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Glucocorticoid withdrawal in systemic lupus erythematosus: are remission and low disease activity reliable starting points for stopping treatment? A real-life experience

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ABSTRACT

Objectives To evaluate the proportion of patients who have successfully withdrawn glucocorticoids (GCs) in a longitudinal cohort of patients with systemic lupus erythematosus (SLE) over a period of 6 years; to evaluate patient characteristics during GC withdrawal in relation to existing definitions of remission and Lupus Low Disease Activity State (LLDAS); and to evaluate the occurrence of flares after GC withdrawal.

Methods Patients who attempted GC withdrawal were identified for the cohort, and the following information was assessed during withdrawal attempts: date of last disease flare, disease activity and damage and ongoing treatment. Information regarding the occurrence of disease flares after GC withdrawal was also recorded for patients who successfully stopped treatment.

Definitions of remission were applied to GC withdrawal in line with European consensus criteria (Definitions of remission in SLE [DORIS]) and LLDAS in line with the Asian Pacific Lupus Consortium definition.

Results 148 patients were involved in the study; GC withdrawal was attempted in 91 patients (61.5%) with 77 patients (84.6%) successfully stopping GCs. At the beginning of the GC reduction, the majority of patients were in complete or clinical remission (48.9% and 39.6%, respectively). Disease activity was significantly lower in patients who successfully stopped GCs, and the proportion of patients in complete remission was higher (54.2%) with respect to patients who failed in their attempt. Among patients who stopped GCs, 18 flares were recorded after a median of 1 year. The time period since the last flare was shorter in patients who experienced flares with respect to patients who did not flare (mean 0.93 years vs 6.0, p<0.001).

Conclusions GC withdrawal is an achievable goal in SLE and may be attempted after a long-term remission or LLDAS to protect the patient from disease flares.

Key messages

What is already known about this subject?

- At present, the decision to withdraw glucocorticoids (GCs) in systemic lupus erythematosus (SLE) is left to the judgement and experience of the treating physician who is required to weigh up the individual risk of disease flares against GC-related damage.
- A significant proportion of patients are kept on GCs by their treating physician despite clinical remission, particularly if there is a history of severe organ involvement.

What does this study add?

- We demonstrated that GCs tapering and complete withdrawal is an achievable goal in patients with SLE.

How might this impact on clinical practice?

- Long-term remission or Lupus Low Disease Activity State can be considered a reliable starting point for GCs tapering.
- Disease flares after GCs withdrawal are not common, and they can occur both early and a long time after stopping GCs.

INTRODUCTION

Glucocorticoids (GCs) have been used in systemic lupus erythematosus (SLE) treatment since the late 1940s[1] and still remain a cornerstone of SLE treatment despite advances in immunosuppressive therapies.

While pulse GCs are able to rapidly control disease activity, their effect is not maintained in the long term. Therefore, a chronic low-dose treatment is continued for many years,[2] particularly in patients with a relapsing–remitting course who experience several disease flares.

Observations of SLE cohorts demonstrate that up to 88% of patients are treated with GCs, and between 57% and 86% of patients undergo long-term treatment.[1 3 4]

In a recent survey of existing practice patterns in the treatment of patients with SLE by Canadian rheumatologists, approximately one-quarter of responders stated that they prescribed low-dose prednisone indefinitely to approximately 6%–10% of their patients.[5]

Chronic GC therapy is, however, associated with many side effects, in particular an increased risk of osteoporosis and avascular osteonecrosis, infections, diabetes, cardiovascular disease, cataract and glaucoma and also neuropsychiatric disorders, such as depression, hypomania and overt psychosis.[6–11]

Thus, treat-to-target recommendations suggest GC withdrawal where possible, or alternatively dosage reduction to ≤5 mg prednisone equivalent/day as an important target of the treatment plan.[12]

Strategies aimed to reduce GC use through the universal prescription of hydroxychloroquine, the early use of immunosuppressive drugs together with the use of pulses of GCs and maintenance therapy with ≤5 mg/day have demonstrated success in reducing GC-related damage without increasing damage due to SLE.[13]

Some studies have reported complete GC withdrawal, especially in lupus nephritis (LN).[14–19] There is, however, a lack of data available in terms of which patients may represent ideal candidates for GC withdrawal and how to carry out a GC withdrawal programme.

At present, in the majority of cases, the decision to withdraw GCs is left to the judgement and experience of the treating physician who is required to weigh up the individual risk of disease flares against GC-related damage.

For LN, European Renal Association–European Dialysis and Transplant Association (EULAR-ERA/EDTA) recommendations suggest that a gradual withdrawal of GCs is attempted in patients who have been in remission for at least 3 years after induction therapy.[20]

According to a recent internet-based survey of 130 clinicians from 30 countries, a longer duration of clinical remission (>5 years) with normal serology is associated with approximately a 35% likelihood of GC withdrawal; however, a significant proportion of patients are kept on GCs by their treating physician despite clinical remission, particularly if there is a history of severe organ involvement. From the same survey, serology emerged as the main influencer for the physician's decision to withdraw GCs.[21]

Definitions of remission and low disease activity have recently been developed in SLE.[22 23] This study's hypothesis is that such conditions might also represent the optimal moment to begin steroid withdrawal in clinical practice.

This study aims to: evaluate the proportion of patients who successfully withdraw GCs in a prospective cohort of SLE patients over a period of 6 years; evaluate the main characteristics of patients at GC withdrawal in terms of existing definitions of remission and low disease activity (Lupus Low Disease Activity State (LLDAS)); and evaluate the occurrence of flares after GC withdrawal.

METHODS

This study is a retrospective analysis of prospectively collected data from a monocentric longitudinal cohort of patients with SLE that began in 2012. Patients fulfilling the 1997 revised ACR criteria for SLE were enrolled in this cohort. Patients were considered eligible according to the following criteria:

- Undergoing ongoing GC therapy at study baseline (2012).
- Having at least two assessments/year from 2012 to 2017.
- Completing clinical and serological data (anti-dsDNA, C3 and C4) at each specialist appointment.

Ethical approval for this study was obtained from the Institutional Review Board and a local ethics committee approved the study; each patient signed the informed consent for the use of clinical and laboratory data for study purposes.

Definitions and outcomes

Patients who attempted GC withdrawal have been categorised into two groups: successful withdrawal and unsuccessful withdrawal. Withdrawal was defined successful when a patient was able to reduce the dosage of GC until complete stopping without having disease flares during the dose reduction.

Last disease flare, disease activity and damage and ongoing treatment were assessed for these patients; the occurrence of disease flares after GC withdrawal was recorded for the patients who successfully stopped treatment.

Disease activity was assessed at each visit using the Safety of Estrogens in Lupus Erythematosus National Assessment -systemic lupus erythematosus disease activity index (SELENA-SLEDAI), while organ damage was assessed annually with the American College of Rheumatology/Systemic Lupus International Collaborating Clinics Damage Index (ACR-SLICC/DI); remission has been defined according to European consensus criteria (DORIS) and low disease activity (LLDAS) defined according to Asian Pacific Lupus Consortium criteria.[22 23] Considering the overlapping between the LLDAS and remission definitions, in the cohort description, patients fulfilling LLDAS but not remission criteria (LLDAS not remission) and patients fulfilling both criteria were indicated separately.

Disease flares have been defined according to the SELENA-SLEDAI flare index as mild/moderate flares or severe flares.

The treating physician decided when and how to stop GC in agreement with the patient, and there was not a predefined protocol for GC tapering.

Statistical analysis

Variables were described in terms of mean and SD or median and 25th–75th percentiles depending on variable distribution. T-test and the non-parametric Wilcoxon test have been used to investigate differences between groups

of patients. Cross-tabulated data have been analysed by χ^2 test or Fisher's test when the expected cell count was less than 5.

The association between successful GC withdrawal and the occurrence of flares and different types of disease status, disease activity, organ damage and duration from last flare has been evaluated by logistic regression analysis. The following variables were included in the univariate analysis: age, disease duration, complete remission on treatment (yes/no), clinical remission on treatment (yes/no), SLEDAI at the physician's decision to stop GC, baseline SLICC, duration from last flare, type of organ involvement (cumulative) and ongoing therapy at the physician's decision to stop GC.

The same variables were considered for the derivation of a propensity score used to estimate the adjusted probability of experiencing a flare between the subgroup of GC-free patients versus the rest of the cohort.

Factors with a p<0.1 at univariate analysis were considered for inclusion into multivariate models.

Statistics were performed using the STATA software. P values less than 0.05 were considered statistically significant.

RESULTS

From the whole cohort (n=310), GC-free patients at the cohort entry (n=47), patients with incomplete follow-up (n=53) and patients with incomplete data (n=30) have been excluded from this analysis. A total of 148 patients have been included. Their epidemiological and clinical characteristics at study entry are summarised in table 1. In short, patients were predominantly Caucasians (98.6%), at study entry the mean age was 42.2±12.5 and disease duration was 13.9±9.1 years; as expected, musculoskeletal manifestations (76.3%) were the most prevalent manifestations during the disease course and approximately half the patients had a history of haematological, cutaneous or renal manifestations (57.5%, 56.2% and 53.4%, respectively).

Table 1 Characteristics of the cohort

	Whole cohort (N=148)
Age at study entry (mean±SD)	42.2±12.5
Disease duration at study entry (mean±SD) at study entry	13.9±9.2
Cumulative organ involvement	
Musculoskeletal involvement (ever)	76.3%
Haematological involvement (ever)	57.5%
Skin involvement (ever)	56.1%
Kidney involvement (ever)	53.3%
Serositis (ever)	21.6%
Neuropsychiatric involvement (ever)	12.8%
Constitutional symptoms: fever and weight loss (ever)	6.8%
Ongoing therapies	
Hydroxychloroquine	76.3%
Traditional immunosuppressants	36.5%
Azathioprine	10.4%
Mycophenolate	15.0%
Metotrexate	4.8%
Cyclosporine	2%
Tacrolymus	4.9%
Biological drugs	12.9%
SLICC/DI at study entry (median (IQR))	0 (0–1)
SLICC/DI at last observation (median (IQR))	0 (0–2)

Clinical characteristics at GC withdrawal

GC withdrawal was attempted in 91 patients (61.5%) during the 6 years of follow-up; the median daily dosage of GC in use when GC tapering was started was 5 mg/prednisone equivalent (IQR 2.5–5), and the median time required to completely withdrawn GC resulted 11 months (IQR 6–15).

GCs were successfully stopped in 77 patients (84.6%), while 14 (15.4%) patients were not able to discontinue treatment due to symptom flares during the period of reduction (mainly arthralgias and fatigue). The mean yearly rate of GC discontinuation therefore resulted in 8.7%.

Table 2 reports the characteristics of patients for whom GC withdrawal was attempted at the time of the physician's decision. Patients who attempted GC withdrawal were slightly younger (mean 40.7±12 years vs 44.6±13, p=0.06) with less organ damage (mean SLICC 0 0–1) vs 1 0–2), p=0.033), while disease duration was similar to the group who had never attempted GC withdrawal.

When physicians opted to begin GC reduction, disease activity was generally low (median SLEDAI 2 (0–2)), and only a few patients (6.6%) had SLEDAI >4. The majority of patients were in LLDAS (97%); among those, complete remission or clinical remission were fulfilled in 48.9% and 39.6%, respectively, while only a minority were in LLDAS but not in remission (9.9%).

When comparing patients who successfully stopped GCs with patients who failed in their attempt, disease activity when the physician decided to begin GC reduction was significantly lower in the first group (mean SLEDAI 1.31±1.1 vs 2.57±2.1, p=0.01); indeed, the proportion of patients in complete remission was higher (54.2%) in patients who successfully stopped GCs, while fewer patients were on clinical remission (37.3%) or in LLDAS (6.8%). By logistic regression, the state of being in complete remission and the SLEDAI score were associated with an increased likelihood of successfully stopping

Table 2 Characteristics of patients at the physician's decision to stop GCs

	Patients who attempted GCs stopping (n=91)	Patients who successfully stopped GCs (n=77)	Patients who were unable to stop GC (n=14)
SLEDAI (median (IQR))	2 (0–2)	0 (0–2)*	2 (2–2)
SLEDAI >4, n (%)	6 (6.6)	4 (5.2)	2 (14.3)
Complete remission, n (%)	44 (48.3)	42 (54.2)†	3 (21.4)
Clinical remission, n (%)	36 (39.6)	29 (37.3)‡	9 (64.3)
LLDAS (not remission), n (%)	9 (9.9)	7 (9.2)	2 (14.3)
LLDAS, n (%)	89 (97.8)	75 (97)	14 (100)
Duration from last flare, years (median (IQR))	3 (2–6.5)	4 (2–7)	3 (2–7)
HCQ, %	74.2	78	
IS, %	37	34	
Biological, %	4.7	4	
	Patients who flared after GCs stopping (n=18)	Patients who did not flare after GCs stopping (n=59)	
SLEDAI (median (IQR))	2 (1–4)§	2 (0–2)	
SLEDAI >4, n (%)	3 (16.6)¶	**1 (1.7)**	
Complete remission, n (%)	8 (44.4)	33 (55.9)	
Clinical remission, n (%)	5 (27.8)	24 (40.6)	
LLDAS (not remission), n (%)	4 (22.2)**	3 (5.08)	
LLDAS, n (%)	16 (94.1)	58 (98.3)	
Duration from last flare, years (median (IQR))	1.5 (0.5–4)††	5 (2–10)	
HCQ, %	73.3	74.5	
IS, %	26	41	
Biological, %	0	6	

*With respect to patients who failed, p=0.01
†With respect to patients who failed, p=0.02.
‡With respect to patients who failed, p=0.04.
§With respect to patients who did not flare, p=0.008.
¶With respect to patients who did not flare, p=0.004.
**With respect to patients who did not flare p=0.02.
††With respect to patients who did not flare, p<0.001

GCs (OR 4.29, p=0.035; OR 0.7, p=0.023 4.4, respectively); however, at the multivariate analysis, this significance is lost (table 3).

Moreover, in patients who successfully stopped GCs, the time period since the last flare was longer (5.21±0.64 vs 4.57±1.45 years), even though this difference was not statistically significant (table 2).

Flares after GC withdrawal

For those patients who successfully stopped GCs, over a median follow-up period of about 2 years a total of 18 flares were recorded involving 23% of patients.

In the subgroup of patients who had never attempted GC withdrawal during the 6-year period of follow-up, about 69.8% of patients experiences at least one flare; in particular, a total of 46 flares were recorded and four patients were chronically active.

Attempting to compare the probability of experiencing a flare in the GC-free subgroup versus patients who had never attempted GC withdrawal over the whole 6-year follow-up period and using a propensity score adjustment, probabilities were significantly different with a mean difference of about −19.9 (95% CI −36.4 to −0.03).

For patients who successfully stopped GCs, in 13 cases (72.2%) flares were mild, while in five cases (27.7%), a major flare occurred. Moreover, the reintroduction of GCs was necessary in almost all patients (94.4%). Flares were articular in six cases (33.3%), cutaneous in three cases (16.6%), renal in four cases (22.2%), haematological in three cases (16.6%), serositis in one case (5.5%) and neurological in one case (5.5%). Flares occurred after a median of 1 (0–2) year after GC withdrawal and after a maximum of 5 years.

Table 2 reports characteristics of patients at the physician's decision to stop GCs who experienced flares in comparison with the whole group. In short, patients who experienced a disease flare after GC withdrawal presented a higher disease activity (as expressed by the mean

Table 3 Univariate and multivariate analysis for predictors of successful GC stopping and flares after GC withdrawal

Successful GC withdrawal	OR	P value	CI
Disease duration	1.00	0.87	0.91 to 1.128
Complete remission	4.25	**0.03**	1.19 to 16.6
Clinical remission	0.36	**0.05**	0.09 to 1.06
LLDAS (not remission)	0.69	0.56	011 to 3.28
SLEDAI	0.70	**0.02**	0.52 to 0.95
Duration from last flare	1.00	0.87	0.90 to 1.12
SLICC	0.63	**0.05**	0.39 to 1.01
Multivariate analysis			
Complete remission	0.40	0.69	0.004 to 38.9
Clinical remission	0.19	0.23	0.009 to 3.84
SLICC	0.59	0.09	0.32 to 1.08
SLEDAI	0.69	0.35	0.31 to 1.51
Flare after GC withdrawal			
Disease duration	1.01	0.76	0.94 to 1.07
Complete remission	0.73	0.58	0.25 to 2.18
Clinical remission	0.53	0.29	0.16 to 1.79
LLDAS (not remission)	4.47	0.07	0.89 to 22.4
SLEDAI	1.43	**0.03**	1.03 to 1.98
Duration from last flare	0.78	**0.03**	0.63 to 1.96
SLICC	0.45	0.27	0.10 to 1.86
Multivariate analysis			
SLEDAI	1.11	0.61	0.72 to 1.0
Duration from last flare	0.8	0.05	0.64 to 1.8

GC, glucocorticoid.

SLEDAI and the percentage of patients with SLEDAI >4) when the physician decided to start GC withdrawal.

The time period since the last flare was shorter in patients who flared (median 2[1–4] vs median 4[2–9] years, p<0.001); lower SLEDAI scores and longer time period from the last flare were associated with lower likelihood of flare after GC withdrawal (OR 1.43, p=0.031 and OR 0.78, p=0.033 respectively); no differences were observed in terms of disease status or ongoing treatments at the time of GC withdrawal.

In the multivariate analysis, only the time period since the last flare remained the most important determiner of disease flare (table 3).

DISCUSSION

GC tapering and withdrawal are considered one of the main targets of SLE management. While GC tapering is a well-consolidated practice in SLE management, there is little guidance in terms of how and when to stop GCs; thus, the decision to begin GC withdrawal is determined principally by the physician's experience.

A recent survey showed that clinicians' preferences in withdrawing GCs in patients with SLE in clinical remission are highly variable: serological abnormalities, previous disease severity and duration of remission are the most recurrent variables that influence this decision.[21]

Definitions for disease remission and LLDAS have recently been proposed and validated as meaningful targets to be pursued in SLE management; indeed, sustained remission and LLDAS have been associated with less organ damage accrual and better quality of life.[15 24–30] This study's hypothesis is therefore that such conditions might also be considered an effective starting point for GC withdrawal in clinical practice.

The aim of this study is to describe GC withdrawal rate in a real-life setting of patients with SLE as well as the variables that most likely influenced the decision to stop GCs and the occurrence of flares after GC withdrawal; this study also aims to assess the possible role of LLDAS and remission definitions to start GC withdrawal.

This study found that GC withdrawal was attempted in the majority of patients in this cohort during the observation period (61.5%), and in many cases (85.7%), GC withdrawal was successful, thus demonstrating that GC-free remission is an achievable goal in SLE; indeed, only 15.4% of patients failed to stop GCs due to the emergence of subjective complaints (fatigue and arthralgia) or a disease flare during reduction.

Overall, the patients at study entry were young, with a long disease duration and a full-blown disease history making this cohort well representative of the disease in Caucasian patients.

Data on the frequency of GC withdrawal in SLE are scarce and extremely heterogeneous; the main literature is summarised in table 4.[14–17 24 31–34] The prevalence of GC-free patients in SLE cohorts is highly variable in the literature; one of the lowest frequencies is reported by Steiman *et al*, who described prolonged remission lasting for ≥5 years while taking no medications in less than 3% of the cohort;[15] similarly, Zen *et al*[31] and Urowitz *et al*[32] reported a frequency of GC-free patients of less than 10%.

In 2013, Zahr *et al* reported that the dose of prednisone was reduced to <5 mg/day in 11% of the visits of the Hopkins Lupus cohort and 55% of patients successfully remained below 5 mg for at least 1 year; ongoing cutaneous or arthritis activity were associated with unsuccessful reduction, while lack of disease activity was the only major clinical variable that significantly predicted successful reduction.[35]

A greater experience can be found in LN, where GC withdrawal seems to be more common; the first successful experience of GC withdrawal in LN was reported by Ponticelli *et al* in 1988[36]; thereafter, the same group confirmed the results in a larger study with long-term follow-up where 32% of patients were able to completely withdraw GCs and immunosuppressive drugs. Interestingly,

Table 4 Frequency of GCs-free patients in the cohorts reported in the literature

Author, year	Ref	Study design	Percentage of patients GC free	Note
Ponticelli, 1988	36	Prospective	50	Only LN
Drenkard, 1996	14	Prospective	23	
Formiga, 1999	33	Prospective	24	Remission for at least 1 year
Pons-Estel, 2004	34	Prospective	20.2	
Urowitz, 2005	32	Prospective	6.5	Complete remission for at least 1 year
Moroni, 2006	17	Retrospective	26.6	Only LN
Moroni, 2013	16	Prospective	32	Only LN
Steiman, 2014	15	Prospective	2.4	
Zen, 2017	27	Prospective	7.1	
Petri, 2018	24	Prospective	13	Of follow-up months

GC, glucocorticoid.

Moroni *et al* did not find significant differences in the clinical presentation, histological characteristics or the type of induction therapy between patients who were able to stop treatment and those who were not, with the exception of a higher activity index in the latter.[16]

In this cohort, we observed a higher percentage of patients in whom GC withdrawal is attempted, which may reflect the increasing knowledge of the long-term harm of even low-dose chronic GC use; this is in line with observations by Zahr *et al* on the increase of the successful tapering of GCs since the year 2000.[35]

These data could be reinforced by the observation that in the majority of our cases GC tapering has been successful and that disease flares after GC withdrawal have been rare and in the majority of the cases mild.

By analysing the physician's triggers for GC withdrawal, this study found that remission (particularly complete remission) is the main driver for attempting GC tapering, while only a minority of patients were presenting some degree of clinical manifestations. At the physician's decision to stop GCs, about one-third of the patients was on immunosuppressants and/or biologicals, thus demonstrating that GC withdrawal can be considered a priority compared with immunosuppressants. Moreover, 76% of patients were on hydroxychloroquine (HCQ), and no differences were observed in term of successful GC withdrawal and risk of flare between HCQ users or not. Considering the importance of HCQ for the disease activity control, one could argue that even more successful GC withdrawal would be expected by increasing the percentage of patients taking this drug.

Data concerning disease flares also confirmed the importance of conducting a disease activity assessment before GC withdrawal; indeed, the risk of flare was significantly influenced by disease activity at the time of the decision to stop GCs.

The time period since the last flare represented another significant factor in the risk of flaring after GC withdrawal. The importance of remission duration as a fundamental driver for a successful outcome is well documented in the literature.[24 25 27 32]

Interestingly, the state of being in clinical remission, in complete remission or in LLDAS at the time of the physician's decision to stop GCs does not constitute a different risk in terms of disease flare; this is a crucial point demonstrating that all such conditions might be similarly considered a valid starting point for treatment tapering and withdrawal.

Important information for a successful GC withdrawal in clinical practice can be drawn from the above data: the ideal situation to start GC withdrawal is a patient with low disease activity and who has not experienced a recent disease flare; therefore, sustained disease remission or LLDAS constitutes optimal conditions for considering to start treatment tapering.

The limitations of this study are as follows: first, the follow-up after GC withdrawal is variable and short on average (1–5 years), thus late flares might be missed by the analysis. Moreover, our data are derived from a real-life practice from a tertiary referral centre enrolling mainly Caucasian patients; thus, their direct applicability could be limited to this setting. Lastly, we have to acknowledge that the relatively small sample size (especially in subgroups analysis) could be a limitation by inflating the risk of a type I error.

Despite such limitations, we hope that these data might be useful to treating physicians as an initial input on when the right moment could be to attempt GC withdrawal.

In conclusion, GC tapering and complete withdrawal can be achievable and sustainable in patients with SLE and might be attempted after a long-term remission or LLDAS to protect the patient as much as possible from disease flares. Disease flares are not common in this subset of patients and can occur both early and a long time after stopping GCs, thus, close disease monitoring after GC withdrawal is necessary.

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