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Gradual Glucocorticosteroid Withdrawal Is Safe in Clinically Quiescent Systemic Lupus Erythematosus

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Objectives. Patients with systemic lupus erythematosus (SLE) are usually treated with glucocorticosteroids even during periods of clinically quiescent disease. A recent study showed that abrupt glucocorticoid withdrawal was associated with an increased likelihood of flare in the next 12 months. The aim of the present study was to assess clinical flare rates and damage accrual in patients who tapered glucocorticosteroids gradually.

Methods. Patients from the Toronto Lupus Clinic with 2 consecutive years of clinically quiescent disease were retrieved from the database. Individuals who maintained a low prednisone dose (5 mg/day) comprised the maintenance group, whereas patients who gradually tapered prednisone within these two years comprised the withdrawal group. All individuals were followed for 2 years after prednisone discontinuation or the corresponding date for the maintenance group. Propensity score matching was implemented to adjust for certain baseline differences. Outcomes included clinical flares and damage accrual.

Results. Of 270 eligible patients, 204 were matched (102 in each group). Flare rate (any increase in clinical SLE Disease Activity Index 2000) was lower in the withdrawal group both at 12 (17.6% versus 29.4%; $P = 0.023$) and 24 months (33.3% versus 50%; $P = 0.01$). Moderate to severe flares (requiring systemic treatment escalation) were not different at 12 months (10.8% versus 13.7%; $P = 0.467$) but were less frequent at 24 months (14.7% versus 27.5%; $P = 0.024$). Damage accrual was less frequent in the withdrawal group (6.9% versus 17.6%; $P = 0.022$). No predictors for clinical flares were identified.

Conclusion. Gradual glucocorticoid withdrawal is safe in clinically quiescent SLE and is associated with fewer clinical flares and less damage accrual at 24 months.

INTRODUCTION

Glucocorticosteroids remain the cornerstone of treatment in systemic lupus erythematosus (SLE), not only for the management of active disease but also as maintenance in clinically quiescent patients, albeit in lower doses (1,2). Approximately 50% to 85% of patients with lupus are regularly administered glucocorticosteroids in large cohorts, even during periods of mild disease activity (3–5). Their long-term side effects are widely recognized; however, many patients continue low-dose glucocorticosteroids indefinitely either by preference or by physician's advice. The latter seems to occur infrequently, as shown by a recent study from Manchester in the United Kingdom in which the vast majority of physicians (>90%) were willing to reduce or withdraw prednisone before immunosuppressives and antimalarials in cases of prolonged clinical inactivity (6). This approach seems justified by studies demonstrating significant damage accrual with doses as low as 4.42 mg/day of prednisone (time-adjusted over a median of 3.6 years) (7), whereas a chronic 5 mg/day dose is enough to induce a reduction in bone mineral density and increased fracture risk during the treatment period (8), although other studies did not confirm these findings for doses of up to 6 mg/day (9). As such, the latest European League Against Rheumatism recommendations suggest glucocorticoid withdrawal when possible (1).

The rate of withdrawal has not been defined yet. A recent randomized clinical trial (Evaluation of the Discontinuation of Maintenance Corticosteroid Treatment in Quiescent Systemic Lupus [CORTICOLUP]) from France demonstrated an increased possibility of clinical flare over the next 12 months in patients who discontinued low-dose prednisone (5 mg/day) abruptly (compared

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with patients who maintained the 5-mg/day dose) (10). At the University of Toronto Lupus Clinic (UTLC), we follow a different approach on glucocorticosteroid tapering, which mandates a gradual decrease in the daily prednisone dose over many months even at the level of 5 mg/day. The aim of the present study was to evaluate this approach as per its ability to decrease damage accrual and minimize flares compared with patients who maintained a low prednisone dose.

PATIENTS AND METHODS

The UTLC has currently enrolled 2080 patients since its establishment in 1970. All patients fulfilled the revised American College of Rheumatology criteria for SLE classification or had three criteria and a supportive kidney biopsy (11). Patients are followed regularly at 2- to 6-month intervals according to a standardized research protocol, which is regularly updated. The protocol captures demographic, clinical, laboratory, and therapeutic variables together with the major comorbidities. All data are entered and stored in an electronic database for further analysis. All individuals have provided written informed consent for studies being conducted at the UTLC, and this study was approved by the University Health Network Research Ethics Board (11-0397).

For the purpose of the present study, UTLC patients with prolonged clinical remission for a continuous period of 2 years for the first time during their disease course were retrieved from the database. Remission was defined based on a clinical SLE Disease Activity Index 2000 (SLEDAI-2K) of 0 that remained stable over those 2 years. Isolated serologic activity (abnormal levels of anti–double-stranded DNA (dsDNA) antibodies and/or low levels of complement C3/C4) was allowed. Patients should be receiving prednisone (5 mg/day) at the beginning of the observation period, and antimalarials and immunosuppressives in stable or lower doses were allowed. During these 2 years, patients remained at stable doses of prednisone (5 mg/day, maintenance group) or were instructed to gradually taper glucocorticosteroids in order to discontinue (withdrawal group). These patients reduced their prednisone dose by 1 mg/day in 7 weeks' time as follows:

- Week 1: usual dose (5 mg/day) for 6 days and reduced dose (4 mg/day) for Day 7.
- Week 2: usual dose (5 mg/day) for 5 days and reduced dose (4 mg/day) for 2 days.
- Week 3: usual dose (5 mg/day) for 4 days and reduced dose (4 mg/day) for 3 days, and so on.

Following this approach, each patient reaches the first reduced dose at Week 7 and remains at the same dose until her/his next clinic visit or continues to the next lower level according to the clinical condition. At the next clinic visit, she/he is instructed to continue tapering, aiming at the next lower level. Based on this schedule, our patients discontinue prednisone approximately in 9 to 18 months depending on the frequency of the clinic visits, possible development of withdrawal symptoms, and personal preferences.

The index date (baseline) was defined as the end of the first prolonged (2 consecutive years) clinical remission for the maintenance group and the date patients discontinued prednisone for the withdrawal group. All patients were followed for 2 years after the index date. The study design is schematically shown in Figure S1.

Outcomes included the proportion of patients who experienced flares within the two years of follow-up defined by the following:

- Any increase in clinical SLEDAI-2K (excluding serology).
- Any increase in clinical SLEDAI-2K accompanied by escalation in treatment with glucocorticosteroids, antimalarials, or immunosuppressives.
- Any increase of 4 or more in clinical SLEDAI-2K.

All outcomes (flare by the aforementioned definitions) were assessed at 12 and 24 months after the index date. Damage accrual at the end of follow-up (24 months) was also assessed based on the Systemic Lupus International Collaborating Clinics Damage Index (SDI) (12).

Patients from both groups who experienced a clinical flare and/or increased the doses of prednisone, antimalarials, or immunosuppressives during the observation period were excluded from this analysis. However, the patients who did not have a 2-year remission after commencing glucocorticosteroid tapering were studied separately and compared with individuals who maintained a low prednisone dose (5 mg/day); these patients were followed for 2 years for the same outcomes as above. This approach allowed for the identification of the "success rate" of the gradual tapering approach.

Descriptive statistics were used to describe the cohort characteristics and outcome rates; the mean ± SD and count (percentage) are provided for continuous and categorical variables, respectively. Variables were further compared by Student's *t* test, analysis of variance, and χ^2 test.

Because of differences in the baseline characteristics of the groups, we performed a propensity score–matching (PSM) analysis. The independent variables that were used for calculating the propensity score included sex, age (at SLE diagnosis and at index), Black race, inception status (follow-up started within 12 months of SLE diagnosis), disease duration, SDI (at index date), SLEDAI-2K (at inception and index dates), adjusted mean SLEDAI-2K for the first 5 years of observation in our clinic and for the last 2 years prior to the index date, serology at index date (low complement C3/C4 and/or abnormal anti-dsDNA antibodies), cumulative dose of glucocorticosteroids up to the index date, antimalarials and immunosuppressives at index date, history of prior renal and/or central nervous system (CNS) involvement, and duration of the clinical remission prior to the index date. The caliper used was 0.2 multiplied by the logit of propensity score from a logistic regression

using the aforementioned independent variables, which is considered optimal for observational studies (13). The dependent variable used in the calculation of propensity score was the group membership (whether patients maintained or withdrew prednisone). Differences between matched patients were compared by standardized difference of means and variance ratios.

In order to confirm the results in the entire cohort, we also performed an inverse probability of treatment weighting analysis (IPTW) (14).

PSM based on the same variables was applied to patients who had a shorter clinical remission (for two clinic visits and not 2 years) and maintained or gradually tapered their low-dose prednisone (5 mg/day).

In order to quantify the impact of withdrawal on the possibility of flare, we performed a Cox proportional regression analysis for the outcome of first flare between the groups (conditional on matched pairs). A step-down covariate selection method was used in the multivariable analysis; covariates were selected out one by one with largest *P* value until the smallest Akaike information criterion was reached.

Statistical analysis was performed with SAS 9.4; $P < 0.05$ was considered significant.

RESULTS

Maintenance versus withdrawal. A total of 270 individuals satisfied the inclusion criteria. One hundred fifty-six patients maintained low-dose prednisone (5mg/day) for 2 years before the index date (baseline). One hundred fourteen patients discontinued prednisone gradually without flare in 11.9 ± 5.6 months. All 114 patients decreased their prednisone from 5 mg/day to 4 mg/day in 4.8 ± 2.4 months. The time for complete withdrawal (from 5 mg/day to 0 mg/day) was 7.6 ± 2.7 months for 62 patients and 17.1 ± 3 months for the remaining 52 patients depending on the frequency of clinic visits, development of withdrawal symptoms, and/or patient preferences. Patient characteristics at baseline are shown in Supplementary Table 1.

After PSM, 204 patients were retained (102 in each group). There were no significant baseline differences between groups (details in Table 1).

Outcomes (flare rates and damage accrual) are shown in Table 2. Regarding any increase in clinical SLEDAI-2K or an increase of 4 or more, patients in the withdrawal group developed significantly fewer flares at 24 months after index date. Approximately half of these flares (23/51 and 19/34 in the maintenance and withdrawal groups, respectively) were mild and managed with topical treatment and/or nonsteroidal anti-inflammatory drugs only. For the entire period of follow-up (24 months), mild flares were observed in 23 patients with skin involvement (10 and 13 in the maintenance and withdrawal groups, respectively), 11 with hematologic involvement (isolated leukopenia or thrombocytopenia; five and six in the maintenance and withdrawal groups, respectively), eight with mild arthritis (seven and one in the maintenance and withdrawal groups, respectively) and two with mild vasculitic lesions (one in each group). None of these comparisons (by organ system) reached statistical significance.

Regarding moderate to severe flares requiring escalation in systemic therapy, there were fewer flares in the withdrawal

Table 1. Demographic, clinical, serological, and therapeutic characteristics of the patients at baseline

Variable	Maintenance Group (n = 102)	Withdrawal Group (n = 102)	SMD	Variance Ratio	*P* Value
Female sex	92 (90.2)	89 (87.3)	-	-	0.884
Black	12 (11.8)	8 (7.8)	-	0.88	0.317
Age, years	44.1 ± 15.4	41.7 ± 12.9	0.17	1.07	0.242
Disease duration, years	12.8 ± 10	11.7 ± 7.9	0.12	1.1	0.292
Duration of clinical remission, years	3.6 ± 2.6	3.6 ± 2.2	0.01	0.7	0.967
SLEDAI-2K	1.7 ± 1.5	1.6 ± 1.5	0.08	0.91	0.577
Adjusted mean SLEDAI-2K for the first 5 years since enrollment	3.5 ± 1.9	3.1 ± 1.9	0.23	1.05	0.075
History of lupus nephritis[a]	37 (36.3)	41 (40.2)	-	0.99	0.572
History of CNS involvement[b]	34 (33.3)	28 (27.5)	-	0.93	0.396
Low C3/C4	42 (41.2)	41 (40.2)	-	1	0.866
Anti-dsDNA (+)	45 (44.1)	40 (39.2)	-	1.04	0.484
SDI	1.2 ± 1.4	1.0 ± 1.5	0.13	0.68	0.352
Cumulative glucocorticoid dose,[c] g	30.6 ± 24.4	25.5 ± 22.6	0.22	1.17	0.062
Antimalarials	67 (65.7)	67 (65.7)	-	0.88	1.000
Immunosuppressives	51 (50)	44 (43.1)	-	0.98	0.25

Categorical variables are presented as n (%), continuous variables are presented as mean ± SD.
Abbreviation: SDI, Systemic Lupus International Collaborating Clinics Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; SMD, standardized mean difference.
[a] Based on renal biopsy demonstrating lupus nephritis or abnormal proteinuria (>0.5g/day) in two consecutive visits treated with glucocorticosteroids and immunosuppressives by the attending physician.
[b] Based on any central nervous system involvement treated with glucocorticosteroids and/or immunosuppressives by the attending physician.
[c] From first clinic visit up to the index date (in prednisone equivalent).

Table 2. Flare rates at 12 and 24 months and damage accrual at 24 months

	Maintenance Group (n = 102)	Withdrawal Group (n = 102)	*P* Value
Flares at 12 months			
Flare (first definition)[a]	30 (29.4)	18 (17.6)	0.023
Flare (second definition)[b]	14 (13.7)	11 (10.8)	0.467
Flare (third definition)[c]	12 (11.8)	7 (6.9)	0.197
Flares at 24 months			
Flare (first definition)[a]	51 (50)	34 (33.3)	0.01
Flare (second definition)[b]	28 (27.5)	15 (14.7)	0.024
Flare (third definition)[c]	27 (26.5)	13 (12.7)	0.013
Damage accrual at 24 months			
Related to glucocorticosteroids	12 (11.8)	3 (2.9)	0.02
Not related to glucocorticosteroids	7 (6.9)	4 (3.9)	0.317
Increase in SDI	18 (17.6)	7 (6.9)	0.022

Abbreviation: SDI, Systemic Lupus International Collaborating Clinics Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000; SMD, standardized mean difference.
Data are given as n (%).
[a] Any increase in clinical SLEDAI-2K (excluding serology).
[b] Any increase in clinical SLEDAI-2K plus treatment escalation (for glucocorticosteroids, antimalarials or immunosuppressives).
[c] Any increase ≥4 in clinical SLEDAI-2K.

group (14.7% versus 27.5%; *P* = 0.024) at 24 months. The nature of these flares was mostly cutaneous manifestations (12 [11.8%] versus 6 [5.9%] for the maintenance and withdrawal groups, respectively) and polyarthritis (7 [6.9%] versus 5 [4.9%], respectively]. Renal flares were observed in six (5.9%) and two (2%) patients, whereas central nervous system involvement occurred in one (1%) and two (2%) patients in the maintenance and withdrawal groups, respectively. None of these comparisons (by organ system) reached statistical significance.

Regarding flares at 12 months, there were no significant differences in moderate to severe and flares with an increase of 4 or more in SLEDAI-2K. Total flares (any increase in SLEDAI-2K) were fewer in the withdrawal group (17.6% versus 29.4%; *P* = 0.023) (Table 2).

More patients in the maintenance group accrued new damage (expressed by any increase in SDI) at 24 months (17.6% versus 6.9%; *P* = 0.022). The majority of the patients developed glucocorticoid-dependent damage (11.8% versus 2.9%; *P* = 0.02), whereas there were no significant differences regarding glucocorticoid-independent damage (6.9% versus 3.9%; *P* = 0.317).

Predictors of clinical flare. The multivariable Cox proportional regression analysis for the identification of predictors for clinical flare did not reveal any of the studied variables to independently affect the possibility of flare (Table 3).

Table 3. Univariable and multivariable Cox proportional regression analysis for the earliest clinical flare

	Univariable Analysis			Multivariable Analysis		
Predictors	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Age at onset	1.004	0.98-1.029	0.742	-	-	-
Age at baseline	1.001	0.978-1.025	0.912	-	-	-
Disease duration at baseline	0.99	0.945-1.038	0.683	-	-	-
Adjusted mean SLEDAI-2K in 5 years since first clinic visit	0.911	0.743-1.117	0.372	-	-	-
Low C3/C4 at baseline	1.583	0.769-3.262	0.213	-	-	-
Abnormal anti-dsDNA at baseline	1.286	0.639-2.585	0.481	-	-	-
Low C3/C4 and abnormal anti-dsDNA	1.444	0.617-3.379	0.3964	-	-	-
SDI	1.007	0.796-1.275	0.952	-	-	-
Cumulative glucocorticoid dose up to baseline (grams)	1.008	0.99-1.026	0.38	1.016	0.994-1.039	0.144
Antimalarials at baseline	0.933	0.451-1.934	0.853	-	-	-
Immunosuppressives at baseline	0.643	0.278-1.485	0.301	-	-	-
History of CNS involvement	1.125	0.574-2.206	0.732	-	-	-

Abbreviation: CI, confidence interval; dsDNA, double-stranded DNA; SDI, Systemic Lupus International Collaborating Clinics Damage Index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index-2000.

Flare rates in patients with shorter clinical remission (<2 years). We also analyzed an additional 263 patients with clinical remission for two consecutive visits but not 2 years who were treated with prednisone 5 mg/day (stable dose for these two visits). Of these patients, 107 maintained their prednisone dose and 156 were instructed to start tapering despite not having 2 years of clinical remission. All individuals were followed for 2 years after the second clinic visit. One hundred seventy patients (85 pairs) were propensity score–matched on the basis of the same variables that were used for the main study groups (details in supplementary Table 2). During the follow-up period, the flare rates (defined as any increase in clinical SLEDAI-2K or systemic treatment escalation) were identical (57/85 [67.1%] versus 57/85 [67.1%]) in the two groups. At the end of follow-up, 31 patients (36.5%) had successfully discontinued prednisone and another 51 (60%) were taking 2.5 mg/day or less.

IPTW analysis. The IPTW analysis for the entire cohort (n = 270) is provided in the Appendix. Briefly, the outcomes were comparable with the PSM analysis for both the flare rate and the damage accrual. Patients who withdrew glucocorticoids gradually had fewer flares and less damage accrual in the following 2 years from baseline.

DISCUSSION

In the present study, we showed that gradual withdrawal of prednisone was not associated with more flares at 12 and 24 months in patients with clinically quiescent SLE. This finding was reproduced for all applied definitions of flare (any increase in clinical SLEDAI-2K, increase ≥4 in clinical SLEDAI-2K, or any flare with escalation in systemic treatment). Moreover, fewer patients who withdrew from glucocorticosteroids accrued new damage after 24 months of follow-up.

Our findings disagree with those of the CORTICOLUP trial (10). In the French study, all 124 patients had quiescent disease (remission on treatment) for more than 1 year at baseline. Sixty-three patients discontinued prednisone abruptly (with 20 mg/day hydrocortisone for 30 days to avoid adrenal insufficiency), whereas the others continued the 5 mg/day dose. At the end of follow-up (52 weeks), 17/63 (27%) in the withdrawal group and 4/61 (7%) in the maintenance group experienced a flare (relative risk = 0.2; 95% confidence interval = 0.1-0.7; P = 0.003). Flares were defined on the basis of the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA)-SLEDAI Flare Index (SFI) (15). There were no significant differences in damage accrual, whereas most adverse events were recorded in the withdrawal group.

Compared with our cohort, their flare rates at 12 months were slightly less in the maintenance groups (7% versus 13.7%) but significantly more in the withdrawal groups (27% versus 10.8%) based on moderate to severe flares (which resemble the SFI that was used in the French study and the British Isles Lupus Assessment Group [BILAG] A and B flares) (16). At 24 months, the flares were more frequent in the maintenance group (27.5% versus 14.7%; P = 0.024). Regarding any increase in clinical SLEDAI-2K, a definition that captures even very mild flares, the flare rates were significantly less in the withdrawal patients at both 12 and 24 months.

Our withdrawal group did not differ significantly from the French group regarding age, sex, disease duration, mean SLEDAI-2K score, history of lupus nephritis, and serologic activity. On the contrary, the French withdrawal group had less prior CNS involvement (13% versus 27.5%), more frequent use of antimalarials (89% versus 65.7%), and fewer immunosuppressives (25% versus 43.1%). Apart from the differences in the tapering process (gradual withdrawal versus abrupt discontinuation), only the higher rate of immunosuppressive usage could account for the lower flare rates in our cohort. However, given that the use of immunosuppressives was slightly more frequent in our maintenance patients, it seems reasonable that a gradual withdrawal is superior to abrupt discontinuation in such patients.

The French study concluded that maintenance of 5 mg/day of prednisone is superior to withdrawal for preventing flares in clinically quiescent SLE (10). Although we demonstrated opposite results, it is worth noticing that, in both studies, the majority of the withdrawal patients (73% and 82.4%, respectively) did not experience any clinical flare for 12 months after glucocorticoid discontinuation. Moreover, 87% and 89.2%, respectively, did not experience a moderate to severe flare (requiring systemic therapy) for the same time period. As such, the vast majority of the patients remained in clinical remission or in a low disease activity state, which has been shown to confer similar long-term outcomes (regarding both damage accrual and mortality) even after 10 years (17).

Regarding predictors of flare, our Cox regression analysis did not show any of the included variables to be independently associated with increased or decreased risk for subsequent flares. However, certain patient characteristics, such as prolonged clinical and serological inactivity and concomitant treatment with antimalarials and/or immunosuppressives, may be of value in assisting clinical decisions for gradual glucocorticoid withdrawal.

Concerning damage, fewer patients in the withdrawal group acquired new damage compared with those in the maintenance group. As expected, this was particularly evident for the glucocorticoid-related damage. The French study reported only three patients acquiring new damage (all of them in their withdrawal group) (10).

Similar findings were observed for patients who achieved a shorter period of clinical remission (approximately 6 months). Patients who withdrew from prednisone gradually did not experience more flares compared with individuals who maintained 5 mg/day. However, the flare rates were 15% to 20% more in both groups for the same length of follow-up, implying that the duration

of remission is a critical factor for successful glucocorticosteroid tapering. Of note, more than one-third of the patients were able to discontinue glucocorticosteroids in 2 years, and 60% decreased to 2.5 mg/day or less.

The findings of the present study are limited by its observational nature. As such, the decision for maintenance or withdrawal of prednisone was at the discretion of the treating physician and not randomized. Moreover, the rate of glucocorticoid withdrawal was not standardized for all patients. For this reason, we applied PSM for the two patient groups to account for the important covariates potentially impacting the outcomes, such as the nature (previous renal and/or CNS involvement) and the severity (adjusted mean SLEDAI-2K for the first 5 years of observation) of the disease. After matching, the two groups were well balanced regarding the standardized differences for continuous variables and percentages for binary variables at baseline. This strategy reduces the impact of baseline bias (confounding by indication) when estimating causal treatment effects using observational data and highlights the importance of appropriately matching (PSM) patients in observational studies to more closely approximate the patient selection criteria used in randomized clinical trials.

In conclusion, gradual withdrawal of prednisone seems safer than abrupt discontinuation in patients with clinically quiescent SLE and could be attempted because the vast majority of these patients will not develop a moderate to severe flare within 24 months. A randomized controlled trial could confirm whether gradual glucocorticoid tapering is preferable to abrupt withdrawal in such patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Urowitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Tselios, Gladman, Su, Urowitz.
Acquisition of data. Tselios, Gladman, Su, Urowitz.
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APPENDIX : Inverse probability treatment weighting analysis.

We followed the inverse probability treatment weighting (IPTW) approach using the formula "IPTW = $Z/e + (1 - Z)/(1 - e)$", in which Z is the indicator variable of withdrawal or not. We assigned $Z = 1$ for withdrawal patients and $Z = 0$ for nonwithdrawal (maintenance) patients, whereas e is the propensity score from the previous logistic regression model. Withdrawal subjects were assigned a weight equal to the reciprocal of the propensity score, whereas control subjects (nonwithdrawal subjects) were assigned a weight equal to the reciprocal of 1 minus the propensity score. The propensity score and IPTW in the two groups are provided in Appendix Table 1.

As can be seen from the table, less weight was assigned to the maintenance (nonwithdrawal) group and more weight was assigned to the

withdrawal group. All patients (n = 270) were ranked in five even groups (54 patients each) according to the IPTW scores, as seen in the Appendix Table 2.

Patients were compared for the outcomes of flare and damage accrual.

Outcome of flare. As can be seen from Appendix Table 3, withdrawal patients experienced less flares by any applied definition in all IPTW ranks. The only exception was observed for IPTW 1 with regard to the second flare definition. In that case, the extremely low number of patients (n = 5) might have affected the results.

Outcome of damage accrual. As can be seen from Appendix Table 4, withdrawal patients always accrued less damage compared with their maintenance counterparts. The only exceptions were observed in IPTW 1, in which the small number of patients (n = 5) might have affected the results.

Appendix Table 1. Patient distribution in five IPTW quintiles (withdrawal and nonwithdrawal)

	IPTW_rank (Rank for Variable IPTW)					
Withdrawal_pts	0	1	2	3	4	Total
No	49 31.41	29 18.59	25 16.03	27 17.31	26 16.67	156
Yes	5 4.39	25 21.93	29 25.44	27 23.68	28 24.56	114
Total	54	54	54	54	54	270

Abbreviation: IPTW, inverse probability treatment weighting; Withdrawal_pts, patients in whom prednisone was gradually discontinued.

Appendix Table 2. Propensity scores and IPTW comparisons in withdrawal and nonwithdrawal patients (Logistic regression)

Withdrawal_pts	N Obs	Variable	N	N Miss	Minimum	Maximum	Mean	SD
No	156	Propensity Score	156	0	0	0.8	0.3	0.2
		IPTW	156	0	1	5.4	1.7	0.8
Yes	114	Propensity Score	114	0	0.1	1	0.6	0.2
		IPTW	114	0	1	15.8	2.3	1.8

Abbreviation: IPTW, inverse probability treatment weighting; Miss, missing; Obs, observations; Withdrawal_pts, patients in whom prednisone was gradually discontinued.

Appendix Table 3. Flare rates in withdrawal and nonwithdrawal patients stratified by five IPTW ranks

	Flare[a]	Flare[b]	Flare[c]
IPTW 1			
Withdrawal (n = 5)	2 (40)	2 (40)	1 (20)
Nonwithdrawal (n = 49)	21 (42.9)	15 (30.6)	14 (28.6)
IPTW 2			
Withdrawal (n = 25)	8 (32)	6 (24)	5 (20)
Nonwithdrawal (n = 29)	15 (51.7)	10 (34.5)	11 (37.9)
IPTW 3			
Withdrawal (n = 29)	10 (34.5)	5 (17.2)	5 (17.2)
Nonwithdrawal (n = 25)	17 (68)	5 (20)	8 (32)
IPTW 4			
Withdrawal (n = 27)	10 (37)	4 (14.8)	2 (7.4)
Nonwithdrawal (n = 27)	11 (40.7)	9 (33.3)	5 (18.5)
IPTW 5			
Withdrawal (n = 28)	10 (35.7)	3 (10.7)	3 (10.7)
Nonwithdrawal (n = 26)	11 (42.3)	5 (19.2)	5 (19.2)

Abbreviation: IPTW, inverse probability treatment weighting.
Data are given as n (%).
[a]Any increase in clinical SLEDAI-2K (excluding serology).
[b]Any increase in clinical SLEDAI-2K plus treatment escalation (for glucocorticosteroids, antimalarials or immunosuppressives).
[c]Any increase ≥4 in clinical SLEDAI-2K.

Appendix Table 4. Organ damage in withdrawal and nonwithdrawal patients stratified by five IPTW ranks

	SDI Increase	GC-Related	Not GC-Related
IPTW 1			
Withdrawal (n = 5)	1 (20)	0 (0)	1 (20)
Nonwithdrawal (n = 49)	6 (12.2)	1 (2)	5 (10.2)
IPTW 2			
Withdrawal (n = 25)	2 (8)	1 (4)	1 (4)
Nonwithdrawal (n = 29)	5 (17.2)	3 (10.3)	2 (6.9)
IPTW 3			
Withdrawal (n = 29)	2 (6.9)	1 (3.4)	1 (3.4)
Nonwithdrawal (n = 25)	5 (20)	4 (16)	1 (4)
IPTW 4			
Withdrawal (n = 27)	2 (7.4)	1 (3.7)	1 (3.7)
Nonwithdrawal (n = 27)	5 (18.5)	3 (11.1)	2 (7.4)
IPTW 5			
Withdrawal (n = 28)	1 (3.6)	0 (0)	1 (3.6)
Nonwithdrawal (n = 26)	3 (11.5)	1 (3.8)	2 (7.7)

Abbreviation: GC, glucocorticoids; IPTW, inverse probability treatment weighting.
Data are given as n (%).