

Addition of cyclosporine/ tacrolimus for pediatric relapsed lupus nephritis during mycophenolate mofetil maintenance therapy

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Abstract

Objective: We aimed to evaluate the efficacy of low-dose cyclosporine (CsA) or tacrolimus (Tac) in children with proliferative lupus nephritis (PLN) during maintenance therapy.

Methods: A low dose of CsA or Tac was added to 11 children who relapsed during mycophenolate mofetil (MMF) maintenance therapy. Renal remission was analyzed at 3 and 6 months, and at 1, 2, and 3 years after CsA/Tac addition. Adverse effects were recorded.

Results: The clinical response rates were 81.9%, 100%, 90.0%, 100%, and 100% at 3 months, 6 months, 1 year, 2 years, and 3 years after CsA/Tac addition, respectively. Complete renal remission rates were 45.5%, 45.5%, 40.0%, 44.4%, and 71.4% at 3 months, 6 months, 1 year, 2 years, and 3 years after CsA/Tac addition, respectively. None of the patients had severe adverse events.

Conclusion: Low-dose CsA/Tac combined with MMF shows a promising effect in renal remission with acceptable safety in children with PLN. Therefore, this combination would be a good choice for children with lupus nephritis who relapse or have suboptimal MMF maintenance therapy.

Keywords

Lupus nephritis, children, maintenance therapy, cyclosporine, mycophenolate mofetil, renal remission, tacrolimus

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that is characterized by the presence of autoantibodies and multiorgan involvement. Lupus nephritis (LN) has high mortality and morbidity and is a major determinant for long-term outcome.¹ Even renal survival in childhood-onset LN has improved in the past three decades with progressive treatment,² but long-term remission of severe LN remains a major challenge.

The standard therapy for severe LN is induction therapy following maintenance treatment according to guidelines. The mainstay induction therapy for LN is cyclophosphamide (CYP) or mycophenolate mofetil (MMF) plus glucocorticoids. MMF was recently recommended as the first-line choice during the maintenance phase.³ However, there are frequent relapses during the maintenance treatment phase clinically.

The issue remains of how to deal with patients who relapse and have a poor response to MMF treatment during the maintenance period. Switching to CYP therapy may be a choice in this situation, but is not always appropriate considering the potential gonadal toxicity and previous CYP exposure in induction therapy. Recently, tacrolimus (Tac) addition to MMF was reported to have a good response in adults in some small sample studies.^{4,5} Previous studies have reported multitarget therapy with MMF combined with tacrolimus (Tac) in proliferative lupus nephritis (PLN) with good results in the induction period.^{6,7} On the basis of these results and successful experiences of the combination of MMF and calcineurin inhibitors (CNIs) in long-term renal transplantation, the combination of CNIs and MMF might be effective in LN maintenance therapy. However, few data on this combination have been reported, especially in children with LN.

Since 2010 in our department, low-dose cyclosporine (CsA) or Tac has been added for patients with PLN who relapsed during MMF maintenance therapy. We have observed optimistic results with this therapy. This study aimed to summarize our results with low-dose CsA or Tac added in patients with PLN who relapsed during MMF maintenance therapy.

Materials and methods

Patients

From January 2010, patients with PLN who were treated with MMF and CsA/Tac in the maintenance period were retrospectively analyzed. SLE was diagnosed according to American Rheumatologic Association criteria for the diagnosis of SLE.⁸ Nephritis was classified according to the International Society of Nephrology/Renal Pathology Society 2003 classification.⁹ Inclusion criteria were as follows: 1) patients with PLN who achieved complete renal remission after induction therapy; 2) induction therapy was CYP plus steroid or MMF plus steroid, followed by MMF in maintenance therapy; 3) relapse during the maintenance period; and 4) patients were followed up for at least 6 months after CsA/Tac addition. The study was approved by the ethics committee in Shanghai Children's Medical Center. Written informed consent was obtained from the parents of the patients.

With regard to other organs involved in SLE, one of the patients had interstitial lung disease, and one patient was complicated by hypertensive encephalopathy. These patients recovered after induction therapy.

Immunosuppressive protocol

Once LN was diagnosed, CYP was provided as induction therapy intravenously with 0.5 to 0.75 g/m² per month or MMF with dose of 25 to 30 mg/kg (≤ 1500 mg) orally.

Both of these treatments were accompanied by oral prednisone of 1.5 to 2 mg/kg (≤ 60 mg). In patients with nephrotic proteinuria or deteriorative renal function or lupus encephalopathy, a high dose of methylprednisolone (10–15 mg/kg, ≤ 500 mg) was provided continuously for 3 days before CYP or MMF administration. After 6 months of induction therapy, MMF was continued for maintenance therapy. MMF was tapered by 250 mg every 6 months and maintained with a minimum dose of 500 mg. Prednisone was tapered to 1 mg/kg after 3 months of induction therapy and then tapered by 5 mg every 2 weeks until a maintenance dose of 10 mg.

For patients who were in renal relapse during maintenance therapy, a low dose of CsA or Tac was added. CsA 3 mg/kg and Tac 0.05 mg/kg were administered at onset. The maximum dose was 200 mg for CsA and 2 mg for Tac. The dosage was adjusted according to clinical responses and blood concentrations. Normally, trough blood concentrations were maintained below 50 to 100 ng/mL and 4 to 6 ng/mL for CsA and Tac, respectively. The dose of CsA/Tac was then tapered every 3 to 6 months, with a minimum of 100 mg and 1 mg daily for CsA and Tac, respectively. The trough blood concentrations were not monitored if patients were in complete renal remission. The dose of prednisone was also upregulated during renal relapse and tapered to maintenance a dose of 10 mg after a clinical response.

Study assessment and endpoints

Treatment responses were assessed by clinical and laboratory data. Clinical symptoms were evaluated at each visit. Laboratory data, such as urine protein levels, serum creatinine levels, a urinary sediment test, and hematology, were monitored every month. Parameters of complement fragment 3 (C3), the erythrocyte sediment

rate, and anti-nuclear antibody titers were evaluated every year. These parameters were re-evaluated in case of fluctuation of disease. Complete renal remission was defined as proteinuria < 0.3 g/1.73 m²/day, urine blood cells < 5 /high power field, and a normal renal glomerular filtration rate. Partial renal remission was defined as $> 50\%$ improvement of proteinuria and serum creatinine levels.¹⁰ A clinical response included partial and complete renal remission. Renal relapse was defined as an increase in proteinuria > 0.5 to 1.0 g/day and/or an increase of $> 25\%$ serum creatinine levels.¹¹ The primary outcome was complete renal remission at 3 and 6 months, at 1, 2, and 3 years, and at the end of the follow-up period.

Statistical analysis

Continuous variables are summarized using descriptive statistics. Comparisons of various laboratory parameters between baseline and at different time intervals were performed by one-way analysis of variance using SPSS for Windows, Version 15.0 (Chicago, IL, USA). $P < 0.05$ was considered to be statistically significant.

Results

Patients' characteristics

We enrolled 11 patients. The baseline demographics and clinical data before addition of CsA/Tac are shown in Table 1. There were eight girls and three boys, and the mean (standard deviation) age was 10.5 ± 3.2 years (4–14 years). The mean duration of LN was 36.5 ± 2.8 months (8–84 months). Nine patients received a renal biopsy and were classified as three with type III, five with type IV, and one with IV + V (Table 1). During induction therapy, seven patients achieved complete renal remission within 6 months, three

Table 1. Patients' characteristics at baseline before CsA/Tac addition.

Patient	1	2	3	4	5	6	7	8	9	10	11
Sex	M	M	F	F	F	F	F	F	M	F	F
Body Weight (kg)	50-55	50	60	50	45	50	45-50	20	30	35	45
Age of onset (years)	13	10	14	8	7	14	12	4	9	12	13
LN duration (months)	35	84	9	48	70	78	24	19	22	10	43
Pathology	IV	/	IV	III	/	IV	III	III	IV+V	IV	IV
Therapy before CsA/Tac	Pred + CYP MMF	MP, Pred + CYP MMF	MP, Pred + CYP MMF	Pred + CYP MMF	Pred + CYP MMF	Pred + CYP MMF	Pred + CYP MMF	Pred + CYP MMF	Pred + CYP MMF	Pred + CYP MMF	Pred + CYP MMF
Adjunctive therapy	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ	ACEI+ HCQ
MMF duration (months)	28	38	3	33	19	36	24	19	22	10	43
Baseline at time of CsA/Tac addition											
MMF dose (g)	1.5	1.5	1.5	1	1	1.5	0.5	0.5	0.75	1	0.5
Pred dose (mg)	30	30	30	15	15	10	10	20	20	30	20
Proteinuria (mg/24 h)	5898	4258	13,311	2975	1024	4800	874	2994	3434	5249	619
Urine RBC (/HPF)	30-40	5-7	5-6	5-8	3-6	3-5	3-5	8-11	15-20	4-5	1-3
Scr ($\mu\text{mol/L}$)	67	47	68	47	36	87	48	26	40	35	74
eGFR (mL/min/1.73 m^2)	95	125	92	110	140	72	110	150	120	135	83
Alb (g/L)	25.5	35.4	28.9	38.7	37	31.9	33	34.5	26	35.5	41
DsDNA	+	-	+	+	+	+	+	+	+	+	+
ANA	1:320	1:320	1:320	1:1000	1:1000	1:1000	1:320	1:320	1:1000	1:1000	1:1000
C3 (g/L)	0.74	0.8	0.6	0.41	0.99	0.86	0.91	0.43	0.44	0.92	0.52
ESR (mm/h)	12	11	30	15	47	30	7	15	39	15	10
PLT ($\times 10^9/\text{L}$)	357	337	280	320	271	350	354	240	231	258	221
CsA or Tac	CsA	Tac	Tac	CsA	CsA	CsA	Tac	Tac	Tac	Tac	Tac

CsA: cyclosporine; Tac: tacrolimus; M: male; F: female; LN: lupus nephritis; MMF: mycophenolate mofetil; Pred: prednisone; RBC/HPF: red blood cells/high power field; Scr: serum creatinine; eGFR: estimated glomerular filtration rate; Alb: albumin; DsDNA: double-stranded DNA; ANA: anti-nuclear antibody; C3: complement fragment 3; ESR: erythrocyte sediment rate; PLT: blood platelets; CYP: cyclophosphamide; ACEI: angiotensin-converting enzyme inhibitor; HCQ: hydroxychloroquine.

achieved complete renal remission between 6 and 12 months, and one achieved complete remission after 15 months of treatment. Six patients received CYP therapy before MMF and CsA/Tac therapy. Five patients had CsA added and six had Tac added. All of these 11 patients were administered an angiotensin-converting enzyme inhibitor and hydroxychloroquine as adjunctive therapy. Seven (63%) patients experienced nephrotic range proteinuria and two had slightly decreased renal function. Eight patients had low complement fragment (C3) concentrations. The median duration of follow-up was 44.0 ± 17.2 months, and it ranged from 6 to 60 months.

Clinical response after CsA/Tac addition

In patients with relapse during MMF therapy, CsA or Tac addition resulted in rapid and effective renal remission.

Proteinuria and the SLE disease activity index were significantly decreased 3 months after CsA/Tac addition (both $P < 0.05$,

Table 2). C3 levels were improved after 1 year of combination therapy ($P < 0.05$ vs baseline).

Nine patients reached complete or partial renal remission at 3 months after CsA/Tac addition (Table 3). At 6 months, a clinical response occurred in all 11 patients, and five patients had complete renal remission and six had partial renal remission. In the subsequent follow-up, a high rate of renal remission still remained. Figure 1 shows the individual response of each parameter of proteinuria, serum creatinine, C3, and the erythrocyte sediment rate from baseline to different intervals after CsA/Tac addition.

One patient presented with deteriorative renal function and refractory hypertension at 1 year, and thus there was obvious rebound of proteinuria and serum creatinine levels. This patient was discharged at that time as requested by the parents for economic reasons. He was lost to follow-up. Another patient was lost to follow-up after 2 years. These two patients had partial

Table 2. Comparison of clinical data between baseline and different time intervals after CsA/Tac addition.

	Baseline (n = 11)	3 months (n = 11)	6 months (n = 11)	1 year (n = 10)	2 years (n = 9)	3 years (n = 7)
Proteinuria (mg/24 h)	$3430 \pm 581^*$	1214 ± 491	442 ± 99	821 ± 421	728 ± 243	361 ± 168
Scr ($\mu\text{mol/L}$)	53 ± 5.6	46 ± 4.0	44.6 ± 5.0	61.8 ± 15.2	50.3 ± 5.9	50 ± 5.1
C3 (g/L)	$0.75 \pm 0.08^*$	/	/	0.91 ± 0.03	0.90 ± 0.06	0.95 ± 0.07
ESR (mm/h)	24.5 ± 5.3	/	/	22.3 ± 7.2	13.7 ± 1.7	16.1 ± 4.3
SLEDAI	$11.1 \pm 3.7^*$	5.0 ± 2.5	2.1 ± 1.5	3.8 ± 1.6	1.2 ± 1.1	1.1 ± 1.2

* $P < 0.05$, baseline versus the other groups.

CsA: cyclosporine; Tac: tacrolimus; Scr: serum creatinine; C3: complement fragment 3; ESR: erythrocyte sediment rate; SLEDAI: systemic lupus erythematosus disease activity index.

Table 3. Clinical response after addition of CsA/TaC.

	3 months (n = 11)	6 months (n = 11)	1 year (n = 10)	2 years (n = 9)	3 years (n = 7)
CR	5 (45.5)	5 (45.5)	4 (40.0)	4 (44.4)	5 (71.4)
PR	4 (36.4)	6 (54.5)	5 (50.0)	5 (55.6)	2 (28.6)
NR	2(18.1)	0	1 (10)		

Values are n (%). CsA: cyclosporine; Tac: tacrolimus; CR: complete renal remission; PR: partial renal remission; NR: no response.

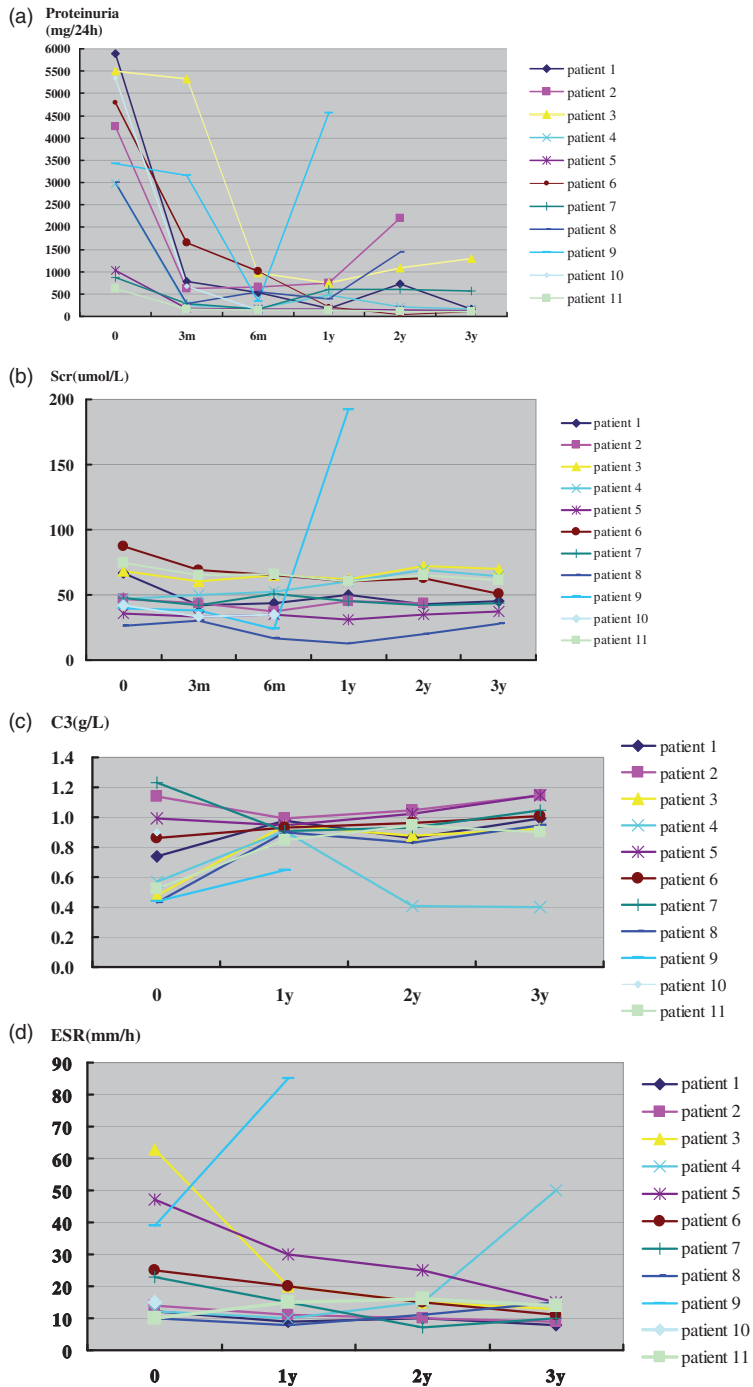


Figure 1. Individual treatment response from baseline to 3 months, 6 months, and 1, 2, and 3 years after CsA/Tac addition. (a) Proteinuria; (b) serum creatinine levels; (c) C3 levels; (d) ESR. CsA: cyclosporine; Tac: tacrolimus; C3: complement fragment 3; ESR: erythrocyte sediment rate.

renal remission at the last visits. At the last visit, seven patients were in complete renal remission and two patients were in partial renal remission. All of these patients presented with stable serum creatinine levels.

Adverse events

There were no severe adverse events, and no patients discontinued combination therapy because of safety reasons. One patient presented with pulmonary infection and recovered after anti-infection therapy. Another patient presented with elevated transaminase levels, which were reduced to normal after glutathione therapy.

Discussion

In our study, for patients with PLN who relapsed during MMF maintenance therapy, a low dose of CsA/Tac addition resulted in rapid and long-term renal remission with acceptable safety. All of the patients showed at least partial renal remission to CsA/Tac addition. Complete renal remission occurred in 45.5% patients at 6 months after CsA/Tac addition. This rate reached 71.4% after 3 years of CsA/Tac addition. During LN treatment, the aim of maintenance therapy is to sustain renal remission by preventing relapse and achieve the best long-term outcome. However, for patients who relapse or have suboptimal MMF therapy, there are limited options available for better renal remission.

CsA and Tac are potent immunosuppressive agents and are the standard of care for immunosuppression after kidney transplantation. CsA/Tac also has the unique ability to stabilize the podocyte actin cytoskeleton by inhibiting dephosphorylation and degradation of synaptopodin. Synaptopodin is an actin-associated protein that regulates cell shape and motility and organization of the podocyte foot processes.¹² Therefore, CsA/Tac is used to

reduce proteinuria in glomerular disease. A previous study reported that CsA administered continuously as induction and maintenance therapy was as effective as CYP in 19 patients with LN.¹³ Some recent reports showed that multitarget of MMF, Tac, and prednisone in PLN is superior to classical CYP induction therapy.^{6,7} Application and efficacy of CsA/Tac in maintenance therapy has not been as well reported. Lanata et al.⁴ reported that addition of Tac to seven patients with LN experienced treatment failure by MMF, with one patient in complete remission and three in partial remission. However, Tac toxicity appeared to be prevalent in their study. The probable reason for this finding is because they used a slightly high dosage from 2 to 8 mg and had high blood concentrations. Mok et al.⁵ reported a low-dose MMF and Tac combination in 21 patients with LN who failed to adequately respond to standard regimens. Two thirds of their patients improved after 12 months, but longer term efficacy and safety need to be confirmed. All of these previous findings were from adults with LN and data in children with LN are lacking.

In our study of childhood PLN, with relapse during MMF maintenance therapy, the combination of low-dose CsA/Tac and MMF resulted in rapid and long-term renal remission. Infection is the main side effect under combination immunosuppression of a CNI and Tac. In this study, the onset dose was no more than 200 mg and 2 mg for CsA and Tac, and the trough blood levels were below 50 to 100 ng/mL and 4 to 6 ng/mL for CsA and Tac, respectively. The dose of MMF during maintenance therapy was no more than 1500 mg. Therefore, under a low-dose combination of CsA/Tac and MMF, there were no severe infections.

Chronic CNI nephrotoxicity is a concern with using CsA/Tac therapy. This therapy was relatively safe with a low dosage and low blood concentrations. A previous study

reported 19 Japanese patients who were treated with corticosteroids and Tac, with trough blood Tac levels of 3.9 ± 1.5 ng/mL.¹⁴ After a mean follow-up of 42 months, they achieved satisfactory control of disease activity with stable serum creatinine levels. Another study investigated the clinical outcomes of 29 Chinese patients with LN who were treated with Tac for 46.0 ± 37.9 months.¹⁵ The target 12-hour trough blood tacrolimus level in this previous study was 4 to 6 µg/L, which achieved satisfactory suppression of proteinuria and stable renal function. Additionally, MMF and Tac are used together for a synergistic effect in organ transplantation with good long-term allograft survival, and lower dosages of Tac can be used for maintenance to reduce its long-term nephrotoxicity. All of the above-mentioned evidence shows acceptable safety for addition of Tac in LN maintenance therapy.

A limitation of this study was the small number of patients. In addition, because this was a retrospective study with follow-up for 5 years, our findings need to be confirmed in a further large-sample study with a longer follow-up. Finally, there was no re-biopsy after CsA/Tac addition for several years.

In conclusion, low-dose CsA/Tac combined with MMF shows promising effects in renal remission with acceptable safety in children with PLN. This combination would be a good choice for children with LN who relapse or have suboptimal MMF maintenance therapy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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