Glucocorticoid Discontinuation in Patients With Systemic Lupus Erythematosus With Prior Severe Organ Involvement: a Single-center Retrospective Analysis

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Abstract

Background:

Long-term glucocorticoid use in systemic lupus erythematosus (SLE) may have significant side effects; however, glucocorticoid discontinuation is occasionally associated with disease flare-ups. Therefore, we evaluated the risk factors for disease flares and the flare rate upon glucocorticoid tapering in patients with prior severe organ involvement.

Methods:

Patients with SLE with glucocorticoid tapering at our institution were retrospectively analyzed. We divided the patients according to the presence of prior severe organ involvement and compared flare rates and time to first flare after glucocorticoid discontinuation. Furthermore, we determined risk and protective factors for flares after glucocorticoid discontinuation.

Results:

A total of 309 patients with SLE were screened; 298 had prednisolone tapered to less than 7.5 mg/day and 75 had glucocorticoid discontinuation. Overall, 73 patients met the inclusion criteria; 49 were classified as SLE with prior severe organ involvement. No statistical differences were noted in the 52-week flare rate and time to first flare after glucocorticoid discontinuation between patients with and without prior severe organ involvement (52-week flare rate: 16.7% vs. 18.2%, p = 1.0; time to first flare: 322 [280, 1169] vs. 385 [304, 2345] days, p = 0.33). Hypocomplementemia, elevated anti-dsDNA antibody titers of more than twice the upper limit of the laboratory reference range, and positive anti-Smith/anti-ribonucleoprotein antibody were negatively associated with flare-free remission.

Conclusion:

Glucocorticoid discontinuation can often be achieved in patients with SLE without increasing flare risk in most patients with prior severe organ involvement, especially when the disease is clinically and serologically stable.

Background

Glucocorticoids have been used as the mainstay of treatment for systematic lupus erythematosus (SLE), with a majority of patients undergoing long-term treatment. In a previous study of 215 patients with SLE, 214 patients used glucocorticoids for SLE treatment and 86% used glucocorticoids as maintenance therapy [1]. Glucocorticoids are associated with several long-term side effects, such as hypertension, diabetes, infection, and osteoporosis. As the cumulative glucocorticoid dosage increases, the rate of organ damage increases simultaneously [2]. It is noteworthy that even small amounts of glucocorticoids (prednisolone [PSL] equivalent > 2.5 mg/day) are associated with organ damage, including osteoporosis, fractures, and infection [3-5].

Treat-to-target in SLE aims to use the lowest possible glucocorticoid dose to control disease activity and to discontinue glucocorticoids as soon as feasible [6]. The European League Against Rheumatism (EULAR) also recommends reduction of glucocorticoid dose to < 7.5 mg/day (PSL equivalent) or discontinuation of glucocorticoid once disease activity has stabilized [7].

Many clinical trials have investigated the possibility of glucocorticoid discontinuation. Masthian et al. compared SLE flare rates between patients who abruptly discontinued glucocorticoids and those who were maintained on low-dose glucocorticoids (PSL equivalent 5 mg/day) and found that the low-dose maintenance group had a lower flare rate [8]. However, these data are difficult to apply in clinical practice, given that in our clinical practice, we follow stable patients every three months and gradually taper off low-dose glucocorticoid to avoid flare. Although gradual glucocorticoid discontinuation has been suggested and can be successful [9-11], to the best of our knowledge, the predictive factors for subsequent flare-free state have not been elucidated to date.

In addition, SLE patients with severe organ involvement tend to start treatment with high-dose glucocorticoids, and many clinicians hesitate to taper or discontinue glucocorticoids in such patients, so glucocorticoid-induced organ damage tend to be more severe. Little is known about glucocorticoid discontinuation in patients with prior severe organ involvement.

To address this gap in knowledge, this study investigated the difference in flare-free remission rate and flare-free duration in the presence of prior severe organ involvement and aimed to determine the factors contributing to a flare-free state after glucocorticoid discontinuation.

Methods

Study design and participants

This study was a single-center retrospective analysis conducted using electronic health records of SLE patients who were followed up at a Japanese tertiary teaching hospital between January 2006 and March 2021. Patients were followed up for more than 52 weeks at our institution, and at least 6 months of follow-up was completed after glucocorticoid discontinuation.

SLE diagnosis

SLE diagnosis was based on the 1997 American College of Rheumatology (ACR), Systemic Lupus International Collaborating Clinics (SLICC) 2012, and 2019 EULAR-ACR classification criteria [12-14]. We used three major classification criteria when enrolling SLE patients because we had previously established that diagnoses based solely on the 2019 EULAR-ACR classification criteria could occasionally miss SLE patients with a low anti-nuclear antibody titer [15].

Glucocorticoid tapering and data collection

Glucocorticoids were gradually tapered off after the patients attained clinical remission. The timing and speed of glucocorticoid tapering was determined by the treating rheumatologists.

For each patient, we collected demographic information (age at glucocorticoid discontinuation, sex, height, weight, body mass index, and ethnicity), date of SLE onset, organ-specific manifestations (joint and muscular, mucocutaneous, hematological manifestation, serositis, renal manifestation, class of lupus nephritis, and neurological manifestation), positive autoantibodies (anti-nuclear antibody, anti-double stranded DNA [anti-ds-DNA] antibody, anti-Smith [anti-Sm] antibody, anti-Ro/SSA antibody, anti-ribonucleoprotein [anti-RNP] antibody, lupus anticoagulant, anti-cardiolipin [CL] antibody, and anti-CLβ2GPI antibody), and prior treatment regimen (glucocorticoid dosage, treatment with methylprednisolone [mPSL] pulse therapy, and treatment with immunosuppressive agents, biologics, and cytotoxic agents). The following data were collected at 52 and 26 weeks before glucocorticoid discontinuation, on the day of glucocorticoid discontinuation, and at 26 and 52 weeks after glucocorticoid discontinuation: C3 and C4 level; anti-dsDNA antibody titer; Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI); Lupus Low Disease Activity State (LLDAS) achievement; glucocorticoid dose; and immunosuppressive, biological, or cytotoxic agent use.

Furthermore, we followed the included patients and monitored the occurrence of SLE flares until the time to first flare after glucocorticoid discontinuation or until the end of the study period (March 31, 2021).

We defined patient with any of the following conditions as patient with prior severe organ involvement: renal manifestation (protein urea level > 0.5 g/24 h, cellular casts due to lupus, or biopsy proven lupus nephritis), neuropsychiatric SLE (delirium, psychosis, seizure, myelitis, or peripheral/cranial neuropathy due to lupus), prior treatment with mPSL pulse therapy, prior treatment with PSL 1 mg/kg/day, and prior treatment with rituximab (RTX) or cyclophosphamide (CY).

We divided the patients into the following two groups: patients with SLE with prior severe organ involvement and patients with SLE without prior severe organ involvement. Then, we compared the flare rates and flare-free duration after glucocorticoid discontinuation between the two groups.

The study protocol was in accordance with the ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki. The study was approved by the Ethics Committee of St. Luke's International Hospital (approval no. 20-R-23). Written informed consent was obtained from all participants in this study.

Definition of SLE flare-up

SLE flares were defined as new British Isles Lupus Assessment Group index category A in at least one organ system or initiation of new immunosuppressants. Immunosuppressants were defined as any of the following: tacrolimus (Tac), cyclosporin (CyA), mycophenolate mofetil (MMF), mizoribine (MZR), CY, azathioprine (AZA), belimumab, RTX, methotrexate, sulphasalazine, iguratimod, and bucillamine.

Definition of LLDAS

We evaluated LLDAS at each time point in the study (52 and 26 weeks before glucocorticoid discontinuation, on the day of glucocorticoid discontinuation, and 26 and 52 weeks after glucocorticoid discontinuation) because maintenance of LLDAS is related to reduced damage accrual in patient with SLE.

We considered patients in LLDAS if they achieved all of the following: (1) SLEDAI-2K ≤ 4, with no disease activity in the major organ systems (renal, central nervous, and cardiopulmonary system, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity; (2) no new SLE disease activity; (3) SELENA-SLEDAI physician global assessment score ≤ 1; (4) current PSL (or equivalent) dose ≤ 7.5 mg/day; and (5) well-tolerated standard maintenance doses of immunosuppressive drugs and biological agents [16].

Statistical analysis

For descriptive statistics, categorical data are presented as number and percentages and continuous data are presented as median values and interquartile range. We used Fisher's exact test to compare qualitative variables and the Mann–Whitney U test to compare continuous variables. We also analyzed differences in time to first flare after glucocorticoid discontinuation between the groups using the Kaplan–Meier method and log rank test. A univariate Cox proportional hazard model was used to calculate the hazard ratio for flares after glucocorticoid discontinuation. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander (version 2.5-1) designed to add statistical functions frequently used in biostatistics.

Results

At our institution, 309 patients with SLE were treated with glucocorticoids and were followed up for more than 52 weeks between January 2006 and March 2021. Of these, 298 (96.4%) had their PSL tapered to ≤7.5 mg/day, and 75 (24.3%) discontinued glucocorticoids and completed at least 6 months of follow-up. Two patients were excluded due to missing data on prior treatment regimens. Finally, 73 patients were included in our study, of which, 49 were classified as having SLE with prior severe organ involvement and the remaining 24 were classified as having SLE without prior severe organ involvement (Figure 1). Baseline characteristics of each study group are summarized in Table 1.

Table 1

Demographic and clinical characteristics of patients with SLE with and without prior severe organ involvement

	Patient with SLE without prior severe organ involvement (n = 24)	Patient with SLE with prior severe organ involvement (n = 49)	p value
Demographics			
Age at time of GC discontinuation	44.00 [38.00, 51.75]	45.00 [35.00, 54.00]	0.97
Female ratio (%)	24 (100.0)	46 (93.9)	0.55
BMI	20.08 [18.14, 22.17]	19.51 [17.91, 21.11]	0.66
Ethnicity			
Japanese	21 (87.5)	48 (98.0)	0.06
Non-Japanese Asian	3 (12.5)	1 (2.0)	
Disease duration before GC discontinuation (days)	2379 [1547, 3345]	4367 [1881, 6683]	0.06
Organ involvement			
Joints and muscles	22 (91.7)	38 (77.6)	0.20
Skin/mucous membranes	20 (83.3)	39 (81.2)	1
Hematologic abnormalities	14 (58.3)	32 (65.3)	0.61
Serositis	7 (29.2)	7 (14.3)	0.20
Renal manifestation	0 (0.0)	35 (71.4)	<0.01
Lupus nephritis class			
Class III/IV	0 (0.0)	13 (37.1)	
Non-class III/IV	0 (0.0)	12 (34.3)	
No data	0 (0.0)	10 (28.6)	
Neurological manifestation	0 (0.0)	6 (12.2)	0.17
Laboratory data			
anti-dsDNA Ab	13 (54.2)	35 (71.4)	0.19
anti-Sm Ab	2 (8.3)	8 (16.7)	0.48

anti-Ro/SSA Ab	11 (45.8)	22 (46.8)	1
anti-RNP Ab	5 (23.8)	13 (31.0)	0.77
Lupus anticoagulant	3 (12.5)	8 (16.7)	0.74
anti-CL Ab	3 (13.6)	18 (37.5)	0.052
anti-CL β2GPI Ab	2 (9.5)	3 (6.5)	0.65
Prior treatment regimen			
PSL 1 mg/kg/day	0 (0.0)	29 (59.2)	<0.01
mPSL pulse therapy	0 (0.0)	16 (32.7)	<0.01
Maximum GC dose (mg/day) *	20 [10, 25]	60 [40, 60]	<0.01
B-cell targeting/cytotoxic agent	0 (0.0)	4 (8.2)	0.30
RTX	0 (0.0)	1 (2.0)	1
CY	0 (0.0)	4 (8.2)	0.30

Values are number (%) or median [interquartile range]

Ab = antibody; aPL = antiphospholipid antibody; BMI = body mass index; CL = cardiolipin; CY = cyclophosphamide; GC = glucocorticoid; mPSL = methylprednisolone; PSL = prednisolone; RNP = ribonucleoprotein; RTX = rituximab; SLE = systemic lupus erythematosus

*prednisolone equivalent (mg/day)

There were no statistically significant differences in age at the time of glucocorticoid discontinuation, female ratio, body mass index, and antibody profiles (anti-dsDNA antibody, anti-Sm antibody, anti-Ro/SSA antibody, anti-RNP antibody, lupus anticoagulant, anti-CL antibody, anti-CLβ2GPI antibody) between the two groups. Although disease duration before glucocorticoid discontinuation tended to be longer in patients with prior severe organ involvement, no statistical differences were noted (4367 [1881–6683] vs. 2379 [1547–3345] days, p = 0.06). The maximum dose of glucocorticoids (PSL equivalent) was higher in patients with prior severe organ involvement than in those without (60 [40–60] vs. 20 [10–25] mg/day, p < 0.01). The detailed treatment regimen during the follow-up period is summarized in Table 2 and Additional file 1. On the day of glucocorticoid discontinuation, SLE patients with prior severe organ involvement tended to use hydroxychloroquine (HCQ), Tac, CyA, MMF, AZA, but no statistical difference was noted. MZR is an inhibitor of purine synthesis, with a mechanism of action similar to that of MMF, and is a widely used medication in Japan. Since we have proven the efficacy of MZR in IgG4-related disease with multiple organ involvement and of MZR/tacrolimus combination therapy in lupus nephritis [17, 18], the use of MZR tended to be higher in patients with prior severe organ involvement than in those without, but no statistical differences were noted. As shown in Table 3 and Additional file 2, on the day of

glucocorticoid discontinuation, median SLENA-SLEDAI was 0.0 [0.0, 2.0] in patients with prior severe organ involvement and 0.0 [0.0, 0.0] in patients without prior severe organ involvement.

Table 2

Treatment regimen on the day of glucocorticoid discontinuation

Treatment regimen	SLE without prior severe organ involvement (n = 24)	SLE with prior severe organ involvement (n = 49)	P value
GC dosage (mg/day) *	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	N/A
HCQ	10 (41.7)	26 (53.1)	0.46
Tac	5 (20.8)	20 (40.8)	0.12
CyA	0 (0.0)	1 (2.0)	1.0
MMF	0 (0.0)	6 (12.2)	0.17
MZR	3 (12.5)	14 (28.6)	0.15
AZA	0 (0.0)	2 (4.1)	1.0
MTX	3 (12.5)	2 (4.1)	0.32
SASP	2 (8.3)	0 (0.0)	0.11
IGU	0 (0.0)	1 (2.0)	1.0
BUC	1 (4.2)	0 (0.0)	0.33
BEL/RTX/CY/PE/IVIg	0 (0.0)	0 (0.0)	NA

Values are number (%) or median [interquartile range]

AZA = azathioprine; BEL = belimumab; BUC = bucillamine; CyA = cyclosporin; CY = cyclophosphamide; GC = glucocorticoid; HCQ = hydroxychloroquine; IGU = iguratimod; IVIg = intravenous immunoglobulin; MMF = mycophenolate mofetil; MTX = methotrexate; MZR = mizoribine; PE = plasma exchange; RTX= rituximab; SASP = salazosulfapyridine; SLE = systemic lupus erythematosus; Tac = tacrolimus
*prednisolone equivalent (mg/day)

Table 3

Flare ratio, complement/anti-dsDNA antibody level, and disease activity on the day of glucocorticoid discontinuation in both patient groups

	SLE without prior severe organ involvement (n = 24)	SLE with prior severe organ involvement (n = 49)	p value
Flare-free duration after GC discontinuation (days)	385 [304, 2345]	322 [280, 1169]	0.33
Flare rate within 52 weeks after GC discontinuation*	4 (18.2)	8 (16.7)	1.0
C3 (mg/dL)	90.00 [81.00, 102.50]	82.50 [67.75, 97.25]	0.05
C4 (mg/dL)	20.00 [14.50, 27.50]	18.00 [13.50, 20.00]	0.03
Anti-dsDNA antibody (IU/mL)	3.50 [1.50, 5.25]	6.00 [3.00, 14.50]	0.04
GC dosage (mg/day) **	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	N/A
SELENA-SLEDAI	0.00 [0.00, 0.00]	0.00 [0.00, 2.00]	0.05
LLDAS achievement ratio	23 (95.8)	46 (93.9)	1

Values are number (%) or median [interquartile range]

BILAG = British Isles Lupus Assessment Group Index; GC = glucocorticoid; LLDAS = lupus low disease activity state; N/A = not applicable; SLE = systemic lupus erythematosus; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index; PSL = prednisolone

*We excluded 3 patients (1 patient with prior severe organ involvement and 2 patients without prior severe organ involvement) from the assessment of flare rate within 52 weeks after glucocorticoid discontinuation because of incomplete follow-up.

**prednisolone equivalent (mg/day)

SLE flare rate (overall)

Prior severe organ involvement did not affect the time to first flare after glucocorticoid discontinuation, as this time was 322 (280–1169) days in patients with prior severe organ involvement vs. 385 (304–2345) days in those without prior severe organ involvement (p = 0.33; Table 3).

As shown in Figure 2a, more than 80% of the patients achieved 52 weeks of flare-free remission and more than 70% achieved 1000 days of flare-free remission after glucocorticoid discontinuation. When we compared patients by the presence or absence of prior severe organ involvement, the flare-free rate after glucocorticoid discontinuation in patients with prior severe organ involvement was lower than that in patients without prior severe organ involvement in the first year. However, the flare rate stabilized over

time (Figure 2a), and the log rank test results showed that there was no statistical difference between the two groups by the end of the follow-up period (p = 0.73).

We defined resuming glucocorticoids as another definition of flare and assessed glucocorticoid-free remission rate. As shown in Figure 2b, although patients with prior severe organ involvement tended to restart glucocorticoids, no statistical difference was noted between the two groups (p = 0.74).

SLE flare rate (52 weeks)

Of the 73 patients, 1 patient with prior severe organ involvement and 2 patients without prior severe organ involvement did not complete the entire 52-week follow-up after glucocorticoid discontinuation, and these patients could not be monitored for SLE flares during the follow-up. Therefore, we excluded these 3 patients from the 52-week evaluation for SLE flare rates. Of the remaining 70 patients, 8 (16.7%) with prior severe organ involvement and 4 (18.2%) without prior severe organ involvement had flares during the 52 weeks of follow-up after glucocorticoid discontinuation; however, no statistical difference was noted between these patients (p = 1.0; Table 3).

A detailed electronic record search revealed that most flares were mild. However, 3 patients (6.3%) with prior severe organ involvement and 1 patient (4.5%) without prior severe organ involvement experienced a lupus nephritis flare or a lupus flare that necessitated re-initiation of glucocorticoid therapy at a dose of >0.5 mg/kg/day. Of the 3 patients with prior severe organ involvement, 1 experienced a lupus nephritis flare 280 days after glucocorticoid discontinuation and was managed by restarting PSL at 25 mg/day, adding tacrolimus, and subsequently tapering prednisolone to 2.5 mg/day. The second patient experienced a flare of lupus myopathy 313 days after glucocorticoid discontinuation. Although the patient had to start PSL at 40 mg/day, the dose was subsequently decreased to 6 mg/day. The third patient experienced a mild flare of lupus nephritis 70 days after glucocorticoid discontinuation and was initiated on belimumab.

The one patient without prior severe organ involvement experienced fever, arthritis, leukocytopenia, and thrombocytopenia on day 301 after glucocorticoid discontinuation and was managed by restarting mPSL at 30 mg/day. Prednisolone was discontinued 251 days after the occurrence of first flare. The details of each flare are summarized in Additional file 3.

Risk factors for flares after glucocorticoid discontinuation

We evaluated the risk factors for flares after glucocorticoid discontinuation. As shown in Table 4, flare rate was not affected by the presence of prior severe organ involvement (patients with flare 68.4% vs. patients without flare 66.7%, p = 1.0), renal manifestation (47.4% vs. 48.1%, p = 1.0) or neurological manifestation (0.0% vs. 11.1%, p = 0.33), history of PSL treatment more than 1 mg/kg/day (42.1% vs. 38.9%, p = 1.0), mPSL pulse therapy (21.1% vs. 22.2%, p = 1.0), or B cell targeting/cytotoxic agent (0.0% vs. 7.4%, p = 0.57).

Factors that negatively affected flare-free remission after discontinuation were: hypocomplementemia (patient with flare 50.0% vs. patient without flare 23.1%, p = 0.04), elevated anti-dsDNA antibody titer at more than twice the upper limit of the laboratory reference range on the day of glucocorticoid discontinuation (55.6% vs. 12.0%; p = 0.02), positive anti-Sm (31.6% vs. 7.5%, p = 0.02), and anti-RNP antibodies (64.7% vs. 15.2%, p < 0.01).

Factors that tended to decrease the flare-free ratio, but without statistical significance possibly due to the small sample size, were: SLE duration of more than 5000 days (patient with flare 15.8% vs. patient without flare 38.9%, p = 0.09), HCQ treatment on the day of glucocorticoid discontinuation (36.8% vs. 53.7%, p = 0.29), and LLDAS achievement on the day of glucocorticoid discontinuation (89.5% vs. 96.3%, p = 0.28). We then evaluated these variables using the Cox proportional hazard model, which showed that flare rate was not influenced by the presence of prior severe organ involvement (hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.44–3.17, p = 0.73), renal manifestations (HR 1.22, 95% CI 0.48–3.10, p = 0.67), neurologic manifestations (not applicable), history of PSL treatment more than 1 mg/kg/day (HR 1.16, 95% CI 0.46–2.91, p = 0.76), mPSL pulse therapy (HR 0.97, 95% CI 0.32–2.95, p = 0.95), or B-cell targeting or cytotoxic agent use (not applicable).

Cox proportional hazard model analysis also demonstrated that hypocomplementemia on the day of glucocorticoid discontinuation (HR 3.77, 95% CI 1.43–9.90, p < 0.01), elevated anti-dsDNA antibody titer more than twice the upper limit of the laboratory reference range (HR 4.84, 95% CI 1.27–18.41, p = 0.02), anti-Sm antibody positivity (HR 3.50, 95% CI 1.31–9.35, p = 0.01), and anti-RNP antibody positivity (HR 6.80, 95% CI 2.36–19.63, p < 0.01) were risk factors for flares after glucocorticoid discontinuation. Cox proportional hazard model analysis suggested that SLE duration of >5000 days (HR 0.43, 95% CI 0.12–1.48, p = 0.18), HCQ use (HR 0.75, 95% CI 0.29–1.97, p = 0.56), and LLDAS achievement (HR 0.25, 95% CI 0.06–1.1, p = 0.07) on the day of glucocorticoid discontinuation were possible protective factors for flare-free remission after discontinuation; however, significant differences were not noted.

Table 4

Risk factors for flares after glucocorticoid discontinuation

Factor	Fisher's exact test			Cox proportional hazard model	
	Flare (−) (n = 54)	Flare (+) (n = 19)	p value	Hazard ratio	p value (95% CI)
Prior severe organ involvement	36 (66.7)	13 (68.4)	1.0	1.19	0.73 (0.44–3.17)
Renal manifestations	26 (48.1)	9 (47.4)	1.0	1.22	0.67 (0.48–3.10)
Neurological manifestations	6 (11.1)	0 (0.0)	0.33	N/A	N/A
History of treatment with PSL 1 mg/kg/day	21 (38.9)	8 (42.1)	1.0	1.16	0.76 (0.46–2.91)
History of treatment with mPSL pulse therapy	12 (22.2)	4 (21.1)	1.0	0.97	0.95 (0.32–2.95)
History of treatment with: B-cell targeting/cytotoxic medication	4 (7.4)	0 (0.0)	0.57	N/A	N/A
Hypocomplementemia on the day of glucocorticoid discontinuation	12 (23.1)	9 (50.0)	0.04	3.77	<0.01 (1.43–9.90)
Elevated anti-dsDNA antibody of twice above ULN of laboratory reference range on the day of glucocorticoid discontinuation	3 (12.0)	5 (55.6)	0.02	4.84	0.02 (1.27-18.41)
Duration of SLE >5000 days	21 (38.9)	3 (15.8)	0.09	0.43	0.18 (0.12–1.48)
Anti-Smith antibody	4 (7.5)	6 (31.6)	0.02	3.50	0.01 (1.31–9.35)
Anti-Ro/SSA antibody	22 (42.3)	11 (57.9)	0.29	2.19	0.10 (0.87–5.55)
Anti-RNP antibody	7 (15.2)	11 (64.7)	<0.01	6.80	<0.01 (2.36-19.63)

HCQ use on the day of glucocorticoid discontinuation	29 (53.7)	7 (36.8)	0.29	0.75	0.56 (0.29–1.97)
Achievement of LLDAS on the day of glucocorticoid discontinuation	52 (96.3)	17 (89.5)	0.28	0.25	0.07 (0.06–1.1)

Values are number (%) unless otherwise specified.

HCQ = hydroxychloroquine; LLDAS = lupus low disease activity state; mPSL = methylprednisolone; N/A = not applicable; PSL = prednisolone; RNP = ribonucleoprotein; SLE = systemic lupus erythematosus, ULN = upper limit of normal

Discussion

Our findings showed that more than 95% (298 of 309 patients with SLE followed for more than 52 weeks at our institution) of patients with SLE could achieve a good response with a PSL dose of ≤7.5 mg/day at least once. Therefore, as recommended by EULAR, SLE treatment with PSL at ≤7.5 mg/day is a realistic goal for most patients with SLE [7]. Furthermore, glucocorticoid discontinuation was achieved in 75 of 309 patients (24.3%) with SLE. Of the 73 patients included in our study, more than 80% achieved 52 weeks of flare-free remission and more than 70% achieved 1000 days of flare-free remission after glucocorticoid discontinuation. These results were not influenced by the presence of prior severe organ involvement. Furthermore, our results suggested that hypocomplementemia and elevated anti-dsDNA antibody titer at more than twice the upper limit of the laboratory reference range on the day of glucocorticoid discontinuation as well as positive anti-Sm antibodies and anti-RNP antibodies can be risk factors for flares after glucocorticoid discontinuation.

Mathian et al. reported that 27% of patients with SLE experienced disease flares after glucocorticoid discontinuation; however, their findings are not applicable to our study population as they abruptly discontinued glucocorticoids in the previous study [8].

Goswami et al. reported that 20.9% of patients with SLE experienced disease flares after gradual glucocorticoid discontinuation at a median follow-up of 539 days [9], whereas Tani et al. reported that 23% of patients with SLE experienced a flare after glucocorticoid tapering over a median follow-up of 2 years [10]. In addition, Zen et al. reported that 21.8% of patients with SLE achieved prolonged complete remission after corticosteroid discontinuation for 5 years [11]. These flare rates are in agreement with the rates noted for our cohort for both the patient groups.

This study showed that glucocorticoid doses can be safely tapered in patients with and without prior severe organ involvement. Regarding the risk factors for flares after glucocorticoid discontinuation, our results suggest that hypocomplementemia and elevated anti-dsDNA antibody at more than twice the

upper limit of the laboratory reference range on the day of glucocorticoid discontinuation as well as positive anti-Sm antibodies and anti-RNP antibodies may be important factors in this regard.

As suggested by the SLICC classification criteria, we used anti-dsDNA antibody titers at more than twice the upper limit of the laboratory reference range as a risk factor for flares because low titers of anti-dsDNA antibody have low sensitivity for SLE activity [13].

A previous study on B-cell depression therapy illustrated that the one-year flare rates were higher in SLE patients with anti-RNP or anti-Sm antibody positivity than in patients without anti-RNP or anti-Sm antibody positivity [19]. This is possibly due to the fact that anti-RNP/Sm antibodies are produced by long-lived plasma cells [20] that cannot be fully eliminated by rituximab, similar to that in the case with glucocorticoids [21-23].

LLDAS achievement on the day of glucocorticoid discontinuation was not statistically significant because more than 90% of the patients achieved LLDAS on the day of glucocorticoid discontinuation. Nevertheless, on the day of glucocorticoid discontinuation, LLDAS achievement ratio was higher in patients without flares than in patients with flares (96.3% vs. 89.5%), thus LLDAS should be targeted before glucocorticoid discontinuation.

Previous reports have suggested that HCQ reduces the flare risk and mortality of SLE patients [24-26]. However, HCQ use on the day of discontinuation was not a significant predictive factor of flare-free state, probably because of the lower HCQ prescription ratio due to the formulary restrictions until 2016. Nevertheless, HCQ use was higher in patients in the flare-free group (53.7%) than in patients in the flare group (36.8%). In Japan, HCQ was approved for SLE in 2015, and the 2-week dosing period restrictions were removed in 2016. Of the 75 patients who discontinued glucocorticoid, 48 discontinued glucocorticoid between 2016 to 2020 (after the approval of HCQ) and 66.0% of them used HCQ on the day of glucocorticoid discontinuation. This prescription rate of HCQ was consistent with that stated in the Hopkins Lupus Cohort report, which included 2054 patients with SLE with an HCQ prescription rate of 64.4% [27].

In addition, our data showed that the number of patients who achieved disease stability after glucocorticoid discontinuation increased after HCQ approval. Of the 75 patients who discontinued glucocorticoids, 8 discontinued glucocorticoids between 2006 and 2010, 19 between 2011 and 2015, and 48 between 2016 and 2020. Therefore, the glucocorticoid discontinuation rate and flare-free remission rate after glucocorticoid discontinuation are expected to increase in the future.

Currently, many clinicians, including our group, are attempting to reduce or discontinue the use of glucocorticoids, immunosuppressants, and biologic agents to avoid the associated adverse effects and reduce the medical burden and pregnancy-related complications [8-11, 28-30].

Treatment with glucocorticoids is associated with many side effects, and even small amounts of glucocorticoids (prednisolone [PSL] equivalent > 2.5 mg/day) are associated with osteoporosis and an

increased risk of fractures [5]. The management of glucocorticoid-related adverse events is reported to cost approximately $21,824.68/year/patient for peptic ulcers, $26,471.80/year/patient for nonfatal myocardial infarctions, and $18,357.90/event for fractures [31]. Furthermore, glucocorticoids not only impose a financial burden on patients but also increase the rate of all-cause mortality as the cumulative glucocorticoid dosage increases [32].

In addition, glucocorticoid use during pregnancy is related to adverse pregnancy outcomes, including increased ratio of preterm birth and orofacial clefts [33, 34]. Therefore, reduction of glucocorticoid dosage is recommended according to the 2016 EULAR recommendation for use of antirheumatic drugs before and during pregnancy and lactation [35] and the 2020 ACR guideline for management of reproductive health in rheumatic and musculoskeletal diseases [36]. As we have previously proven that patients with SLE can have favorable pregnancy outcomes even with prior severe organ involvement [37], glucocorticoid discontinuation may further improve pregnancy outcomes.

Glucocorticoid discontinuation can be achieved in an increasing number of patients with SLE with the current treatment regimens, and the presence of prior severe organ involvement does not influence the 52-week flare-free remission after glucocorticoid discontinuation.

Rheumatologists should aim to taper glucocorticoid dosages as much as possible in patients with SLE. We believe that our results support the idea that more patients with SLE, including those with prior severe organ involvement, can achieve freedom for glucocorticoid use, thereby reducing glucocorticoid-related adverse events, financial burden, and adverse pregnancy outcomes.

The limitations of this study include its single-center retrospective cohort study design that included a limited number of patients and thus could not exclude cofounders. Second, since we included sulphasalazine, iguratimod, and bucillamine as immunosuppressants, we might have overestimated the flare rate after glucocorticoid discontinuation. Finally, we could not include patients on belimumab therapy on the day of glucocorticoid discontinuation. Belimumab has only been available to patients in Japan since 2017; therefore, in the future we will need to re-analyze the data in patients treated with belimumab.

Conclusions

Our results suggest that more than 80% of patients who gradually discontinued glucocorticoid achieved 52 weeks of flare-free remission even with prior severe organ involvement. Hypocomplementemia and elevated anti-dsDNA antibody titers of more than twice the upper limit of the laboratory reference range on the day of glucocorticoid discontinuation were risk factors for subsequent flares.

List Of Abbreviations

Ab: antibody

ACR: American College of Rheumatology

AZA: azathioprine

BEL: belimumab

CL: cardiolipin

CY: cyclophosphamide

CyA: cyclosporin

EULAR: European League Against Rheumatism

GC: glucocorticoid

HCQ: hydroxychloroquine

HR: hazard ratio

LLDAS: Lupus Low Disease Activity State

MMF: mycophenolate mofetil

mPSL: methylprednisolone

MZR: mizoribine

PSL: prednisolone

RNP: ribonucleoprotein

RTX: rituximab

SELENA-SLEDAI: Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index

SLE: systemic lupus erythematosus

SLICC: Systemic Lupus International Collaborating Clinics

Sm: Smith

Tac: tacrolimus

Declarations

Ethics approval and consent to participate:

The study was approved by the Ethics Committee of St. Luke's International Hospital (approval no. 20-R-23). Written informed consent was obtained from all participants in this study.

Consent for publication:

Written informed consent was obtained from all participants in this study.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests:

MO has received speaking fees and/or honoraria from Eli Lilly and Company, Santen Pharmaceutical, Mitsubishi Tanabe Pharma, Pfizer, and Abbott Japan. Other authors declare that they have no competing interests.

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Authors' contributions:

TN was involved in study conception and design, acquisition of the data, data analysis, drafting the manuscript, and final approval of the article. SF was involved in acquisition of the data, statistical advice, and approval of the final article. YI, MS, and HT were involved in acquisition of the data, and final approval of the article. MO was involved in study conception and design, drafting the manuscript, and final approval of the article. All authors read and approved the final manuscript.

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Figures

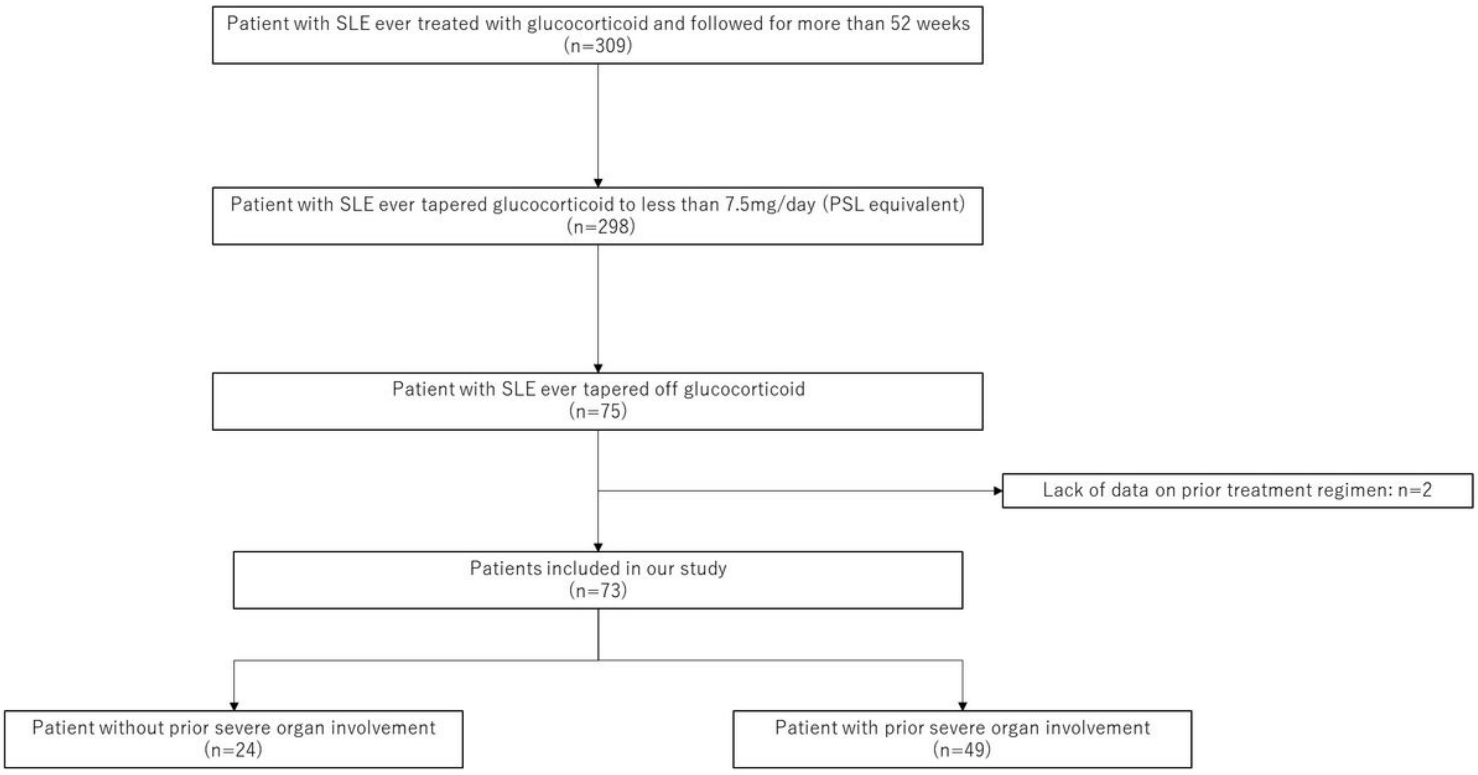

Figure 1

Patient flowchart A total of 309 patients with SLE were treated with glucocorticoids and were followed up for > 52 weeks. Of these, 298 had their PSL dosage tapered to ≤ 7.5 mg/day and 75 discontinued glucocorticoids. Two patients were excluded from the study because of the lack of data on prior treatment regimen. Among the 73 patients finally included in our study, 49 were classified as having SLE

with prior severe organ involvement and the remaining 24 were classified as having SLE without prior severe organ involvement.

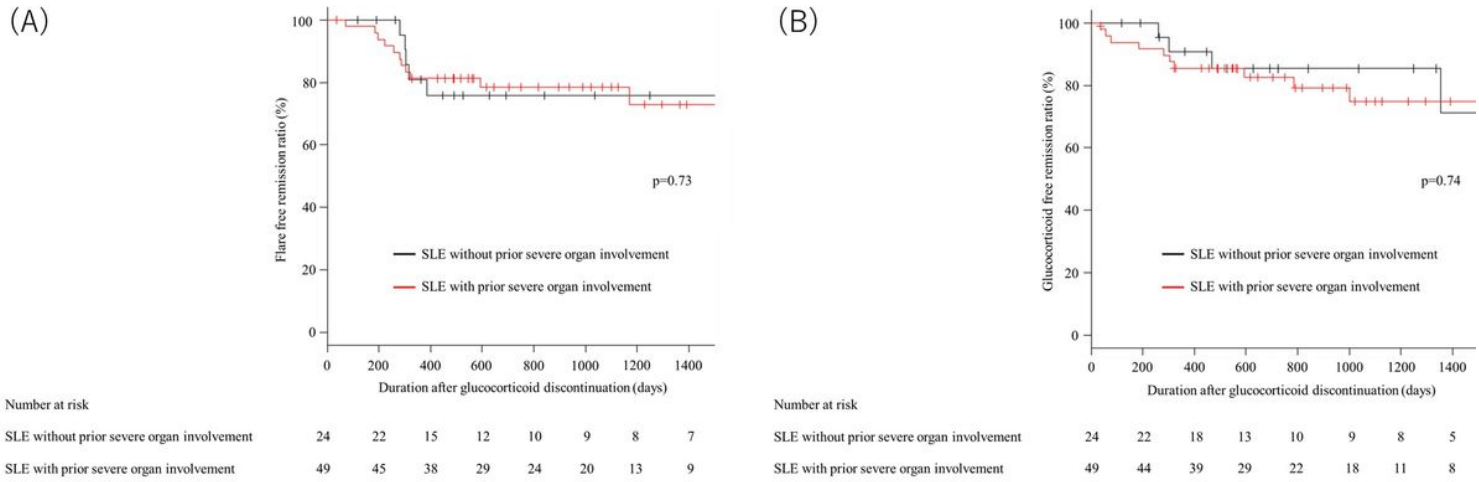

Figure 2

Kaplan–Meier curve for flare-free/glucocorticoid-free remission rate after glucocorticoid discontinuation a: Kaplan–Meier curve for flare-free remission rate after glucocorticoid discontinuation b: Kaplan–Meier curve for glucocorticoid-free remission rate after glucocorticoid discontinuation

Supplementary Files

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