Serious Infection Rates among Patients with Systemic Lupus Erythematosus Receiving Corticosteroids and Immunosuppressants

Candace H. Feldman, MD, MPH1,2
Linda T. Hiraki, MD, SM, ScD3
Wolfgang Winkelmayer, MD, ScD4
Francisco M. Marty, MD, MS5
Jun Liu, MD, MPH6
Jessica M. Franklin, PhD6
Daniel H. Solomon, MD, MPH1,6
Seoyoung C. Kim, MD, MSCE1,2,6
Karen H. Costenbader, MD, MPH1,2

1Brigham and Women’s Hospital, Division of Rheumatology, 2Harvard School of Public Health, 3Hospital for Sick Children, Division of Rheumatology, 4Stanford School of Medicine, Division of Nephrology, 5Brigham and Women’s Hospital, Division of Infectious Disease, 6Brigham and Women’s Hospital, Division of Pharmacoepidemiology and Pharmacoeconomics

Evidence Based Medicine


Infections and Medication Use

• Previous RCTs and small academic cohort studies describe increased infection rates in SLE associated with corticosteroids and other immunosuppressants
• Prior studies limited by:
  – small sample sizes
  – exclusions by disease severity
  – restrictions on concurrent medication use
  – short follow-up
  – self-reported data
  – primary focus on drug efficacy
• Precedent in RA to use nationwide administrative databases to examine infection risk factors, but no parallel large cohort studies to date in SLE

Aim

• To examine the sociodemographics and incidence rates of serious infections requiring hospitalization in a nationwide cohort of SLE and lupus nephritis patients newly starting SLE-specific medications

Infections in SLE and LN Patients

• Serious infections are a leading cause of hospitalization and mortality in SLE patients
  – Up to 50% have a severe infection during disease course
• Lupus nephritis (LN) patients may be particularly vulnerable
• Likely related both to impaired immune function and to immunosuppressant use
• Little known about the sociodemographic distribution of serious infections in SLE and LN patients
• Many serious bacterial, fungal, viral and mycobacterial infections described in SLE patients, but few population-based studies with power to examine incidence rates in setting of medication use

Disclosures

• None

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Methods: Study Population

- Medicaid Analytic eXtract (MAX): billing claims and demographics for all Medicaid enrollees from 47 states and Washington, DC from 2000-2006
- Medicaid is largest public health insurance program in U.S., covering >60 million low-income individuals

Methods: Patient Identification

- Prevalent SLE
  - Defined as age 18-65 with ≥3 ICD-9 codes for SLE (710.0) each ≥30 days apart from hospital discharge diagnoses or physician visit claims
- Prevalent lupus nephritis (LN)
  - Defined by ≥2 ICD-9 codes for nephritis, proteinuria and/or renal failure, on or after SLE diagnosis and ≥30 days apart
  - PPV 80%


Methods: New Users

- Patients identified with prevalent SLE or LN with ≥6 months of continuous enrollment with no use of SLE-specific drug during that period “new users”:
  - Hydroxychloroquine (HCQ) alone
  - Oral or intravenous corticosteroids (CS) + HCQ
  - Immunosuppressants (IS): mycophenolate mofetil, mycophenolic acid, oral or intravenous cyclophosphamide, azathioprine, cyclosporine, or tacrolimus + HCQ
  - CS + IS simultaneously + HCQ
  - New use of CS, IS, or CS+IS regardless of preexisting HCQ use

Methods: Covariates

- Demographics
  - Age and sex
  - Race/ethnicity (White, African American, Hispanic, Asian, Native American)
  - U.S. geographic region
- Area-level socioeconomic status (SES)
  - Previously validated county-level composite measure using U.S. Census variables at the ZIP code level
- SLE-specific risk adjustment index
  - A SLE-specific severity of illness index using ICD-9 codes for comorbidities; superior to Charlson index in stratifying SLE patients by in-hospital mortality risk


Methods: Outcome Definition

- Serious infections requiring hospitalization
- Defined using ICD-9 discharge diagnoses:
  - Bacterial: cellulitis, endocarditis, pneumonia, pyelonephritis, septic arthritis, osteomyelitis, bacteremia, listeriosis
  - Viral: cytomegalovirus, influenza, herpes zoster
  - Fungal: Systemic candidiasis, cryptococcosis, aspergillosis, histoplasmosis, pneumocystosis
  - Mycobacterial: TB, atypical mycobacteria
- Previously validated in an administrative database (PPV>80%)

Methods: Assessment of Outcome

- Cohort of SLE and LN new users of HCQ, CS, IS, or CS+IS
- Exposure lag and extension periods of 7 days each
- Censored after first infection, drug switch, death, disenrollment or end of follow-up period
Stratified serious infections requiring hospitalization by medication use, infection subtype and sociodemographic factors
• Calculated incidence rates (IR) of serious infections and incident rate ratios (IRR) with 95% CI adjusting for covariates, using Poisson regression

Methods: Statistical Analyses

Results: Serious Infections
• 28,803 SLE patients (23,671 person-years follow-up)
  - 3,502 (12.2%) with serious infections
    • 93% Bacterial
    • 4% Fungal
    • 2% Viral
    • 1% Mycobacterial
• 5,140 LN patients (3,600 person-years follow-up)
  - 1,348 (26.2%) with serious infections
    • 92% Bacterial
    • 5% Fungal
    • 3% Viral
    • 1% Mycobacterial
• Predominant infections
  • Bacterial- pneumonia, cellulitis and bacteremia; fungal-systemic candidiasis; viral- herpes zoster; mycobacterial-tuberculosis

Results: Baseline Characteristics

Incident Rates of All Serious Infections

Sociodemographics of Infections

Adjusted IRRs by Sociodemographic Group

* Incidence rates (IR) per 100 person-years
** Incidence rate ratios (IRR) adjusted for age, sex, race/ethnicity, region, area SES, and SLE-specific index
Results Summary

- Significant burden of serious infections requiring hospitalization: 12.2% of SLE patients and 26.2% of LN patients; predominately bacterial infections
  - Prevalence highest among 51-64 year-olds, Whites, African Americans, Native Americans, patients from lower SES areas and with higher SLE-specific risk adjustment indices
- Incidence rates of serious infection highest among CS users
  - > 20 infections/100 person-years among SLE patients
  - > 40 infections/100 person-years among LN patients
- In SLE patients, 4.2 times higher rate, and in LN a 2.6 times higher rate of infections among CS users compared to HCQ
  - Infection rates among SLE patients on IS were 1.5 times higher and among LN patients on CS+IS, 2.9 times higher than those on HCQ alone

Limitations

- Confounding by indication and contraindication
- No clinical information available on disease activity
- Possible misclassification of drugs and exposure risk windows, however minimized given new use design
- Separate IS drugs were not investigated individually
- Relatively short follow-up time among IS users and IS and CS combined users
- Low income population with high burden of disease; may not be globally generalizable

Conclusions

- In this large, nationwide, diverse cohort of SLE patients, we found a significant burden of serious infections, particularly bacterial, and among patients with LN
- First documentation of infection rates in a SLE cohort this size; found to be strikingly high
  - Compared to RA patients on CS in a similar size cohort, we found nearly 5 times higher IRs among SLE patients and 10 times higher IRs in those with LN
- Demonstrated an increased rate of infection among SLE new users of IS, and SLE and LN new users of CS+IS
- Further research needed to examine infection risk by specific IS drug, and by infection subtype

Future Directions

- Propensity score-adjusted analyses to compare incidence rates of serious infections by specific medication use
- Further assessment of corticosteroid use according to administration route, dose and duration
- Examination of medication switchers in addition to new users

Thanks

- Mentors: Dr. Karen Costenbader, Dr. Daniel Solomon, Dr. Seoyoung Kim
- Funded by the Lupus Foundation Career Development Award and the NIH-NIAMS T32 AR007530
SLE Characteristics by Medication Use

<table>
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<tr>
<th></th>
<th>HCQ (n=8,016)</th>
<th>CS (n=12,136)</th>
<th>IS (n=3,165)</th>
<th>CS+IS (n=1,486)</th>
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<tbody>
<tr>
<td>Age- mean (SD)</td>
<td>39.7 (13.1)</td>
<td>38.9 (12.3)</td>
<td>38.1 (12.6)</td>
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<td>Follow-up, mean months (SD)</td>
<td>10.8 (14.4)</td>
<td>10.9 (15.4)</td>
<td>5 (8.2)</td>
<td>3 (3.7)</td>
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<tr>
<td>Sex- N (%):</td>
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<tr>
<td>Female</td>
<td>7576 (94.5)</td>
<td>15116 (93.7)</td>
<td>2910 (91.9)</td>
<td>104 (7.4)</td>
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<td>Race/Ethnicity</td>
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<tr>
<td>White</td>
<td>3052 (38.1)</td>
<td>5489 (34.6)</td>
<td>1105 (34.9)</td>
<td>371 (25)</td>
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<td>African American</td>
<td>2881 (35.9)</td>
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<td>1139 (35.9)</td>
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<td>Hispanic</td>
<td>1206 (15)</td>
<td>2361 (14.5)</td>
<td>544 (16.2)</td>
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<td>Asian</td>
<td>149 (4.4)</td>
<td>672 (4.2)</td>
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<td>Native American</td>
<td>100 (1.3)</td>
<td>237 (1.5)</td>
<td>66 (2.1)</td>
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<td>Region</td>
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<td>Northeast</td>
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<td>6653 (41.2)</td>
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<td>West</td>
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<td>2651 (16.4)</td>
<td>821 (25.9)</td>
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<tr>
<td>Midwest</td>
<td>1159 (14.5)</td>
<td>487 (15.4)</td>
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<td>Area SES</td>
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<tr>
<td>High</td>
<td>3877 (50)</td>
<td>7462 (49)</td>
<td>1536 (52)</td>
<td>867 (61.8)</td>
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<td>Low</td>
<td>3680 (50)</td>
<td>7046 (51)</td>
<td>1409 (48)</td>
<td>525 (38.2)</td>
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LN Characteristics by Medication Use

<table>
<thead>
<tr>
<th></th>
<th>HCQ (n=807)</th>
<th>CS (n=3,272)</th>
<th>IS (n=665)</th>
<th>CS+IS (n=396)</th>
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<tbody>
<tr>
<td>Age- mean (SD)</td>
<td>36.6 (11.3)</td>
<td>34.4 (12.8)</td>
<td>32.9 (12.5)</td>
<td>29.9 (11.2)</td>
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<tr>
<td>Follow-up, mean months (SD)</td>
<td>7.7 (11.4)</td>
<td>10.1 (13.6)</td>
<td>4.3 (6.7)</td>
<td>3.1 (1.7)</td>
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<tr>
<td>Sex- N (%):</td>
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<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>739 (91.6)</td>
<td>2949 (90.1)</td>
<td>599 (90.1)</td>
<td>350 (88.4)</td>
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<td>Race/Ethnicity</td>
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<tr>
<td>White</td>
<td>291 (37.1)</td>
<td>709 (21.7)</td>
<td>132 (19.9)</td>
<td>65 (16.4)</td>
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<td>African American</td>
<td>353 (43.7)</td>
<td>1650 (50.4)</td>
<td>286 (40)</td>
<td>178 (45)</td>
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<td>Hispanic</td>
<td>125 (15.5)</td>
<td>538 (16.4)</td>
<td>135 (20.3)</td>
<td>83 (21)</td>
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<tr>
<td>Asian</td>
<td>52 (6.4)</td>
<td>101 (3.8)</td>
<td>60 (9)</td>
<td>19 (9.9)</td>
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<tr>
<td>Native American</td>
<td>13 (1.6)</td>
<td>44 (1.3)</td>
<td>15 (2.3)</td>
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<td>699 (21.4)</td>
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<tr>
<td>South</td>
<td>307 (38)</td>
<td>1345 (41.1)</td>
<td>261 (39.3)</td>
<td>131 (34.6)</td>
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<td>West</td>
<td>207 (25.7)</td>
<td>662 (20.2)</td>
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<td>Midwest</td>
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<tr>
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<td>296 (47.5)</td>
<td>147 (38.7)</td>
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