Sir,
Tacrolimus (Tac) is a T-cell-specific calcineurin inhibitor which prevents activation of helper T cells, thereby inhibiting transcription of the early activation genes of interleukin (IL)-2 and suppressing the production of tumor necrosis factor-α, IL-1β and IL-6 [1]. Thus, Tac is expected to have clinical benefits in patients with rheumatic diseases including systemic lupus erythematosus (SLE). Indeed, to date, several articles have described the efficacy of Tac in patients with difficult SLE [2, 3]. Recently, Tac combined with prednisolone (PDN) has been successfully administered without serious adverse effects, as induction and maintenance treatment for patients with proliferative and membranous lupus nephritis [2–6]. However, to our knowledge, the efficacy of Tac monotherapy in the treatment of patients with lupus nephritis has not been reported. We encountered a Japanese female patient with long-standing SLE, in whom relatively low-dose Tac monotherapy for disease flare was effective and safe.

A 38-year-old Japanese female with a 24-year history of long-standing SLE with lupus nephritis suddenly developed significant proteinuria (~1 g/day), arthralgia, hypocomplementemia and elevation of serum anti-dsDNA antibody titers. When she was 14 years old, active SLE with nephrotic-range proteinuria occurred. Percutaneous renal biopsy revealed Class IVb diffuse proliferative lupus nephritis. She was administered three courses of methylprednisolone pulse therapy followed by oral PDN combined with a 12-week course of cyclophosphamide (CPA) [7]. Thereafter, CPA was replaced by azathioprine, and the concomitantly administered PDN was tapered. The SLE activity, both clinical and serological, was under reasonably good control during maintenance therapy. The second renal biopsy, performed 12 months after the initial biopsy, revealed marked improvement to Class II lupus nephritis. After a 2-year treatment, PDN was successfully discontinued, and she remained free of SLE/lupus nephritis signs for the past 20 years or more.

Although her blood pressure and renal function were normal at the time of the flare, significant proteinuria associated with hypocomplementemia and elevation of serum anti-dsDNA antibody titer developed 3 months prior to the time of presentation. However, the patient strongly refused to take PDN, mainly because of the cosmetic adverse effect. In this context, we decided to treat her with Tac monotherapy. After obtaining written informed consent, Tac was administered at a dose of 3 mg/day (0.06 mg/kg) once daily after the evening meal [4–6]. If the Tac-resistant flare persisted, PDN was scheduled to start for treating the flares.
Response to the treatment is shown in Table 1. The outcome measures, such as the severity of proteinuria as estimated using the urinary protein/creatinine ratio (U-prot./cre.), the serum C3 level, the serum complement hemolytic activity (CH50), the serum creatinine level and the SLE activity as assessed using the European Consensus Lupus Activity Measurement (ECLAM) index [8] were prospectively examined at baseline and after 1, 3, 6 and 12 months of treatment. At 1 month after the start of the protocol, a significant decrease in the ECLAM index was noted. After 3 months of treatment, the improvement in the ECLAM index was associated with a significant decrease in the U-prot./cre. ratio and marked recovery of hypocomplementemia. After 6 months of treatment, a tendency toward a marked decrease in the serum anti-dsDNA antibody titer was observed, with the serum creatinine level remaining unchanged. The blood levels of Tac in the patient were maintained at relatively low levels of <5.0 ng/mL. No adverse reaction to the Tac treatment was observed, except for mild periocular herpes which occurred at 6 months of treatment and was easily treated with vidarabine ointment. At present, after 14 months of treatment, she is free from SLE lupus nephritis signs except for the slight increase in serum anti-dsDNA antibody titer as a result of the treatment with 3 mg/day of Tac monotherapy.

The efficacy and safety of Tac monotherapy for patients with focal segmental glomerulosclerosis so far has been reported [9]. We confirmed the efficacy of Tac, even when used as the sole therapy, for decrease in proteinuria as well as favorable changes in the immunological parameters in this patient’s flare. Concerning its rapid anti-proteinuric effects, Tac has been reported to reduce proteinuria and mesangial alterations due to its suppressive effects on glomerular expression of interferon-γ messenger RNA in rat models [10]. This laboratory observation would warrant its use in the treatment of patients with lupus nephritis [2–6], although this remains speculative. On the other hand, the safety of Tac treatment is important since some patients which exhibited Tac-related nephrotoxicity did not always necessarily have high blood levels of the drug [3]. Although we did not perform a renal biopsy in this patient at the time of the flare, her renal function remained normal during the treatment. Based on recent clinical experiences, we speculated that once-daily administration of Tac might be beneficial for preventing progression of nephrotoxicity since once-daily administration of low doses of Tac could shorten exposure to the drug, although this remains to be examined in future studies [4–6]. We believe that this letter, even though dealing with only one case, might lend further support to the efficacy of Tac monotherapy for selected patients with lupus nephritis. Further studies are, however, needed on a large number of patients, including histological evaluation following Tac treatment, to confirm our preliminary observation.

Tac, even when used as the sole therapy, may be potentially effective for the treatment of selected patients with lupus nephritis.

Conflict of interest statement. None declared.

References

3. Tse KC, Lam MF, Tang SCW et al. A pilot study on tacrolimus treatment in membranous or quiescent lupus nephritis with proteinuria resistant to angiotensin inhibitor or blockade. Lupus 2007; 16: 46–51

Table 1. Sequential changes in the outcome measures of the patient with SLE who received Tac monotherapy at the flare

<table>
<thead>
<tr>
<th>Variable</th>
<th>At –3 months</th>
<th>At baseline</th>
<th>At 1 month</th>
<th>At 3 months</th>
<th>At 6 months</th>
<th>At 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-prot./cre.</td>
<td>0.51</td>
<td>1.05</td>
<td>1.07</td>
<td>0.35</td>
<td>0.25</td>
<td>0.23</td>
</tr>
<tr>
<td>Serum C3 level (mg/dL)</td>
<td>40</td>
<td>41</td>
<td>56</td>
<td>60</td>
<td>79</td>
<td>83</td>
</tr>
<tr>
<td>Serum CH50 value (IU/mL)</td>
<td>13.5</td>
<td>20.2</td>
<td>28.7</td>
<td>31.1</td>
<td>41.3</td>
<td>39.9</td>
</tr>
<tr>
<td>Serum anti-dsDNA (IU/mL)</td>
<td>145.4</td>
<td>109.9</td>
<td>124.9</td>
<td>123.1</td>
<td>61.1</td>
<td>43.9</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.46</td>
<td>0.49</td>
<td>0.45</td>
<td>0.51</td>
<td>0.58</td>
<td>0.41</td>
</tr>
<tr>
<td>Trough blood level of Tac (ng/mL)</td>
<td>Not done</td>
<td>Not done</td>
<td>2.7</td>
<td>3.4</td>
<td>4.6</td>
<td>3.1</td>
</tr>
<tr>
<td>ECLAM index</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*anti-dsDNA, anti-dsDNA antibody titer; Trough blood level of Tac, 12 hours post-dosing of Tac.

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