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J. Little

B. Parker

M. Lunt

J. G. Hanly

M. B. Urowitz

See next page for additional authors

Authors

J. Little, B. Parker, M. Lunt, J. G. Hanly, M. B. Urowitz, A. E. Clarke, J. Romero-Diaz, C. Aranow, M. Mackay, I. N. Bruce, and +32 additional authors

RHEUMATOLOGY

Original article

Glucocorticoid use and factors associated with variability in this use in the Systemic Lupus International Collaborating Clinics Inception Cohort

Jayne Little[1,2], Ben Parker[2], Mark Lunt[1], John G. Hanly[3], Murray B. Urowitz[4], Ann E. Clarke[5], Juanita Romero-Diaz[6], Caroline Gordon[7,8], Sang-Cheol Bae[9], Sasha Bernatsky[10], Daniel J. Wallace[11], Joan T. Merrill[12], Jill Buyon[13], David A. Isenberg[14], Anisur Rahman[14], Ellen M. Ginzler[15], Michelle Petri[16], Mary Anne Dooley[17], Paul Fortin[18], Dafna D. Gladman[4], Kristjan Steinsson[19], Rosalind Ramsey-Goldman[20], Munther A. Khamashta[21], Cynthia Aranow[22], Meggan Mackay[22], Graciela S. Alarcón[23], Susan Manzi[24], Ola Nived[25], Andreas Jönsen[25], Asad A. Zoma[26], Ronald F. van Vollenhoven[27], Manuel Ramos-Casals[28], Guillermo Ruiz-Irastorza[29], Sung Sam Lim[30], Kenneth C. Kalunian[31], Murat Inanc[32], Diane L. Kamen[33], Christine A. Peschken[34], Soren Jacobsen[35], Anca Askanase[36], Jorge Sanchez-Guerrero[37] and Ian N. Bruce[1,2]

Abstract

Objectives. To describe glucocorticoid (GC) use in the SLICC inception cohort and to explore factors associated with GC use. In particular we aimed to assess temporal trends in GC use and to what extent physician-related factors may influence use.

[1]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK, [3]Division of Rheumatology, Department of Medicine and Department of Pathology, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, Nova Scotia, [4]Lupus Program, Centre for Prognosis Studies in The Rheumatic Disease and Krembil Research Institute, Toronto Western Hospital, University of Toronto, Toronto, Ontario, [5]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada, [6]Instituto Nacional de Ciencias Médicas y Nutrición, Immunology and Rheumatology, Mexico City, Mexico, [7]Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, [8]Rheumatology department, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK, [9]Department of Rheumatology, Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, [10]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, Quebec, Canada, [11]Cedars-Sinai Medical Centre, David Geffen School of Medicine at UCLA, Los Angeles, CA, [12]Department of Clinical Pharmacology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [13]Division of Rheumatology, Department of Medicine, New York School of Medicine, NY, USA, [14]Centre for Rheumatology, Department of Medicine, University College London, London, UK, [15]Department of Medicine, SUNY Downstate Medical Center, Brooklyn, NY, [16]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [17]Thurston Arthritis Research Center, University of North Carolina, Chapel Hill, NC, USA, [18]Division of Rheumatology, Centre Hospitalier Universitaire de Québec et Université Laval, Québec City, Canada, [19]Center for Rheumatology Research, Landspitali University hospital, Reykjavik, Iceland, [20]Division of Rheumatology, Feinberg School of Medicine, Northwestern University Chicago, IL, USA, [21]Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, King's College London School of Medicine, London, UK, [22]Feinstein Institute for Medical Research, Manhasset, NY, [23]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [24]Lupus Center of Excellence, Allegheny Health Network, Pittsburgh, PA, USA, [25]Department of Clinical Sciences, Rheumatology, Lund University, Lund, Sweden, [26]Lanarkshire Centre for Rheumatology, Hairmyres Hospital, East Kilbride, UK, [27]Unit for Clinical Therapy Research (ClinTRID), Karolinska Institute, Stockholm, Sweden, [28]Josep Font Autoimmune Diseases Laboratory, IDIBAPS, Department of Autoimmune Diseases, Hospital Clínic, Barcelona, [29]Autoimmune Diseases Research Unit, Department of Internal Medicine, BioCruces Health Research Institute, Hospital Universitario Cruces, University of the Basque Country, Barakaldo, Spain, [30]Division of Rheumatology, Emory University School of Medicine, Atlanta, GA, [31]University of California San Diego School of Medicine, La Jolla, CA, USA, [32]Division of Rheumatology, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey, [33]Department of Medicine, Medical University of South Carolina, Charleston, SC, USA, [34]Department of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada, [35]Department of Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [36]Hospital for Joint Diseases, New York University, Seligman Centre for Advanced Therapeutics, New York, NY, USA and [37]Department of Rheumatology, Mount Sinai Hospital and University Health Network, University of Toronto, Toronto, Ontario, Canada

CLINICAL SCIENCE

Methods. Patients were recruited within 15 months of diagnosis of SLE from 33 centres between 1999 and 2011 and continue to be reviewed annually. Descriptive statistics were used to detail oral and parenteral GC use. Cross sectional and longitudinal analyses were performed to explore factors associated with GC use at enrolment and over time.

Results. We studied 1700 patients with a mean (S.D.) follow-up duration of 7.26 (3.82) years. Over the entire study period, 1365 (81.3%) patients received oral GCs and 447 (26.3%) received parenteral GCs at some point. GC use was strongly associated with treatment centre, age, race/ethnicity, sex, disease duration and disease activity. There was no change in the proportion of patients on GCs or the average doses of GC used over time according to year of diagnosis.

Conclusion. GCs remain a cornerstone in SLE management and there have been no significant changes in their use over the past 10–15 years. While patient and disease factors contribute to the variation in GC use, between-centre differences suggest that physician-related factors also contribute. Evidence-based treatment algorithms are needed to inform a more standardized approach to GC use in SLE.

Key words: systemic lupus erythematosus, glucocorticoids, epidemiology

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Rheumatology key messages

- According to year of diagnosis, over 15 years, GC use has not reduced in the SLICC inception cohort.
- Significant variation in GC use exists between treatment centres, even after adjusting for patient factors.
- New therapies and RCTs exploring GC dosing are needed to optimize GC use in SLE.

Introduction

Glucocorticoids (GCs) have been used in the treatment of SLE for >60 years. Despite their widespread use, there are only a limited number of small scale clinical trials [1–3] and observational studies [4–9] exploring the most effective mode, dose or regimen of administration. This limited evidence, combined with the inherent heterogeneity of the disease, means than guidelines for the use of GCs in SLE are not very specific [10–16]. As such, there are significant differences in opinion on the use of GCs in SLE [17–19]. Most observational studies describing GC use in SLE are limited to single centres, small cohorts or SLE disease subgroups [20–23].

A number of factors are likely to influence GC use. These include patient-related factors (e.g. disease phenotype/severity, comorbidities and personal preference) and patient-independent factors (e.g. health care setting and opinions of the treating physician). Two survey-based studies suggest that prescribing may be more influenced by patient-independent factors, such as geographical location [17, 18].

The aims of this study were to describe GC use in detail in a large international SLE inception cohort and to explore variations in GC practice between treatment centres. Finally we aimed to explore what other patient dependent and independent factors are associated with GC use in SLE and to determine whether there was any temporal trend towards more modest GC use over the study period.

Methods

SLICC inception cohort

The Systemic Lupus International Collaborating Clinics (SLICC) consortium includes 33 centres across North America, Europe and Asia. Patients were recruited to the Inception Cohort between 1999 and 2011. All patients were recruited within 15 months of confirming four ACR Classification Criteria for SLE [24]. Case report forms (including demographic, disease, treatment and co-morbidity details) were completed at enrolment and annually thereafter. Disease activity was quantified using the SLEDAI-2K [25] and the classic BILAG disease activity index [26]. Data were submitted to the co-ordinating centres at the University of Toronto, Toronto, Ontario, Canada and Dalhousie University, Halifax, Nova Scotia, Canada. For this analysis, patients with a minimum of one follow-up assessment (in addition to the enrolment assessment) were included.

Ethics

The study was approved by the institutional research ethics boards of participating centres in accordance with the Declaration of Helsinki's guidelines for research in humans.

Descriptive analyses of GC use

Information on GC use was recorded at enrolment (past and current use) and at each annual assessment visit, including the dose, duration and type of oral (PO) GC courses. From this data it was possible to calculate the average daily and total cumulative PO GC doses as well as the total time/proportion of time spent on PO GCs over each follow-up interval (FUI; defined as the time from one assessment to the next). PO doses were transformed into prednisolone equivalents. The number and dose of parenteral GC pulses were also recorded at baseline and at each follow-up assessment but transformation to prednisolone equivalents was not possible, as specific GC type was not collected for these episodes. Descriptive

statistics were used to report the proportions of patients receiving GCs at enrolment (PO and parenteral), the proportion of FUIs where GC had been given and the average doses received at enrolment and within FUIs. Average dose descriptions exclude patients/FUIs where dose was zero and are reported as median [interquartile range (IQR)].

Cross-sectional analyses of factors associated with GC use at enrolment

Potential factors that might influence the use of GCs were defined *a priori* from our review of the literature: demographic details including age, sex and race/ethnicity (grouped into Caucasian, Asian, Hispanic, African ancestry and other), disease activity (SLEDAI-2K), disease phenotype including presence or absence of active renal disease (active nephritis or any renal manifestation of the SLEDAI-2K). We also included comorbidities including diabetes mellitus, hypertension, BMI, concomitant medications (antimalarial yes/no and/or immunosuppressant yes/no), date of diagnosis and treatment centre. Univariable analyses were performed to explore the association between each of these predictor variables and the following GC outcomes: (1) taking PO GCs at enrolment (yes/no); (2) average daily dose of PO GC at enrolment; (3) received parenteral GCs prior to enrolment (yes/no); and (4) total dose of parenteral GC received prior to enrolment.

Logistic and linear regression models were used for binary outcomes (1 and 3) and continuous outcomes (2 and 4—log transformed data), respectively. For each outcome, predictor variables significant at univariable analysis ($P < 0.20$) were entered into multivariable models using forwards stepwise selection to create the final models ($P < 0.05$). Linear regression results were back transformed and converted to percentage dose changes for ease of interpretation. Tests for interactions between sex and other independent variables were performed, as was quadratic transformation of BMI to explore a possible curvilinear relationship with GC use.

To illustrate differences in GC use between centres, we defined a hypothetical 'typical' patient and used the weightings generated by each model to describe the probable GC use by this 'typical' patient at each treatment centre. The 'typical' patient was defined (according to the median/modal values of the predictor variables in the cohort overall) as a 33-year-old Caucasian female with disease duration of 0.4 years, no active renal disease, hypertension or diabetes, a SLEDAI2K score of 4 and taking an antimalarial but no immunosuppressive treatment.

Longitudinal analysis of factors associated with GC use over time

Random effect modelling was used to explore the relationship between the same predictor variables (age, sex, race/ethnicity, diagnosis date and treatment centre were fixed; all other predictor variables were time-variant) with the following outcome descriptions of GC use over time: (1) PO GCs received during preceding FUI (yes/no); (2) average daily PO GC dose over preceding FUI; (3)

parenteral GCs received during preceding FUI (yes/no); and (4) total dose of parenteral GC received over preceding FUI.

The GC outcomes were calculated over individual FUIs, and therefore a patient with an enrolment and three follow-up assessments would contribute data from three FUIs to the longitudinal analysis.

Outcomes 2 and 4 were again log transformed and final models were generated through the same process of initial univariable testing and forwards selection. Quadratic transformation of BMI was also tested, as were interaction terms. For descriptions of probable GC use in the hypothetical typical patient, the definition was adapted to a 37 year old female with disease duration of 4.7 years and SLEDAI2K score of 2, to reflect the median/modal values of these variables in the cohort over time.

Sensitivity analyses

To further explore the effect of disease activity and phenotype, sensitivity analyses were run on all final models: inclusion of the BILAG total score; replacement of the total SLEDAI-2K score with individual components of the score (selected from arthritis, rash, myositis, serositis, active neurological disease, thrombocytopenia, low complement and increased dsDNA binding through univariable testing ($P < 0.20$) and forwards stepwise selection ($P < 0.05$)). We also examined the influence of body weight on all final models.

Missing data

Less than 5% of the data was missing for all variables apart from height, weight and blood pressure. These were replaced with the average from preceding and subsequent visits or alternatively the preceding or subsequent visit where possible. Complete case analysis was then performed, accepting the minimal remaining missing data.

Results

Patients

Of 1848 patients recruited to the SLICC Inception Cohort, 1700 (92%) had a minimum of one follow-up visit and are included in these analyses. Patient characteristics are summarized in Table 1. These 1700 patients provided data on 10 745 FUIs with a mean (S.D.) total time in the study of 7.26 (3.82) years. The median (IQR) length of these FUIs was 372 (341–427) days.

Descriptive analysis of GC prescription

At enrolment, 1189 (69.98%) patients were taking PO GC at a median (IQR) daily dose of 20.0 (10.0– 30.0) mg; 414 (24.4%) patients were receiving $\geqslant 30$ mg/day. The proportion of patients receiving PO GC decreased in later FUIs. For example, by the fifth follow-up assessment, 610/1076 patients (56.90%) had used PO GC over the preceding FUI, of whom 129 (12.0%) had taken GC for some and 481 (44.7%) for all of the preceding FUI. Similarly the median (IQR) daily GC dose decreased from 10.0 (5.0–15.0) mg at follow-up 1 to 5.5 (4.6–10.0) mg at

TABLE 1 Demographic and baseline disease characteristics of study population

Characteristic (n = 1700 unless stated otherwise)	n (%)/* median (IQR)
Age (n = 1699), years	33.0 (24.5–43.7)*
Gender	
Female	1506 (88.6)
Male	194 (11.4)
Enrolment location	
Canada	397 (23.4)
USA	463 (27.2)
Mexico	210 (12.4)
Europe	470 (27.7)
Asia	160 (9.4)
Race/ethnicity	
Caucasian	843 (49.6)
Hispanic	262 (15.4)
Asian	254 (14.9)
African origin	278 (16.4)
Other	63 (3.7)
Disease activity/phenotype	
SLEDAI-2K (n = 1693)	4 (2–8)*
SLICC/ACR-Damage Index ⩾1	391 (23.0)
Active renal disease[a]	436 (25.7)
Anti-dsDNA positive (n = 1541)	613 (39.8)
Low complement (n = 1548)[b]	582 (37.6)
Medication use	
Oral GC use prior to enrolment (n = 1699)	1189 (70.0)
Average GC dose[c] (n = 1179), mg/day	20.0 (10.0–30.0)*
Highest GC dose[c] (n = 1183), mg/day	40.0 (20.0–60.0)*
Immunosuppressant use	684 (40.2)
Antimalarial use	1152 (67.8)
Co-morbidities	
Hypertension (n = 1683)	758 (45.0)
Diabetes mellitus (n = 1682)	61 (3.6)
Current smoker (n = 1698)	252 (14.8)
Post-menopausal (n = 1506)[d]	213 (14.1)
BMI, mean (S.D.) (n = 1672), kg/m²	25.7 (5.9)

*Values are in median (IQR). [a]Active nephritis or any renal item on SLEDAI-2K (haematuria, proteinuria, pyuria or casts). [b]Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory. [c]Average/highest GC doses of zero excluded from calculation. [d]Percentage of women. IQR, interquartile range.

follow-up 5 [mean (S.D.) duration in study at follow-up 1 and 5 = 384 (57) and 1860 (155) days, respectively].

Of the 10732 (99.9%) FUIs in which the proportion of time on GCs could be calculated, all of the time had been spent on PO GC in 4946 (46.1%) and none of this time had been spent on PO GC in 4265 (39.7%); in 1521 (14.2%) FUIs a proportion of the period had been spent on PO GCs. Therefore, 558 (32.8%) patients spent their entire study period on PO GCs, 807 (47.5%) spent part of the entire study period on PO GC and 335 (19.7%) never received PO GC therapy (differences in demographic and disease characteristics of these three groups can be seen in supplementary Table S1, available at *Rheumatology* online).

Regarding parenteral GC, at enrolment 235 (13.8%) patients had received at least one dose at a median (IQR) total dose of 1.5 (0.7–3.0) g. Parenteral GCs were given between subsequent visits in 458 (4.26%) FUIs at a median (IQR) total dose of 0.5 (0.12–2.0) g. Patients who had parenteral GCs also received a median (IQR) total PO GC dose of 3.4 (0.5–6.2) g in the same FUI. Overall more PO GC was received during those FUIs where higher doses of parenteral GC were also received (Table 2). This was also true in the group who had <250 mg of parenteral GC, which was likely to have been intra-muscular and/or intra-articular GCs.

Factors associated with GC use at enrolment and over time

Treatment centre

There was a significant association between treatment centre and all four measures of GC use at enrolment and over time in both univariable (Tables 3 and 4) and multivariable analyses ($P < 0.0001$) (Table 5). There were a number of centres where GC use differed significantly from the overall cohort, as can be seen in the variability of average daily PO GC dose between the centres (Table 6). At enrolment the mean (95% CI) average daily PO GC dose in the cohort overall was 13.03 (13.01–13.06) mg. The mean dose within individual centres was significantly different in 25 of the 33 centres with mean average doses ranging from 4.54 (4.26–4.83) to 19.84 (17.5–22.5) mg. Similar variability was seen in the longitudinal analysis of PO GC dose and also in all three other GC outcome measures at enrolment and over time (supplementary Tables S2 and S3, available at *Rheumatology* online).

Age, sex and race/ethnicity

We found strong inverse associations between age and PO GC use in both univariable (Tables 3 and 4) and multivariable (Table 5) analyses. Older age was associated with reduced odds of receiving PO GCs and lower PO GC dose. For example, in longitudinal analyses the odds of receiving PO GCs reduced with each additional year of age (OR = 0.98, 95% CI: 0.96, 0.99) and there was a small reduction in dose used (% change = 0.66, 95% CI: 0.31, 1.01). There was also a greater odds of men receiving PO GC (OR = 3.90, 95% CI: 2.19, 6.94) and men also took higher doses (% change = 16.85, 95% CI: 2.79, 32.83) in longitudinal analysis. When we added body weight to the final longitudinal models, the dose difference between men and women was no longer significant (% change = 13.32, 95% CI: −0.64, 29.24) but men were still more likely to be taking PO GC steroids (OR = 4.02, 95% CI: 2.24, 7.22). Hispanics, Asians and patients of African origin all had greater odds of receiving PO GCs than Caucasians both at enrolment and over time. Race/ethnicity was also associated with PO GC dose over time, for example, Hispanics had higher odds of using PO GCs (OR = 2.46, 95% CI: 0.87, 6.95) and at higher average doses than Caucasians (% change = 36.07, 95% CI:

TABLE 2 Oral glucocorticoid exposure over follow-up intervals, grouped by total parenteral glucocorticoid dose received over follow-up interval

Total dose of parenteral GC, mg[a]	n (%) of FUI where PO GCs have been used	Median point estimates[b]			
		Total PO GC dose, mg	Average daily PO GC dose, mg	Maximum daily PO GC dose, mg	Total time on PO GC, days
>1000 (n = 182)	172 (94.5)	5503	15.0	30	371
250–1000 (n = 90)	80 (88.9)	4663	10.0	30	365
<250 (n = 175)	109 (62.3)	2688	7.5	10	336
0 (n = 10287)	6097 (59.3)	2450	6.0	10	364
P-value for between group comparisons	<0.001*	<0.001**	<0.001**	<0.001**	0.015**

[a]Information on total parenteral GC dose available for 10 734 follow-up intervals. [b]Median values calculated from those FUIs where PO GCs have been used; that is, dose or duration equal to zero not included in the calculation. *Chi-square. **Kruskal–Wallis. FUI: follow-up interval; GC: glucocorticoid; PO: oral.

1.65, 82.15). There were no significant associations between age, sex or race and parenteral GC use (frequency or dose) either at enrolment or over time, nor did we find any significant interactions between sex and other independent variables.

Other factors

Longer disease duration was associated with lower GC use by most of the measures used to assess PO and parenteral use (Table 5). Overall disease activity (SLEDAI-2K score) was positively associated with the frequency and dose of PO GC and the frequency (but not dose) of parenteral GC in cross-sectional and longitudinal analyses. Active renal disease was also associated with PO GC use (frequency and dose) at enrolment (not over time) but had no associations with parenteral GC use. We also found a number of positive associations between hypertension and diabetes mellitus and GC use but no associations with BMI. Antimalarial use had a negative association with a number of GC measures whereas immunosuppressant use showed positive associations with all four measures at enrolment and over time. For example the OR (95% CI) for receiving parenteral GC at enrolment if on an antimalarial was 0.63 (0.46, 0.86) and if on an immunosuppressant was 2.06 (1.52, 2.80). Sensitivity analyses incorporating BILAG score (supplementary Table S3, available at *Rheumatology* online) or significant SLEDAI 2K components (results available) supported our primary models.

Diagnosis date

When we examined GC use according to year of diagnosis, there were no significant associations between date of diagnosis and any of the four GC outcomes in either cross-sectional or longitudinal analysis (Tables 3 and 4).

Discussion

There is growing evidence that lower doses of GCs may be as effective for the treatment of SLE while incurring fewer adverse events [6–9]. As such, a number of review and guidance articles have advocated more judicious use of GC [27–31]. We have observed that PO GCs were used frequently in this international SLE cohort with 32.8% of patients spending their entire observation period on GC therapy. Also, high doses [32] were commonly used with 24.4% of patients receiving ⩾30 mg/day at enrolment. Of note, we found no association between date of diagnosis and any of the GC outcomes suggesting that the aspiration for more judicious use has not yet translated into changes in routine clinical practice over the past 10–15 years. It should, however, be noted that in this time period very few new therapies or therapeutic paradigms have gained widespread use, but recent results from a phase III trial of belimumab suggest this may have some GC-sparing effects [33].

Previous survey-based studies have found geographical variation in GC use [18] and have found associations between GC prescribing and physician-related factors such as specialty and years of experience [17]. We found significant associations between all four GC measures and treatment centre at enrolment and over time. A number of factors are likely to contribute to this between-centre variability, for example, the local health-care system (e.g. universal coverage *vs* insurance-based systems), socioeconomic status, availability of GC-sparing agents and cultural acceptance of GC use. Data on these factors were not collected and therefore they were absent from our models, but even within countries or regions (e.g. Canada and Europe), where confounding from such factors should be less marked, there was still significant variation in GC use. This real-world variation between centres requires further exploration but lends support to the hypothesis that GC use is still driven by patient-independent factors to a significant degree. Such patient-independent heterogeneity in GC use will contribute to 'noise' in multicentre clinical trials and will increase the likelihood of type 2 errors occurring. Our observations suggest that in such multicentre trials some

TABLE 3 Univariate analysis of factors associated with oral glucocorticoid use within the SLICC inception cohort

	At enrolment		Over time	
Received PO GCs (yes/no)	**OR (95% CI)**	***n***	**OR (95% CI)**	***N***
Age, years	0.97 (0.96, 0.98)	1698	0.87 (0.85, 0.88)	11 428
Sex, male	1.94 (1.34, 2.83)	1699	5.09 (2.72, 9.51)	11 437
Ethinicity/race[a]				
Hispanic	5.79 (3.90, 8.58)	1699	13.25 (7.63, 23.01)	11 437
Asian	7.71 (4.96, 12.00)		41.38 (23.39, 73.21)	
African origin	2.97 (2.16, 4.01)		12.98 (7.49, 22.51)	
Other	1.86 (1.07, 3.25)		2.94 (1.06, 8.17)	
Diagnosis date	1.00 (1.00, 1.00)	1699	1.00 (1.00, 1.00)	11 437
Disease duration (years)	0.73 (0.54, 0.98)	1699	0.80 (0.78, 0.81)	11 437
Hypertension[b]	1.65 (1.33, 2.04)	1683	1.94 (1.62, 2.32)	11 431
Diabetes[c]	0.88 (0.51, 1.51)	1682	0.79 (0.54, 1.14)	11 437
BMI	0.97 (0.95, 0.99)	1671	0.98 (0.96, 1.00)	11 371
BMI^2	1.00 (1.00, 1.00)	1671	1.00 (1.00, 1.00)	11 371
On antimalarial (yes/no)	0.65 (0.52, 0.82)	1699	1.11 (0.91, 1.36)	11 437
On immunosuppressant (yes/no)	8.50 (6.33, 11.41)	1679	8.65 (7.08, 10.58)	11 437
SLEDAI-2K score	1.12 (1.09, 1.15)	1693	1.12 (1.09, 1.14)	11 312
Active renal disease (yes/no)	6.25 (4.40, 8.88)	1699	2.77 (2.15, 3.56)	11 437
Overall treatment centre effect	*P* < 0.0001[d]	1699	*P* < 0.0001[d]	1699
Average daily dose of PO GC (mg)	**% change (95% CI)**	***n***	**% change (95% CI)**	***N***
Age, years	−0.89 (−1.21, −0.56)	1178	−2.13 (−2.46, −1.81)	6441
Sex (male)	8.20 (−4.80, 22.96)	1179	15.43 (0.46, 32.64)	6450
Ethnicity/race[a]				
Hispanic	47.08 (30.61, 65.62)		41.40 (24.45, 60.65)	
Asian	13.19 (0.54, 27.44)	1179	23.00 (8.35, 39.62)	6450
African origin	18.59 (5.03, 33.91)		42.18 (24.90, 61.84)	
Other	14.27 (−9.60, 44.43)		12.40 (−12.66, 44.66)	
Diagnosis date	−0.003 (−0.006, 0.001)	1179	0.00 (−0.00, 0.01)	6450
Disease duration (years)	−44.12 (−50.53, −36.87)	1179	−7.29 (−7.98, −6.59)	6450
Hypertension[b]	32.82 (21.92, 44.70)	1172	20.16 (12.93, 27.85)	6449
Diabetes[c]	−10.41 (−29.29, 13.50)	1166	11.54 (1.77, 22.24)	6450
BMI	0.07 (−0.70, 0.85)	1161	0.26 (−0.39, 0.92)	6414
BMI^2	0.00 (−0.01, 0.01)	1161	0.00 (−0.01, 0.01)	6414
On antimalarial (yes/no)	−34.26 (−39.82, −28.19)	1177	−18.70 (−24.30, −12.68)	6450
On immunosuppressant (yes/no)	44.61 (32.89, 57.37)	1177	44.43 (35.44, 54.01)	6450
SLEDAI-2K score	3.85 (3.10, 4.60)	1175	3.40 (2.71, 4.10)	6388
Active renal disease (yes/no)	76.36 (61.81, 92.22)	1179	29.00 (19.56, 39.18)	6450
Overall treatment centre effect	*P* < 0.0001[d]	1699	*P* < 0.0001[d]	1699

[a]Cf. Caucasian. [b]Defined as systolic blood pressure ⩾130 mmHg or diastolic blood pressure ⩾90 mmHg or taking anti-hypertensive medication. [c]Defined as any past or current history of diabetes. [d]Overall variation between treatment centres shown here as *P*-values for chi-square test. Further detail of between centre differences (in multivariable analyses) shown in Table 6. *n*: number of patients; *N*: number of follow up intervals; PO: oral; GC: glucocorticoid.

period of standardization of GC use may be necessary to address such variation prior to randomization. In addition, international consensus guidelines for GC use in different clinical situations, for example, LN and arthritis, may go some way towards reducing the observed variability.

There was significant race/ethnic variation in PO GC use, with higher use amongst non-Caucasians. Race/ethnicity may reflect socioeconomic status at the individual or population level and PO GC may be a favoured treatment option for uninsured individuals or in poorer countries due to its relatively low cost. There was also significantly higher frequency and dosing of GCs in male

patients. Gender differences in the SLE phenotype are well recognized [34], for example, lower incidence of musculoskeletal features, RP, alopecia and photosensitivity but more nephritis, serositis and discoid lupus in men. However, whether men experience higher disease activity, damage accrual or mortality is more contentious with inconsistent findings across several studies [35–42]. In the SLICC cohort we found no difference in disease activity between men and women (data on file) although more men had active renal disease at enrolment: OR (95% CI) [age/race adjusted logistic regression] = 1.80 (1.49, 2.90). Our analyses adjusted for such confounding, but despite

TABLE 4 Univariate analysis of factors associated with parenteral glucocorticoid use within the SLICC inception cohort

	At enrolment		Over time	
Received parenteral GCs (yes/no)	OR (95% CI)	*n*	OR (95% CI)	*N*
Age, years	0.99 (0.98, 1.00)	1699	0.98 (0.97, 0.99)	11 468
Sex (male)	1.31 (0.90, 1.90)	1700	1.03 (0.66, 1.59)	11 477
Ethnicity/race[a]				
Hispanic	0.85 (0.55, 1.26)		0.54 (0.35, 0.83)	
Asian	1.68 (1.18, 2.38)	1700	0.85 (0.57, 1.28)	11 477
African origin	1.53 (1.08, 2.16)		1.74 (1.21, 2.49)	
Other	1.09 (0.54, 2.21)		1.72 (0.88, 3.36)	
Diagnosis date	1.00 (1.00, 1.00)	1700	1.00 (1.00, 1.00)	11 477
Disease duration, years	0.88 (0.61, 1.27)	1700	0.87 (0.85, 0.90)	11 477
Hypertension[b]	1.89 (1.46, 2.45)	1683	1.50 (1.19, 1.88)	11 471
Diabetes[c]	1.50 (0.82, 2.77)	1682	2.00 (1.51, 2.63)	11 477
BMI	1.00 (0.98, 1.02)	1672	1.00 (0.98, 1.02)	11 410
BMI^2	1.00 (1.00, 1.00)	1672	1.00 (1.00, 1.00)	11 410
On antimalarial (yes/no)	0.56 (0.43, 0.72)	1697	0.78 (0.61, 1.00)	11 477
On immunosuppressant (yes/no)	2.61 (2.01, 3.40)	1697	2.48(1.96, 3.14)	11 477
SLEDAI-2K score	1.06 (1.03, 1.08)	1693	1.08 (1.06, 1.11)	11 347
Active renal disease (yes/no)	1.84 (1.40, 2.41)	1700	1.32 (1.00, 1.75)	11 477
Overall treatment centre effect	*P* < 0.0001[d]	1699	*P* < 0.0001[d]	1699
Total dose of GC, mg	% change (95% CI)	*n*	% change (95% CI)	*N*
Age, years	−1.45 (−2.79, −0.09)	235	−2.74 (−3.87, −1.59)	549
Sex (male)	64.13 (−1.30, 172.92)	235	40.21 (−12.74, 125.28)	550
Ethnicity/race[a]				
Hispanic	217.33 (77.91, 466.03)		185.31 (75.40, 364.10)	
Asian	25.29 (−23.11, 104.13)		36.32 (−12.18, 111.61)	550
African origin	51.70 (−5.92, 144.60)	235	42.30 (−2.67, 108.06)	
Other	4.30 (−62.03, 186.46)		138.40 (21.23, 368.83)	
Diagnosis date	−0.01 (−0.02, 0.01)	235	−0.01 (−0.02, 0.01)	550
Disease duration, years	6.20 (−38.28, 82.71)	235	−10.80 (−14.02, −7.47)	550
Hypertension[b]	68.70 (15.72, 145.97)	233	38.02 (5.40, 80.72)	549
Diabetes[c]	−18.03 (−64.55, 89.54)	235	30.01 (4.61, 61.58)	396
BMI	−1.74 (−4.49, 1.09)	233	−0.90 (−3.06, 1.32)	548
BMI^2	−0.02 (−0.07, 0.02)	233	−0.01 (−0.04, 0.03)	548
On antimalarial (yes/no)	−45.73 (−62.19, −22.10)	235	−42.13 (−56.37, −23.23)	550
On immunosuppressant (yes/no)	194.01 (104.83, 322.02)	235	276.02 (192.45, 383.48)	550
SLEDAI-2K score	2.03 (−0.65, 4.79)	235	3.72 (0.98, 6.53)	545
Active renal disease (yes/no)	103.63 (40.98, 194.12)	235	124.68 (66.55, 203.10)	550
Overall treatment centre effect	*P* < 0.0001[d]	1699	*P* < 0.0001[d]	1699

[a]Cf. Caucasians. [b]Defined as systolic blood pressure ⩾130 mmHg or diastolic blood pressure ⩾90 mmHg or taking anti-hypertensive medication. [c]Defined as any past or current history of diabetes. [d]Overall variation between treatment centres shown here as *P*-values for chi-square test. Further detail of between centre differences (in multivariable analyses) shown in Table 6. *n*: number of patients; *N*: number of follow up intervals; GC: glucocorticoid.

this, a gender difference in GC use persisted. This may therefore reflect differences due to patient choices or physicians' therapeutic strategies in men and women. For example, men may be less concerned about weight gain and physicians may have more concerns about osteoporosis in women. Similarly physicians may hold a perception that males with SLE require more aggressive treatment or men may choose to stay on GCs if they are working in manual occupations.

Our study has some strengths and limitations that are worth consideration. As far as we are aware, this is the first time that the use of GCs and factors associated with their use have been described in a large international SLE cohort. The large cohort size and long follow-up from early in the disease course allowed us to adjust for a range of potential confounders and also explore variations related to between- and within-centre differences in a real world setting for several different measures of GC use. We were limited in not being able to include factors related to socioeconomic status, as these data were not routinely collected. As such we recognize that unmeasured confounding may account for some of the inter-centre

TABLE 5 Significant factors associated with glucocorticoid use in the SLICC Inception Cohort in final multivariable models

	At enrolment	Over time
Oral		
On GCs (yes/no)	OR (95% CI)	OR (95% CI)
Age, years	0.99 (0.98, 1.00)	0.98 (0.96, 0.99)
Sex (male)	2.35 (1.47, 3.74)	3.90 (2.19, 6.94)
Ethnicity/race[a]		
Hispanic	2.16 (1.05, 4.45)	2.46 (0.87, 6.95)*
Asian	3.28 (1.77, 6.09)	3.73 (1.74, 7.98)
African origin	2.42 (1.62, 3.61)	4.65 (2.68, 8.08)
Other	1.56 (0.81, 3.02)	2.20 (0.89, 5.42)*
Disease duration, years	0.48 (0.32, 0.72)	0.81 (0.79, 0.83)
Hypertension[b]	—	1.89 (1.56, 2.30)
On immunosuppressant (yes/no)	7.07 (5.04, 9.92)	8.72 (7.03, 10.83)
SLEDAI-2K	1.08 (1.04, 1.12)	1.09 (1.06, 1.12)
Active renal disease (yes/no)	1.85 (1.16, 2.94)	—
Overall treatment centre effect	$P < 0.0001$[d]	$P < 0.0001$[d]
Daily GC dose, mg	% difference (95% CI)	% difference (95% CI)
Age, years	−0.72 (−1.02, −0.42)	−0.66 (−1.01, −0.31)
Sex (male)	—	16.85 (2.79, 32.83)
Ethnicity/race[a]		
Hispanic	—	36.07 (1.65, 82.15)
Asian	—	−3.63 (−20.51, 16.82)*
African origin	—	15.80 (1.06, 32.68)
Other	—	1.59 (−19.74, 28.59)*
Disease duration, years	−42.95 (−49.02, −36.16)	−6.63 (−7.39, −5.87)
Hypertension[b]	18.76 (9.55, 28.73)	20.90 (13.77, 28.46)
Diabetes[c]	—	10.02 (1.01, 19.82)
On antimalarial (yes/no)	−21.47 (−27.72, −14.67)	−13.28 (−19.08, −7.07)
On immunosuppressant (yes/no)	28.05 (18.42, 38.46)	36.00 (27.75, 44.79)
SLEDAI-2K	0.84 (0.04, 1.65)	2.25 (1.58, 2.93)
Active renal disease (yes/no)	22.42 (10.83, 35.23)	—
Overall treatment centre effect	$P < 0.0001$[d]	$P < 0.0001$[d]
Parenteral		
Received GC (yes/no)	OR (95% CI)	OR (95% CI)
Disease duration (years)	—	0.88 (0.86, 0.91)
Hypertension[b]	1.53 (1.13, 2.07)	1.41 (1.13, 1.76)
Diabetes[c]	—	1.45 (1.13, 1.86)
On antimalarial (yes/no)	0.63 (0.46, 0.86)	—
On immunosuppressant (yes/no)	2.06 (1.52, 2.80)	12.18 (1.73, 2.76)
SLEDAI-2K	1.06 (1.04, 1.09)	1.09 (1.07, 1.12)
Overall treatment centre effect	$P < 0.0001$[d]	$P < 0.0001$[d]
Total dose, mg	% difference (95% CI)	% difference (95% CI)
Disease duration (years)	—	−9.35 (−12.27, −6.34)
On antimalarial (yes/no)	−36.26 (−55,96, −7.76)	—
On immunosuppressant (yes/no)	94.61 (33.81, 183.06)	158.98 (102.39, 231.39)
Overall treatment centre effect	$P < 0.0001$[d]	$P < 0.0001$

[a]Cf. Caucasians. [b]Defined as systolic blood pressure $\geqslant 130$ mmHg or diastolic blood pressure $\geqslant 90$ mmHg or taking anti-hypertensive medication. [c]Defined as any past or current history of diabetes. [d]Overall variation between treatment centres shown here as *P*-values for chi-square test. Further detail of between centre differences shown in Table 6. *Non-significant. GC: glucocorticoid.

variation observed. No data were collected on the specific formulation of parenteral GCs and we were therefore unable to calculate a standardized dose. Although we recognize that some parenteral doses will not have bioequivalence, it is likely that a significant majority of the parenteral GCs used will be methylprednisolone or triamcinolone, which are bioequivalent, minimizing the impact of this limitation. Another major strength is the low level of missing data in the cohort although we also recognize that the annual data collection may introduce some recall bias on the part of the patient and physician when completing details of steroid courses.

We have therefore found significant between-centre variation across a range of different measures of GC use

TABLE 6 Average mean daily oral GC dose of hypothetical typical patient at each treatment centre at enrolment and over time

Treatment centre	Mean average daily PO GC dose at enrolment, mg (95% CI)	Mean average daily PO GC dose between assessments, mg (95% CI)
Cohort overall	13.03 (13.01, 13.06)	3.64 (3.63, 3.66)
USA		
1	13.10 (12.81,13.39)	3.59 (3.45, 3.74)
2	14.60 (11.42, 18.68)	**6.18 (3.73, 10.24)**
3	**17.72 (17.38, 18.68)**	**4.49 (4.34, 4.65)**
4	**10.05 (9.71, 10.40)**	**2.54 (2.39, 2.69)**
5	NA[a]	6.81 (0.71, 65.67)
6	13.30 (12.65, 13.99)	**2.62 (2.46, 2.79)**
7	**11.75 (11.42, 12.08)**	**2.88 (2.78, 2.98)**
8	**17.76 (17.06, 18.49)**	**4.06 (3.84, 4.29)**
9	**13.44 (13.21, 13.67)**	3.61 (3.50, 3.73)
10	**7.22 (7.00, 7.46)**	**2.06 (1.96, 2.16)**
11	**13.78 (13.24, 14.33)**	**3.05 (2.87, 3.24)**
12	**19.52 (18.57, 20.51)**	**5.27 (4.77, 5.82)**
13	14.98 (12.92, 17.38)	2.52 (1.71, 3.72)
Europe		
14	13.34 (12.68, 14.04)	**4.16 (3.67, 4.73)**
15	**17.65 (15.86, 19.64)**	**4.87 (4.06, 5.83)**
16	**8.02 (7.75, 8.30)**	3.42 (3.22, 3.63)
17	**7.91 (7.80, 8.03)**	**3.99 (3.92, 4.07)**
18	**9.31 (8.95, 9.68)**	**3.33 (3.18, 3.49)**
19	**10.59 (10.15, 11.06)**	**3.03 (2.88, 3.19)**
20	**12.12 (11.33, 12.95)**	3.51 (3.18, 3.88)
21	**19.84 (17.50, 22.50)**	**1.66 (1.10, 2.51)**
22	**11.89 (11.17, 12.65)**	**4.15 (3.82, 4.50)**
23	**10.40 (10.11, 10.70)**	**3.14 (3.03, 3.25)**
24	15.50 (10.77, 22.31)	3.69 (2.40, 5.67)
25	**4.54 (4.26, 4.83)**	**1.80 (1.61, 2.01)**
26	**5.21 (3.61, 7.52)**	**4.47 (3.88, 5.15)**
27	**11.77 (11.66, 11.88)**	**4.36 (4.31, 4.42)**
Canada		
28	**16.00 (15.84, 16.17)**	**2.54 (2.50, 2.59)**
29	**18.46 (18.32, 18.61)**	**4.59 (4.53, 4.65)**
30	**16.27 (15.99, 16.56)**	**1.90 (1.85, 1.95)**
31	12.21 (8.46, 17.64)	3.73 (1.76, 7.93)
Other		
32	**14.59 (14.50, 14.68)**	**3.59 (3.55, 3.62)**
33	**11.53 (11.46, 11.60)**	**3.88 (3.83, 3.92)**

For the cross sectional analysis of PO GC dose at enrolment, a typical patient is defined as a 33-year-old Caucasian female with disease duration of 0.4 years, no active renal disease, hypertension or diabetes, SELDAI2K score of 4 and taking an antimalarial but no immunosuppressive treatment. For the longitudinal analysis of PO GC dose over time, a typical patient is defined as a 37-year-old Caucasian female with disease duration of 4.7 years, no active renal disease, hypertension or diabetes, a SELDAI2K score of 2 and taking an antimalarial but no immunosuppressive treatment. Results in bold show where GC use at a centre differs significantly from the cohort overall (i.e. the confidence intervals do not overlap). [a]No data (only one patient receiving PO GC in this centre, for whom no dose data available). GC: glucocorticoid.

in SLE patients. Several patient-related factors such as age, gender, race/ethnicity, disease activity and renal involvement explain part of this variation; however, our models suggest that physician-dependent factors still have a major influence in determining GC use. We also found no major change in GC use over the past 15 years and so current standard of care remains dependent on GC use. New therapies will be needed to provide better, GC sparing/avoiding approaches to SLE management. Taken together, the challenge now will be to develop better evidence-based treatment algorithms to optimize GC use, reduce variation and minimize GC harm in SLE. Such an approach will also likely contribute to a more consistent 'standard of care' and thus improve the likelihood of success in future clinical trials.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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