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Relationship between Prednisone, Lupus Activity and Permanent Organ Damage

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Abstract

Background—Corticosteroids are the mainstay for treatment of systemic lupus erythematosus (SLE). The potential role of corticosteroid use on the pathogenesis of permanent organ damage requires appropriate adjustment for confounding by disease activity. We estimate the effect of corticosteroids (prednisone dose) on permanent organ damage among persons with SLE.

Methods—We identified 525 incident SLE patients in the Hopkins Lupus Cohort. At each visit, clinical activity indices, laboratory data, and treatment were recorded. The study population was followed from the month after the first visit until June 29 2006, irreversible organ damage, death, loss to follow-up, or receipt of pulse methylprednisolone therapy. We estimated the effect of cumulative average dose of prednisone on organ damage using a marginal structural model to adjust for time-dependent confounding by indication due to SLE disease activity.

Findings—Compared with non prednisone use, the hazard ratio (95% confidence interval) of organ damage for prednisone was 1.16 (0.59, 2.20) for cumulative average doses >0–180 mg/month, 1.50 (0.67, 3.39) for >180–360 mg/month, 1.64 (0.67, 4.06) for >360–540 mg/month, and 2.51 (1.02, 6.19) for >540 mg/month. In contrast, standard Cox regression models estimated higher hazard ratios at all dose levels.

Interpretation—Our results suggest that low doses of prednisone do not result in a substantially increased risk of irreversible organ damage.

Keywords

causal modeling; marginal structural model; systemic lupus erythematosus; corticosteroid treatment; long-term prednisone therapy; permanent organ damage

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I, Mae Thamer, the first author state that I had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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BACKGROUND

SLE is a chronic systemic autoimmune disease of unknown etiology that is characterized by a relapsing-remitting course.¹ In the past 40 years, prognosis for patients with SLE has improved; the 10-year survival is now approximately 90%.¹ Despite improved survival rates, organ damage occurs in 50% of all patients within 5 years of the diagnosis of SLE.² Corticosteroids are the mainstay of therapy for SLE, with the route of administration and dosage schedule dependent on the severity and distribution of organ involvement. Corticosteroids have both anti-inflammatory and immunosuppressive actions in SLE; however, numerous adverse effects result from corticosteroid use itself. Some complications associated with corticosteroid therapy are reversible (e.g., obesity, diabetes, hypertension), while others including avascular necrosis, osteoporotic fractures, and cataracts represent irreversible damage.

Recent studies found an association between prednisone therapy and permanent organ damage.^{3,4,5} However, because high SLE disease activity leads independently to treatment with corticosteroids and to organ damage,⁶ the association observed in these studies might be explained by uncontrolled confounding by indication rather than by a true effect of prednisone use on organ damage. Further, because SLE disease activity is affected by prior prednisone use and is on the causal pathway between prednisone use and organ damage, standard statistical methods may fail to appropriately adjust for this confounding by indication even if disease severity were perfectly measured.⁷

We estimated the effect of prednisone therapy on organ damage in a study in which the indication for prednisone therapy was carefully measured. We adjusted for confounding by indication using inverse probability weighting of marginal structural models, a statistical method that appropriately adjusts for measured confounders affected by prior therapy.⁸

METHOD

Data source

The Hopkins Lupus Cohort is a prospective longitudinal study of lupus activity, organ damage, and quality of life in SLE patients⁹ who have been evaluated and treated by one of us (MP) for two decades.^{10,11} At each visit, clinical activity indices, laboratory data, and treatment are recorded. The cohort database is continually updated including sociodemographic information, medical and reproductive history, SLE complications, and treatment. The information regarding corticosteroid use and organ damage is recorded since the date of SLE diagnosis. The average daily dose of prednisone is recorded for each patient.

Patient selection criteria and study design

We identified 525 incident SLE patients who were diagnosed within 6 months of their first visit with MP. Each patient was followed from the month after the first visit (baseline) until June 29 2006, irreversible organ damage (141), death (12), loss to follow-up (defined as absence of visit for 1 ½ year or more) (200), or receipt of pulse methylprednisolone therapy, whichever occurred first. (Pulsed-dose methylprednisone treatment is an infrequent form of prednisone therapy and therefore our analysis focuses on oral prednisone therapy only.) Only 31 patients were censored because of pulse methylprednisolone therapy and including them in the analysis did not materially affect our findings. The mean study follow-up time was 58 months (4.8 years) and the maximum follow-up time was 227 months (18.9 years).

Study variables

The primary outcome of interest was a new diagnosis of organ damage during the follow-up. At each visit, irreversible organ damage was measured using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI). The SDI has 41 items in 12 domains which measure irreversible organ damage occurring since the onset of SLE.^{12,13}

We defined cumulative average prednisone dose for a given patient at a given month as the total number of milligrams of prednisone taken up to that month divided by the number of months. For simplicity of presentation, we categorized cumulative prednisone dose as follows: 0 mg/month, >0 – 180 mg/month, >180 – 360 mg/month, >360 – 540 mg/month, and >540 mg/month.

The main potential confounder was SLE disease activity. At each visit, SLE disease activity was measured as the average score from the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).¹⁴ Missing dates of SLE diagnosis (8.7% of cases) and organ damage (2.2% of cases) were assigned to baseline, and missing months of organ damage (16% of cases) were assigned to June of that year as in other studies.³

Statistical analysis

We estimated the effect of cumulative average log prednisone dose on time to first organ damage by fitting a time-varying Cox model. Because adding the time-varying confounders as covariates in the model may introduce bias,¹⁵ we adjusted for confounding by indication by weighting each subject in each risk set by the inverse of the estimated probability of having received his or her own treatment history. Unlike conventional methods for confounding adjustment that add the time-dependent confounders as covariates in the model, the weighted approach appropriately adjusts for measured time-dependent confounders that are affected by prior prednisone therapy (i.e., SLE disease activity). Our hazard ratio estimate can be interpreted as the net effect of prednisone dose only under the assumption of no unmeasured confounding at all times, as well as the conditions of positivity, consistency, and no misspecification of both the weighted Cox model and the models used to estimate the inverse probability weights (see below). These assumptions are less restrictive than those of conventional unweighted analyses, which require the absence of confounding by time-dependent covariates affected by previous treatment. Under the assumption listed above, the parameters from the weighted Cox model equal those of a marginal structural Cox model.¹⁶ The 95% confidence interval around the hazard (rate) ratio was based on a robust variance estimator.

The denominators of the inverse probability weights were estimated by fitting three nested models: 1) a logistic regression model to estimate the probability of a visit in each month of follow-up; 2) a logistic regression model to estimate the probability of receiving prednisone treatment among person-months with a visit; and 3) a linear regression model to estimate each patient's density (assumed to be normal) of log prednisone dose among person-months with a visit and with prednisone treatment. All models included the baseline variables age at SLE diagnosis, gender, race/ethnicity, SLE disease activity at baseline, organ damage score at baseline (although the official definition of SDI is damage *since* lupus diagnosis, we used organ damage events prior to diagnosis as a baseline measure of severity of illness), and prednisone dose at baseline; the time-varying covariate SLE disease activity score; and months since last visit as well as product terms between months since last visit and baseline variables. To adjust for potentially informative censoring, we also estimated the censoring weights using the predicted values from pooled logistic regression models. Both the prednisone treatment and censoring weights were stabilized,^{17,18} and their product was used

to fit the weighted regression model to estimate the risk of organ damage. The mean weight was 0.99 with a range of 0.01 – 10.0. Analyses were done with SAS (version 9.1).

Role of the funding source

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FINDINGS

Table 1 summarizes the characteristics of the 525 patients included in this study. Ninety percent were female, 56% were white, and 48% were not prescribed prednisone at their first visit. Sixty-one percent had no organ damage at their first visit, while the remaining 40% had 1 or more organ damage events prior to lupus diagnosis. Almost half of all patients (46%) had not been prescribed prednisone at one year after their first visit; by ten years, only 15% had never received prednisone (Table 2). Similarly, the proportion of patients who received middle range doses (i.e., >0 – 180 and >180 – 360 mg/months) increases over time. However, the proportion of patients receiving higher doses (especially a cumulative dose >540 mg/month) decreases over time. No patients survived for ten or more years with a cumulative prednisone dose of >540 mg/month (or a cumulative total dose of >64.8 grams). The higher the mean SLE disease activity score, the higher the average prednisone per month (Table 3) that was prescribed.

Of the 525 patients, 141 had an organ damage event during follow-up. Table 4 shows the distribution and hazard ratios and 95% confidence intervals (CI) of organ damage for several levels of cumulative average dose of prednisone compared with no prednisone use. Both the weighted and unweighted (conventionally-adjusted) models show that the risk of organ damage increases with dose. However, the weighted model that appropriately adjusts for measured confounders estimated a lower risk at all dose levels. In the weighted model, the hazard ratios ranged from 1.16 (0.59, 2.20) for >0–180 mg/month to 2.51 (1.02, 6.19) for >540 mg/month. In the unweighted model, the hazard ratios ranged from 2.01 (1.11, 3.63) for >0–180 mg/month to 4.10 (1.74, 9.65) for >540 mg/month.

Results in Table 4 did not materially change when we added the 8 patients who died before any evidence of organ damage as cases, when we used the most recent 3-month average of prednisone dose (versus the cumulative average from baseline), or when we controlled for pulse methylprednisolone therapy as a confounder (versus censoring patients) (see Table 5 for these results). Results were also similar when we assumed no organ damage at baseline for all patients (as whatever damage existed might not have been caused by lupus). We also conducted sensitivity analyses using different dose categories and without a log transformation of dose, and the conclusion was similar: clearly increased risk of organ damage for cumulative average doses greater than approximately 500 mg/month.

INTERPRETATION

Our findings suggest that the risk of irreversible organ damage increases with prednisone dose. Compared with no prednisone use, the increase in risk is small or inexistent for a cumulative average dose below 180 mg/month, and two-fold for a cumulative average dose greater than 540 mg/month, which is equivalent to a cumulative total dose of 19 grams in 3 years, 32.4 grams in 5 years or 64.8 grams in 10 years.

The increase in risk with higher prednisone doses might be explained by unmeasured confounding by indication if our measurements of severity were not able to fully capture the indications for high prednisone doses. However, we believe that the most important confounders were captured from the clinical and laboratory information that is recorded the Hopkins Lupus Cohort database. Furthermore, a better measurement of confounding by indication would have resulted in an even lower risk for low prednisone doses.

In an earlier analysis, Gladman et al. also examined the pattern of accumulation of damage in an inception cohort of patients with SLE followed yearly for at least 15 years, and identified organ damage that might be related to corticosteroid therapy.⁴ The authors concluded that a significant proportion of the damage both early and late could be attributed to corticosteroid therapy, although the majority of damage occurred at 15 years. Our results also suggest that since organ damage varies widely depending on the dose of corticosteroids used and the extent of lupus disease,³ corticosteroids might have important mechanisms of action apart from anti-inflammatory and immunosuppressive actions in SLE. Therefore, effective treatment for SLE patients receiving prednisone doses above a cumulative threshold of 540 mg/month must require new corticosteroid-sparing therapies that treat disease activity while minimizing organ damage due to high cumulative prednisone exposure.

In contrast to our weighted estimates, our standard models show a much higher risk of organ damage for all levels of prednisone dose. Previous studies,^{3,4,6,11} also analyzed using conventional methods, had similar findings. Relevant differences between the weighted and conventional estimates have been also found in other clinical areas,^{19,20,21,22,23} and can be explained by the inability of standard methods to appropriately adjust for time-dependent confounders that are affected by prior treatment.

Due to the low number of organ damage events, we had to aggregate all organ damage events. Future research to determine the relative contribution of corticosteroids to the pathogenesis of specific types of organ damage is warranted because some studies have suggested that certain types of organ damage might be more likely to be caused by prednisone dose. Zonana-Nacach et al, for example, found that cumulative prednisone dose was significantly associated with the development of osteoporosis fractures (RR=2.5, 95% CI 1.7, 3.7), symptomatic coronary artery disease (RR=1.7, 95% CI 1.1, 2.5) and cataracts (RR=1.9, 95% CI 1.4, 2.5).³ Each additional 2-month exposure to high-dose prednisone was associated with a 1.2 fold increase in the risk of both avascular necrosis (95% CI 1.1, 1.4) and stroke (95% CI 1.0, 1.5).

In conclusion, our results suggest that low doses of prednisone do not result in a substantially increased risk of irreversible organ damage. Clinicians treating lupus patients might consider either tapering prednisone or introducing other immunosuppressive therapies to “steroid spare.” A better understanding of the relationship between corticosteroid therapy, SLE disease activity, and organ damage will hopefully provide a basis for improving current treatment guidelines for SLE, and highlight the urgent need to develop corticosteroid-sparing therapies.

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REFERENCES

1. Goldblatt F, Isenberg DA. New therapies for systemic lupus erythematosus. Clin Exp Immunology. 2005; 140:205–212.

2. Karlson EW, Daltroy LH, Lew RA, Wright EA, et al. The relationship between of socioeconomic status, race and modifiable risk factors to outcomes in patients with systemic lupus erythematosus. *Arthritis Rheum.* 1997; 40:47–56. [PubMed: 9008599]
3. Zonana-Nacach, a; Barr, SG.; Magder, LS.; Petri, M. Damage in systemic lupus erythematosus and its association with corticosteroids. *Arthritis Rheum.* 2000; 43:1801–1808. [PubMed: 10943870]
4. Gladman DD, Urowitz MB, Rahman P, Ibanez D, Tam LS. Accrual of organ damage over time in patients with systemic lupus erythematosus. *J Rheumatol.* 2003; 30:1955–1959. [PubMed: 12966597]
5. Toloza SM, Roseman JM, Alarcón GS, et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA): XXII. Predictors of time to the occurrence of initial damage. *Arthritis Rheum.* 2004; 50:3177–3186. [PubMed: 15476246]
6. Nossent JC. LDICC/ACR damage index in Afro-Caribbean patients with systemic lupus erythematosus: changes in and relationship to disease activity, corticosteroid therapy and prognosis. *J Rheumatol.* 1998; 25:654–659. [PubMed: 9558165]
7. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology.* 2004; 15:615–625. [PubMed: 15308962]
8. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the joint effect of non randomized treatments. *J Am Stat Assoc.* 2001; 96:440–448.
9. Petri M. Hopkins Lupus Cohort. 1999 update. *Rheum Dis Clin North Am.* 2000; 26:199–213. [PubMed: 10768209]
10. Petri M. Lupus in Baltimore: evidence-based 'clinical pearls' from the Hopkins Lupus Cohort. *Lupus.* 2005; 14:970–973. [PubMed: 16425579]
11. Petri M, Barr SG, Zonana-Nach A, Magder L. Measures of disease activity, damage, and health status: the Hopkins Lupus Cohort experience. *J Rheumatol.* 1999; 26:502–503. [PubMed: 9972995]
12. Gladman D, Ginzler E, Goldsmith C, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. *Arthritis Rheum.* 1996; 39:363–369. [PubMed: 8607884]
13. Gladman DD, Urowitz MB, Goldsmith CH, et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. *Arthritis Rheum.* 1997; 40:809–813. [PubMed: 9153540]
14. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum.* 1992; 35:630–640. [PubMed: 1599520]
15. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology.* 2004; 15:615–625. [PubMed: 15308962]
16. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology.* 2000; 11:550–560. [PubMed: 10955408]
17. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men. *Epidemiology.* 2000; 11:561–570. [PubMed: 10955409]
18. Hernán MA, Brumback B, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med.* 2002; 21:1689–1709. [PubMed: 12111906]
19. Hernán MA, Brumback B, Robins JM. Marginal structural models to estimate the causal effect of Zidovudine on the survival of HIV-positive men. *Epidemiology.* 2000; 11:561–570. [PubMed: 10955409]
20. Choi HK, Hernán MA, Seeger JD, Robins JM, Wolfe F. Methotrexate and mortality in patients with rheumatoid arthritis: a prospective study. *Lancet.* 2002; 359:1173–1177. [PubMed: 11955534]
21. Cook NR, Cole SR, Hennekens CH. Use of a marginal structural model to determine the effect of aspirin on cardiovascular mortality in the physicians' health study. *Am J Epidemiology.* 2002; 155:1045–1053.

22. Hernan MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med.* 2002; 21:689–1709. [PubMed: 11870810]
23. Cole SR, Hernan MA, Robins JM, et al. Effect of highly active antiretroviral therapy on time to acquired immunodeficiency syndrome or death using marginal structural models. *Am J Epidemiology.* 2003; 158:687–694.

Table 1

Demographic and clinical characteristics of study population (n = 525).

	N	%
Gender		
F	472	89.9
M	53	10.1
Race/Ethnicity		
White	294	56.0
African American	196	37.3
Other	35	6.7
Age at SLE diagnosis, years		
10 to 25	113	21.5
26 to 40	230	43.8
41 to 76	182	34.7
Year of SLE diagnosis		
Before 1990	64	12.2
1990 to 1999	236	45.0
2000 to 2006	225	42.9
Prednisone dose at first visit (mg/month)		
0	254	48.4
>0–180	62	11.8
>180 –360	48	9.1
>360 –540	34	6.5
>540	127	24.2
Lupus disease activity at first visit (SLEDAI score)		
0	153	29.1
1 to 2	137	26.1
3 to 4	112	21.3
≥5	123	23.4
Organ damage score at first visit (SDI index)		
0	318	60.6
1	118	22.5
2	52	9.9
≥3	37	7.0

SLEDAI = Systemic Lupus Erythematosus Disease Activity Index

SDI = Systemic Lupus International Collaborating Clinics / American College of Rheumatology Damage Index

Table 2

Percentage of patients by cumulative prednisone dose by duration of SLE.

	Years after first visit for SLE			
	1	3	5	10
Cumulative prednisone dose (mg/month)				
0	45.7 (0)	30.6 (0)	28.1 (0)	15.4 (0)
>0–180	15.1 (0–2.2)	34.7 (0–6.5)	40.4 (0–10.8)	57.7 (0–21.6)
>180–360	17.8 (2.2–4.3)	19.4 (6.5–14.0)	21.1 (10.8–21.6)	23.1 (21.6–43.2)
>360–540	8.9 (4.3–6.5)	9.9 (14.0–19.0)	8.8 (21.6–32.4)	3.9 (43.2–64.8)
>540	12.6 (>6.5)	5.4 (>19)	1.8 (>32.4)	0 (>64.8)
<i>no. of patients</i>	<i>438</i>	<i>222</i>	<i>114</i>	<i>26</i>

() indicate cumulative prednisone dose in grams.

Table 3

Lupus disease activity and prescribed prednisone dose during the study period (n = 21,801 patient months).

Mean SLE activity and (SLEDAI)	Prednisone dose (mg/month)	% of patient months
0	95.5	42.6
1 to 2	120.9	25.3
3 to 4	194.0	17.5
>=5	317.6	14.6

Table 4

Hazard ratio of organ damage (n = 141) by cumulative average dose of prednisone.

Cumulative average prednisone dose (mg/month)	% of patient months	no. of events	Unadjusted model		Conventionally-adjusted model*		Weighted model*	
			HR	95 % CI	HR	95 % CI	HR	95 % CI
0	35.9	34	<i>Ref</i>		<i>Ref</i>		<i>Ref</i>	
>0-180	37.0	49	1.58	1.00 2.50	2.01	1.11 3.63	1.16	0.59 2.29
>180-360	14.9	29	2.10	1.24 3.55	2.46	1.17 5.16	1.50	0.67 3.39
>360-540	6.7	18	3.04	1.67 5.53	3.54	1.55 8.12	1.64	0.67 4.06
>540	5.5	21	4.19	2.35 7.47	4.10	1.74 9.65	2.51	1.02 6.19

* Adjusted for age, sex, race/ethnicity, baseline prednisone dose, baseline SLE activity, baseline organ damage, and time-varying covariates.

HR: hazard ratio; CI: confidence interval

Table 5

Secondary analyses estimating hazard ratio of organ damage by cumulative prednisone dose.

Cumulative average prednisone dose (outcome death or organ damage)	Unadjusted model		Conventionally-adjusted model		Weighted model	
	HR	95% CI	HR	95% CI	HR	95% CI
0 dose	<i>Ref</i>		<i>Ref</i>		<i>Ref</i>	
>0–180 mg/month	1.44	0.92 2.24	1.78	1.00 3.18	1.06	0.55 2.06
>180–360 mg/month	2.13	1.29 3.51	2.39	1.17 4.87	1.53	0.69 3.38
>360–540 mg/month	2.93	1.64 5.21	3.33	1.49 7.47	1.58	0.65 3.84
>540 mg/month	4.22	2.43 7.32	4.08	1.78 9.34	2.63	1.09 6.32
Average 3-month prednisone dose (censoring at pulse methylprednisolone therapy) ~	Unadjusted model		Conventionally-adjusted model		Weighted model	
0 dose	HR	95% CI	HR	95% CI	HR	95% CI
>0–180 mg/month	<i>Ref</i>		<i>Ref</i>		<i>Ref</i>	
>180–360 mg/month	1.73	1.01 2.95	1.45	0.81 2.59	1.14	0.65 1.98
>360–540 mg/month	2.28	1.22 4.25	1.83	0.95 3.50	1.67	0.88 3.18
>540 mg/month	1.57	0.64 3.86	1.24	0.49 3.16	0.91	0.33 2.47
Cumulative average prednisone dose (controlling for pulse methylprednisolone therapy) *	Unadjusted model		Conventionally-adjusted model		Weighted model	
0 dose	HR	95% CI	HR	95% CI	HR	95% CI
>0–180 mg/month	<i>Ref</i>		<i>Ref</i>		<i>Ref</i>	
>180–360 mg/month	1.93	1.16 3.22	1.78	1.01 3.16	1.01	0.53 1.93
>360–540 mg/month	2.87	1.61 5.11	3.49	1.56 7.78	1.21	0.55 2.63
>540 mg/month	4.24	2.44 7.35	4.36	1.90 9.99	1.51	0.64 3.57
					2.49	1.06 5.89

~ adjusted for previous cumulative prednisone dose up to last three months.

* total organ damage events = 150.