Corticosteroid use in childhood-onset systemic lupus erythematosus – practice patterns at four pediatric rheumatology centers

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Abstract

Objective

To evaluate corticosteroid prescribing patterns in childhood-onset systemic lupus erythematosus (SLE), comparing four academic pediatric rheumatology practices.

Methods

Patients with childhood-onset SLE (n=72) treated at four large pediatric rheumatology centers were studied at 3-month intervals for 18 months. Information on medication use, disease activity as measured by the SLEDAI and the SLAM; and disease damage by the SLICC/ACR Damage Index was collected.

Results

At the time of enrollment, patients at each center were similar for disease duration, age, frequency of renal involvement and disease damage. Prednisone (mean 9 mg/day) was continued during 72% of periods of inactive disease for at least 3 months (SLEDAI=0). Centers differed in the use of intravenous pulse methylprednisolone ($p<0.0001$). Even when adjusted for between-center differences in patient weight, race and disease activity, centers also significantly differed in the dose of prednisone ($p<0.05$). The center with the largest between-patient variability in the dose of prednisone prescribed to its patients showed the smallest between-patient variance in patient disease activity.

Conclusions

Corticosteroids are commonly used for the treatment of childhood-onset SLE, even when the disease is inactive. There appears to be important between-center differences in the use of intravenous and oral corticosteroids for childhood-onset SLE therapy that cannot be explained by patient disease activity corticosteroid prescribing patterns influence disease control. Further studies are needed to determine whether differences in practice patterns lead to significant differences in longer-term disease outcomes with childhood-onset SLE.

Key words

SLE, children, prednisone, corticosteroids, treatment patterns.

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Introduction

Corticosteroids are one of the mainstays for the treatment of childhood-onset systemic lupus erythematosus (SLE) (1). For childhood-onset SLE therapy, prednisone doses are increased with disease flares and then gradually decreased over several months in an effort to avoid re-appearance of flare. In contrast to adults with SLE, previous studies suggested that the vast majority of children with SLE are treated with oral and sometimes intravenous corticosteroids over prolonged periods of time (2). Previous research also showed that damage, likely secondary to corticosteroid use, is more frequent in children than adults with SLE (3). Although patient-tailored use of corticosteroids in childhood-onset SLE appears to be of great clinical relevance, knowledge about the optimal dosing of corticosteroids based on patient disease features has not been well examined, and there are no generally accepted guidelines of how to best use corticosteroids in childhood-onset SLE.

The objectives of this pilot study were: 1) to evaluate corticosteroid prescribing patterns in childhood-onset SLE, comparing four academic pediatric rheumatology practices; 2) to assess whether differences in steroid use influence disease control and damage. We also set out to determine if there were 3) clinically important differences in the use of intravenous and oral corticosteroids between treatment centers, and 4) whether these differences in corticosteroid use could be attributed to patient clinical or laboratory features. This research may provide an initial step in developing evidence-based criteria for the dosing of corticosteroids in childhood-onset SLE.

Methods

Patients

Children fulfilling classification criteria for SLE prior to the age of 16 years (4) were recruited from four pediatric rheumatology centers during visits to the out-patient clinics in a consecutive fashion. The two U.S. and the two Canadian centers were chosen according to their size and the availability of standardized clinic documentation to ensure accurate documentation of the patients' disease course prior to enrollment to the study. Each center was asked to contribute about 20 patients to over a 12-month period, starting 2002. Patients were evaluated every 3 months for 18 months. Eligible patients were 18 years or younger at the time of study enrollment and had no other chronic diseases besides childhood-onset SLE.

Measures

In addition to patient demographics, prior organ involvement with childhood-onset SLE was recorded, with focus on renal and neuropsychiatric SLE. At each study visit, all prescribed medications were recorded, and any changes of medications at the end of the visit were noted. In cases where the prednisone dosages changed between study visits, we assumed that such a change occurred at 6 weeks after a preceding study visit, unless more specific information was provided. Alternate doses and twice or trice daily doses of prednisone were converted to once daily prednisone doses by using 50%, 200% and 300% of the respective prednisone dose.

Results of laboratory testing performed as part of childhood-onset SLE clinical care were recorded. They included anti-ds-DNA antibodies, complement levels, urinalyses and microscopy, complete blood counts, ESR, liver function tests and renal panels.

Disease activity was measured using the Systemic Lupus Erythematosus Disease Activity Index (5) (SLEDAI: range 0-104; 0 = inactive disease) and the Systemic Lupus Activity Measure (6, 7) (SLAM: range 0-86; 0 = inactive disease). The two disease activity indices differ in that the SLEDAI only considers objectively verifiable SLE features while the SLAM also includes subjective SLE symptoms such as fatigue, myalgias, or arthralgias. These two disease activity indices were completed to allow for the consideration of subjective and objective SLE signs and symptoms in the physician's decisions for medication changes.

At each study visit, physicians were asked about their opinion as to whether

there was a major or minor disease flare, no change in disease activity, or even improvement (major, minor) since the last study visit.

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) (8) was completed at the time of enrollment to the study and at the final study visit.

Statistical analysis

For the analysis patients recruited in Chicago, Cincinnati, Toronto and Vancouver are referred to as patients from Center 1, 2, 3 or 4, respectively.

Numerical variables were summarized by mean ± standard error (SE); and binary and categorical variables were summarized by frequency (in percent). In cross-sectional studies, analysis of variance (ANOVA) tests and Pearson Chi square tests were used to assess the center effect for numerical and categorical variables, respectively. In longitudinal and cross-sectional studies, we applied mixed effect models to assess associations between primary measures and major fixed effects of interest (9). In particular, the primary measures were oral corticosteroid dosages and disease activity; and the major fixed effects of interest were time (a 7-level categorical factor of months 0, 3, 6, 9, 12, 15 and 18), center (a 4-level categorical factor of centers 1-4), and their interaction (time x center). A random effect (*i.e.* patients) was used in the mixed effect model to account for "within-patient" correlation caused by repeated observations over time. Controlling/adjusting covariates such as demographics of patients were also included in the mixed effect modes. Under the mixed effect model framework, we further performed *post hoc* comparisons of means of primary measures cross-sectionally between centers and longitudinally between months. Tukey's methods were used to adjust for *post hoc* multiple comparisons and ensure an overall 5% of type I error. Total "between-patient" variances of oral corticosteroid dosages and disease activity and their proportions in each center were also estimated under the mixed effect model framework as an alternate approach to assess the relationship of changes in disease control and distribution (variation) of corticosteroid doses over time.

Statistical computations were performed using SAS version 9.1 (SAS, Cary, NC) software. Figures were plotted using Splus version 6.2 (Insightful Corp, Durham, NC) software. p-values <0.05 were considered statistically significant.

Ethic review

The study was approved by the institutional review or research ethic boards of the participating pediatric rheumatology centers. Informed consent and assent was sought from all participants prior to the study procedures.

Results

Patients and baseline disease features

From four pediatric rheumatology centers 72 patients with childhood-onset SLE (female: male = 59: 13) with a mean ± SE age of 14.8±0.3 years and mean ± SE disease duration of 2.82±0.4 years were recruited (Table I). Patients were studied for up to 18 months, and data from 108 patient years of follow-up were considered in the analysis. There were 11 (15%) Hispanic patients included in the study. At the time of diagnosis with childhood-onset SLE, the global disease activities (mean ± SE) of the patients were 15±1 and 12±0.7 using SLEDAI and SLAM, respectively; their average ± SE renal disease activity as measured by the renal domain score of the SLEDAI was 3.6±0.5, without important differences between centers (p=0.09).

At the time of enrollment, biopsy-proven lupus nephritis was present in 51 (51/72 = 71%) of the patients. There were no important between-center differences in prior organ involvement (including lupus nephritis) or the presence of antiphospholipid antibodies. Constitutional symptoms (mainly fatigue) as measured by the SLAM were similar among the patients followed at the various sites at the time of enrollment. The same was true for laboratory abnormalities based on laboratory testing results included in the SLAM or the SLEDAI, respectively.

Disease course and medication use during the study

Medication use at the four centers is summarized in Table II. There were no important between-center differences in the use of hydroxychloroquine or immunosuppressive medications. However, centers differed in the frequency of prescribing non-steroidal anti-inflammatory medications, aspirin and the use of intravenous corticosteroids (all p<0.0001 using mixed models).

At all centers, the vast majority of patients were treated with oral or intravenous corticosteroids (Table II). During the entire 108 patient-years of follow-up considered in the study, there were 76 patient-years (76/108=70%) during which oral corticosteroids (prednisone) were prescribed for childhood-onset SLE treatment, although disease activity of most patients was well-controlled during the study [mean score ± SE of the SLEDAI: 3.1±0.05; range: 0-18; mean score ± SE of the SLAM: 3.3±0.06; range: 0-21].

Physicians reported 43 flares (40 minor and 3 major flares by Likert scale), occurring in 28 patients during the study. At the time of physician identified flares, there was a mean ± SE increase of the SLEDAI score from the previous study visit of 2±0.09 to a mean SLEDAI score of 6±0.07; similarly the mean SLAM score increased by 1.7±0.07 to a mean SLAM score of 5.6±0.07 with flares. With disease flares, the daily dose of prednisone was increased by (mean ± SE) 3 mg±0.3 (range 0-30 mg), resulting in a mean ± SE daily dose of 15±0.4 mg of prednisone prescribed to patients with flares.

Effect of change of disease activity on prednisone use

Irrespective of center, a patient's dose of prednisone at the time of discharge from a study visit was found positively associated with his/her previous disease activities as measured by the SLEDAI at the current visit, and SLEDAI scores at the time of study visits 3 and 6 months ago (p<0.05). Similar results were found when the SLAM was used as a measure of disease activity, or when subgroup analysis of patients with renal, serologic or hematologic, or

constitutional features of disease activity were considered (all $p<0.05$).

Use of oral corticosteroids at the time of maximal disease activity

The dose of prednisone prescribed at the time of the highest disease activity for each patient was determined, in an effort to determine doses of prednisone given by the pediatric rheumatologists in the setting of active disease.

On average, the highest SLEDAI score was 4.5, 6.6, 6.7 and 8.4, respectively, for patients followed at centers 1 through 4, without significant differences among centers ($p=0.08$). However, there were statistically significant differences of the means of the prednisone doses (weight adjusted) at that time of the highest SLEDAI score (Centers 1 through 4: 21 mg, 19 mg, 13 mg, and 5 mg; $p=0.03$ using mixed models). Similar between-center differences in the use of prednisone were found when SLAM scores were used to identify peak disease activities ($p=0.0013$).

Use of oral corticosteroids at the time of minimal disease activity

During the 34.25 patient-years of follow-up with inactive disease (SLEDAI 0) oral corticosteroids were prescribed

Table I. Patient characteristics at the time of study enrollment[†].

Variable	Category	Total (n=72)	Center 1 (n=22)	Center 2 (n=16)	Center 3 (n=19)	Center 4 (n=15)	*p*-value[‡]
Demographics							
Gender	Female	82%	86%	88%	74%	80%	NS*
Race	White	42%	64%	50%	16%	33%	0.0006
	Black	22%	22%	44%	21%	0%	
	Asian	29%	14%	6%	53%	47%	
	Other	7%	0.00%	0.00%	10.53%	20.00%	
Ethnicity – Hispanics[Δ]		11 (15%)	9	0	1	1	
Age at enrollment (years)		14.8 ± 0.3	15.6 ± 0.3	15.4 ± 0.8	13.5 ± 0.6	14.5 ± 0.8	NS
Disease duration (years)		2.8 ± 0.4	3.8 ± 0.9	2.7 ± 1.1	2.1 ± 0.5	2.5 ± 0.6	NS
Disease activity as measured by the SLEDAI at diagnosis[#]		15 ± 1.0	16 ± 2.3	12 ± 1.5	16 ± 1.8	15 ± 1.8	NS
Disease activity as measured by the SLAM at diagnosis[%]		12 ± 0.7	12 ± 1.4	14 ± 1.2	12 ± 1.2	13 ± 1.4	NS
Treatment history since the diagnosis with SLE							
Oral or intravenous pulse corticosteroids		92%	91%	81%	95%	100%	NS
Oral corticosteroids		86%	73%	81%	95%	100%	0.0204
Intravenous pulse corticosteroids		25%	64%	19%	0%	7%	<0.0001
Disease activity & damage the time of enrollment							
Frequency of disease damage (SDI[$] > 0)		18%	27%	25%	6 %	10%	NS
Frequency of renal damage (SDI renal >0)		8%	9%	19%	5%	0%	NS
Disease activity as measured by the SLEDAI		3.4 ± 0.05	3.2 ± 0.09	3.3 ± 0.24	4.1 ± 0.23	2.8 ± 0.22	NS
Disease activity as measured by the SLAM		3.3 ± 0.06	2.6 ± 0.11	5.1 ± 0.40	3.2 ± 0.21	2.4 ± 0.17	NS

*NS: not significant
[Δ] all other patients were of non-Hispanic ethnicity
[#] SLEDAI: Systemic Lupus Erythematosus Disease Activity Index
[%] SLAM: Systemic Lupus Assessment Measure
[$] SDI: Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Disease Damage Index
[†]Values in cells are frequency (in %) for categorical variables and mean (SE) for numerical variables. [‡]*p*-values are from Pearson chi square tests for categorical variables and ANOVA tests for numerical variables; and *p*-values.

Table II. Disease features and treatments during the study[†].

Variable	Total (n=72)	Center 1 (n=22)	Center 2 (n=16)	Center 3 (n=19)	Center 4 (n=15)	*p*-value[‡]
Oral corticosteroids (prednisone)	92%	95%	88%	90%	93%	NS
Intravenous pulse corticosteroids	19%	59%	0%	0%	7%	0.0000
Nonsteroidal anti-inflammatory medication	24%	46%	26%	0%	21%	0.0001
Hydroxychloroquine	97%	95%	94%	100%	100%	NS
Immunosuppressives[§]	43%	32%	50%	58%	33%	NS
Antihypertensives	19%	18%	19%	32%	7%	NS

For additional legend please see Table I
[†]Values in cells are frequency (in %). [‡]*p*-values are from Pearson chi square tests; and *p*-values <0.05 indicate a significant center effect. [§]Methotrexate, azathioprine, mycophenolate mofetil, intravenous cyclophosphamide.

Table III. Use of oral corticosteroids despite prolonged periods of inactive disease*.

	Center 1§	Center 2§	Center 3§	Center 4§	All centers
1. SLEDAI score = 0†					
After 2 consecutive study visits in 3-month intervals (n of inactive periods = 25 among 23 patients)					
Number of inactive periods	5	8	5	7	25
Number (%) of inactive periods using oral prednisone	3 (60%)	6 (75%)	3 (60%)	6 (86%)	18 (72%)
Daily dose of prednisone (mg) of periods using prednisone#	24 ± 12	7 ± 3	8 ± 1	5 ± 2	9 ± 8
CHANGE of daily dose of prednisone (mg)#	-5 ± 4	-1 ± 4	0 ± 0	-1 ± 0.5	-2 ± 2
After 3 consecutive study visits in 3-month intervals (n of inactive periods = 14 among 13 patients)					
Number of inactive periods	2	5	2	5	14
Number (%) of inactive periods using oral prednisone	1 (50%)	4 (80%)	1 (50%)	4 (80%)	10 (71%)
Daily dose of prednisone (mg)	12	4 ± 1	15	4 ± 1	6 ± 4
CHANGE of daily dose of prednisone (mg)	-3	0	0	-1 ± 1	-1 ± 1
2. SLAM score = 0‡					
After 2 consecutive study visits in 3-month intervals (total inactive periods = 21 among 19 patients)					
Number of inactive periods	4	1	9	7	21
Number (%) of inactive periods using oral prednisone	3	1	6	6	16
Daily dose of prednisone (mg) of periods using prednisone	11 ± 1	5	11 ± 6	3 ± 1	8 ± 5
CHANGE of daily dose of prednisone (mg)	-1 ± 1	± 0	-2 ± 2	-1 ± 1	-1 ± 2
After 3 consecutive study visits in 3-month intervals (n of inactive periods = 8 among 8 patients)					
Number of inactive periods	2	0	4	2	8
Number (%) of inactive periods using oral prednisone	2		3	2	7
Daily dose of prednisone (mg) of periods using prednisone	9 ± 1		13 ± 1	2 ± 0.5	9 ± 5
CHANGE of daily dose of prednisone (mg)	-1 ± 1		-2 ± 1	-1 ± 1	-1 ± 1

†Oral corticosteroids were prescribed to patients with SLEDAI scores of '0' during 333 of a total of 411 (81%) patient months of inactive disease. Details on prednisone use despite inactive disease during 2 or 3 consecutive visits is shown in Panel 1.
‡Oral corticosteroids were prescribed to patients with SLAM scores of '0' during 268 or the 288 patient months (93%). Details on prednisone use despite inactive disease during 2 or 3 consecutive visits is shown in Panel 2.
*One patient may contribute more than one inactive period (episode or event).
#Values in the same row are mean ± SE of the daily dose of prednisone.

81% (333/ 411) of the time. When using the SLAM scores of '0' to define inactive disease, then there were 24 patient-years of inactive disease with 93% (22.33/24) patient-years during which oral corticosteroids were prescribed.

We then examined the doses of prednisone prescribed to patients with inactive disease activity for at least 3 or 6 months, *e.g.* SLEDAI scores or SLAM scores of '0' during two or more consecutive study visits (Table III). Among a total of 25 episodes of inactive disease for 3 months, *e.g.* SLEDAI scores of '0' on two consecutive visits, there were 18 (72%) episodes during which prednisone was prescribed at mean ± SE of daily dose of 9 mg ± 8. Results were similar when the SLAM was used to define inactive disease (Table III). As is also shown in Table III, prednisone was often continued even with inactive disease for at least 6 months' duration, *e.g.* SLEDAI scores of '0' or SLAM scores of '0' on three consecutive visits.

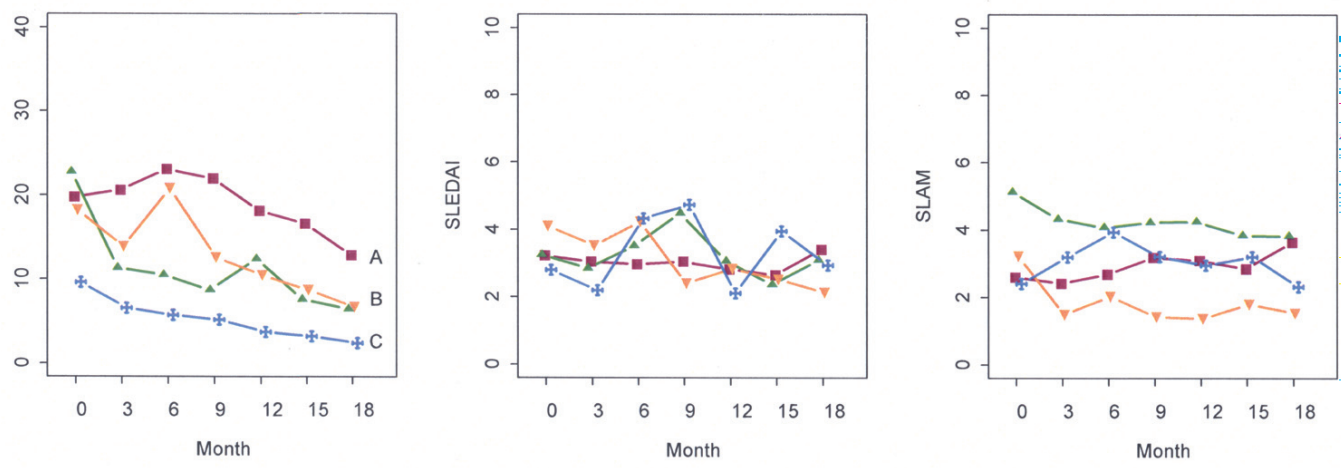
Center differences of stability (variation) of disease activity vs. corticosteroid doses during the study

Despite similar average disease activity of the patients followed at each of the four centers (as measured by the mean SLEDAI and SLAM scores), there were large between-center differences in the average prescribed daily dose of prednisone. Center 1 used pulse intravenous methylprednisolone more frequently during the study and had the highest average dose of daily prednisone. This is depicted in Figure 1, upper panel. Of note trends in theses differences persisted even if only White patients were considered as is shown in Figure 1, lower panel.

The relationship between changes of disease activity and the prescribed dose of prednisone was further examined for differences between centers. This was done by assessing between-patient variability, *e.g.* variance of prednisone and disease activity, respectively, between patients of a given center. As is shown in Table IV, there are discrepancies of between-patient variability of disease activity and of prednisone dosages among the centers. Center 1 exhibited the smallest between-patient variance of SLEDAI scores, accounting for 8% of the entire (centers 1 to 4) between-patient variance in SLEDAI scores. When using the SLAM to measure disease activity, center 1 contributed 12% of the between-patient variance in disease activity. However, the between-patient variance of prednisone dose at center 1 was the largest, accounting for 62% of the entire (centers 1 to 4) between-patient variance of prednisone. Conversely, although center 4 had the largest between-patient variance of disease activity (SLEDAI, SLAM) among centers 1 through 4, the between-patient variance of prednisone dose was the smallest in center 4.

Despite the observed differences in prednisone use in relation to disease activity among the four centers, there were no significant trends among centers for the accrual of new damage during the study (Table IV).

Upper panel – All patients



Lower panel –White patients only

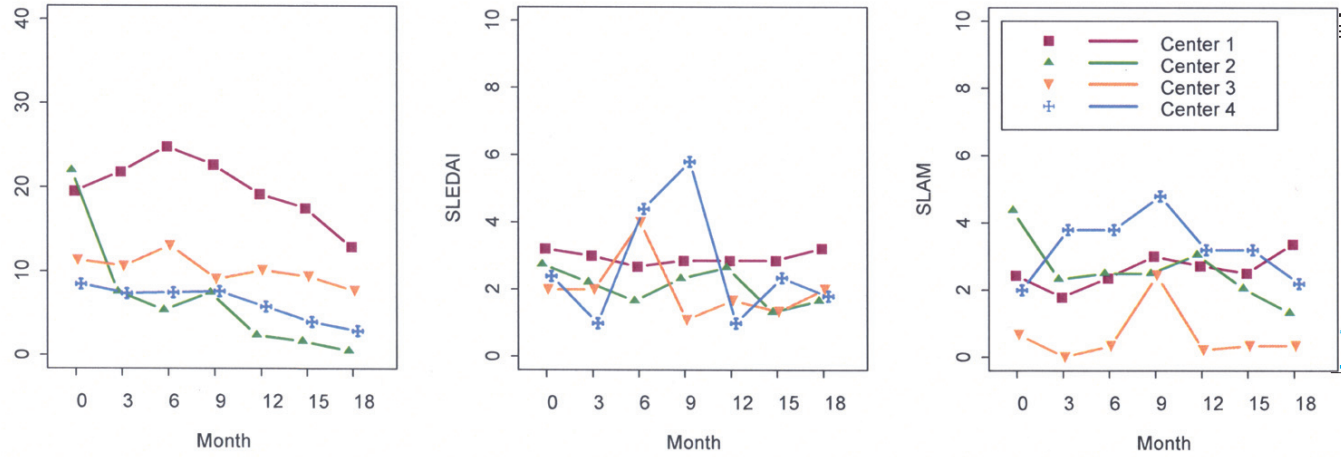


Fig. 1. Changes of oral corticosteroids and disease activity during the study by center during the study.
72 Patients were followed for 18 months. Plots in the upper panel consider all patients (n=72) enrolled in the study; and plots in the bottom lower panel consider only the subset of White patients (n=51). Upper panel plots depict the daily dose of prednisone, disease activity as measured by the SLEDAI and disease activity as measured by the SLAM. Irrespective of disease activity measures, there are no differences in disease activity, but there are statistically significant differences in the daily dose of prednisone (left upper plot): "A" indicates prednisone doses in center 1 as the highest in most of months except months 0 and 6; a "B" indicates doses in centers 2 and 3 are the same and both centers use significantly higher prednisone doses than center 4; and a "C" indicates Center 4 uses significantly lower prednisone doses than the other three centers. All means were compared using a Tukey's multiple comparison method under a mixed effect model framework; and $p<0.05$ indicated a statistical significance.

Discussion

Children and adolescents with SLE are often treated with corticosteroids for prolonged periods of time. This study supports that there are significant differences between different pediatric rheumatology centers in the use of oral and intravenous corticosteroids for these patients that cannot be explained by patient disease activity or baseline disease features. Notably, such differences in treatment approach appeared to affect disease control with childhood-onset SLE, as is supported by the relative contribution of each center to the variability of disease activity and prednisone doses.

The benefits and potential threats from using corticosteroids in childhood-onset SLE have long been recognized. Corticosteroids dramatically improve the clinical manifestations of SLE, but short-term and long-term side effects are distressing to the patient, present a major management problem, and are sometimes fatal (10). Contrary to adults with SLE (11), almost all children with childhood-onset SLE are exposed to high-dose oral corticosteroids for a prolonged period of time (3). Oral corticosteroids are the drugs of choice for SLE-associated skin, serosal, pulmonary, hematologic, renal, and cerebrovascular disease (12). Corticosteroids are used in combination with immunosuppressive drugs for severe organ involvement (13, 14). Since the 1970s, so-called pulse steroids, *i.e.* intravenously administered methylprednisolone at a dose of 10-30 mg/kg (max 1 gram), have been used mainly for severe disease exacerbation (12, 15).

Despite their proven benefits, corticosteroids also appear to contribute disease damage with SLE (16-19). The cumulative dose of oral corticosteroids for the treatment of SLE patients is significantly associated with the development of osteoporotic fractures,

Table IV. Center differences in corticosteroid use – relationship to disease control and damage during the study.

Variable	Total (n=72)	Center 1 (n=22)	Center 2 (n=16)	Center 3 (n=19)	Center 4 (n=15)
Prednisone					
Mean (SE) of prednisone dose (mg)†	13.54 ± 1.24	19.38 ± 1.92	12.64 ± 2.44#	13.33 ± 2.15#	5.86 ± 2.37#&$
Between-patient variance in prednisone dose (mg)‡	306.51 (100%)	190.41 (62%)	38.16 (12%)	45.50 (15%)	32.43 (11%)
Disease Activity					
Between-patient variance in the SLEDAI summary score‡	16.52 (100%)	1.32 (8%)	5.28 (32%)	3.70 (22%)	6.23 (38%)
Between-patient variance in the SLAM summary score‡	29.01 (100%)	3.55 (12%)	17.53 (60%)	1.16 (4%)	6.77 (23%)
Disease Damage§					
SDI > 0 at month 0 (n=11)	17.74%	27.27%	25.00%	5.55%	10.00%
SDI = 0 at month 0 and SDI =0 at 18 months (n =39)	62.90%	54.55%	50.00%	77.78%	70.00%
SDI = 0 at month 0 & SDI > 0 at 18 months (n=12)	19.36%	18.18%	25.00%	16.67%	20.00%

For additional legend please see Table I

† Means ± SE of prednisone dose are estimated after adjusting for weight in mixed effect models; *post hoc* comparison of means are performed using Tukey's multiple comparison methods; "#", "&" and "$" indicate means are different between Center 1 *vs*. Center 2, Center 1 *vs*. Center 3 and Center 1 *vs*. Center 4, respectively.

‡ Values in cells are means of between patient variance of each center and its percentage (in parenthesis) of the total between patient variance. All means are estimated from mixed effect models.

§ The association between disease damage (using SDI) and center is insignificant with a p-value = 0.5587 using a Pearson chi-square test.

coronary artery disease, cataracts, and avascular necrosis (11). The role of the dose, high versus low, of corticosteroids, and the role of intravenous pulse corticosteroids as a factor precipitating avascular necrosis and osteoporosis remains controversial (20, 21).

The use of different dosages of oral corticosteroids, the pattern in which they are given (*i.e*. daily versus alternate day) with or without i.v. pulses is essentially empirical, since the evidence to support physician preferences is sparse (22). In the absence of available evidence-based standards, expert consensus has been used to develop prednisone recommendations for adults with SLE (23). These recommendations were developed mainly because the practice variation in the use of oral corticosteroids (used as standard background therapy) among adult SLE experts created problems when conducting clinical trials (24). The results of our study suggest that these published recommendations for adult SLE are quite different from the current use of prednisone in childhood-onset SLE, limiting the utility of these recommendation or future clinical trials including children. For example, in adults, discontinuation of any steroids is suggested as quickly as 18 weeks after a severe, life-threatening complication of SLE, with tapering initiated as early as two weeks after the initial flare. This is very different from the long-term use of corticosteroids in the presented cohort.

We do not believe that differences in the ethnic and racial composition of the cohorts between centers have importantly influenced our findings as the observed trends persisted even when only white patients were considered in the analysis. Additionally, our previous research suggests that, corrected for differences in disease activity, patient race is not an important predictor of the prednisone dose used for treatment (2). Access to medical therapy with chronic diseases is similar in the U.S. and Canada for children, even those from low-income families, thus unlikely contribute to the differences in corticosteroid use observed in this study.

Of great interest, our data show considerable differences in the practice patterns among pediatric rheumatology centers is associated with differences in disease control. Given our previous research, suggesting that disease control is a critical for the avoidance of permanent disease damage (2), we consider this observation provides an important argument for promoting the development of evidence-based guidelines for corticosteroids use in childhood-onset SLE. Unfortunately, but likely because our study was small in size, we were unable to show that differences in corticosteroid use might result in differences in disease damage accrual over time. Thus, additional research with larger sample sizes in larger diverse patient populations with childhood-onset SLE is required to address this important research question.

There are limitations to our study. The relatively small sample size and short duration of this pilot study and, on average, well-controlled disease likely led to underestimation of the variance in corticosteroid use between centers. Because the centers participating in this study have dedicated childhood-onset SLE clinics and follow an excess of 600 childhood-onset SLE patients, a lack of expertise in treating childhood-onset SLE is not likely to be a reason for the observed differences in corticosteroid use among the participating centers. Additionally, we assumed that alternate-day prednisone dosing and multiple doses of prednisone could be converted in once-daily regimens without adjustment for potential differences in prednisone exposure (pharmacokinetics). This was done because the relative efficacy of split and alternate day prednisone therapy compared to once daily prednisone has not been well examined, and insufficient data are available how this would affect SLE disease control.

The current pilot study is not suited to propose the best use of corticosteroids in childhood-onset SLE. However, we

provide initial evidence that differences in practice patterns influence disease control (variability of disease activity) over time, suggesting that evidence-based use aimed at optimal short-term disease control and avoidance of long-term damage might improve the prognosis of childhood-onset SLE. Evidence-based corticosteroid dosing regimens for children are still lacking but are appear warranted given pronounced differences in practice patterns with impact on patient short and possibly longer-term prognosis. Additional research in larger groups of childhood-onset SLE patients that considers immunologic and pharmacologic variations in the response to corticosteroids as they pertain to SLE (25, 26) are needed to elucidate the best use of corticosteroids in children with SLE.

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