4.05	0.358/ 0.514
1 month postoperative	17.26±3.58/17.70±4.16	17.68±3.87/17.97±3.93	0.265/ 0.434
6 months postoperative	17.43±3.09/18.24±3.89	18.08±3.13/18.54±3.77	0.114/ 0.478
12 months postoperative	16.35±4.14/17.06±4.21	18.45±3.52/18.96±4.10	0.012/ 0.039

Table 6: Comparison of immunological indicators of children in the two studied groups

Parameter	MMF group n=38	Control group n=38	*P*-value
$CD3^+$ T cell (%)			
Pretreatment	42.62±6.63	41.74±6.36	0.557
Post-treatment	53.54±7.88	50.37±8.14	0.089
$CD4^+$ T cell (%)			
Pretreatment	24.69±4.43	25.76±4.38	0.293
Post-treatment	34.24±3.98	32.82±3.49	0.066
$CD8^+$ T cell (%)			
Pretreatment	33.31±3.06	34.35±3.23	0.154
Post-treatment	26.41±3.46	28.83±3.42	0.003
CD4/CD8 ratio			
Pretreatment	0.62±0.17	0.66±0.16	0.294
Post-treatment	1.09±0.19	1.03±0.22	0.207
NK cell (%)			
Pretreatment	6.24±1.88	6.59±1.92	0.425
Post-treatment	10.51±2.22	9.39±2.39	0.038

In the MMF group, there were 4 cases of pneumonia, 13 cases of acute bronchitis, 9 cases of acute upper respiratory tract infection, and 2 cases of fungal infection within 1 year of treatment, while there were 6 cases of pneumonia, 16 cases of acute bronchitis, 15 cases of acute upper respiratory tract infection, 3 cases of fungal infection, and 1 case of acute lymphadenitis in the control group. In the MMF group, 5 patients were administered with oral nifedipine for elevated blood pressure during the pulse therapy, 4 cases with transient elevation of IOP, and 1 case with leukopenia, while there were 6 cases with elevation of IOP, no elevation of blood pressure and leukopenia in the control group. There were no complications such as acute pancreatitis, gastrointestinal bleeding and perforation, nervous system dysfunction (convulsions, mental changes and behavioral abnormalities) and arrhythmia.

T lymphocyte subset levels in peripheral blood

Before treatment, there were no statistically significant differences in $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes, $CD4^+/CD8^+$ ratio and NK cell levels of peripheral blood between the two groups of patients ($p > 0.05$). After treatment, peripheral blood $CD3^+$ while $CD4^+$ T lymphocytes, $CD4^+/CD8^+$ ratio and NK cell levels in the two groups of children were significantly increased, and $CD8^+$ T lymphocyte level markedly reduced ($p < 0.05$). MMF group had a significantly lower level of $CD8^+$ T lymphocyte ($p = 0.003$) and a significantly higher level of NK cell ($p = 0.038$) after treatment compared with control group, but

there were no statistically significant differences between the groups for the remaining indicators ($p > 0.05$, Table 6).

DISCUSSION

Children with SLE account for 15 - 20% of all SLE patients. Pediatric SLE is characterized by a more serious onset, a higher risk for involvement of multiple organs, and a more dangerous progression than adult SLE. GC is mainly used as traditional medication. However, due to the factors related to the children's growth and development period, it is necessary to try to reduce the dosage of hormones as much as possible, while at the same time achieving effective treatment. Hormones combined with immunosuppressants improve the efficacy and reduce the dosage of hormones. Immunosuppressants used in clinical practice include CTX, MMF, cyclosporine A and azathioprine, and of the three, CTX has greater toxic and side effects, especially gonadal damage, and the individual concentration of cyclosporin A varies significantly. It has also been reported that the recurrence rate is higher after the drug withdrawal [11,12].

MMF is an immunosuppressant used to prevent rejection reactions after organ transplantation, and whose mechanism of action is to selectively inhibit the classical synthesis pathway of guanine in lymphocytes by reversibly inhibiting hypoxanthine mononucleotide deoxygenase. It does not affect the purine salvage synthesis pathway, and the lymphocytes do not have salvage synthesis pathway but the classic synthesis pathway. So MMF can selectively inhibit the proliferation of lymphocytes [13,14].

In recent years, MMF has been clinically applied in the treatment of multiple autoimmune diseases, and a previous study demonstrated that MMF reduced the production of autoantibodies and anti-DNA antibodies by resisting the proliferation of B and T cells in the treatment of LN, thereby reducing the immune complexes deposited in the kidneys, and also delaying the progression of kidney damage [15]. Recently, MMF being utilized as the first-line treatment for proliferative LN has been confirmed by the guidelines in the United States and Europe [16].

In active pSLE, children with overexpression of IFN regulatory gene in the peripheral blood mononuclear cells account for approximate 90 % [17]. The IFN pathway not only increases the understanding of the pathogenesis of SLE, but also has guiding significance for clinical treatment. The original literature on the IFN pathway in pSLE patients confirmed that the IFN pathway activity was downregulated in 3 patients receiving intravenous methylprednisone pulse therapy. Subsequent studies have also indicated that intravenous methylprednisone pulse therapy continuously inhibited the signal of the IFN gene pathway in the active pSLE, while oral conventional doses of GC did not produce such effects [18, 19]. The biological half-life of methylprednisolone is 18 - 36 h, and the inhibition time for HPA axis is 1.25 - 1.50 d. During the pulse therapy, the blood drug concentration rises rapidly and decreases rapidly, and the maintenance time is short. During the intermittent period, oral low-dose GC reduces the inhibitory effect on the hypothalamus-pituitary-adrenal cortex axis, so that the body has the opportunity to self-adjust, recover and reduce the inhibition of the secretion of adrenocorticotropic hormone (ACTH) in the adenohypophysis, thereby also reducing the atrophy of the fascicular and reticular zones of the adrenal cortex due to insufficient ACTH without causing adrenal crisis.

The present study indicated that SLEDAI score was lower in the MMF group than that in the control group at 6 months and 12 months after treatment, and compared with control group, MMF group showed a higher level of complementary C3, and a lower level of 24-h urine protein level 6 months after treatment. Besides, clinical effectiveness in MMF group was higher than in control group. The results suggest that methylprednisolone combined with MMF can rapidly control symptoms early, while intermittent oral low-dose GC (7.5 - 10.0 mg/d) makes the dosage of oral steroid for maintenance treatment smaller, with lower blood drug concentration during the intermittent period. The risk exists in the methylprednisolone therapy, which is more likely to induce or aggravate infection during the pulse phase, induce or aggravate digestive tract ulcers, bleeding and perforation, acute pancreatitis, as well as increase the risk of cardiovascular and cerebrovascular diseases [20,21]. In the present study, infection frequency in the MMF group was lower than in the control group; also BMI, TG, FBG and IOP levels were lower in MMF group than those in the control group, suggesting that MMF has higher safety profile.

After treatment, peripheral blood $CD3^+$ and $CD4^+$ T lymphocytes, $CD4^+/CD8^+$ ratio and NK cell levels in the two groups of children were significantly increased, while the $CD8^+$ T lymphocyte level declined. Compared with the control group, MMF group had a lower level of

$CD8^+$ T lymphocyte (p = 0.003) and a higher level of NK cell (p = 0.038) after treatment. The results demonstrated that MMF used in the treatment of SLE can effectively regulate the patient's cellular immune function and improve clinical efficacy.

The present study is a retrospective study with few children enrolled, a short follow-up period and incomprehensive follow-up content, and the long-term prognosis of the children was not analyzed. Therefore, in the future, large-sample, multi-center long-term follow-up studies are needed to verify the conclusions of the present study.

CONCLUSION

Following methylprednisolone pulse therapy, MMF combined with low-dose methylprednisolone lowers symptoms, and reduces renal injury in the treatment of pSLE, when compared with oral GC and transitional reduction. It is also safer, and potentially regulates the patient's cellular immune function.

DECLARATIONS

Acknowledgement

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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