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Abstract

Objectives

To describe glucocorticoid (GC) use in the Systemic Lupus International Collaborating Clinics (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.

Methods

Patients were recruited within 15 months of diagnosis of SLE from 33 centres between 1999 – 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 (SD) 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.

Conclusions

GCs remain a cornerstone in SLE management and there have been no significant changes in their use over the last 10-15 years. Whilst 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 standardised approach GC use in SLE.

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Key Words:

- Systemic Lupus Erythematosus
- Glucocorticoids
- Epidemiology

INTRODUCTION:

Glucocorticoids (GCs) have been used in the treatment of systemic lupus erythematosus (SLE) for more than 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 GCs use over the study period.

PATIENTS AND METHODS

SLICC inception cohort

The 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 4 American College of Rheumatology (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 SLE Disease Activity Index 2000 (SLEDAI-2K)[25] and the 'classic' British Isles Lupus Assessment Group's (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 was 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 (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 & 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, body mass index (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 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)
4) Total dose of parenteral GC received prior to enrolment

Logistic and linear regression models were used for binary outcomes (1 & 3) and continuous outcomes (2 & 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)
4) Total dose of parenteral GC received over preceding FUI

The GC outcomes were calculated over individual FUIs, therefore a patient with an enrolment and 3 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: 1) Inclusion of the BILAG total score 2) 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 and 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.

RESULT

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 summarised in table 1. These 1700 patients provided data on 10745 FUIs with a mean (SD) 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 prescribing

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 ≥30mg/day. The proportion of patients receiving PO GC decreased in later FUIs. For example, by the 5th 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 follow-up 5 (mean (sd) 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 3 groups can be seen in supplementary table 1).

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 <250mg of parenteral GC which are 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 & 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 3 other GC outcome measures at enrolment and over time (supplementary table 2).

Age, sex and race/ethnicity

We found strong inverse associations between age and PO GC use in both univariable (Tables 3 & 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: 95% CI = 0.98: 0.96, 0.99) and there was a small reduction in dose used (0.66 [0.31, 1.01] %). There was also a greater odds of men receiving PO GC (OR: 95%CI = 3.90: 2.19, 6.94) and men also took higher doses (16.85 [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 (13.32 (-0.64, 29.24) %) but men were still more likely to be taking PO GC steroids (OR: 95%CI = 4.02: 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: 95%CI = 2.46 (0.87, 6.95) and at higher average doses than Caucasians

(36.07 [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 2.06 (1.52, 2.80) if on an immunosuppressant. Sensitivity analyses incorporating BILAG score (supplementary table 3) 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 & 4).

DISCUSSION

There is growing evidence that lower doses of GCs may be as effective for the treatment of SLE whilst 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 ≥30mg/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, however 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 was not collected therefore they were absent from our models, however 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 period of standardisation of GC use may be necessary to address such variation prior to randomisation. The development of international guidelines for GC use in different clinical situations, for example lupus nephritis 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 amongst male patients. Gender differences in the SLE phenotype are well recognised [34] e.g. lower incidence of musculoskeletal features, Raynaud's phenomenon, 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 however despite 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 which 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 has 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 this

data was not routinely collected. As such we recognise that unmeasured confounding may account for some of the inter-centre variation observed. No data was collected on the 'type' of parenteral GC and we were therefore unable to calculate a standardised dose. Although we recognise that some parenteral doses will not have bioequivalence, it is likely that a significant majority of the parenteral GC used will be methylprednisolone or triamcinolone, which are bioequivalent, minimising the impact of this limitation. Another major strength is the low level of missing data in the cohort although we also recognise 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 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.

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Key Messages:

1) Over 15 years GC use has not reduced in the SLICC inception cohort.

2) Significant variation in GC use exists between treatment centres, even after adjusting for patient factors.
3) New therapies and RCTs exploring GC dosing are needed to optimise GC use in SLE

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n = 1700 unless stated otherwise	n (%) / * median (IQR)
Age (years) (n=1699)	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 Ψ	436 (25.7)
Anti-dsDNA positive (n=1541)	613 (39.8)
Low complement (n=1548) †	582 (37.6)
Medication use	
Oral GC use prior to enrolment (n=1699)	1189 (70.0)
Average GC dose (mg/day) (n=1179) ‡	20.0 (10.0-30.0) *
Highest GC dose (mg/day) (n=1183) ‡	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) §	213 (14.1)
Body mass index (kg/m2) (n=1672)	25.7 (5.9) ¢

Table 1: Demographic and baseline disease characteristics of study population

SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC, Systemic Lupus Erythematosus International Collaborating Clinics; ACR, American College of Rheumatology; GC, glucocorticoid.

* Median (IQR)

Ψ Active nephritis or any renal item on SLDEAI-2K (haematuria, proteinuria, pyuria or casts)

† Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory

‡ Average/maximum GC doses of zero excluded from calculation

§ Percentage of women

¢ Mean (SD)

Total dose of parenteral GC (mg) *	Number (%) of FUI where PO GC have been used	Median Point Estimates ¢			
		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 ‡

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

GC, glucocorticoid; FUI, follow up interval; PO, oral

* Information on total parenteral GC dose available for 10,734 follow-up intervals

¢ Median values calculated from those FUIs where PO GC have been used; i.e. dose or duration equal to zero not included in the calculation.

† Chi 2 ‡ Kruskal-Wallis

		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)	11428
Sex (male)		1.94 (1.34-2.83)	1699	5.09 (2.72, 9.51)	11437
Ethnicity/ Race §	Hispanic	5.79 (3.90, 8.58)		13.25 (7.63, 23.01)	
	Asian	7.71 (4.96, 12.00)		41.38 (23.39, 73.21)	
	African origin	2.97 (2.16, 4.01)	1699	12.98 (7.49, 22.51)	11437
	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)	11437
Disease duration (years)		0.73 (0.54, 0.98)	1699	0.80 (0.78, 0.81)	11437
Hypertension †		1.65 (1.33-2.04)	1683	1.94 (1.62, 2.32)	11431
Diabetes ‡		0.88 (0.51-1.51)	1682	0.79 (0.54, 1.14)	11437
BMI		0.97 (0.95-0.99)	1671	0.98 (0.96, 1.00)	11371
BMI^2		1.00 (1.00-1.00)	1671	1.00 (1.00, 1.00)	11371
On antimalarial (yes/no)		0.65 (0.52-0.82)	1699	1.11 (0.91, 1.36)	11437
On immunosuppressant (yes/no)		8.50 (6.33-11.41)	1679	8.65 (7.08, 10.58)	11437
SLEDAI-2K score		1.12 (1.09-1.15)	1693	1.12 (1.09, 1.14)	11312
Active renal disease (yes/no)		6.25 (4.40-8.88)	1699	2.77 (2.15, 3.56)	11437
Overall treatment centre effect		p< 0.0001 ¢	1699	p< 0.0001 ¢	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 §	Hispanic	47.08 (30.61, 65.62)		41.40 (24.45, 60.65)	
	Asian	13.19 (0.54, 27.44)		23.00 (8.35, 39.62)	
	African origin	18.59 (5.03, 33.91)	1179	42.18 (24.90, 61.84)	6450
	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 †		32.82 (21.92, 44.70)	1172	20.16 (12.93, 27.85)	6449
Diabetes ‡		-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 ¢	1699	p< 0.0001 ¢	1699

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

PO, oral; GC, glucocorticoid; SLICC, Systemic Lupus International Collaborating Clinics; BMI, body mass index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000

n = number of patients, N = number of follow up intervals

§ C.f. Caucasian

† Defined as systolic blood pressure ≥130mmHg or diastolic blood pressure ≥90mmHg or taking anti-hypertensive medication.

‡ Defined as any past or current history of diabetes

¢ Overall variation between treatment centres shown here as p-value for Chi^2 test. Further detail of between centre differences (in multivariable analyses) shown in table 6.

		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)	11468
Sex (male)		1.31 (0.90, 1.90)	1700	1.03 (0.66, 1.59)	11477
Ethnicity / Race §	Hispanic	0.85 (0.55, 1.26)	1700	0.54 (0.35, 0.83)	11477
	Asian	1.68 (1.18, 2.38)		0.85 (0.57, 1.28)	
	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)	11477
Disease duration (years)		0.88 (0.61, 1.27)	1700	0.87 (0.85, 0.90)	11477
Hypertension †		1.89 (1.46, 2.45)	1683	1.50 (1.19, 1.88)	11471
Diabetes ‡		1.50 (0.82, 2.77)	1682	2.00 (1.51, 2.63)	11477
BMI		1.00 (0.98, 1.02)	1672	1.00 (0.98, 1.02)	11410
BMI^2		1.00 (1.00, 1.00)	1672	1.00 (1.00, 1.00)	11410
On antimalarial (yes/no)		0.56 (0.43, 0.72)	1697	0.78 (0.61, 1.00)	11477
On immunosuppressant (yes/no)		2.61 (2.01, 3.40)	1697	2.48(1.96, 3.14)	11477
SLEDAI-2K score		1.06 (1.03, 1.08)	1693	1.08 (1.06, 1.11)	11347
Active renal disease (yes/no)		1.84 (1.40, 2.41)	1700	1.32 (1.00, 1.75)	11477
Overall treatment centre effect		p< 0.0001 ¢	1699	p< 0.0001 ¢	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 §	Hispanic	217.33 (77.91, 466.03)	235	185.31 (75.40, 364.10)	550
	Asian	25.29 (-23.11, 104.13)		36.32 (-12.18, 111.61)	
	African origin	51.70 (-5.92, 144.60)		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†		68.70 (15.72, 145.97)	233	38.02 (5.40, 80.72)	549
Diabetes ‡		-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 ¢	1699	p< 0.0001 ¢	1699

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

GC, glucocorticoid; SLICC, Systemic Lupus International Collaborating Clinics; BMI, body mass index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000

n = number of patients, N = number of follow up intervals

* OR / % Change amongst all non-Caucasian race/ethnic groups compared with Caucasians

† Defined as systolic blood pressure ≥130mmHg or diastolic blood pressure ≥90mmHg or taking anti-hypertensive medication.

‡ Defined as any past or current history of diabetes

¢ Overall variation between treatment centres shown here as p-value for Chi^2 test. Further detail of between centre differences (in multivariable analyses) shown in table 6.

	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 § Hispanic	2.16 (1.05, 4.45)	2.46 (0.87, 6.95) *
Ethnicity/ Race § Asian	3.28 (1.77, 6.09)	3.73 (1.74, 7.98)
Ethnicity/ Race § African origin	2.42 (1.62, 3.61)	4.65 (2.68, 8.08)
Ethnicity/ Race § 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 †	-	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 ¢	p< 0.0001 ¢
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 § Hispanic	-	36.07 (1.65, 82.15)
Ethnicity/ Race § Asian	-	-3.63 (-20.51, 16.82) *
Ethnicity/ Race § African origin	-	15.80 (1.06, 32.68)
Ethnicity/ Race § Other	-	1.59 (-19.74, 28.59) *
Disease duration (years)	-42.95 (-49.02, -36.16)	-6.63 (-7.39, -5.87)
Hypertension †	18.76 (9.55, 28.73)	20.90 (13.77, 28.46)
Diabetes ‡	-	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 ¢	p< 0.0001 ¢
Parenteral		
Received GC (yes/no)	**OR (95% CI)**	**OR (95% CI)**
Disease duration (years)	-	0.88 (0.86, 0.91)
Hypertension †	1.53 (1.13, 2.07)	1.41 (1.13, 1.76)
Diabetes ‡	-	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 ¢	p< 0.0001 ¢
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 ¢	p< 0.0001

Table 5: Significant factors associated with glucocorticoid use in the SLICC Inception Cohort in final multivariable models.

GC, glucocorticoid; SLICC, Systemic Lupus International Collaborating Clinics; BMI, body mass index; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000

* Non-significant

¢ Overall variation between treatment centres shown here as p-value for Chi^2 test. Further detail of between centre differences shown in table 6.

† Defined as systolic blood pressure ≥130mmHg or diastolic blood pressure ≥90mmHg or taking anti-hypertensive medication.

‡ Defined as any past or current history of diabete

	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		†			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)**

Table 6: Average mean daily oral glucocorticoid dose of a hypothetical 'typical' patient at each treatment centre at enrolment and over time

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).

† No data (only one patient receiving PO GC in this centre, for whom no dose data available)

Supplementary table 1: Demographic and disease characteristics of patients grouped according to proportion of study time spent on oral glucocorticoids						
	Proportion of time in study spent on PO GCs n (%) / * median (IQR)					
	All		**Some**		**None**	
		n		n		n
Age (years)	31.4 (23.9-41.4) *	558	31.5 (23.6-43.2) *	806	37.9 (29.0-47.6) *	335
Gender		558		806		335
Female	472 (84.6)		720 (89.2)		314 (93.7)	
Male	86 (15.4)		87 (10.8)		21 (6.3)	
Enrolment location		558		806		335
Canada	65 (11.7)		229 (28.4)		103 (30.8)	
USA	98 (17.6)		243 (30.1)		122 (36.4)	
Mexico	82 (14.7)		126 (15.6)		2 (0.6)	
Europe	221 (39.6)		144 (17.8)		105 (31.3)	
Asia	92 (16.5)		65 (8.1)		3 (0.9)	
Race/Ethnicity		558		806		335
Caucasian	213 (38.2)		370 (45.9)		260 (77.61)	
Hispanic	96 (17.2)		151 (18.7)		15 (4.5)	
Asian	123 (22.0)		114 (14.1)		17 (5.1)	
African origin	110 (19.7)		135 (16.7)		33 (9.85)	
Other	16 (2.9)		37 (4.6)		10 (3.0)	
Disease activity/phenotype						
SLEDAI-2K	4 (2-8) *	556	4 (2-8) *	803	2 (0-4) *	334
SLICC/ACR-Damage Index ≥1	153 (27.4)	556	180 (22.3)	803	58 (17.3)	334
Active renal disease Ψ	174 (31.2)	558	243 (30.1)	806	19 (5.7)	335
Anti-dsDNA positive	227 (43.2)	525	313 (44.0)	712	73 (24.0)	304
Low complement †	240 (45.5)	528	289 (40.3)	717	53 (17.5)	303
Medication use						
Immunosuppressant use	300 (53.8)	558	346 (42.9)	807	38 (11.3)	335
Antimalarial use	364 (65.2)	558	530 (65.7)	807	258 (77.0)	335
Co-morbidities						
Hypertension	278 (49.9)	557	358 (44.8)	799	122 (37.3)	327
Diabetes Mellitus	20 (3.6)	551	27 (3.4)	798	14 (4.2)	333
Current smoker	88 (15.8)	556	116 (14.4)	807	48 (14.3)	335
Post-menopausal §	60 (12.7)	472	89 (12.4)	720	64 (20.4)	314
Body mass index (kg/m2)	25.1 (5.4) ¢	547	25.9 (5.9) ¢	796	26.5 (6.5) ¢	329

SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC, Systemic Lupus Erythematosus International Collaborating Clinics; ACR, American College of Rheumatology; GC, glucocorticoid.
* Median (IQR)
Ψ Active nephritis or any renal item on SLDEAI-2K (haematuria, proteinuria, pyuria or casts)
† Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory
§ Percentage of women
¢ Mean (SD)

Supplementary table 2: GC use by a hypothetical 'typical' patient at each treatment centre

Cross-sectional analysis at enrolment

('Typical' patient 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)

	Probability patient is on PO GC at enrolment (95% CI)	Probability parenteral GC received prior to enrolment (95% CI)	Mean total parenteral GC dose prior to enrolment (mg) (95% CI)
Cohort overall	0.49 (0.43, 0.54)	0.09 (0.07, 0.11)	542 (518, 567)
USA			
1	0.36 (0.10, 0.62)	0.61 (0.00, 0.12)	880 (431, 1797)
2	0.25 (-0.34, 0.84)	†	†
3	0.29 (0.05, 0.53)	**0.03 (-0.00, 0.06)**	987 (464, 2097)
4	0.76 (0.48, 1.03)	0.11 (0.01, 0.21)	**142 (69, 189)**
5	**0.02 (-0.06, 0.10)**	†	†
6	**0.05 (0.00, 0.10)**	0.10 (0.02, 0.18)	**83 (40, 172)**
7	**0.11 (0.03, 0.19)**	**0.01 (-0.01, 0.02)**	1000 (61, 16234)
8	0.38 (0.08, 0.68)	0.08 (0.00, 0.16)	874 (420, 1820)
9	**0.09 (0.03, 0.15)**	0.13 (0.07, 0.19)	**128 (104, 158)**
10	**0.24 (0.03, 0.44)**	0.17 (0.05, 0.29)	750 (504, 1116)
11	**0.25 (0.02, 0.48)**	0.04 (-0.01, 0.09)	655 (36, 11766)
12	0.83 (0.52, 1.15)	†	†
13	**0.07 (-0.10, 0.25)**	0.04 (-0.4, 0.12)	983 (55, 17648)
Europe			
14	**0.95 (0.78, 1.12)**	0.27 (0.06, 0.49)	**1757 (1099, 2808)**
15	0.31 (-0.13, 0.75)	0.06 (-0.05, 0.17)	1912 (110, 33255)
16	0.74 (0.44, 1.04)	0.06 (-0.01, 0.13)	898 (339, 2378)
17	0.41 (0.23, 0.58)	0.08 (0.03, 0.13)	694 (540, 892)
18	0.66 (0.37, 0.94)	0.12 (0.02, 0.21)	551 (361, 840)
19	0.65 (0.37, 0.93)	0.03 (-0.01, 0.08)	367 (136, 993)
20	0.82 (0.53, 1.11)	†	†
21	**0.05 (-0.07, 0.18)**	0.03 (-0.04, 0.11)	2312 (133, 40289)
22	**0.83 (0.57, 1.09)**	0.07 (-0.03, 0.17)	1135 (254, 5058)
23	0.48 (0.23, 0.73)	0.04 (-0.00, 0.08)	**148 (69, 317)**
24	0.72 (-0.06, 1.50)	0.64 (0.09, 1.20)	717 (175, 2940)
25	0.35 (-0.04, 0.74)	0.22 (0.04, 0.41)	711 (379, 1332)
26	**0.11 (-0.03, 0.25)**	0.04 (-0.04, 0.11)	100 (6, 1623)
27	0.58 (0.43, 0.72)	**0.28 (0.20, 0.36)**	**541 (496, 591)**
Canada			
28	**0.03 (0.01, 0.05)**	0.07 (0.03, 0.10)	**1358 (1095, 1684)**
29	0.41 (0.26, 0.56)	0.05 (0.02, 0.08)	**157 (120, 205)**
30	**0.03 (0.01, 0.06)**	**0.02 (0.00, 0.05)**	782 (425, 1438)
31	0.16 (-0.29, 0.61)	0.43 (-0.03, 0.89)	333 (131, 850)
Other			
32	0.39 (0.12, 0.66)	**0.04 (0.02, 0.06)**	**1048 (866, 1268)**
33	**0.92 (0.84, 1.00)**	0.10 (0.06, 0.14)	521 (463, 586)

Longitudinal analysis over total study period

('Typical' patient 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)

	Probability PO GC received between assessments (95% CI)	Probability patient received parenteral GC between assessments (95% CI)	Mean total parenteral GC dose between assessments (mg) (95% CI)
Cohort overall	0.39 (0.33, 0.46)	0.015 (0.011, 0.019)	300 (295, 307)
USA			
1	0.65 (0.40, 0.91)	0.006 (-0.000, 0.012)	**635 (341, 1181)**
2	0.53 (-0.25, 1.31)	†	†
3	0.58 (0.30, 0.86)	0.006 (0.001, 0.012)	**777 (507, 1189)**
4	**0.91 (0.79, 1.03)**	0.016 (0.001, 0.031)	273 (176, 423)
5	**0.06 (-0.19, 0.30)**	0.019 (-0.032, 0.069)	862 (39, 19080)
6	**0.14 (0.01, 0.27)**	0.025 (0.008, 0.042)	**132 (108, 160)**
7	**0.29 (0.12, 0.46)**	**0.003 (-0.000, 0.006)**	252 (130, 489)
8	0.67 (0.39, 0.95)	0.011 (0.001, 0.021)	**487 (319, 745)**
9	**0.24 (0.10, 0.38)**	0.031 (0.016, 0.046)	**61 (55, 67)**
10	0.51 (0.22, 0.79)	0.021 (0.006, 0.036)	273 (221, 337)
11	0.52 (0.21, 0.83)	0.013 (0.001, 0.025)	162 (84, 311)
12	**0.94 (0.82, 1.07)**	0.004 (-0.005, 0.014)	1449 (66, 32017)
13	0.21 (-0.22, 0.63)	†	†
Europe			
14	**0.98 (0.93, 1.04)**	0.032 (-0.010, 0.075)	**1078 (470, 2335)**
15	0.60 (0.10, 1.09)	0.005 (-0.006, 0.015)	2044 (95, 44151)
16	**0.90 (0.77, 1.04)**	0.020 (0.001, 0.040)	429 (250, 736)
17	0.69 (0.54, 0.85)	0.007 (0.003, 0.011)	274 (228, 328)
18	**0.86 (0.71, 1.01)**	0.012 (0.002, 0.022)	**440 (319, 608)**
19	**0.86 (0.71, 1.01)**	0.009 (0.000, 0.018)	**50 (326, 767)**
20	**0.94 (0.83, 1.05)**	†	†
21	**0.15 (-0.17, 0.48)**	†	†
22	**0.94 (0.84, 1.04)**	0.008 (-0.002, 0.018)	671 (266, 1693)
23	0.76 (0.57, 0.94)	0.014 (0.005, 0.024)	**142 (115, 176)**
24	0.89 (0.53, 1.26)	†	†
25	0.64 (0.24, 1.04)	0.018 (-0.003, 0.038)	392 (200, 770)
26	0.28 (-0.02, 0.58)	†	†
27	**0.82 (0.73, 0.91)**	**0.065 (0.043, 0.087)**	307 (298, 317)
Canada		,	
28	**0.09 (0.04, 0.14)**	**0003 (0.001, 0.005)**	**393 (310, 497)**
29	0.70 (0.57, 0.83)	**0.005 (0.002, 0.008)**	**131 (112, 154)**
30	**0.11 (0.04, 0.17)**	**0.004 (0.001, 0.006)**	225 (155, 326)
31	**0.39 (-0.41, 1.19)**	†	†
Other			
32	0.68 (0.44, 0.93)	**0.004 (0.002, 0.006)**	**946 (853, 1050)**
33	**0.97 (0.95, 1.00)**	0.008 (0.004, 0.012)	**447 (406, 491)**

Results in bold show where GC use at a centre differs significantly from the cohort overall (i.e. the confidence intervals do not overlap).
† No pulsed GC received at this centre
‡ No data (only one patient receiving PO GC in this centre, for whom no dose data available)