Longterm Data on Disease Flares in Patients with Proliferative Lupus Nephritis in Recent Years

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ABSTRACT. ***Objective.*** To examine the disease flare rate in lupus nephritis (LN), focusing on renal flares, and the factors associated with relapse risk in recent years.

Methods. We analyzed data on 139 Chinese patients with class III/IV ± V LN diagnosed from January 1983 to December 2013. We also compared data before and after 1998, when maintenance immunosuppression was changed from azathioprine (AZA) to mycophenolic acid (MPA).

Results. Over 112.5 ± 88.4 months, 135 episodes of renal flare occurred, giving a flare rate of 0.108 episodes per patient-year. The renal relapse-free survival rate was 96%, 90%, 86%, 80%, 69%, and 57% after 1, 2, 3, 4, 5, and 10 years, respectively, calculated from the start of induction treatment. Reduced risk of flare was associated with MPA maintenance (OR 0.314, 95% CI 0.099–0.994, p = 0.049), complete remission after induction immunosuppression (OR 0.329, 95% CI 0.133–0.810, p = 0.016), and diagnosis after 1998 (OR 0.305, 95% CI 0.133–0.700, p = 0.005). Relapse-free survival was significantly better in patients treated with prednisolone and MPA as maintenance immunosuppression (91% after 5 yrs and 83% after 10 yrs, respectively) compared with prednisolone and AZA (70% and 52%, respectively, p = 0.044). LN diagnosed in 1998–2013 showed 5-year and 10-year relapse-free survival rates of 93% and 86%, respectively, compared with 81% and 66%, respectively (p = 0.017) for LN that presented in 1983–1997.

Conclusion. Our data show a relatively low flare rate for LN in the more recent era, attributed to effective induction of immunosuppression and MPA as maintenance treatment. (First Release July 1 2017; J Rheumatol 2017;44:1375–83; doi:10.3899/jrheum.170226)

Key Indexing Terms:
RELAPSE LUPUS NEPHRITIS MYCOPHENOLIC ACID

Lupus nephritis (LN) is an important cause of renal failure in Asian countries[1]. Advances in immunosuppressive therapies over the past few decades have led to improvements in short-term and longterm clinical outcomes[2,3,4,5,6,7,8,9,10,11,12]. However, renal flares portend unfavorable renal survival, and the prevention of disease flares remains challenging[1,13,14,15]. Reported rates of disease flares ranged from 20% to 40% at 5 years. Factors associated with increased risk of flares were African American descent, younger age at presentation, failure to achieve complete remission, and persistent serological and histological activity[16,17,18,19,20,21,22]. However, much of the data came from older studies in which cyclophosphamide (CYC) was the predominant induction (and sometimes maintenance) immunosuppressive treatment together with corticosteroids[13,14,23,24]. Treatment of severe LN has evolved considerably over the past few decades, and mycophenolic acid (MPA) is increasingly used both for active disease and for longterm maintenance. Improvements in short- and medium-term outcomes due to advances in immunosuppressive regimens and general medical care could affect the disease flare rate, especially because patients survive longer now compared with earlier days[21,25,26,27,28]. Further, racial and/or ethnic variations have been demonstrated in LN regarding response to treatment and also renal flare rate, and there are data to suggest higher flare rates in African Americans and Hispanics compared with whites[16,20,29]. There is also relatively little information on Asian patients. One previous study reported that the cumulative risk of renal flare was 28% at 36 months and 44% at 60 months in Asian patients who received CYC-azathioprine (AZA) as induction-maintenance treatment[30]. Given this backdrop of confounding information, and the considerable change of immunosuppressive treatment over the past few decades, there is insufficient knowledge on disease flare rate and the risk factors based on longterm followup data in the current era.

Low-dose prednisolone (PRED) with either AZA or MPA for variable durations is the mainstay of maintenance immunosuppressive regimens to prevent disease flares in patients with LN, but the comparative efficacy of AZA and

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MPA remains controversial. While the Aspreva Lupus Management Study (ALMS) showed superiority of MPA over AZA in preventing disease flares during a followup period of 36 months in patients who had responded to induction immunosuppression with corticosteroids and either CYC or MPA, results from the MAINTAIN study showed similar efficacy between MPA and AZA, albeit in a much smaller number of patients[31,32]. That the MAINTAIN trial included primarily white patients while ALMS included 43% white, 33% Asian, and 24% patients of African or Hispanic descent was another factor that might have contributed to the different conclusions in the 2 studies. The objective of our study was to examine the disease flare rate focusing on renal flares, and the factors associated with relapse risk, in the present era.

MATERIALS AND METHODS

Patients. The case records were reviewed of all patients with kidney biopsy showing class III/IV ± V LN from January 1983 to December 2013 and under the care of the systemic lupus erythematosus (SLE) clinic at Queen Mary Hospital, Hong Kong. We excluded patients with pure class V LN from analysis because the natural history of the clinical course is different from that of proliferative LN. All were "incident" patients referred to our clinic for management of LN. The diagnosis of SLE was according to the 1982 revised American College of Rheumatology classification[33], and the histological classification of biopsy findings was based on the 1982 World Health Organization classification for LN until 2004, when the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification was adopted[34]. All renal biopsies were reported by the same renal pathologist, and biopsies prior to 2004 were reviewed and reclassified according to the ISN/RPS 2003 classification. This retrospective study was done in accordance with the Declaration of Helsinki and was approved by the University of Hong Kong/Hong Kong Hospital Authority Wester Cluster Institutional Review Board (approval number: UW11-115).

Immunosuppressive treatment and followup schedule. Patients with class III/IV ± V LN in our center were treated with corticosteroid and either CYC or MPA (available since 1998) under standard treatment and tapering protocols[2]. PRED was started at 0.8 mg/kg/d and reduced by 5 mg/d every 2 weeks to reach 5–7.5 mg/d at 6 months. CYC was given orally at 1.5–2 mg/kg/d for 6 months. MPA treatment was started at 1 g twice daily of mycophenolate mofetil (MMF) or 720 mg twice daily of MPA sodium and the dose remained unchanged for 6 months. Anti-CD20 therapy was not used in our center because it was not a reimbursed item. Patients who could not tolerate MMF at 1.5 g/d or MPA sodium at 1080 mg/d during the induction phase were excluded from analysis (6 patients) because these patients did not have exposure to MPA comparable to the other patients. Some required a change to other immunosuppressive medications because of persistent gastrointestinal intolerance. The period of induction immunosuppression was defined as the first 6 months. Initial maintenance immunosuppression (i.e., commencing at the seventh month after starting induction therapy) consisted of low-dose PRED at < 5 mg/d and either MPA or AZA. The target dose of MMF was 1.5 g per day during the first 6 months of maintenance immunosuppression, 1.25 g per day during the subsequent 6 months, and 1–1.25 g per day up to the end of the second year after diagnosis. The same rate of dose tapering was adopted in patients treated with MPA sodium. The dose of AZA was 2 mg/kg/d during the first 6 months of maintenance immunosuppression, and 1.25 to 1.5 mg/kg/d during the second year after diagnosis. Subsequent rate of dose tapering for the immunosuppressive medications varied between patients depending on clinical stability and prior history of disease flares, and were subject to clinicians' discretion. All patients were treated with hydroxychloroquine 200–400 mg/d and angiotensin-converting enzyme/angiotensin receptor blockers unless contraindicated. Patients were seen at 2- to 14-week intervals depending on their clinical status. The following clinical variables were monitored at every visit: urinalysis, blood pressure, complete blood picture, renal and liver biochemistry, anti-dsDNA (measured by ELISA; BioRad), C3 levels (measured by nephelometry; Beckman Coulter), and proteinuria. Glucose and lipid profile were measured every 6 months. Only patients with followup of at least 12 months from commencement of induction immunosuppressive treatment were included in our study.

Renal flare in patients who had responded to immunosuppressive treatment for active LN was defined as increase in urine protein to over 1 g/24 h in patients with proteinuria < 0.5 g/24 h or increase of urine protein by 1 g/24 h or more in patients with proteinuria above 0.5 g/24 h, and/or increase in serum creatinine by 15% or more compared with stable level during remission, with or without serological activity. All renal flares were confirmed with renal biopsy unless patients had contraindications for biopsy.

Complete renal remission (CR) was defined as reduction in urine protein excretion to < 0.5 g/day together with improved or stable renal function, the latter indicated by a serum creatinine level not higher than 115% of baseline value. Partial renal remission was denoted by a decrease in urine protein excretion of ≥ 50% and in the nonnephrotic range, together with improved or stable renal function. Extrarenal flares were defined as measurable increases in disease activity (involving new or worsened clinical/laboratory findings) in 1 or more organ systems other than the kidneys that necessitated an increase in the daily dose of PRED by 10 mg for more than 2 weeks and/or an increase in the dose of concomitant immunosuppressive medication[35]. Factors associated with renal and extrarenal flares were sought, and data on LN diagnosed before or after 1998 were compared, because standard initial maintenance therapy was AZA in the former period and MPA in the latter period, both combined with low-dose PRED. We also compared the characteristics of patients who relapsed within or beyond 3 years after the last nephritic episode (referred to as early relapses and late relapses, respectively).

Statistical analysis. Categorical variables were expressed as frequencies (percentages). Continuous variables were expressed as mean (SD) or median (range), and compared with the Student t test or Mann-Whitney U test, where appropriate. The flare rates were expressed as episodes per patient-years, and the flare rates between different eras were compared with Poisson regression adjusted for total patient-years at risk. The factors associated with renal flares were assessed by univariate then multivariate analysis. The relapse-free survival rates were estimated by Cox-regression model. All statistical analyses were performed by SPSS version 18. P values of 0.05 (2-tailed) were considered statistically significant.

RESULTS

The study included 139 patients with proliferative LN (Table 1). A total of 135 episodes of renal flare and 29 episodes of extrarenal flare occurred during a mean followup of 115.2 ± 90.2 months. Among the 135 episodes of renal flares, 71 episodes (52.6%) were class IV, 17 episodes (12.6%) were class III, and 47 episodes (34.8%) were class III/IV ± V, and all were biopsy-proven. The 29 episodes of extrarenal flare included 23 (79.3%) cutaneous/articular flares, 4 (13.8%) hematological flares, and 2 (6.9%) cerebral SLE flares. The durations of MPA and AZA treatment were 58.6 ± 46.1 months and 70.4 ± 61.2 months, respectively.

The overall renal flare rate was 0.108 relapse per patient-year. The renal relapse-free survival rate was 96%, 90%, 86%, 80%, 69%, and 57% after 1, 2, 3, 4, 5, and 10

Table 1. Clinical characteristics of 139 patients with class III/IV ± V lupus nephritis (LN).

Characteristics	Value
Age, yrs, mean (SD)	34.9 (11.4)
Sex, n (%)	
Female	122 (87.8)
Male	17 (12.2)
Duration of followup, mos, mean (SD)	115.2 (90.2)
Class of LN at presentation, n (%)	
III	14 (10.1)
IV	92 (66.2)
III + V or IV + V	33 (23.7)
Baseline laboratory measures, mean (SD)	
Urinary protein excretion, g/d	4.6 (3.6)
Serum creatinine, mol/l	105.8 (57.8)
Serum C3, mg/dl	51.4 (27.2)
Serum anti-dsDNA, IU/ml	160.8 (194.0)

Normal ranges: anti-dsDNA, < 30 IU/ml; C3, 76–150 mg/dl.

years, respectively, calculated from the start of induction treatment. The renal flare rate was significantly lower in the period 1998 to 2013 compared with 1983 to 1997, at 0.085 episode per patient-year (95% CI 0.062–0.114) and 0.125 flare per patient-year (95% CI 0.101–0.154), respectively (p = 0.034). CR rates were similar for the 2 periods (47% and 49%, respectively; p = 0.735).

Univariate analysis showed that factors associated with lower risk of renal relapse included older age (OR 0.967, 95% CI 0.942–0.992; p = 0.011), serum creatinine at presentation (OR 0.991, 95% CI 0.985–0.997; p = 0.004), induction treatment with MPA (OR 0.365, 95% CI 0.165–0.870; p = 0.013), maintenance treatment with MPA (OR 0.319, 95% CI 0.154–0.664; p = 0.002), achievement of CR (OR 0.473, 95% CI 0.251–0.892; p = 0.021), and the later treatment era 1998–2013 (OR 0.284, 95% CI 0.156–0.518; p < 0.001; Table 2). Multivariate analysis showed that the remaining factors associated with significantly lower renal flare rate were higher serum creatinine at presentation (OR 0.989, 95% CI 0.981–0.997; p = 0.006), achievement of CR (OR 0.329, 95% CI 0.133–0.810; p = 0.016), maintenance with MPA (OR 0.314, 95% CI 0.099–0.994; p = 0.049), and later treatment era (OR 0.305, 95% CI 0.133–0.700; p = 0.005). For extrarenal flares, only higher levels of C3 at presentation were associated with reduced risk of flare (OR 0.963, 95% CI 0.934–0.994, p = 0.021). The choice of immunosuppression did not appear to make a significant difference in the risk of extrarenal flares (p > 0.05 for all; Table 3). We found no association between the age of onset (OR 1.0, 95% CI 0.9–1.1; p = 0.938) and anti-ENA status (OR 1.4, 95% CI 0.6–3.4; p = 0.41) with relapse.

Patients treated with MPA as maintenance immunosuppression had superior relapse-free survival rates compared to patients taking AZA maintenance (91% after 5 yrs and 83% after 10 yrs, vs 70% and 52%, respectively; p = 0.044; Figure 1A). Also, the relapse-free survival rate was higher in the post-MPA era (1998–2013; 93% after 5 yrs and 86% after 10 yrs, vs 81% and 66%, respectively, in 1983–1997, p = 0.017; Figure 1B). Renal survival rate was not related to the number of flares among patients who experienced no flare, 1 flare, or > 1 flare (10–yr renal survival rate of 95.0%, 97.1%, and 95.7% for subjects with no, 1, or > 1 flare, and 20–yr renal survival rate of 95.0%, 88.3%, and 80.6%, respectively; p > 0.05 among the 3 groups; Figure 2).

There were 56 episodes of early relapse, defined as occurring within the first 3 years after induction treatment, and 79 episodes of late relapse (Table 4). Prior CR was present in 44.3% of late relapse and 25.0% of early relapse (p = 0.022). Serum creatinine level at diagnosis of relapse was higher in late relapses compared with early relapses (104.2 ± 65.2 μmol/l vs 86.2 ± 26.2 μmol/l; p = 0.029). The dose of PRED at the time of flare was higher in early relapse (8.9 ± 3.0 mg/d vs 6.9 ± 2.8 mg/d in late relapse; p = 0.002). Fourteen patients had late relapse after complete discontinuation of maintenance immunosuppressive agents (12 were taking AZA previously and 2 were taking MPA). The occurrence of late relapse was less frequent in 1998–2013 compared with 1983–1997, with incidence rates of 0.043 episodes/patient-year (95% CI 0.025–0.060) and 0.079 episodes/patient-year (95% CI 0.058–0.099), respectively (p = 0.013). There was no difference between the 2 time periods regarding the incidence rate of early relapse, at 0.043 episodes/patient-year (95% CI 0.025–0.060) for 1998–2013 and 0.046 episodes/patient-year (95% CI 0.031–0.062) for 1983–1997 (p = 0.753).

DISCUSSION

Our data show that the risk of renal flare in patients with a history of LN has decreased considerably over the past few decades, and the reduction of flare rate is associated with the use of MPA as maintenance immunosuppression. All the patients included in our study had prior biopsy-proven severe LN, but the overall renal flare rate was relatively low and compared favorably to data presented in earlier reports[16,18,20,29,36]. Our data highlight the importance of MPA maintenance and the achievement of satisfactory renal response with induction immunosuppression as important factors for the low flare rate. Maintenance therapy with MPA was associated with 5- and 10-year relapse-free survival rates of 95% and 89%, which was significantly better than maintenance with AZA. The data from ALMS, based on 36 months of followup after the induction phase, demonstrated that maintenance immunosuppressive treatment with MPA was superior to AZA in reducing disease flares, including renal flares[31]. We previously also reported on the tolerability and efficacy of MPA as longterm maintenance immunosuppression, with a followup of 91.9 ± 47.7 months[37]. We suggest that CYC should be considered in patients presenting with low glomerular filtration rate (GFR) due to severe active

Table 2. Predictors of renal flares in 139 patients with lupus nephritis by univariate and multivariate analysis.

Predictor Variables	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Sex (male vs female)	1.611 (0.642–4.040)	0.310	1.395 (0.449–4.338)	0.565
Age	0.967 (0.942–0.992)	0.011	1.000 (0.968–1.034)	0.986
Baseline laboratory measures				
Serum creatinine	0.991 (0.985–0.997)	0.004	0.989 (0.981–0.997)	0.006
Urinary protein excretion	1.009 (0.913–1.116)	0.861	1.055 (0.939–1.185)	0.370
Anti-dsDNA level	1.001 (1.000–1.003)	0.137	1.002 (1.000–1.004)	0.056
C3 level	0.998 (0.985–1.012)	0.787	0.994 (0.979–1.009)	0.402
Induction treatment †				
PRED + CYC, n = 64	1.000	—	1.000	—
PRED + MPA, n = 75	0.365 (0.165–0.870)	0.013	1.775 (0.622–5.062)	0.283
Maintenance treatment ††				
PRED + AZA, n = 85	1.000	—	1.000	—
PRED + MPA, n = 54	0.319 (0.154–0.664)	0.002	0.314 (0.099–0.994)	0.049
Use of antimalarial	0.672 (0.253–1.785)	0.426	0.588 (0.189–1.828)	0.359
History of renal relapse	0.703 (0.385–1.286)	0.253	0.975 (0.464–2.048)	0.946
Treatment outcome#				
Complete renal remission	0.473 (0.251–0.892)	0.021	0.329 (0.133–0.810)	0.016
Partial renal remission	2.111 (0.909–4.901)	0.082	2.032 (0.737–5.601)	0.170
Treatment era				
Before MPA available (i.e., 1983–1997)	1.000	—	1.000	—
After MPA available (i.e., 1998–2013)	0.284 (0.156–0.518)	< 0.001	0.305 (0.133–0.700)	0.005

†PRED + CYC as reference group. †† PRED + AZA as reference group. # Treatment failure as reference group. AZA: azathioprine; CYC: cyclophosphamide; MPA: mycophenolic acid; PRED: prednisolone.

Table 3. Predictors of extrarenal flares in 139 patients with lupus nephritis by univariate and multivariate analysis.

Predictor Variables	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Sex (male vs female)	1.608 (0.563–4.595)	0.375	1.140 (0.214–6.070)	0.878
Age	0.962 (0.925–1.001)	0.056	0.973 (0.926–1.021)	0.264
Baseline laboratory measures				
Serum creatinine	0.996 (0.988–1.005)	0.408	1.002 (0.991–1.014)	0.678
Urinary protein excretion	0.926 (0.804–1.066)	0.285	0.841 (0.663–1.065)	0.150
Anti-dsDNA level	1.002 (0.999–1.004)	0.160	1.001 (0.998–1.003)	0.636
C3 level	0.976 (0.955–0.998)	0.032	0.963 (0.934–0.994)	0.021
Induction treatment †				
PRED + CYC, n = 64	1.000	–	1.000	–
PRED + MPA, n = 75	1.385 (0.613–3.127)	0.433	3.832 (0.584–25.14)	0.162
Maintenance treatment ††				
PRED + AZA, n = 85	1.000	–	1.000	–
PRED + MPA, n = 54	1.080 (0.442–2.640)	0.866	0.637 (0.107–3.794)	0.621
Use of antimalarial	1.082 (0.302–3.881)	0.903	0.858 (0.138–5.334)	0.870
History of renal relapse	0.500 (0.229–1.089)	0.081	1.345 (0.422–4.283)	0.616
Treatment era				
1983–1997	1.000	–	1.000	–
1998–2013	1.004 (0.463–2.181)	0.991	0.490 (0.112–2.141)	0.343

†PRED + CYC as reference group. †† PRED + AZA as reference group. AZA: azathioprine; CYC: cyclophosphamide; MPA: mycophenolic acid; PRED: prednisolone.

disease, often associated with much change in the kidney biopsy, in view of the aggressive disease and the potent immunosuppressive effect of CYC[38]. However, the racial origin of patients should be taken into account in the choice of therapy, because CYC-based induction therapy was associated with an inferior response rate (irrespective of presenting renal function) compared with MMF, as demonstrated in ALMS. While subgroup analysis of patients in ALMS who presented with estimated GFR (eGFR) below 30 ml/min suggested a faster improvement of eGFR in patients treated with MMF compared with CYC, the sample size was small (20 MMF and 12 CYC) and the renal response rate did

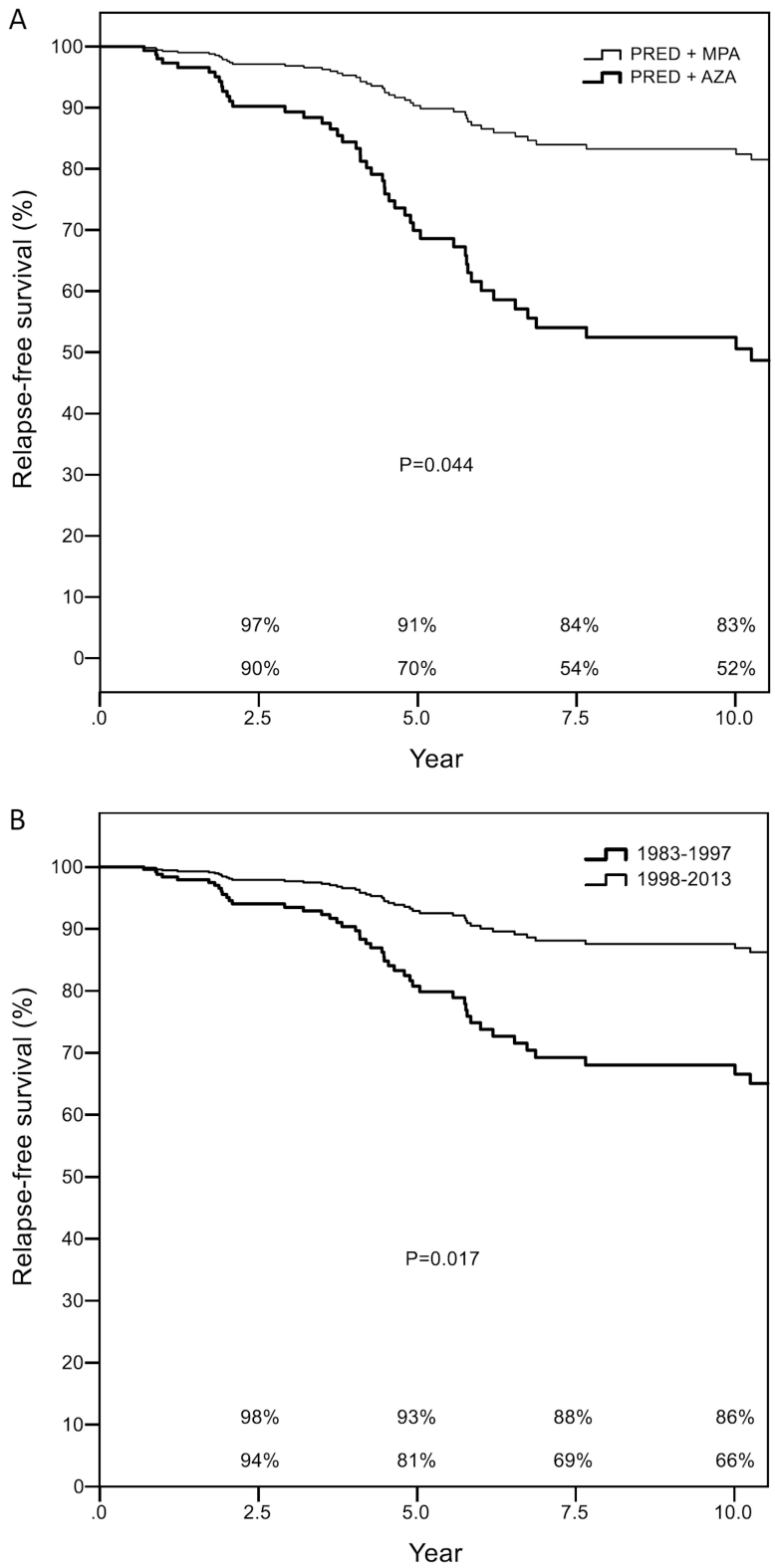

Figure 1. Relapse–free survival of (A) patients with lupus nephritis who received prednisolone (PRED) plus mycophenolic acid (MPA) or PRED plus azathioprine (AZA) as maintenance immunosuppression; (B) patients with lupus nephritis according to time of presentation (1983–1997 or 1998–2013).

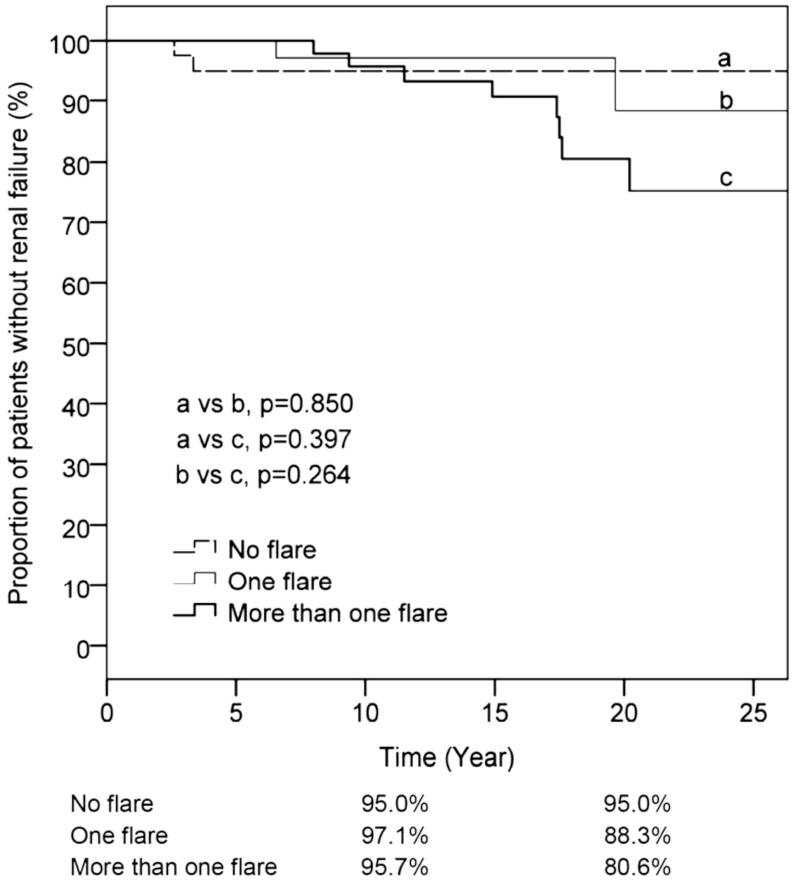

Figure 2. Renal survival in patients with lupus nephritis according to the number of episodes of renal flare.

not differ between the 2 groups[39]. In our present analysis, we did not observe any difference in flare rate between patients treated with various induction immunosuppressive agents. Importantly, more effective prevention of renal flares is beneficial to longterm renal survival because repeated renal flares result in progressive attrition of nephron mass and reduction of renal reserve[15].

We found that achievement of CR after induction immunosuppression was associated with a lower risk of renal relapse compared with patients who failed to achieve a satisfactory treatment response, as in previous reports[16,21]. In this context, high response rates to induction immunosuppressive treatments including corticosteroids and either CYC or MPA have been reported in Chinese patients with LN[2,7,8]. We also observed that a higher serum creatinine level at presentation was associated with lower flare rates. One possible explanation is the immunosuppressive effect of chronic renal insufficiency[16,36,40]. The lack of relationship between renal survival rate and the number of flares could be attributed to the high efficacy of prompt induction therapy in Chinese patients, thus minimizing the amount of nephron loss. Nevertheless, the data do suggest a higher renal survival rate after 20 years in patients who did not experience any disease flare, and so the effect of flare number might become evident with a bigger sample size. An additional consideration is whether longterm treatment with MPA could have a separate beneficial effect on the progression of renal fibrosis, as suggested by *in vitro* and animal data[41,42,43,44,45]. Notwithstanding, we did not observe major differences in the histological features on repeat biopsies between patients treated with different maintenance agents. This is not surprising because renal fibrosis is a complex process that might be affected by various factors such as prior immunosuppressive treatments, previous renal inflammation, and blood pressure control.

It is of interest to note that late relapses seem to have become less frequent in the recent era of 1998–2013 compared with the earlier time frame of 1983–1997, while the results show that the choice of induction or maintenance therapy appears to have little effect on the timing of relapse. This would suggest that in the current era, with MPA being the predominant maintenance immunosuppressive treatment, when remission is achieved it is often well sustained. Nevertheless, one should also be cautious in the interpretation

Table 4. Clinical characteristics of early relapses (within 3 yrs) and late relapses (beyond 3 yrs) in 139 Chinese patients with lupus nephritis (LN).

Characteristics	Early Relapses, n = 56	Late Relapses, n = 79	p
Class of LN in preceding episode, n (%)			
Class IV	27 (48.2)	44 (55.7)	0.391
Class III	6 (10.7)	11 (13.9)	0.580
Class III + V or IV + V	23 (41.1)	24 (30.4)	0.199
Treatment outcome in preceding episode, n (%)			
Complete renal remission	14 (25.0)	35 (44.3)	0.022
Partial renal remission	33 (58.9)	56 (70.9)	0.149
Baseline laboratory measures, mean (± SD)			
Urine protein, g/d	4.4 ± 3.7	4.6 ± 3.0	0.188
Serum creatinine, μmol/l	86.2 ± 26.2	104.2 ± 65.2	0.029
Serum C3, mg/dl	50.7 ± 22.3	52.2 ± 23.6	0.593
Anti-dsDNA, IU/ml	183.8 ± 200.0	149.9 ± 184.7	0.207
Induction treatment used in preceding episode of LN, n (%)			
PRED + CYC	39 (69.6)	65 (82.3)	0.085
PRED + MPA	17 (30.4)	14 (17.7)	
Maintenance treatment used in preceding episode of LN, n (%)			
PRED + AZA	45 (80.4)	69 (87.3)	0.270
PRED + MPA	11 (19.6)	10 (12.7)	
Dose of treatment at relapse, mg/d, mean (± SD)			
PRED, mg/d	8.9 ± 3.0	6.9 ± 2.8	0.002
MPA, mg/d	1099.2 ± 675.6	1135.6 ± 534.8	0.895
AZA, mg/d	72.5 ± 24.2	70.7 ± 49.1	0.880

AZA: azathioprine; CYC: cyclophosphamide; MPA: mycophenolic acid; PRED: prednisolone.

of data, because the improved relapse rates in the latter era might also be related to advances in medical care such as increased use of renin-angiotensin blockers and hydroxychloroquine. We observed a relatively low incidence of nonrenal flares, which were not related to the type of induction or maintenance immunosuppression. In this regard, phenotypic segregation into renal versus extrarenal manifestations has been reported in Chinese patients with SLE and has been attributed to variations in genetic predisposition[46]. Our observation of different risk factors for renal and extrarenal relapses is in line with such a hypothesis, and requires further elucidation.

While relapses were associated with treatment noncompliance, this issue appeared to be less problematic in our locality (Chinese population in general); our outpatient attendance rates were over 99% and thus the effect of treatment noncompliance on disease relapse cannot be assessed in this cohort. Other potential confounders include changes in severity and outcome over time, especially the severity of disease at presentation, because earlier presentation is associated with more favorable response to therapy. Our present data showed similar levels of serum creatinine and proteinuria at presentation for the 2 time periods (serum creatinine 103.1 ± 63.1 μmol/l and 106.4 ± 60.9 μmol/l, and proteinuria 4.6 ± 3.6 g/d and 4.3 ± 3.5 g/d, for patients who presented in 1983–1997 and 1998–2013, respectively; p = 0.69 and 0.56, respectively, for the 2 periods), suggesting that the renal flares in the 2 periods were of similar severity. One should also appreciate that progress in general medical care might have resulted in an improvement in the outcome of patients with LN, but such a confounding effect has been minimized by adjustment for the treatment era in our multivariate analysis. In our study, 24-h urine protein excretion instead of spot urine-to-protein ratio was used to assess proteinuria because the latter was not available in the first period. While spot urine protein-to-creatinine ratio is definitely more convenient compared with 24-h urine collection, its accuracy in predicting the level of 24-h urine protein excretion is at best moderate despite a correlation between the 2 variables[47]. It should be noted that our study included only Chinese patients and so the results may not be extrapolated to other racial or ethnic groups, although the data from ALMS do suggest that the superior efficacy of MPA compared with AZA in the prevention of renal flares is applicable to other patient groups[31]. Whether the inclusion of biologics in the treatment of LN would further reduce the disease flare rate is another area that warrants exploration. Based on preliminary experience, the use of anti-CD20 therapy should reduce the flare rate in selected patients.

The rate of renal flare in patients with LN has decreased considerably in more recent years, and is likely attributed to improved response to induction immunosuppression and MPA maintenance.

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