Safety and potential efficacy of tacrolimus for treatment of lupus nephritis with persistent proteinuria

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Abstract

Objectives

To evaluate the safety and potential efficacy of tacrolimus for the treatment of patients with lupus nephritis and persistent proteinuria.

Methods

A total of 23 Japanese patients with lupus nephritis (21 females / 2 males) were enrolled in this study. Patients were administered tacrolimus at a dose of 2-3 mg once daily after the evening meal for 6 months. The dose of tacrolimus was unchanged throughout the study period. Concomitant prednisolone therapy was unchanged or gradually tapered, while other immunosuppressants were stopped at the start of tacrolimus treatment.

Results

Tacrolimus was well tolerated, and none of the patients developed adverse drug reactions that required discontinuation of the study. Daily urinary protein loss, the U-prot/U-creat ratio, and serum albumin were significantly improved after 4 months, 3 months, and 1 month of treatment with tacrolimus ($p<0.05$), respectively, and the improvement persisted until 6 months. The serum complement hemolytic activity (CH50), complement C3 level, and CRP level were also significantly improved after treatment with tacrolimus ($p<0.05$). Improvement of the U-prot/U-creat ratio was most prominent for patients who were in WHO class IV.

Conclusion

Tacrolimus is safe and effective as maintenance therapy for patients with lupus nephritis, at least for 6 months. A larger randomised, controlled trial over a longer period is needed to confirm these results.

Key words

Lupus nephritis, calcineurin inhibitor, maintenance therapy, immunosuppressant, complement.

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Introduction

Systemic lupus erythematosus (SLE) is a prototypic systemic autoimmune disease that is characterised by the appearance of a variety of autoantibodies and subsequent immune complex deposition, culminating in chronic inflammation that affects multiple organs (1). Renal involvement has been demonstrated in up to 60% of SLE patients at some stage of their disease, and it is one of the most important factors with regard to both morbidity and mortality (2).

Standard therapy for proliferative lupus nephritis is the combination of a corticosteroid and immunosuppressive agents. Long-term efficacy has only been demonstrated for cyclophosphamide (CY)-based regimens, but these are associated with severe toxicity such as ovarian failure and an increased risk of secondary malignancy (3-5). Therefore, less toxic treatment with equal efficacy needs to be developed. Contreras *et al*. reported that azathioprine (AZA) and mycophenolate mofetil (MMF) showed superior efficacy and safety over quarterly intravenous CY as maintenance therapy (6).

Tacrolimus is a T cell-specific calcineurin inhibitor that has a similar immunosuppressive action to that of cyclosporine A (CsA) (7). It forms a complex with immunophilin FK506-binding protein 12 and inhibits the phosphatase activity of calcineurin, resulting in decreased IL-2 transcription and inhibition of T cell activation. Tacrolimus also inhibits the production of TNF-α and INF-γ by activated T cells. *In vivo* and *in vitro* studies have shown that tacrolimus is 10 to 100 times more potent than CsA. Tacrolimus has not only been used to prevent allograft rejection after solid organ transplantation, but also to manage graft-versus-host disease in patients undergoing allogeneic hematopoietic stem cell transplantation (8). Recently, tacrolimus has been successfully employed to treat rheumatoid arthritis (RA), which is the most common autoimmune disorder. A number of reports, including those of randomised controlled trials, have demonstrated the efficacy of oral tacrolimus in patients with active RA that is refractory to disease-modifying anti-rheumatic drugs (DMARDs) or in patients who cannot tolerate treatment with DMARDS (9-14). Tacrolimus was also reported to be effective for inclusion body myositis with autoimmune features (15).

However, only a few uncontrolled pilot studies have been reported with respect to the use of tacrolimus for SLE. It was shown to be effective as remission induction therapy in 9 patients with diffuse proliferative lupus nephritis (16) as well as for maintenance therapy in 6 patients with paediatric-onset lupus nephritis (17). Tacrolimus was also reported to be effective in two small studies of 6 and 18 patients with membranous lupus nephritis (18, 19). Furthermore, combination therapy with tacrolimus, MMF, and corticosteroids was recently reported to be more effective than intravenous CY as remission induction therapy for class V + IV lupus nephritis (20).

To further confirm the efficacy and safety of tacrolimus for the treatment of lupus nephritis, we conducted the present clinical study in 23 patients with lupus nephritis and persistent proteinuria. To our knowledge, this is the largest study of such patients reported so far.

Patients and methods

Patients

This was a multi-centre open-label prospective 6-month observational study performed from 2007 to 2008 during normal clinical practice. The inclusion criteria were as follows: 1) an age of 15 years or more, 2) a diagnosis of SLE (patients who fulfilled four or more of the American College of Rheumatology criteria (21) for diagnosing of SLE), and 3) persistent proteinuria despite treatment with corticosteroids and/or immunosuppressants. Exclusion criteria included the following: 1) pregnancy, 2) previous treatment with tacrolimus, 3) intravenous CY within 12 weeks before the study, 4) steroid pulse therapy within 4 weeks before the study, 5) a serum creatinine level ≥2 mg/dl, 6) serum transaminase levels ≥100 U/L, 7) moderate to severe cardiac dysfunction, and 8) known allergy to tacrolimus. All of the participants were Japanese nationals and were managed

at Kyushu University Hospital or its affiliated hospitals for at least 6 months after the initiation of tacrolimus therapy. Informed consent was obtained from all patients.

Treatment protocol

Tacrolimus was administered at a dose of 2-3 mg once daily after the evening meal for 6 months. The dose of tacrolimus was unchanged throughout the study period. The dose of concomitantly administered prednisolone was also not changed or was gradually tapered throughout the study period, depending on each patient's clinical status. Other immunosuppressants, such as AZA, mizoribine, CsA, or CY, were stopped and the patient was switched to tacrolimus without a washout-period at study entry.

Clinical assessment

For safety evaluation, blood pressure was measured at monthly intervals. Laboratory tests were also performed, including hematology tests (red blood cell count, hemoglobin, hematocrit, platelet count, leukocyte count, and differential leukocyte count), biochemistry tests (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, g-glutamyl transpeptidase, total bililubin, cholesterol, triglycerides, glucose, blood urea nitrogen, uric acid), and serum electrolytes (Na, K, Cl, Ca, and P). All adverse events were examined and those for which a causal relationship to tacrolimus could not be excluded by the investigator were classified as adverse drug reactions.

For evaluation of efficacy, the daily urinary protein loss, the severity of proteinuria as estimated from the urinary protein/creatinine ratio (U-prot/U-creat ratio), urinary sediment parameters, the serum creatinine level, serum titers of anti-dsDNA antibody (ELISA), serum C3 and C4 levels, serum complement hemolytic activity (CH50), and the serum CRP level were measured at monthly intervals. Last observation carried forward analysis was performed.

Tacrolimus monitoring

The whole blood trough tacrolimus level was monitored by microparticle enzyme immunoassay (Abbott IMx), at monthly intervals after starting tacrolimus treatment.

Table I. Baseline characteristics of 22 patients who completed 6 months of treatment with tacrolimus.

Female/Male	20/2
Age at entry (years) (median, range)	34.5 (17-61)
Duration of SLE (years)	11.7 ± 7.4
Proteinuria	
U-prot/U-creat ratio	2.52 ± 1.24
Daily protein loss (g/day)*	1.64 ± 1.94
Urinary sediment**	
Red cells (/HPF)	10.5 ± 13.6
Cellular casts (%)	44.4
Renal histology (WHO class)	
III	3
III+V	1
IV	6
IV+V	1
V	5
Undetermined	6
Serum creatinine (mg/dl)	0.91 ± 0.35
Serum albumin (g/dl)	3.28 ± 0.57
Serum C3 (mg/dl)	73.8 ± 30.3
Serum CH50 (U/ml)	33.4 ± 16.5
Anti-dsDNA (IU/ml)	50.6 ± 58.3
Serum CRP (mg/dl)	0.39 ± 0.50
Induction therapy	
PSL only	13
PSL+cyclophosphamide	2
PSL+mizoribine	2
PSL+cyclosporine	3
PSL+mycophenolate mofetil	1
None	1
Maintenance therapy	
PSL only	11
PSL+mizoribine***	6
PSL+cyclosporine***	3
PSL+azathioprine***	1
None	1
PSL dose (mg/day)	11.5 ± 8.5

All patients were followed at outpatient clinics. Except for "age at entry", data are expressed as the mean ± SD.
* In 10/22 patients, daily urinary protein loss was measured.
** In 9/22 patients, urinary sediment was assessed.
*** These immunosuppressive agents were switched to tacrolimus at study entry.

Statistical analysis

Results are expressed as the mean ± standard deviation (SD). Wilcoxon's signed rank test was used for comparison between baseline values and those obtained at each time point during the study. Statistical tests were two-sided and $p<0.05$ was taken to indicate statistical significance.

Results

Patient characteristics

Table I shows baseline characteristics of the 22 patients with lupus nephritis who completed the 6-month study. They consisted of 20 females and 2 males with a median age of 34.5 (range: 17 to 61 years) and a disease duration of 11.7±7.4 years at study entry. One patient did not complete the study because of poor compliance with the specified regimen. The severity of proteinuria was estimated by the U-prot/U-creat ratio in all of the patients and by daily measurement of urinary protein loss in 10 patients. Urinary sediment was assessed in 9 patients. Histologic examination of renal biopsy specimens was done in 16 out of 22 patients (3 patients were WHO class III, 1 was WHO class III+V, 6 were WHO class IV, 1 was WHO class IV+V, and 5 were WHO class V). At entry into the study, the patients only had renal manifestations of SLE apart from two patients with a butterfly rash and thrombocytopenia.

Before remission induction therapy, the baseline proteinuria and serum creatinine level were 3.70±3.99 g/day and 0.86±0.32 mg/dl, respectively. For induction of remission, 13 patients were treated with corticosteroid therapy alone, 2 received a corticosteroid plus intravenous cyclophosphamide, 2 received a corticosteroid plus mizoribine, 3 were given a corticosteroid plus cyclosporine, and 1 had a corticosteroid plus MMF. After remission induction therapy, immunosuppressants were stopped in 3 patients and were added or changed in 5 patients. The dosage and the duration of cyclosporine therapy were 150.0±38.2 mg/day and 25.6±23.3 months, respectively. The interval between remission induction therapy and the start of tacrolimus treatment was 51.0±43.1 months. Proteinuria was increasing in 5 patients and was stable in 17 patients at the start of tacrolimus treatment.

Safety

Tacrolimus was well tolerated, and none of the patients developed adverse drug reactions that required its discontinuation during the 6-month study period.

Adverse drug reactions occurred in 10 out of 22 patients (45.5%). Infections were diagnosed in 3 patients (13.6%), including urinary tract infection, salivary gland infection, and herpes simplex virus infection of the right cheek. These infections were not serious and resolved after treatment with antimicrobial or antiviral agents. One patient developed a tremor that required reduction of the tacrolimus dose. Worsening of hypertension and fatigue occurred in one patient each. An increase of serum creatinine by more than 30% was seen in 4 patients (18.2%), but the average serum creatinine level of all patients was unchanged by tacrolimus treatment. In 10 patients whose creatinine clearance was monitored there was no significant change between baseline and 6 months of tacrolimus treatment (data not shown). A decrease of the haemoglobin level by more than 1 g/dl was seen in one patient.

One female patient withdrew from the study because of poor compliance and not due to side effects.

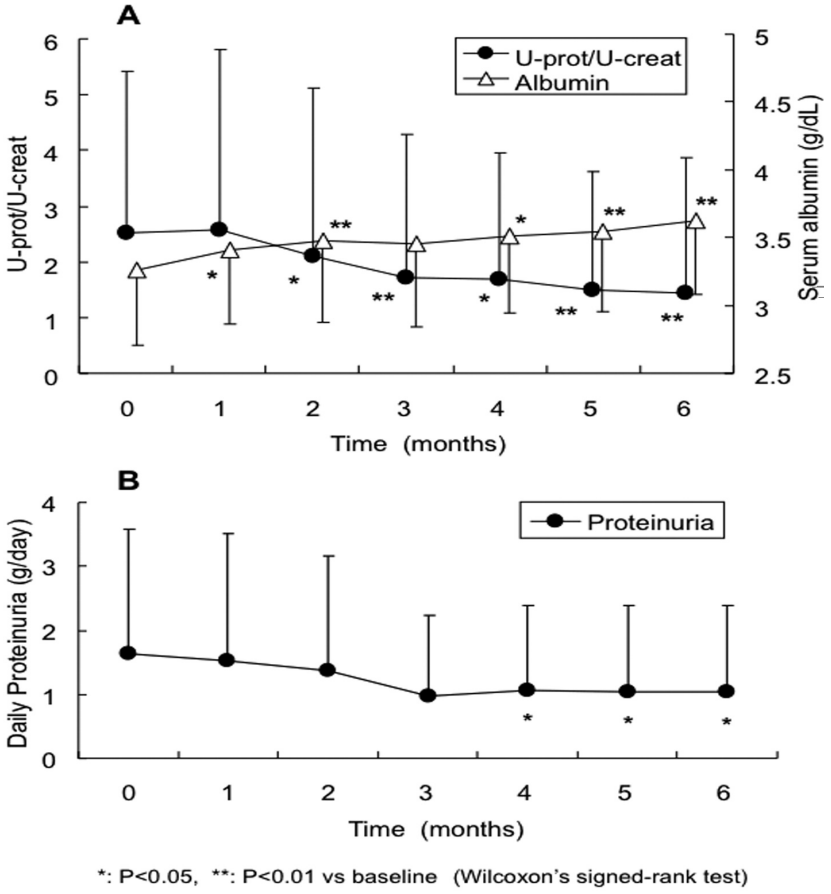

Fig. 1. Evaluation of proteinuria in 22 lupus patients during tacrolimus treatment. Urinary protein loss was evaluated from the U-prot/U-creat ratio (A) or from 24-hour urinary protein excretion (B). Values are shown as the mean ± SD and the significance of improvement was assessed by Wilcoxon's signed rank test (*p<0.05, **p<0.01).

Response of proteinuria

As shown in Figure 1A, the U-prot/U-creat ratio at baseline was 2.52±2.89 and it decreased significantly to 2.11±3.01 by 2 months after the start of the study (p<0.05). This significant decrease of the U-prot/U-creat ratio continued until 6 months (1.43±2.43) (p<0.05). In order to more precisely estimate the effect of tacrolimus on lupus nephritis, daily urinary protein loss was measured in 10 patients (Fig. 1B). The baseline protein loss was 1.64±1.94 g/day, which decreased significantly to 1.05±1.34 g/day after 4 months (p<0.05), and the improvement was maintained at 6 months (1.04±1.35 g/day) (p<0.05). Two of these 10 patients achieved complete remission, with a daily urinary protein loss of less than 0.1 g/day. Analysis of the sediment showed that red cells decreased from 10.5±13.6 /high power field (HPF) before treatment to 5.9±8.4/HPF at 6 months although the difference did not reach statistical significance (p=0.25). Cellular casts (containing granulocytes, white cells, and red cells) were positive in 44.4% and 22.2% of the patients before treatment and at 6 months, respectively. Extra-renal manifestations of SLE were also improved by tacrolimus.

Response of serological markers and changes of the prednisolone dose

There was significant improvement of the serum albumin, complement, and CRP levels (Fig. 1A, Table II). As shown in Figure 1A, serum albumin level increased significantly from as early as 1 month after the start of tacrolimus therapy (from 3.28±0.57 g/dl at baseline to 3.42 ± 0.55 g/dl, p<0.05). The serum albumin level increased gradually throughout the 6-month study period and reached 3.64±0.55 g/dl at 6 months, which was significantly higher

Table II. Adverse drug reactions.

Event	No. of patients (%)
Urinary tract infection	1 (4.5)
Salivary gland infection	1 (4.5)
Herpes simplex infection	1 (4.5)
Tremor	1 (4.5)
Fatigue	1 (4.5)
Hypertension	1 (4.5)
Creatinine increased	4 (18.2)
Hemoglobin decreased	1 (4.5)

than at baseline ($p<0.01$). Table II shows that serum CH50 and C3 values were 33.4±16.5 U/ml and 73.8±30.3 mg/dl at baseline, respectively, both of which increased significantly after 2 months to reach 36.3±14.4 U/ml and 81.1±27.9 mg/dl, respectively ($p<0.05$). The effect of tacrolimus on these complement parameters continued until 6 months (38.1±12.6 U/ml for CH50 and 79.7±26.9 mg/ml for C3). Although there was an increase, the C4 level did not improve significantly after 6 months. The serum CRP level was significantly decreased compared with that at baseline after 3 months and 6 months (both $p<0.05$).

The corticosteroid dose showed a decrease from 11.5±8.5 mg/day at baseline to 10.0±5.7 mg/day after 6 months of treatment with tacrolimus, but the difference was not statistically significant.

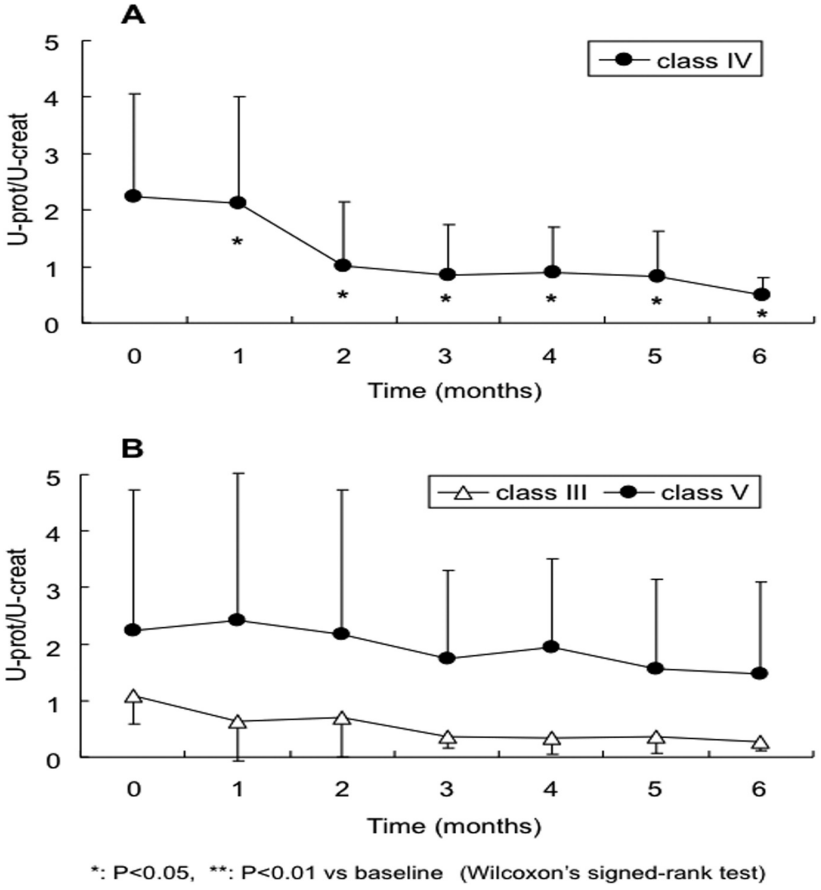

Fig. 2. Evaluation of proteinuria during tacrolimus treatment in patients with WHO class IV nephritis (A) and in patients with WHO class III or V nephritis (B). Values are shown as the mean ± SD for the U-prot/U-creat ratio. (*$p<0.05$, **$p<0.01$). Data from a patient who was WHO class III + V were included among both those for WHO class III and WHO class V. Data from a patient who was WHO class IV + V were included among those for both WHO class IV and WHO class V.

Stratification of patients to assess the efficacy of tacrolimus

Stratification of the patients revealed a number of factors that predicted a better response of lupus nephritis. First, the improvement of the U-prot/U-creat ratio was greater for 7 patients in WHO class IV (Fig. 2A). In these patients, the U-prot/U-creat ratio was 2.25±1.81 at baseline and showed a rapid and significant decrease from as early as 1 month after starting tacrolimus treatment to reach 0.43±0.33 at 6 months ($p<0.05$). Although there was also improvement of the U-prot/U-creat ratio for the 4 patients in WHO class III and the 7 patients in WHO class V, the changes after tacrolimus treatment were not significant (Fig. 2B). However, all 4 patients in WHO class III and 6 out of 7 patients in WHO class V showed improvement of the U-prot/U-creat ratio at 6 months. Second, the improvement of complement, CRP, and anti-dsDNA antibody was more pronounced in patients with abnormal levels of these parameters at baseline (Table III). CRP was normalised after 1 month, followed by improvement of C3 and CH50 at 2 months and improvement of C4 at 5 months ($p<0.05$). Significant improvement of these markers was maintained at 6 months, except in the case of C3. The anti-dsDNA antibody level was normalised at 1 month and 6 months ($p<0.05$). Six out of 16 patients with an increase of anti-dsDNA antibody (>10 IU/ml) achieved normalisation at 6 months.

Tacrolimus concentration

The tacrolimus concentration was measured in 7 patients and the whole blood tacrolimus level was 4.03±1.49 ng/ml at 1 month. The tacrolimus levels of these patients showed almost no changes thereafter until the end of the study (data not shown).

Discussion

Treatment of lupus nephritis consists of an intensive remission induction therapy, followed by long-term and less intensive maintenance therapy. The standard regimen for induction of remission includes prednisolone combined with CY as daily oral therapy or intravenous pulse therapy (3, 22). The efficacy of MMF for remission induction therapy has also been reported (23, 24). With regard to maintenance therapy, pulse CY has been recommended (25), while MMF and AZA are also considered to be good options (6, 26). In patients with SLE, proteinuria sometimes persists or relapses following the resolution of acute nephritis after remission induction therapy. Up to 20% of patients with lupus nephritis are reported to be resistant to initial immunosuppressive therapy (27). Resistance to conventional immunosuppressive agents is a major risk

Table III. Change in immunological markers after tacrolimus treatment in all the patients enrolled in the study.

	n	baseline	1 month	2 month	3 month	4 month	5 month	6 month
C3 (mg/dL)	22	73.8±30.3	78.2 ± 31.3	81.1 ± 27.9*	81.1 ± 27.0*	81.3 ± 28.0	80.9 ± 26.2*	79.7 ± 26.9
C4 (mg/dL)	20	15.9±11.0	15.6 ± 11.7	17.0 ± 11.7	17.5 ± 11.9	17.0 ± 11.2	17.2 ± 11.1	17.1 ± 10.9
CH50 (U/mL)	21	33.4±16.5	34.5 ± 16.3	36.3 ± 14.4*	37.1 ± 13.5*	36.2 ± 13.5	37.3 ± 13.2*	38.1 ± 13.0*
CRP (mg/dL)	20	0.39±0.50	0.34 ± 0.44	0.32 ± 0.54	0.22 ± 0.38*	0.22 ± 0.38	0.16 ± 0.19	0.13 ± 0.18*
anti-dsDNA (U/mL)	21	50.6±58.3	43.0 ± 47.4	41.4 ± 58.5	44.4 ± 54.2	51.5 ± 70.2	46.7 ± 65.3	43.1 ± 54.5

Data are expressed as mean ± SD. *: $p<0.05$ *vs*. baseline (Wilcoxon's signed-rank test)

Table IV. Change in immunological markers after tacrolimus treatment in the patients whose baseline values were abnormal.

	n	baseline	1 month	2 month	3 month	4 month	5 month	6 month
C3 (mg/dL)	14	54.2 ± 13.6	58.1 ± 14.2	64.3 ± 15.5*	65.6 ± 17.5*	65.5 ± 16.9*	65.6 ± 14.6*	64.1 ± 14.4
C4 (mg/dL)	14	9.7 ± 4.6	9.1 ± 4.7	10.6 ± 4.6	11.1 ± 4.8	11.0 ± 4.3	11.1 ± 4.2*	11.1 ± 4.0*
CH50 (U/mL)	10	19.1 ± 7.5	20.5 ± 7.8	24.2 ± 6.9*	26.1 ± 7.8*	25.0 ± 6.0*	26.9 ± 7.1*	28.6 ± 7.4**
CRP (mg/dL)	8	0.83 ± 0.53	0.58 ± 0.57*	0.45 ± 0.54**	0.41 ± 0.54*	0.24 ± 0.23*	0.21 ± 0.20*	0.13 ± 0.10*
anti-dsDNA (U/mL)	16	64.5 ± 60.6	54.1 ± 49.3*	52.6 ± 63.3	55.7 ± 57.7	65.1 ± 75.7	57.7 ± 71.6	51.7 ± 60.0*

Data are expressed as mean ± SD. *: $p<0.05$, **: $p<0.01$ *vs*. baseline (Wilcoxon's signed-rank test)

factor for eventual deterioration of renal function and a poor prognosis (28-30). It is therefore important to establish effective rescue therapy for such patients.

In the present study, we assessed the safety and efficacy of tacrolimus for patients with lupus nephritis that was resistant to conventional maintenance therapy. Twenty-two patients who had persistent or relapsed lupus nephritis were treated with tacrolimus at 2-3 mg/day for 6 months.

With respect to safety, almost all of the subjects tolerated the medication well.

Adverse drug reactions were observed in 45.5% of the patients. The common reactions were infections and an increase of serum creatinine, which are known to be adverse reactions caused by tacrolimus. Three patients (13.6%) had minor infections. In other studies of RA or SLE, infection occurred in 3.6-18.5% of the patients (9-14, 17-19). An increase of creatinine was observed in 18.2% and 1.8-14.8% of the patients in this and other studies (9-14, 17-19), respectively.

The effects of tacrolimus in our patient population can be summarised as follows. 1) Renal involvement (estimated either by daily urinary protein loss or the U-prot/U-creat ratio was significantly improved after 4 months and 2 months, respectively, with the improvement persisting after 6 months of tacrolimus therapy. 2) Serological markers (C3, C4, CH50, albumin, anti-dsDNA antibody, and CRP) were also improved. 3) Tacrolimus was safe and well tolerated (22/23 patients were still taking it at the end of the 6-month study period). 4) The U-prot/U-creat ratio was most significantly improved in patients with WHO class IV lupus nephritis. 5) In patients with WHO class III (n=4) or WHO class V (n=7) nephritis, there was no significant improvement. However, tacrolimus also seemed to be effective for these types of lupus nephritis, because all but one of the patients showed improvement of the U-prot/U-creat ratio at 6 months. A large-scale study would be needed to clarify the efficacy of tacrolimus for patients in WHO class III and WHO class V.

This study showed that, there were no differences of the response to tacrolimus in relation to previous treatment (data not shown). Among 3 patients who had previously been treated with adequate doses of CsA, 2 patients showed improvement of the U-prot/U-creat ratio at 6 months.

Only reports of a few preliminary and uncontrolled studies are available with respect to the efficacy of tacrolimus for patients with lupus nephritis. In nine patients with proliferative lupus nephritis (WHO class IV), tacrolimus combined with oral prednisolone was reported to have been useful for remission induction therapy (16). Regarding maintenance therapy for lupus nephritis, tacrolimus has been shown to be effective in 6 young patients (17) and in 6 patients with membranous or quiescent lupus nephritis (18). Recently, tacrolimus was also reported to be effective in 18 patients with membranous lupus nephritis (19). Our study enrolled 23 patients with lupus nephritis, and to our knowledge, this is the largest-scale study of tacrolimus in such patients to date. In addition, the effect of tacrolimus itself was directly assessed in our study, because the dose of prednisolone was unchanged or tapered and other concomitant immunosuppressive agents were stopped at the initiation of tacrolimus treatment.

Tacrolimus is a calcineurin inhibitor that shares a similar immunosuppressive mechanism with CsA (another calcineurin inhibitor). A number of open-labelled uncontrolled studies have indicated the effectiveness of CsA for lupus nephritis (31-33). One randomised controlled trial demonstrated that the efficacy of CsA or AZA combined with prednisolone as maintenance therapy was equal for preventing the flare-up of diffuse proliferative lupus nephritis (34). Taken together, these findings suggest that calcineurin inhibitors like tacrolimus and CsA could be a useful option for the treatment of lupus nephritis.

In conclusion, the present study provided evidence that tacrolimus is safe and effective for lupus nephritis with persistent proteinuria, at least as maintenance therapy for 6 months. The improvement of proteinuria was most pronounced among patients in WHO class IV. However, this study may have had some bias because it was an open-label, observational, and short-term trial. Randomised controlled trials with a longer duration and larger patient population are needed to confirm the efficacy of tacrolimus for maintenance therapy of lupus nephritis and to clarify the histological types (WHO class IV, etc.) of nephritis that are more suitable for treatment with tacrolimus.

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