Comparison of short interval and low dose (SILD) with high dose of cyclophosphamide in the susceptibility to infection in SLE: a multicentrereal-world study

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ABSTRACT

Objective Infection is a major cause of death in patients with SLE. This study aimed to explore the infection rate in patients with SLE receiving a low dose of intravenous cyclophosphamide (IV-CYC).

Methods Clinical parameters of 1022 patients with SLE from 24 hospitals in China were collected. Patients were divided into the short-interval and lower-dose (SILD, 400 mg every 2 weeks) IV-CYC group and the high-dose (HD, 500 mg/m² of body surface area every month) IV-CYC group. The clinical data and infection rate between the two groups were compared.

Results Compared with HD IV-CYC, the infection rate of the SILD IV-CYC group was significantly lower (13.04% vs 22.27%, p=0.001). Respiratory tract infection (10.28% vs 15.23%, p=0.046) and skin/soft tissue infection (1.78% vs 4.3%, p=0.040) were significantly decreased in the SILD IV-CYC group. Moreover, infections occurred most likely in patients with SLE with leucopenia (OR 2.266, 95% CI 1.322 to 3.887, p=0.003), pulmonary arterial hypertension (OR 2.756, 95% CI 1.249 to 6.080, p=0.012) and >15 mg/day of glucocorticoid (OR 2.220, 95% CI 1.097 to 4.489, p=0.027).

Conclusions SILD IV-CYC showed a lower frequency of infection events than high-dose IV-CYC in patients with SLE.

INTRODUCTION

SLE is a serious systemic and chronic auto-immune disease with various clinical features that continue to pose a challenge to developing effective treatments with minimal side effects. It is known that 11%–45% of patients

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WHAT IS ALREADY KNOW ON THIS TOPIC

⇒ Infection is the major cause of death in patients with SLE.

⇒ Cyclophosphamide is one of the most acknowledged and effective treatments for patients with SLE, while it can increase the susceptibility to infection.

WHAT THIS STUDY ADDS

⇒ Short-interval and lower-dose cyclophosphamide (SILD IV-CYC) results in less infection susceptibility compared with high-dose cyclophosphamide.

⇒ More infections occurred in patients with SLE with leucopenia, pulmonary arterial hypertension and on glucocorticoids.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ SILD IV-CYC was superior to high dose at less risk of infection.

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with SLE develop severe infections during treatment.[1] In recent decades, numerous studies have presented that infection is one of three major causes of death in patients with SLE.[2–4] Some research has also shown that some patients have even experienced more than one severe infection.[2 5] Impaired immune functions involving the innate and adaptive immune system are the intrinsic factors of infection vulnerability in patients with SLE.[6–8] Moreover, the use of immunosuppressants markedly elevates the risk of infection. To better manage and improve the
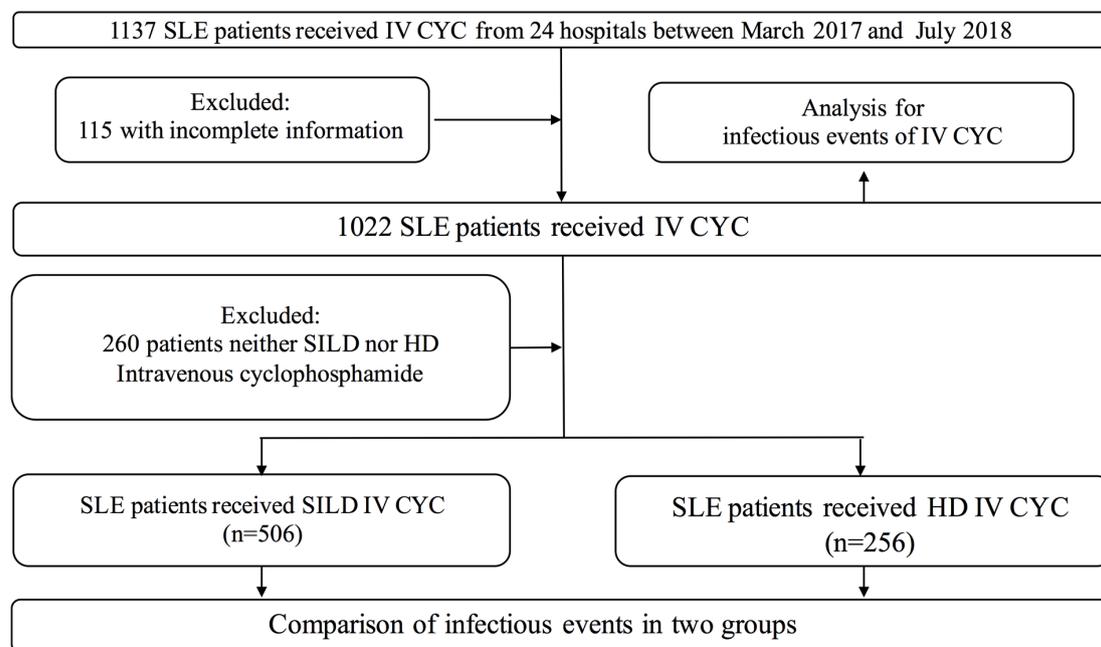
Figure 1 Flow diagram of the selection of patients with SLE. HD IV-CYC, high-dose intravenous cyclophosphamide; IV-CYC, intravenous cyclophosphamide; group 1, the SILD IV-CYC group, short-interval and lower-dose intravenous cyclophosphamide fortnightly with a fixed dose of 400 mg; group 2, the HD IV-CYC group, high-dose intravenous cyclophosphamide monthly at a dose of 500 mg/m^2 of body surface area; n, number of patients; SILD IV-CYC, short-interval and lower-dose intravenous cyclophosphamide.

prognosis of patients with SLE, we conducted a retrospective, real-word, multicentre study on the infection of patients with SLE receiving intravenous cyclophosphamide (IV-CYC) in China.

MATERIALS AND METHODS
Patient population
A total of 1137 patients who visited 24 hospitals covering 17 provinces in China from March 2017 to July 2018 were screened (depicted in figure 1) for this study (SILD cohort). All patients with SLE were diagnosed according to the 1997 revised classification criteria of the American College of Rheumatology[9] and received IV-CYC. Their medical histories were collected by retrospective survey in the inpatient and outpatient electronic medical records of patients. We excluded 115 patients with incomplete information. Patients in combination with CYC and other immune suppressants (mycophenolate mofetil, azathioprine, ciclosporin, tacrolimus, methotrexate, leflunomide, rituximab, etc) were also excluded from the study. Patients who received glucocorticoid pulse therapy were acceptable. The initial dose of prednisone was 40–60 mg/day in these patients. Finally a total of 1022 patients were included in the study. Of these patients, 506 received short-interval and lower-dose (SILD) IV-CYC treatment every 2 weeks at a fixed dose of 400 mg,[10 11] and 256 patients were treated with the high-dose (HD) IV-CYC at a dose of 500 mg/m^2 of body surface area every month.[12 13]

Data collection
The collected demographic data included gender, age of enrolment, age of onset, systemic manifestation (eg, lupus nephritis, neuropsychiatric SLE, interstitial pneumonia, pulmonary arterial hypertension, leucopenia, etc), white cell count, neutrophil count, lymphocyte count, IV-CYC duration, accumulated dose of CYC, glucocorticoid and immunosuppressive agents before intravenous cyclophosphamide, as well as any comorbidities (diabetes mellitus, hypertension, coronary heart disease, hyperlipidaemia, etc) and infection site (respiratory system, digestive system, urinary system, skin, septicaemia, etc). The glucocorticoid pulse therapy, the initial dose of glucocorticoids and the dosage of glucocorticoids at the time of infection were also recorded. The cumulative doses and duration of CYC was from the day of initiation of CYC to the day of infection occurred.

Statistical analysis
Infection events occurring during IV-CYC treatment of the remaining 1022 patients with SLE were recorded, including infection site, duration and cumulative dose of CYC, and risk factors. A comparison of infectious events was made between the SILD IV-CYC group and the HD IV-CYC group.

Patients with an infection that did not require antibiotic treatment were considered to have a mild infection. Those who were treated with antibiotics were regarded as having a moderate infection. Severe infection refers to an infection that leads to hospitalisation, prolonged hospitalisation, life-threatening illness or death.

The Statistical Product and Service Solutions (SPSS) V.26.0 was used to analyse the data. Continuous variables were presented as median (IQR), and statistical significance between two groups was assessed using a Mann-Whitney U test. Categorical data were expressed as absolute count (percentage), and comparison between two groups were made by χ^2 or Fisher's exact test. A stepwise multivariate logistic regression analysis was used to determine the risk factors for infections, and the ORs of the infection event risk and its 95% CIs were calculated. In univariate analysis, the factors related to infection at $p<0.15$ and diabetes mullitus were entered into the multivariate logistic model. The threshold of significance was set to $p<0.05$.

RESULTS

The characteristics of patients with SLE are shown in table 1, with the average patient age being 39.00 (30.00–50.00). The duration and cumulative dose of CYC were 6.00 (3.00–10.00) months and 4.80 (2.40–8.00) g, respectively. The most common disease presentations were lupus nephritis (LN) and neuropsychiatric SLE, as well as those impacting the haematologic system and respiratory system. As shown in table 1, there was no significant difference in age, gender, duration of CYC, cumulative dose of CYC, glucocorticoid treatment dose or organ involvement between the patients receiving SILD IV-CYC and HD IV-CYC.

Table 1 Baseline characteristics of patients with SLE in this study

	Total patients with SLE (N=1022)	SILD IV-CYC (n=506)	HD IV-CYC (n=256)	P value (SILD vs HD)
Sex (female:male)	934:88	463:43	234:22	0.964
Age (years)	39.00 (30.00–50.00)	40.00 (31.00–51.00)	39.00 (30.00–50.00)	0.699
Age onset (years)	31.00 (23.00–42.00)	32.00 (24.00–43.00)	31.50 (23.00–42.00)	0.421
CYC course (months)	6.00 (3.00–10.00)	6.00 (3.00–10.63)	6.00 (4.00–8.75)	0.471
Accumulated dose of CYC (g)	4.80 (2.40–8.00)	4.80 (2.40–8.40)	5.60 (3.20–8.00)	0.139
Glucocorticoid dose (mg/day)	20.00 (10.00–40.00)	20.00 (10.00–45.00)	18.75 (10.00–35.00)	0.089
Lupus nephritis	573 (56.07)	269 (53.16)	149 (58.20)	0.187
Leucocytopaenia	110 (10.76)	66 (13.04)	32 (12.5)	0.832
Neutrocytopaenia	20 (1.96)	7 (1.38)	3 (1.17)	1.000
Lymphocytopaenia	42 (4.11)	23 (4.55)	10 (3.91)	0.682
Interstitial lung disease	80 (7.83)	45 (8.89)	16 (6.25)	0.204
Pulmonary arterial hypertension	46 (4.50)	26 (5.14)	7 (2.73)	0.124
NPSLE	143 (13.99)	70 (13.83)	30 (11.72)	0.414
Diabetes mellitus	41 (4.01)	19 (3.75)	10 (3.91)	0.918
Decreased C3	495 (48.43)	249 (49.21)	118 (46.09)	0.416
Decreased C4	427 (41.78)	186 (36.76)	110 (42.97)	0.097
Increased anti-dsDNA antibody	317 (31.02)	149 (29.45)	77 (30.08)	0.857
SLEDAI	6.00 (2.00–10.00)	6.00 (2.00–10.00)	6.00 (2.00–9.00)	0.316
HCQ	881 (86.20)	450 (88.93)	221 (86.33)	0.295
Glucocorticoid pulse therapy	109 (10.67)	52 (10.28)	27 (10.55)	0.908
Immunosuppressants before IV-CYC				
MMF	148 (14.48)	80 (15.81)	39 (15.23)	0.836
AZA	15 (1.47)	11 (2.17)	2 (0.78)	0.269
CSA	23 (2.25)	13 (2.57)	7 (2.73)	0.893
TAC	10 (0.98)	9 (1.78)	1 (0.39)	0.210
MTX	16 (1.57)	10 (1.98)	4 (1.56)	0.908
LEF	50 (4.89)	29 (5.73)	11 (4.30)	0.402
RTX	7 (0.68)	4 (0.79)	1 (0.39)	0.864

Data were presented as median (IQR) or count (percentage).
AZA, azathioprine; C3, complement 3; C4, complement 4; CSA, ciclosporin; CYC, cyclophosphamide; dsDNA, double-stranded DNA; HCQ, hydroxychloroquine; HD, high dose; IV-CYC, intravenous cyclophosphamide; LEF, leflunomide; MMF, mycophenolate mofetil; MTX, methotrexate; NPSLE, neuropsychiatric SLE; RTX, rituximab; SILD, short interval, lower dose; SLEDAI, Systemic Erythematosus Disease Activity Index; TAC, tacrolimus.

Table 2 Sites and severity of infection for patients with SLE in each group

	SILD IV-CYC (N=506)		HD IV-CYC (N=256)		
	n	%	n	%	P value
Infection	66	13.04	57	22.27	**0.001***
Infection sites					
Respiratory tract	52	10.28	39	15.23	**0.046***
Skin and soft tissue	9	1.78	11	4.30	**0.040***
Urinary tract	5	0.99	3	1.17	1.000
Gastrointestinal tract	3	0.59	5	1.95	0.173
Other (haematologic, central nervous, etc)	4	0.79	2	0.78	1.000
Multiple sites	11	2.17	6	2.34	0.881
Severity of infection					
Mild infection	30	5.93	24	9.38	0.080
Moderate infection	24	4.74	22	8.59	**0.035***
Severe infection	12	2.37	11	4.30	0.142

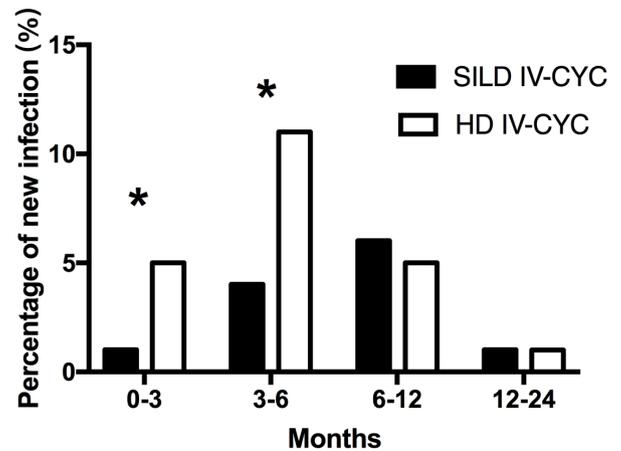*P value <0.05. All p values less than 0.05 which is significant are in bold.
HD IV-CYC, high-dose intravenous cyclophosphamide;
SILD IV-CYC, short-interval and lower-dose intravenous cyclophosphamide.

	0-3 (M)	3-6 (M)	6-12 (M)	12-24 (M)
SILD IV-CYC (n = 506)	7 (1.38%)	22 (4.35%)	30 (5.93%)	7 (1.38%)
HD IV-CYC (n = 256)	13 (5.08%)	28 (10.94%)	14 (5.47%)	2 (0.78%)
P value	0.003	0.001	0.797	0.725

Figure 2 Comparison of the rates of new infection in patients with SLE undergoing SILD IV-CYC and HD IV-CYC treatments. HD IV-CYC, high-dose intravenous cyclophosphamide; M, months; SILD IV-CYC, short-interval lower-dose intravenous cyclophosphamide.

Infection events in patients with SLE

Infections occurred in 177 (17.32%) of the 1022 patients with SLE included in this study. The most frequently recorded sites of infection were the respiratory tract (12.82%), followed by the skin/soft tissue (2.54%), the urinary tract (1.17%) and the gastrointestinal tract (0.98%). Of these 177 patients, 23 patients experienced more than one infection episode and 17 patients even had two sites of infection during IV-CYC treatment.

The short-interval, lower-dose intravenous cyclophosphamide group showed less infection than the high-dose group

As depicted in table 2, the infection risk was found to be lower in patients who received SILD IV-CYC compared with those treated with HD IV-CYC (13.04% vs 22.27%, p=0.001). The respiratory tract was the most common site of infection in both groups. In the SILD IV-CYC group, the risk of developing either a respiratory tract infection (10.28% vs 15.23%, p=0.046) or skin/soft tissue infection (1.78% vs 4.3%, p=0.040) was significantly decreased. No difference in susceptibility to infection could be detected in the urinary tract, gastrointestinal, central nervous system or bloodstream between the two groups. Although there is no significant difference in the occurrence of mild infection (5.93% vs 9.38%) and severe infection (2.37% vs 4.30%) between the two groups, the moderate

infection rate was lower in the SILD IV-CYC group (4.74% vs 8.59%, p=0.035).

Most of the infections occurred within 6 months (104/177, 58.76%) and 1 year (167/177, 94.35%) of IV-CYC injection. After 6 months of IV-CYC injection, the infection rates in the SILD group and the HD group were 5.73% (29/506) and 16.02% (41/256) (p=0.000), respectively, and after 12 months of IV-CYC injection, the infection rates in the SILD group and HD group were 11.66% (59/506) and 21.48% (55/256), respectively. During the treatment period of 0 to 6 months, the infection events in the HD IV-CYC group increased significantly compared with the SILD IV-CYC group (figure 2).

In addition, when a multivariate analysis was performed (table 3), the risk of infection in patients with SLE who received HD IV-CYC was found to be twice than that of those who had received SILD IV-CYC (OR 2.018, 95% CI 1.315 to 3.097, p=0.001).

Other risk factors of infection

As shown in table 3, patients with SLE who also had leucopaenia (OR 2.266, 95% CI 1.322 to 3.887, p=0.003) or pulmonary arterial hypertension (OR 2.756, 95% CI 1.249 to 6.080, p=0.012) were more susceptible to infection. There was no significant difference in glucocorticoid usage between patients with SLE who developed infections and those who did not. However, all of the patients with SLE were divided into three groups according to the dosage of glucocorticoids they received: those free of glucocorticoids, glucocorticoids ≤15 mg/day and glucocorticoids >15 mg/day. The multivariate

Table 3 Risk factors for infection in patients with SLE receiving IV-CYC

	Univariate analysis			Multivariate analysis	
	With infection (n=177)	Without infection (n=845)	P value	OR (95% CI)	P value
Age, years	36.00 (29.00–50.00)	39.00 (30.00–50.00)	0.161		
Sex (female:male)	162:15	772:73	0.943		
CYC course (months)	7.00 (5.00–12.00)	6.00 (2.00–9.00)	**0.000**	0.964 (0.876 to 1.060)	0.446
CYC accumulation (g)	6.40 (4.45–9.00)	4.80 (1.80–8.00)	**0.000**	1.092 (0.964 to 1.236)	0.166
LN	110 (62.15)	463 (54.79)	0.073	1.246 (0.826 to 1.878)	0.294
NPSLE	24 (13.56)	119 (14.08)	0.855		
Leucopaenia	28 (15.82)	82 (9.70)	**0.017**	**2.266 (1.322 to 3.887)**	**0.003***
Neutropaenia	7 (3.95)	13 (1.54)	0.035	1.159 (0.258 to 5.199)	0.847
Lymphocytopaenia	14 (7.91)	28 (3.31)	**0.005**	1.371 (0.565 to 3.327)	0.485
ILD	16 (9.04)	64 (7.57)	0.509		
PAH	15 (8.47)	31 (3.67)	**0.005**	**2.756 (1.249 to 6.080)**	**0.012***
Diabetes mellitus	10 (5.65)	31 (3.67)	0.222	1.635 (0.633 to 4.224	0.310
SLEDAI	6.00 (2.00–10.00)	6.00 (2.00–10.00)	0.451		
CYC protocols					
SILD	13.04% (66/506)	86.96% (440/506)	**0.001**	**2.018 (1.315 to 3.097)**	**0.001***
HD	22.27% (57/256)	77.73% (199/256)			
Glucocorticoid pulse therapy	20 (11.30)	89 (10.53)	0.764		
Glucocorticoid dose (mg)	22.0 (10.0–40.0)	20.0 (10.0–45.0)	0.871		
Group 1 (without Pred)	22 (12.43)	128 (15.15)			
Group 2 (≤15 mg/day)	57 (32.20)	278 (32.90)		1.802 (0.865 to 3.753)	0.116
Group 3 (>15 mg/day)	98 (55.37)	439 (51.95)		**2.220 (1.097 to 4.489)**	**0.027***

Data were presented as median (IQR) or n count (percentage).
*P value <0.05. All p values less than 0.05 which is significant are in bold.
CYC, cyclophosphamide; HD, high dose; ILD, interstitial lung disease; IV-CYC, intravenous cyclophosphamide; LN, lupus nephritis; NPSLE, neuropsychiatric SLE; PAH, pulmonary arterial hypertension; Pred, prednisone; SILD, short interval lower dose; SLEDAI, Systemic Erythematosus Disease Activity Index.

logistic regression analysis found that when the dose of glucocorticoid was >15 mg/day, the risk of infection was higher (OR 2.220, 95% CI 1.097 to 4.489, p=0.027). Other factors that were valuable in univariate analysis, including CYC accumulation, CYC duration and lymphocytopaenia, did not confer any additional infection risk.

DISCUSSION

Infection is one of the most critical causes of death in patients with SLE. This study is a real-world, multicentre study that has shown the infection risk associated with IV-CYC. Consistent with various studies,[14 15] leucopaenia, lymphopaenia and neutropaenia are associated with an increased risk for infection in patients with SLE. Our results confirm that patients with SLE who also have leucopenia are more vulnerable to infection after receiving IV-CYC.

Along with the impaired immune functions associated with SLE, the use of immunosuppressive drugs containing CYC additionally increases the susceptibility to infection in patients with SLE.[16 17] CYC is one of the most acknowledged and successful therapies for treating SLE, especially

for severe, organ-threatening SLE, and has been shown to dramatically improve the prognosis of these patients. Since the 1970s, a series of clinical trials carried out by the National Institutes of Health have shown that the intermittent infusions of CYC with prednisone was superior to a single application of prednisone.[12 13 18] When CYC was first used to treat SLE, HD IV-CYC was the standard therapy for LN in the induction phase. In recent years, many studies have demonstrated that SILD IV-CYC is also efficacious, and there was no difference between the SILD IV-CYC and HD IV-CYC groups in SLE disease control.[10 11 19 20] However, the side effects of long-term exposure to CYC have been shown to include infection, bone marrow damage, malignancy, ovarian dysfunction and haemorrhagic cystitis at any therapeutic dose. The infection occurring in associated with CYC treatment could be fatal for patients with SLE. Our previous randomised, single-centre study showed that patients with SLE receiving SILD CYC treatment had fewer infection events compared with the HD CYC group; however, the differences did not reach statistical significance.[10] In the Euro-Lupus Nephritis Trial study, episodes of severe

infection were more than twice as frequent in the HD CYC group.[11] In the present study, we have shown that the risk of infection was significantly lower in patients with SLE in the SILD IV-CYC group than in the HD IV-CYC group. The infection risk of HD IV-CYC is 2.018 times higher than that of SILD IV-CYC after adjusting by the duration and accumulated dose of CYC, pulmonary arterial hypertension, leucopaenia and lymphocytopaenia.

In addition, we observed that patients who received IV-CYC with glucocorticoids >15 mg/day had a higher infection risk. Our data also showed that most infections occurred within the first 6 months of IV-CYC treatment. This may be due to most patients with SLE also being on glucocorticoids >15 mg/day in addition to IV-CYC during the first 6 months of the induction phase. Fortunately, patients who received SILD IV-CYC remained at low infection risk throughout our study.

Our study has inherent limitations of retrospective research. First of all, it was not recorded for research purposes, and some clinical details such as infectious organisms are incomplete. Second, the regimens of glucocorticoids were inconsistent in the study, and some patients also received intravenous pulse methylprednisolone therapy at the beginning of the treatment. Glucocorticoids at the time of infection were analysed; however, the cumulative and average dose of glucocorticoids and other factors which may affect the risk of infection could not be obtained. Last, patients who lost follow-up were excluded, and there might be some selection bias among the study subjects.

In summary, we found that the infection rate of patients with SLE treated with SILD IV-CYC is much lower than that of patients treated with HD IV-CYC. This indicates that SILD IV-CYC could be a better option in the treatment of patients with SLE.

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REFERENCES
1 Teh CL, Wan SA, Ling GR. Severe infections in systemic lupus erythematosus: disease pattern and predictors of infection-related mortality. *Clin Rheumatol* 2018;37:2081–6.
2 Cervera R, Khamashta MA, Font J, *et al*. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison

of early and late manifestations in a cohort of 1,000 patients. *Medicine* 2003;82:299–308.

3 Thomas G, Mancini J, Jourde-Chiche N, *et al*. Mortality associated with systemic lupus erythematosus in France assessed by multiple-cause-of-death analysis. *Arthritis Rheumatol* 2014;66:2503–11.

4 Wang Z, Wang Y, Zhu R, *et al*. Long-term survival and death causes of systemic lupus erythematosus in China: a systemic review of observational studies. *Medicine* 2015;94:e794.

5 Feldman CH, Hiraki LT, Winkelmayer WC, *et al*. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. *Arthritis Rheumatol* 2015;67:1577–85.

6 Suárez-Fueyo A, Bradley SJ, Tsokos GC. T cells in systemic lupus erythematosus. *Curr Opin Immunol* 2016;43:32–8.

7 Ghobadi MZ, Izadi S, Teymoori-Rad M, *et al*. Potential role of viral infection and B cells as a linker between innate and adaptive immune response in systemic lupus erythematosus. *Immunol Res* 2021;69:196–204.

8 Mevorach D. Clearance of dying cells and systemic lupus erythematosus: the role of C1q and the complement system. *Apoptosis* 2010;15:1114–23.

9 Hochberg MC. Updating the American College of rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.

10 Zhang XW, Li C, Ma XX, *et al*. Short-interval lower-dose intravenous cyclophosphamide as induction and maintenance therapy for lupus nephritis: a prospective observational study. *Clin Rheumatol* 2014;33:939–45.

11 Houssiau FA, Vasconcelos C, D'Cruz D, *et al*. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus nephritis trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;46:2121–31.

12 Austin HA, Klippel JH, Balow JE, *et al*. Therapy of lupus nephritis. controlled trial of prednisone and cytotoxic drugs. *N Engl J Med* 1986;314:614–9.

13 Boumpas DT, Austin HA, Vaughn EM, *et al*. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. *Lancet* 1992;340:741–5.

14 Merayo-Chalico J, Gómez-Martín D, Piñeirúa-Menéndez A, *et al*. Lymphopenia as risk factor for development of severe infections in patients with systemic lupus erythematosus: a case-control study. *QJM* 2013;106:451–7.

15 Dias AMB, do Couto MCM, Duarte CCM, *et al*. White blood cell count abnormalities and infections in one-year follow-up of 124 patients with SLE. *Ann N Y Acad Sci* 2009;1173:103–7.

16 Mok CC, Tse SM, Chan KL, *et al*. Effect of immunosuppressive therapies on survival of systemic lupus erythematosus: a propensity score analysis of a longitudinal cohort. *Lupus* 2018;27:722–7.

17 Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. *Lupus* 2013;22:1286–94.

18 Donadio JV, Holley KE, Ferguson RH, *et al*. Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. *N Engl J Med* 1978;299:1151–5.

19 Houssiau FA, Vasconcelos C, D'Cruz D, *et al*. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus nephritis trial. *Arthritis Rheum* 2004;50:3934–40.

20 Martin-Suarez I, D'Cruz D, Mansoor M, *et al*. Immunosuppressive treatment in severe connective tissue diseases: effects of low dose intravenous cyclophosphamide. *Ann Rheum Dis* 1997;56:481–7.