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ORIGINAL ARTICLE

Treatment of children with Henoch-Schönlein purpura nephritis with mycophenolate mofetil

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Abstract
Background Henoch–Schönlein purpura (HSP) can progress to Henoch–Schönlein purpura nephritis (HSPN), and the most effective management remains unclear. Our aim was to evaluate the efficacy of mycophenolate mofetil (MMF) for treating pediatric patients with HSPN and nephrotic-range proteinuria.
Methods Twelve children, seven boys and five girls, mean age 8.33 (range 6–12) years at the time of HSPN diagnosis with nephrotic-range proteinuria, were treated with MMF. All patients failed steroid treatment, and mean proteinuria at the time of MMF initiation was 5.6 g/d. MMF dosage ranged from 20 to 25 mg/kg per day. Patients also received an angiotensin-converting enzyme inhibitor (cliazapril) at MMF initiation. Mean follow-up was 3.9 (range 2.3–5.5) years.
Results All patients responded to MMF at a mean of 2.5 (range 1–4 months). Among the 12 patients, MMF was administered for 10 months in five, 12 months in six, and 15 months in one. At last follow-up, all patients had negative proteinuria and normal renal function, and no relapses were noted. No serious adverse effects of MMF were noted in any patient.
Conclusion MMF is useful for treating pediatric patients with HSPN and nephrotic-range proteinuria.

Keywords Henoch–Schönlein nephritis · Mycophenolate mofetil · Nephrotic syndrome

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Introduction

Henoch–Schönlein purpura (HSP) is the most common childhood vasculitis, with an incidence of approximately 10:100 000 children and a slight male predominance (1.5:1) [1]. HSP is most commonly self-limiting; however, a small number of children will progress to a severe form of the disease, with renal involvement [HSP nephritis (HSPN)], which may result in renal failure [2–4]. HSPN is a result of deposition of immunoglobulin A (IgA) immune complexes in the kidney, and renal histological and immunofluorescence microscopic findings are the same as those seen in patients with IgA nephropathy [1]. The severity of renal symptoms at onset is known to be the best prognostic factor for HSP in children, and patients presenting with nephrotic-range proteinuria have the highest risk of poor long-term renal outcome [1, 4].

Corticosteroids are used to treat patients with severe abdominal pain, nephritis, and central nervous system involvement; however, studies have not supported their routine use [5]. The most appropriate management of HSPN remains uncertain. Early active treatment is warranted if severe symptoms continue, whether the pathological renal changes are severe or not [3, 4]. Immunosuppressive drugs such as cyclosporin A, cyclophosphamide, azathioprine, and steroid pulse therapy have been used to treat severe and rapidly progressive HSPN; however, reports are typically single case studies or small case series, and the drugs are not without significant side effects [6–11].

Mycophenolate mofetil (MMF) is an immunosuppressant that inhibits both T- and B-lymphocyte proliferation and is used to prevent and treat allograft rejection [12], glomerulonephritis due to systemic lupus erythematosus [13], vasculitis [14], IgA nephropathy [15], and membranous nephropathy [16], and to treat patients with frequently relapsing steroid-dependent and steroid-resistant nephrotic

syndrome [15, 17, 18]. There are some reports of the successful use of MMF for IgA nephropathy in adults [15, 19]. However, there are only a few reports of the use of MMF to treat HSP [20] and HSPN [21, 22].

The purpose of this report was to describe the successful treatment with MMF of 12 children with severe HSPN.

Patients and methods

Patients

This is a single-center, retrospective analysis of 12 patients (seven boys, five girls) with a mean age of 8.33 (range 6–12) years at the time of HSP diagnosis. Renal biopsies were performed on all patients within 6 weeks of the initial diagnosis and were graded according to the International Study of Kidney Diseases in Children (ISKDC) classification [23].Three patients were categorized as grade IIB, five as grade IIIA, two as grade IIIB, and two as grade IV. No biopsies were performed after MMF treatment because proteinuria had decreased, and parents of the children declined in all cases. No patient exhibited renal failure or hypertension at the HSPN onset. Mean proteinuria of the 12 children 4 weeks after the initial diagnosis (the time MMF was begun) was 5.56 g/day (range 2.9–7.3 g/day). In addition, all patients had hematuria (3+) by dipstick and >100 erythrocytes per high power field on microscopic examination. The records of 16 children who were treated with cyclophosphamide (CTX) were also reviewed and compared. This study was approved by the Institutional Review Board of our hospital, and because of its retrospective nature, the requirement of patient informed consent was waived.

Treatment

Prior to MMF treatment, all patients were found to be resistant to steroid therapy. Patients were initially treated with prednisolone 1.5 mg/kg orally, three times a day for 2 weeks. If nephrotic-range proteinuria persisted, subsequent methylprednisolone pulse therapy 15–30 mg/kg per day for 3 days, maximum dose 0.5 g, was administered twice in the following 2 weeks. If the there was still no response after the second course of methylprednisolone and the child's parents refused cyclophosphamide (CTX) because of the significant side effects, children were treated with MMF orally. MMF dosage ranged from 20 to 25 mg/kg per day administered in a divided dose (morning and evening on an empty stomach). At the same time, because all patients had received steroid pulse therapy, all received prednisone 2 mg/kg orally every other day, which was tapered and discontinued after 4–6 months. MMF tapering was begun after 6 months and was then discontinued 10–15 months later if the proteinuria became negative. After a diagnosis of HSPN was confirmed, all patients were given heparin 0.5 mg/kg per day for 1 week, orally administered dipyridamole vitamin D 300 U/day and calcium for 6 months, and an angiotensin-converting enzyme (ACE) inhibitor (cilazapril) at a dosage of 0.5 mg/kg per day for 1 year. For CTX treatment, management consisted of 10–12 mg/kg per day for two consecutive days four to six times within a period of 2 weeks. The same treatment regime was repeated after 2–3 months. If necessary, it was repeated a third time 2–3 months after the second course. During treatment, laboratory testing every 3 months included measuring urine protein, serum creatinine, serum total protein, albumin, glutamate pyruvate transaminase (GPT), aspartate transaminase (AST), and glomerular filtration rate [GFR; determined by ^{99m} Tc-diethylenetriamine pentaacetic acid (DTPA) ECT>]. After MMF discontinuation, patients were seen every 3 months and laboratory testing performed every 6 months. Any MMF side effects were noted and documented. The mean follow-up was 3.9 (range 2.3-5.5) years. All data from HSPN onset until the end of the follow-up were analyzed.

Statistical analysis

Continuous data were summarized by mean and standard deviation (SD), and categorical data were summarized as the count of each category. The differences in repeated measurements between several time points were tested with Friedman's test, and differences in repeated measurements between every two time points were tested with the Wilcoxon signed rank test. A p value<0.05 was considered statistically significant. All analyses were performed using the SPSS 15.0 statistics software (SPSS Inc, Chicago, IL, USA).

Results

Characteristics of the 12 children are presented in Table 1. In all children, no change in proteinuria was noted after initial steroid therapy (5.7 g/d pretreatment vs. 5.6 g/d posttreatment, p=0.717) . Cases 3, 4, 5, 6, 9, and 11 were noted to have hyperfiltration (GFR >120 ml/min/1.73 m^2; normal range 80–120 ml/min/1.73 m^2).

All patients responded (i.e., proteinuria decreased to a minimum of 50% of pretreatment level) MMF treatment at a mean of 2.5 (range 1–4) months. Mean duration of steroid and MMF administration were 5.12 and 12.42 months, respectively (Fig. 1). An obvious response was seen within 3 months of beginning MMF in two patients (1 and 5), with a decrease in proteinuria to <1.5 g/d. In the other patients, the decrease in proteinuria was more gradual (Fig. 2). The mean duration for return to negative proteinuria for the 12 patients was 11±1.7 months. The longest duration for

Table 1 Patient characteristics

Patient	Age (year)	Gender	ISKDC	Proteinuria at onset (g/d)	Laboratory findings before MMF				Laboratory findings at the end of follow-up				Time to negative proteinuria (months)	Follow-up (years)
					Proteinuria (g/day)`	Serum albumin (g/L)	Serum creatinine (μmol/L)	GFR (ml/min/1.73 m^2)	Proteinuria (g/day)	Serum albumin (g/L)	Serum creatinine (μmol/L)	GFR (ml/min/1.73 m^2)		
1	6	F	IIIA	4.1	3.9	25	75	101	0.2	38	52	110	9	5.5
2	7	F	IIB	5.7	5.9	24	68	96	0.2	39	62	87	10.5	5.1
3	8	M	IIIA	7.2	7.3	20	43	166[b]	0.3	36	71	123	13	4.7
4	12	F	IIB	6.5	6.4	26	85	135[b]	0.4	40	45	120	14	4.7
5	9	M	IIIA	3.8	3.7	24	56	140[b]	0.2	45	48	96	9	4.2
6	10	M	IV	6.2	7.2	21	77	128[b]	0.1	47	62	89	11	4
7	9	M	IIIA	3.3	2.9	27	62	98	0.2	46	55	105	11	3.8
8	8	F	IV	5.6	4.5	22	55	109	0.2	44	52	98	10.5	3.7
9	7	F	IIIB	5.9	5.8	30	62	127[b]	0.3	48	49	130	13	3.6
10	6	M	IIIA	7.1	6.2	23	48	116	0.2	40	66	108	12	2.8
11	9	M	IIIB	6.9	7.1	20	68	160[b]	0.1	46	70	98	9	2.7
12	9	M	IIB	5.5	5.8	25	57	107	0.4	42	56	115	10	2.3
Summary	8.3±1.7	7 boys 5 girls	3 IIB 5 IIIA 2 IIIB 2 IV	5.7±1.3	5.6±1.5	23.9±3.0	63.0±12.2	123.6±23.4	0.2±0.1	42.6±3.9[a]	57.3±8.7	106.6±13.6[a]	11±1.7	3.9±1.0[a]

ISKDC International Study of Kidney Diseases in Children, *MMF* mycophenolate mofetil, *GFR* glomerular filtration rate

[a] Significant difference compared with before MMF

[b] Hyperfiltration (GFR >120 ml/min/1.73 m^2 ; normal range 80–120 ml/min/1.73 m^2)

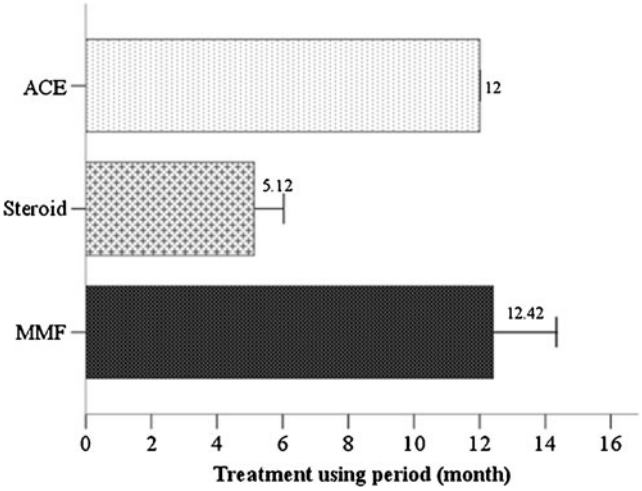

Fig. 1 Summary of treatment periods. MMF, mycophenolate mofetil; ACE, angiotensin converting enzyme

proteinuria to return to normal values was 15 months (patient 4). At all time points, mean proteinuria was significantly decreased compared with the prior time point (Fig. 2). Among the 12 patients, MMF was administered for 10 months in five, 12 months in six, and 15 months in one (Table 1). ACE-inhibitor dose was not adjusted according to proteinuria because blood pressures were within the normal range and because ACE-inhibitor dose was low.

No significant change in white blood cell (WBC) count was observed between pretreatment and 1-month posttreatment (Table 2). However, WBC counts 3, 6, 9, and 12 months after MMF therapy were significantly decreased compared with pretreatment and 1-month posttreatment values. No significant change in WBC count was observed at 6, 9, and 12 months posttreatment.

At the end of follow-up after completion of MMF treatment, the mean proteinuria level had decreased from 5.61 g/day to 0.2 g/day ($p<0.001$), GFR significantly decreased from 123.6 to 106.6 ml/min/1.73 m^2 ($p=0.032$), and serum albumin significantly increased from 23.9 g/L to 42.6 g/L ($p<0.001$). No significant difference was observed between serum creatinine levels before and after MMF treatment (Table 1).

No serious complications developed in any patient during MMF treatment. Four patients developed diarrhea at MMF treatment onset, and it resolved within 3–5 days without treatment. In three patients, an increase in GPT was noted, which returned to a normal level after 6 months without and special therapy. As of last follow-up, no relapses were noted, GFR and serum creatinine and albumin levels of all patients were within the normal range, and no patient exhibited significant edema. A comparison of the MMF and CTX groups is presented in Table 3. No significant difference was observed in age and gender between groups. However, a significant difference in ISKDC classification was observed ($p=0.002$). Pretreatment proteinuria in the MMF group was significantly higher than in the CTX group (5.7 g/day vs. 4.4 g/day, $p=0.03$). No significant difference in proteinuria was observed at posttreatment; however, a significantly greater decrease in proteinuria from pretreatment was observed in the MMF group (3 months, −3.6 g/day vs. −2.6 g/day, $p=0.008$; 6 months, −4.6 vs. −3.4, $p=0.012$; 9 months, −5.1 vs. −3.9, $p=0.015$; 12 months, −5.4 vs. −4.2, $p=0.022$).

Discussion

There is no clear consensus on how to treat patients with HSPN, although nephrotic syndrome has been shown to be a risk factor for poor long-term outcome [2, 3, 5]. Many treatments, such as pulse steroids, immunosuppressives (azathioprine, cyclophosphamide, chlorambucil), plasmapheresis, and tonsillectomy, either alone or in various

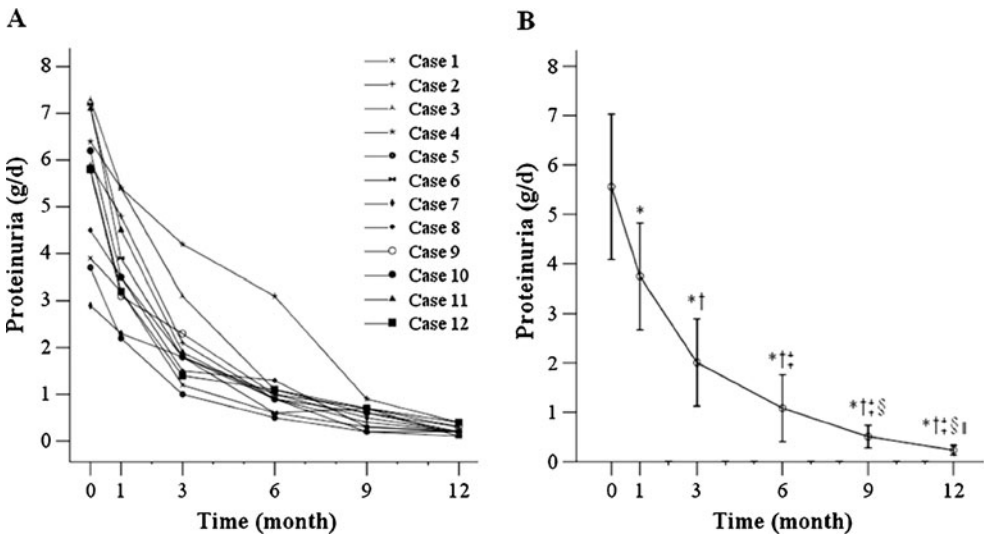

Fig. 2 Decrease in proteinuria after mycophenolate mofetil (MMF) initiation. *Significant difference compared with proteinuria before MMF. †Significant difference compared with proteinuria 1 month after beginning MMF. ‡Significant difference compared with proteinuria 3 months after beginning MMF. §Significant difference compared with proteinuria 6 month after beginning MMF. ‖Significant difference compared with proteinuria 9 months after beginning MMF

Table 2 Summary of white blood cell counts (cell number x 10^9/L)

Patient	Time after MMF treatment (month)					
	0	1	3	6	9	12
1	12.5	11.2	9.5	8.6	6.7	7.4
2	13.2	13.5	9.1	8.8	8.4	6.8
3	10.5	11.2	10.3	9.1	9.5	5.9
4	12.8	10.3	8.7	8.6	7.5	8.8
5	15.8	11.2	10.5	9.9	5.8	6.1
6	13.4	13.3	9.6	9.2	6.7	5.8
7	13.9	12.5	8.4	8.5	8.8	7.8
8	11.2	9.8	8.8	9.4	9.1	8.1
9	14.2	12.4	10.2	6.8	7.5	8.3
10	13.6	11.4	9.5	7.6	8.8	7.9
11	11.9	10.6	7.9	7.4	8.2	6.8
12	12.8	11.2	8.2	7.9	5.8	6.7
Summary	13.0±1.4	11.6±1.1	9.2±0.9[a, b]	8.5±0.9[a, b]	7.7±1.3[a, b]	7.2±1.0[a, b, c]

MMF mycophenolate mofetil

[a]Significant difference compared with before MMF

[b]Indicates a significant difference compared with 1 month after beginning MMF

[c]Indicates a significant difference compared with 3 months after beginning MMF

combinations, have been used to treat HSPN with varying results [5, 8, 24, 25]. Results of the study reported here indicated that MMF was effective for treating patients with HSPN with nephrotic-range proteinuria who were resistant to steroid therapy. In all patients, urine protein levels returned to normal, all patients achieved stable remission, and no patient developed MMF dependence. MMF has been used as a therapeutic agent for certain renal diseases in adults [12–14, 16]; however, its use for HSPN treatment is only beginning to be examined. MMF has been used successfully for treating persistent proteinuria in patients with IgA nephropathy [17], and the fact that HSPN exhibits the same renal pathological changes as IgA nephropathy suggests that it may be effective in patients with HSPN. Until this report, most reports regarding successful use of MMF for treating HSPN have been individual case reports [21, 22]. The largest case series of MMF treatment for HSP was of six children, reported by Nikibakhsh et al. in 2010 [20]. In that series, all children had severe manifestations of HSP, but only one had progressed to nephrotic-range

Table 3 Comparison of MMF and CTX groups

		MMF (n=12)	CTX (n=16)	p-value
Age (year)		8.3 ± 1.7	8.1 ± 1.9	0.706
Gender	Female	5 (41.7%)	9 (56.3%)	0.704
	Male	7 (58.3%)	7 (43.8%)	
ISKDC	IIB	3 (25.0%)	5 (31.3%)	0.002*
	IIIA	5 (41.7%)	0 (0.0%)	
	IIIB	2 (16.7%)	11 (68.8%)	
	IV	2 (16.7%)	0 (0.0%)	
Proteinuria (g/d)				
Pretreatment		5.7 ± 1.3	4.4 ± 1.4	0.030*
Posttreatment	1 month	3.8 ± 1.1	3.2 ± 1.1	0.106
	3 months	2.0 ± 0.9	1.8 ± 0.9	0.428
	6 months	1.1 ± 0.7	1.0 ± 0.6	0.511
	9 months	0.5 ± 0.2	0.5 ± 0.3	0.577
	12 months	0.2 ± 0.1	0.2 ± 0.2	0.617
Proteinuria change (compared with pretreatment)	1 month	−1.9 ± 0.8	−1.2 ± 0.8	0.051
	3 months	−3.6 ± 1.1	−2.6 ± 0.8	0.008*
	6 months	−4.6 ± 1.3	−3.4 ± 1.1	0.012*
	9 months	−5.1 ± 1.2	−3.9 ± 1.2	0.015*
	12 months	−5.4 ± 1.3	−4.2 ± 1.3	0.022*

MMF, mycophenolate mofetil, CTX, cyclophosphamide, ISKDC, International Study of Kidney Disease in Children

*p<0.05, indicates a significant difference was observed between groups

proteinuria. All patients were resistant to steroid therapy, and all responded to MMF within 1 month of treatment initiation (one case within 48 h and 1 within 1 week). MMF dose used in our study is that recommended by the Chinese Medical Association for treating refractory nephropathy and lupus.

In our patients, we began MMF after 4 weeks of failed steroid therapy, which is earlier than the typical 2 months of prednisone oral administration. The importance and efficacy of early therapy of severe HSPN was illustrated by Tanaka et al. [25], who treated nine patients with nephrotic-range proteinuria with prednisone and cyclophosphamide orally within 1 month of HSPN diagnosis. Eight patients were ISKDC grade IIIB and one was grade IVB. At a mean follow-up of 78 months, all except two patients exhibited negative proteinuria, and no patient showed renal impairment. A retrospective study by Deng et al. [26] in 2011 of 180 children with varying HSPN severity also indicated that early intensive treatment was associated with improved outcomes.

In our study, three patients were ISKDC grade IIB, and the amount of proteinuria was not remarkably different than that of ISKDC grades III and IV patients (patient 4 was ISKDC grade IIB and had the worst proteinuria). All patients received MMF at the same point (immediately after steroid therapy failure), and the grade IIB patient recovered more slowly than the grades III and IV patients. This finding is similar to that reported by Ronkainen et al. [6] using cyclosporin A to treat HSPN. Wakaki et al. [27] studied 42 children with HSPN who presented with a nephrotic state in the early phase of the disease. With a mean follow-up of 6.2 years, multivariate logistic regression analysis revealed that a nephrotic state lasting >3 months had a significant adverse effect on renal outcomes, whereas initial renal insufficiency, renal pathological findings, age at onset, and type of treatment did not. Other authors also reported good outcomes using cyclosporin A to treat HSPN, though some patients become cyclosporine-A-dependent. Our findings suggest that pathological changes may not be a useful indicator for beginning therapy; rather, urine protein levels should be used.

All our patients received an ACE inhibitor, which is known to reduce proteinuria and provide protection against deterioration of renal function in various kidney diseases [28]. We began the ACE inhibitor 4 weeks from the initial diagnosis of HSPN, at the same time MMF was started. We cannot, however, discriminate between reduced proteinuria due to ACE inhibitor and that due to MMF. ACE inhibitors may reduce GFR, as they cause vasodilatation in the efferent glomerular arterioles [29].

Reported side effects and adverse reactions to MMF include hyperglycemia, hypomagnesemia, hypocalcemia, hyperkalemia, increase in blood urea nitrogen, and pleural effusion [30]. Side effects in our patients were minimal, and the drug was well-tolerated at the dosage used. The ideal length of MMF treatment for HSPN patients is not known. We planned the treatment time to be 9–15 months, but this was modified according to clinical symptoms of individual patients.

The primary limitations of this study are the small number of patients, lack of a control group, and no follow-up renal biopsies after treatment. In addition, patients were treated with an ACE inhibitor in addition to MMF, and it cannot be ruled out that improvement was due to the ACE inhibitor and/or a synergistic effect of the ACE inhibitor and MMF. However, our previous experience has shown that an ACE inhibitor alone did not yield good results, and the dosage of ACE inhibitor used in this study was low. Despite these shortcomings, our results indicate that MMF is effective for treating HSPN.

Conclusions

Results of this study indicate that MMF is effective for treating patients with HSPN and nephrotic-range proteinuria. Based on these results, further study with a larger, randomized patient series and longer follow-up are warranted.

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