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Original article

Combination of tacrolimus and mycophenolate mofetil in persistent proteinuria due to refractory childhood lupus nephritis

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ABSTRACT

Background: Children with lupus nephritis particularly, diffuse proliferative and membranous glomerulonephritis, may necessitate potent immunosuppressive medications and occasionally combined therapy.

Objective: To report the beneficial effects of tacrolimus (TAC) in children with refractory lupus nephritis from a single tertiary pediatric rheumatology clinic.

Methods: This is a retrospective case series of children with refractory lupus nephritis treated with TAC after failure of aggressive immunosuppressive treatment. All patients were evaluated at the time of initiation of TAC and at last follow-up visit by assessing the following response parameters: cSLE Disease Activity Index (SLEDAI), urine protein/creatinine ratio, urine sediments, serum albumin, complement (C_3 and C_4), anti-double-stranded DNA (dsDNA) antibody levels, and renal function assessed by glomerular filtration rate (eGFR).

Results: Three children (two girls and one boy) with lupus nephritis and persistent nephrotic-range proteinuria failed prednisone treatment as well as sequential treatment of cyclophosphamide, mycophenolate mofetil (MMF), and rituximab. When TAC was administered along with MMF and prednisone, all patients showed improvement in response parameters, namely, SLEDAI, serum albumin, and proteinuria, and prednisone doses were significantly weaned off and discontinued in two patients. However, eGFR remained stable during the treatment period. TAC was well tolerated, and no adverse effects were observed.

Conclusion: TAC combined with MMF can be considered as an alternative therapeutic option for children with refractory lupus nephritis particularly those with persistent nephrotic-range proteinuria.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multiorgan involvement; the onset and clinical features of childhood SLE (cSLE) are often aggressive and require an intensive therapy [1,2]. Lupus nephritis is one of the major clinical features of SLE, occurring in up to 60% of children with SLE. It can be subclinical but occasionally present with body edema due to nephrotic-range proteinuria, hypertension, and renal impairment [3,4].

Although there is no available cure for SLE presently, several drugs are useful in controlling the disease and contributed to a favorable outcome. Children with lupus nephritis, especially diffuse proliferative and membranous glomerulonephritis, may necessitate potent immunosuppressive medications such as cyclophosphamide (CYC) or mycophenolate mofetil (MMF) and occasionally rituximab (RTX) [5,6]. However, one third of such patients might either have frequent disease flares or be resistant to the treatment with disease progression [7,8].

Tacrolimus (TAC) recently gained much attention in the treatment of adult patients with refractory lupus nephritis and children with a nephrotic syndrome [9–11]. However, the available published data in childhood lupus nephritis are limited [12–14].

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Herein, we present three children with refractory lupus nephritis who were treated successfully with TAC. Furthermore, we reviewed all published articles on the treatment of childhood lupus nephritis with TAC.

2. Patients and methods

This is a retrospective case series of patients with refractory childhood lupus nephritis seen at King Faisal Specialist Hospital and Research Center (KFSH-RC), Riyadh. Medical records were reviewed for demographic data, clinical and laboratory parameters, histopathology and imaging findings, and response to TAC. All patients were evaluated at the time of initiation of TAC treatment, then after 3 and 6 months, and at the last follow-up visit by assessing the following response parameters: cSLE Disease Activity Index (SLEDAI), urine protein/creatinine ratio, urine sediments, serum albumin, complement (C_3 and C_4), anti-double-stranded DNA (dsDNA) antibody levels, and renal function assessed by estimated glomerular filtration rate (eGFR).

3. Results

Table 1 shows the clinical and laboratory findings of the three patients with refractory lupus nephritis.

3.1. First case

A 13-year-old girl was diagnosed with SLE at the age of 8 years on the basis of constitutional symptoms, malar rash, oral ulceration, and arthritis. She had leukopenia, elevated antinuclear antibody (ANA), high anti-ds DNA antibody levels, and low complement (C_3 and C_4) levels. Other results revealed a high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) 39 mm/h and 22 mg/L, respectively. She also had evidence of nephritis manifested with hematuria and nephrotic-range proteinuria. Renal biopsy proved lupus nephritis class IV. Interestingly, her mother is a known case of SLE with nephritis. She was started on prednisone (1 mg/kg/day), hydroxychloroquine (5 mg/kg/day), and azathioprine (AZA) (2 mg/kg/day).

In the early disease course, she developed heart failure due to moderate mitral valve regurgitation and required Lasix (2 mg/kg/day) and enalapril (0.2 mg/kg/day).

Because of cardiac involvement and persistent heavy proteinuria (632 mg/mmol), treatment was switched from AZA to CYC and RTX; she completed six doses of monthly CYC (750 mg/m^2/dose), and two doses of RTX (350 mg/m^2/dose), followed by MMF (600 mg/m^2 12 h). She was maintained on hydroxychloroquine and variable of prednisone depending on the disease activity. Unfortunately, she had partial improvement with persistent heavy proteinuria, and then, oral TAC at 0.1 mg/kg/day was added to MMF, hydroxychloroquine, and prednisone. Three months later, she showed significant improvement in all parameters and allowed prednisone discontinuation.

3.2. Second case

A 13-year-old girl presented to the local hospital with features of nephrotic syndrome and was treated with prednisone 60 mg/m^2/day for 4 weeks; she did not show improvement, and the renal biopsy performed proved lupus nephritis class IV. Interestingly, she did not have extra-renal manifestations of lupus, but laboratory investigations revealed positive ANA (1:160) and low C_3 (0.8). Oral prednisone was continued, and MMF (600 mg/m^2 12 h) was added along with hydroxychloroquine (5 mg/kg/day). Despite the treatment, she had progressive disease course with hypertension and impaired renal function. Accordingly, MMF was replaced with six doses of monthly CYC (750 mg/m^2/dose) and two doses of RTX (350 mg/m^2/dose). Proteinuria and hypoalbuminemia improved partially but with progressive renal impairment. Consequently, TAC (0.1 mg/kg/day) was added to her treatment regimen. Two months later, she showed good improvement in all parameters including renal function, and she was able to stop prednisone for the first time since her disease onset. During TAC treatment, she had urinary tract infection (UTI), wherein a proper oral antibiotic was administered for efficiently treating *Escherichia coli*.

3.3. Third case

A 14-year-old boy was diagnosed at the age of 11 years with SLE on the basis of mucocutaneous manifestations, leukopenia, autoimmune hemolytic anemia diagnosed by the direct Coombs test, thrombocytopenia, positive ANA, high anti-dsDNA antibody levels, and low C_3 and C_4 levels with hematuria and proteinuria. Renal biopsy proved lupus nephritis class III. He was treated with prednisone (2 mg/kg/day), hydroxychloroquine (5 mg/kg/day), and AZA (2 mg/kg/day). Owing to partial response, treatment was switched from AZA to MMF (600 mg/m^2 12 h).

Table 1
Baseline clinical and laboratory findings of three patients with refractory lupus nephritis.

	Case I	Case II	Case III
Age (Years)/Gender	13/Female	12/Female	14/Male
Age at onset (SLE) (Years)	8	11	8
Lupus nephritis (ISN/RPS)	IV	IV	IV/V
Extra-renal	Mucocutaneous Musculoskeletal Hematological	Hematological	Mucocutaneous Musculoskeletal Hematological
Urine Pr/Cr ratio (mg/mmol) [a]	424	120	629
Urine sediments	5 RBC, 5 WBC+ Hyaline cast	Negative	>50 RBC, 5 WBC+ Granular cast
C_3 g/L (0.9–1.8)	0.79	1	0.8
C_4 g/L (0.1–0.4)	0.3	0.4	0.1
eGFR min/ml/1.73 m^2	157	43	162
Serum albumin mg/L	30	34	27
Anti-dsDNA antibody (<200)	1280	Negative	456
Daily Steroid dose (mg)	10	5	5
Previous medications	MMF, RTX, CYC, IVIG	MMF, RTX, CYC, IVIG	MMF, RTX, CYC, IVIG
SLEDAI	9	4	14

C_3, complement 3; C_4, Complement 4; dsDNA, double-stranded DNA; AZZ, azathioprine; CYC, cyclophosphamide; RTX, rituximab; MMF, mycophenolate mofetil; IVIG, intravenous immunoglobulin; SLEDAI, systemic lupus erythematosus disease activity index.

[a] Urine protein/creatinine ratio (<30 mg/mmol).

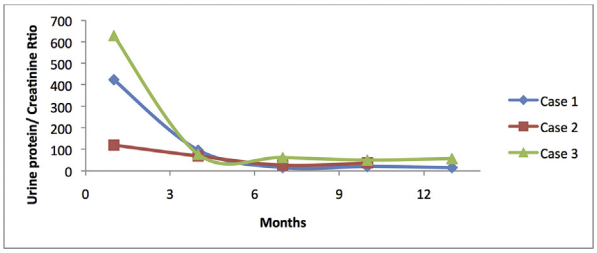

Fig. 1. Changes in urine protein/creatinine ratio during the treatment period.

Two years later, he presented with nephritic/nephrotic manifestations; hence, renal biopsy was repeated and showed lupus nephritis class IV and V. Accordingly, MMF was replaced by CYC (750 mg/m^2/dose), for six doses monthly, and then another six doses for every 3 months; then, he was maintained on MMF but showed partial response. He required two cycles of RTX (350 mg/m^2/dose) but showed suboptimal improvement. Then, TAC (0.1 mg/kg/day) was added to MMF, and he showed good improvement.

3.4. Clinical assessment

All patients showed improvement in response parameters, namely, SLEDAI, serum albumin, and urine protein/creatinine ratio (Fig. 1). However, eGFR remained stable during the treatment period. Prednisone was weaned gradually and was stopped in two patients. TAC was well tolerated, and no significant adverse effects were observed except in one patient who had simple UTI. Table 2 summarizes the results of response to TAC during the follow-up period.

Table 2
Summarized results of response to tacrolimus during the follow-up period.

	Baseline	3 months	6 months	Last follow-up visit
Urine Pr/Cr ratio				
Case I	424	127	18	70
Case II	126	69	23	37
Case III	629	76	62	49
C_3/C_4				
Case I	0.76/0.3	0.76/0.28	0.9/0.39	0.9/0.2
Case II	1.0/0.46	1.1/0.48	0.9/0.37	1.0/0.4
Case III	0.8/0.1	1.05/0.1	1.22/0.13	1.37/0.21
eGFR				
Case I	157	130	–	165
Case II	43	51	49	52
Case III	206	260	230	239
Serum albumin				
Case I	30	36.8	40	40
Case II	34	39	43	44
Case III	19	28	41	42
Anti-dsDNA antibody				
Patient I	1280	–	–	348
Patient II	–	–	–	–
Patient III	456	–	296	–
SLEDAI				
Case I	9	6	0	0
Case II	4	0	0	0
Case III	14	0	0	0
Prednisone daily dose				
Case I	10	5	0	0
Case II	5	0	0	0
Case III	5	5	5	5

C_3, complement 3; C_4, Complement 4; eGFR, estimated glomerular filtration rate; dsDNA, double-stranded DNA; SLEDAI, systemic lupus erythematosus disease activity index.

4. Discussion

Management of lupus nephritis remains a great challenge particularly in children with active nephritis and persistent heavy proteinuria [14]. CYC and MMF are still considered as the induction therapy for proliferative lupus nephritis, but MMF is considered as a suitable maintenance therapy. Additionally, MMF might be the preferred induction and maintenance therapy for membranous lupus nephritis [15]. By this approach, the disease relapse rate reduced and the outcome improved significantly. Despite that, renal flare can occur in up to 50% during the maintenance treatment. Thus, in active nephritis or persistent proteinuria, immunosuppressive drugs can be switched to another agent within 3–6 months of treatment [15,16]. Although, evidence is limited, combination of RTX and MMF or CYC might provide efficacious therapeutic effect for refractory cases of SLE including nephritis. However, it was associated with a high rate of infection [17,18].

TAC recently showed encouraging results suggesting its efficacy in adult patients with refractory lupus nephritis, especially in reducing proteinuria [9,19].

The available data in childhood lupus nephritis are limited. Almost all published data came from one institution. Tanaka et al. followed a cohort of children with lupus nephritis treated with TAC; the results suggest that TAC is beneficial with low cytotoxicity [12,13]. A new treatment option in patients who were refractory to the standard treatment is the multitarget treatment such as a combination of TAC and MMF [20,21].

Our patients had refractory lupus nephritis with persistent heavy proteinuria showing partial response to sequential CYC, MMF, and RTX treatment. Fortunately, combined treatment of TAC and MMF showed beneficial therapeutic effect within 3 months of treatment. This regimen led to complete remission of proteinuria and constant improvement in eGFR. Furthermore, prednisone was discontinued in two patients. Interestingly, none of them had relapses after initiation of this regimen until the last follow-up visit.

Evidence is limited for the use of TAC for treating childhood lupus nephritis. However, if a patient with cSLE with heavy proteinuria resists the standard induction treatment within 6 months, it is worth considering TAC as an alternative therapeutic option. This work had several limitations; it included a small number of patients. Moreover, it is an open uncontrolled study with patients treated in an unblinded manner.

Conflicts of interest

The authors have nothing to disclose related to this work. This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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