

Risk of Serious Infection for Patients with Systemic Lupus Erythematosus Starting Glucocorticoids with or without Antimalarials

Lisa J. Herrinton, Liyan Liu, Robert Goldfien, M. Alex Michaels, and Trung N. Tran

ABSTRACT. Objective. To compare serious infection risk for systemic lupus erythematosus (SLE) patients starting glucocorticoids (GC), antimalarials (AM), or their combination.

Methods. We conducted a new-user, historical cohort study, Kaiser Permanente Northern California, 1997–2013. Cox proportional hazards analysis was used to calculate adjusted HR and 95% CI.

Results. The study included 3030 patients with SLE followed an average of 4 years. Compared with patients starting AM without GC (9 infections/1461 patient-yrs), the HR for the risk of infection was 3.9 (95% CI 1.7–9.2) for those starting GC \leq 15 mg/day without AM (14 infections/252 patient-yrs), while it was 0.0 (0 infections/128 patient-yrs) for those starting the combination. We split the 14 patients with a serious infection and with GC $<$ 15 mg/day into 2 groups: $<$ 7.5 and \geq 7.5–15 mg/day. The HR for $<$ 7.5 mg/day was 4.6 (95% CI 1.8–11.4) and for \geq 7.5–15 mg/day, 3.1 (95% CI 1.0–9.7). For patients starting GC $>$ 15 mg/day (reflecting more severe SLE), the risk of infection was nearly the same for the combination of GC and AM (9 infections/135 patient-yrs) and GC alone (41 infections/460 patient-yrs), but the combination users had evidence of more severe disease. Patients with SLE had a 6- to 7-fold greater risk of serious infection than the general population.

Conclusion. Our findings suggest that the benefits of AM treatment for SLE may extend to preventing serious infections. Although the study included $>$ 3000 patients, the statistical power to examine GC dosages $<$ 15 mg/day was poor. (First Release July 1 2016; J Rheumatol 2016;43:1503–9; doi:10.3899/jrheum.150671)

Key Indexing Terms:

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Systemic lupus erythematosus (SLE) primarily affects women of childbearing age and is associated with significant adverse events, with infections and cardiovascular disease the leading causes of death^{1,2,3}. Antimalarials (AM) such as hydroxychloroquine (HCQ) and immunosuppressive medica-

tions are frequently used to treat SLE. Evidence suggests that use of GC contributes to the increased risk of serious infections, while the effect of AM on risk of infection is not fully documented^{4,5,6,7,8,9,10,11,12,13}. As a consequence, physicians vary in their prescribing habits, and patient continuation of HCQ is poor in some settings¹⁴.

We conducted a new-user, historical cohort study of Kaiser Permanente Northern California members to estimate the relationship of SLE and its treatments on risk of serious infections.

MATERIALS AND METHODS

Our study was approved by the local institutional review board at the Kaiser Foundation Research Institute.

Overview and setting. The study was set in the 3.5 million membership of the Kaiser Permanente Medical Care Program, Northern California. The program provides prepaid, comprehensive, integrated care to one-third of the population in its service areas. Kaiser Permanente is a capitated, staff model plan. Compared with patients whose medical insurance is through other companies, Kaiser Permanente members have greater racial diversity, lower mean income, lower college attainment, more obesity, and similar smoking habits¹⁵.

We used methods developed for comparative effectiveness and safety research¹⁶ to compare serious infection risk in patients with SLE who were new users of GC, AM, or their combination. To define new use, we required a clearance period without use of a study drug before the start of observation

From the Division of Research, Kaiser Permanente Northern California; Department of Rheumatology, The Permanente Medical Group, Oakland, California; Patient Safety Department, AstraZeneca/MedImmune; Observational Research Center, AstraZeneca, Gaithersburg, Maryland, USA.

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L.J. Herrinton, PhD, Division of Research, Kaiser Permanente Northern California; L. Liu, MD, Division of Research, Kaiser Permanente Northern California; R. Goldfien, MD, Department of Rheumatology, The Permanente Medical Group; M.A. Michaels, MD, Patient Safety Department, AstraZeneca/MedImmune; T.N. Tran, MD, PhD, Observational Research Center, AstraZeneca.

Address correspondence to L.J. Herrinton, Division of Research, Kaiser Permanente, 2000 Broadway Ave., Oakland, California 94612, USA.

E-mail: Lisa.Herrinton@kp.org

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for outcomes. Compared with prevalent-user designs, new-user designs more closely resemble clinical trials in that patients have no immediate history of exposure to the study treatments before the start of followup. However, implementation of the clearance period, typically 6–12 months, can greatly reduce the sample size. For this reason, we conducted a second, prevalent-user analysis (not requiring a clearance period), data for which is presented online as Supplementary Material at jrheum.org.

We compared new users of AM with new users of GC monotherapy and new users of combination therapy (GC plus AM), with stratification by dosage of GC (≤ 15 mg/day and > 15 mg/day). We considered 15 mg/day the cutpoint to provide adequate study power to evaluate milder SLE. Although the approved disease indications for AM and lower dosages of GC are not exactly the same, in community practice, the regimens are accepted alternative treatments. For this reason, we compared (1) AM monotherapy with (2) GC ≤ 15 mg/day monotherapy, and (3) the combination of AM plus GC ≤ 15 mg/day. We separately compared GC > 15 mg/day monotherapy with the combination of GC > 15 mg/day and AM, to focus analysis on patients with more severe disease.

Study population. Kaiser Permanente members aged ≥ 18 years during 1996–2013, who had ≥ 1 physician diagnosis of SLE [International Classification of Disease, Volume 9 (ICD-9) codes 710.0], were included in the study. We required the inpatient visits for SLE to have been recorded as a primary or secondary diagnosis, and we required the outpatient diagnosis to have been recorded by a specialist in rheumatology, nephrology, or dermatology. We also required a minimum of 12 months of continuous enrollment preceding the first dispensing of AM or GC. For GC dosages ≥ 7.5 mg/day, we required only 1 dispensing. For GC dosages < 7.5 mg/day, which are given for many diseases, we required a minimum of 2 dispensings. The 12-month continuous enrollment period enabled assessment of baseline covariates and exclusion of patients with a history of serious infection or cancer (ICD-9 140-209). Because of this condition, the first date of entry into the study was January 1, 1997.

In addition to the comparison between new users of AM and GC, we also compared the risk of serious infections for patients in the SLE cohort with risk of serious infections for controls selected from general Kaiser Permanente members without SLE. Controls were required to have had 12 months of continuous enrollment, and they were individually matched at a ratio of 10:1 to the patients with SLE by age, sex, and year of entry into the study. For this analysis, we examined risk of infection for patients with SLE during the first period of current use of AM or GC and during the first period of non-use of any SLE-related drug.

Data collection. Data were obtained from Kaiser Permanente North California's computerized clinical information systems and the electronic medical records, which provide detailed, comprehensive information about patient demographics, diagnoses, encounters, procedures, and therapies. The data are primarily used to provide clinical care and only secondarily to generate insurance claims.

Serious infections were defined from ICD-9 codes (Supplementary Table 1). We included patients who had infection recorded as a primary discharge diagnosis and were hospitalized for at least 3 days with their infections, or were treated with intravenous anti-infective agents, or had infection recorded as the cause of death. Death information was available from the California Death Master File through 2012, in state mortality data, and through 2013 in Kaiser Permanente mortality data.

Patient demographics were obtained from membership data. Race/ethnicity was defined as Asian, African American, Hispanic, white, and other. The pharmacy information system is the gold standard for gathering inpatient and outpatient information. We recorded dispensings, dosages, and days of supply for AM and GC drugs, and the immunosuppressants mycophenolate mofetil (MMF), azathioprine (AZA), methotrexate (MTX), cyclophosphamide (CYC), cyclosporine (CSA), and belimumab. SLE-related visits were ascertained from inpatient and outpatient ICD-9 diagnoses recorded during the year before cohort entry. From these data, we computed the Charlson comorbidity index (continuous), history of cardio-

vascular (yes/no) and renal disease (yes/no), and the number of ambulatory visits (continuous) in the year before cohort entry to specialists in rheumatology, nephrology, pulmonology, and neurology. Laboratory data were accessed to obtain the most recent information, preceding cohort entry, on serum creatinine, hematocrit, and white blood cell counts.

To characterize the patients, we also ascertained any past positive laboratory result recorded in the computerized data (including results recorded before the start of the 12-month continuous enrollment period) for complement C3 and C4, antinuclear antibody (ANA), anti-dsDNA, antiphospholipid antibody, anti-Sm, anti-Ro or La, and rheumatoid factor; typically, these tests are requested by physicians during periods of disease activity.

Exposure assessment. A treatment episode was defined as a period of use of a drug regimen with a precisely defined start date^{17,18}. To prevent immortal time bias¹⁹, patients were required to have had the SLE diagnosis recorded before the dates of initiation of their first treatment episode. A treatment episode ended when the patient switched to a new regimen, did not have the agent dispensed again within 30 days after the supply of the drug ended, or received a diagnosis for a serious infection. The pharmacy variable days-supply was used to estimate the intended duration of each dispensing, and the patient was given a 30-day grace period to refill the dispensing. Thus, duration of use was defined as the date of dispensing plus days-supply plus 30-day grace period. If the patient received a new dispensing of the medication before the days-supply was exhausted, the excess supply was carried over. If patients were dispensed new drugs before the supplies of the preceding drugs had been exhausted, they were assumed to have had added a concomitant drug, which was defined as a new regimen.

We allowed patients to contribute more than 1 treatment episode (and accounted for this in the analysis). All treatment episodes were mutually exclusive in time. We required a 6-month clearance period, without AM or GC treatment, before the start of a new qualifying treatment episode.

Data analysis. For each treatment episode, followup began on the date of initiation of a treatment episode and continued for a maximum of 1 year. Followup ended on the date of the first occurrence of serious infection, Day 365, the treatment episode end date, a diagnosis of cancer (ICD-9 140-209), disenrollment, death, or the end of the study (December 31, 2013), whichever occurred first. Patients using GC who switched their dosages between the 2 exposure categories (≤ 15 mg/day; > 15 mg/day) were censored on the date of switch. We followed the patients for a maximum of 365 days to enhance the validity of the study by limiting the effect of time-varying covariates^{20,21,22}.

The crude incidence rate was computed using the number of eligible infections in the numerator and patient-years of followup in the denominator. Cox proportional hazards analysis was used to estimate the HR, after adjustment for confounding factors.

The following were examined as potential confounding factors: age (continuous), sex, and race/ethnicity (5 classes); year of cohort entry; Charlson comorbidity index (continuous), which identifies both comorbidities and SLE-related complications; history of renal disease (ICD-9 580-599); serum creatinine (low, normal), hematocrit (low, normal, high), white blood cell count (low, normal, high); and current use of other immunosuppressants (i.e., MMF, AZA, MTX, CYC, CSA, and belimumab; any/none). Potential confounding factors were included in the Cox proportional hazards analysis if they were considered clinically important by the study rheumatologist, were associated with the treatment group in the univariate analysis, or, when included in the Cox model, resulted in a substantive change to the HR.

We used a robust sandwich estimator that accounted for clustering of infections within patients to estimate the 95% CI²³. We compared the risk of serious infection in patients with SLE to risk in the general health plan membership, after adjustment for age, sex, and race/ethnicity.

RESULTS

The final cohort for analysis was composed of 3030 new users who contributed 5490 treatment episodes (Supple-

Table 1. Demographics and comorbidities of 3030 patients in relation to glucocorticoid (GC) and antimalarial (AM) treatment used during the first eligible treatment episode.

Characteristic	Milder SLE		More Severe SLE		
	AM Only, n = 1271 (42%)	AM + GC, ≤ 15 mg/day, n = 165 (5%)	GC ≤ 15 mg/day Only, n = 262 (9%)	AM + GC, > 15 mg/day, n = 277 (9%)	GC > 15 mg/day Only, n = 1055 (35%)
Year of cohort entry					
1997–2000	22	32	28	24	24
2001–2004	21	20	23	22	22
2005–2008	24	28	23	24	22
2009–2013	33	20	26	30	32
Age at cohort entry, yrs					
≤ 44	52	58	43	65	45
45–65	39	35	41	30	39
> 65	9	7	16	5	16
Sex					
Male	8	11	13	13	12
Female	92	89	87	87	88
Race-ethnicity					
Asian	15	28	16	27	18
African American	18	16	23	21	19
Hispanic	22	21	21	18	24
White	38	30	36	29	36
Other	7	5	4	5	3
Charlson Index ≥ 2	18	16	36	25	33
Positive laboratory test results					
ANA	93	91	89	93	89
Anti-dsDNA	89	89	82	92	85
APL*	40	30	34	44	41
Anti-Sm	63	54	47	60	53
Anti-Ro (SSA)/Anti-La (SSB)	64	52	55	66	55
RF	70	64	61	70	62
Use of other immunosuppressants**	9	21	36	24	24
History of renal disease	12	16	24	22	30
Test result, mean (SD)					
Serum creatinine	0.8 (0.7)	0.9 (0.7)	1.2 (1.6)	0.9 (0.7)	1.3 (1.8)
Hematocrit	38.2 (4.0)	37.2 (4.3)	37.0 (5.2)	35.8 (5.2)	36.3 (5.5)
WBC	5.7 (2.2)	5.6 (2.3)	6.7 (2.9)	5.7 (2.9)	7.0 (3.9)

*Includes positivity to dilute Russell's viper venom time and partial thromboplastin time. **Mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, cyclosporine, and belimumab. SLE: systemic lupus erythematosus; ANA: antinuclear antibody; APL: antiphospholipid antibody; RF: rheumatoid factor; WBC: white blood cell count.

mentary Figure 1). The average length of observation for defining treatment episodes was 4.0 years per patient (total, 12,120 patient-yrs), with 2435 patient-years (20%) involving treatment with AM, GC, or the combination. The majority of patients with SLE were positive for ANA or dsDNA.

AM were used by 85% of patients not using GC or using GC ≤ 15 mg/day. In contrast, for those using GC > 15 mg/day, only 21% used AM (Table 1).

Risk of serious infections for patients with SLE compared with general health plan members. For current users of AM and GC, the rate of serious infection was 2.6 per 100 patient-years, compared with the rate in the general health plan population of 0.4 per 100 patient-years, after accounting for differences in age, sex, and race/ethnicity corresponding to an adjusted HR of 6.6 (95% CI 4.5–9.5). This HR includes the effects of the disease and its treatment (Table 2). The HR

comparing risk of infection in patients with SLE without current drug use (AM, GC, or other SLE-related treatments) to that in the general health plan members was 6.0 (95% CI 4.2–8.5).

Comparison of risk of serious infection for new users of GC compared with new users of AM. Compared with patients with SLE starting AM without GC (9 infections/1461 patient-yrs), the HR was 3.9 (95% CI 1.7–9.2) for those starting GC ≤ 15 mg/day without AM (14 infections/252 patient-yrs; average GC dosage, 8 mg/day), while no infections were observed for patients (128 patient-yrs) with exposure to the combination of AM plus GC ≤ 15 mg/day (HR 0.0; 95% CI, 0.0–0.8; Table 3; and Supplementary Table 2). During the maximum 1-year followup period, the average durations of use of the 3 treatment regimens were 169 days for AM without GC, 134 days for GC ≤ 15 mg/day without AM, and 145 days for the combination of AM plus GC

Table 2. Adjusted HR for the relationship of SLE with at least 1 serious infection, 3030 patients with SLE and 30,300 general members of Kaiser Permanente (KP).

Cohort	No. Patients with ≥ 1 Serious Infection	Patient-yrs	Crude Incidence Rate per 100 Patient-yrs	Adjusted HR*	95% CI
KP general population	103	27,901	0.4	1.0	Ref.
SLE with current AM and GC exposure	39	1526	2.6	6.6	4.5–9.5
SLE without current SLE drug use**	52	2090	2.5	6.0	4.2–8.5

*Adjusted for age (continuous), sex (M/F), and race/ethnicity (5 classes). **For this analysis, we examined risk of infection for patients with SLE during the first period of current use of AM or GC, and during the first period of non-use of any SLE-related drug. Nonusers included only patients who were not current users of any SLE-related drug on the day of the risk set or during the preceding 30 days, including AM, GC, and the following medications: mycophenolate mofetil, azathioprine, methotrexate, cyclophosphamide, cyclosporine, and belimumab. SLE: systemic lupus erythematosus; AM: antimalarials; GC: glucocorticoids.

Table 3. Adjusted HR for the relationship of serious infection with new use of glucocorticoid (GC) compared with antimalarial (AM) therapy.

Current Medication*	No. Serious Infections	Patient-yrs	Crude Incidence Rate per 100 Patient-yrs	Average Dosage, mg/day		Adjusted HR**	95% CI
				AM	GC		
Milder SLE							
AM without GC	9	1461	0.6	360 \pm 148	—	1.0	Ref.
GC \leq 15 mg/day without AM	14	252	5.6	—	8 \pm 3	3.9	1.7–9.2
GC \leq 15 mg/day + AM	0	128	0.0	367 \pm 147	7 \pm 3	0.0	0.0–0.8
More severe SLE							
GC > 15 mg/day without AM	41	460	8.9	—	41 \pm 27	1.0	Ref.
GC > 15 mg/day + AM	9	135	6.6	373 \pm 107	37 \pm 37	1.1	0.5–2.3

*For each drug regimen, patients contributed to risk sets formed while the patients were current users of the drug regimens and during the 30 days following their last days of drug supply. **Adjusted for age (continuous), race/ethnicity (white/Asian, African American, Hispanic), cohort entry year (continuous), Charlson Comorbidity Index (continuous), renal disease (yes/no), hematocrit (≤ 33 , 34–39, ≥ 40), and current therapy using other immunosuppressants (yes, no). SLE: systemic lupus erythematosus.

≤ 15 mg/day. In an exploratory analysis, we re-ran this model after splitting the 14 patients with a serious infection and with GC < 15 mg/day into 2 smaller groups: < 7.5 mg/day and ≥ 7.5 –15 mg/day. The HR for the < 7.5 mg/day subgroup was 4.6 (95% CI 1.8–11.4) and for the ≥ 7.5 –15 mg/day subgroup was 3.1 (95% CI 1.0–9.7). The wide and overlapping CI of the HR indicate the lack of power in the new-user analysis to differentiate between < 7.5 mg/d and ≥ 7.5 –15 mg/day GC in contrast with AM.

The HR for those starting GC > 15 mg/day with AM (9 infections/135 patient-years) was 1.1 (95% CI 0.5–2.3) compared with those starting GC > 15 mg/day without AM (41 infections/460 patient-yrs; Table 3; and Supplementary Table 2). As in Table 4, about 30% of patients with serious infections who started GC > 15 mg/day without AM used a third SLE-related drug, compared with 77% of patients with serious infection cases who started the combination GC > 15 mg/day plus AM. The analysis was adjusted for use of a third SLE-related drug, but because of sample size limitations, the adjustment was coded simply as any third drug versus none. During the maximum 1-year followup period, the average durations of use were 111 days for GC > 15 mg/day with AM and 83 days for GC > 15 mg/day without AM.

Table 4. Concomitant SLE-related drug use among new users of glucocorticoid (GC) > 15 mg/day who developed a serious infection. Data are percentages.

Concomitant Medication	GC > 15 mg/day with AM, n = 9	GC > 15 mg/day without AM, n = 41
None	22	71
Azathioprine	44	10
Mycophenolate mofetil	33	7
Cyclophosphamide	0	7
Methotrexate	0	2
Cyclosporine	0	2
Total	100	100

AM: antimalarials.

As provided in Supplementary Table 2, risk of serious infection was increased for patients with renal disease (HR 5.3, 95% CI 2.8–10.2), hematocrit below 34% (HR 2.6, 95% CI 1.5–4.5), Hispanics (HR 1.8, 95% CI 1.1–3.1), and possibly African Americans (HR 1.9, 95% CI 1.0–3.3).

The results of the prevalent user analysis are provided in the online Supplementary Material and are consistent with the new-user analysis presented here.

DISCUSSION

In this community-based study of 3030 patients with SLE, we observed a 6- to 7-fold increased risk of serious infections in patients with SLE compared with general members of the Kaiser Permanente population, including those with and without current use of SLE-related medications. We further observed that SLE patients starting GC \leq 15 mg/day without AM had a 4-fold greater risk of serious infection than did patients with SLE starting AM treatment, and had a greater risk than patients with SLE starting GC \leq 15 mg/day combined with AM. Results for the 2 smaller subgroups (those receiving \leq 7.5 mg/day and those receiving $>$ 7.5–15 mg/day) were also consistent with the results of the \leq 15 mg/day subgroup without AM. However, the small sample size of each group did not permit comparison between them. In the prevalent-user analysis (online Supplementary Material), which had a greater sample size, patients with SLE who took current GC monotherapy at all dosages were also found to have had a greater risk of serious infections than those with current AM monotherapy (Supplementary Table A1), which confirmed findings of the new-user analysis. Among patients using GC \leq 15 mg/day, the average duration of AM use was similar across exposure groups and was long enough (134 to 169 days) to produce a clinical benefit²⁴.

The results were more complex for new users of GC $>$ 15 mg/day, for whom the risk of serious infections appeared to be similar between those starting and not starting concomitant AM. These patients likely had more severe SLE. Those who combined GC $>$ 15 mg/day with AM had greater use of other SLE-related drugs, such as AZA and MMF, than those who used GC $>$ 15 mg/day without AM (78% vs 30%). Although we attempted to adjust for current use of any other SLE-related drug, residual confounding may have occurred as a result of differences in disease severity, adverse effects of the additional SLE-related drugs, or both. We could not further adjust for disease severity, agent, dosage, or duration of drug treatment, because the number of exposed study patients was too few, despite the large base population.

AM therapy is known to reduce disease flares and improve renal disease in SLE^{25,26,27}, and could reduce infection risk through these mechanisms. In addition, AM are known to have antiinfective effects beyond their antiparasitic effects¹. For SLE with nephritis, the American College of Rheumatology clinical practice guideline recommends the use of AM as background therapy for all cases lacking a contraindication (Level C evidence)²⁸. A guideline for SLE without nephritis has not been published, but the use of AM has evolved since the 1990s, and they are now used as background therapy for all patients with SLE who do not have a contraindication of allergy or retinal disease²⁹. Nonetheless, AM therapy is not always prescribed, and when it is, the patient does not always adhere to treatment. The rate of nonadherence in SLE has been reported to range from 3% to 76% in 1 review¹⁴, while in our health plan, AM treatment was used about 50% of the time.

The HR we observed of 6.6 (95% CI 4.5–9.5) for the association of SLE with risk of serious infection is consistent with findings from Bernatsky and colleagues⁹, whose clinic-based study included 9547 patients with SLE, with 64 having infection listed as the cause of death. The study reported unadjusted standardized mortality ratios of 5.0 (95% CI 3.7–6.7) for infection including septicemia and 2.6 (95% CI 1.6–4.0) for pneumonia, through comparison of deaths of patients with SLE to those in the underlying population. The inverse association we observed between AM therapy and risk of serious infection was similar to the findings of Feldman and colleagues¹³, who used the Medicaid Analytic eXtract database (2000–06) to identify 33,565 patients with SLE. In that study, the HR comparing drug users to never users was 1.5 (95% CI 1.4–1.6) for GC (any dosage) and 0.73 (95% CI 0.68–0.77) for HCQ, the most predominant AM.

Our study is also consistent with the findings from Tektonidou and colleagues¹⁰, who analyzed rates of hospitalization for infection using 9000 patients with SLE who had infection and who were included in the National Inpatient Sample data (1996–2011). Relative risks ranged from 5.7 (95% CI 5.5–6.0) for pneumonia to 9.8 (95% CI 9.1–10.7) for urinary tract infection, although the patients with SLE included in the hospital-based study likely had more severe disease than those in our community-based study. In addition, the study is consistent with a population-based inception cohort that observed a 2.5-fold (95% CI 1.8–3.4) increased risk of herpes zoster³⁰. A small clinic-based cohort study observed that AM protected against major infections (OR 0.1, 95% CI 0.0–0.2)⁶. AM were associated with lower mortality in the LUMINA cohort (OR 0.3, 95% CI 0.1–0.9)⁸, and Grupo Latino Americano de Estudio del Lupus Eritematoso cohort (HR 0.62, 95% CI 0.39–0.99)¹². Moreover, the dose-response relationship of GC with risk of infection is consistent with prior reports³¹.

We observed that patients with SLE without current use of medication were at a striking 6-fold increased risk of serious infection (95% CI 4.2–8.5), which could result from their underlying SLE or factors that predispose to discontinuation of therapy, such as frailty.

Earlier studies of SLE have been set in clinic populations^{4,5,6}, have used inpatient data only¹⁰, or have ascertained infections using death certificates only^{7,8,9,10,12}. Referral to specialized clinics often could not be well-characterized, resulting in the potential for referral bias. In studies of death certificates, cause-of-death coding can be imprecise, with appreciable numbers of infection-related deaths attributed to the proximate cause of SLE³².

A key limitation of our study was the lack of detail on the severity and activity of SLE. Our community-based clinicians do not record disease activity into an established measure such as the Systemic Lupus Erythematosus Disease Activity Index score. Nor could we adjust for SLE-related laboratory test results, because they were performed infrequently during

the 12-month continuous enrollment period preceding the start of followup. We used a control group of patients taking GC to control somewhat for differences in disease severity and activity between AM users and nonusers. In addition, we compared users of combination therapy to users of GC monotherapy, and we compared the dosage and duration of therapy among these users. We separated patients using GC ≤ 15 and > 15 mg/day, with the idea that patients treated with ≤ 15 mg/d have milder disease. However, choosing GC dosage involves the physician's judgment and other factors. GC dosage is only a proxy for disease activity, and while we expect correlation between GC dosage and disease activity, the correlation is not perfect. Neither could we adjust for laboratory results or lung involvement, because too few patients with SLE had laboratory testing or specialist visits during the year preceding the start of followup, when confounding factors were obtained. Consequently, differences in SLE activity between exposure groups may partly explain the study findings.

The choice of using 15 mg/day as the cutoff point for high- and low-dosage GC in the new-user analysis was primarily to obtain adequate statistical power, and the findings may vary subject to the choice of dosage cutoff. Finally, although we required a specialist's diagnosis of SLE, study resources did not permit validation of its diagnosis, and it is possible that some cases were misdiagnosed or had comorbid rheumatoid arthritis.

The Kaiser Permanente membership is broadly representative of the underlying population of insured patients in Northern California¹⁵, and community-based populations typically include patients with less severe disease than would be observed for referral populations. Consistent with the other population-based studies, most of the patients with SLE were women, with an overrepresentation of African Americans^{33,34}.

Risk of serious infection was increased 6- to 7-fold for patients with SLE, including those without current use of medications, compared with the general population. This risk was increased with use of GC compared with those who started AM alone. AM are known to reduce the risk of nephritis in SLE and are recommended as background therapy for patients with SLE nephritis. The results presented here give evidence that AM might reduce the risk of infection, supporting greater use of AM in SLE, including those with and without nephritis.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

REFERENCES

1. Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. *Lupus* 2013;22:1286–94.
2. Nikpour M, Gladman DD, Urowitz MB. Premature coronary heart disease in systemic lupus erythematosus: what risk factors do we understand? *Lupus* 2013;22:1243–50.
3. Ippolito A, Petri M. An update on mortality in systemic lupus erythematosus. *Clin Exp Rheumatol* 2008;5 Suppl 51:S72–9.
4. Bosch X, Guilabert A, Pallarés L, Cerveral R, Ramos-Casals M, Bové A, et al. Infections in systemic lupus erythematosus: a prospective and controlled study of 110 patients. *Lupus* 2006;15:584–9.
5. Gladman DD, Hussain F, Ibanez D, Urowitz MB. The nature and outcome of infection in systemic lupus erythematosus. *Lupus* 2002;11:234–9.
6. Ruiz-Irastorza G, Olivares N, Ruiz-Arruza I, Martínez-Berrioxoa A, Egurbide MV, Aguirre C. Predictors of major infections in systemic lupus erythematosus. *Arthritis Res Ther* 2009;11:R109.
7. Alarcón GS, McGwin NG Jr., Bastian HM, Roseman J, Lisse J, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups. VIII. Predictors of early mortality in the LUMINA cohort. *Arthritis Care Res* 2001;45:191–202.
8. Alarcón GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alén J, Bastian HM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (LUMINA L). *Ann Rheum Dis* 2007;66:1168–72.
9. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Gladman DD, et al. Mortality in systemic lupus erythematosus. *Arthritis Rheum* 2006;54:2550–7.
10. Tektonidou MG, Wang Z, Dasgupta A, Ward MM. Burden of serious infections in adults with systemic lupus erythematosus. A national population-based study, 1996–2011. *Arthritis Care Res* 2015;67:1078–85.
11. Jacobsen S, Petersen J, Ullman S, Junker P, Voss A, Rasmussen JM, et al. Mortality and causes of death of 513 Danish patients with systemic lupus erythematosus. *Scand J Rheumatol* 1999;28:75–80.
12. Shinjo SK, Bonfá E, Wojdyla D, Borba EF, Ramirez LA, Scherbarth HR, et al, for the Grupo Latino Americano de Estudio del Lupus Eritematoso (Gladel). AM treatment may have a time-dependent effect on lupus survival: data from a multinational Latin American inception cohort. *Arthritis Rheum* 2010;62:855–62.
13. Feldman CH, Hiraki LT, Winkelmayer WC, Marty FM, Franklin JM, Kim SC, et al. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. *Arthritis Rheumatol* 2015;67:1577–85.
14. Costedoat-Chalemeau N, Pouchot J, Guettrot-Imbert G, Le Guern V, Leros G, Marra D, et al. Adherence to treatment in systemic lupus erythematosus patients. *Best Pract Res Clin Rheumatol* 2013;27:329–40.
15. Gordon NP. How does the adult Kaiser Permanente membership in Northern California compare with the larger community? [Internet. Accessed April 27, 2016.] Available from: [www.dor.kaiser.org/external/uploadedFiles/content/research/mhs/_2011_Revised_Site/Documents_Special_Reports/comparison_kaiser_vs_nonKaiser_adults_kpnc\(1\).pdf](http://www.dor.kaiser.org/external/uploadedFiles/content/research/mhs/_2011_Revised_Site/Documents_Special_Reports/comparison_kaiser_vs_nonKaiser_adults_kpnc(1).pdf)
16. Stürmer T, Jonsson Funk M, Poole C, Brookhart MA. Nonexperimental comparative effectiveness research using linked healthcare databases. *Epidemiology* 2011;22:298–301.
17. Herrinton LJ, Curtis JR, Chen L, Liu L, Delzell E, Lewis JD, et al. Study design for a comprehensive assessment of biologic safety using multiple healthcare data systems. *Pharmacoepidemiol Drug Saf* 2011;20:1199–209.

18. Grijalva CG, Chen L, Delzell E, Baddley JW, Beukelman T, Winthrop KL, et al. Initiation of tumor necrosis factor- α antagonists and the risk of hospitalization for infection in patients with autoimmune disease. *JAMA* 2011;306:2331–9.
19. Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf* 2007;16:241–9.
20. Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ; British Society for Rheumatology Biologics Register Control Centre Consortium; British Society for Rheumatology Biologics Register. Serious infection following anti-tumor necrosis factor alpha therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum* 2007;56:2896–904.
21. Dixon WG, Watson K, Lunt M, Hyrich KL, Silman AJ, Symmons DP; British Society for Rheumatology Biologics Register. Rates of serious infection, including site specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2006; 54:2368–76.
22. Curtis JR, Xi J, Patkar N, Xie A, Saag KG, Martin C. Drug-specific and time-dependent risks of bacterial infection among patients with rheumatoid arthritis who were exposed to tumor necrosis factor alpha antagonists. *Arthritis Rheum* 2007;56:4226–7.
23. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. *J Am Stat Assoc* 1989;84:1974–8.
24. Tett SE, Cutler DJ, Day RO, Brown KF. Bioavailability of hydroxychloroquine tablets in healthy volunteers. *Br J Clin Pharmacol* 1989;27:771–9.
25. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. *N Engl J Med* 1991;324:150–4.
26. Tsakonas E, Joseph L, Esdaile JM, Choquette D, Sénécal JL, Cividino A, et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. *Lupus* 1998;7:80–5.
27. Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody-positive patients. *Curr Rheumatol Rep* 2011;13:77–80.
28. Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al; American College of Rheumatology. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res* 2012;64:797–808.
29. Sugai DY, Gustafson CJ, De Luca JF, Davis SA, Jorizzo JL, O'Rourke KS, et al. Trends in the outpatient medication management of lupus erythematosus in the United States. *J Drugs Dermatol* 2014;13:545–52.
30. Chen HH, Chen YM, Chen TJ, Lan JL, Lin CH, Chen DY. Risk of herpes zoster in patients with systemic lupus erythematosus: a three-year follow-up study using a nationwide population-based cohort. *Clinics* 2011;67:1177–82.
31. Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. *Ann Rheum Dis* 2012;71:1128–33.
32. Abu-Shakra M, Novack V. Mortality and multiple causes of death in systemic lupus erythematosus — role of the death certificate. *J Rheumatol* 2012;39:458–60.
33. Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The incidence and prevalence of systemic lupus erythematosus, 2002–2004: The Georgia Lupus Registry. *Arthritis Rheumatol* 2014;66:357–68.
34. Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. *Arthritis Rheumatol* 2014;66:369–78.