Case Report
 Tacrolimus ameliorates proteinuria in Chinese pediatric lupus nephritis patients

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Abstract: Few studies have reported treatment with tacrolimus (TAC) for Chinese pediatric lupus nephritis (PLN). Therefore, this study aims to investigate the effects of TAC in Chinese PLN. A 12 month retrospective analysis was performed from Children’s Hospital of Fudan University. Data on the clinical characteristics and serologic lupus activity were assembled. The baseline characteristics of the patients were: complement component 3 (C3), 0.64 ± 0.36 g/L; complement component 4 (C4), 0.13 ± 0.09 g/L; the 50% hemolytic complement (CH50), 29.14 ± 21.59 U/ml; erythrocyte sedimentation rate (ESR), 48.43 ± 28.16 mm/h; platelets (PLT), 167.00 ± 87.82 10^9/L; 24 h urine protein, 3.07 ± 1.33 g; prednisolone (PDN) dose, 52.57 ± 7.16 mg/d. After 12 month treatment with TAC, C3, and CH50 levels were increased than baseline (P < 0.05). ESR, 24 hour urine protein and PDN dose were decreased than baseline (P < 0.05). No serious adverse reactions were found. In conclusion, TAC could ameliorate proteinuria and reduce PDN dose in Chinese PLN patients.

Keywords: Tacrolimus, proteinuria, pediatric, lupus nephritis, real world study

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by the production of a large number of autoantibodies in the blood, which deposits in the vascular beds of target tissues and organs including glomeruli and the renal microvasculature, leading to systemic inflammation and lupus nephritis (LN) [1-4].

Pediatric systemic lupus erythematosus (PSLE) is a disease with a prevalence of 4.7 per 100,000 children, where higher frequency of LN is observed in children than adults. It is generally believed that LN lesions could affect prognosis and proteinuria is an important risk factor for progression of renal disease in patients with LN. Therefore, controlling proteinuria is particularly important in treating pediatric lupus nephritis (PLN) [5].

Although corticosteroids and immunosuppressants are widely used to treat PLN, more than a few resistant cases have been experienced. A new treatment has been strongly sought in the clinical setting [6].

Tacrolimus (TAC) is a medication that induces an immunosuppressive effect, and in recent years it has been widely used in the treatment of SLE [7, 8]. However, the experience of TAC in Chinese PLN is very limited. This study aims to investigate the effect of TAC in Chinese PLN.

Material and methods

Patients

All data were all from real world studies. Patients, younger than 18 years of age, who were diagnosed by LN and on treatment with tacrolimus as therapy, were included in our study. Patients were excluded if they had other serious diseases. PLN patients in Children’s Hospital of Fudan University were studied for treatment dates between January 2015 and December 2017, retrospectively. The present study was approved by the Research Ethics Committee of Children’s Hospital of Fudan University.
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Main outcome variable and procedures

A systematic review of patient files, using a standard data collection protocol, was carried out. Data were gathered from the beginning of TAC treatment to the 12 month endpoint, defined as last follow-up. Clinical characteristics included sex, age, renal biopsies, TAC dose, complement component 3 (C3), complement component 4 (C4), the 50% hemolytic complement (CH50), erythrocyte sedimentation rate (ESR), platelets (PLT), 24 h urine protein and prednisolone (PDN) dose at the beginning of TAC treatment (0 month), treatment with TAC for 6 months (6 month) and treatment with TAC for 12 months (12 month). Data on clinical characteristics and serologic lupus activity were obtained from medical records, which were measured by the automatic biochemical analyzer.

Statistical analysis

Data are expressed as mean ± standard error (SE). Statistical analyses were performed using General Linear Model for repeated measurement. A value of $P < 0.05$ was considered statistically significant.

Results

Summary of clinical characteristics

Clinical characteristics are summarized in Table 1. Seven Chinese PLN patients including three boys and four girls from Children's Hospital of Fudan University were available for investigate the effects of TAC in PLN. Their ages were from 9.2 to 17.5. Renal biopsies showed one III, four IV-G, and two V. During follow-up time, TAC dose were 2-3 mg/d. The baseline characteristics of the patients were: C3, 0.64 ± 0.36 g/L; C4, 0.13 ± 0.09 g/L; CH50, 29.14 ± 21.59 U/ml; ESR, 48.43 ± 28.16 mm/h; PLT, 167.00 ± 87.82 10^9/L; 24 h urine protein, 3.07 ± 1.33 g; PDN dose, 52.57 ± 7.16 mg/d.

Changes in C3, C4 and CH50 after TAC treatment

As illustrated in Figure 1, the C3, C4, and CH50 exhibited remarkably higher level at 6 month when compared to 0 month ($P < 0.05$). This indicated that TAC could significantly improve the low level of C3, C4, and CH50 after treatment with TAC for 6 months in PLN. At 12 month, the level of C3, and CH50 were still higher than 0 month ($P < 0.05$). This showed that TAC could increase C3, and CH50 level after treatment with TAC for 12 months.

Changes in ESR and PLT after TAC treatment

In Figure 2, ESR after treatment with TAC for 6 months and 12 months were all decreased compared with baseline, 0 month ($P < 0.05$). Thus, the results indicated that administration of TAC significantly decreased the level of ESR in PLN. However, no significant difference was found between baseline and treatment with TAC for 6 or 12 months in terms of the level of PLT.

Changes in 24 hour urine protein and PDN dose after TAC treatment

The 24 hour urine protein and PDN dose after treatment with TAC for 6 months and 12 months were all decreased compared with baseline ($P < 0.05$), as shown in Figure 3, indicating that TAC could ameliorate 24 hour urine protein and reduce PDN dose in PLN.

Discussion

PSLE is a relatively common and life-threatening autoimmune disease in children and it triggers systemic organ damage, especially LN which is found more frequently (in about 70% of cases) in childhood-onset disease than in adult-onset SLE [9]. LN is one of the complications significantly impacting on prognosis, its treatment is crucial for improving the care of PSLE patients. In addition, proteinuria is an important risk factor for the progression of renal disease in patients with LN. Therefore, controlling proteinuria is particularly important in treating PLN [5].

TAC is a calcineurin inhibitor and the main immunophilin of TAC is FK-506-binding protein 12 (FKBP-12) in T cells. The complex of TAC and FKBP-12 inhibits calcineurin phosphatase, an essential enzyme for the activation of nuclear factor of activated T cells (NF-AT) [10]. NF-AT is an important transcription factor for the transcription of cytokine genes in T cells. Thus, TAC inhibits the transcription of T cell cytokines like interleukin-2 (IL-2) and interferon-γ (IFN-γ) [10]. TAC affects the growth and differentiation of...
Table 1. Summary of clinical characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Renal biopsies</th>
<th>TAC Dose (mg/d)</th>
<th>C3 (g/L)</th>
<th>C4 (g/L)</th>
<th>CH50 (U/ml)</th>
<th>ESR (mm/h)</th>
<th>PLT (10^9/L)</th>
<th>24 h Urine protein (g)</th>
<th>PDN (mg/d)</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Baseline</td>
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<td>Baseline</td>
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<td>Baseline</td>
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<tr>
<td>1</td>
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<td>9.2</td>
<td>IV-G</td>
<td>3</td>
<td>0.33</td>
<td>1.32</td>
<td>0.05</td>
<td>0.24</td>
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<td>39</td>
</tr>
<tr>
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<td>V</td>
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<td>1.43</td>
<td>0.02</td>
<td>0.28</td>
<td>6</td>
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<tr>
<td>3</td>
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<td>13</td>
<td>V</td>
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<tr>
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<td>F</td>
<td>15.5</td>
<td>IV-G</td>
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<td>1.32</td>
<td>0.24</td>
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<td>1.87</td>
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<td>6</td>
<td>F</td>
<td>17.5</td>
<td>III</td>
<td>2-3</td>
<td>0.88</td>
<td>1.1</td>
<td>0.18</td>
<td>0.15</td>
<td>49</td>
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<tr>
<td>7</td>
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<td>IV-G</td>
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<td>0.19</td>
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</table>

Baseline: before TAC treatment; last visit: treatment with TAC for 12 months; M: male; F: female.
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T-and B-lymphocytes, thereby, inhibiting immunity [11-13]. Until now, TAC has been used for renal transplant patients [14-19], liver transplant patients [20-25], lung transplant patients [26], idiopathic membranous nephropathy patients [27], nephritic syndrome patients [28], and systemic-onset juvenile idiopathic arthritis patients [29]. In addition, TAC has been widely used in the treatment of SLE [7, 8, 30]. However, TAC research in PLN is very limited. The present study aims to investigate the effect of TAC in Chinese PLN patients.

In this study, seven Chinese PLN patients treating with TAC for 12 months were analyzed. Clinical characteristics were collected from the beginning of TAC treatment to the 12 month endpoint. TAC could increase C3, and CH50 level and decrease ESR level after treatment with TAC for 12 months. Significantly, TAC could ameliorate 24 h urine protein and reduce PDN dose in PLN. PLN patients undergo prolonged and repeated steroid therapy, increasing the risk of obesity, cushingoid appearance, osteoporosis, hypertension, infections, growth retardation and psychological problems. Moreover, 

Figure 1. Changes in C3, C4, and CH50 after TAC treatment. A. Changes of C3 of every patient. B. Mean ± SE of C3. C. Changes of C4 of every patient. D. Mean ± SE of C4. E. Changes of CH50 of every patient. F. Mean ± SE of CH50. 0 month: before TAC treatment; 6 month: treatment with TAC for 6 months; 12 month: treatment with TAC for 12 months. *P < 0.05 vs. 0 month.
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Figure 2. Changes in ESR and PLT after TAC treatment. A. Changes of ESR of every patient. B. Mean ± SE of ESR. C. Changes of PLT of every patient. D. Mean ± SE of PLT. 0 month: before TAC treatment; 6 month: treatment with TAC for 6 months; 12 month: treatment with TAC for 12 months. *P < 0.05 vs. 0 month.

Figure 3. Changes in 24 hour urine protein and PDN dose after TAC treatment. A. Changes of 24 hour urine protein of every patient. B. Mean ± SE of 24 hour urine protein. C. Changes of PDN dose of every patient. D. Mean ± SE of PDN dose. 0 month: before TAC treatment; 6 month: treatment with TAC for 6 months; 12 month: treatment with TAC for 12 months. *P < 0.05 vs. 0 month, #P < 0.05 vs. 6 month.
proteinuria is an important risk factor for the progression of renal disease in PLN patients. Hence, TAC is a better choice of treatment in Chinese PLN by ameliorating 24 h urine protein and reducing PDN dose.

However, there are several limitations. First, it is a retrospective study. Second, it was only possible to include seven Chinese PLN patients. Therefore, further multicenter and prospective study with more Chinese PLN patients will be urgently needed.

In conclusion, TAC is a better choice of treatment in Chinese PLN by ameliorating 24 h urine protein and reducing PDN dose.

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Disclosure of conflict of interest

None.

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