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ORIGINAL ARTICLE

Glucocorticoid, immunosuppressant, hydroxychloroquine monotherapy, or no therapy for maintenance treatment in systemic lupus erythematosus without major organ manifestations

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Abstract

Objective To study maintenance therapy after achievement of the lowest possible disease activity in systemic lupus erythematosus (SLE) without major organ manifestations.

Methods We retrospectively evaluated patients with SLE who visited our hospital from Jan 2015 to Feb 2018 and were taking prednisolone (PSL) < 10 mg/day. After excluding those with neuropsychiatric SLE or severe lupus nephritis, patients were divided into four groups according to their maintenance monotherapy treatment, namely, prednisolone (PSL), immunosuppressant (IS), hydroxychloroquine (HCQ), and no drugs. The groups were then compared with regard to cumulative flare rate and changes in SLE Disease Activity Index (SLEDAI).

Results There were 47 patients on PSL, 10 on IS, 5 on HCQ, and 11 on no drugs. Flare rate was higher in the no drug group, and no patients with the IS or HCQ group experienced a flare ($p = 0.003$). A reduction in SLEDAI was only seen in the IS and HCQ groups ($p = 0.05$ and $p = 0.03$, respectively). There were no differences in adverse events among groups during the study period.

Conclusions Our results suggest that the cessation of all drugs is associated with disease flare for SLE patients without major organ manifestations. IS or HCQ monotherapy might be a reasonable maintenance strategy comparing with steroid monotherapy.

Key Point
• *Immunosuppressant or hydroxychloroquine monotherapy appears to be a reasonable maintenance strategy.*

Keywords Hydroxychloroquine · Immunosuppressive agents · Relapse · Systemic lupus erythematosus

Introduction

Glucocorticoids (GC), immunosuppressants (IS), and hydroxychloroquine (HCQ) are cornerstones of systemic lupus erythematosus (SLE) treatment [1], and these drugs are largely used to alleviate symptoms and suppress disease activity. According to a strategy proposed in 2014, after achieving clinical remission or the lowest possible disease activity, the goal should be the lowest GC dosage needed to control disease and, if possible, complete withdrawal of GCs during maintenance therapy [2]. This strategy further mentioned that preventing flares should be the therapeutic goal for reducing damage accrual. In clinical practice, physicians combine these drugs to control disease activity and subsequently reduce the GC dose to as low as possible. After achieving very-low dose GC, however, it has not been clarified which drugs, including GC, IS, and HCQ, should be continued to prevent flares, especially in patients with nonmajor organ manifestations. There is evidence that HCQ prevents flares, but the effect of HCQ monotherapy on disease flare prevention has not been well investigated [3]. Furthermore, an international task force, definitions of remission in SLE (DORIS), recently proposed that complete remission should be strictly defined as the total absence of clinical activity without the use of medication for SLE, including GC and IS [4, 5]. However, few data are available on the withdrawal of GC, IS, or even HCQ in patients with nonmajor organ manifestations [6, 7].

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Here, we performed a retrospective study to compare flare rates and changes in disease activity when these drugs were used as monotherapy or withdrawn for maintenance therapy in SLE patients without major organ manifestations.

Materials and methods

Patients

We performed a retrospective study of Japanese patients who met the American College of Rheumatology (ACR) classification criteria for SLE [8] and who visited St. Marianna University Hospital from Jan 2015 through Feb 2018. Observation was made from the earliest point to the latest point when they visited from Jan 2015 to Feb 2018. Thus, the baseline point in this study was the earliest point in the observational periods. All the patients who were selected in this study were treated by rheumatologist (board-certified rheumatologist in Japan College of Rheumatology) and SLE experts. Patients who were taking prednisolone (PSL) at < 10 mg/day were selected and divided into two groups whether they were taking any drugs or not. Then, they were divided into four groups according to their maintenance treatment regimen, namely, PSL, IS, HCQ, and no treatment. Patients with any combination therapy were excluded. Since HCQ was not approved in Japan until 2015, those in the HCQ group had newly started HCQ during this study period. We compared their clinical characteristics up to Feb 2018. Patients were excluded if they had neuropsychiatric SLE [9], lupus nephritis class III or IV [10], or any manifestations that were categorized as severe activity according to the British Society for Rheumatology guideline for the management of SLE in adults [1]. Among the 154 patients identified as having SLE, 81 had been treated with PSL at more than 10 mg/day or by combination treatment with PSL plus IS or HCQ and were excluded. Finally, we evaluated 47 on PSL, 10 on IS, 5 on HCQ, and 11 on no drugs.

This study was approved by the Ethics Committee of St. Marianna University School of Medicine (approval number 3305). Because the study was conducted under a retrospective cohort design that did not conduct any investigations/interventions besides those for clinical use, written informed consent was not required, in accordance with the guidelines of the Japanese Ministry of Health, Labour and Welfare. This study was carried out as per routine clinical care, and medication was initiated at the discretion of the attending physician.

Data collection

Clinical information was obtained at baseline and at the last visit. Data included demographic and clinical features, PSL dose, and SLE Disease Activity Index (SLEDAI) [11]. Changes in SLEDAI were compared between the baseline and the last visit. Incidence of flare during the observation period was determined using the SLE Flare Index (SFI) by chart review [12]. Patients in this study experienced moderate/mild and severe flares of SFI.

Statistical analysis

Continuous values are shown as mean ± standard deviation. Differences between groups were analyzed using the Mann-Whitney *U* test or Kruskal-Wallis test for nonparametric data and the chi-squared or Fisher's exact test for categorical data. The cumulative flare rate was calculated using the Kaplan-Meier method, and differences between the two groups were tested using the log-rank test.

Results

Baseline clinical characteristics

Clinical features at baseline between patients with any drugs and no drugs are shown in Table 1, and we found no significant difference between these groups. We next investigated baseline clinical features among the four groups depending on the treatments (Table 2). The length of the observation periods did not significantly differ among the groups (mean 14.9 months). Patients in the PSL monotherapy group had longer disease duration ($p = 0.03$) than those in the other groups. Most patients in all groups mainly manifested skin involvement, arthritis, and cytopenia. Mean PSL dose in the PSL mono group was 5.9 mg/day.

Cumulative flare rate and change in SLEDAI

We next examined the flare rate between patients with any drugs and no drugs (Fig. 1a). A significantly higher flare rate was observed in the no drugs group than any drugs group ($p < 0.0001$); however, there was no significant difference between them in the SLEDAI change from baseline (Fig. 1b). We further examined the flare rate depending on the treatments (Fig. 2a) and found flare rate was significantly higher in the no drugs group than other groups ($p = 0.003$). There was no significant difference among the PSL-mono, IS-mono, and HCQ-mono groups. The SLEDAI was significantly reduced in the IS-mono and HCQ-mono groups compared with the no drugs and PSL groups ($p = 0.04$ and $p = 0.02$, respectively) (Fig. 2b).

Cumulative flare rate and the last initial treatment before study enrolment

To investigate the influence of the previous treatment on results, we reviewed the last initial treatment before the

Table 1 Baseline clinical characteristics

Clinical features	No drugs ($n = 11$)	Any drugs ($n = 62$)	p
Sex (female), *n* (%)	10 (90.1)	57 (91.9)	0.90
Age (years)	53.8 ± 16.6	47.9 ± 15.1	0.46
Disease duration (months)	90.0 ± 70.7	181.2 ± 292.2	0.41
Observation (months)	14.0 ± 3.9	14.9 ± 5.6	0.80
WBC (× 1000/μL)	4.6 ± 2.2	5.4 ± 2.1	0.40
Hb (g/dL)	12.2 ± 1.7	12.1 ± 1.7	0.56
Plt (× 10^4/μL)	21.3 ± 9.5	21.7 ± 5.8	0.90
SLEDAI	2.3 ± 3.5	1.7 ± 1.5	0.89
Proteinuria (g/gCr)	0.1 ± 0.3	0.1 ± 0.2	0.91
eGFR (mL/min/1.73 m^2)	70.6 ± 20.0	76.6 ± 26.2	0.85
CRP (mg/dL)	0.8 ± 2.2	0.3 ± 0.6	0.92
CH50 (U/mL)	37.3 ± 8.8	34.5 ± 10.3	0.12
Anti-Sm antibody-positive, *n* (%)	1 (9.1)	8 (12.9)	0.72
Anti-dsDNA antibody (IU/mL)	19.3 ± 39.2	15.3 ± 31.7	0.26
Anti-cardiolipin antibody (IU/mL)	8.8 ± 1.8	6.9 ± 3.3	0.68
Lupus anticoagulant-positive, *n* (%)	4 (36.3)	10 (16.1)	0.11
Organ manifestations			
Skin, *n* (%)	2 (18.2)	14 (22.5)	0.74
Arthritis, *n* (%)	3 (27.3)	10 (16.1)	0.37
Cytopenia, *n* (%)	3 (27.3)	14 (22.6)	0.73
Serositis, *n* (%)	2 (18.2)	5 (8.1)	0.29
LN class II, *n* (%)	0	5 (8.1)	0.32
Class V, *n* (%)	1 (9.1)	7 (11.3)	0.82
Others, *n* (%)	0	7 (14.9)	0.24
PSL (mg/day)	–	5.9 ± 3.0	–
MMF use, *n* (%)	–	4 (6.4)	–
TAC use, *n* (%)	–	3 (4.8)	–
CyA use, *n* (%)	–	3 (4.8)	–
MTX use, *n* (%)	–	–	–
AZP use, *n* (%)	–	–	–

Values indicate mean ± standard deviation unless otherwise indicated

WBC white blood cells, *Hb* hemoglobin, *Plt* platelets, *GFR* glomerular filtration rate, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *CRP* c-reactive protein, *dsDNA* double-stranded DNA, *LN* lupus nephritis, *PSL* prednisolone, *MMF* mycophenolate mofetil, *TAC* tacrolimus, *CyA* cyclosporine, *MTX* methotrexate, *AZA* azathioprine

study period (Fig. 3). In patients in the no drugs group, three patients (27.3%) had been treated with PSL-mono, three (27.3%) with PSL + IS, and five (45.5%) with no drugs. These three subgroups showed no statistically significant differences in the rate of flares, albeit that numbers were low (66.7%, 33.3%, and 40%, respectively). Most of the PSL-mono group had been treated with PSL-mono previously (97.8%), and seven patients (15.2%) experienced flare; the one patient in the PSL-mono group who had been treated with PSL + IS also experienced flare during observation. Among the ten patients in the IS-mono group, two had been treated with PSL-mono previously and the other eight had been treated with PSL and IS. No patient in the IS-mono group experienced a flare. None of the five patients in the HCQ-mono group had been previously treated, and none of them experienced a flare.

In summary of flare rate by the last treatment provided, patients in the PSL-mono group had a higher flare rate than those in the IS-mono group regardless of the previous treatment. No patient with HCQ had been previously treated, and none experienced flare during observation.

Adverse events

Table 3 summarizes adverse events (AEs) over the study period. There were no deaths or serious AEs. Increases in steroid-related metabolic markers, including low-density

Table 2 Baseline clinical features

Clinical features	No drugs ($n = 11$)	PSL-mono ($n = 47$)	IS-mono ($n = 10$)	HCQ-mono ($n = 5$)	p
Sex (female), *n* (%)	10 (90.1)	44 (93.6)	8 (80.0)	5 (100.0)	0.37
Age (years)	53.8 ± 16.6	49.0 ± 14.7	48.5 ± 18.5	36.8 ± 5.3	0.26
Disease duration (months)	90.0 ± 70.7	226.0 ± 334.3	72.1 ± 74.1	61.3 ± 75.2	0.03*
Observation (months)	14.0 ± 3.9	14.7 ± 4.5	18.1 ± 8.6	10.5 ± 7.0	0.17
WBC (× 1000/μL)	4.6 ± 2.2	5.7 ± 2.2	5.1 ± 2.2	3.7 ± 0.9	0.08
Hb (g/dL)	12.2 ± 1.7	12.4 ± 1.5	10.6 ± 2.5	12.6 ± 0.7	0.09
Plt (× 10^4/μL)	21.3 ± 9.5	21.5 ± 5.9	23.5 ± 5.5	20.9 ± 4.9	0.60
SLEDAI	2.3 ± 3.5	1.9 ± 3.8	1.8 ± 1.0	2.0 ± 2.2	0.12
Proteinuria (g/gCr)	0.1 ± 0.3	0.1 ± 0.3	0.4 ± 0.6	0.4 ± 0.5	0.11
eGFR (mL/min/1.73 m^2)	70.6 ± 20.0	75.2 ± 27.4	77.5 ± 24.3	88.6 ± 16.6	0.50
CRP (mg/dL)	0.8 ± 2.2	0.3 ± 0.6	0.1 ± 0.1	0.1 ± 0.1	0.49
CH50 (U/mL)	37.3 ± 8.8	36.3 ± 10.7	28.4 ± 12.6	32.5 ± 12.0	0.22
Anti-Sm antibody-positive, *n* (%)	1 (9.1)	3 (6.3)	4 (60.0)	1 (20.0)	0.11
Anti-dsDNA antibody (IU/mL)	19.3 ± 39.2	10.9 ± 14.3	37.7 ± 70.5	11.5 ± 11.2	0.61
Anti-cardiolipin antibody (IU/mL)	8.8 ± 1.8	8.3 ± 2.7	19.5 ± 36.0	8.3 ± 0.6	0.82
Lupus anticoagulant-positive, *n* (%)	4 (36.3)	7 (14.8)	2 (20.0)	1 (20.0)	0.61
Organ manifestations					
Skin, *n* (%)	2 (18.2)	11 (23.4)	1 (10.0)	2 (40.0)	0.93
Arthritis, *n* (%)	3 (27.3)	7 (14.9)	2 (20.0)	1 (20.0)	0.83
Cytopenia, *n* (%)	3 (27.3)	12 (25.5)	2 (20.0)	0	0.91
Serositis, *n* (%)	2 (18.2)	4 (8.5)	1 (10.0)	0	0.93
LN class II, *n* (%)	0	2 (4.3)	2 (20.0)	1 (20.0)	0.88
Class V, *n* (%)	1 (9.1)	4 (8.6)	2 (20.0)	1 (20.0)	0.97
Others, *n* (%)	0	7 (14.9)	0	0	0.67
PSL (mg/day)	–	5.9 ± 3.0	–	–	–
MMF use, *n* (%)	–	–	4 (40.0)	–	–
TAC use, *n* (%)	–	–	3 (30.0)	–	–
CyA use, *n* (%)	–	–	3 (30.0)	–	–
MTX use, *n* (%)	–	–	–	–	–
AZP use, *n* (%)	–	–	–	–	–

Values indicate mean ± standard deviation unless otherwise indicated

PSL prednisolone, *IS* immunosuppressant, *HCQ* hydroxychloroquine, *mono* monotherapy, *WBC* white blood cells, *Hb* hemoglobin, *Plt* platelets, *GFR* glomerular filtration rate, *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index, *CRP* c-reactive protein, *dsDNA* double-stranded DNA, *LN* lupus nephritis, *PSL* prednisolone, *MMF* mycophenolate mofetil, *TAC* tacrolimus, *CyA* cyclosporine, *MTX* methotrexate, *AZA* azathioprine

*PSL vs. IS, $p < 0.05$

lipoprotein cholesterol and hemoglobin A1C, were observed in the PSL-mono group.

Discussion

Our results suggest that patients who were treated with IS-mono and HCQ-mono had a significant reduction in SLEDAI. Cessation of all drugs might lead to an increased risk of disease flare. In contrast, IS or HCQ monotherapy may represent reasonable maintenance strategies to prevent flares in SLE patients without major organ manifestations for a short observation period.

According to the British Society for Rheumatology guideline for the management of SLE in adults [1], patients with moderate disease activity should be treated with PSL < 0.5 mg/kg/day plus HCQ and/or IS. After stable remission is achieved, physicians should aim to reduce and stop drugs, except HCQ. However, the order of drug reduction or cessation is not specifically mentioned. One prospective study reported that HCQ reduced flares, but 50% of subjects also used GC, and it is therefore unclear which drug is more effective in reducing flare when used as monotherapy [3]. In Japan, since HCQ was not approved until 2015, we were able to evaluate the efficacy of IS-mono and PSL-mono on disease flare.

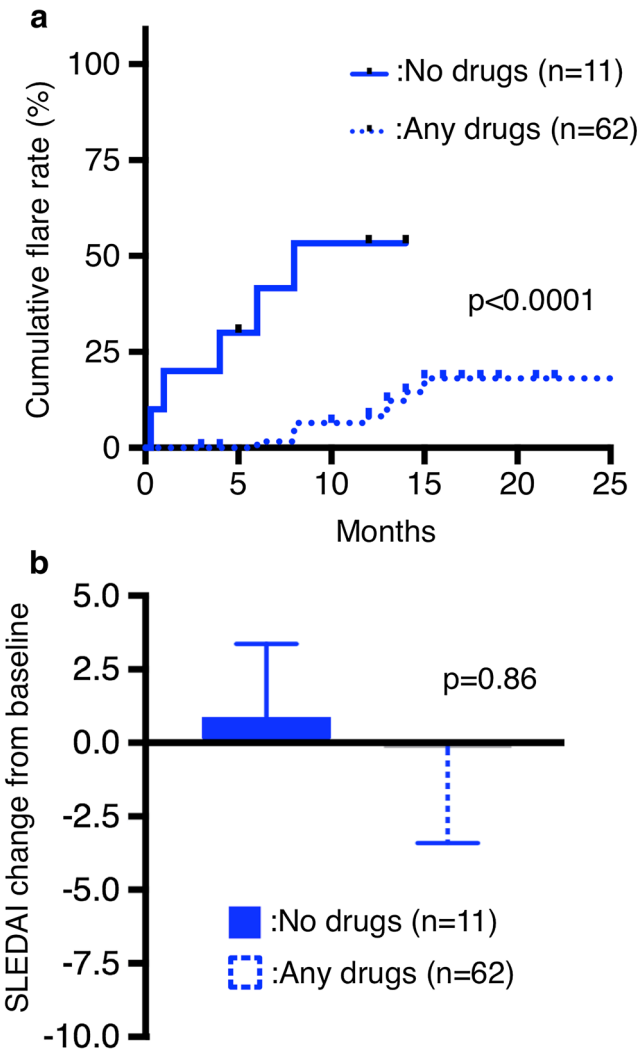

Fig. 1 Cumulative flare rate and change in SLEDAI for patients with no drugs and any drugs. Cumulative flare rate (**a**) and SLEDAI change from baseline (**b**) are shown. SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

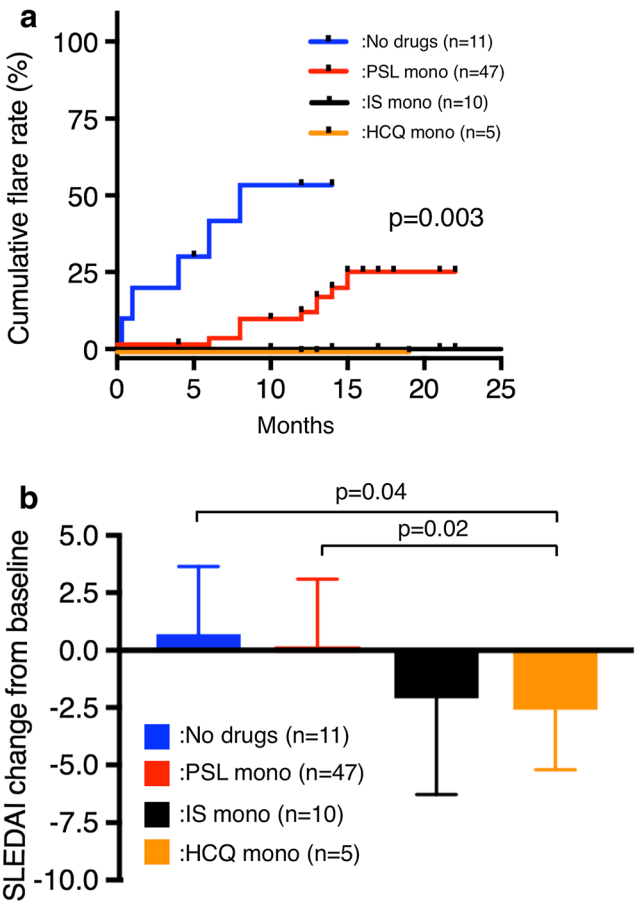

Fig. 2 Cumulative flare rate and change in SLEDAI for each treatment. Cumulative flare rate (**a**) and SLEDAI change from baseline (**b**) are shown. PSL, prednisolone; IS, immunosuppressant; HCQ, hydroxychloroquine; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index

Our results suggest that IS and HCQ monotherapy might have superior efficacy to PSL monotherapy regarding reduction of flare incidence and SLEDAI. Since the last treatment before this study might have influenced the results, we also analyzed flare rates by the previous treatment. In that analysis, regardless of any previous treatment, patients treated with IS monotherapy experienced the lowest flare rate for the maintenance phase among monotherapies. No patient with HCQ had been previously treated, and none experienced flare during observation. IS or HCQ monotherapy therefore appears to be the most effective in suppressing flare in our study.

Discontinuation of all drugs without disease flare is a desirable outcome in SLE treatment. DORIS recently defined complete remission to include a clinical SLEDAI = 0, physician's global assessment < 0.5 cm, PSL = 0 mg/day, no IS, and serological stability [4, 5]. One randomized pilot study comparing PSL monotherapy with no drugs in patients with lupus nephritis class III/IV/V in maintenance phase concluded that there was no significant difference in flare rate [13]. Regarding nonmajor organ manifestations, however, the possibility of a complete withdrawal of therapy while minimizing the risk of flare remains unclear. Few data are available about withdrawal of therapy in SLE without major organ manifestation [14–17]. In a cohort of 667 SLE patients, 156 (23%) were able to stop therapy and maintain remission for a mean of 5.8 years. Steiman et al. reported that 2.4% of SLE patients took no medications for ≥ 5 years, while Zen et al. reported the complete withdrawal of therapy in 7.1% of SLE patients for ≥5 years. Our results suggest that patients who had been previously treated with PSL monotherapy or PSL + IS experienced a 50% risk of flare over a mean observation period of 14.0 months if they discontinued all drugs. Allowing that patient number in the HCQ monotherapy group was low ($n = 5$), our findings may suggest that HCQ monotherapy should be used as minimal maintenance therapy [1, 4, 5].

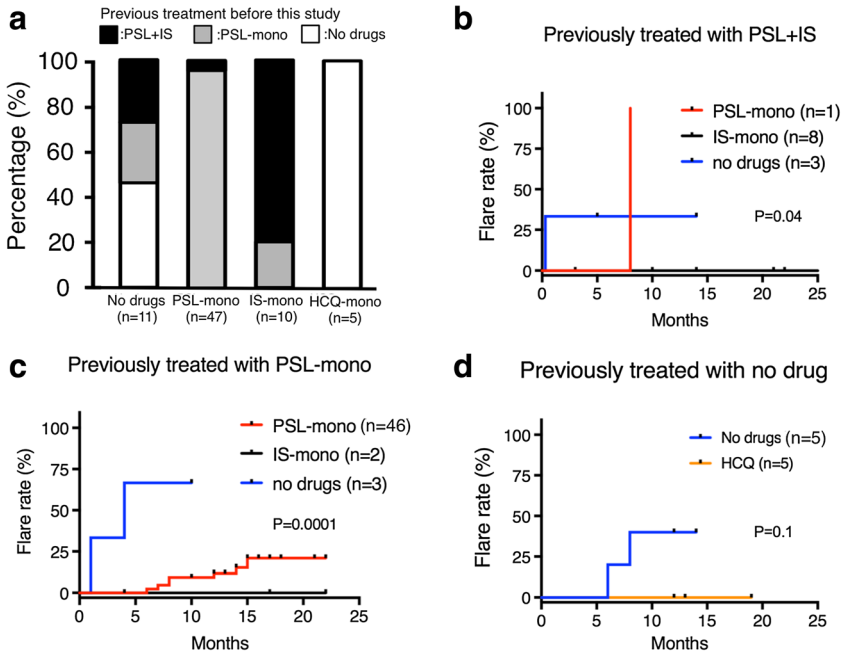

Fig. 3 Cumulative flare rate by previous treatment. Previous treatment (**a**) and cumulative flare rate in patients who had previously been treated with PSL + IS (**b**), PSL-mono (**c**), and no drugs (**d**). PSL, prednisolone; IS, immunosuppressant; HCQ, hydroxychloroquine

This study is limited by its single-center nature, retrospective observational design, relatively short observation period, and small sample size. Statistical significance might not have been reached because of the small sample size. Furthermore, treatment strategy was changed at the discretion of the attending physicians, which may have influenced the results. Since the flare was counted by chart review, it poses the risk of missing flares. This study was conducted retrospectively, and enrolled patients were very small; therefore, adverse events were not accurately collected. Confirmation of our findings will require a multicenter prospective study.

In conclusion, these findings suggest that cessation of all drugs increases the risk of disease flare for SLE patients without major organ manifestations. As monotherapy, IS or HCQ may be a reasonable maintenance strategy comparing with steroid, but further insight into this aspect is left to future work.

Table 3 Adverse events

	No drugs ($n = 11$)	PSL mono ($n = 47$)	IS mono ($n = 10$)	HCQ mono ($n = 5$)	p
Death	0	0	0	0	–
Serious adverse event	0	0	0	0	–
Infection (total)	1 (9.1)	3 (6.4)	1 (10.0)	0	0.87
Respiratory infection	1 (9.1)	1 (2.1)	1 (10.0)	0	0.52
Urinary tract infection	0	2 (4.2)	0	0	0.53
Gastrointestinal					–
Nausea	0	0	1 (10.0)	1 (20.0)	0.61
Diarrhea	0	0	0	0	–
Laboratory data					
Leukopenia, WBC count < 4000/μL	1 (10.0)	1 (2.1)	3 (30.0)	0	0.09
Anemia, Hb < 11.0 g/dL	0	2 (4.2)	1 (10.0)	0	0.90
Thrombocytopenia, Plt count < 10×10^4/μL	0	0	0	0	–
Abnormal liver function test	0	1 (2.1)	1 (10.0)	0	0.71
HbA1c increasing	0	3 (6.4)	0	0	0.89
LDL-C increasing	0	6 (12.8)	0	0	0.77

WBC white blood cells, *Hb* hemoglobin, *Plt* platelets, *HbA1c* hemoglobin A1C, *LDL-C* low-density lipoprotein cholesterol

Compliance with ethical standards

This study was approved by the Ethics Committee of St. Marianna University School of Medicine (approval number 3305).

Disclosures None.

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