Steroid-Sparing Effect of Tacrolimus in the
Maintenance Phase of Systemic Lupus
Erythematosus: A Single-Center, Prospective Study

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Abstract

Objective: The purpose of this study was to prospectively assess the steroid-sparing effect and safety of Tacrolimus (TAC) combination treatment during the maintenance phase of SLE.

Methods: Thirty-eight patients were studied over a 1-year period from 2009 to 2012. If manifestations of mild active SLE, such as skin eruptions, arthritis, or asymptomatic nephritis, worsened and/or decreasing levels of serum complement (C3c) were observed, TAC combination treatment (from 1 mg to 5 mg once daily) was carried out. This was accomplished by adding TAC to the patient’s existing treatment regimen and decreasing in the usage of prednisolone (PSL). Scores on the SLE Disease Activity Index (SLEDAI), PSL dosage, and proteinuria, serum levels of C3c, anti-dsDNA levels were researched.

Results: Twenty-eight patients received to TAC combination therapy. 1) The PSL dose was decreased from 11.7 ± 5.6 to 8.2 ± 4.2 mg/day (P<0.001). 2) The serum concentration of C3c increased and levels of anti-dsDNA antibodies decreased 3) Scores on the SLEDAI modified from 6.2 ± 3.7 to 2.6 ± 2.3 (P<0.001). There were no significant differences in proteinuria. In contrast, eight patients did not respond and/or had worsening SLE, and two patients discontinued treatment because of an adverse effect such as rhabdomyolysis or muscle cramps. No patients had complications of an abnormal urinalysis, and none progressed to renal failure with or without requiring dialysis.

Conclusions: TAC combination treatment may have a useful steroid-sparing effect, as it does not worsen disease activity and is safe for SLE patients during the maintenance phase.

Keywords: systemic lupus erythematosus, tacrolimus, maintenance phase, steroid-sparing effect
Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by a deviant production of autoantibodies and immune complexes.[1][2][3] Although corticosteroids (CSs) and immunosuppressant medications are widely used for treatment, which increases the rates of induction and maintenance therapy, more than a few refractory cases and adverse events have been reported with their use. Therefore, a new treatment modality has been actively sought in the clinical setting.[4] Tacrolimus (TAC) is a comparatively new type of drug that an immunosuppressive effect was prompted, specifically by inhibiting the calcineurin pathway in T cells and reducing following inflammatory cytokine production.[5][6][7] TAC has been accepted for use worldwide in organ transplantation and for the treatment of autoimmune diseases, [8][9][10][11] including myasthenia gravis. [12]

More recently, in 2006, Japan was the first country to approve TAC for the treatment of lupus nephritis in patients with intolerance to the previous standard treatment. However, reports regarding the use of TAC in SLE patients with/without renal involvement have been limited. Moreover, long-term, large observational studies during the maintenance phase of SLE are rare. Accordingly, this study was conducted to clarify the steroid-sparing effect and safety of TAC in such patients.

Subjects and Methods

This study was a single-center, open-label, prospective, 52-week observational study, which took place from April 2009 to March 2012 in a typical clinical practice. Thirty-eight SLE patients who fulfilled the American College of Rheumatology’s 1997 revised criteria for the classification of SLE were enrolled. [13] We defined the case that passed from initial treatment more than one year as Maintenance phase. If clinical symptoms (for example, headache, arthritis, rash alopecia, mucosal ulcers and fever) worsened and/or decreasing levels of serum complement were detected, TAC was added to the patient’s extant treatment regimen, and the dose of prednisolone (PSL) was decreased. The patients were administered TAC at a dose of 1–3 mg (with the exclusion of 5 mg in one case) once per day in the evening for 52 weeks. TAC dosage was not adjusted to body weight. TAC trough blood levels adjusted a dose to become the range of
5-10ng/ml. The inclusion requirements for this study were as follows: 1) Maintain the dosage of steroid at the same level for 3 months after study entry with no additional usage of immunosuppressive drugs; and clinical symptoms (for example, headache, arthritis, rash alopecia, mucosal ulcers and fever) worsened and/or decreasing levels of serum complement were detected. 2) Discontinue the administration of cyclophosphamide and rituximab at least 1 month before study entry; 3) Discontinue the administration of cyclosporine A, methotrexate, mycophenolate mofetil, and azathioprine at the time of study entry; 4) Continue the administration of mizoribine for 6 out of 8 subjects because the combined use of TAC and mizoribine is well tolerated for lupus nephritis induction therapy and appears to be highly efficacious; 5) Maintain the amount of immunosuppressive drugs (mizoribine) used throughout the study. [14] According to the pointing out, it becomes the bias. The utility of the therapy with mizoribine and TAC has been already reported. It is naturally desirable we discontinue mizoribine, and to switch to TAC. Because efficacy of the mizoribine combination therapy was reported, only mizoribine enabled TAC and combination. Apparently, SLE patients with major organ disease were excluded and only those with constitutional, skin, joints disease were included in the study.

Disease activity and clinical responses were investigated using the SLE Disease Activity Index (SLEDAI) at 0 and 52 weeks. [15] The final efficacy evaluation of TAC was determined based on whether a patient satisfied all of the following criteria: 1) a decrease in the SLEDAI score at 52 weeks compared to week zero (baseline); 2) continuation of TAC at 52 weeks; and 3) no increase in CS dose and no addition of immunosuppressive drugs. Safety was researched by examining clinical signs and symptoms in combination with laboratory findings, including the following: complete blood count, general biochemistry (including estimated glomerular filtration rate; eGFR), serum glucose, serum C3 concentration (normal range: 86-160 mg/dl), serum anti-double-stranded (ds) DNA antibody level (measured by radioimmunoassay) (normal range: <12 IU/ml), urinalysis, chest X-ray, and additional appropriate tests in cases of suspected adverse events. Each physician involved in this study independently decided on the continuation or discontinuation and the TAC dosage adjustments to reach a therapeutic blood level of 5 to 10 ng/ml.

For statistical analysis, we made use of a paired t-test and Wilcoxon’s test for comparisons between pre- and post-tacrolimus administration periods. A p value of <0.05 was regarded as a statistically significant. The mean score on the SLEDAI at baseline was 6.2 ± 3.7. The disease activity of the enrolled patients was mild to moderate. All of the patients used CS in combination with TAC from
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baseline, and the mean dose of prednisolone was 11.7 ± 5.6 mg/day. The mean
dose of TAC at the beginning of treatment was 2.80 ± 0.65 mg/day. This study
proceeded under the approval of Showa University Bio-Ethical Committee (No.
1195).

Results
Patient profiles

Thirty-eight SLE patients were registered in this study. The patient
demographics and baseline characteristics are summarized in Table 1. The mean
age was 44.0 ± 15.6 years old, and 28 patients (73.6%) were female. Regarding
subtypes of the disease, 50% of the patients had renal involvement. Most patients
had used CS (11.7 ± 5.6 mg/day) and immunosuppressants, such as mizoribine
(MZB), cyclosporine A (CyA), cyclophosphamide (CPA), azathioprine (AZA),
methotrexate (MTX), mycophenolate mofetil (MMF), and rituximab (RTX), had
also been used in 30 cases. The mean score on the SLEDAI at baseline was 6.2 ±
3.7. The disease activity of the enrolled patients was mild to moderate. All of the
patients used CS in combination with TAC from baseline, and the mean dose of
prednisolone was 11.7 ± 5.6 mg/day. The mean dose of TAC at the beginning of
treatment was 2.80 ± 0.65 mg/day. Clinical manifestations before TAC treatments
included headache in 7 patients, skin eruptions in 6, fever in 5, alopecia in 5,
arthritis in 3, and mucosal ulcer in 2. Seven people who presented with the
symptom of the headache were all lupus headache, and there were not the patients
who presented with other neuropsychiatric sign. Sixteen patients with
serological-only activity who were stated on TAC. (Table 1)

Steroid-sparing effect and effect on disease activity

In the 37 patients who continued treatment for 52 weeks, the mean CS dose was
successfully reduced from 11.7 ± 5.6 to 8.2 ± 4.2 at 52 weeks (p<0.001).(Fig. 1)
Four of 37 patients were on prednisolone 20 mg/day or more at the time of entry.
The clinical characteristics of those 4 patients were the continuation of lupus
nephritis in 2 patients. Two cases were type IV and type III of lupus nephritis,
respectively. However, it was 0.5<g/day the level of proteinuria in 2 cases, a
gradual decrease in the amount of prednisolone causing a rash in 1 patient and
significant general malaise in the other patient. Therefore, discontinuation of
prednisolone for these cases was not possible. The amount of prednisolone for the
above 4 patients was gradually decreased one month after tacrolimus initiation.
The administration of prednisolone was successfully decreased to 5-10 mg/day as
of 52 weeks in 3 out of 4 cases. There were no cases that were able to stop a
steroid, and the case that reached PSL<5g/day was 7 cases. Efficacy assessments indicated that the SLEDAI scores significantly improved (p<0.001, paired t-test).(Fig 2) Although 28 patients improved in their SLEDAI scores, 8 patients did not respond and/or experienced worsening of their SLE.

One patient discontinued treatment because of adverse events, and another reduced treatment but continued it. TAC administration was continued in 37 patients. The mean anti-dsDNA antibody level, as a typical indicator of immunological parameters reflecting disease activity, was also reduced at 52 weeks compared to baseline. The mean serum C3 concentration was 74.7 ± 21.8 mg/dl immediately before starting TAC, and it increased to 86.4 ± 17.8 mg/dl after 52 weeks; this difference was significant (p=0.006). There were also changes in normal ranges. The mean proteinuria (creatinine correction) was 0.31 ± 0.70 g/g Cr immediately before starting TAC, and it was 0.31 ± 0.47 after 52 weeks; this difference was not significant (p=0.47). Although serum levels of creatinine were significantly different between before and after treatment (from 0.72 ± 0.28 to 0.78 ± 0.37, p=0.038), eGFR was a trend for worsening of eGFR, but is not significantly different (p=0.055). Overall, disease activity of SLE and blood and urine studies did not worsen during this study. (Table 2)

Safety

Physician-determined definitive or unquestionable adverse drug events related to TAC were observed in 2 patients (5.3%) over 52 weeks (Table 3), and 2 patients discontinued treatment. Patient 1 noted rhabdomyolysis beginning 7 days after starting treatment with TAC, but the symptoms improved after discontinuing treatment. This might have been caused by drug interaction due to the simultaneous use of statins. The blood tacrolimus level for patient 1 was 6.7 ng/mL, which was not a high level. Although patient 2 noted muscle cramps 11 months after starting treatment with TAC, she improved after decreasing the TAC dose. The patient’s serum tacrolimus level was 7.4 ng/mL, which was not a high level; therefore, it was unlikely that the adverse effect was due to the serum levels of tacrolimus. No patients who experienced complications from adverse events had an abnormal urinalysis, and none progressed to renal failure with or without requiring dialysis. The statin used 14/38 (36.8%), ARB/ACE in 13/38 (34.2%) as we showed it in Table 1. During the study, the statin continued other than a case who had Rhabdomyolysis. ARB/ACE continued all cases. And there was not the case that started statin, ARB/ACE newly.
Discussion

In this paper, we demonstrated that TAC is both steroid sparing in effect and safe to use as treatment during the maintenance phase in SLE patients in a clinical setting. TAC was effective at decreasing disease activity during the maintenance phase of SLE, as observed at 52 weeks, without requiring an increase in CS dose for 28 of 38 patients (73.7%) in our study. Moreover, regarding safety, non-severe side effects were observed in only two patients (5.3%) over the 52-week period. The results of our prospective study indicate that TAC is an effective agent for treating SLE. Duddrige and Powell administered TAC to three SLE patients and found that cutaneous vasculitis, leukopenia, arthritis, and hypocomplementemia improved in two patients. [16] In 2006, Maruoka et al. reported that TAC was effective for treating a patient with lupus cystitis. [17] Subsequently, several reports have noted the efficacy of TAC for nephritis.[18][19][20]

Maintenance therapy of SLE has been reported only in studies of patients with lupus nephritis or without lupus nephritis,[21][22][23] and in a small group study and a short-duration study.[24][25] Thus, there have been no previous assessments of long-term TAC therapy in a larger group of SLE patients with/without nephropathy, as performed in this study. We demonstrated that treatment with TAC for 52 weeks maintains suppression of disease activity in SLE patients with/without renal involvement so that decreasing the CS dose was possible.

Limitations. In designing our study, consecutive patients were enrolled during specific periods to avoid selection bias, which differs from many of the aforementioned case series. The patients were assigned to groups according to the decisions of the involved physicians, not by randomization. Our survey focused on the real world, ordinary practice of TAC treatment for SLE; thus, a fully randomized study would not have been well shaped to our purposes, nor would it have been suitable for our investigation of the dose optimization of TAC to ensure its steroid-sparing effect and safety for all patients. For the patients whom activity of the SLE cannot control though use a middle dosage of steroid and/or an immunosuppressive drug collected it, and number of cases decreased. SLE is the heterogeneous disease, and this is a limit in this study. We increase number of cases, and it will be thought that nephropathy presence or absence, the comparison in the presence or absence of other clinical manifestations is necessary in future. Each physician carefully ascertained the dosage of TAC upon considering multiple factors for each patient, including disease activity, complications, age,
and renal function. In this study, the statistical significant difference is absent, but a tendency to exacerbation includes renal function. When we use TAC, we need attention.

Clinical trials including patients with rheumatoid arthritis have shown that the main adverse reactions caused by TAC are renal impairment, hypertension, glucose intolerance, and gastrointestinal symptoms.[26] In our study, adverse events were observed in two patients; however, these symptoms were reversible, improving after the discontinuation of TAC. The reason for this difference between patients with SLE and those with rheumatoid arthritis is not known, but the different underlying diseases, patient ages, and concurrent treatments (e.g., nonsteroidal anti-inflammatory drugs) might have played a role.

Conclusions

In conclusion, TAC combination therapy may be useful in decreasing steroid doses. It does not worsen disease activity and is safe for SLE patients during the maintenance phase. TAC could be one of the newest pragmatic treatment options for the maintenance phase of SLE. However, for severe, active conditions, the efficacy of TAC is considered limited at its current dose and usage recommendations.

Contributors. K.O. and Y.M. planned this study, performed statistical analyses. YM is responsible for the overall content as guarantor. S.I. and S.S. contributed to methods and discussion. N.O., S.I., T.T., M.U., H.F. and R.Y. provided administrative support. T.K. gave methodological advice and supervised all statistical procedures. All authors approved final manuscript.

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Patient consent. Obtained.

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**References**


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Figure 1. Decrease of prednisolone dose during tacrolimus therapy in eight systemic lupus erythematosus (SLE) patients. The mean (±SD) dose of prednisolone was 11.5 ± 5.6 mg/day before tacrolimus treatment and decreased significantly (p<0.001) to 8.2 ± 4.2 mg/day after 1 year.
Figure 2. Decrease of SLEDAI score during tacrolimus therapy in eight systemic lupus erythematosus (SLE) patients. The mean (±SD) SLEDAI score was 6.2 ± 3.7 before tacrolimus treatment and decreased significantly (p<0.001) to 2.6 ± 2.3 after 1 year.

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