Pediatric Systemic Lupus Erythematosus in Thammasat University Hospital

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Systemic lupus erythematosus (SLE) is a common autoimmune disease in children. Current standard therapies carry high adverse effects. Refractory SLE to conventional therapies is not uncommon. Rituximab, anti-CD20 monoclonal antibody, has been used as an adjunctive therapy in children with refractory SLE with limited reports. This study described pediatric SLE patients in a single center, Thailand. To determine the clinical manifestations, treatments, and outcome of SLE patients, the authors retrospectively studied 19 patients (age <15 years) diagnosed with SLE at Thammasat University hospital, from January 01, 2002 through March 31, 2010. The mean age was 12.9 ± 1.6 years; mean follow-up 3.3 ± 2.6 years. Seventeen (89.5%) patients were female. Clinical manifestations were hematological (89.5%), dermatologic (73.7%), and renal involvement (68.4%). SLE was diagnosed 1 year after systemic onset juvenile rheumatoid arthiris in one patient. Lupus nephritis (LN) class II was observed in 30.8%, class III (15.4%), and class IV (53.8%) of patients with LN. Overall, mean SLEDAI score at presentation was 14.9 ± 2.2 and significantly decreased to 6.8 ± 1.6 ($p < 0.0001$) at 1 month after treatment. Complete remission at 1 year demonstrated in 11 (68.7%) patients. Infection was the most common complication followed by ophthalmological complications. All patients survived during follow-up period. Rituximab induced remission of SLE after refractory diffuse alveolar hemorrhage in one patient, and rapidly progressive glomerulonephirits leading to end stage renal failure in one patient. Clinical outcome of pediatric SLE was favorable in the present study. Complications from corticosteroid and anti-inflammatory therapy were high. Rituximab may be a good adjunctive therapy for refractory SLE in children. Large controlled trials to establish safety profile and optimal regimen of rituximab in childhood SLE are required.

Keywords: *Systemic lupus erythrematosus, Lupus nephritis, Optic neuritis, Diffuse alveolar hemorrhage, Asian, Children, Rituximab, IV pulse cyclophosphamide, Systemic onset juvenile Rheumatoid arthritis, Hydroxychlorquine, Chloroquine maculopathy*

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease. Childhood-onset SLE is more severe and carries a worse prognosis than in adult-onset disease[1]. The prognosis for pediatric SLE has improved dramatically over the last 20 years attributable to early diagnosis, and improved anti-inflammatory therapy[2]. However, these treatments produce severe complications especially corticosteroid-related adverse effects, gonadal toxicity, and infections from cyclophosphamide. Infection remains the most common cause of both morbidity and mortality for children and adult SLE[2,3]. Disease activity is one of major determinants for poor disease outcome[4]. Innovative approaches are used for patients with SLE who do not response to conventional therapy. Rituximab, anti-CD20 monoclonal antibody, has been used as an adjuctive therapy in refractory SLE in children with limited reports[5-8]. The present study reported a case series of pediatric SLE patients from a hospital in suburban area of Patumthani province, Thailand. The authors reported clinical manifestations, treatments, complications, and outcomes. The authors also demonstrated a successful treatment of refractory SLE in 2 patients with rituximab.

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Material and Method

Patients

Medical records of pediatric patients (0-15 years) newly diagnosed as SLE at the Thammasat University Hospital from January 01, 2002 through March 31, 2010 were retrospectively reviewed. This study was approved by the ethic committee of the

Faculty of Medicine, Thammasat University. All patients were diagnosed according to the criteria of the American Rheumatism Association's (ARA) revised criteria for the diagnosis of SLE[9].

The demographic data include sex, onset age, age of diagnosis, duration of follow-up and family history was recorded. The initial presentations including the ARA criteria and other symptoms were recorded. The laboratory data at diagnosis of SLE were collected as follows: anemia (Hb<10g/dL, Hct<30%), leucopenia (<4,000/mm^3), lymphopenia (<1500/mm^3), thrombocytopenia (<100,000/mm^3), positive anti-nuclear antibody (ANA), anti-double strand DNA (anti ds-DNA), anti-smith antibody (anti-Sm), low complement component 3 (C3 <0.9 mg/dL), low complement component 4 (C4 <0.1mg/dL), elevated erythrocyte sediment rate (ESR) (>20 mm at 1 h), proteinuria (24-h urine protein > 4 mg/m^2/h), nephrotic range proteinuria (24-h urine protein >40 mg/m^2/h) and active urine sediment (hematuria, >5 RBCs/high power field; leucocyturia, >5 WBCs/high power field; and/or cellular cast).

The clinical diagnosis of lupus nephritis (LN) required the presence of active urinary sediment, proteinuria, and/or raised serum creatinine levels. Glomerular filtration rate (GFR) was estimated by creatinine clearance at the time of diagnosis. An estimated GFR (eGFR) was derived by the height index formula of Schwartz[10]. All patients with lupus nephritis were renal biopsied. Renal biopsy specimens were examined by light and immunofluoresence microscopy. The histological observation were categorized according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 reclassification[11]. End-stage renal disease (ESRD) was defined as the time of initiation of dialysis.

The clinical course and outcome were classified and defined as follows:

Active disease or non-response was defined as no change in clinical status.

Complete renal remission was defined as eGFR >90 ml/min/1.73m^2, a decrease of at least 50% of urine protein/creatinine ratio (UPCI) with a ratio <0.2, and inactive urine sediment at 24 weeks after treatment[12].

Partial renal remission was defined as 25% increase of eGFR if base line level was abnormal and/or a decrease of at least 50% of UPCI with a ratio between 0.2 and 2 and/or a change from active to inactive urinary sediment (hematuria, ≤ 5 RBCs/high power field; leucocyturia, ≤ 5 WBCs/high power field; and/or no cellular cast at 24 weeks after treatment[12].

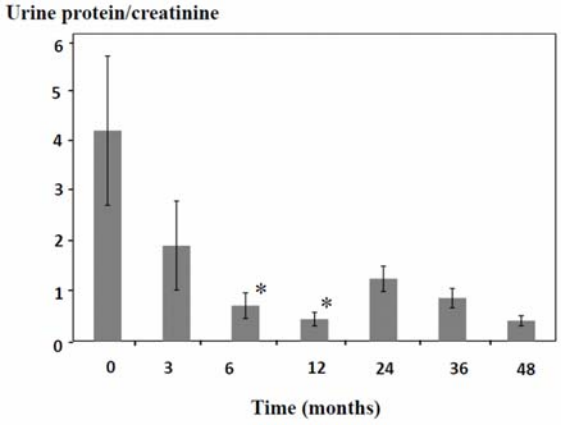

Fig. 1 Urine protein/creatinine ratio (mg/mg) calculated from spot morning urine at different time points during treatment of lupus nephritis. Data presented as mean ± SE **p < 0.05

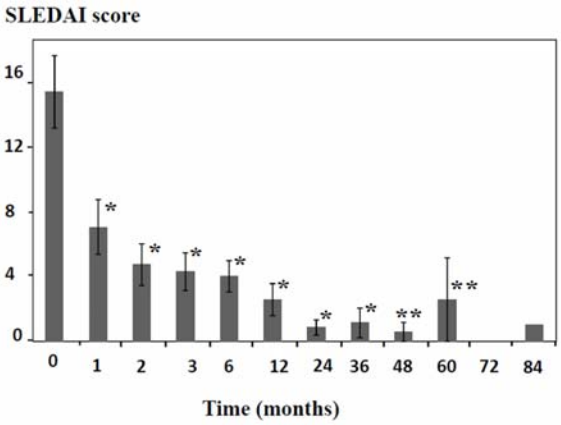

Fig. 2 The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score demonstrated the clinical activity during and after treatment. Data presented as mean ± SE *p < 0.0001, *p < 0.05

Remission was defined as absence of A and B scores on the British Isles Lupus Assessment Group system (BILAG 2004)[13].

Relapse was defined as recurrences of clinical disease and the worsening of C3/C4 and serology.

The clinical activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score during and after treatment[14]. *Infection* was defined as infection needed to be hospitalized. Adverse effects of medications were recorded.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) or median (range). SLEDAI score and UPCI are expressed as mean ± standard error of mean (SE). The differences between the two groups were compared using paired T-test. The mortality rate was defined as the number of deaths divided by the total number of patients.

Results

Nineteen patients, 17 female (89.5%) with mean (± SD) age at diagnosis of 12.9 ± 1.6 years (range, 7.8-15.0 years), were enrolled. Mean (± SD) period of follow-up was 3.3 ± 2.6 years (range, 6-84 months). Patient characteristics are shown in Table 1.

Clinical manifestation

The presenting symptoms including ARA criteria and other manifestations at diagnosis are summarized in Table 2. Hematological, dermatologic and renal involvement were the major clinical manifestations presenting in 17 (89.5%), 14 (73.7%), and 13 (68.4%) patients, respectively. Anemia was identified in 12 (63.2%) patients (Table 3). Eleven patients had hemolytic anemia with positive direct coombs' test. One patient had anemia of chronic disease. Only 3 (15.8%) patients had leucopenia at the time of diagnosis of SLE. One patient presented with thromobocytopenia one year prior to a diagnosis of SLE. One patient had antiphospholipid syndrome secondary to SLE as demonstrated by thrombotic microangiopathy in renal histology and positive anticardiolipin and lupus anticoagulant 12 weeks apart.

Renal system was common organ involvement in the present study. All thirteen patients with renal manifestation had proteinuria (Table 3, Fig. 1). Of these, 8 (61.5%) patients had non-nephrotic range proteinuria and 5 (38.5%) had nephrotic range proteinuria (Table 4). Nine (69.2%) patients with renal manifestation had microscopic hematuria. All thirteen patients received kidney biopsies at the time of diagnosis. They were classified as LN class II in 4 (30.8%), class III in 2 (15.4%) and class IV in 7 (53.8%) patients. Mean of creatinine clearance of patients with LN class II and III were 111 ± 14 and 112 ± 11ml/min/1.73m^2, respectively (Table 4). Four patients with LN class IV had scarring on renal biopsy according to the ISN classification of class III/IV active/chronic lupus nephritis. All patients with LN class IV had proteinuria, microscopic hematuria and hypertension. Two patients with LN class IV presented with rapidly-progressive glomerulonephritis. Of these, one required hemodialysis at the time of diagnosis.

Skin and mucocutaneous manifestation included malar rash in 8 (42.1%) patients, alopecia in 4 (21.1%), discoid rash in 4 (21.1%), photosensitivity in 2 (10.5%), vasculitis in 1 (5.2%), and oral ulcer in 1(5.2%) patient (Table 2). Musculoskeletal involvement was

Table 1. Patient characteristic

Characteristic		Patients (Total = 19) n (%)
Gender	Female	17 (89.5)
	Male	2 (10.5)
Age at onset (yr, mean ± SD)		12.6 ± 1.9
Age at diagnosis (yr, mean ± SD)		12.9 ± 1.6
Follow up duration (yr, mean ± SD)		3.3 ± 2.6
Family history of SLE		3 (15.8)

Table 2. Presenting symptoms

Category		Patients (Total = 19) n (%)
ARA criteria		
Malar rash		8 (42.1)
Discoid rash		4 (21.1)
Photosensitivity		2 (10.5)
Oral Ulcer		1 (5.2)
Arthritis		4 (21.1)
Serositis	Pleuritis	1 (5.2)
	Pericarditis	6 (31.6)
Renal disorder		13 (68.4)
Neurological disorder		3 (15.8)
Hematological disorder		17 (89.5)
Immunological disorder		9 (47.4)
Anti-nuclear antibody		16 (84.2)
Others		
Prolonged fever		4 (21.1)
Alopecia		4 (21.1)
Lymphadenopathy		3 (15.8)
Weight loss		3 (15.8)
Ascites		2 (10.5)
Hepatomegaly		1 (5.2)
Gastric hemorrhage		1 (5.2)
Lupoid hepatitis		1 (5.2)
Pulmonary hemorrhage		1 (5.2)
Skin vasculitis		1 (5.2)

Abbreviations: ARA, American Rheumatism Association; ANA, anti-nuclear antibody

Table 3. Laboratory data at diagnosis in SLE patients

Data	Patients (Total=19) N (%)
Proteinuria	13/19 (68.4)
Microscopic hematuria	9/19 (47.4)
Anemia	12/19 (63.2)
Positive direct coombs' test	11/19 (57.9)
Leucopenia	3/19 (15.8)
Lymphopenia	3/19 (15.8)
Thromobocytopenia	4/19 (21.1)
Anti-dsDNA	7/19 (36.8)
Anti-Sm	1/10 (10.0)
Anticardiolipin	2/10 (20.0)
Lupus anticoagulant	3/9 (66.7)
LE cell	3/5 (60.0)
Low serum C3	11/19 (57.9)
Low serum C4	4/10 (40)
Elevated ESR	10/11 (90.9)

Abbreviations: SLE, systemic lupus erythematosus; Anti-Sm, anti-Smith antibody; ESR, erythrocyte sedimentation rate

identified in 4 (21.1%) patients who presenting with bilateral symmetrical arthritis. Three patients had lymphadenopathy at cervical region (2) and intra-abdominal region (1). The enlarged lymphatic nodes disappeared after corticosteroid therapy.

Neurologic involvement was a presentation in 3 patients. Two had generalized tonic clonic seizure from cerebritis. One patient presented with bilateral eye pain and poor vision due to optic neuritis. All patients received echocardiography. Six (31.6%) patients had pericardial effusion. Of these, one patient had pericardial effusion, myocarditis and endocarditis called pancarditis. Four (21.0%) patients presented with gastrointestinal symptoms. One patient presented with ascites and severe acute abdominal pain. His abdominal tenderness required emergency abdominal exploration to exclude surgical conditions. He was diagnosed with lupus peritonitis.

Respiratory system involvement was identified in only 2 patients. Of these, 1 patient presented with acutely life-threatening diffuse alveolar hemorrhage (DAH) required mechanical respiratory support. Weight loss was the most common non-specific symptoms. One patient had prolonged fever, generalized lymphadenopathy, thrombocytopenia, splenomegaly and was diagnosed with systemic onset juvenile rheumatoid arthritis (JRA) one year prior to diagnosis of SLE.

Laboratory data

Anti-nuclear antibody (ANA) was determined in all patients. Sixteen (84.2%) patients had ANA titer $\geq$ 1: 80. Thirteen patients had ANA titer $\geq$ 1:320. The characteristic of ANA included speckle pattern in 9 patients, homogenous pattern (7) and peripheral pattern (3) and data unavailable in 4 patients. Anti-double stranded DNA (Anti ds-DNA) was determined in all patients with positive results in 7 (36.8%) patients. Serum C3 and C4 were determined in 19 and 10 patients respectively. Low serum C3 and C4 levels were presented in 11 (57.9%) and 4 (40%) patients, respectively (Table 2). Mean SLEDAI score was 14.9 $\pm$ 2.2 at the time of diagnosis (Fig. 2).

Treatment and outcome

Most patients received oral corticosteroid. Fourteen patients received hydroxychloroquine. Other treatments were demonstrated in Table 5. Disease activity was evaluated by SLEDAI as shown in Fig. 2. Overall, all patients did response to therapy as demonstrated by a significant decreasing of SLEDAI score from 14.9 $\pm$ 2.2 to 6.8 $\pm$ 1.6 ($p < 0.0001$) at 0 and 1 month, respectively and 4.6 $\pm$ 1.2 at 2 months. At 1 year after therapy, 11 of 16 patients had complete remission with absence of As and Bs score of BILAG 2004 index. Four patients relapsed at 2.7 $\pm$ 1.2 years after the disease onset.

Twelve patients with LN responded to therapy with decreasing of UPCI (Fig. 1). Four patients with LN class II received oral prednisolone 1-2 mg/kg/day. Two of them also received pulse methylprednisolone (pulse MP, 30 mg/kg/dose, maximum 1 g) for 3 consecutive days at the beginning for lupus peritonitis and pericarditis. Their initial UPCI significantly decreased from 0.9 $\pm$ 0.1 to 0.26 $\pm$ 0.04 ($p < 0.05$) and 0.2 $\pm$ 0.02 ($p < 0.05$) at 6 and 12 months after therapy, respectively. All of them had complete renal remission at 24 weeks. Of two patients with LN class III, one had complete renal remission and one had partial renal remission with prednisolone 0.5 mg/kg/day at 6 months. Seven patients with LN class IV was treated with a conventional regimen including oral predinisolone 2 mg/kg/day and monthly intravenous cyclophosphamide (IV CYC) for 6 months followed by quarterly dosing for 2 years. Six patients received pulse MP for 3 consecutive days at a time of diagnosis. Duration of follow-up was 3.0 $\pm$ 2.5 years. All patients did response to therapy. Their UPCI significantly decreased from 5.7

Table 4. Clinical characteristic and laboratory data at the time of initial renal biopsy

Characteristic	Class II n (%)	Class III n (%)	Class IV n (%)
Number of patients	4	2	7
Age at onset (yr, mean ± SD)	13.9 ± 1.4	11.1 ± 4.2	13.4 ± 1
Hypertension	0 (0)	1 (50)	7 (100)
Microscopic hematuria	0 (0)	2 (100)	7 (100)
Proteinuria	4 (100)	2 (100)	7 (100)
24 hr urine protein (mg/m^2/h)			
4 - 40	4 (100)	0 (0)	4 (57.1)
> 40	0 (0)	2 (100)	3 (42.9)
Creatinine clearance (ml/min/1.73m^2)			
≥90	4 (100)	2 (100)	2 (28.6)
≥20 to <90	0 (0)	(0) 0	3 (42.8)
<20	0 (0)	(0) 0	2 (28.6)
Scarring on renal biopsy*	0 (0)	(0) 0	4 (66.7)

*Scarring defined according to ISN classification of class III/IV active/chronic lupus nephritis [11]

Table 5. Treatment of SLE

Medications	Patients (total=19) N (%)
Oral prednisolone	19 (100)
Hydroxychloroquine	14 (73.7)
Pulse methylprednisolone	12 (63.2)
Pulse cyclophosphamide	9 (47.4)
Azathioprine	4 (21.1)
NSAID	3 (15.8)
Plasma exchange	3 (15.8)
Rituximab	2 (10.5)
Methotrexate	1 (5.3)

± 1.4 to 0.9 ± 0.4 ($p < 0.05$), eGFR significantly increased from 53.2 ± 47.8 to 113.1 ± 82.9 ml/ 1.73m^2/min ($p < 0.05$), and SLEDAI score significantly decreased from 19.6 ± 4.0 to 5.1 ± 1.4 ($p < 0.0001$) at 24 weeks after therapy. Two patients presented with RPGN. Of these, one patient responded to 3 doses of pulse MP, plasmapheresis, and pulse IV CYC as demonstrated by decreasing of UPCI from 9.4 to 0.2 and increasing eGFR from 9.4 to 88.6 ml/1.73m^2/min at 24 weeks. Another patient with RPGN, LN class IV-G (A/C) and pancarditis received plasmapheresis, pulse MP and IV CYC at the beginning. This patient did not response to these intensive therapies as demonstrated by unusual persistently high SLEDAI score at 25, 1 month later. One infusion of rituximab 375 mg/m^2 induced rapid decreasing of SLEDAI score from 25 to 14 in two months. Then, she was treated with oral prednisolone and pulse CYC for 18 courses. She was hemodialysis-dependent for 6 months. Two years later, she had eGFR of 114.3 ml/1.73m^2/min, UPCI of 1.47, SLEDAI score of 4 and normal echocardiography.

Two patients with cerebritis did response to pulse MP and oral prednisolone 2 mg/kg/day. A patient with bilateral optic neuritis received pulse MP for 3 consecutive days followed by monthly doses for 12 months in conjunction with pulse CYC for 12 months followed by quarterly doses for a total of 22 courses and azathioprine for 3 years. She had permanent blindness of her left eye.

One patient presented with DAH which was refractory to 4 sessions of plasmapheresis, pulse MP and pulse CYP, but responded to one infusion of rituximab 375 mg/m^2. This patient developed herpes zoster infection and bacterial septicemia at 2 and 3 months after receiving rituximab, respectively.

Sixteen patients with hematological involvement also had other major organ involvement. Hematological abnormalities improved after high dose of oral corticosteroid and immunosuppressive drugs. One patient with antiphospholipid syndrome and LN class IV received low molecular weight heparin followed by long-term warfarin. She received pulse MP and pulse CYC for LN class IV. Her eGFR gradually increased from 34 to 58 ml/min/1.73m^2 at 24 weeks. Three patients presented with ascites, hepatomegaly, gastric bleeding, lupus peritonitis also had LN. These gastrointestinal manifestations improved after treatment of LN. Lupus peritonitis dramatically responded to pulse MP 3

consecutive days.

Complications and adverse effects

Infection was the leading complication during treatment of SLE (Table 6). The common sites of infections were respiratory system, skin, urinary tract and gastrointestinal tract, respectively. They had community-acquired infections. Prednisolone dose was 0.9 ± 0.6 mg/kg/day, while they developed infections. Six (55%) episodes of infections were accompanied with lymphopenia (Table 6). All patients recovered from infections after receiving appropriated antibiotics. Ophthalmological complications were identified in 6 (32%) patients. They were cataract in 4 patients, chloroquine maculopathy (1) and permanent blindness from optic neuritis (1). Hemorrhagic cystitis was not observed in patients received pulse CYC. All patients survived at the time of last follow-up.

Discussion

The present study reported a cohort of children with SLE from a hospital in suburban area, Thailand. This group of patients had demographic data, clinical presentation and laboratory data comparable to previous studies in Asia[2,15,16]. Similar to previous studies, hematological and renal involvements are the most common manifestations in the present study[2,15,16]. The 11.3% incidence of neurological disorder in the present study was underestimated because standard neuropsychological test to detect cognitive dysfunction was not performed in our patients. The authors reported a coexistence of JRA and SLE in the same patient which rarely seen in children. There are a few publications reporting this particular overlap[17-20]. However, systemic-onset JRA and SLE occurring in the same patient is very rare[21]. Our patient developed systemic-onset JRA at the age of 12; this diagnosis was made after ruling out other conditions including SLE and hematologic malignancy. One year later, he developed typical clinical and serological evidences of lupus including seroconversion from an ANA-negative to ANA-positive and normal C3 level to low C3 level, autoimmune hemolytic anemia and neurological involvement. The underlying mechanism of the coexistence of JRA and SLE remained unknown. Clinical presentation of this patient should alert a pediatrician that a high index of suspicious is necessary when a patient diagnosed with systemic-onset JRA has recurrence of symptoms so that diagnosis of SLE is not missed.

Pediatric SLE management is based on results from small pediatric cohort studies, clinical experience, and large randomized controlled trials in adults. As a result of the shortage of clinical controlled trials in children, treatment protocols vary between different centers. The present study demonstrated a good clinical outcome of SLE patients with selected regimens as demonstrated by a complete remission rate of 69% at 1 year after therapy. The SLEDAI was employed to evaluate disease activity during treatment. Overall, SLEDAI score significantly decreased within 1 months after starting therapies. This finding suggested that a persistently high SLEDAI score at 1 month after therapy should alert physician to evaluate possible causes including patient compliance or a benefit of adjunctive treatments. Based on a research supporting the central role of B cells in the pathogenesis of SLE, medications specifically targeting B cells are developed. Rituximab is a chimeric mouse-human monoclonal antibody against human CD20 which is a cell surface marker specific to B cells[22]. It has been used as an adjunctive therapy in adult SLE patients with severe disease and refractory to traditional immunosuppressive drugs with good results[23-25]. The study showing efficacy of rituximab in children SLE is limited[6-8]. In the present study, the authors presented clinical experience on rituximab as an adjunctive therapy in 2 pediatric SLE patients.

LN class IV presented with RPGN, renal failure leading to hemodialysis dependence is not uncommon in children. A full recovery of renal function in patient with ESRD and hemodialysis dependent is rare. To date, several studies support the efficacy of rituximab as an adjunctive treatment for severe LN in children[6-8]. Nwobi et al reported good benefit of two to four doses of rituximab in eighteen children with SLE after demonstrating resistance or toxicity to conventional regimens. However, renal function of three hemodialysis-dependent patients in this report did not fully recover. In the present study, the authors reported a single dose of rituximab induced significant decreasing of SLEDAI score in one patient presented with RPGN and LN LN class IV-G (A/C). This patient had refractory SLE and persistently high SLE score at 1 month after conventional therapy including pulse CYC, pulse MP and plasmapheresis. It is likely that rituximab has contributed to the remission in this patient since other previous treatments have failed to induce remission and decrease SLEDAI score when used alone. To the best of our knowledge, the present study firstly reported a child who became hemodialysis independent 6 months after receiving a combination of

Table 6. Infections during treatment of SLE

Patient	Immunosuppressive drugs	Infections	Treatment	Outcome	Leucopenia (WBC<4000 cells/mm^3)	Lymphopenia (L<1,500 cells/mm^3)	Neutropenia (PMN<1,500 cells/m^3)
1	Prednisolone oral	Herpes zoster	Acyclovir	Recovered	No	Yes	No
2	Pulse CYC* Prednisolone oral	Pneumonia	Ceftriaxone, Ciprofloxacin				
		Varicella and Pneumonia	Ceftriaxone, Meropenem, Acyclovir	Recovered	No	Yes	No
3	Pulse MP** Prednisolone oral	Pneumonia	Ceftriaxone	Recovered	No	No	No
4	Pulse CYC Pulse MP Prednisolone oral	Dengue hemorrhagic fever	Intravenous fluid therapy	Recovered	No	Yes	No
5	Prednisolone oral	Pharyngitis	Ceftriaxone	Recovered	No	No	No
6.	Pulse CYC Pulse MP Prednisolone oral	Urinary tract infection	Ceftriaxone	Recovered	No	Yes	No
		Sinusitis	Augmentin	Recovered	No	No	No
7	Prednisolone oral Methotrexate	Herpes zoster	Acyclovir	Recovered	No	No	No
8	Rituximab Pulse MP Pulse CYC Prednisolone oral	Herpes zoster	Acyclovir	Recovered	Yes	Yes	No
9	Pulse MP Pulse CYC Prednisolone oral	Infective diarrhea	Norfloxacin	Recovered	No	Yes	No

*Pulse CYC, pulse cyclophosphamide; **Pulse MP, pulse methylprednisolone

rituximab and conventional therapy. Serious adverse effect of rituximab is severe infection leading to death[7]. Our patient did not experience major infection within 3 years after receiving rituximab.

Diffuse alveolar hemorrhage (DAH) is a rare but life-threatening complication of SLE. The incidence of DAH is approximately 1.9% of Chinese SLE patients[26]. It should be considered in patients with SLE who presented with dyspnea, unexplained anemia and new radiographic chest infiltrates. Mortality from DAH remains high approximately 50%[27]. To date there is no standard regimen for DAH secondary to SLE given a lack of controlled clinical trials. In general, early pulse MP is recommended[28,29]. Intravenous CYC has been used to treat DAH in modern practice[27]. Although, controlled clinical trials have failed to show any benefit of plasmapheresis in SLE overall[30], However, plasmapheresis may have a role in life-threatening DAH[31,32]. Recently, Liang et al. reported a successful treatment of refractory DAH secondary to SLE with mesenchymal cord blood stem cell transplantation[33]. The present study reported refractory DAH after plasmapheresis, pulse MP, and IV CYC. This patient needed to be re-intubation due to recurrent alveolar bleeding even after such intensive therapies. Apparently, an infusion of rituximab could stop alveolar bleeding and allowed patient to be independent from mechanical respirator. Thus, it is likely that rituximab has contributed to the remission in this patient since other previous treatments have failed to induce remission when used alone. To date, only one study have reported a treatment of DAH with rituximab in conjunction with other therapies[27]. However, a patient reported by Todd et al. received many SLE medications including rituximab at the same time. Thus, it appeared rather difficult to attribute DAH improvement to the use of rituximab only in that patient. The present study suggested that rituximab may be a useful agent for SLE-associated DAH.

The authors have demonstrated a benefit of rituximab to induce remission in two patients with renal failure and acute life-threatening diffuse alveolar hemorrhage which resistant to conventional therapy. Given a risk of human antichimeric antibody, fatal complications and a cost issue, large controlled studies are needed to established safety profile and optimal regimen of rituximab when used in children with SLE.

The present study reported a small group of patients with short duration of follow-up leading to an unusual zero of mortality rate. Previous large study in Asian reported approximately 77.5% of mortality rate at 10 years[2]. A major morbidity of our patients was ophthalmologic complications including cataract, chloroquine maculopathy, and blindness from optic neuritis. Cataract is a common side effect of corticosteroid. A high dose of oral corticosteroid is required for induction of remission in severe SLE. However, the goal should be to get disease under control with minimal side effect. A high dose corticosteroid should be weaned over the following 6-8 weeks to a dose of 0.5 mg/kg/day to prevent serious side effects including infection, growth inhibition, avascular necrosis and cataract[34]. Hydroxychloroquine has antiinflammatory, antithrombotic, antihyperlipidemic effects and has been shown to reduce damage accrual in patients with SLE[35]. Our patient with abnormal renal function developed chloroquine maculopathy despite of bi-annual eye exam including retinal examination, and Amsler grid testing as recommended by the American academy of ophthalmology for high-risk patients[36]. Early recognition of retinopathy followed by discontinue medicine is the best way to prevent permanent vision loss. Thus, our finding suggested that quarterly eye examination should be considered in high-risk patients.

Ultimate goal of SLE treatment is to improve long-term patient survival. Infection is a major cause of morbility and mortality in SLE patients[2,37]. It is the most common complication in the present study. Major risk factors for infection in SLE are corticosteroid and immunosuppressive drugs including pulse CYC. There is an enormous effort to identify effective drugs to increase remission rate of severe SLE and minimize side effects of drugs. Several studies in adult demonstrated both superior and comparable effect of mycophenolate mofetil (MMF) to IV CYC for induction treatment of LN class III through V[38,39]. In addition, MMF appeared to be more efficacious, safer, and less infectious rate than IV CYC in maintenance phase in adult LN[40,41]. Controlled clinical trials comparing IV CYC and MMF in both induction phase and maintenance phase in pediatric patients are needed.

Conclusions

The authors demonstrated a good outcome of SLE treatment in pediatric patients from a single center. Infection was the most common cause of morbidity followed by ophthalmologic complications. Rituximab may be a good adjunctive therapy for refractory SLE. Large controlled trials to establish safety profile and optimal regimen of rituximab in childhood SLE is required.

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โรคลูปัสในเด็กที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติ์

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โรคลูปัสเป็นโรคออโต้อิมมูนที่เกิดจากความผิดปกติในระบบภูมิคุ้มกันที่พบได้บ่อยในเด็ก การรักษาในปัจจุบันได้ผลดีแต่มีผลข้างเคียงจากยามาก โดยเฉพาะจากยาสเตียรอยด์และยากดภูมิต้านทาน การทำให้โรคสงบเป็นปัจจัยหนึ่งที่มีผลต่อการพยากรณ์โรค รายงานการใช้ยารักษาภาวะที่โรคไม่ตอบสนองต่อการรักษามาตรฐานในผู้ป่วยเด็กมีจำกัด ผู้นิพนธ์ทำการศึกษาย้อนหลัง ลักษณะโรคลูปัส ผลการรักษาและภาวะแทรกซ้อนในผู้ป่วยเด็กอายุน้อยกว่า 15 ปี ที่รับการรักษาที่โรงพยาบาลธรรมศาสตร์เฉลิมพระเกียรติระหว่างวันที่ 1 มกราคม พ.ศ. 2545–31 มีนาคม พ.ศ. 2553 ผู้ป่วย 19 ราย อายุเฉลี่ย 12.9 $\pm$ 1.6 ปี มาติดตามการรักษาเฉลี่ยนาน 3.3 $\pm$ 2.6 ปี ผู้ป่วยมีความผิดปกติของหลายระบบเมื่อแรกวินิจฉัย ได้แก่ ระบบโลหิตพบร้อยละ 89.5 ระบบผิวหนังร้อยละ 73.7 ระบบไตร้อยละ 68.4 ผู้นิพนธ์รายงานผู้ป่วย 1 ราย ที่ได้รับการวินิจฉัยโรค systemic onset juvenile rheumatoid arthritis 1 ปีก่อนได้รับการวินิจฉัยโรคลูปัส ลักษณะทางพยาธิวิทยาของไตได้แก่ พยาธิสภาพกลุ่ม 2 ร้อยละ 30.8 พยาธิสภาพกลุ่ม 3 ร้อยละ 15.4 พยาธิสภาพกลุ่ม 4 ร้อยละ 53.8 การรักษาโรคลูปัสได้ผลดีอย่างเห็นได้ชัดเมื่อเวลา 1 เดือน โดยผู้ป่วยมีค่าแสดงการกำเริบของโรค (SLEDAI) ลดลงอย่างมีนัยสำคัญทางสถิติกล่าวคือ SLEDAI ลดจาก 14.9 $\pm$ 2.2 ที่แรกวินิจฉัยเป็น 6.8 $\pm$ 1.6 ที่ 1 เดือน ($p < 0.0001$) เมื่อประเมินที่เวลา 1 ปีหลังการรักษาพบว่าผู้ป่วยร้อยละ 68.7เข้าสู่ภาวะโรคสงบ ภาวะแทรกซ้อนที่เกิดขึ้นในผู้ป่วยระหว่างการรักษาคือภาวะติดเชื้อ โดยผู้ป่วยร้อยละ 47.4 ต้องนอนโรงพยาบาลเนื่องจากการติดเชื้อ ภาวะแทรกซ้อนทางตาพบในผู้ป่วยร้อยละ 32 ได้แก่ ต้อกระจกจากยา prednisolone จอประสาทตาเสื่อมจากยา hydroxychlorquine และตาบอดจากโรคลูปัสเอง ผู้ป่วยทุกรายรอดชีวิตเมื่อสิ้นสุดการศึกษา ผู้นิพนธ์รายงานการทำให้โรคสงบจากการใช้ยา rituximab ในผู้ป่วย 2 ราย ซึ่งไม่สนองตอบต่อการรักษาโดยวิธีมาตรฐาน รายแรกมีภาวะไตวายเรื้อรังและรายที่ 2 มีภาวะเลือดออกในปอด