Published in final edited form as:

Lupus. 2019 July ; 28(8): 977–985. doi:10.1177/0961203319856088.

Real-world electronic health record identifies antimalarial underprescribing in patients with lupus nephritis

Wenlu W Xiong, MD¹, JB Boone, MD², Lee Wheless, MD, PhD³, Cecilia P. Chung, MD, MPH², Leslie J. Crofford, MD², and April Barnado, MD, MSCI²

¹Department of Medicine, Rush University Medical Center, Chicago, Illinois, USA

²Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

³Department of Dermatology, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Summary

Antimalarials (AMs) reduce disease activity and improve survival in patients with systemic lupus erythematosus (SLE), but studies have reported low AM prescribing frequencies. Using a real-world electronic health record (EHR) cohort, we examined if patient or provider characteristics impacted AM prescribing. We identified 977 SLE cases, 94% of whom were ever prescribed an AM. Older patients and patients with SLE nephritis were less likely to be on AMs. Current age (OR = 0.97, $p < 0.001$) and nephritis (OR = 0.16, $p < 0.001$) were both significantly associated with ever AM use after adjustment for sex and race. Of the 244 SLE nephritis cases, only 63% were currently on AMs. SLE nephritis subjects who were currently prescribed AMs were more likely to be followed by a rheumatologist than a nephrologist and less likely to have undergone dialysis or renal transplant (all $p < 0.001$). Non-current vs. current SLE nephritis AM users had higher serum creatinine ($p < 0.001$), higher urine protein ($p = 0.05$), and lower hemoglobin levels ($p < 0.01$). As AMs reduce disease damage and improve survival in patients with SLE, our results demonstrate an opportunity to target future efforts to improve prescribing rates among multi-specialty providers.

Keywords

systemic lupus erythematosus; electronic health records; antimalarials; lupus nephritis

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multi-system, autoimmune disease that can cause significant morbidity and mortality. Antimalarials (AMs) reduce disease activity with most studies showing a 50% reduction in disease activity.^{1–10} AMs improve survival^{11–13} with one large US cohort study showing a significantly higher mortality rate of 17% in patients not treated with AMs compared to 5% in patients treated with AMs.¹³ AMs

Corresponding Author: April Barnado, MD, MSCI, Address: 1161 21st Avenue South, T3113 MCN, Nashville, TN 37232, Telephone: (615) 322 – 4746, Fax: (615) 322 6248, april.barnado@vumc.org.

The Authors declare that there is no conflict of interest.

also improve renal outcomes in SLE nephritis.^{14,15} Based on this evidence, the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) guidelines recommend the use of hydroxychloroquine (HCQ) in the management of SLE,¹⁶ while the American College of Rheumatology (ACR) recommends HCQ in all SLE patients with nephritis unless contraindicated.¹⁷

Cohort studies, however, have shown that AMs are not universally prescribed with rates ranging from 66 to 79%^{18, 19} and an even lower rate of 38%²⁰ when prescription fill data is examined. Barriers to prescribing AMs including patient, disease, and prescriber factors have not been fully examined. Using a real-world, electronic health record (EHR) cohort, we investigated if demographic, clinical, or prescriber characteristics impacted AM prescribing frequency in SLE.

Methods

After approval from the Institutional Review Board of Vanderbilt University Medical Center (VUMC) (#141222), we used Vanderbilt's de-identified electronic health record (EHR), called the Synthetic Derivative,²¹ with over 2.8 million subjects and decades of follow-up to assemble our SLE cohort. VUMC's patient population derives from a large area of the southern United States due to its position as a tertiary care center and is predominantly Caucasian (81%). All available EHR data is included in the Synthetic Derivative, such as diagnostic and procedure billing codes, demographics, inpatient and outpatient notes from Vanderbilt providers, laboratory values, and imaging and pathology reports. Medication data was collected from both inpatient and outpatient electronic prescribing systems and a natural language processing program called MedEx. MedEx recognizes medication names and specifications, such as dose, frequency, route, and duration, within free-text records and displays this information for each subject in the Synthetic Derivative.^{22, 23} The text of the medical record in the Synthetic Derivative is entirely searchable, allowing specific keywords to be captured and highlighted for targeted chart review. Not included in the Synthetic Derivative are scanned records from other healthcare systems.

Our previously validated algorithm of 4 or more counts of the SLE International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) code of 710.0 and antinuclear antibody (ANA) positive titer of 1:160 or higher while excluding dermatomyositis and systemic sclerosis ICD-9 codes was used to identify potential SLE cases in the Synthetic Derivative.²⁴ All subjects were then confirmed on chart review as a SLE case if diagnosed with SLE by a specialist (rheumatologist, dermatologist, or nephrologist). Subjects excluded had alternative autoimmune diagnoses (i.e. cutaneous or drug-induced SLE), uncertainty in diagnosis, or missing notes. On chart review, we also collected age at time of analysis (current age), sex, race/ethnicity, presence of SLE nephritis, and specialist(s) managing SLE. Data on race/ethnicity obtained from the Synthetic Derivative was a combination of self-report and administrative entry. EHR race/ethnicity data has been previously validated and shown to correlate with genetic ancestry.²⁵ SLE nephritis was defined as a positive renal biopsy or clinical diagnosis by a specialist (rheumatologist or nephrologist). Patients with multiple classes (i.e. class IV + V) were

grouped with the lower class (i.e. class IV) except for where noted for class I and II subjects. Each SLE nephritis case was reviewed for having ever undergone renal transplant and/or dialysis. Our primary outcome was ever use of AMs. We assessed for ever use of AMs from inpatient and outpatient electronic prescribing systems and MedEx, described above. Antimalarials included in the medication search were “hydroxychloroquine,” “plaquenil,” “HCQ,” “PLQ,” “chloroquine,” “quinacrine,” and “aralen.” If the subject was ever prescribed an AM, the specialist who documented in a clinical note as prescribing the AM was counted as the managing specialist. If the subject was never prescribed an AM, the specialist following the patient was counted as not having prescribed the AM. If a patient was being followed by multiple SLE specialists and not prescribed an AM, the specialist was recorded as “multiple” to assign responsibility to all providers. This “multiple” category was created because it was easy to identify which specialist prescribed the AM if there were multiple specialists; however, it was not easy to discern which specialist was responsible for not prescribing an AM if there were multiple specialists.

Using a cross-sectional analysis, current AM use was assessed by whether AMs were recorded from a specialist visit closest to October 1, 2015. As our validated SLE algorithm incorporates ICD-9 codes, we restricted dates to before October 1, 2015, the date when US medical systems transitioned from ICD-9 to ICD-10 codes. Laboratory data on creatinine (Cr), white blood cell (WBC) count, hemoglobin (Hgb), and platelet (Plt) count were also recorded from the clinic visit closest to October 1, 2015.

We evaluated for differences in SLE cases ever/currently prescribed AMs vs. those never prescribed AMs using the Mann-Whitney U test for continuous variables and chi-square or Fisher’s exact test for categorical variables. Cases with missing demographic and clinical data race were excluded from analyses using those covariates. We performed logistic regression to estimate the association between nephritis and managing specialty and AM prescribing, adjusting for demographics, using odds ratios (ORs) and 95% confidence intervals. Analyses were conducted in R version 3.5.1.

Results

SLE EHR cohort

Using our algorithm of 4 counts of the SLE ICD-9 code and ANA 1:160, we identified a cohort of 1147 potential SLE cases. Upon chart review, 977 cases were confirmed to have a diagnosis of SLE. Of the remaining cases, 109 did not have SLE, 26 had an unclear diagnosis of SLE, 31 had missing specialist notes to confirm a diagnosis, and 4 had no clinical notes in the EHR. Our positive predictive value (PPV) for this algorithm was 90%, which is consistent with the previously published PPV of 89%.²⁴ Of the 977 cases, 90% were female with the majority being Caucasian (68%) and the remainder African American (27%), Hispanic (3%), and Asian (2%), which reflects the demographics of middle Tennessee (Table 1). The mean current age was 51 ± 17 , and the mean age at first SLE ICD-9 code was 39 ± 16 . SLE cases had a mean EHR follow-up of 9 years. There were 915 (94%) cases whose specialist was a rheumatologist, 29 (3%) a nephrologist, 7 (1%) a dermatologist, and 23 (2%) had multiple specialists.

Ever AM use in SLE cases

Ever use of AMs in the 977 SLE cases was 94%. SLE cases who were ever vs. never prescribed AMs are shown in Table 2. Current age, gender, and race/ethnicity were not significantly different among cases ever vs. never prescribed AMs in univariate analyses. SLE cases who were ever prescribed AMs were more likely to be managed by a rheumatologist than a nephrologist or multiple providers as compared to cases not prescribed AMs ($p < 0.001$). In a logistic regression model for ever AM use, adjusting for sex and race/ethnicity, current age became significant ($OR = 0.96, 0.94 - 0.98, p < 0.01$) as well as managing specialty ($p < 0.01$) (Supplemental Table 1A). Older cases had lower odds of being prescribed AMs. Cases following primarily with nephrology had a markedly lower odds of being prescribed AMs compared to cases following primarily with rheumatology or dermatology (Supplemental Table 1A).

SLE cases who were never prescribed AMs were more likely to have nephritis compared to SLE cases who were ever prescribed AMs (59% vs. 23%, $p < 0.001$). In a logistic regression model adjusting for sex and race/ethnicity, current age ($OR = 0.97, 95\% \text{ CI } 0.95 - 0.99, p < 0.001$) and nephritis ($OR = 0.16, 0.08 - 0.29, p < 0.001$) were both significantly associated with ever AM use (Supplemental Table 1B). Both older and nephritis cases had lower odds of being prescribed AMs.

SLE nephritis cases

With lower AM prescribing in the SLE nephritis subjects, we then examined these 244 subjects. Characteristics of the SLE nephritis cases are displayed in Table 3. Of these cases, 188 (77%) had biopsy-proven SLE nephritis, 43 (18%) had no biopsy, and 13 (5%) had missing data on how the diagnosis was reached. The majority of biopsies were class IV ($n = 54, 32\%$) followed by class V ($n = 51, 31\%$), class III ($n = 39, 23\%$), class II ($n = 22, 13\%$), and class I ($n = 2, 1\%$). Of the 54 class IV subjects, 18 were class IV + V. Of the 37 class III subjects, 9 were class III + V and 1 class III + IV. Of the 24 class II subjects, 1 had class II + III and 1 class II + V. These subjects were grouped with class III and V subjects, respectively. Of the 3 class I subjects, 1 had class I + III, and this subject was grouped with class III subjects.

The mean age at first SLE ICD-9 code of SLE nephritis cases was 32 ± 15 , and the mean current age was 43 ± 16 . SLE nephritis cases were 89% female. Distribution by race was 47% Caucasian, 44% African American, 6% Asian, and 3% Hispanic. Among the SLE nephritis cases, 78% were followed by rheumatology, 12% nephrology, 2% dermatology, and 8% multiple specialties. There were 91 subjects (38%) who had ever received dialysis and 50 (21%) who had ever undergone a kidney transplant.

Ever AM use in SLE nephritis cases

We compared SLE nephritis cases that were ever vs. never prescribed AMs in Supplemental Table 2. Of the 244 SLE nephritis cases, 86% were ever prescribed AMs. There were no significant differences in sex, race/ethnicity, method of SLE nephritis diagnosis, or nephritis class in SLE nephritis cases never vs. ever prescribed AMs. SLE nephritis cases who were never prescribed AMs were significantly older (53 ± 20 vs. $42 \pm 14, p = 0.01$). SLE nephritis

subjects who were ever prescribed AMs were more likely to be managed by a rheumatologist than a nephrologist or multiple providers compared to cases not prescribed AMs ($p < 0.001$). Adjusting for sex and race/ethnicity, current age (OR = 0.94, 0.89 – 0.98, $p = 0.01$) and managing specialty (OR = 0.009, 0.0008 – 0.005, $p < 0.001$) were both significantly associated with ever AM use (Supplemental Table 3). Older SLE nephritis cases and cases following primarily with nephrology had a lower odds of being prescribed AMs. Cases who never prescribed AMs were more likely to have received dialysis ($p < 0.001$) or renal transplant ($p < 0.001$) compared to those ever prescribed AMs.

Current AM use in SLE nephritis cases

In a cross-sectional analysis, we investigated additional factors, including lab values, that could impact AM prescribing in SLE nephritis patients. Of the 241 SLE nephritis patients with available AM data, 153 (63%) were current users, and 88 (37%) were former or never users. Of the 57 cases who were former users, reasons for discontinuation were provided for 16 patients shown in Supplemental Table 4. Eye toxicity was cited as the reason for discontinuation in 5 cases, cardiomyopathy in 2 cases, and medication inefficacy in 2 cases, while other reasons were documented in single cases.

There were no differences in sex or race/ethnicity between SLE nephritis cases who were or were not currently prescribed AMs (Table 4). Current users were significantly younger than non-current users (39 ± 14 vs 50 ± 17 years, $p < 0.001$). Cases that were currently prescribed AMs were more likely to be managed by a rheumatologist than a nephrologist or multiple providers compared to cases not prescribed AMs ($p < 0.001$). Cases not currently prescribed AMs were more likely to have received dialysis (64% vs. 23%, $p < 0.001$) or renal transplant (42% vs. 8%, $p < 0.001$) compared to those currently prescribed AMs. Serum creatinine (1.8 ± 2.6 vs. 3.0 ± 3.2 , $p < 0.001$) and urine protein/creatinine ratio (1.4 ± 2.6 vs 3.0 ± 6.3 , $p = 0.05$) were both significantly lower in SLE nephritis cases with current compared to not current AM use. Hemoglobin was significantly higher in SLE nephritis cases with current use of AMs vs. non-current use (12.1 ± 2.1 vs. 11.2 ± 2.3 , $p < 0.01$). White blood cell and platelet counts were not significantly different between current and non-current AM users ($p = 0.32$, $p = 0.21$).

We performed a similar analysis of current AM use in SLE subjects without nephritis (Supplemental Table 5). Of the 700 SLE subjects with available medication data, 533 (76%) were current users and 167 (24%) were former users. Similar to the results for SLE nephritis subjects, SLE subjects currently prescribed AMs were younger than SLE subjects not currently prescribed AMs (52 ± 16 vs. 56 ± 15 , $p < 0.001$). There were no significant differences in sex and race/ethnicity. SLE subjects who were currently prescribed AMs had a lower white blood cell count (6.6 ± 2.9 vs. 7.3 ± 3.2 , $p = 0.02$) with no significant differences in serum creatinine, hemoglobin, or platelet levels. For the 167 subjects who had their AMs discontinued, reasons are shown in Supplemental Table 6 with the most common being patient preference ($n = 28$) followed by rash ($n = 19$) and gastrointestinal symptoms ($n = 16$).

Discussion

Using a large EHR-based cohort with real-world data, we found 94% of all SLE subjects were ever prescribed an AM. SLE nephritis subjects, however, were less likely to have been prescribed AMs. SLE nephritis subjects who followed with a nephrologist or who had ever undergone dialysis or renal transplant were less likely to be prescribed AMs. Antimalarial prescribing is important as AMs improve renal outcomes^{14,15} and survival in SLE.^{11–13} By identifying gaps in AM prescribing, we can target efforts to improve clinical outcomes in SLE.

Our large EHR study builds on studies investigating AM prescribing practices, which use traditional cohort studies or administrative databases. Studies have recorded lower rates of AM prescribing but used different methods to capture AM use. A Danish registry study reported 38% of newly diagnosed SLE cases were prescribed and then filled AMs in the first year.²⁰ In contrast to our study, the Danish study captured not only prescribing but pharmacy fill data, which may explain the lower result in their study compared to our study, which did not capture pharmacy fill data. Further, the Danish study included only newly diagnosed cases. A Canadian study of 10 SLE cohorts recorded 66% of SLE subjects were ever exposed to AMs based on cohort collection data.¹⁸ The recruitment was over a 12-year window as opposed to our decades-long data.¹⁸ The University of California, San Francisco (UCSF) SLE Outcomes Study reported HCQ prevalence of 55 per 100 person-years.²⁶ The study, however, used patient-reported questionnaires and not clinical data. Lastly, 79% of patients in a Spanish cohort study¹⁹ were reported to have ever been exposed to AMs based on cohort collection data. These results were closest to our findings. While we and other studies examined physician prescribing patterns through medical records and electronic prescribing systems^{18, 19, 29, 31, 32}, we were not able to access medication refill data to assess medication adherence. Medication non-adherence is a problem among patients with SLE.^{27,28} Low AM adherence has been previously described with most patients not adhering to an AM within the first year of starting therapy.²⁸

In our study, age and type of specialist were both significantly associated with whether AMs were ever prescribed. Older subjects were less likely to ever be prescribed AMs, as demonstrated by other studies.²⁰ These studies propose that patients who are diagnosed with SLE at a younger age tend to have more active disease compared to patients who are diagnosed at an older age.²⁹ Older SLE subjects may also not have been prescribed AMs, as there were less data and guidelines at the time that supported AM prescribing. Further, age has been reported as a risk factor for ocular toxicity related to AM use,³⁰ which may have influenced prescribing patterns.

Subjects who were prescribed AMs were much more likely to be followed by a rheumatologist than a nephrologist or dermatologist. Despite a strong association between nephrology and ever AM use, we had a small number of patients following primarily with nephrology resulting in a wide confidence interval in our model. Nonetheless, this association was also noted in the UCSF SLE Outcomes Study, where subjects whose primary SLE provider was a rheumatologist were more likely to use AMs compared to subjects who followed primarily with generalists or nephrologists.²⁶ A Swiss study also

reported significantly higher AM prescribing rates in rheumatologists as compared to nephrologists, immunologists, and internists.³¹ In contrast, a Spanish study of SLE patients diagnosed and managed by internal medicine reported 81% of SLE patients were prescribed AMs in the first year with no difference between patients with and without SLE nephritis.³² Rheumatologists may be more comfortable prescribing AMs due to guidelines and their use in other rheumatologic diagnoses. Nephrologists would have fewer indications for AMs and less familiarity with their use. Of note, the Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group (KDIGO) published guidelines³³ recommending AMs in all SLE nephritis patients in the same year as the ACR.¹⁷

With nephrologists less likely to prescribe AMs, we then examined current AM use among SLE nephritis subjects in a cross-sectional analysis to uncover specific factors influencing prescribing patterns. Only 63% of SLE nephritis subjects were currently prescribed AMs compared to 76% of SLE subjects without nephritis. Our results agree with a Danish administrative database study, where subjects with renal disease were less likely to be started on AMs.²⁰

In our study, SLE nephritis subjects who were not currently prescribed AMs were more likely to have undergone dialysis or renal transplant. To determine whether renal function was driving this finding, we examined serum creatinine and urine protein to creatinine ratios. Subjects not currently prescribed AMs had significantly higher serum creatinines and urine protein to creatinine ratios compared to subjects currently prescribed AMs. We cannot determine if this worse renal function was the reason or the result of not being currently prescribed AMs, as only one subject had clinical documentation for “renal toxicity” as the reason for discontinuing AMs.

Renal function may impact prescribing patterns as AMs are excreted renally. Renal disease can increase circulating levels of AMs and is a risk factor for ocular toxicity from AMs.¹² Since nephrologists are more likely to see patients with more severe renal disease, nephrologists may have concerns for increased risk of ocular toxicity in these patients and prescribe AMs less frequently. Further, some sources suggest that AMs should be dose-adjusted for decreased renal function and in end stage renal disease^{34, 35} although decreased renal function is not a contraindication to AM use. Currently, the ACR SLE nephritis treatment guidelines recommend that all SLE nephritis patients receive AMs unless otherwise contraindicated.¹⁷ The ACR, however, does not detail specific contraindications, leaving these up to interpretation. Some providers may interpret impaired renal function as a contraindication.

Given the improvement in renal response, relapses, and accrued renal damage with AMs, EULAR/ERA-EDTA recommends AMs for all SLE nephritis patients with normal baseline ophthalmological exam and suggests the dose may need to be adjusted when glomerular filtration rate is less than 30 ml/min.¹⁶ Despite the importance of being on AMs regardless of renal function, SLE nephritis patients were less frequently prescribed them. Of the SLE nephritis patients ever on dialysis, 77% were ever prescribed an AM and 38% currently prescribed an AM. As more dialysis patients were ever vs. currently prescribed AMs, the AMs were stopped at some point. While the rationale for discontinuing the AMs was not

documented in the EHR for all patients, we speculate that providers may assume that SLE nephritis patients on dialysis have reduced disease activity and do not need AMs. A recent systematic review of SLE nephritis patients with ESRD suggests this may not always be the case as 37.5% of the studies demonstrated disease activity to be the same or higher after development of ESRD.³⁶ Future studies could directly assess knowledge of nephrologists in management of SLE nephritis subjects and their concerns regarding use of AMs.

Of the renal transplant SLE subjects, 68% were ever prescribed an AM and only 26% currently prescribed an AM. Documentation was only provided for 16 subjects on why the AM was discontinued. We hypothesize that there may be concern among nephrologists of AMs interfering with transplant medications or that transplant medications may control a patient's SLE with AMs not being needed. There is a lack of literature and guidelines on use of AMs in SLE patients who have undergone renal transplant. There are also few studies that examine extrarenal disease activity in SLE renal transplant recipients. Case series report mixed findings of no subjects having extrarenal disease activity after renal transplant to over half of subjects having extrarenal disease activity.^{36, 37–41}

Another hypothesis for decreased AM prescribing was physician concern for ocular toxicity. Ophthalmology guidelines report risk of toxicity for hydroxychloroquine under 1% for up to 5 years of use and under 2% for up to 10 years.³⁰ These guidelines also report both older age and renal disease as risk factors for ocular toxicity³⁰ and could explain lower prescribing rates in these groups. In our study, only 5 of the SLE nephritis cases and 12 of the SLE cases without nephritis had documented ocular toxicity as the reason for discontinuation, so we doubt that this clinical reason was the sole driver of our findings.

While our study examined AM prescribing patterns in SLE using a large, novel EHR cohort, there are limitations to our study. This was a single center study in a large academic center, limiting its generalizability. Our EHR does not include outside records and medications prescribed at other hospitals or clinics. These outside records and medications would then cause us to underestimate AM prescribing. Further, we had missingness in the data, notably with some subjects not seen by a specialist to confirm their diagnoses or confirm current AM use. However, only 31 subjects were excluded due to not having a specialist confirmed diagnosis, and only 4 subjects were excluded due to no available clinical notes in the EHR. SLE disease activity and damage index scores were not included in our analyses, as these measures are not routinely collected in clinical practice and available in the EHR. Since the algorithm for our cohort relied on ICD-9 codes, which transitioned to ICD-10 codes on October 1, 2015, we only analyzed AM prescribing patterns until 2015. More recent prescribing rates could be higher with a longer presence of both rheumatology and nephrology guidelines. Our current study may then underestimate AM prescribing rates. Lastly, we could not capture refill data to assess AM adherence. Despite these limitations, the EHR can be used to capture real-world prescribing patterns using longitudinal data over decades of follow-up.

In conclusion, we found a high percentage of SLE patients have been prescribed AMs at some point in their disease course. In contrast, SLE nephritis patients, which represent a particularly vulnerable population with a significant disease burden, are less frequently

prescribed AMs. As AMs reduce renal damage in SLE nephritis, our results demonstrate an opportunity to target efforts to improving AM prescribing rates. Future studies are needed to directly assess barriers to prescribing AMs among multi-specialty providers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support:

Supported by grants NIH/NICHD 5K12HD043483–12 (Barnado), NIH/NIAMS 1 K08AR072757–01 (Barnado), NIH/NIGMS R01 GM126535 (Chung), NIH/NIAMS K23AR064768 (Chung), and the Rheumatology Research Foundation K Supplement (Chung)

References

1. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis*. 2010; 69: 20–8. [PubMed: 19103632]
2. Canadian Hydroxychloroquine Study G. A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. *N Engl J Med*. 1991; 324: 150–4. [PubMed: 1984192]
3. Meinao IM, Sato EI, Andrade LE, Ferraz MB, Atra E. Controlled trial with chloroquine diphosphate in systemic lupus erythematosus. *Lupus*. 1996; 5: 237–41. [PubMed: 8803897]
4. Williams HJ, Egger MJ, Singer JZ, et al. Comparison of hydroxychloroquine and placebo in the treatment of the arthropathy of mild systemic lupus erythematosus. *J Rheumatol*. 1994; 21: 1457–62. [PubMed: 7983646]
5. Tsakonas E, Joseph L, Esdaile JM, 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. [PubMed: 9541091]
6. Wozniacka A, Lesiak A, Narbutt J, McCauliffe DP, Sysa-Jedrzejowska A. Chloroquine treatment influences proinflammatory cytokine levels in systemic lupus erythematosus patients. *Lupus*. 2006; 15: 268–75. [PubMed: 16761500]
7. Costedoat-Chalumeau N, Amoura Z, Hulot JS, et al. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. *Arthritis Rheum*. 2006; 54: 3284–90. [PubMed: 17009263]
8. Levy RA, Vilela VS, Cataldo MJ, et al. Hydroxychloroquine (HCQ) in lupus pregnancy: double-blind and placebo-controlled study. *Lupus*. 2001; 10: 401–4. [PubMed: 11434574]
9. Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum*. 2006; 54: 3640–7. [PubMed: 17075810]
10. Cortes-Hernandez J, Ordi-Ros J, Paredes F, et al. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. *Rheumatology (Oxford)*. 2002; 41: 643–50. [PubMed: 12048290]
11. Hernandez-Cruz B, Tapia N, Villa-Romero AR, Reyes E, Cardiel MH. Risk factors associated with mortality in systemic lupus erythematosus. A case-control study in a tertiary care center in Mexico City. *Clin Exp Rheumatol*. 2001; 19: 395–401. [PubMed: 11491494]
12. Ruiz-Irastorza G, Egurbide MV, Pijoan JI, et al. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. *Lupus*. 2006; 15: 577–83. [PubMed: 17080912]
13. Alarcon GS, McGwin G, Bertoli AM, 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. [PubMed: 17389655]

14. Kasitanon N, Fine DM, Haas M, Magder LS, Petri M. Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. *Lupus*. 2006; 15: 366–70. [PubMed: 16830883]
15. Barber CE, Geldenhuys L, Hanly JG. Sustained remission of lupus nephritis. *Lupus*. 2006; 15: 94–101. [PubMed: 16539280]
16. Bertsias G, Ioannidis JP, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis*. 2008; 67: 195–205. [PubMed: 17504841]
17. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. *Arthritis Care Res (Hoboken)* 2012; 64: 797–808. [PubMed: 22556106]
18. Bernatsky S, Peschken C, Fortin PR, et al. Medication use in systemic lupus erythematosus. *J Rheumatol*. 2011; 38: 271–4. [PubMed: 21078722]
19. Pego-Reigosa JM, Rua-Figueroa I, Lopez-Longo FJ, et al. Analysis of disease activity and response to treatment in a large Spanish cohort of patients with systemic lupus erythematosus. *Lupus*. 2015; 24: 720–9. [PubMed: 25516473]
20. Norgaard JC, Stengaard-Pedersen K, Norgaard M, de Thurah A. Antimalarials in the treatment of systemic lupus erythematosus: a registry-based cohort study in Denmark. *Lupus*. 2015; 24: 299–306. [PubMed: 25318969]
21. Roden DM, Pulley JM, Basford MA, et al. Development of a large-scale de-identified DNA biobank to enable personalized medicine. *Clin Pharmacol Ther*. 2008; 84: 362–9. [PubMed: 18500243]
22. Xu H, Stenner SP, Doan S, et al. MedEx: a medication information extraction system for clinical narratives. *J Am Med Inform Assoc*. 2010; 17: 19–24. [PubMed: 20064797]
23. Jiang M, Wu Y, Shah A, et al. Extracting and standardizing medication information in clinical text - the MedEx-UIMA system. *AMIA Jt Summits Transl Sci Proc*. 2014; 2014: 37–42. [PubMed: 25954575]
24. Barnado A, Casey C, Carroll RJ, et al. Developing Electronic Health Record Algorithms that Accurately Identify Patients with Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)*. 2017; 69: 687–93. [PubMed: 27390187]
25. Dumitrescu L, Ritchie MD, Brown-Gentry K, et al. Assessing the accuracy of observer-reported ancestry in a biorepository linked to electronic medical records. *Gent Med*. 2010; 12: 648–50.
26. Schmajuk G, Yazdany J, Trupin L, Yelin E. Hydroxychloroquine treatment in a community-based cohort of patients with systemic lupus erythematosus. *Arthritis Care Res*. 2010; 62: 386–92.
27. Marengo MF, Waimann CA, de Achaval S, et al. Measuring therapeutic adherence in systemic lupus erythematosus with electronic monitoring. *Lupus*. 2012; 21: 1158–65. [PubMed: 22588588]
28. Feldman CH, Collins J, Zhang Z, et al. Dynamic patterns and predictors of hydroxychloroquine nonadherence among Medicaid beneficiaries with systemic lupus erythematosus. *Semin Arthritis Rheum*. 2018; 48: 205–13. [PubMed: 29458974]
29. Cervera R, Doria A, Amoura Z, et al. Patterns of systemic lupus erythematosus expression in Europe. *Autoimmun Rev*. 2014; 13: 621–9. [PubMed: 24418306]
30. Marmor MF, Kellner U, Lai TY, et al. Recommendations on Screening for Chloroquine and Hydroxychloroquine Retinopathy (2016 Revision). *Ophthalmology*. 2016; 123: 1386–94. [PubMed: 26992838]
31. Ribi C, Trendelenburg M, Gayet-Ageron A, et al. The Swiss Systemic lupus erythematosus Cohort Study (SSCS) - cross-sectional analysis of clinical characteristics and treatments across different medical disciplines in Switzerland. *Swiss Med Wkly* 2014; 144: w13990. [PubMed: 25115978]
32. Ruiz-Irastorza G, García M, Espinosa G, et al. Patterns of drug therapy in newly diagnosed Spanish patients with systemic lupus erythematosus. *Clin Exp Rheumatol*. 2016; 34: 466–72. [PubMed: 26940538]
33. Chapter 12: Lupus nephritis. *Kidney Int Suppl* (2011) 2012; 2: 221–32. [PubMed: 25018937]

34. Jallouli M, Galicier L, Zahr N, et al. Determinants of hydroxychloroquine blood concentration variations in systemic lupus erythematosus. *Arthritis Rheumatol.* 2015; 67: 2176–84. [PubMed: 25989906]
35. Lee JY, Luc S, Greenblatt DJ, Kalish R, McAlindon TE. Factors associated with blood hydroxychloroquine level in lupus patients: renal function could be important. *Lupus.* 2013; 22:541–2. [PubMed: 23396569]
36. Mattos P, Santiago MB. Disease activity in systemic lupus erythematosus patients with end-stage renal disease: systematic review of the literature. *Clin Rheumatol.* 2012; 31: 897–905. [PubMed: 22415467]
37. Barrera-Vargas A, Quintanar-Martinez M, Merayo-Chalico J, Alcocer-Varela J, Gomez-Martin D. Risk factors for systemic lupus erythematosus flares in patients with end-stage renal disease: a case-control study. *Rheumatology (Oxford).* 2016; 55: 429–35. [PubMed: 26396262]
38. Kang SH, Chung BH, Choi SR, et al. Comparison of clinical outcomes by different renal replacement therapy in patients with end-stage renal disease secondary to lupus nephritis. *Korean J Intern Med.* 2011; 26: 60–7. [PubMed: 21437164]
39. Correia P, Cameron JS, Ogg CS, et al. End-stage renal failure in systemic lupus erythematosus with nephritis. *Clin nephrol.* 1984; 22: 293–302. [PubMed: 6396007]
40. Cheigh JS, Stenzel KH, Rubin AL, Chami J, Sullivan JF. Systemic lupus erythematosus in patients with chronic renal failure. *Am J Med.* 1983; 75: 602–6. [PubMed: 6353915]
41. Krane NK, Burjak K, Archie M, O'Donovan R. Persistent lupus activity in end-stage renal disease. *Am J Kidney Dis.* 1999; 33: 872–9. [PubMed: 10213642]

Table 1.

SLE case characteristics.

SLE cases (n = 977)	
Age at first SLE ICD-9 code, mean $\pm$ SD (years)	39 $\pm$ 16
Current age, mean $\pm$ SD (years)	51 $\pm$ 17
Sex, n (%)	881 (90%)
Female	95 (10%)
Male	
Race/ethnicity ^a , n (%)	626 (68%)
Caucasian	247 (27%)
African American	31 (3%)
Hispanic	22 (2%)
Asian	
SLE nephritis ^b , n (%)	244 (25%)
Managing specialist ^c , n (%)	915 (94%)
Rheumatology	29(3%)
Nephrology	7(1%)
Dermatology	23 (2%)
Multiple	

^a51 cases with missing race^bSLE nephritis defined as a positive renal biopsy or clinical diagnosis by a rheumatologist or nephrologist^c3 cases with missing specialist

Table 2.

SLE cases ever prescribed AMs vs. never prescribed antimalarials.

SLE cases (n = 977)	Ever Prescribed Antimalarials (n = 917)	Never Prescribed Antimalarials (n = 60)	p value ^a
Current age, mean $\pm$ SD (years)	50 $\pm$ 16	55 $\pm$ 21	0.10
Sex, n (%)			
Female	827 (90%)	54 (90%)	0.94
Male	89 (10%)	6 (10%)	
Race/ethnicity ^b , n (%)			
Caucasian	593 (68%)	33 (59%)	0.19
African American	226 (26%)	21 (37%)	
Hispanic	29 (3%)	2 (4%)	
Asian	22 (3%)	0 (0%)	
SLE nephritis, n (%)			
Absent	705 (77%)	24 (41%)	<0.001
Present	210(23%)	34 (59%)	
Managing specialist ^c , n (%)			
Rheumatology	891 (97%)	24 (40%)	< 0.001
Nephrology	16 (2%)	13 (22%)	
Dermatology	7(1%)	0 (0%)	
Multiple	0 (0%)	23 (38%)	

^aChi-square or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables^b51 cases with missing race/ethnicity^c3 cases with missing specialist. Specialist indicates provider managing the patient's SLE. Multiple indicates a subject was following with multiple specialists.

Table 3.

SLE nephritis case characteristics.

SLE nephritis cases (n = 244)	
Current age, mean $\pm$ SD (years)	43 $\pm$ 16
Sex, n (%)	216(89%)
Female	28(11%)
Male	
Race/ethnicity ^a , n (%) Caucasian	112(47%)
African American	103 (44%)
Hispanic	8 (3%)
Asian	14 (6%)
Diagnosis method, n (%) Biopsy	188(77%)
Clinical diagnosis	43 (18%)
Missing	13 (5%)
Nephritis class ^b , n (%)	2 (1%)
I	22 (13%)
II	39 (23%)
III	54 (32%)
IV	51(31%)
V	
Managing specialist ^c , n (%) Rheumatology	189 (78%)
Nephrology	28 (12%)
Dermatology	4 (2%)
Multiple	20 (8%)
Dialysis ^d , n (%)	91 (38%)
Renal transplant ^e , n (%)	50(21%)

^a7 cases with missing race/ethnicity^b20 cases with missing biopsy class. Patients with multiple classes were grouped with the lower class except for where noted for class I and II subjects. 1 case with class I + III (grouped with class III), 1 with class II + III (grouped with class III), 1 with class II + V (grouped with class V), 9 with III + V, 1 with III + IV, 18 with IV + V.^c3 cases with missing specialist. Specialist indicates provider managing the patient's SLE. Multiple indicates a subject was following with multiple specialists.^d3 cases with missing dialysis data^e2 cases with missing transplant data

Table 4.

SLE nephritis cases with current vs. not current antimalarial use.

SLE nephritis cases (n = 244 ^a)	Currently Prescribed Antimalarials (n = 153)	Not Currently Prescribed Antimalarials (n = 88)	p value ^b
Current age, mean ± SD (years)	39 ± 14	50 ± 17	< 0.001
Sex, n (%) ^c			
Female	134 (88%)	79 (90%)	0.61
Male	19 (12%)	9 (10%)	
Race/ethnicity ^d , n (%)			
Caucasian	73 (49%)	37 (43%)	0.44
African American	60 (40%)	42 (49%)	
Hispanic	5 (3%)	3 (4%)	
Asian	11 (8%)	3 (4%)	
Managing specialist ^e , n (%)			
Rheumatology	142 (93%)	46 (54%)	< 0.001
Nephrology	10 (6%)	17 (20%)	
Dermatology	1 (1%)	3 (4%)	
Multiple	0 (0%)	19 (22%)	
Dialysis, n (%)			
Absent	118 (77%)	31 (36%)	< 0.001
Present	35 (23%)	56 (64%)	
Renal transplant, n (%)			
Absent	140 (92%)	51 (58%)	< 0.001
Present	13 (8%)	37 (42%)	
Serum creatinine, mean ± SD	1.8 ± 2.6	3.0 ± 3.2	< 0.001
Urine protein/creatinine ratio, mean ± SD	1.4 ± 2.6	3.0 ± 6.3	0.05
WBC count, mean ± SD	7.4 ± 5.4	8.1 ± 4.9	0.32
Hemoglobin, mean ± SD	12.1 ± 2.1	11.2 ± 2.3	< 0.01
Platelet count, mean ± SD	240 ± 91	224 ± 93	0.21

^a 3 cases with missing AM data^b Chi-square or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables^c 7 cases with missing race/ethnicity^d 6 cases with missing specialist. Specialist indicates provider managing the patient's SLE. Multiple indicates a subject was following with multiple specialists.