Pre-emptive immunosuppressive treatment for asymptomatic serological reactivation may reduce renal flares in patients with lupus nephritis

Desmond Y. H. YAP[1], Lorraine P. Y. KWAN[1], Maggie M. K. MA[1], Maggie M. Y. MOK[1], Gary C. W. CHAN[1], Tak Mao CHAN[1]

[1]Division of Nephrology, Department of Medicine, The University of Hong Kong, Hong Kong

Running title: pre-emptive treatment of serological reactivation in lupus nephritis

Correspondence

Prof. Tak Mao CHAN, Department of Medicine, Queen Mary Hospital 102 Pokfulam Road, The University of Hong Kong, Hong Kong.

Tel: 852-22554542 Fax: 852-28725828 Email: dtmchan@hku.hk

Abstract

Objective: Serological activity may precede clinical flares of lupus nephritis (LN) but the management of asymptomatic serological reactivation (ASR) remains undefined.

Methods: We conducted a retrospective analysis of 138 episodes of ASR, which included 53 episodes in which immunosuppression was increased pre-emptively and 85 episodes in which treatment was unaltered. Pre-emptive immunosuppressive treatment comprised increasing the dose of prednisolone to approximately 0.5 mg/kg/D, and in patients already on mycophenolate mofetil (MMF) or azathioprine (AZA) increasing the dose to 1.5 g/D and 100 mg/D respectively.

Results: 32 episodes of renal flare occurred during follow-up (88.8±77.3 and 82.8±89.7 months in the pre-emptive group and controls respectively), following 5 (9.4%) of pre-emptively treated ASR and 27 (31.8%) of untreated ASR (HR=0.3, CI 0.1-0.7, P=0.012). Pre-emptive treatment was associated with superior survival free of renal relapse (99%, 92% and 90% at 6-, 12- and 24-month respectively, compared with 94%, 69% and 64% in controls, p=0.011), while survival rate free of extra-renal relapse was similar in the two groups. Pre-emptively treated patients who did not develop renal flares showed better renal function preservation (eGFR slope +0.54±0.43 ml/min/1.73m^2/year, compared with -2.11±0.50 and -1.00±0.33 ml/min/1.73m^2/year respectively in controls who did or did not develop subsequent renal flares, p=0.001 and 0.012 respectively). Pre-emptive treatment was associated with increased incidence of gastrointestinal side-effects attributed to MMF (p=0.031), while infection rate did not differ between the two groups.

Conclusion: Pre-emptive moderate increase of immunosuppression for ASR in LN patients may reduce renal flares and confer benefit to long-term renal function.

Key Messages

- Pre-emptive treatment of asymptomatic serological reactivation in lupus nephritis may reduce flare.
- Pre-emptive treatment of asymptomatic serological reactivation in lupus nephritis may confer long-term renal benefits.

Keywords: asymptomatic, serological reactivation, pre-emptive treatment, lupus nephritis

Introduction

Lupus nephritis (LN) is a serious organ involvement in patients with systemic lupus erythematosus (SLE) and portends undesirable clinical outcomes [1-3]. The current standard-of-care induction regimen for active severe LN are high-dose corticosteroids combined with either mycophenolate mofetil (MMF) or cyclosphophamide (CYC), followed by low-dose corticosteroids plus either MMF or azathioprine (AZA) as long-term maintenance immunosuppression to prevent relapse[4-7]. Disease relapses are still common and repeated flares have a negative impact on long-term renal survival[8]. Prediction and prevention of flares remain challenging. Although serial monitoring of serological parameters such as anti-dsDNA and C3 can reflect disease activity in most SLE patients, their usefulness in guiding treatment decisions remains controversial[9-12]. While serological reactivation may precede clinical flares, a considerable portion of patients who show serological reactivation could remain clinically stable for years[9-12]. Pre-emptive increase in immunosuppression for all patients with asymptomatic serological reactivation (ASR) might 'over-treat' some patients leading to an increased risk of adverse effects such as infections and metabolic complications[13-15]. It has been reported that a short-course moderate-dose corticosteroids could prevent severe flares in SLE patients who were serologically active but clinically stable[16, 17]. However, small numbers of patients were involved in these studies and the durations of follow-up relatively short; and the effect of pre-emptive treatment on long-term flare risk and renal outcomes were not examined. Furthermore, disease flare rate has changed considerably over time with MMF increasingly used as maintenance treatment[15, 18, 19]. Against this background, the objective of

this study was to examine the impact of pre-emptive immunosuppressive treatment on subsequent flare rate and renal outcome in LN patients who experienced ASR.

Patients and methods

Patients

The case records of all biopsy-proven LN patients followed at the SLE clinic of Queen Mary Hospital during the period of June 1993 to May 2015 were reviewed. Asymptomatic serological reactivation (ASR) was defined as absence of renal or systemic manifestations of active SLE and either 1) increase of anti-dsDNA antibody titre from negative (<40 IU/mL) to >100 IU/mL or 2) when baseline anti-dsDNA level was ≥40 IU/mL, a two-fold increase of anti-dsDNA antibody titre to >100 IU/mL, with or without subnormal serum complement level. Patient characteristics and clinical events including renal and extra-renal flares and serial serum creatinine levels were retrieved. This study was approved by the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster Hospitals (IRB HKU/HAHKW).

Induction and maintenance immunosuppression and follow-up schedule

Standard immunosuppressive treatment protocols were used in all patients with biopsy-proven Class III/IV/V LN. Induction treatment for Class III/IV±V LN was prednisolone (PRED) (0.8 mg/kg/D) plus either oral CYC (1-1.5 mg/kg/D) before 1998 or MMF (1 g bid) after 1998 for six months, followed by low-dose PRED (5-7.5 mg/D) plus either AZA (2 mg/kg/D) or MMF (0.75 g bid) which were gradually tapered[15, 19, 20]. All patients were given anti-malarial treatment unless contraindicated. Patients were seen at 2- to 14-week intervals depending on their clinical

status. Complete blood counts, renal and liver biochemistry, anti-dsDNA antibody and C3 levels, urine protein/creatinine ratio and clinically significant events were monitored at every visit.

Pre-emptive immunosuppressive treatment for Asymptomatic Serological Reactivation (ASR)

The decision to initiate pre-emptive immunosuppressive treatment to some patients with ASR based on physician discretion. The dosage and tapering of medications were in accordance with the following protocol when a patient was assigned to the pre-emptive treatment group. PRED dose was increased to 0.4-0.5 mg/kg/D, then reduced by 5 mg/D every 2 weeks to reach 15 mg/D, and then by 2.5 mg/D every 2 weeks to reach 5 mg/D. In patients who were already on MMF or AZA, MMF dose was increased to 1.25-1.5 g per day and AZA dose was increased to 100 mg/D, and maintained for a minimum of 12 weeks before gradual reduction back to the original dosage. There was no cross-over between the patients who have or have not received pre-emptive treatments (i.e. subsequent ASR will also be managed in the same way according to their initial assignment) to enable subsequent analysis on clinical flare rates and long-term renal outcomes. Patients were seen at least once every 4 weeks with the standard surveillance parameters monitored. Patients with ASR but did not receive pre-emptive increase of immunosuppression were seen every 4-6 weeks.

Primary and secondary outcomes

Primary outcome was the occurrence of renal flare as defined by an increase in proteinuria to over 1 g/D and/or increase of serum creatinine by 15% or more of baseline value, and confirmed

with kidney biopsy. Secondary outcomes included extra-renal flares, serological parameters, slope of estimated glomerular filtration rate (eGFR) over time, and the occurrence of adverse events including infections and treatment associated adverse effects. Extra-renal flares were new or worsened clinical/laboratory findings indicative of increased disease activity in one or more organ systems other than the kidneys, that were considered clinically significant and warranted a change or increase in treatment[21].

Statistical Analysis

Continuous variables were expressed as mean (S.D.) or median (range), and compared with Student's t-test or Man-Whitney test where appropriate. Categorical variables were expressed as frequency (percentages), and compared with Chi-square or Fisher-Exact test where appropriate. The slopes of eGFR over time was calculated from 6-monthly eGFR for those who completed 5 years of follow-up after the onset of ASR and compared between different patient groups using regression analysis[22]. Longitudinal values were logarithmic transformed and compared with ANCOVA. All statistical analyses were performed with SPSS version 23.0 and p-values were two-sided.

Results

Patient characteristics

138 episodes of ASR occurred in 98 LN patients during the study period, and the follow-up duration was 22206.7 patient-months (Table 1). The doses of PRED, MMF, and AZA at the onset of ASR were 6.3±2.1 mg/D, 0.904±0.262 g per day, and 64.1±20.3 mg/D respectively. 53 episodes (in 38 patients) were treated with pre-emptive increase of immunosuppression while 85 episodes (in 60 patients) were not. Follow-up duration after ASR was 88.8±77.3 months in the pre-emptive group and 82.8±89.7 months in untreated controls. Patients who received pre-emptive treatment had significantly lower C3 levels compared with untreated controls (55.5±25.1 mg/dL vs. 76.2±22.3 mg/dL, $p<0.001$), while anti-dsDNA titres were similar in the two groups (191.8±111.2 IU/mL vs. 153.1±75.2 IU/mL, $p=0.120$). PRED dose was increased to 24.1±6.2 mg/D; MMF dose was increased to 1411.3±540.6 mg/D; AZA dose was increased to 85.4±22.5 mg/D.

Longitudinal change of serological parameters

Pre-emptive immunosuppressive treatment was associated with a reduction of anti-dsDNA titre from 191.8±111.2 IU/mL to 73.7±54.0 IU/mL after 12 months and 62.2±51.7 IU/mL after 24 months ($p<0.001$ compared with baseline for both), and increasing C3 level from 55.5±25.1 mg/dL to 65.9±23.0 mg/dL after 12 months and 70.6±25.0 mg/dL after 24 months ($p=0.006$ and 0.002 respectively compared with baseline) (Figure 1, A&B). In the untreated group there was

no significant change over time for anti-dsDNA titre (153.1±75.0 IU/mL vs. 121.9±94.0 IU/mL vs. 127.7±104.9 IU/mL at baseline and after 12 and 24 months respectively, p=0.077 and 0.243 compared with baseline) and C3 level (76.2±22.0 mg/dL vs. 73.5±21.0 mg/dL vs. 78.4±26.3 mg/dL, at baseline and after 12 and 24 months respectively, p=0.249 and 0.857 compared with baseline).

Renal and non-renal flares

Patients who received pre-emptive treatment for ASR showed significantly better survival free of renal relapse than untreated controls (99% vs. 94% after 6 months, 92% vs. 69% after 12 months, and 90% vs. 64% after 24 months respectively, p=0.011) (Figure 2, A). Renal flares occurred after 5 (9.4%) of pre-emptively treated 53 ASR episodes, at 16.8±5.0 months. 27 (31.8%) episodes of renal flare developed at 10.7±5.0 months after the 85 untreated ASR episodes. Pre-emptive treatment was associated with a lower cumulative incidence of renal flares compared with untreated controls (0% vs. 12.9%, 3.8% vs. 28.2%, and 9.4% vs. 31.8% after 6, 12 and 24 months respectively; p=0.007, <0.001, and 0.003 respectively) (HR=0.3 in the pre-emptive treatment group, CI 0.1-0.7, P=0.012) (Table 2). For the pre-emptive group, 4 out of 5 subsequent renal flares had repeat biopsy (all Class IV LN). For the control group, 25 out of 27 subsequent renal flares had repeat biopsy (16 were Class IV, 7 were Class III+V or IV+V, 2 were pure Class V). The number of ASR needed-to-treat to prevent one episode of renal flare was 11.7. Extra-renal flares occurred at 12.0±5.1 months after 12 ASR episodes (cerebral lupus n=1; hematological n=5; arthritis n=6) in the pre-emptive group, and at 8.8±3.1 months after 13 untreated ASR episodes (hematological n=3; arthritis n=10). Survival free of extra-renal flares

was similar between the pre-emptive treatment group and untreated controls (95% vs. 93%, 90% vs 92%, and 82% vs. 88% after 6, 12 and 24 months respectively, p=0.389) (Figure 2, B).

Renal function

Baseline eGFR was similar between the pre-emptive treatment group and untreated controls (86.1±26.5 ml/min/1.73m^2 vs. 85.9±26.0 ml/min/1.73m^2 respectively, p=0.970). At 5 years after ASR, eGFR was higher in the pre-emptive treatment group (90.9±22.5 ml/min/1.73m^2 vs. 80.1±28.1 ml/min/1.73m^2 in untreated controls, p=0.043). Pre-emptively treated patients who did not develop renal flares had significantly higher eGFR than untreated patients who subsequently developed renal flares (91.9±20.4 ml/min/1.73m^2 vs. 71.2±24.4 ml/min/1.73m^2, p=0.01), while their eGFR was similar to untreated patients without renal flare (82.9±28.8 ml/min/1.73m^2, p=0.195) (Figure 3A). Pre-emptively treated patients who did not develop renal flare showed better eGFR slope (+0.54±0.43 ml/min/1.73m^2/year) compared with untreated patients with or without subsequent renal flare (-2.11±0.50 and -1.00±0.33 ml/min/1.73m^2/year respectively, p=0.001 and 0.012). Slope of eGFR over time was similar between pre-emptively treated patients without or with subsequent renal flares (+0.54±0.43 and -2.07±1.69 mL/min/1.73m^2 per year respectively, p=0.130) (Figure 3B). The 5-year renal survival rate was 86% in pre-emptively treated patients with renal flare and 100% in those without renal flare. Corresponding rates were 100% and 86% respectively in untreated controls (p>0.05 for both).

Adverse Events

The adverse events were summarized (Table 3). Hospitalization and infection rates did not differ between the pre-emptive treatment and the untreated groups ($p>0.05$ for all). All episodes of infection were successfully managed with appropriate anti-microbials and had not resulted in any mortality. More gastrointestinal disturbance was noted in patients who received pre-emptive treatment (5 episodes vs. 1 episode in the untreated group, $p=0.031$), and all were related to MMF and resolved with dose reduction. None of the patients developed new onset diabetes or worsening of hypertension.

Discussion

Since relapses are common in the natural disease course of LN maintenance immunosuppression is given to LN patients for variable durations. Not uncommonly during the long-term maintenance phase patients develop ASR. How ASR should be managed is a clinically pertinent question that remains unanswered. Previous studies on pre-emptive increase in corticosteroid dose in the face of serological activity involved relatively few patients with short follow-up, and most patients were treated with low-dose corticosteroids with or without AZA[16, 17]. The impact of pre-emptive treatment on long-term flare risk and renal outcomes was not examined. An important finding from the present study was that ASR when left untreated was associated with a considerable risk of renal flares, which was over 30% in the subsequent 24 months. Furthermore, approximately 80% of the renal relapses were severe proliferative LN which could portend an unfavorable long-term prognosis[23]. While the risk of clinical flares following ASR seems significant, it is prudent to minimize the potential adverse effects of increasing immunosuppression. We therefore examined whether a moderate increase in the dose of conventional immunosuppressive drugs would be able to reduce the flare rate without leading to excessive treatment-associated adverse effects. The data suggested that this approach, with the drug dosing adopted in our protocol being approximately half of the dose used for the treatment of an active nephritic flare, may be effective in reducing the occurrence of subsequent renal flares, and thereby reduce the negative impact of renal flares on long-term renal survival.

Selection bias is a potential confounder in retrospective studies. The data suggested that the pre-emptive treatment group was serologically more active than the untreated group as indicated by

the lower level of complements. It remained possible that the pre-emptive group, with lower serum complements, renders it more worrisome for relapse and thus prompted the attending physician to initiate treatment. Despite the more active serology, the renal flare rate was lower in the pre-emptive treatment group, which lent additional support to the efficacy of intervention. Up to 90% of pre-emptively treated patients remained relapse-free after 24 months, which was significantly superior to controls. The sustained effect on relapse prevention might also be related to the gradual tapering schedule of corticosteroids compared with previous reports[16], and also the dosage increase in concomitant immunosuppressive medications such as MMF and AZA. The improvement of serological markers only in the intervention group was consistent with the treatment effect. Of interest was the lack of impact of pre-emptive treatment on extra-renal flares. Other investigators have also reported that a moderate increase of corticosteroid dose alone might be ineffective in preventing arthritic and cutaneous flares[16]. The absence of treatment effect could be related to the overall low incidence of extra-renal flares in our patients, or differences in pathogenic mechanisms between renal and non-renal lupus.

Repeated renal flares lead to cumulative attrition of nephron mass and progressive reduction of renal reserve that results in unfavorable long-term renal survival[8]. Our data suggested that pre-emptive treatment of ASR could benefit long-term renal preservation through the prevention of LN flares. While the two groups had similar eGFR at the time of ASR, the pre-emptive treatment group showed significantly better eGFR after 5 years, and patients without subsequent renal flare showed stable eGFR over time.

It could be challenging to decide on the immunosuppressive dose that could confer efficacy while minimizing potential side-effects. The data showed that the drug doses chosen in the pre-emptive protocol were relatively safe, which is important in informing future prospective trials. With regard to frequency, the incidence rate of infections was similar between the pre-emptive group and controls. With regard to severity, the infections that occurred in the pre-emptive group were relatively mild and responded to antimicrobials. More gastrointestinal disturbance was noted in the pre-emptive group which could be related to the increased dose of MMF or AZA. Notwithstanding, since cumulative corticosteroid exposure correlated with damage accrual, the impact of pre-emptive treatment on long-term toxicities such as osteoporosis and cardiovascular risk can only be determined with long-term follow-up [24].

Conclusion

Pre-emptive immunosuppressive treatment with moderate increase of immunosuppression for ASR that occurred in LN patients receiving maintenance immunosuppressive treatment may be effective in preventing renal flares thus contributing to the long-term preservation of renal function, and should be further investigated with prospective randomized control trials.

Acknowledgement

N. A.

Conflict of Interest statement

The results presented in this paper have not been published previously in whole or part, except in abstract format. The authors declared no conflict of interest.

Funding statement

This project did not receive any funding support.

References

1. Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. Nephrol Dial Transplant 2012;27:3248-3254.

2. Bomback AS, Appel GB. Updates on the treatment of lupus nephritis. J Am Soc Nephrol 2010;21:2028-2035.

3. Saxena R, Mahajan T, Mohan C. Lupus nephritis: current update. Arthritis Res Ther 2011;13:240.

4. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64:797-808.

5. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771-1782.

6. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guidelines for Glomerulonephritis. Kidney Int Suppl 2012;2:139-274.

7. Mok CC, Yap DY, Navarra SV, et al. Overview of lupus nephritis management guidelines and perspective from Asia. Nephrology 2014;19:11-20.

8. Parikh SV, Nagaraja HN, Hebert L, Rovin BH. Renal flare as a predictor of incident and progressive CKD in patients with lupus nephritis. Clin J Am Soc Nephrol 2014;9:279-284.

9. Gripenberg M, Helve T. Outcome of systemic lupus erythematosus. A study of 66 patients over 7 years with special reference to the predictive value of anti-DNA antibody determinations. Scand J Rheumatol 1991;20:104-109.

10. ter Borg EJ, Horst G, Hummel EJ, Limburg PC, Kallenberg CG. Measurement of increases in anti-double-stranded DNA antibody levels as a predictor of disease exacerbation in systemic lupus erythematosus. A long-term, prospective study. Arthritis Rheum 1990;33:634-643.

11. Esdaile JM, Abrahamowicz M, Joseph L, et al. Laboratory tests as predictors of disease exacerbations in systemic lupus erythematosus. Why some tests fail. Arthritis Rheum 1996;39:370-378.

12. Pan N, Amigues I, Lyman S, et al. A surge in anti-dsDNA titer predicts a severe lupus flare within six months. Lupus 2014;23:293-298.

13. Austin HA, 3rd, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986;314:614-619.

14. Gourley MF, Austin HA, 3rd, Scott D, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996;125:549-557.

15. Yap DY, Ma MK, Mok MM, Tang CS, Chan TM. Long-term data on corticosteroids and mycophenolate mofetil treatment in lupus nephritis. Rheumatology (Oxford) 2013;52:480-486.

16. Tseng CE, Buyon JP, Kim M, et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:3623-3632.

17. Bootsma H, Spronk P, Derksen R, et al. Prevention of relapses in systemic lupus erythematosus. Lancet 1995;345:1595-1599.

18. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 2011;365:1886-1895.

19. Chan TM, Tse KC, Tang CS, Mok MY, Li FK. Long-term study of mycophenolate mofetil as continuous induction and maintenance treatment for diffuse proliferative lupus nephritis. J Am Soc Nephrol 2005;16:1076-1084.

20. Chan TM, Li FK, Tang CS, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000;343:1156-1162.

21. Ruperto N, Hanrahan LM, Alarcon GS, et al. International consensus for a definition of disease flare in lupus. Lupus 2011;20:453-462.

22. Armitage P. Statistical methods in medical research. Malden, Massachusetts, USA: Blackwell Science, 2002.

23. Appel GB, Cohen DJ, Pirani CL, Meltzer JI, Estes D. Long-term follow-up of patients with lupus nephritis. A study based on the classification of the World Health Organization. Am J Med 1987;83:877-885.

24. Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. Arthritis Rheum 2000;43:1801-1808.

Table 1. Clinical characteristics of 98 lupus nephritis patients with asymptomatic serological reactivation.

	Pre-emptive treatment (n=38)	**No pre-emptive treatment (n=60)**	**P-value**
Sex (M/F)	4/34	9/51	0.525
Age (year)	40.0±11.9	40.5±12.1	0.838
Duration of SLE (year)	21.6±7.4	21.8±7.2	0.869
SLE onset before 16 years old	4 (10.5%)	10 (16.7%)	0.397
Class of lupus nephritis on initial presentation			
Class III or IV	23(60.5%)	40 (66.7%)	0.536
Class III/IV±V	3 (7.9%)	8 (13.3%)	0.521
Class V	8 (21.1%)	10 (16.7%)	0.585
Class II	4 (10.5%)	2 (3.3%)	0.203
History of prior renal flares			
None	6 (15.8%)	18 (30.0%)	0.111
One renal flare	22 (57.9%)	25 (41.7%)	0.117
More than one renal flare	10 (26.3%)	17 (28.3%)	0.828
Maintenance treatment			
PRED alone	19 (50.0%)	32 (53.3%)	0.807
PRED+MMF	11 (28.9%)	9 (15.0%)	0.104
PRED+AZA	8 (21.1%)	19 (31.7%)	0.232
Adjunctive treatment			
Anti-malarials	23 (60.5%)	30 (50.0%)	0.410
ACEI or ARB	26 (68.4%)	42 (70.0%)	0.870
Laboratory parameters during asymptomatic serological reactivation			
Baseline serum creatinine (μmol/L)	79.2±31.5	82.7±38.8	0.188
Baseline Proteinuria (g/d)	0.27±0.16	0.40±0.51	0.862
Baseline Anti-dsDNA (IU/mL)	191.8±111.2	153.1±75.2	0.120
Baseline C3 (mg/dL)	55.5±25.1	76.2±22.3	<0.001
SELENA-SLEDAI score	3.1±1.3	2.9±1.1	0.469

AZA=azathioprine; MMF=mycophenolate mofetil; PRED=prednisolone

Table 2. Impact of pre-emptive immunosuppressive treatment given for asymptomatic serological reactivation on the incidence of subsequent renal flares.

	Pre-emptive treatment (53 episodes)	**No pre-emptive treatment (85 episodes)**
Renal flare within 6 months	0 (0%)	11 (12.9%)
No renal flare within 6 months	53 (100%)	74 (87.1%)
Renal flare within 12 months	2 (3.8%)	24 (28.2%)
No renal flare within 12 months	51 (96.2%)	61 (71.8%)
Renal flare within 24 months	5 (9.4%)	27 (31.8%)
No renal flare within 24 months	48 (90.6%)	58 (68.2%)

Table 3. Adverse events experienced by lupus nephritis patients who have or have not received pre-emptive immunosuppressive treatment for asymptomatic serological reactivation.

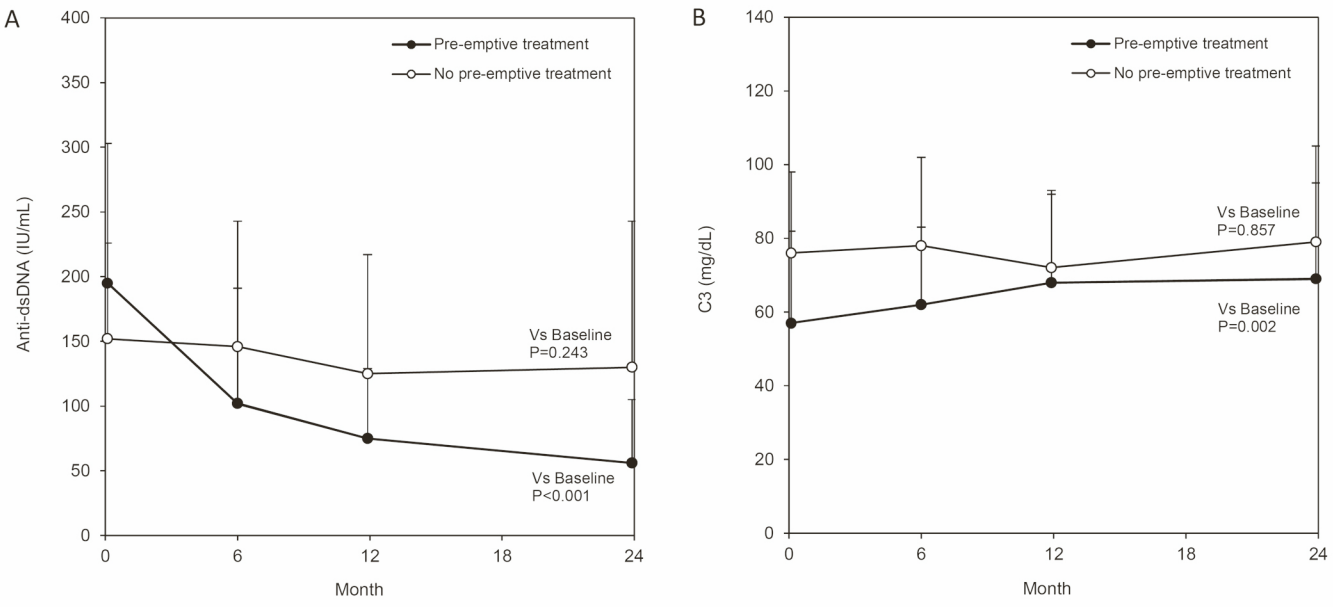
	Pre-emptive treatment (53 episodes)	**No pre-emptive treatment (85 episodes)**	**p-value**
Incidence rate of hospitalization (episode/patient-month)	0.004	0.003	0.483
Infection (episodes)	11	8	0.076
Upper respiratory infection	3	3	
Pneumonia	1	1	
Facial wart	1	1	
Herpes zoster	2	2	
Urinary tract infection	4	1	
Gastrointestinal disturbance (episodes)	5	1	0.031

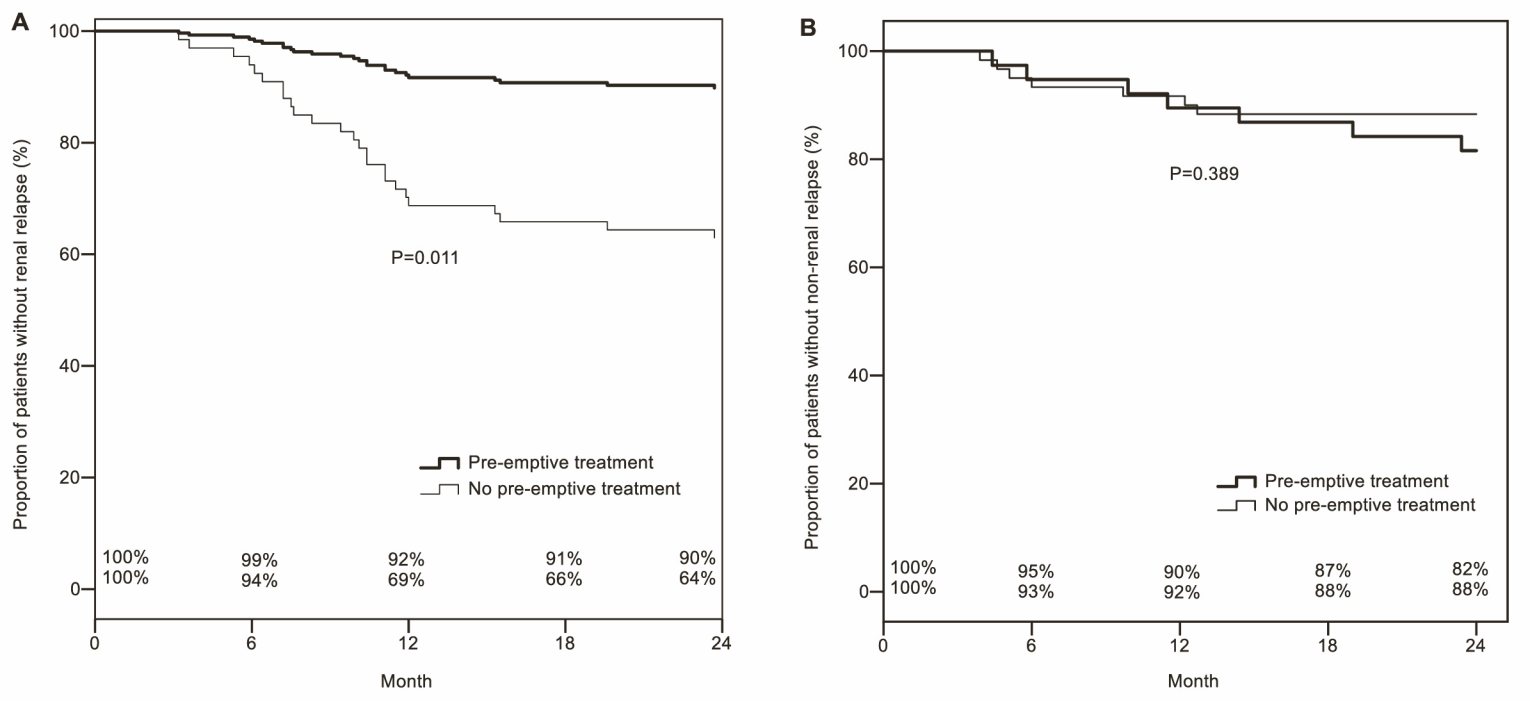
Figure Legends

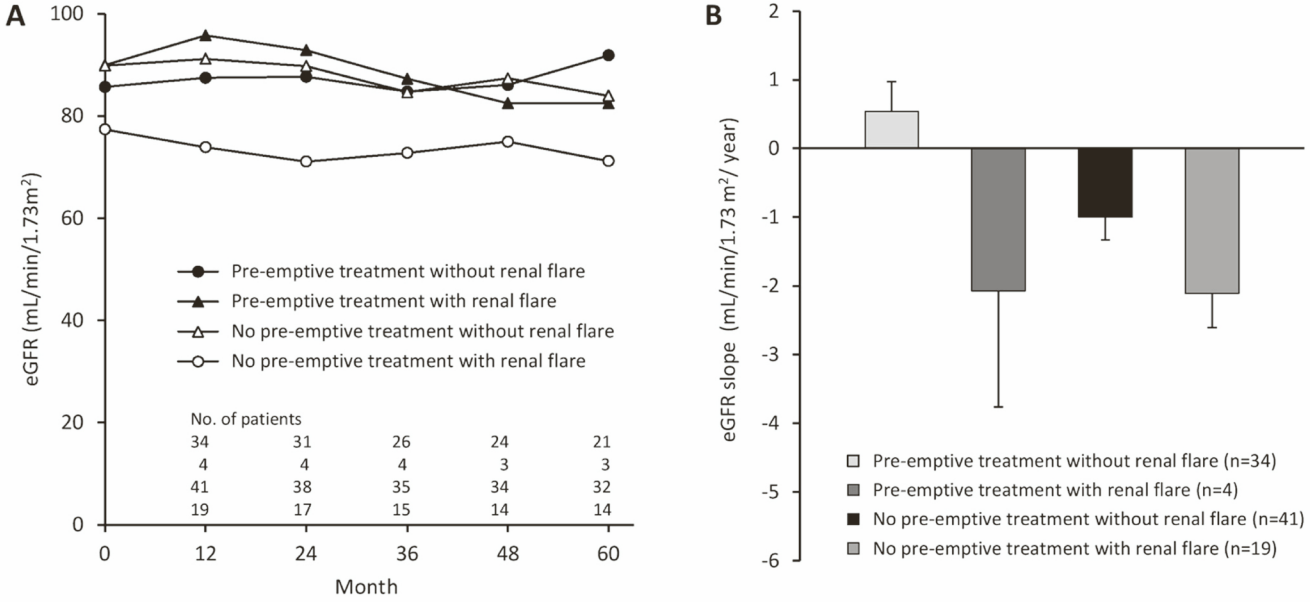
Figure 1. Serial changes in (A) anti-dsDNA and (B) C3 levels in lupus nephritis patients who had or had not received pre-emptive immunosuppressive treatment for asymptomatic serological reactivation.

Figure 2. Impact of pre-emptive immunosuppressive treatment for asymptomatic serological reactivation on survival free of (A) renal and (B) extra-renal relapse in lupus nephritis patients.

Figure 3. (A) Change of eGFR over time and (B) slope of eGFR over time in lupus nephritis patients who had or had not received pre-emptive immunosuppressive treatment for asymptomatic serological reactivation.


A
Anti-dsDNA (IU/mL)
400
350
300
250
200
150
100
50
0
Pre-emptive treatment
No pre-emptive treatment
Vs Baseline
P=0.243
Vs Baseline
P<0.001
0
6
12
18
24
Month
B
C3 (mg/dL)
140
120
100
80
60
40
20
0
Pre-emptive treatment
No pre-emptive treatment
Vs Baseline
P=0.857
Vs Baseline
P=0.002
0
6
12
18
24
Month


A
Proportion of patients without renal relapse (%)
100
80
60
40
20
0
P=0.011
Pre-emptive treatment
No pre-emptive treatment
100%
100%
99%
94%
92%
69%
91%
66%
90%
64%
0
6
12
18
24
Month
B
Proportion of patients without non-renal relapse (%)
100
80
60
40
20
0
P=0.389
Pre-emptive treatment
No pre-emptive treatment
100%
100%
95%
93%
90%
92%
87%
88%
82%
88%
0
6
12
18
24
Month


A
100
80
60
40
20
0
eGFR (mL/min/1.73m²)
Pre-emptive treatment without renal flare
Pre-emptive treatment with renal flare
No pre-emptive treatment without renal flare
No pre-emptive treatment with renal flare
No. of patients
34 31 26 24 21
4 4 4 3 3
41 38 35 34 32
19 17 15 14 14
0 12 24 36 48 60
Month
B
2
1
0
-1
-2
-3
-4
-5
-6
eGFR slope (mL/min/1.73 m²/ year)
Pre-emptive treatment without renal flare (n=34)
Pre-emptive treatment with renal flare (n=4)
No pre-emptive treatment without renal flare (n=41)
No pre-emptive treatment with renal flare (n=19)