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Influence of renal complications on the efficacy and adverse events of tacrolimus combination therapy in patients with systemic lupus erythematosus (SLE) during a maintenance phase: a single-centre, prospective study

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ABSTRACT

Objectives: The study investigated whether renal complications affected the efficacy and safety of tacrolimus combination therapy in patients with systemic lupus erythematosus (SLE) during a maintenance phase.

Methods: Fifty-seven patients with SLE (A: 30 cases with renal complication, B: 27 cases without renal complications) were included. The presence of renal complications was defined as proteinuria ≥0.5 g/day and lupus nephritis on renal biopsy. Major outcome measures included SLE disease activity index (SLEDAI), steroid dose, serum anti-dsDNA Ab, C3 and creatinine (Cr) levels and estimated glomerular filtration rate (eGFR). The patient's background factors included age, gender, disease duration and ACE-I/angiotensin II receptor blocker and statin therapies. We compared these outcome measures pre treatment and after 1 year of treatment.

Results: The SLEDAI and serum C3 levels improved in both groups from pretreatment period to post-treatment period: from 7.2±5.0 to 2.8±2.3 in A and 6.4±3.8 to 2.4±2.2 in B, p<0.001, and from 65.9±24.6 to 77.7 ±18.2 mg/dL in A and 81.8±23.0 to 90.6±19.4 mg/dL in B, p=0.002, respectively. The anti-dsDNA antibody level was reduced, and the serum Cr and eGFR levels were slightly elevated. No patients developed end-stage renal failure that required artificial dialysis.

Conclusions: Tacrolimus combination therapy had additive beneficial effects on reduced proteinuria and increased serum C3 levels in patients with SLE with renal complications during a maintenance phase.

KEY MESSAGES

- Tacrolimus combination therapy had additive beneficial effects and increased serum C3 levels in SLE patients with or without renal complications during a maintenance phase.
- Tacrolimus reduced the steroid dosage, improved the SLEDAI and reduced anti-dsDNA antibody levels in patients with or without renal complications.
- Notably, serum Cr and eGFR levels were mildly elevated.

BACKGROUND

Systemic lupus erythematosus (SLE) is an autoimmune disease that results in the production of several autoantibodies.[1 2] SLE treatment largely consists of remission induction therapy and maintenance therapy. Immunosuppressive drugs and high-dose steroid therapy are generally used for remission induction therapy, although the therapy regimen depends on the type of renal lesions. Standard therapies include the immunosuppressive drugs intravenous cyclophosphamide (IVCY)[3] and mycophenolate mofetil (MMF).[4] One recent study reported the use of tacrolimus (TAC) for multitarget therapy,[5] while azathioprine (AZA), MMF and rituximab (RTX) are often used for maintenance therapy.[6] However, the primary disease sometimes relapses even with the use of AZA or MMF. Additionally, side effects such as bone marrow suppression and infectious diseases can occur. Moreover, in some cases steroid use must be discontinued or reduced due to conditions such as a slight fever, rash, a feeling of malaise and abnormal test values.

TAC is widely used as an immunosuppressive drug after organ transplantation, including kidney[7] and liver.[8] TAC is also attracting attention due to its immunosuppressive

effect, and therefore is used for the treatment of various autoimmune diseases, such as rheumatoid arthritis,[9] polymyositis[10] and myasthenia gravis.[11] Moreover, TAC is used in Japan for the treatment of lupus nephritis[12] and SLE without renal lesions.[13] The efficacy of TAC against lupus nephritis has been reported in a number of articles to date. However, only a few reports have investigated cases of non-lupus nephritis. The efficacy of TAC has been validated in both diseases, but differences in efficacy and safety due to the presence or absence of renal lesions have not been reported. Some studies have reported the use of TAC during the maintenance therapy period. For example, one small-scale study reported an approximately 6-month observation period,[14] and a clinical practice report of 38 cases used TAC for 1 year.[15] However, there have not been reports of a large-scale clinical practice study, such as the inclusion of more than 50 cases followed up for 1 year. However, one report suggested that the long-term use of TAC caused renal dysfunction.[16] Therefore, this study examined whether TAC combination therapy affected efficacy and safety due to the presence or absence of renal lesions during maintenance therapy in patients with SLE.

METHODS

Patients with SLE in maintenance therapy undergoing outpatient treatment were enrolled at the Division of Rheumatology, Department of Medicine, Showa University School of Medicine. The study was conducted from 1 January 2009 to 30 April 2013 with a 52-week observation period. A single centre prospective study was used as the study design. Patients with SLE diagnosed according to the 1997 revised criteria for the classification of SLE from the American College of Rheumatology were eligible for enrolment.[17] The criterion used to enrol patients was daily steroid consumption below the limit of ≤20 mg/day of prednisolone. The initial dose of TAC was defined as 1–2 mg/day; this amount was adjusted to achieve blood trough levels of 5–10 ng/mL at 12 h after medication, with a maximum dose of 4 mg/day.[6] The dose of steroid prescribed during the observation period was not changed, but it could be tapered or discontinued based on the attending doctor's judgement. When adverse effects appeared (ie, eruption, cytopenia or liver damage), the patient was switched from the previous immunosuppressive drug to TAC. Moreover, we added TAC to the regimens of patients who had used a current immunosuppressive drug for more than 6 months but showed evidence of the lack of the drug's effectiveness because TAC would not reduce the steroid's efficacy or induce adverse effects in combination with the immunosuppressive drug. The SLE disease activity index (SLEDAI) was used to assess disease activity. A case was defined as possessing renal lesions when the urine protein levels were ≥0.5 g/day and lupus nephritis was observed by renal biopsy.[13] All other cases were defined as non-renal lesions.

The following background factors were examined: age, sex, height, weight, SLE disease duration, the dose of steroids prescribed at the beginning of TAC combination therapy, the presence or absence of angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin II receptor blocker (ARB), the presence or absence of statin use, the presence or absence of steroid-pulse therapy during the remission induction period, prednisolone dosage prior to TAC treatment (1 year, 6 months, 3 months or 1 month) and the types of immunosuppressive drugs used previously. The body mass index (BMI) was calculated based on height and weight. The following measurements were examined: serum C3 levels before and 52 weeks after TAC treatment (normal range: 86–160 mg/dL), anti-ds DNA antibody titres (measured by radioimmunoassay, normal range: <12 IU/mL), serum creatinine levels and the estimated glomerular filtration rate (eGFR). Additionally, we also investigated the presence or absence of SLE relapse during the observation period (ie, whether the patient developed end-stage renal disease (ESRD) or was treated with artificial dialysis) and TAC side effects.

Patients with renal lesions were defined as group A, while patients without renal lesion were defined as group B. The following discontinuation criteria were defined: the presence of TAC side effects, a patient proceeding to ESRD, a patient starting artificial dialysis, an increase in the amount of steroids due to primary disease relapse, an increase or initiation of an immunosuppressive drug regimen, patient relocation resulting in the inability to visit the hospital or the submission of a proposal of discontinuation by the patient.

The analysis was performed via comparisons between the group of survivors and the group of non-survivors. Statistical tests included Fisher's exact probability test, Welch's t test and χ^2 for independence tests, as well as repeated measures analysis of covariance. The significance level was set to 5%. The statistical analysis was performed with the JMP10 software (2012 SAS Institute, Japan, Tokyo, Japan). This study was conducted with the approval of the Bio-Ethical Committee of Showa University School of Medicine (No. 1195). We acquired written informed consent from all patients enrolled in the study.

RESULTS

The basic patient population included 30 patients and 27 patients who were classified into groups A and group B, respectively (table 1). The histological types of renal lesions in group A included eight patients with Type II, one patient with Type II+V, three patients with Type III, two patients with Type III+V, five patients with Type IV, four patients with Type IV+V and seven patients with Type V (table 2). The immunosuppressive drugs IVCY, ciclosporin A, AZA, mizoribine (MZR), methotrexate, RTX and MMF were used prior to the initiation of TAC treatment. There were no significant differences in the

Table 1 Patient characteristics before treatment

	Renal (+)	Renal (–)	p Value
N	30	27	
Age (years, mean±SD)	42.2±15.7	37.7±13.2	0.23*
Sex (male/female)	8/22	3/24	0.29†
Disease duration (years, mean±SD)	8.6±6.0	7.1±8.7	0.45*
BMI (mean±SD)	20.2±3.8	20.9±3.1	0.49*
Dose of TAC at start (mg/day, mean±SD)	1.6±0.9	1.7±0.7	>0.05*
Dosage of PSL at start (mg/day, mean±SD)	13.2±9.2	12.6±7.8	>0.05*
Rate of ACE/ARB use	15/30 (50.0%)	6/27 (22.2%)	0.028†
Rate of statin use	11/30 (36.7%)	6/27 (22.2%)	0.184†

*Analysis by Welch's t test.†Analysis by Fisher's exact probability test.
ARB, angiotensin II receptor blocker; BMI, body mass index; PSL, prednisolone; TAC, tacrolimus.

presence or absence of renal lesions (p=0.305) (table 3). MZR and AZA were concomitantly used as immunosuppressive drugs after the initiation of TAC treatment, but there were no significant differences in the presence or absence of renal lesions (p=0.429) (table 4).

Significant improvements in the SLEDAI were observed in each group before and after treatment: from 7.2±5.0 (mean±SD) to 2.8±2.3 in group A (p=0.000) and from 6.4±3.8 to 2.4±2.2 in group B (p=0.000) (table 5). A repeated measures analysis of variance (ANOVA) revealed no interaction, but a significant difference before and after treatment was confirmed (p=0.000) regardless of the presence of renal lesions (p=0.367). Serum C3 levels improved from 65.9±24.6 mg/dL to 77.7 ±18.2 mg/dL before and after treatment in group A (p=0.002), but showed only a slight improvement in group B (from 81.8±23.0 mg/dL to 90.6±19.4 mg/dL), with no significant difference found before and after treatment (p=0.065). A repeated measures ANOVA revealed no interaction, but a significant difference was confirmed before and after treatment (p=0.002) regardless of the presence of renal lesions (p=0.006). The dose of prednisolone decreased from 13.2±9.2 mg/day to 7.4 ±4.0 mg/day (p=0.0004) in the A group and from 12.6 ±7.8 mg/day to 7.4±4.0 mg/day in the B group (p=0.003), thereby demonstrating a significant difference before and after treatment (p=0.000). However, there were no significant differences based on the presence or absence of renal lesions (p=0.836). The anti-ds DNA antibody titre in the A group decreased from 56.7 ±99.0 IU/mL to 33.3±56.8 IU/mL, which was not significant but represented a downward trend (p=0.057). The anti-ds DNA antibody DNA titre decreased significantly in the B group from 30.9±33.2 IU/mL to 18.4 ±18.6 IU/mL (p=0.007). A repeated measures ANOVA revealed no interaction, but a significant difference before and after the treatment was confirmed (p=0.027). However, there was no significant difference based on the presence or absence of renal lesions (p=0.186). Serum Cr levels were slightly elevated, with a significant increase from 0.76±0.31 mg/dL to 0.82±0.42 mg/dL (p=0.029) in the A group and from 0.65±0.21 mg/dL to 0.68 ±0.23 mg/dL (p=0.040) in the B group regardless of the presence of renal lesions (p=0.011). The eGFR level decreased slightly from 57.9±9.68 mL/min/1.73 m^2 to 57.0±9.79 mL/min/1.73 m^2 (p=0.0029) in the A group and from 59.4±9.27 mL/min/1.73 m^2 to 58.4±9.26 mL/min/1.73 m^2 in the B group regardless of the presence of renal lesions (p=0.001). No significant differences were observed between the two groups in the following background factors: age, sex, disease duration, BMI, the dose of TAC and steroids at the beginning of TAC treatment and the presence or absence of combinational statin use. However, a significant difference was observed in the combinational use of ACE and ARB (p=0.028), which was prescribed more often in the A group (table 5).

Although the patients were prescribed a relatively high dose of glucocorticoid at the initiation of TAC treatment,

Table 2 Histological type of kidney lesions in Group A

Type	n
I	8
II+V	1
III	3
III+V	2
IV	5
IV+V	4
V	7

Table 3 Breakdown of combination treatment with immunosuppressive agents prior to tacrolimus treatment

	Renal (+)	Renal (–)
IVCY	10	5
CyA	10	10
AZA	5	10
MZR	8	6
MTX	1	5
RTX	0	1
MMF	2	2

p=0.305.χ^2 for independent test.
AZA, azathioprine; CyA, ciclosporin A; IVCY, intravenous cyclophosphamide; MMF, mycophenolate mofetil; MTX, methotrexate; MZR, mizoribine; RTX, rituximab.

Table 4 Breakdown of combination treatment with immunosuppressive agents after tacrolimus treatment

	Renal (+)	Renal (−)
MZR	8	5
AZA	0	1

p=0.429.
Fisher's exact probability test.
AZA, azathioprine; MZR, mizoribine.

they were not in the midst of tapering glucocorticoid after the induction of remission (table 6).

The patients had remarkable improvement of symptoms including headache, arthritis, rash, alopecia, mucosal ulcer and fever among the components of SLEDAI. Moreover, the examination found improvement of haematuria, pyuria, hypocomplementaemia and anti-DNA antibody among close to half of the patients. On the other hand, thrombocytopenia was not improved although leucopenia was improved (table 7).

Side effects were observed in one patient in the A group (pruritus) and four patients in the B group (rhabdomyolysis, muscle cramp, alopecia and diarrhoea observed in all patients), all of which improved following treatment discontinuation. The patient who developed rhabdomyolysis in the B group used statin concomitantly, which increased the likelihood that this side effect was caused by statin monotherapy or the concomitant use of statin and TAC. No patients developed ESRD or required artificial dialysis. Moreover, none of the patients experienced a relapse of the primary disease, required an increase in the dosage of steroids or required an increase or new initiation of the immunosuppressive drugs that were used concomitantly.

DISCUSSION

This study demonstrated that TAC combination therapy had additional beneficial effects on increased serum C3 levels in patients with SLE with or without renal complications during a maintenance phase in a clinical setting. TAC effectively decreased disease activity during the maintenance phase of SLE during our 52-week observation period without requiring an increase in the corticosteroid and/or immunosuppressants dose in our study. Moreover, non-severe side effects were observed in only five patients (5.3%) during the 52-week period. The results of our prospective study indicated that TAC is an effective agent for the treatment of SLE. Duddrige and Powell administered TAC to three patients with SLE and found that cutaneous vasculitis, leucopenia, arthritis and hypocomplementaemia improved in two patients.[2] Maruoka *et al*[18] reported that TAC effectively treated a patient with lupus cystitis. Subsequently, several reports noted the efficacy of TAC for nephritis.[19–21] Maintenance therapy of SLE was previously reported only in studies of patients with or without lupus nephritis,[12 13 22] including one small group study and one short-duration study.[14 15] No previous assessments of

Table 5 Clinical feature and laboratory data before and after tacrolimus treatment

	Renal (+)			Renal (−)			Interaction	Variation between individuals	Intraindividual variability
	Pre	Post	p Value	Pre	Post	p Value	p Value	p Value	p Value
Disease activity index (SLEDAI) at start (mean±SD, range)	7.2±5.0	2.8±2.3	0.000	6.4±3.8	2.4±2.2	0.000	0.793	0.367	0.000
Prednisolone dosage (mean±SD, mg/day)	13.2±9.2	7.4±4.0	0.0004	12.6±7.8	7.4±4.0	0.0025	0.776	0.836	0.000
Anti-ds-DNA antibody titre (mean±SD, IU/mL)	56.7±99.0	33.3±56.8	0.057	30.9±33.1	18.4±18.6	0.0065	0.506	0.186	0.027
Serum C3 concentration (mean±SD, mg/dL)	65.9±24.6	77.7±18.3	0.0022	81.8±23.6	90.6±19.4	0.065	0.647	0.006	0.002
Serum creatinine level (mg/dL)	0.76±0.31	0.82±0.42	0.029	0.65±0.21	0.68±0.23	0.040	0.591	0.147	0.011
eGFR (mL/min/1.73 m^2	57.9±9.7	57.0±9.8	0.0029	59.7±9.3	58.4±9.3	0.0013	0.772	0.571	0.000
Dosage of TAC (mg/day)	1.6±0.9	3.0±0.7	0.000	1.7±0.7	2.8±0.6	0.000	0.350	0.805	0.000
Protein urea (g.gCr)	1.9±5.6	0.78±1.3	0.14	0.07±0.21	0.0±0.0	0.05	0.352	0.25	0.026

eGFR, estimated glomerular filtration rate; SLEDAI, systemic lupus erythematosus disease activity index; TAC, tacrolimus.

Table 6 Prednisolone dosage before treatment with tacrolimus

	Renal (+)	Renal (−)
Before 1 year	12.5±9.9	9.6±8.5
Before 6 months	15.7±12.4	8.8±5.0
Before 3 months	12.8±7.5	9.8±6.2
Before 1 month	11.7±6.6	11.2±6.8
At start	13.2±9.2	12.6±7.8
	p Value	
Interaction	0.052	
Variation between individuals	0.089	
Intraindividual variability	0.42	

long-term TAC therapy were reported in a larger group of patients with SLE with and without renal complications, as performed in this study. We investigated whether renal complication affected the efficacy and safety of TAC combination therapy in patients with SLE during a maintenance phase.

Our study had several limitations. Our study enrolled consecutive patients during specific periods to avoid selection bias, which differed from many of the aforementioned case series. A significant difference was observed in the combinational use of ACE-I and ARB. The patients were assigned to groups according to the decisions of the involved physicians, and not by randomisation. Our survey focused on real-world scenarios and the ordinary practice of TAC treatment for SLE. Therefore, a fully randomised study would not have suited our purposes, and it would not have been suitable for our investigation into the dose optimisation of TAC to ensure its efficacy and safety for all patients with and without renal complications. The number of cases of patients for whom SLE activity could not be controlled through the use of a middle dose of steroids and/or an immunosuppressive drug has decreased. SLE is a heterogeneous disease, and this characteristic is a limitation of this study. Each physician carefully ascertained the dose of TAC after considering multiple factors for each patient, including disease activity, complications such as hypertension, diabetes mellitus and hyperlipidaemia age, renal function, serum concentrations of TAC and complications due to other collagen diseases.

Table 7 Components of SLEDAI before and after treatment of tacrolimus

	Pre	Post
Headache	7	1
Arthritis	3	0
Rash	6	0
Alopecia	5	0
Mucosal ulcer	2	0
Fever	5	1
Haematuria	7	3
Pyuria	14	7
Low complement	22	13
Anti-DNA antibody	23	11
Leucopenia	4	0
Thrombocytopenia	1	1

SLEDAI, systemic lupus erythematosus disease activity index.

Clinical trials that included patients with rheumatoid arthritis demonstrated that the main adverse reactions caused by TAC were renal impairment, hypertension, glucose intolerance and gastrointestinal symptoms.[23] Adverse events were observed in three patients in our study, and renal function was mildly elevated.[24] However, these symptoms were reversible and improved after the discontinuation of TAC. The reason for this difference between patients with SLE and rheumatoid arthritis is not known, but the different pathologies underlying the diseases, patient ages and concurrent treatments (eg, non-steroidal anti-inflammatory drugs) might have played a role.

CONCLUSION

TAC combination therapy had additive beneficial effects and increased serum C3 levels in patients with SLE with or without renal complications during a maintenance phase. TAC reduced the steroid dosage, improved the SLEDAI and reduced anti-dsDNA antibody levels in patients with or without renal complications. Notably, serum creatinine and eGFR levels were mildly elevated.

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Patient consent Obtained.

Ethics approval This study was conducted with the approval of the Bio-Ethical Committee of Showa University School of Medicine (No. 1195). We acquired written informed consent from all patients enrolled in the study.

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