Long-term data on tacrolimus treatment in lupus nephritis

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Abstract

Objective. Calcineurin inhibitors are effective immunosuppressants. They also reduce proteinuria in glomerular diseases but are potentially nephrotoxic. Short-term data suggest that tacrolimus (TAC) combined with corticosteroids is effective in LN, but long-term data are lacking. This study examined the long-term outcomes and tolerability of TAC for the treatment of LN.

Methods. We retrospectively reviewed 29 LN patients who received TAC treatment for 46.9 months (± 37.9).

Results. In 17 patients with class III/IV or V LN and persistent proteinuria ≥ 2 g/day despite induction immunosuppression, response rates after 12 and 24 months of add-on TAC treatment were 66.7% and 80.0%, respectively. In 10 patients with nephrotic syndrome due to class V LN who were given prednisolone and TAC as initial treatment, the response rate was 60.0% and 90.0% after 12 and 24 months, respectively. TAC facilitated steroid minimization in two patients with lupus podocytopathy. As a group, proteinuria decreased from 3.6 g/day (± 2.6) to 1.0 (± 1.1) (P < 0.05). Four patients developed end-stage renal failure, with 3-, 5- and 8-year renal survival rates of 93%, 83% and 83%, respectively. In the remaining patients, serum creatinine and estimated GFR remained stable after 36 months. One patient with pre-existing chronic renal failure developed TAC nephrotoxicity. Four renal flares occurred, all associated with low TAC blood levels. Six patients (20.1%) had deterioration of hypertension and one patient (3.4%) had new-onset diabetes mellitus. Six patients (20.1%) had infections that required hospitalization. Two deaths occurred: one due to pneumonia and one to breast cancer.

Conclusion. The results suggest efficacy of TAC in LN, especially in reducing proteinuria, and its role as a long-term maintenance agent warrants further investigation.

Key words: long-term, lupus, nephritis, tacrolimus.

Introduction

LN is a severe manifestation in patients with SLE and is an important cause of renal failure in some racial groups. The current standard-of-care induction immunosuppressive treatment for severe proliferative LN includes corticosteroids combined with either CYC or MMF/mycophenolic acid sodium, while low-dose corticosteroids plus either MMF or AZA for variable duration is commonly used as maintenance therapy [1–3]. Previous studies have shown that corticosteroids combined with CYC or MMF have a response rate of 55–90% at 6 months [4–6]. A significant proportion of patients show persistent proteinuria despite standard induction and maintenance immunosuppressive treatment. Protracted significant proteinuria is associated with vascular complications and unfavourable renal prognosis [7, 8]. Therefore alternative treatments are being sought to reduce the prevalence of persistent proteinuria in patients with LN.

Calcineurin inhibitors are effective immunosuppressive medications with a proven track record in the prevention of organ transplant rejection. The effect of these drugs on the podocyte translates into clinically significant proteinuria reduction in various chronic glomerular diseases such as membranous nephropathy and focal segmental
glomerulosclerosis [3, 9–13]. Long-term treatment is often required since early discontinuation of therapy is associated with a high incidence of proteinuria relapse. Compared with ciclosporin, the first calcineurin inhibitor that was widely used, tacrolimus (TAC) has fewer cosmetic adverse effects and less gingival hyperplasia, which are obvious advantages in lupus patients, who are mostly young females. However, calcineurin inhibitors can induce or exacerbate hypertension and TAC is diabetogenic, especially when given together with moderate- to high-dose corticosteroids. Furthermore, these drugs are potentially nephrototoxic and chronic nephrotoxicity is often subclinical in its early stage. There are emerging data on the use of dual immunosuppression with corticosteroids and TAC for class III/IV or V LN, and on triple immunosuppression that includes corticosteroids, TAC and MMF for class III/IV and V disease [14–18]. While short-term data suggest efficacy and tolerability of TAC in proliferative and/or membranous LN, long-term data are lacking. With this background we examined clinical outcomes and tolerability data in LN patients who have been given TAC as long-term treatment.

Methods

Patients

The case records of all patients with biopsy-proven LN who were followed at the SLE Clinic of Queen Mary Hospital, Hong Kong, during the period 2003–13 were reviewed. The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster Hospitals and informed consent was obtained from all participants. Patients who had received TAC treatment for ≥6 months were included. Data were retrieved from patients’ case records and from the Hospital Authority Computer Management System archive. The histological findings of LN were classified according to the International Society of Nephrology/Renal Pathology Society 2003 classification [19, 20].

Immunosuppressive treatments for LN

First-line induction treatment for class III/IV and V LN is prednisolone and MMF. Patients with class V LN and nephrotic syndrome (proteinuria >3 g/day) were randomized to receive treatment with either the above immunosuppressive regimen or corticosteroids and TAC in a prior clinical study [21]. Prednisolone dose and tapering schedule were identical for all patients, commencing at 0.8 mg/kg/day then reduced by 5 mg/day every 2 weeks to reach 5–7.5 mg/day at ~6 months, then maintained for at least 6 months before further tapering according to clinical status. The target MMF dose was 2 g/day in the first 6 months, 1.5 g/day in the following 6 months and 1.25–1.5 g/day in the second year. In patients with class III/IV or V LN, TAC was added when, after 6 months of induction immunosuppressive treatment, patients showed persistent proteinuria >2 g/day over 3 months without a decreasing trend. TAC was also used in patients with relapsing steroid-dependent lupus podocytopathy. TAC was initiated at ~0.07 mg/kg/day, given as two divided doses separated by 12 h. The target serum 12-h trough TAC level was 4–6 μg/l.

Concomitant treatment

All patients with class III/IV or V LN had the maximum tolerated dose of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker before the addition of TAC and the dosages of these agents were kept unchanged during follow-up except titration for blood pressure control. Other anti-hypertensive medications were prescribed as indicated, aiming for a systolic reading of <130 mmHg and a diastolic reading of <85 mmHg. Patients with a low-density lipoprotein (LDL) cholesterol level of >3.4 mmol/l and/or triglyceride >2.0 mmol/l were treated with a statin or fibrate, respectively.

Follow-up schedule

Patients were seen at intervals of 2–14 weeks depending on their clinical status. Clinically significant events, blood pressure, urinalysis, complete blood count, renal and liver biochemistry, anti-dsDNA and C3 levels were monitored at every visit. The estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease Study (MDRD) equation validated in Chinese patients [22]. Twenty-four-hour urine protein excretion, fasting glucose and lipid profile were measured at least once every 6 months.

Study outcomes

Complete renal response was defined as a reduction of proteinuria to <0.5 g/day, with improved or stable renal function indicated by a serum creatinine level <115% of the baseline level. Partial renal response was defined as a decrease in urine protein excretion of at least 50% and non-nephrotic (<3 g/day) proteinuria with improved or stable renal function. Other study outcomes included disease flares, adverse events (including drug-induced nephrotoxicity), serological parameters, glycaemic and lipid profiles and blood pressure control. Renal relapse was defined by deterioration of proteinuria and/or serum creatinine and was confirmed with kidney biopsy.

Statistical analysis

Continuous variables were expressed as mean (s.d.) unless otherwise specified and were compared using the paired t-test or Wilcoxon signed-rank test where appropriate. Categorical variables were expressed as frequency or percentage and were compared with Pearson’s χ² test or Fisher’s exact test where appropriate. The slope of the change of eGFR over time was examined by linear regression. Patient and renal survival were assessed by actuarial analysis and compared by log-rank test. All statistical analyses were performed with PASW for Windows 18.0 (SPSS, Chicago, IL, USA) and a two-sided P-value < 0.05 was considered statistically significant.
Results

Patient characteristics
Twenty-nine patients fulfilled the selection criteria and were included for analysis (Table 1). Follow-up duration after starting TAC treatment was 46.9 months (S.D. 37.9) (1363 patient-months). TAC was used as add-on therapy in 17 patients with class III/IV or V LN who showed persistent proteinuria despite conventional immunosuppressive treatment as described in the Methods section (group I). Ten patients with nephrotic syndrome due to class V LN received corticosteroids and TAC as their initial treatment (group II). Two patients had lupus podocytopathy. TAC treatment duration was >12 months in 21 patients (72.4%), >24 months in 19 patients (65.5%) and >36 months in 18 patients (62.1%). The TAC dose at 6 and 12 months was 3.39 mg/day (S.D. 1.91) and 3.41 (S.D. 1.72), respectively, achieving a 12-h blood trough level of 4.72 mg/l (S.D. 2.90) and 4.17 (S.D. 1.91), respectively. Both the dose and blood level of TAC remained stable over time.

Renal parameters
In group I (class III/IV or V with persistent proteinuria) the complete response rate was 40.0% and the complete or partial response rate was 66.7% after 12 months of TAC treatment. Corresponding response rates were 46.7% and 80.0%, respectively, after 24 months. Mean time to achieve renal response was 13.8 months (S.D. 9.7). In group II (class V with nephrotic syndrome) the complete response rate was 30.0% and the complete or partial response rate was 50.0% after 12 months of TAC treatment. Corresponding response rates were 50.0% and 90.0%, respectively, after 24 months. Mean time to achieve renal response was 18.0 months (S.D. 4.9). In the two patients with lupus podocytopathy and relapsing steroid-responsive nephrotic syndrome, the dose of maintenance prednisolone was reduced from 15 mg/day to 7.5 mg/day after the addition of TAC.

Considering all 29 patients together as a group, proteinuria decreased from 3.6 g/day (S.D. 2.6) to 1.0 (S.D. 1.1) after 36 months of TAC treatment (P < 0.05) (Fig. 1A). Eleven patients (37.9%) had proteinuria reduced by >50% after 6 months of TAC treatment. Serum creatinine and eGFR remained stable during follow-up and the values at 36 months showed no significant difference compared with baseline values (P = 0.072 and 0.083) (Fig. 1A). The numerical improvement in the slope of eGFR change over time after TAC treatment did not reach statistical significance (−8.5 ml/min/1.73 m²/month before vs 8.8 (S.D. 7.1) after TAC treatment, P = 0.099) (Fig. 2). Four patients developed end-stage renal failure (ESRF) after 27.4 months (S.D. 25.1). Compared with the other 25 patients, these patients [class IV LN (n = 3), class V LN (n = 1)] had significantly lower baseline renal function [eGFR 21.2 ml/min/1.73 m² (S.D. 8.2) vs 72.0 (S.D. 20.4), P = 0.001; serum creatinine

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<tr>
<th>Table 1 Characteristics of 29 patients who received long-term tacrolimus treatment for LN</th>
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<td>Age, mean (s.d.), years</td>
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<td>Sex, female/male, n/n</td>
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<td>Duration of SLE before TAC treatment, mean (s.d.), months</td>
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<td>Clinical parameters prior to initiation of TAC, mean (s.d.)</td>
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LDL: low-density lipoprotein; pred: prednisolone; TAC: tacrolimus.

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Baseline (before TAC treatment) proteinuria, anti-dsDNA and C3 did not differ between patients who progressed to and those who did not develop ESRF (all \( P \)-values > 0.05). The 3-, 5- and 8-year renal survival rates were 93%, 83% and 83%, respectively (Fig. 3).

Other clinical parameters
Anti-dsDNA remained stable while C3 level increased during follow-up [84.6 mg/dl (s.d. 26.2) at 36 months vs 70.4 (s.d. 20.1) at baseline, \( P = 0.02 \) (Fig. 1B). There was no significant change in fasting blood glucose, LDL cholesterol, triglycerides or systolic and diastolic blood pressure during follow-up (Fig. 1C and D).

Four episodes of renal flare occurred [class IV LN (n = 3), lupus podocytopathy (n = 1)], giving a renal flare rate of 1 in 312 patient-months. All episodes were associated with trough TAC levels <3 mg/l. There were three episodes of extrarenal flare, with two episodes occurring after attempted discontinuation of TAC treatment. All three episodes responded to increase in corticosteroids.

**Adverse events and tolerability of TAC treatment**
After starting TAC therapy, six patients had increased blood pressure and three showed an increase in LDL cholesterol that responded to increase in respective treatments (Table 2). One patient had new-onset diabetes. One patient with impaired renal function showed features compatible with chronic TAC nephrotoxicity on renal biopsy. Infections that required hospitalization occurred in six patients during the 1363 patient-months of TAC exposure and two patients died (one from pneumonia and the other from breast cancer).

**Discussion**
There have been reports of the efficacy of combined calcineurin inhibitor and corticosteroid treatment for LN [14–16, 18, 21, 26]. The results are not unexpected in view of the proven immunosuppressive efficacy of this family of drugs. Their direct action on the podocyte, stabilizing its actin cytoskeleton, accounts for the proteinuria-lowering effect and adds to the role of calcineurin inhibitors in the management of chronic glomerular diseases [25]. Long-term treatment is often required since there is a high incidence of relapse after treatment discontinuation. However, with prolonged treatment duration there is concern about potential nephrotoxicity. While the short-term efficacy of prednisolone and TAC have been reported in both proliferative and membranous LN [14–18, 21, 26], there is little long-term data on the efficacy and tolerability of TAC treatment in LN patients.
In view of its dual immunosuppressive and proteinuria-reducing actions, we have chosen to add TAC in the treatment of patients with membranous LN and excess proteinuria or those with proliferative LN who show persistent proteinuria despite conventional therapy. Our results demonstrate the efficacy of TAC in reducing proteinuria and, in patients with proliferative LN, the potential benefit of TAC as add-on therapy in improving treatment outcome. Importantly, the efficacy was sustained with continuous treatment. The high response rates were also notable, being >80% in both proliferative and membranous LN after 12 months of TAC treatment. While ~40% of patients had proteinuria reduced by half compared with baseline after 6 months of TAC treatment, the mean treatment duration to achieve complete or partial response was >1 year, implying that the rate of improvement is variable and could be slow in some patients.

We set our target 12-h trough blood TAC level at 4–6 ng/l, with the objective of minimizing the risk of nephrotoxicity, since many patients with LN have impaired renal function, which increases their susceptibility to the nephrotoxic effects of drugs. With actual achieved trough TAC levels of 4–5 ng/l, the majority of patients had stable serum creatinine and eGFR during prolonged follow-up. However, the single patient who showed features compatible with chronic TAC nephrotoxicity underlines the importance of vigilance in the prevention and early detection of this complication. Since patients with established chronic renal impairment could be on a course of progressive renal function deterioration prior to the addition of TAC, in order to ascertain whether TAC might exert any negative impact on renal prognosis we compared the slope of change in eGFR over time before and after TAC therapy. While the numerical improvement in renal functional status after TAC treatment did not reach statistical significance, the results did not suggest deterioration of renal function after the addition of TAC and were thus reassuring.

With therapeutic drug level monitoring we observed a relatively low relapse rate while patients were on TAC treatment, and all renal flares were associated with inadequate drug levels. The disease stability conferred by TAC is corroborated by the improvements in serological parameters, especially the increase in C3 level. The preliminary experience in two patients with relapsing steroid-dependent lupus podocytopathy suggests that TAC can serve as a steroid-sparing agent in this setting.

Our present data show that the long-term use of TAC is quite well tolerated in most patients. Yet despite the relatively low target TAC blood level, well-established drug-related adverse events still occurred, such as hypertension, dyslipidaemia and diabetes mellitus. While these side effects responded promptly to treatment, it would be advisable to defer the addition of TAC in patients with suboptimal control of blood pressure or diabetes mellitus. Due to the small sample size and the retrospective nature of this study, it is not possible to compare the risk of infection between TAC and other immunosuppressive regimens in LN patients. Nonetheless, the incidence of infectious complications did not appear excessive.

In summary, our results suggest that TAC is effective in the treatment of LN, especially in patients with severe or persistent proteinuria. Therapeutic drug level monitoring is important to minimize drug-related adverse effects. Further studies are required to define the characteristics of patients who would benefit most from the incorporation of TAC in long-term maintenance treatment.

### Rheumatology key messages

- Add-on tacrolimus reduces proteinuria in proliferative LN patients not responsive to standard treatments.
- Corticosteroids and tacrolimus is effective initial treatment for membranous LN with nephrotic syndrome.

### Acknowledgements

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### Disclosure statement

The authors have declared no conflicts of interest.

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