Online supplement for Risk of Serious Infection in Patients with Systemic Lupus Erythematosus Starting Glucocorticoids with or without Antimalarials, *The Journal of Rheumatology*, doi:10.3899/150671

PREVALENT USER ANALYSIS

The prevalent user analysis examined a wide range of drugs, comparing current users (new and prevalent) to SLE patients without current use of any drug. Belimumab, cyclophosphamide, and cyclosporine were rare during the study period and therefore were not examined as main effects.

Because the effective sample size was greater, we used a somewhat more specific definition of eligibility for the prevalent user analysis. We required ≥2 physician diagnoses (inpatient or outpatient) of SLE (ICD-9 codes 710.0). In addition, we required patients to have either a positive ANA or a positive double-stranded (ds) DNA test indicating SLE (83% had a positive test); and we required patients to have had at least one dispensing of any SLE-related drug, rather than antimalarials or glucocorticoids alone.

Patients entered follow-up on their cohort entry date. Follow up ended at the first occurrence of serious infection, diagnoses of rheumatoid arthritis (ICD-9 714) or cancer (ICD-9 140-209), disenrollment, death, or the end of the study (December 31, 2012). A key difference between the new user and prevalent user design was that the prevalent user analysis followed patients for infection across multiple years and multiple drug exposures, while the new user design follows patients for a maximum of one year after the start of each new episode of antimalarials or glucorticoids.

In the prevalent user analysis, SLE patients with current use of antimalarials had a lower risk of infection than those with no current use of any SLE medication (HR was 0.4, 95% CI 0.3–0.6).

With glucorticoid monotherapy, risk increased with dosage from no increase with <7.5 mg/d (HR 1.0, 95% CI 0.6–1.6) to a 50% increase with glucorticoid of 7.5 to 15 mg/d (HR 1.5, 95% CI 1.0–2.3) to a 70% increase with glucorticoids >15 mg/d (HR 1.7, 95% CI 1.2-2.4) (Table A.1). Risks associated with disease-modifying antirheumatic drugs (DMARDs), used as monotherapies, were not appreciably different from risk with no current medication, although these comparisons were limited by small numbers.

Risk was similar for SLE patients without current medication exposure and those using combination glucocorticoids ≤15 mg/d plus antimalarials or immunosuppressants. The HR for the combination of glucocorticoids >15 mg/d with azathioprine, compared with patients not using current medications, was 4.6 (95% CI 2.8–7.7), while the HRs for the combination of glucocorticoids >15 mg/d with mycophenolate mofetil and methotrexate had somewhat wide confidence intervals and were similar to the HR for glucocorticoids >15 mg/d used as monotherapy.

Prevalent user studies can be biased because long-term drug users typically are healthier than non-users[1]. On the other hand, drug use can serve as a marker of active SLE, although we adjusted for relevant specialist visits and laboratory tests. The findings of this prevalent user analysis are similar to those of the new-user analysis presented in the main body of this report, suggesting that these biases were small relative to the main effects of SLE, glucocorticoids, and antimalarials on risk of serious infection. They are also similar to a prevalent user analysis of 40,678 SLE patients in the Medicaid Analytic Extract database (2000–2006), in which antimalarial users had a reduced risk of infection compared to non-users (HR 0.73, 95% CI 0.68–

0.77).[2] Furthermore, the dose-response relationship of glucocorticoids on risk of infection is consistent with prior reports[3–5], demonstrating the external validity of the study. The consistency of the prevalent and new user analyses, together with the greater statistical efficiency of the prevalent user analysis, strengthens the evidence that antimalarials reduce the risk of infection. We recommend greater use of antimalarials in SLE patients with and without nephritis.

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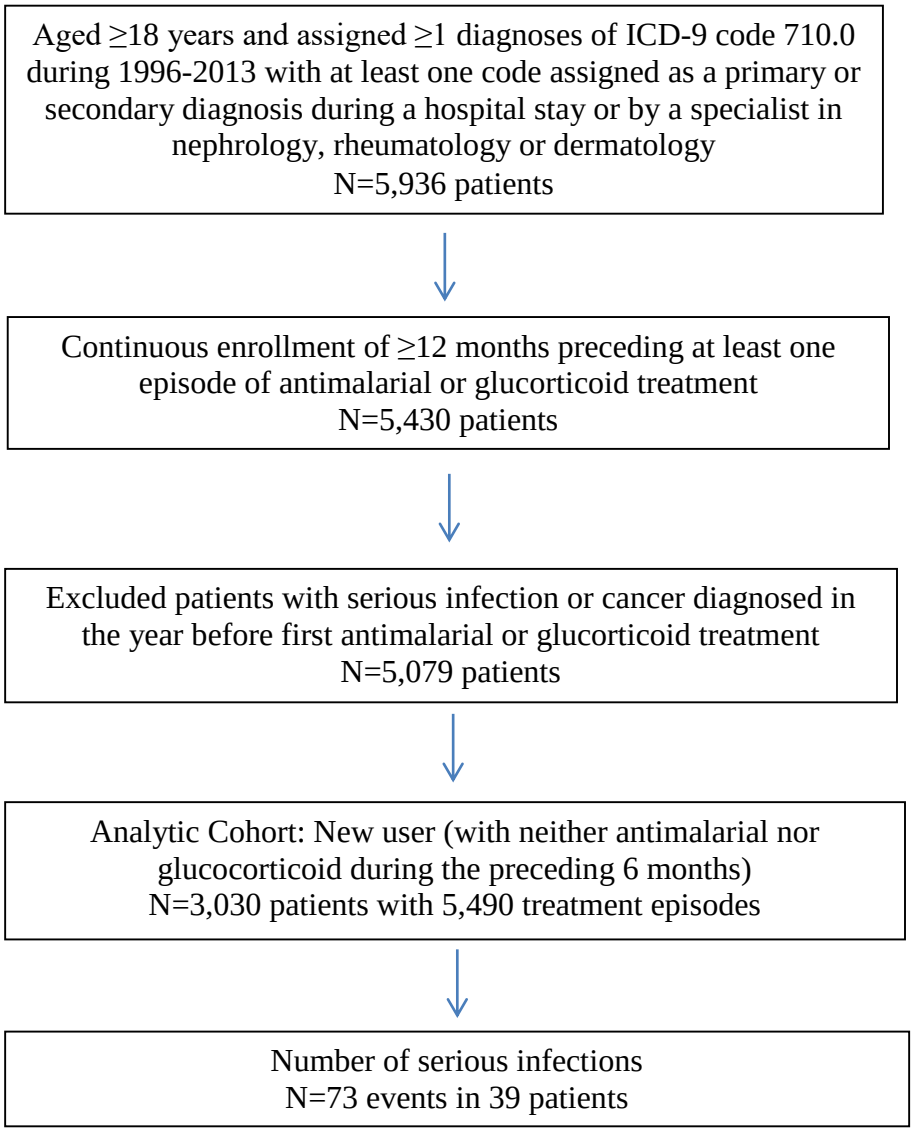
Supplementary Table 1. ICD-9 codes included in the operational definition of infection.

Category	**ICD-9 codes**
Intestinal infectious diseases	001-009
Zoonotic and other bacterial diseases	021, 032.81, 033–035, 036.0, 036, 036.42, 038, 040, 041, 526.4, 528.4, 540, 566, 567, 569.5, 569.61, 572
Syphillis and other venereal diseases	090–099
Spirochetal diseases	100
Infectious diseases of the CNS	049.0, 320, 321, 323, 324
Disorders of the eye and adnexa	372.0, 376.0
Otitis media and mastoiditis	381.5, 382, 383.0, 383, 383.9
Endocarditis and myocarditis	421, 422.92
Infectious diseases of the respiratory system excluding pneumonia and influenza	461, 462, 466, 472, 473, 475, 478.21, 478.22, 478.24, 510, 513
Pneumonia	481, 482, 483, 485, 486,
Infectious diseases of the genitourinary system	590, 597, 599.0, 601.2, 608.4, 611.0, 614.3, 614.4
Infectious diseases of skin	680, 681, 682, 684, 686, 686.8, 686.9
Infection related to arthropathy, fasciitis, and osteomyelitis	711, 728.86, 730
Bacteremia	790.7
Post-traumatic wound infection	958.3
Device-associated infections	996.6
Post-operative infection	998.5

ICD: International Classification of Disease; CNS: central nervous system.

Supplementary Figure 1. Study population



ICD: International Classification of Disease.

Supplementary Table 2. New-user analysis; full-model results. Adjusted hazard ratio for the relationship of serious infection with new use of glucorticoid (GC) compared with antimalarial (AM) therapy.

Variable	HR	95% CI
Antimalarial monotherapy	1.0 (reference)	
GC ≤15 mg/d + antimalarial	0.0	0.0 – 0.8
GC ≤15 mg/d monotherapy	3.9	1.7 – 9.2
GC >15 mg/d + antimalarial	4.5	1.7 – 11.8
GC >15 mg/d monotherapy	4.2	2.0 – 8.8
Year (continuous)	1.0	1.0 – 1.0
Age (per year)	1.0	1.0 – 1.0
Charlson (per unit)	1.2	1.0 – 1.3
Other SLE therapy (y/n)	1.1	0.7 – 1.9
Renal disease (y/n)	5.3	2.8 – 10.2
African American	1.9	1.0 – 3.3
Hispanic	1.8	1.1 – 3.1
White or Asian	1.0 (reference)	
Hematocrit <34%	2.6	1.5 – 4.5
Hematocrit 34–39%	1.0 (reference)	
Hematocrit ≥40%	1.7	0.9 – 3.2

SLE: systemic lupus erythematosus.

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Supplementary Table A1. Prevalent user analysis: Adjusted* hazard ratio for the relationship of current use of monotherapy with risk of serious infection among patients with SLE.**

Current medication	No. of serious infections	Patient-years	Crude incidence rate (IR), %	Adjusted HR,%	95% CI
SLE without current medication	146	7,555	1.9	1.0	Ref.
SLE with current monotherapy					
Antimalarial	58	4,584	1.3	0.4	0.3–0.6
GC <7.5 mg/d	13	453	4.6	1.0	0.6–1.6
GC 7.5-15 mg/d	31	602	5.0	1.5	1.0–2.3
GC >15 mg/d	89	1,016	8.8	1.7	1.2–2.4
Azathioprine	16	542	3.0	1.2	0.7–1.9
Mycophenolate mofetil	16	519	3.1	1.2	0.8–1.9
Methotrexate	4	274	1.5	0.6	0.2–1.8
GC ≤15 mg/d combined with…					
Antimalarial	13	662	2.0	1.0	0.6–1.6
Azathioprine	12	258	4.7	1.2	0.6–2.3
Mycophenolate mofetil	7	259	2.7	1.0	0.7–1.6
Methotrexate	4	130	3.1	1.3	0.4–4.3
GC >15 mg/d combined with …***					
AM monotherapy	0	6	0	0	—
Azathioprine	34	208	16.4	4.6	2.8–7.7
Mycophenolate mofetil	15	238	6.3	1.6	0.9–3.0
Methotrexate	7	67	10.5	2.5	0.9–6.7

*Adjusted for each of the other drug regimens, age (continuous), sex (M/F), race/ethnicity (five classes); cohort entry year; Charlson comorbidity index (continuous), and renal disease (yes/no ICD-9 580-599); the number of visits (continuous) in the year before cohort entry to rheumatology, nephrology, pulmonology, neurology, and hematology; serum creatinine (continuous), hematocrit (continuous), white blood cell count (continuous), complement C3 and C4 (continuous); and number of positive tests (continuous) from among ANA, anti-dsDNA, APL, anti-Sm, anti-Ro or La, and RF. **For each drug regimen, patients contributed to risk sets formed while the patients were a current user of the drug regimens and during the 30 days following their last days of drug supply. Otherwise, they contributed to risk sets "without current medication. ***Glucocorticoids (GC) >15 mg/d combined with azathioprine included 7 patient-years (no events) with antimalarial exposure; combined with mycophenolate mofetil, 3 patient-years (no events) with antimalarial exposure; and combined with methotrexate, 4 patient-years (no events) with antimalarial exposure.