Risk factors for the flare of systemic lupus erythematosus and its influence on prognosis: a single-center retrospective analysis

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Abstract

Objectives: To explore the risk factors for systemic lupus erythematosus (SLE) flare and their impact on prognosis.

Methods: The clinical characteristics, laboratory results, and treatment plans of 121 patients with SLE flare were retrospectively analyzed. Ninety-eight SLE outpatients with sustained remission during the same period were selected as controls. Logistic multivariate regression analysis was employed to screen for risk factors for SLE flare.

Results: Infection, thrombocytopenia, arthritis, anti-nucleosome antibodies positive, anti-β2-glycoprotein I (IgG) antibodies positive, and patient’s self-discontinuation of medicine maintenance therapy might be risk factors for SLE flare. Patients who discontinued medicine maintenance therapy by themselves had a significantly higher rate of severe SLE flare than patients with regular medicine maintenance therapy \( (P = 0.033) \). The incidence of anemia associated with SLE \( (P = 0.001) \), serositis \( (P = 0.005) \), and pulmonary hypertension \( (P = 0.003) \) in patients who discontinued medicine maintenance therapy were significantly higher than patients with regular medicine maintenance therapy. SLE patients with regular medicine maintenance therapy for less than 3 years had a higher risk of pulmonary hypertension than those with regular medicine maintenance therapy longer than 3 years \( (P = 0.034) \).

Conclusions: The accompanying thrombocytopenia, arthritis, anti-nucleosome antibodies positive and anti-β2-glycoprotein I (IgG) antibodies positive at the onset of SLE may affect the prognosis of SLE. Patient’s self-discontinuation of medicine maintenance therapy is the main cause of SLE flare, which may induce severe flare in SLE patients and lead to a significantly higher incidence of pulmonary hypertension.

Keywords: Systemic lupus erythematosus, Flare, Infection, Therapy, Pulmonary hypertension

Background

Systemic lupus erythematosus (SLE) is a serious chronic autoimmune disease, which can involve multiple organs and cause systemic damage. Although the treatment of SLE has been improving, most patients still go through alternating courses of flare and remission. Flare is an important factor for organ damage and poor prognosis of SLE [1], as the same time, it also brings heavy psychological burden to patients [2]. Therefore, remission achievement and its maintenance have become central in the management of SLE patients. At present, the cause of SLE flare is still unclear, but infection is considered to be a possible reason [3, 4], because it could lead to more frequent hospitalization and higher mortality [4]. In China, the main cause of death in SLE patients has changed from renal and central nervous system complications in 1980’s to infections since 1996 to date [5, 6], which may be associated with the longer course of glucocorticoids and immunosuppressive treatments in SLE patients [6]. In recent years, several studies [7, 8]...
showed that patients could benefit from reducing or discontinuing the maintenance therapy with glucocorticoids, when SLE patients reached complete remission. Moreover, the recommendations for the management of SLE underline the importance of glucocorticoids progressive tapering until withdrawal [8]. However, only a few SLE patients without both glucocorticoids and immunosuppressants maintenance therapy could still stay at persistent remission [9–11]. A china cohort also showed that only 14.7% of patients successfully stopped both glucocorticoids and immunosuppressants during follow-up [9]. These suggest that the medicine maintenance therapy, especially the maintenance therapy of immunosuppressants in remission [11], is also related to SLE flare. So far, there is no relevant research on the correlation between medicine maintenance therapy and SLE flare, and it is unknown how long the medicine maintenance therapy needs to last. However, it is important to identify which patients are likely to have SLE flare, and what is the heterogeneity of the clinical manifestations or serum indicators in these patients, which is of great significance for the management of SLE patients in remission period. Therefore, this study retrospectively analyzed the clinical characteristics and treatments of patients with SLE flare in our center, to screen for risk factors for SLE flare and explore the impact for discontinuation of medicine maintenance therapy on the prognosis of SLE.

**Study subjects**
The clinical data of patients with SLE treated in the First Affiliated Hospital of Fujian Medical University from January 2013 to December 2018 were retrospectively analyzed. They met the SLE American College of Rheumatology (ACR) classification criteria [12]. Patients who met the following criteria were included in the SLE flare group: (1) patients aged 18 years or older, (2) patients were initially diagnosed with SLE in our hospital, (3) patients who achieved complete or clinical remission after initial treatment of SLE, (4) patients should be followed up at least three times a year, and (5) patients with SLE flare for the first time after complete or clinical remission and re-hospitalized for treatment. SLE patients who were followed up in outpatient clinic during the same period, met criteria 1 to 4 and were still in complete or clinical remission at the last follow-up were selected as the comparison group. Patients with pregnancy and other autoimmune diseases were excluded.

**Methods**
**Definition of disease activity, remission and flare**
SLE disease activity was measured based on the systemic lupus erythematosus disease activity index 2000 (SLEDAI-2 K) developed by the International Clinical Collaboration Group for SLE [13]. SLE organ damage was evaluated with the SLE damage index (SDI) developed by the Systemic Lupus Erythematosus International Collaborating Clinics (SLICC)/ACR [14].

Complete remission of SLE [15] was defined as SLEDAI-2 K of 0 in corticosteroid-free and immunosuppressant-free patients (antimalarials allowed), clinical remission as serological active clinical quiescent disease (SACQD) according to SLEDAI-2 K ≤ 4 in corticosteroid-free patients or patients on prednisone 1–5 mg/day, (stable immunosuppressants and antimalarials allowed) [15].

The definition of SLE flare, including the definitions of mild to moderate flare and severe flare, referred to the SELENA-SLEDAI flare index [16]. SLE flare was defined as one or more of the following: 1) the SLEDAI-2 K instrument score increase, 2) new or worse activity, medication changes, and new or worsening symptoms and organ damage attributable to lupus. Mild to moderate flares were defined as one or more of the following: a) greater than 3-point increment in SLEDAI-2 K instrument score, with total score less than 12; b) new or worsening discoid, photosensitive, or other rash attributable to lupus (including lupus profundus, cutaneous vasculitis, or bullous lupus), nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, or fever not attributable to infection; c) increase in prednisone dosage but not greater than 0.5 mg/kg of body weight per day; and d) initiation of therapy with either hydroxychloroquine or nonsteroidal anti-inflammatory drugs, without an increase in prednisone dosage. Severe flares were defined as one or more of the following: a) SLEDAI-2 K instrument score greater than 12; b) new or worsening central nervous system involvement, vasculitis, glomerulonephritis, myositis, thrombocytopenia (platelet count < 60 × 10^9 cells/L), or hemolytic anemia (hemoglobin level < 70 g/L or decrease in hemoglobin level > 30 g/L over a 2-week period), each requiring doubling of corticosteroid dosage to a final dosage greater than 0.5 mg/kg per day or acute hospitalization; c) any manifestation requiring an increase in dosage of prednisone or equivalent drug to greater than 0.5 mg/kg per day, or initiation of therapy with cyclophosphamide, azathioprine, mycophenolate mofetil, or methotrexate; and d) hospitalization for lupus activity.

Patients with Pulmonary hypertension were diagnosed based on right heart catheterization or echocardiography (peak tricuspid regurgitation velocity > 3.4 m/s) [17], and those with left heart disease and pulmonary thrombosis were excluded.

**Data collection**
The following clinical data were collected: sex, age, disease duration, clinical symptoms, treatment plans, treatment duration and laboratory indicators, including complete blood count, urinalysis, liver and kidney function, antinuclear antibodies (ANA), anti-double-stranded
DNA antibodies (ds-DNA), anti-ribonucleoprotein (anti-RNP) antibodies, anti-Smith (anti-SM) antibodies, anti-Sjogren’s syndrome A antibodies (anti-SSA), anti-Sjogren’s syndrome B antibodies (anti-SSB), antinucleosome antibodies (AnuA), anti-ribosomal RNP antibody, anti-cardiolipin antibodies (aCL), anti-\(\beta\)2-glycoprotein I (anti-\(\beta\)2GPI) antibodies and lupus anticoagulants (LAs). ANA was measured by a standardized ELISA, the results were in the format of the absorbance value of sample / the cut off value (s/co). ANA in serum present in titer > 1.0 s/co defined as positive. While ds-DNA in serum present in titer > 100 IU/ml defined as positive, measured by a standardized ELISA. The SLEDAI-2K score and SDI of all the patients at each hospitalization and outpatient follow-up were recorded, and the SDI increment (\(\text{SDI}_{2}-\text{SDI}_{1}\)), which was the difference between the SDI at the rehospitalization of a patient with flared SLE and the SDI at the last time of achieving complete or clinical remission of SLE, was calculated.

Statistical analysis
SPSS 20.0 was used for statistical processing. Quantitative data that conformed to the normal distribution were analyzed using Student’s t-test. The Mann–Whitney U-test was used for data that were not normally distributed. Qualitative data were analyzed using the \(\chi^2\) test or Fisher’s exact probability test. \(P < 0.05\) represented statistical significance. Factors with \(P < 0.1\) in univariate analysis were input into the multivariate model to screen for possible risk factors using the logistic multivariate regression analysis, in which test the significance was set to 5%. The Kaplan-Meier test was used to estimate the survival of all patients.

Results
Clinical manifestations, laboratory examinations, and treatments of the flared group and the comparison group
From January 2013 to December 2018, 121 patients were included in the SLE flare group, including 113 females and 8 males with an age of 39.9 ± 13.1 (mean ± SD) years and a disease duration of 93.2 ± 80.1 (mean ± SD) months. Ninety-eight patients were included in the comparison group, including 84 females and 14 males with an age of 39.9 ± 13.1 (mean ± SD) years and a disease duration of 93.2 ± 80.1 (mean ± SD) months. The SLE flare group had a significantly longer disease course than the comparison group \((P < 0.001)\). At the initial onset of SLE, the SLEDAI-2K score of the SLE flare group and the comparison group were 11.6 ± 4.1 (mean ± SD) and 10.4 ± 4.2 (mean ± SD) points, respectively, with no significant difference \((P > 0.05)\). The incidence of infection in the SLE flare group was significantly higher than that in the comparison group \((54/121 \text{ vs } 2/98, P < 0.001)\) (Table 1). There was no significant difference \((P > 0.05)\) in the incidence of clinical symptoms at the initial onset of SLE between the two groups of patients, which included fever, rash, arthritis, oral ulcer, hair loss, serositis, leukopenia, thrombocytopenia, lupus nephritis, Neuropsychiatric lupus, lupus pneumonia, cardiac damage, and lupus-related gastrointestinal damage. In the flared group, there were 6 patients with secondary antiphospholipid syndrome (APS), while none of the comparison group had APS \((P < 0.05)\) (Table 1).

The autoantibody profile at the onset of SLE is laid out in Table 1. In the SLE flare group, the positive rates of anti-SM antibodies (28.9%), AnuA (38%) imunoglobulin G (IgG)-antircardiolipin (aCL) antibodies (5.0%), IgG-anti-\(\beta\)2-GPI antibodies (16.5%), and LA (10.7%) were higher than in the comparison group \((all P < 0.05)\) (Table 1).

All patients received glucocorticoids (orally or intravenously) at the time of initial treatment. The starting dose of glucocorticoids in the flared group was 0.9 ± 0.9 mg/kg/d (mean ± SD), 23 of them had an initial starting dose of glucocorticoids exceeding 0.8 mg/kg/d, 98 patients used hydroxychloroquine for initial treatment, and 49 patients received combined immunosuppressants treatment, include cyclophosphamide (CTX), mycophenolate mofetil (MMF), azathioprine (AZA), methotrexate (MTX), cyclosporine A (CsA) and tacrolimus (FK-506) (Table 1). The starting dose of glucocorticoids in the comparison group was 0.9 ± 0.4 mg/kg/d (mean ± SD), and 21 patients had an initial starting dose of glucocorticoids exceeding 0.8 mg/kg/d, 91 patients used hydroxychloroquine for initial treatment, and 70 patients received combined immunosuppressants treatment. In the SLE flare group, only 5 patients achieved complete remission, while 7 patients achieved complete remission in the comparison group. There was no significant difference in the median time of achieving the clinical remission and glucocorticoid accumulation between the two groups. The application rate of immunosuppressants \((P < 0.001)\) and hydroxychloroquine \((P = 0.017)\) in the SLE flare group was lower than that in the comparison group (Table 1). During the follow-up period, the proportion of patients’ self-discontinuation of medicine maintenance therapy in the SLE flare group was significantly higher than that in the comparison group \((P < 0.001)\) (Table 1).

Logistic multivariate regression analysis of risk factors for SLE flare
A model for logistic multivariate regression analysis was established using SLE flare as the dependent variable and using factors with \(P < 0.1\) in univariate analysis as independent variables, which included sex, disease duration, infection, arthritis, thrombocytopenia, antiphospholipid
Table 1 Clinical characteristics and treatment in patients with SLE flare or sustained remission of SLE

|                                | SLE flare group (n = 121 Case) | comparison group (n = 98 Case) | P-value |
|--------------------------------|--------------------------------|-------------------------------|---------|
| **Age (Year), mean (SD)**      | 39.9(13.1)                     | 42.7(13.8)                    | 0.431   |
| **Gender (female/male)**       | 113/8                          | 84/14                         | 0.072   |
| **Disease duration (Month), mean (SD)** | 93.2(80.1)                     | 78.6(44.9)                    | <0.001* |
| **Infection**                  | 54(44.6)                       | 2(2.4)                        | <0.001* |
| **Flare degree**               |                                 |                               |         |
| Mild and moderate SLE flare, n (%) | 28 (23.1)                      |                               |         |
| Severe SLE flare, n (%)        | 93 (76.9)                      |                               |         |
| **Initial symptom, n (%)**     |                                 |                               |         |
| Fever                          | 36(29.8)                       | 32(32.7)                      | 0.662   |
| Rash                           | 68(56.2)                       | 63(64.3)                      | 0.268   |
| Arthritis                      | 67(55.4)                       | 42(42.9)                      | 0.078   |
| oral ulcer                     | 26(21.5)                       | 21(21.4)                      | 1.000   |
| Hair loss                      | 23(19.0)                       | 14(14.3)                      | 0.372   |
| Serositis                      | 24(19.8)                       | 21(21.4)                      | 0.867   |
| Leucopenia a                   | 18(14.9)                       | 14(14.3)                      | 0.755   |
| Thrombocytopenia b             | 19(15.7)                       | 7(7.1)                        | 0.060   |
| Lupus nephritis                | 31(25.6)                       | 28(28.6)                      | 0.648   |
| Neuropsychiatric lupus         | 8(6.6)                         | 7(7.1)                        | 1.000   |
| Lupus pneumonia                | 3(2.5)                         | 0                             | 0.255   |
| Lupus related cardiac damage   | 0                              | 1(1.0)                        | 0.447   |
| Lupus related gastrointestinal damage | 3(2.5)                      | 0                             | 0.255   |
| **Antiphospholipid syndrome**  | 6(5.0)                         | 0                             | 0.034*  |
| SLEDAI-2 k (score), mean (SD)  | 11.6(4.1)                      | 10.4(4.2)                     | 0.800   |

**Initial serological indicators**

|                                | SLE flare group (n = 121 Case) | comparison group (n = 98 Case) | P-value |
|--------------------------------|--------------------------------|-------------------------------|---------|
| ANA (s/co), mean (SD)          | 4.6(2.7)                       | 4.7(3.1)                      | 0.336   |
| ds-DNA (IU/ml), mean (SD)      | 490.8(260.1)                   | 545.4(244.0)                  | 0.919   |
| Anti-RNP, n (%)                | 55(45.4)                       | 42(42.9)                      | 0.785   |
| Anti-SM, n (%)                 | 35(28.9)                       | 14(14.3)                      | 0.014*  |
| Anti-SSA, n (%)                | 82(67.8)                       | 56(57.1)                      | 0.122   |
| Anti-SSB, n (%)                | 27(22.3)                       | 21(21.4)                      | 1.000   |
| Anti-nu, n (%)                 | 46(38.0)                       | 14(14.3)                      | <0.001* |
| Anti-ORNP, n (%)               | 38(29.0)                       | 21(21.4)                      | 0.125   |
| aCL-IgG, n (%)                 | 4(3.3)                         | 7(7.1)                        | 0.226   |
| aCl-IgM, n (%)                 | 6(5.0)                         | 0                             | 0.034*  |
| Anti-β2GPI-IgG, n (%)          | 20(16.5)                       | 7(7.1)                        | 0.040*  |
| LA (n, %)                      | 13(10.7)                       | 0                             | <0.001* |

**Initial treatment**

|                                | SLE flare group (n = 121 Case) | comparison group (n = 98 Case) | P-value |
|--------------------------------|--------------------------------|-------------------------------|---------|
| The median time of achieving the clinical remission (Month), mean (SD) | 3.17 ± 0.70                   | 3.05 ± 0.65                    | 0.661   |
| SLE patients with Complete remission, n (%) | 5(4.1)                         | 7(7.1)                        | 0.380   |
| Glucocorticoid amount (mg/kg/d), mean (SD) | 0.9(0.9)                       | 0.9(0.4)                      | 0.323   |
| initial glucocorticoid amount > 0.8 mg/kg/d, n (%) | 23(19.0)                       | 21(21.4)                      | 0.735   |
| Glucocorticoid cumulative at the time of achieving clinical remission (mg), mean (SD) | 1780.8 ± 1016.1                | 1808.0 ± 1049.3                | 0.416   |
| Hydroxychloroquine, n (%)       | 98(81.0)                       | 91(92.9)                      | 0.017*  |
syndrome, anti-SM antibodies, AnuA, aCL (IgG), anti-β2-GPI (IgG), LA, use hydroxychloroquine for initial treatment, administration of immunosuppressants in initial treatment, patients’ self-discontinuation of medicine maintenance therapy. The results showed that infection, arthritis, thrombocytopenia, AnuA and anti-β2-GPI (IgG) were risk factors for SLE flare, patient’s self-discontinuation of medicine maintenance therapy after clinical remission of SLE would increase the risk of SLE flare, and the use of immunosuppressants and hydroxychloroquine in the initial treatment reduced SLE flare. (Table 2).

A subgroup analysis of patients with initial thrombocytopenia, which were divided into the Flare group and the Stable remission group (Table 3). There were no statistical differences in clinical symptoms and organ damages between the two groups. Glucocorticoid cumulative at the time of achieving clinical remission in the Flare group were less than that in the Stable remission group (1653.7 ± 942.4 mg vs 2384.7 ± 1390.0 mg, P < 0.001), and the proportion of using immunosuppressants in the Flare group were lower than that in the Stable remission group (9 cases, 47.4% vs 7 cases, 100%, P = 0.023). Among them, the use of cyclophosphamide

Table 1 Clinical characteristics and treatment in patients with SLE flare or sustained remission of SLE (Continued)

| Variable                        | SLE flare group (n = 121 Case) | comparison group (n = 98 Case) | P-value |
|---------------------------------|-------------------------------|-------------------------------|---------|
| Immunosuppressive agent treatment, n (%) | 49(40.5)                     | 70(57.9)                     | < 0.001*|
| CTX                             | 13 (10.7)                     | 21 (21.4)                    | 0.837   |
| MMF                             | 9 (7.4)                       | 7 (7.1)                      | 0.275   |
| AZA                             | 10 (8.3)                      | 17 (17.3)                    | 0.663   |
| MTX                             | 11 (9.1)                      | 13 (13.3)                    | 0.647   |
| FK-506                          | 2 (1.7)                       | 8 (8.2)                      | 0.194   |
| CsA                             | 4 (3.3)                       | 4 (4.1)                      | 0.716   |

Treatment during follow-up

| patient’s self-discontinuation of medicine maintenance therapy, n (%) | 65(53.7) | 7(7.1) | < 0.001* |
| Regular maintenance therapy before SLE flare | 56(46.3) | 91(93.8) | < 0.001* |

Prednisone(≤5 mg/d) | 8(6.6) | 24(24.5) |
Prednisone(≤5 mg/d) + HCQ | 20(16.5) | 32(32.7) |
Prednisone(≤5 mg/d) + HCQ + MMF | 6(5.0) | 7(7.1) |
Prednisone(≤5 mg/d) + HCQ + AZA | 9(7.4) | 11(11.2) |
Prednisone(≤5 mg/d) + HCQ + MTX | 10(8.3) | 11(11.2) |
Prednisone(≤5 mg/d) + HCQ + CsA | 2(1.7) | 3(3.0) |
Prednisone(≤5 mg/d) + HCQ + FK-506 | 1(0.8) | 3(3.0) |

N: Number of cases; *= P value < 0.05; a: white blood count < 4.0 × 10^9/L; b: platelet count < 100 × 10^9/L; SLEDAI-2 K Systemic lupus erythematosus disease activity index-2000; ANA antinuclear antibodies; ds-DNA: Anti double-stranded DNA antibody; Anti-RNP anti-ribonucleoprotein antibody; Anti-SSA anti-Smith antibody; Anti-SSB anti-Sjogren’s syndrome antigen B antibody; Anti-nu anti-nucleosome antibody; Anti-β2GPI anti-β2-glycoprotein I antibody; aCL anti-cardiolipin antibody; IgG immunoglobulin G; IgM immunoglobulin M; LA Lupus anticoagulant; HCQ Hydroxychloroquine; CTX Cyclophosphamide; MMF Mycophenolate mofetil; AZA Azathioprine; MTX Methotrexate; CsA Cyclosporine A; FK-506 Tacrolimus

Table 2 Multiple logistic regression analysis of risk factors for SLE flare

| Variable                        | OR    | 95%CI              | P-value |
|---------------------------------|-------|--------------------|---------|
| Infection                       | 31.383| (6.494,151.695)    | < 0.001 |
| Arthritis                       | 2.644 | (1.098,6.369)      | 0.030   |
| Thrombocytopenia                | 4.366 | (1.165,16.366)     | 0.029   |
| Anti-nucleosome antibody        | 2.927 | (1.107,7.740)      | 0.030   |
| Anti-β2-glycoprotein I antibody (IgG) | 5.291 | (1.224,22.875)     | 0.026   |
| Use immunosuppressant for initial treatment | 0.221 | (0.091,0.540) | 0.001 |
| Use Hydroxychloroquine for initial treatment | 0.267 | (0.076,0.936) | < 0.001 |
| Patient’s self-discontinuation of medicine maintenance therapy | 10.463 | (3.786,28.912) | < 0.001 |

OR odds ratio; 95%CI 95% confidence interval
was higher in the Stable remission group. The immunosuppressants used by the patient in the Flare group included CTX in 1, MMF in 1, CsA in 1, AZA in 3, and MTX in 3, while all patients with initial thrombocytopenia of the Stable remission group were treated with CTX.

Another subgroup analysis for patients with first-onset symptoms of arthritis, which were also divided into the Flare group and the Stable remission group. The SLE activity, organ damage, and treatment were compared in the patients with initial arthritis between the two groups, the result shows in (Table 3). Although the mean (SD) age of patients in the Flare group was lower than that of patients in the Stable remission group, the mean (SD) disease course of patients in the Flare group was longer than that of the Stable remission group. There was no statistical difference in clinical symptoms and organ damages between the two groups, however, the initial dose of glucocorticoids, glucocorticoid cumulative at the time of achieving clinical remission, and the proportion of using immunosuppressants in the Flare group were lower than those in the Stable remission group.

Figure 1 shows the Kaplan–Meier curves of the survival rate for patients with SLE who discontinued medicine maintenance therapy by themself and with regular medicine maintenance therapy, and the result showed they had a similar survival time [19.7 ± 0.9 years and 19.1 ± 0.7 years, respectively]. Five patients with SLE flare still die after received intensive treatment such as glucocorticoids or immunosuppressants again. The cause of death in the patients with SLE flare: central systemic involvement in 2, severe autoimmune pancreatitis in 1, severe pulmonary hypertension combine with infection in 1, diffuse alveolar hemorrhage with thrombocytopenia and infection in 1. The other patients with flare who had obtained stable condition after treatment and discharged from the hospital.

The occurrence of risk factors in different degrees of SLE flare
Among 121 patients with SLE flare, the proportion of patient’s self-discontinuation of medicine maintenance therapy (55/93 vs 10/28, \( P = 0.033 \)) and infection (47/93 vs 7/28, \( P = 0.019 \)) in the severe flare group was higher than that in the mild to moderate flare group. There was no significant difference in the incidence of other risk factors between patients with mild to moderate flare and those with severe flare. (Table 4).

### Table 3 Two subgroup analyses of patients with thrombocytopenia and arthritis at onset

|                          | SLE patients with arthritis at onset | SLE patients with thrombocytopenia at onset |
|--------------------------|-------------------------------------|--------------------------------------------|
|                          | Flare group (N = 67)                | Stable remission group (N = 42)            |
|                          | Flare group (N = 19)                | Stable remission group (N = 7)             |
| Age (Year), mean (SD)    | 43(13)                              | 46(8)                                      |
|                          | 0.008                               | 63(9)                                      |
| Gender (female/male)     | 62/5                                | 35/7                                       |
|                          | 0.207                               | 7/0                                        |
| Disease duration (Month), mean (SD) | 108.1(83.5)                          | 72.8(41.6)                                  |
|                          | 0.003                               | 66.6(66.2)                                 |
| SLEDAI-2 K, mean (SD)    | 13.2(4.0)                           | 13.7(4.2)                                  |
|                          | 0.964                               | 17.4(3.4)                                  |
| Initial organ damage     |                                     |                                            |
| Lupus nephritis          | 22(32.8)                            | 21(50.0)                                   |
|                          | 0.107                               | 5(71.4)                                    |
| Neuropsychiatric lupus   | 4(6.0)                              | 0                                           |
|                          | 0.158                               | 3(15.9)                                    |
| Lupus pneumonia          | 2(3.0)                              | 0                                           |
|                          | 0.522                               | 1(5.3)                                     |
| Lupus related cardiac damage | 0                                  | 1(2.4)                                     |
|                          | 0.385                               | 1(14.3)                                    |
| Gastrointestinal damage  | 1(1.5)                              | 0                                           |
|                          | 1.000                               | 0                                           |
| Initial treatment        |                                     |                                            |
| Glucocorticoid amount (mg/kg/d), mean (SD) | 0.82(0.32)                          | 1.05(0.47)                                  |
|                          | < 0.007                             | 1.31(0.24)                                 |
| Glucocorticoid cumulative at the time of achieving clinical remission (mg), mean (SD) | 1653.7(942.4)                          | 2384.7(1390.0)                             |
|                          | < 0.007                             | 2215.7(1112.3)                             |
| Hydroxychloroquine, n (%) | 54(80.6)                            | 38(90.5)                                   |
|                          | 0.188                               | 15(78.9)                                   |
| Immunosuppressors, n (%) | 30(44.8)                            | 28(66.7)                                   |
|                          | 0.031                               | 9(47.4)                                    |
| Patinet’s self-discontinuation of medication maintenance therapy, n (%) | 35(15.0)                            | 0                                           |
|                          | < 0.001                             | 8(42.1)                                    |

\( a \): the immunosuppressors used by the patients included CTX (12 cases), MMF (6 cases), CsA (2 cases), AZA (4 cases), and MTX (6 cases); \( b \): the immunosuppressors included CTX (14 cases), AZA (7 cases), and MTX (7 cases); \( c \): the immunosuppressors included CTX (1 cases), MMF (1 case), CsA (1 case), AZA (3 cases), and MTX (3 cases); \( d \): all patients were treated with CTX.
Relationship between patient’s self-discontinuation of medicine maintenance therapy and prognosis of SLE

Among the 121 patients with SLE flare, 65 patients discontinued medicine maintenance therapy by themself, and the other 56 patients took the glucocorticoid regularly and maintained at the minimum dose (prednisolone ≤5 mg/d), with or without hydroxychloroquine or immunosuppressant. There was no significant difference between patients who discontinued medicine maintenance therapy by themself and received regular maintenance therapy in terms of age, sex, disease duration, SLEDAI-2 K score and therapeutic drugs at the time of onset. However, the proportion of patients with severe flare of SLE was 84.6% in patients who discontinued medicine maintenance therapy by themself, and the proportion of severe flare of SLE in patients with regular maintenance therapy was 67.9% (P = 0.033) (Table 4). There were still two patients discontinued medicine maintenance therapy by themselves, who had SLEDAI-2 K score of 0 and experienced SLE flare for pulmonary hypertension. The symptoms of these patients were relieved after the treatment with glucocorticoids and immunosuppressants. The mean (SD) of SDI values and the SDI increment (SDI₂-SDI₁) at the last hospitalization

Table 4 The occurrence of risk factors in different degrees of SLE flare

| Risk Factor                                                                 | Mild or moderate SLE flare (n = 28) | Severe SLE flare (n = 93) | P-value |
|-----------------------------------------------------------------------------|------------------------------------|--------------------------|---------|
| Infection                                                                   |                                    |                          |         |
| Arthritis, n (%)                                                            | 7(25.0)                            | 47(50.5)                 | 0.019   |
| Thrombocytopenia, n (%)                                                     | 16(57.1)                           | 51(54.8)                 | 1.000   |
| Anti-nucleosome antibody, n (%)                                             | 6(21.4)                            | 13(14.0)                 | 0.378   |
| anti-β2-glycoprotein I antibody (IgG), n (%)                                | 9(32.1)                            | 37(39.8)                 | 0.513   |
| Use immunosuppressant for initial treatment, n (%)                          | 5(17.9)                            | 15(16.1)                 | 0.779   |
| Use Hydroxychloroquine for initial treatment, n (%)                         | 8(28.6)                            | 41(44.1)                 | 0.188   |
| patient’s self-discontinuation of medicine maintenance therapy, n (%)       | 21(75.0)                           | 77(82.8)                 | 0.412   |
| patient’s self-discontinuation of medicine maintenance therapy, n (%)       | 10(35.7)                           | 55(59.1)                 | 0.033   |
of patients who discontinued medicine maintenance therapy by themself was 2.06 ± 1.45 (mean ± SD) points and 1.86 ± 1.26 (mean ± SD) points, respectively, which were significantly higher than those in patients with regular maintenance therapy (P < 0.05) (Table 5). In terms of clinical manifestations, the incidence of serositis, anemia associated with SLE, and pulmonary hypertension were higher in patients who discontinued medicine maintenance therapy by themself than in patients with regular maintenance therapy (P < 0.01) (Table 5), while the incidence of other clinical symptoms was not significantly different between the two groups of patients. In the patients who discontinued medicine maintenance therapy by themself, the main causes of anemia were autoimmune hemolytic anemia in 12, aplastic anemia in 2, anemia secondary to lupus nephritis in 16, chronic anemia in 6. In the patients with regular maintenance therapy, anemia secondary to lupus nephritis in 7, chronic anemia in 5, autoimmune hemolytic anemia in 2.

Effect of maintenance therapy time on the occurrence of pulmonary hypertension, anemia associated with SLE, and serositis at the flare of SLE

According to whether there is anemia, arthritis and pulmonary hypertension at the time of SLE flare, 121 patients were divided into a pulmonary hypertension group and a non-pulmonary hypertension group, a serositis group and a serositis-free group, or an anemia group and an anemia-free group, respectively. Age, disease duration, sex, SLEDAI-2 K score and initial treatment in each group are shown in (Table 6). The proportions of patients with regular maintenance therapy of less than 1 year, 2 years, 3 years, 4 years, and 5 years in each group are listed in (Table 6). Models for logistic multivariate regression analysis were established using pulmonary hypertension, anemia associated with SLE, and serositis as dependent variables and using age, sex, disease duration, SLEDAI-2 K score, initial treatment and regular maintenance therapy of less than 3 years as independent variables. The results showed that SLE patients with regular maintenance therapy of less than 3 years were more prone to pulmonary hypertension [odds ratio (OR) = 2.986, 95% confidence interval (CI) (1.087, 8.202)] (P = 0.034) (Table 7). SLE patients with regular maintenance therapy of less than 1 year were more prone to serositis [odds ratio (OR) = 5.764, 95% confidence interval (CI) (1.642, 20.241)] (P = 0.006). High SLE activity was a risk factor for the occurrence of anemia associated with SLE and serositis, with OR values of 1.134 (95% CI 1.059, 1.214) and 1.156 (95% CI 1.070, 1.248), respectively (P < 0.001) (Table 7).

Discussion

SLE often has a disease process of alternating flare and remission. The cohort study published by Conti et al. showed that the annual flare rate of SLE was 7 to 9.4% [18], and multiple studies have shown that Asian SLE patients have a more severe disease condition, higher flare rate and higher organ damage rate than Caucasian patients [19]. Therefore, it is worthwhile to search for the risk factors for SLE flare and clarify their impact on the prognosis of SLE.

Infection as an important cause of death in SLE patients [5, 6, 20], especially in developing countries. A subsequent meta-analysis published in 2016 [21] provided evidence regarding a significant increase of mortality due to infectious complications, showing 4.98-fold increase in mortality. Meanwhile, infectious agents, including viruses, bacteria, parasites, and fungus, are a pivotal factor for induction of autoimmunity [22], which could lead to SLE flare. Infection also could result in organ damage in SLE patients, and its risk and prevalence are much higher because of the combined with a defective immune system and use of immunosuppressive drugs [3, 22, 23]. Therefore, infection is always a vulnerable point in SLE patients. Early recognition is crucial when considering that this condition is preventable and treatable, especially in the use of appropriate immunosuppressive therapy.

In this study, the occurrence of thrombocytopenia at the onset of SLE was a risk factor for SLE flare, while a cohort study by Minowa et al. [24] show the same results. For SLE patients with organ damage, clinicians usually use a high glucocorticoid starting dose and often in combination with immunosuppressants to achieve the remission of SLE and reduce the possibility of flare [8, 25, 26]. However, if there is blood system involvement, such as thrombocytopenia, the application of immunosuppressants should be chosen more cautiously because of the adverse effects of bone marrow suppression. In this study, we conducted a subgroup analysis of SLE patients with thrombocytopenia, the results showed that the use of immunosuppressants in the Stable remission group was higher than that in the Flare group (7/7 vs 9/19, P = 0.023), and the use of cyclophosphamide was higher in the Stable remission group.

At the same time, our results suggest that that arthritis is also a risk factor for SLE flare, especially patients who are younger at the onset of SLE deserve more attention. In fact, in clinical practice, we have found that the severity of arthritis in SLE patients is relatively mild, and the rate of deformity is significantly lower than that of rheumatoid arthritis. In most cases, the symptoms are quickly relieved after glucocorticoid treatment, so these patients are often overlooked by clinicians, immunosuppressants would not be used for treatment. The
### Table 5  The clinical characteristics in patients with SLE flare

| Characteristic                                      | patient’s self-discontinuation (n = 65 Case) | regular maintenance therapy (n = 56 Case) | P-value |
|-----------------------------------------------------|---------------------------------------------|------------------------------------------|---------|
| **Age (Year), mean (SD)**                           | 38.5(12.5)                                  | 41.6(13.7)                               | 0.396   |
| **Gender (female/male)**                            | 61/4                                        | 52/4                                     | 1.000   |
| **Disease duration (Month), mean (SD)**             | 91.6(82.3)                                  | 95.0(78.1)                               | 0.926   |
| **SLEDAI-2 k of first onset (score), mean (SD)**    | 10.9(3.8)                                   | 12.4(4.4)                                | 0.072   |
| **Initial treatment**                               |                                             |                                         |         |
| glucocorticoid amount (mg/kg/d), mean (SD)          | 0.9(0.3)                                    | 1.0(1.3)                                 | 0.153   |
| Hydroxychloroquine, n (%)                           | 52(80.0)                                    | 46(82.1)                                 | 0.819   |
| Immunosuppressive therapy, n (%)                    | 27(41.5)                                    | 22(39.3)                                 | 0.854   |
| **Regular maintenance treatment**                   |                                             |                                         |         |
| Prednisone(≤5 mg/d)                                 | /                                           | 56                                       | /       |
| Prednisone(≤5 mg/d) + HCQ                           | /                                           | 8                                        | /       |
| Prednisone(≤5 mg/d) + HCQ + MMF                     | /                                           | 20                                       | /       |
| Prednisone(≤5 mg/d) + HCQ + AZA                     | /                                           | 6                                        | /       |
| Prednisone(≤5 mg/d) + HCQ + MTX                     | /                                           | 9                                        | /       |
| Prednisone(≤5 mg/d) + HCQ + CsA                     | /                                           | 10                                       | /       |
| Prednisone(≤5 mg/d) + HCQ + FK-506                  | /                                           | 2                                        | /       |
| Prednisone(≤5 mg/d)HCQ + FK-506                     | /                                           | 1                                        | /       |
| **Characteristics of SLE flare**                    |                                             |                                         |         |
| Flare degree (mild moderate / severe, n/n)          | 10/55                                       | 18/38                                    | 0.033   |
| SLEDAI-2 k (Score), mean (SD)                       | 13.1(6.6)                                   | 10.5(5.6)                                | 0.140   |
| SDI1, mean (SD)                                     | 0.20(0.44)                                  | 0.25(0.48)                               | 0.270   |
| SDI2, mean (SD)                                     | 2.06(1.45)                                  | 1.21(1.07)                               | 0.042*  |
| SDI increment a, mean (SD)                          | 1.86(1.26)                                  | 0.96(0.89)                               | 0.011*  |
| **Clinical symptoms of flare, n (%)**               |                                             |                                         |         |
| Fever                                               | 16(24.6)                                    | 13(23.2)                                 | 1.000   |
| Rash                                                | 17(26.2)                                    | 18(32.1)                                 | 0.548   |
| Arthritis                                           | 12(18.5)                                    | 11(19.6)                                 | 1.000   |
| oral ulcer                                          | 5(7.7)                                      | 5(9.0)                                   | 1.000   |
| Serositis                                           | 26(40.0)                                    | 9(16.1)                                  | 0.005*  |
| Leukopenia                                          | 15(23.1)                                    | 15(26.8)                                 | 0.677   |
| Anemia associated with SLE                          | 36(55.4)                                    | 14(25.0)                                 | 0.001*  |
| Thrombocytopenia                                    | 14(21.5)                                    | 12(21.4)                                 | 1.000   |
| Vascularitis                                        | 10(15.4)                                    | 3(5.4)                                   | 0.086   |
| Lupus nephritis                                     | 38(58.5)                                    | 23(41.1)                                 | 0.069   |
| Neuropsychiatric lupus                              | 11(16.9)                                    | 14(25.0)                                 | 0.368   |
| Lupus pneumonia                                     | 12(18.5)                                    | 7(12.5)                                  | 0.456   |
| Pulmonary hypertension                             | 17(26.2)                                    | 3(5.4)                                   | 0.003*  |
| Lupus related cardiac damage                        | 9(13.8)                                     | 4(7.1)                                   | 0.378   |
| Lupus related gastrointestinal damage               | 8(12.3)                                     | 6(10.7)                                  | 1.000   |

* Number of cases; SLEDAI-2 K Systemic lupus erythematosus disease activity index-2000; SDI systemic lupus international collaborating clinics and the American College of Rheumatology diagnostic and therapeutic criteria committee damage index; SDI1, SDI at the time of complete or clinical response; SDI2, SDI at the last hospitalization; HCQ Hydroxychloroquine; MMF Mycophenolate mofetil; AZA Azathioprine; MTX Methotrexate; CsA Cyclosporine A; FK-506 Tacrolimus. *: SDI2-SDI1, 'SDI at the last hospitalization' – 'SDI at the time of complete or clinical response'. b: white blood count < 4.0 x 10^9/L. c: hemoglobin < 110 g/L. d: platelet count < 100 x 10^9/L. *: P < 0.05
subgroup analysis of SLE patients with arthritis in our study also shows that the proportion of using immunosuppressants in the Stable remission group was much higher than that in the Flare group. SLE patients with arthritis but without organ damage might have received lower-dose glucocorticoid treatments or lack of immunosuppressants treatments, which leads to a higher possibility of flare. During follow-up, SLE patients with arthritis do not have the precise remission criteria similar as rheumatoid arthritis, which depends more on the subjective feelings of the patients, and then a considerable proportion of patients with arthritis may have prematurely down-dosed the immunotherapy strength of SLE before a true remission has been achieved, which eventually results in flare. A study also reveals that SLE patients with arthritis who discontinued or reduce MTX usage were more likely to flare [11].

Clinically, many SLE patients are SACQ. For these patients, it is believed that intensive treatment should not be administered for the purpose of turning serological indicators negative. Previous clinical studies have confirmed that AnuA as a diagnostic indicator of SLE have

Table 6 Distribution of patients with SLE flare

| Pulmonary hypertension | Serositis | Anemia associated with SLE |
|------------------------|----------|---------------------------|
| **Yes (N = 20)**       | **Yes (N = 35)** | **Yes (N = 50)** |
| Age (Year), mean (SD)  | 41.3(11.8) | 39.7(13.4) | 37.7(12.7) | 40.9(12.3) | 37.6(13.8) | 41.6(12.5) |
| Gender (female/male)   | 20/0 | 93/8 | 34/1 | 79/7 | 47/3 | 66/5 |
| Disease duration (Month), mean (SD) | 109.6(79.5) | 89.9(80.2) | 93.1(85.3) | 93.2(78.4) | 86.3(71.1) | 98.0(86.0) |
| SLEDAI-2 K,mean (SD)  | 12.1(8.0) | 11.8(5.9) | 15.2(5.5) | 10.5(6.1) | 14.4(5.8) | 10.1(5.9) |

**Initial treatment**

| Glucocorticoid amount (mg/kg/d), mean (SD) | 0.80(0.22) | 0.95(0.97) | 0.89(0.34) | 0.94(1.04) | 0.88(0.37) | 0.96(1.13) |
| Hydroxychloroquine, n (%) | 18(90.0) | 80(79.2) | 30(85.7) | 68(79.1) | 43(86.0) | 57(77.5) |
| Immunosuppressive therapy, n (%) | 7(35.0) | 42(41.6) | 12(34.3) | 37(43.0) | 19(38.0) | 30(42.3) |
| Regular maintenance treatment, n (%) | 3(15.0) | 53(52.5) | 25(71.4) | 47(54.7) | 14(28.0) | 42(59.2) |
| maintenance therapy < 1 year, n (%) | 6(30.0) | 14(13.9) | 9(25.7) | 11(28.0) | 7(14.0) | 13(18.3) |
| maintenance therapy < 2 years, n (%) | 8(40.0) | 20(19.8) | 11(31.4) | 17(45.9) | 11(22.0) | 17(23.9) |
| maintenance therapy < 3 years, n (%) | 9(45.0) | 25(24.8) | 12(34.3) | 22(56.8) | 13(26.0) | 21(29.6) |
| maintenance therapy < 4 years, n (%) | 14(70.0) | 84(83.2) | 27(77.1) | 71(82.6) | 41(82.0) | 57(80.3) |
| maintenance therapy < 5 years, n (%) | 15(75.0) | 86(85.1) | 29(82.9) | 72(83.7) | 43(86.0) | 58(81.7) |

| Number of cases; SLEDAI-2 K Systemic lupus erythematosus disease activity index-2000

Table 7 Risk factors of pulmonary hypertension, anemia and serositis in SLE flare

| Pulmonary hypertension | Anemia associated with SLE | Serositis |
|------------------------|---------------------------|----------|
| OR 95%CI                | OR 95%CI                  | OR 95%CI |
| Age                    | 1.007 (0.963,1.053)       | 0.978 (0.946,1.012) | 0.979 (0.942,1.018) |
| Gender                 | 0.000 / 0.480 (0.094,2.446) | 0.177 (0.019,1.160) | 0.158 (0.043,0.577) |
| Disease duration       | 1.000 (0.993,1.008)       | 1.002 (0.995,1.008) | 1.003 (0.996,1.010) |
| SLEDAI-2 K             | 1.024 (0.942,1.113)       | 1.134 (1.059,1.214) | 1.156 (1.070,1.248) |
| Glucocorticoid amount  | 0.577 (0.105,3.185)       | 0.784 (0.426,1.442) | 0.889 (0.503,1.609) |
| Hydroxychloroquine     | 0.704 (0.217,2.290)       | 1.722 (0.602,4.963) | 2.085 (0.637,6.821) |
| Immunosuppressive therapy | 0.883 (0.299,2.606) | 0.973 (0.423,2.236) | 0.742 (0.294,1.874) |
| Regular maintenance treatment | 0.158 (0.043,0.577) a | 0.319 (0.141,0.720) f | 0.362 (0.145,0.908) h |
| Maintenance therapy < 1 years | 4.000 (1.232,12.989) b | 0.687 (0.205,2.299) | 5.764 (1.642,20.241) j |
| Maintenance therapy < 2 years | 3.208 (1.129,9.115) c | 0.799 (0.288,2.216) | 2.283 (0.759,6.684) |
| Maintenance therapy < 3 years | 2.986 (1.087,8.202) d | 0.734 (0.266,0.222) | 1.745 (0.584,5.215) |
| Maintenance therapy < 4 years | 2.252 (0.627,8.089) | 0.776 (0.254,2.374) | 1.335 (0.403,4.420) |

a,b,c,d,e,f,g,h,i,j,k,l,m,n,o,p,q,r,s,t,u,v,w,x,y,z,aa,ab,ac,ad,ae,af,ag,ah,ai,aj,ak,al,am,an,ao,ap,aq,ar,as,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,bi,bj,bk,bl,bm,bn,bo,bp,bq,bc,br,bs,at,au,av,aw,ax,ay,az,b,bc,bd,be,bf,bg,bh,
higher sensitivity compared with anti-SM antibodies and a specificity of higher than 90% [27]. It has a certain correlation with disease activity [27] and may be involved in the pathogenesis of organ damage in SLE patients. Our study suggests that AnuA may be a risk factor for SLE flare, so when AnuA in the serum of SLE patients are persistently positive, immunotherapy should not be terminated whether the patient has achieved clinical remission or not.

Anti-β2 glycoprotein-I (β2GPI) is one of the diagnostic antibodies of APS, which have also been detected in a large range of autoimmune diseases, such as SLE [28, 29] and so on. The mechanism of thrombosis induced via the action of anti-β2GPI has been described: this action is mediated by dimerization of β2GPI by platelet factor 4 (PF4) tetramers, dimerization takes place mainly in the presence of anti-β2GPI antibodies which in turn bind to the PF4/β2GPI complexes and activate platelets [29]. In our study, there were a total of 20 patients with IgG subtype of anti-β2GPI positive in the SLE flare group, among them, including 3 cases of hemolytic anemia, 3 cases of interstitial pneumonia, 3 cases of Raynaud’s phenomenon, 2 cases of cerebral infarction, 3 cases of intestinal obstruction secondary to mesenteric vasculitis and thrombosis and 2 cases of pulmonary hypertension, which suggest that vascular disease or microvascular disease may be the main pathological basis of organ damage in these patients. Based on the pathogenic mechanism of anti-β2GPI in vitro, we speculate that it may induce thrombosis or micro thrombosis, which lead to chronic vascular disease and SLE flare. Taraborelli M’s study reveal that a clinically significant antiphospholipid antibody profile is associated with an increased risk of organ damage accrual during a 15-year follow-up in SLE patients [30]. Although we also found that the positive rates of aCL and La in patients with SLE flare were higher than those in patients with SLE remission, multiple regression analysis showed that aCL and LA were not risk factors for SLE flare. It is possible that the binding ability of anti-β2GPI to the target antigen is different from that of other antiphospholipid antibodies, the specific mechanism remains to be studied.

In China, most SLE patients are treated with low-dose glucocorticoids or combined with hydroxychloroquine as maintenance therapy, when they reached clinical remission [2, 9]. Only a few patients are treated with hydroxychloroquine as maintenance therapy alone [9]. Most SLE patients will reduce or stop immunosuppressants when the disease is stabilized. Studies show that SLE patients with low-dose glucocorticoid maintenance therapy have a significantly lower flare rate than patients with discontinuation of medicine maintenance therapy [31, 32]. In fact, most SLE patients require glucocorticoid maintenance therapy to achieve long-term clinical remission, and fewer than 15% of patients without glucocorticoid maintenance therapy have achieved 5-year clinical remission [33]. However, long-term glucocorticoid maintenance therapy greatly increases the incidence of complications, such as infection and osteoporosis, in SLE patients [34], which seriously affect the quality of life of patients. Therefore, the recommendations for the management of SLE suggest that glucocorticoids progressive tapering until withdrawal, when SLE patients reach to complete remission [8]. But little evidence on immunosuppressants withdrawal in remitted patients is available [11].

Patients reducing the dose or stopping a drug altogether is one of the most common causes of flare in Chinese patients with SLE [2]. Poor understanding of the disease and the glucocorticoids as well as the fear of adverse reactions of the drugs are the most common reasons for discontinuation of drug maintenance therapy [2]. Due to the restrictions of medical ethics, it is difficult for clinical research to prospectively observe the effect of termination of drug maintenance therapy on disease progression and long-term prognosis when SLE patients have reached clinical remission. Therefore, there are still many unanswered questions about maintenance therapies for SLE patients, such as whether the drugs can be terminated and what the indicators of drug termination are. This study found that for patients with flared SLE, patient’s self-discontinuation of medicine maintenance therapy demonstrated higher severity of the disease and higher incidence of new organ damage, such as SLE related anemia, serositis and pulmonary hypertension.

It has been reported that the serositis usually related to SLE activity and severity [35–37], especially in nephropathy, interstitial lung disease, pulmonary hypertension and hematologic involvement [35]. Organ damage of SLE patients with serositis were generally more severe than patients without serositis [36]. In our study, we found that the probability of SLE patients complicated with serositis was significantly increased if the duration of medicine maintenance therapy less than 1 year. The systemic damage of SLE was induce by vasculitis and non-inflammatory vascular remodeling [38–40]. Vasculitis is significantly correlated with the activity of SLE [38], while the pathophysiological mechanisms of non-inflammatory vascular remodeling may play an important role when the course of the disease is longer [38, 40], which might act as a key factor in the choice of treatment strategy and the prognosis. Vascular remodeling erodes multiple organs throughout the body along the course of the disease, and they tend to become chronic, requiring long-term drug control or even lifelong medication. Therefore, the maintenance therapy is important, and premature medicine withdrawal can
cause irreversible organ damage and poor prognosis. In our study, if the duration of maintenance treatment less than 3 year, we found that the probability of SLE patients complicated with pulmonary hypertension was significantly increased. These results show that insufficient maintenance treatment may cause more severe SLE activity and organ damage. Meanwhile, more large-scale prospective researches are needed for further exploration.

Although there is no difference in the survival rate between SLE patients who discontinued medicine maintenance therapy by themself and received regular maintenance therapy. This may be related to the fact that the patients included in this study only experienced the first SLE flare. It is a limitation to evaluate the overall prognosis of SLE patients with drug withdrawal.

Conclusion

In conclusion, our study demonstrates that SLE patients with infection, thrombocytopenia, arthritic or positive AnuA/β2GPI(IgG) antibody have an increased risk of SLE flare. Therefore, special attention needs to be paid to these patients during remission. The use of immunosuppressors and hydroxychloroquine during the initial treatment of SLE can lower the risk of flare. Patients with discontinuation of medicine maintenance therapy are prone to more severe flares and organ damage, of which pulmonary hypertension being the most significant. According to the research results, we recommend that SLE patients have regular maintenance therapy for no less than 3 years during remission. Certainly, larger scale clinical studies will be conducive to point out the indication of drug withdrawal.

Abbreviations

SLE: Systemic lupus erythematosus; ACR: American College of Rheumatology; SLEDAI-2K: Systemic lupus erythematosus disease activity index 2000; SDE: Systemic lupus erythematosus damage index; SACCDO: Serological active clinical quiescent disease; ANA: Antinuclear antibodies; ds-DNA: Anti-double-stranded DNA antibodies; anti-RNP: Anti-ribonucleoprotein antibodies; anti-SM: Anti-Smith antibodies; anti-SSA: Anti-Sjogren’s syndrome A antibodies; anti-SSB: Anti-Sjogren’s syndrome B antibodies; AnuA: Anti-nucleosome antibodies; aCL: Anti-cardiolipin antibodies; anti-β2GPI: Anti-β2-glycoprotein I; LAs: Lupus anticoagulants; APS: Antiphospholipid syndrome; PF4: Platelet factor 4

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Authors’ contributions

Contributors All authors as listed below, XZ, LZ, HR, RK, JC, HC, JL, were involved in all the following aspects of the research presented: Substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. XZ was responsible for the intellectual contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. XZ was responsible for the intellectual content of the study. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The studies involving human participants were reviewed and approved by Branch for Medical Research and Clinical Technology Application, Ethics Committee of the First Affiliated Hospital of Fujian Medical University (Grant No. 2018101).

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no conflict of interest.

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