

Medication Use in Systemic Lupus Erythematosus

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ABSTRACT. Objective. To evaluate factors affecting therapeutic approaches used in clinical practice for the management of systemic lupus erythematosus (SLE), in a multicenter cohort.

Methods. We combined data from 10 clinical adult SLE cohort registries in Canada. We used multivariate generalized estimating equation methods to model dichotomized outcomes, running separate regressions where the outcome was current exposure of the patient to specific medications. Potential predictors of medication use included demographic (baseline age, sex, residence, race/ethnicity) and clinical factors (disease duration, time-dependent damage index scores, and adjusted mean SLE Disease Activity Index-2K scores). The models also adjusted for clustering by center.

Results. Higher disease activity and damage scores were each independent predictors of exposure to nonsteroid immunosuppressive agents, and for exposure to prednisone. This was not definitely demonstrated for antimalarial agents. Older age at diagnosis was independently and inversely associated with exposure to any of the agents studied (immunosuppressive agents, prednisone, and antimalarial agents). An additional independent predictor of prednisone exposure was black race/ethnicity (adjusted RR 1.46, 95% CI 1.18, 1.81). For immunosuppressive exposure, an additional independent predictor was race/ethnicity, with greater exposure among Asians (RR 1.39, 95% CI 1.02, 1.89) and persons identifying themselves as First Nations/Inuit (2.09, 95% CI 1.43, 3.04) than among whites. All of these findings were reproduced when adjustment for disease activity was limited to renal involvement.

Conclusion. Ours is the first portrayal of determinants of clinical practice patterns in SLE, and offers interesting real-world insights. Further work, including efforts to determine how differing clinical approaches may influence outcome, is in progress. (First Release Nov 15 2010; J Rheumatol 2011;38:271–4; doi:10.3899/jrheum.100414)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS
IMMUNOSUPPRESSANTS
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The literature on current therapeutic practices in the management of systemic lupus erythematosus (SLE) is limited, but suggests that, even among centers with extensive experience, approaches to SLE treatment are far from homogeneous^{1,2,3}. Our objective was to evaluate factors affecting therapeutic approaches used in clinical practice for the management of SLE, in a multicenter cohort. *A priori*, factors of

potential interest include patient age, race/ethnicity, disease duration, SLE activity, and accumulated damage.

MATERIALS AND METHODS

Subjects. Our study combined data from 10 clinical SLE cohort registries in Canada, under the umbrella of the “Thousand Faces of Lupus” project. Each center enrolls unselected consecutively presenting patients who meet American College of Rheumatology (ACR) criteria for SLE⁴; the enroll-

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Statistical analysis. Descriptive statistics at baseline included age, sex, self-described race/ethnicity, and urban versus rural residence (based on postal code information). We grouped race/ethnicity into white, black, Asian (essentially persons of East Asian origin), and First Nations/Inuit (persons identifying their race/ethnicity as one of the indigenous peoples of Canada)⁵.

In our models, we applied the unstructured covariance structure because the DI and AMS scores were measured repeatedly over time on the same patients (hence correlation had to be accounted for) and the time intervals between the measurements for each patient were not equal (for example, some patients were seen more often than yearly, and others may miss their yearly assessment). The models also adjusted for clustering of subjects by center, and included interaction terms to account for modification of the influence of AMS and DI scores over time.

SLE treatment strategies are not uniform across all disease manifestations, but rather are generally more aggressive for certain forms of disease (e.g., renal). Thus, we performed sensitivity analyses, adjusting for disease activity limited to renal involvement.

There were 1497 subjects contributing data to our study across 2005-2007; 90.2% were female, and the average age at baseline was 44.3 years (95% CI 43.8, 45.0). The race/ethnicity frequencies were as follows: whites 63.9%, Asians 15.8%, blacks 10.6%, First Nations/Inuit 3.7%, and others 6.1%. Based on postal code information, 88% of the subjects resided in an urban center.

Table 1. Baseline clinical factors of the study subjects (n = 1497).

Factors	Mean (SD)	Median
Disease measures		
SLE Disease Activity Index-2000	4.8 (4.7)	4
SLICC/ACR Damage Index	1.4 (1.8)	1
SLE duration, yrs	12.1 (10.1)	10
Drug exposures		
	n	%
Antimalarial agents*	987	66.0
Prednisone	637	42.6
Azathioprine	248	16.6
Mycophenolate	113	7.5
Methotrexate	99	6.6
Cyclophosphamide	17	1.1

10.3% of patient assessments over time). Elevated anti-dsDNA antibodies were documented in 35.2% of patient visits.

Table 2 outlines the results of the separate regressions for immunosuppressive agents, antimalarial agents, and prednisone use. Higher disease activity and damage scores were each independent predictors of exposure to immunosuppressive agents and for exposure to prednisone. This was not definitely demonstrated for antimalarial agents. An additional independent predictor of prednisone exposure was black race/ethnicity. Older age at diagnosis was independently and inversely associated with exposure to any of these agents (immunosuppressive agents, prednisone, and antimalarial agents). Independent of all other factors, exposure to immunosuppressive agents was more common in persons of Asian and of First Nations/Inuit origin.

There was an interaction such that with the passage of time, AMS became a slightly stronger predictor of current immunosuppressive exposure (RR 1.002, 95% CI 1.000, 1.003), but a weaker predictor of prednisone exposure (RR 0.998, 95% CI 0.996, 0.999). Also with the passage of time, the cumulative damage became a less potent correlate of prednisone exposure (RR 0.997, 95% CI 0.995, 0.999).

Independent of all other factors, exposure to mycophenolate was more common both in Asians (RR 1.68, 95% CI 1.10, 2.55) and persons identifying as First Nations/Inuit (1.70, 95% CI 1.03, 2.78) as compared to whites. Exposure to azathioprine was also more common in persons identifying as First Nations/Inuit (1.85, 95% CI 1.30, 2.62). No specific race/ethnicity factors were identified for methotrexate or cyclophosphamide, but relatively infrequent exposures limited precision.

Table 2. Determinants of drug exposures measured across time. Included in the model was an interaction term for time and adjustment mean SLEDAI-2K (for immunosuppressive exposure, RR 1.002, 95% CI 1.000, 1.003; for antimalarial use, RR 1.001, 95% CI 1.000, 1.002; for prednisone exposure, RR 0.998, 95% CI 0.996, 0.999). An interaction term was also included for time and DI (for prednisone use, RR 0.997, 95% CI 0.995, 0.999).

Variable	Any Immunosuppressive		Prednisone		Antimalarial	
	RR	95% CI	RR	95% CI	RR	95% CI
Women	0.87	0.65, 1.16	0.78	0.61, 0.99	1.01	0.89, 1.15
Age at diagnosis	0.99	0.98, 1.00	0.98	0.98, 0.99	0.99	0.98, 1.00
Urban residence	0.91	0.67, 1.23	1.18	0.92, 1.52	1.00	0.90, 1.12
SLE duration at baseline	0.98	0.97, 0.99	0.99	0.98, 1.00	0.99	0.99, 1.00
High school diploma	1.23	0.95, 1.59	0.93	0.74, 1.15	1.03	0.92, 1.15
Race (white is reference)						
Black	0.94	0.67, 1.31	1.46	1.18, 1.81	1.09	0.98, 1.22
Asian	1.39	1.02, 1.89	1.04	0.82, 1.32	1.01	0.91, 1.13
Aboriginal	2.09	1.43, 3.04	1.15	0.83, 1.58	1.01	0.86, 1.18
Other	1.22	0.55, 2.72	0.89	0.62, 1.28	1.02	0.87, 1.18
Adjusted mean SLEDAI-2K	1.05	1.03, 1.07	1.04	1.03, 1.06	0.99	0.98, 1.00
SLICC/ACR DI	1.07	1.01, 1.14	1.13	1.09, 1.16	1.01	0.99, 1.04

SLE: systemic lupus erythematosus; RR: relative risk; SLEDAI-2K: SLE Disease Activity Index 2000; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

All these findings were reproduced when adjustment for disease activity was limited to renal involvement.

DISCUSSION

Our study suggested very clear trends. It is hardly surprising that treatment with both immunosuppressive agents and prednisone is given to patients with most active disease. However, it seems that the presence of cumulative damage may also predict use of these agents, particularly earlier in the SLE course. Interestingly, antimalarial agents were not so clearly related to disease activity or damage, suggesting perhaps that these are used either more universally (that is, regardless of clinical severity) and/or that antimalarial agents are less likely than immunosuppressive agents to be tapered when disease becomes less active. These phenomena may appear intuitive, but they have not been previously studied or demonstrated in clinical practice. Our findings were reproduced when adjustment for disease activity was limited to renal involvement. We did not test if this was true for other organs, such as central nervous system (CNS) involvement, but isolated CNS activity was rare in our population.

The interaction terms showed that with time, cumulative disease activity became increasingly important as a correlate of immunosuppressive exposure, but not prednisone exposure. This would reflect aggressive use of both types of agents in the SLE course, with increasing focus on steroid-sparing agents as the years pass (even in the face of active disease). Our results suggest that patients with early damage are targeted for aggressive treatment with both steroids and immunosuppressants, although as time goes on, damage no longer is correlated with prednisone. This may all seem intuitive, but ours is the first portrayal of these clinical practice patterns.

The reasons behind different patterns of drug use among persons of different race/ethnicity, compared to whites, independent of disease activity or damage, may be more difficult to explain. Partly, this may be because of incomplete adjustment for disease activity, particularly nephritis, since clinical severity varies considerably according to race/ethnicity. Still, the findings remained apparent with adjustment for cumulative activity, as well as specifically for renal disease. It has been shown that blacks (independent of disease activity or damage) may be more resistant to the effects of agents such as cyclophosphamide^{8,9}; this may explain why blacks in our cohort were more likely to be exposed to prednisone than whites. Drug prescription/use may be affected by personal and cultural factors (e.g., patient preferences) not strictly measured in our sample. It should moreover be noted that our study did not account for potential non-adherence, which is at least as common in SLE as in any other chronic disease¹⁰. Some suggest that “ethnic minorities” including blacks may have lower adherence to “steroid-sparing” immunosuppressive agents¹¹ (which may be part of the reason why blacks in our sample were more likely to be taking prednisone than whites). Nonadherence that goes unacknowledged or unrecognized can lead to the addition of multiple drugs¹², and could be a potential mediator of some of our findings, although we were not able to investigate the hypothesis further in this particular study setting.

Adjusted for clinical factors including lupus activity and damage, persons who were older at the time of SLE diagnosis appeared to be less likely to be prescribed nonsteroid immunosuppressive agents, prednisone, or antimalarial agents. This could be because clinicians have more concern over medication-related effects and/or because of beliefs

that elderly-onset SLE is more benign. The latter belief may reflect an understanding that certain manifestations (e.g., nephritis) are less common in this demographic group^{13,14}. However, although some have suggested that disease activity tends to be lower in elderly-onset SLE, damage accrual may be greater¹⁵. Some have argued that the damage seen in this group is more related to age and/or other comorbidity than to SLE itself¹⁶.

We did not establish that residence (urban vs rural location) was itself a predictor of medication exposures. This may reflect the relatively universal access to care that presumably underlies Canada's "comprehensive" healthcare system, although certainly there is evidence that care provision does differ (for example, rural residents are more likely to have inpatient encounters)¹⁷. In part, our failure to find a difference may stem from the difficulty in defining the concept of urban versus rural, which encompasses not only population density, but access to tertiary care services and other resources. Such access-to-care issues are the focus of additional studies by our team members.

Ours is the first portrayal of clinical practice patterns in SLE, and offers interesting real-world insights. Further work, including efforts to determine how differing clinical approaches may influence outcome, is in progress.

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Correction

Medication Use in Systemic Lupus Erythematosus

Bernatsky S, Peschken C, Fortin PR, et al; Canadian Network for Improved Outcomes in Systemic Lupus Erythematosus (CaNIOS). Medication use in systemic lupus erythematosus. *J Rheumatology* 2010;38:271-4. The author name “Christi A. Pineau” should instead be Christian A. Pineau. We regret the error.

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