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Glucocorticoid discontinuation in patients with SLE with prior severe organ involvement: a single-center retrospective analysis

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ABSTRACT

Objective Long-term glucocorticoid use in 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 on glucocorticoid tapering in patients with prior severe organ involvement.

Methods Data of patients with SLE with glucocorticoid tapering at our institution were retrospectively analysed. We divided the patients by the presence of prior severe organ involvement and compared flare rates after glucocorticoid discontinuation. Furthermore, we determined risk factors for flares after glucocorticoid discontinuation.

Results In total, 309 patients with SLE were screened, 73 of whom met the inclusion criteria; 49 were classified as SLE with prior severe organ involvement. No significant differences were noted in the 52-week flare rate after glucocorticoid discontinuation between patients with and without prior severe organ involvement (16.7% vs 18.2%, p=1.0). Hypocomplementaemia, elevated anti-dsDNA antibody titres more than twice the upper limit of the laboratory reference range, positive anti-Smith/anti-ribonucleoprotein antibody, and use of any immunosuppressant on the day of glucocorticoid discontinuation were negatively associated with flare-free remission.

Conclusions Glucocorticoid discontinuation after gradual tapering can often be achieved in patients with SLE, even with prior severe organ involvement, especially when the disease is clinically and serologically stable.

WHAT IS ALREADY KNOWN ABOUT THIS TOPIC

⇒ The impact of glucocorticoid discontinuation in patient with SLE with prior severe organ involvement has been scarcely explored.
⇒ Little is known on the risk/protective factors for flare-free remission after glucocorticoid discontinuation.

WHAT THIS STUDY ADDS

⇒ A substantial proportion of patients with SLE can achieve glucocorticoid-free remission, and the presence of prior severe organ involvement does not preclude flare-free remission after discontinuing glucocorticoids.
⇒ Hypocomplementaemia and elevated anti-dsDNA antibody titre to more than twice the upper limit of the laboratory reference range on the day of glucocorticoid discontinuation, as well as positive anti-Sm/anti-RNP antibodies, and use of any immunosuppressants on the day of glucocorticoid discontinuation can be risk factors for flares after glucocorticoid discontinuation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Our findings suggest that more patients with SLE, including those with prior severe organ involvement, can achieve freedom from glucocorticoid use.

INTRODUCTION

Glucocorticoids have been used as the mainstay of treatment for SLE, with most patients undergoing long-term treatment. In a previous study of 215 patients with SLE, 214 patients used glucocorticoids for SLE treatment, of whom 86% used glucocorticoids as maintenance therapy.[1] Glucocorticoids are associated with long-term side effects such as hypertension, diabetes, infection and osteoporosis. As the cumulative glucocorticoid dosage increases, the rate of organ damage increases.[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) recommends reduction of glucocorticoid dose to <7.5 mg/day (PSL equivalent) or discontinuation of glucocorticoid once the disease activity has stabilised.[7]

Many clinical trials have investigated the possibility of glucocorticoid discontinuation. Mathian *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, since we follow stable patients every 3 months and gradually taper off low-dose glucocorticoid to avoid flare. Although gradual glucocorticoid discontinuation has been suggested and can be successful,[9–12] little is known on the predictive factors for a subsequent flare-free state. In addition, patients with SLE with severe organ involvement start treatment with high-dose glucocorticoids, and many clinicians hesitate to taper or discontinue the glucocorticoids, so glucocorticoid-induced organ damage tends 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 the 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-centre retrospective analysis conducted using electronic health records of patients with SLE 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, and at least 6 months of follow-up was completed after glucocorticoid discontinuation.

SLE diagnosis

The 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.[13–15] We used three major classification criteria when enrolling patients with SLE because we had previously established that diagnoses based solely on the 2019 EULAR-ACR classification criteria could occasionally miss patients with SLE with a low ANA titre.[16]

Glucocorticoid tapering and data collection

Glucocorticoid dose was gradually tapered off after the patients attained clinical remission. Treating rheumatologists were recommended to reduce glucocorticoid dosage according to the glucocorticoid reduction regimen of our instituition (shown in online supplemental table 1), but tapering speed was modified according to the patient's condition and clinical judgement.

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, haematological manifestation, serositis, renal manifestation, class of lupus nephritis, and neurological manifestation), positive autoantibodies (ANA, anti-double stranded DNA (anti-ds-DNA) antibody, anti-Smith (anti-Sm) antibody, anti-SSA/Ro antibody, anti-ribonucleoprotein (anti-RNP) antibody, lupus anticoagulant, anti-cardiolipin (CL) antibody, and anti-CLβ2-glycoprotein I (β2GPI) 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 weeks and 26 weeks before glucocorticoid discontinuation, on the day of glucocorticoid discontinuation, and at 26 weeks and 52 weeks after glucocorticoid discontinuation (we allowed a variation of plus-minus 2 weeks for each time point, except the day of glucocorticoid discontinuation): C3 and C4 level; anti-dsDNA antibody titre; 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 up 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 (31 March 2021).

We defined patients with any of the following conditions as a patient with prior severe organ involvement: renal manifestation (urine protein level >0.5 g/24 hours, 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. 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), ciclosporin (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 weeks and 26 weeks before glucocorticoid

discontinuation, on the day of glucocorticoid discontinuation, and 26 weeks and 52 weeks after glucocorticoid discontinuation) because maintenance of LLDAS is related to reduced damage accrual in patients with SLE. We considered patients to be 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 systems, vasculitis, and fever) and no haemolytic anaemia 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.[17]

Statistical analysis

For descriptive statistics, categorical data are presented as numbers and percentages and continuous data are presented as median values and IQR. We performed Fisher's exact test to compare qualitative variables and the Mann-Whitney U test to compare continuous variables. We also analysed 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 hazards model was used to calculate the hazard ratio (HR) for flares after glucocorticoid discontinuation. A value of $p<0.05$ 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 (V.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 dose tapered to ≤7.5 mg/day, 270 (87.4%) had their PSL dose tapered to ≤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 whom 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). The baseline characteristics of each study group are summarised in table 1.

There were no 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-SSA/Ro antibody, anti-RNP antibody, lupus anticoagulant, anti-CL antibody and anti-CLβ2GPI antibody) between the two groups. Disease duration and total glucocorticoid exposure before

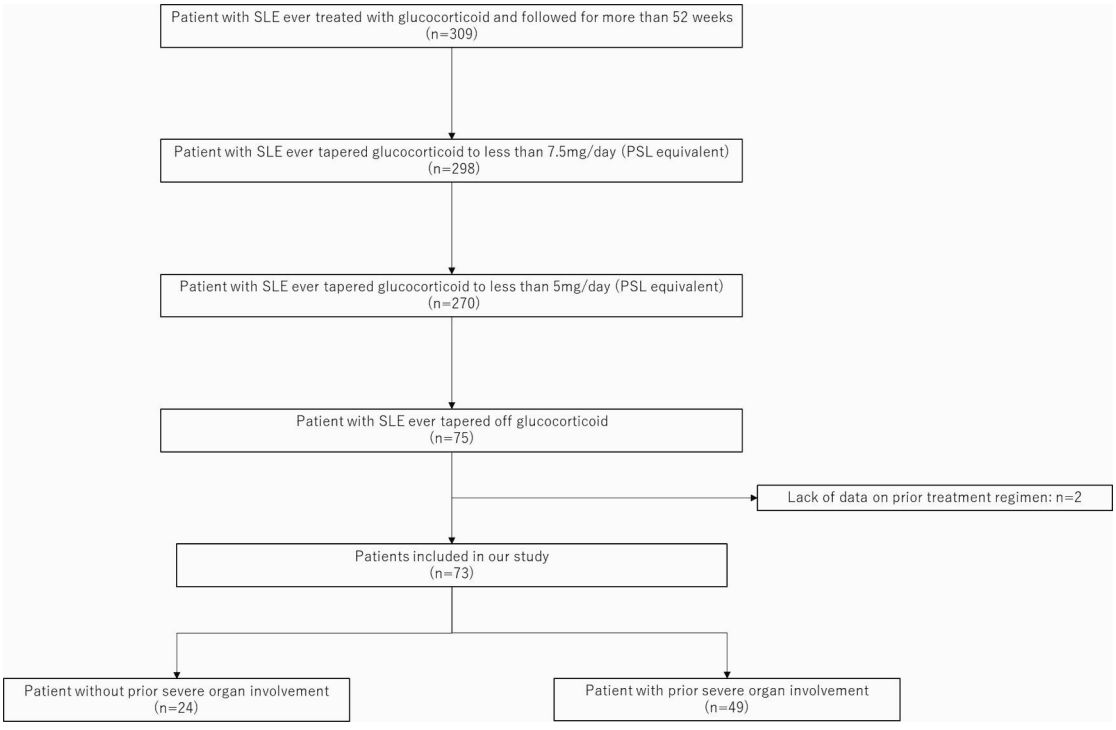

Figure 1 Patient flow chart. A total of 309 patients with SLE were treated with glucocorticoids and were followed up for >52 weeks. Of these, 298 had their PSL dose tapered to ≤7.5 mg/day, 270 (87.4%) had their PSL dose tapered to ≤5 mg/day and 75 discontinued glucocorticoids. Two patients were excluded 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. PSL, prednisolone.

Table 1 Demographic and clinical characteristics of patients with SLE with and without prior severe organ involvement

	Patients with SLE without prior severe organ involvement (n=24)	Patients with SLE with prior severe organ involvement (n=49)	P value
Demographics			
Age at time of GC discontinuation (years)	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 (kg/m^2)	20.08 (18.14, 22.17)	19.51 (17.91, 21.11)	0.66
Ethnicity: Japanese ratio	21 (87.5)	48 (98.0)	0.06
Disease duration before GC discontinuation (days)	2379 (1547, 3345)	4367 (1881, 6683)	0.06
Duration of GC exposure before GC discontinuation (days)	1962 (1180, 2701)	4136 (957, 6683)	0.02
Time needed to discontinue GC from PSL equivalent 5 mg (days)	934 (526, 1591)	777 (350, 1365)	0.33
Organ involvement			
Joints and muscles	22 (91.7)	38 (77.6)	0.20
Skin/mucous membranes	20 (83.3)	39 (81.2)	1
Haematologic 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-SSA/Ro 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

Values are expressed as number (%) or median (IQR)
*Prednisolone equivalent (mg/day).
Ab, antibody; anti-RNP Ab, antiribonucleoprotein antibody; anti-Sm Ab, anti-Smith antibody; BMI, body mass index; CL, cardiolipin; dsDNA, double stranded DNA ; GC, glucocorticoid; mPSL, methylprednisolone; PSL, prednisolone; β2GPI, β2-glycoprotein I.

glucocorticoid discontinuation tended to be longer in patients with prior severe organ involvement (disease duration: 4367 (1881–6683) vs 2379 (1547–3345) days, p=0.06, total glucocorticoid exposure: 4136 (957, 6683) vs 1962 (1180, 2701) days, p=0.02). However, there was no difference in time to discontinue glucocorticoid from PSL equivalent of 5 mg/day between the two groups. (777 (350, 1365) vs 934 (526, 1591) days p=0.33). 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 summarised in table 2 and online supplemental table 2. On the day of glucocorticoid discontinuation, patients

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 expressed as number (%) or median (IQR).
*Prednisolone equivalent (mg/day).
AZA, azathioprine; BEL, belimumab; BUC, bucillamine; CY, cyclophosphamide; CyA, ciclosporin; GC, glucocorticoid; HCQ, hydroxychloroquine; IGU, iguratimod; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; MZR, mizoribine; N/A, not applicable; PE, plasma exchange; RTX, rituximab; SASP, salazosulfapyridine; Tac, tacrolimus.

with SLE with prior severe organ involvement tended to use hydroxychloroquine (HCQ), Tac, CyA, MMF and AZA, but no significant 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/Tac combination therapy in lupus nephritis,[18 19] the use of MZR tended to be higher in patients with prior severe organ involvement than in those without, but no significant differences were noted. As shown in table 3 and online supplemental table 3, 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.

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 and 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

Table 3 Flare-free duration after GC discontinuation, flare ratio within 52 weeks after GC discontinuation, 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 expressed as number (%) or median (IQR)
*We excluded three patients (one patient with prior severe organ involvement and two 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)
dsDNA, double stranded DNA ; GC, glucocorticoid; LLDAS, Lupus Low Disease Activity State; N/A, not applicable; SELENA-SLEDAI, Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index.

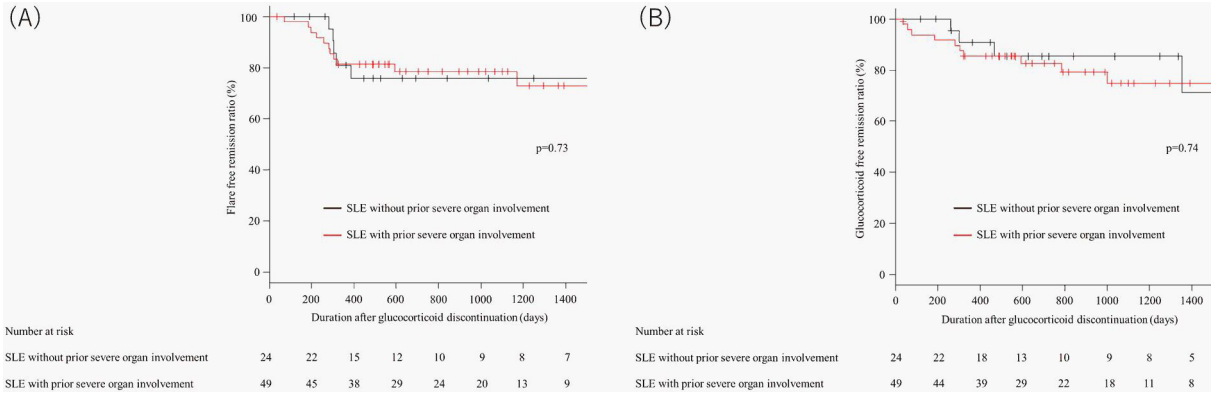

Figure 2 Kaplan-Meier curve for flare-free/glucocorticoid-free remission rate after glucocorticoid discontinuation. (A) Kaplan-Meier curve for flare-free remission rate after glucocorticoid discontinuation. (B) Kaplan-Meier curve for glucocorticoid-free remission rate after glucocorticoid discontinuation.

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 stabilised over time (figure 2A), and the log-rank test results showed that there was no significant 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 significant 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 three 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 significant difference was noted between these patients (p=1.0; table 3).

A detailed electronic record search revealed that most flares were mild. However, three patients (6.3%) with prior severe organ involvement and one 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 three patients with prior severe organ involvement, one experienced a lupus nephritis flare 280 days after glucocorticoid discontinuation and was managed by restarting PSL at 25 mg/day, adding Tac, and subsequently tapering PSL 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. PSL was discontinued 251 days after the occurrence of the first flare. The details of each flare are summarised in online supplemental table 4.

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 hypocomplementaemia (patient with flare 50.0% vs patient without flare 23.1%, p=0.04), elevated anti-dsDNA antibody titre 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), anti-Sm antibody positivity (31.6% vs 7.5%, p=0.02), anti-RNP antibody positivity (64.7% vs 15.2%, p<0.01) and immunosuppressant use on the day of glucocorticoid discontinuation (78.9% vs 55.6%, p=0.10).

Factors that tended to decrease the flare-free ratio, but without statistical significance (possibly due to the small sample size), were SLE duration of >5000 days (patient with flare 15.8% vs patient without flare 38.9%, p=0.09), HCQ treatment on the day of glucocorticoid

Table 4 Risk factors for flares after glucocorticoid discontinuation

Factor	Fisher's exact test			Cox proportional hazards model	
	Flare (–) (n=54)	Flare (+) (n=19)	P value	HR	P value (95% CI)
Prior severe organ involvement	36 (66.7)	13 (68.4)	1.0	1.19	0.73 (0.44 to 3.17)
Renal manifestations	26 (48.1)	9 (47.4)	1.0	1.22	0.67 (0.48 to 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 to 2.91)
History of treatment with mPSL pulse therapy	12 (22.2)	4 (21.1)	1.0	0.97	0.95 (0.32 to 2.95)
History of treatment with: B cell targeting/cytotoxic medication	4 (7.4)	0 (0.0)	0.57	N/A	N/A
Hypocomplementaemia on the day of glucocorticoid discontinuation	12 (23.1)	9 (50.0)	0.04	3.77	<0.01 (1.43 to 9.90)
Elevated anti-dsDNA antibody titre more than twice the limit of laboratory reference range on the day of glucocorticoid discontinuation	3 (12.0)	5 (55.6)	0.02	4.84	0.02 (1.27 to 18.41)
Duration of SLE >5000 days	21 (38.9)	3 (15.8)	0.09	0.43	0.18 (0.12 to 1.48)
Anti-Smith antibody	4 (7.5)	6 (31.6)	0.02	3.50	0.01 (1.31 to 9.35)
Anti-SSA/Ro antibody	22 (42.3)	11 (57.9)	0.29	2.19	0.10 (0.87 to 5.55)
Anti-RNP antibody	7 (15.2)	11 (64.7)	<0.01	6.80	<0.01 (2.36 to 19.63)
HCQ use on the day of glucocorticoid discontinuation	29 (53.7)	7 (36.8)	0.29	0.75	0.56 (0.29 to 1.97)
Immunosuppressant use on the day of glucocorticoid discontinuation	30 (55.6)	15 (78.9)	0.10	3.17	0.04 (1.04 to 9.68)
Achievement of LLDAS on the day of glucocorticoid discontinuation	52 (96.3)	17 (89.5)	0.28	0.25	0.07 (0.06 to 1.1)

Values are expressed as number (%) unless otherwise specified.
HCQ, hydroxychloroquine; LLDAS, Lupus Low Disease Activity State; mPSL, methylprednisolone; N/A, not applicable; PSL, prednisolone; RNP, ribonucleoprotein.;

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 hazards model, which showed that flare rate was not influenced by the presence of prior severe organ involvement (HR 1.19, 95% CI 0.44 to 3.17, p=0.73), renal manifestations (HR 1.22, 95% CI 0.48 to 3.10, p=0.67), neurological manifestations (not applicable), history of PSL treatment more than 1 mg/kg/day (HR 1.16, 95% CI 0.46 to 2.91, p=0.76), mPSL pulse therapy (HR 0.97, 95% CI 0.32 to 2.95, p=0.95), or B cell targeting or cytotoxic agent use (not applicable).

The Cox proportional hazards model analysis also demonstrated that hypocomplementaemia on the day of glucocorticoid discontinuation (HR 3.77, 95% CI 1.43 to 9.90, p<0.01), elevated anti-dsDNA antibody titre more than twice the upper limit of the laboratory reference range (HR 4.84, 95% CI 1.27 to 18.41, p=0.02), anti-Sm antibody positivity (HR 3.50, 95% CI 1.31 to 9.35, p=0.01), anti-RNP antibody positivity (HR 6.80, 95% CI 2.36 to 19.63, p<0.01) and use of any immunosuppressant on the day of glucocorticoid discontinuation (HR 3.17, 95% CI 1.04 to 9.68, p=0.04) were risk factors for flares after glucocorticoid discontinuation. Cox proportional hazards model analysis suggested that SLE duration of >5000 days (HR 0.43, 95% CI 0.12 to 1.48, p=0.18), HCQ use (HR 0.75, 95% CI 0.29 to 1.97, p=0.56) and LLDAS achievement (HR 0.25, 95% CI 0.06 to 1.1, p=0.07) on the day of glucocorticoid discontinuation were possible protective factors for flare-free remission after glucocorticoid discontinuation; however, significant differences were not noted.

DISCUSSION

Our findings showed that 298 of 309 (over 95%) patients with SLE followed up for more than 52 weeks at our institution 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 hypocomplementaemia and elevated anti-dsDNA antibody titre 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.[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] and Tselios *et al* reported a 2-year SLE flare (any increase in clinical SLEDAI +treatment escalation) rate of 14.7% after glucocorticoid discontinuation.[12] In addition, Zen *et al* reported that 21.8% of patients with SLE achieved prolonged complete remission or clinical remission off glucocorticoids after glucocorticoid discontinuation for 5 years.[11] These flare rates agree with the rates noted for our cohort for both patient groups.

This study showed that glucocorticoid doses can be safely tapered in patients whether they had prior severe organ involvement or not. Regarding the risk factors for flares after glucocorticoid discontinuation, Ji *et al* showed a serologically active and clinically stable state was associated with increased risk of flare.[20] This is in line with our results showing that hypocomplementaemia and elevated anti-dsDNA antibody titre more than twice the upper limit of the laboratory reference range on the day of glucocorticoid discontinuation was associated with increased risk of flare. In addition to that, our data suggested that positive anti-Sm antibodies and anti-RNP antibodies may be important risk factors for flare after glucocorticoid discontinuation. As suggested by the SLICC classification criteria, we used anti-dsDNA antibody titres at more than twice the upper limit of the laboratory reference range as a risk factor for flares because low titres of anti-dsDNA antibody have low sensitivity for SLE activity.[14]

A previous study on B cell depression therapy illustrated that the 1 year flare rates were higher in patients with SLE with anti-RNP or anti-Sm antibody positivity than in patients without such antibody positivity.[21] This is possibly because anti-RNP/Sm antibodies are produced by long-lived plasma cells[22] that cannot be fully eliminated by RTX, which is similar to the case with glucocorticoids.[23–25]

Our data suggest that any immunosuppressant use on the day of glucocorticoid discontinuation was associated with increased flare rate after glucocorticoid discontinuation. This may be explained by our method of glucocorticoid and immunosuppressant discontinuation. We attempt to discontinue glucocorticoids initially, followed by immunosuppressants. Therefore, it is quite common for patients on immunosuppressants to experience a flare because their condition is relatively more severe compared with those not on immunosuppressants.

More than 90% of the patients achieved LLDAS on the day of glucocorticoid discontinuation, but achieving LLDAS was higher in patients without flares than in those 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 patients with SLE,[26–28] but 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 the flare-free group (53.7%) than 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 glucocorticoids, 48 did so between 2016 and 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%.[29]

In addition, our data showed that the number of patients who achieved disease stability after glucocorticoid discontinuation increased following 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.[8–12 30–33]

Treatment with glucocorticoids is associated with many side effects, and even small amounts of glucocorticoids (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 non-fatal myocardial infarctions and $18,357.90/event for fractures.[34] 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.[35] In addition, glucocorticoid use during pregnancy is related to adverse pregnancy outcomes, including an increased

ratio of preterm births and orofacial clefts.[36 37] Therefore, reduction of glucocorticoid dosage is recommended according to the 2016 EULAR guidelines for use of antirheumatic drugs before and during pregnancy and lactation[38] and the 2020 ACR guideline for management of reproductive health in rheumatic and musculoskeletal diseases.[39] As we have previously proven that patients with SLE can have favourable pregnancy outcomes even with prior severe organ involvement,[40] 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 from glucocorticoid use, thereby reducing glucocorticoid-related adverse events, financial burden and adverse pregnancy outcomes.

Our study has some strengths. First, the standardised Japanese Healthcare System allowed accurate data acquisition every 1–3 months. In addition, there was a high medication compliance rate among all patients since doctors, nurses and pharmacists directly asked patients to adhere to medication and performed pill counting. The limitations of this study include its single-centre retrospective cohort study design that included a limited number of patients and thus could not exclude cofounders. Second, because we included sulphasalazine, iguratimod and bucillamine as immunosuppressants, we might have overestimated the flare rate after glucocorticoid discontinuation. Third, since our study participants were mostly Japanese, this may restrict the generalisability of our data to other populations. Finally, we could not include patients receiving belimumab therapy on the day of glucocorticoid discontinuation, since this has only been available to patients in Japan since 2017; therefore, in the future, we will need to reanalyse the data of patients treated with belimumab.

In conclusion, 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. Positive anti-Sm/anti-RNP antibody, hypocomplementaemia, elevated anti-dsDNA antibody titres that are more than twice the upper limit of the laboratory reference range, and use of any immunosuppressant on the day of glucocorticoid discontinuation were risk factors for subsequent flares.

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