Understanding Nonadherence with Hydroxychloroquine Therapy in Systemic Lupus Erythematosus

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ABSTRACT. Objective. Hydroxychloroquine (HCQ) is a cornerstone to managing systemic lupus erythematosus (SLE), yet adherence to medication is poor. We sought to measure the association of adherence with 5 "dimensions of adherence" as articulated by the World Health Organization for chronic conditions: the patient's socioeconomic status, and patient-, condition-, therapy-, and healthcare system–related factors. Our longterm goal is to generate evidence to design effective interventions to increase adherence.

Methods. The retrospective cohort study included Kaiser Permanente Northern California patients ≥ 18 years old during 2006–2014, with SLE and ≥ 2 consecutive prescriptions for HCQ. Adherence was calculated from the medication possession ratio and dichotomized as < 80% versus ≥ 80%. Predictor variables were obtained from the electronic medical record and census data. We used multivariable logistic regression to estimate adjusted OR and 95% CI.

Results. The study included 1956 patients. Only 58% of patients had adherence ≥ 80%. In adjusted analyses, socioeconomic variables did not predict adherence. Increasing age (65–89 yrs compared with ≤ 39 yrs: OR 1.44, 95% CI 1.07–1.93), white race ($p < 0.05$), and the number of rheumatology visits in the year before baseline (≥ 3 compared with 0 or 1: OR 1.47, 95% CI 1.18–1.83) were positively associated with adherence. The rheumatologist and medical center providing care were not associated with adherence.

Conclusion. At our setting, as in other settings, about half of patients with SLE were not adherent to HCQ therapy. Differences in adherence by race/ethnicity suggest the possibility of using tailored interventions to increase adherence. Qualitative research is needed to elucidate patient preferences for adherence support. (First Release June 1 2019; J Rheumatol 2019;46:1309–15; doi:10.3899/jrheum.180946)

Key Indexing Terms:
HYDROXYCHLOROQUINE SYSTEMIC LUPUS ERYTHEMATOSUS

In numerous past reports, patients with systemic lupus erythematosus (SLE) have demonstrated poor medication adherence, with about half taking < 80% of their medications as instructed[1]. Adherence to hydroxychloroquine (HCQ) is of special interest because its side effects profile is mild, and the drug is evidenced to be highly effective in correlating directly with reduced SLE disease activity, decreased acute care use, slower progression of lupus nephritis, reduced lupus flares, and lower mortality[2,3].

The World Health Organization (WHO) has articulated 5 "dimensions of adherence" for chronic conditions, categorizing potential barriers to adherence[4]. These include the patient's socioeconomic status, as well as patient-, condition-, therapy-, and healthcare system–related factors. Socioeconomic status refers to a person's wealth, education, and occupation, which reflects economic barriers to care as well as health literacy. Patient factors include beliefs and attitudes regarding treatment, which may be influenced by age and culture. Condition-related factors include comorbidities, functional limitations, and overall complexity of the disease. Therapy-related factors include the complexity of the medication regimen, including co-therapies. Health system factors include integration, care coordination, and access to care. It also

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includes physician workflows and the local context in which the physician works.

Medication adherence can be classified as primary and secondary adherence. Primary adherence is defined as whether patients filled their first prescription, whereas secondary adherence is defined as whether patients continue to fill their prescription over a long period[5]. Primary medication adherence is measured as a single event in time, but secondary medication adherence is a continuous measure and is of more interest in the management of chronic diseases. The reasons for poor adherence to HCQ are not well understood. Qualitative studies have cited the fear of adverse effects and patient perceptions of drug efficacy as important reasons for medication nonadherence[6]. Depression and complex medication regimens are common in SLE, and both are associated with poor adherence[7]. A recent study done in the US Medicaid population has demonstrated that an astounding 85% of patients with SLE were nonadherent to HCQ. Nonadherence was increased in younger patients as well as black and Hispanic patients[8].

Our longterm goal is to develop evidence-based interventions to improve SLE patients' adherence to HCQ. Toward that goal, we conducted a retrospective study to identify factors associated with adherence. We used the WHO framework, together with US Census data and information from the health plan's electronic medical records to assess predictors of HCQ adherence in patients with SLE.

MATERIALS AND METHODS

Setting. Kaiser Permanente Northern California is a comprehensive and integrated healthcare organization with a closed pharmacy system that provides care to 3.8 million members. The region has more than 200 pharmacies available to members, located within outpatient offices and hospitals. Most members (> 95%) obtain their medications through a Kaiser Permanente pharmacy or mail-order system. About two-thirds of patients have a simple, fixed drug copayment ranging from $5 to $20 (all dollars US), while others have coinsurance (e.g., 20%), with out-of-pocket maximums varying by insurance policy. Patients can refill their medications by telephone or through the online patient portal. Our study period, using data during 2006–2014, preceded health insurance expansion under the Affordable Care Act in 2014 and the subsequent changes in health plans that Kaiser Permanente offered. Prior health plans offered individual coverage, employer-sponsored coverage, Senior Advantage Plan for Medicare-eligible patients, and Medicaid.

Study population. The population included in this retrospective cohort study was patients over 18 years of age with 2 recorded diagnosis codes for SLE [International Classification of Diseases, 9th revision (ICD-9) code 710.0], entered by a rheumatologist in an outpatient setting. We only included patients with at least 2 fills for HCQ, which is necessary for calculating medication possession ratio (MPR), our primary outcome. We required the patient to obtain the second fill within 30 days after finishing the pills included in the first fill, as assessed through the day-supply variable. We did not include patients without a refill within 30 days because those patients were more likely to have an HCQ allergy or adverse effect. The date of the second fill was used as the index date. We required patients included in the analysis to be enrolled in the health plan for at least 12 months prior to the index date to assess the patient's baseline health condition and health care use. We excluded patients with contraindications to HCQ, including retinopathy (ICD-9 codes 362.01–362.07, 362.10–362.12), toxic maculopathy (362.55), and allergy (995.27, 995.3, V148, V149), recorded during the 12-month period before the index date.

Data collection. Clinical data used for the study were obtained from the EPIC-based electronic medical record, established in 2005. We also used information from the 2010 census.

Our primary outcome is the rate of secondary adherence as measured by MPR, a well-established measure of medication adherence in electronic database research that has been validated in other chronic diseases[9,10]. MPR is defined as the number of days of dispensed medication (days-supply) divided by the total days of followup. If patients were to refill their medication sooner than the last prescription, patients can have "over-adherence" where the days-supply is greater than the total days of followup, resulting in an MPR > 1. Because of this limitation, the algorithm used to estimate MPR allowed for 7 days of stockpiling, and we did not allow the MPR to rise above 1 on any day. Followup to assess the MPR began on the index date and ended on the date of disenrollment from the health plan or the second anniversary of the index date, whichever was earlier. Adherence to HCQ was dichotomized as MPR < 80% and ≥ 80%, a conventional threshold often used to define adherence in previous studies conducted on insured patient population[10,11].

We used information from the 2010 US Census and from the electronic medical record to assess predictors of adherence. The US Census is a population survey collected every 10 years and provides demographic data by geography. Information on predictors was obtained during the 1-year period before the patient's second HCQ fill. The first dimension of the WHO adherence framework, socioeconomic status, was determined by linking the patient's address code to their census block (comprising about 600–3000 people) and obtaining mean values for the block-group. Variables used included median household income, percent of household income below poverty level, percent unemployment, and percent of adults who completed high school (all quartiles). Patient-related factors included age (≤ 39, 40–49, 50–64, ≥ 65 yrs), sex, race/ethnicity (African American, Asian American, Hispanic, white, multiracial/other, and unknown), and language preference (English, other). Condition-related factors included the Charlson Comorbidity Index (0, 1, ≥ 2), a composite score recording multiple comorbidities such as age, diabetes, liver disease, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease, stroke, and other chronic diseases[12]. We also examined the number of all-cause hospitalizations (0, ≥ 1) and the estimated glomerular filtration rate (eGFR) as an indicator of renal function. Therapy-related factors included prescriptions for SLE drugs, including prednisone (yes, no), mycophenolate mofetil (yes, no), azathioprine (yes, no), cyclophosphamide (CYC; yes, no), and angiotensin-converting enzyme (ACE) inhibitor (yes, no), as well as the number of rheumatology visits (0–1, 2, 3, ≥ 4) in the year prior to index date. We chose these medications to determine both medication complexity as well as the severity of disease, because they are used to treat renal involvement in SLE. Health system–related factors included the rheumatologist who prescribed the HCQ and the medical center at which the patients received their rheumatology care, an overall measure of clinical workflow, leadership, and culture.

Statistical analysis. We used chi-square tests to assess the significance of categorical variables in univariate analysis. For each adherence factor except rheumatologist and medical center, we used the SAS procedure GENMOD to perform logistic regression analysis to estimate the OR and its 95% CI for the association of each factor with HCQ adherence ≥ 80%. We studied crude OR by examining each independent variable one at a time. We then combined variables into an adjusted model, including variables with p values < 0.2 from the unadjusted analyses. Finally, we reduced the adjusted model by removing variables that were not associated with adherence and did not function as confounders with other variables. We used the SAS procedure GLIMMIX to perform logistic regression analysis while accounting for the random effects of rheumatologist and then medical center. This was done by using a binomial distribution with a logit link function. We assessed the fit of each model using the likelihood ratio test, and we compared models using the Akaike information criterion. A p value of 0.05 was chosen as threshold for statistical significance. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc.).

This study was approved by the Institutional Review Board at the Kaiser Foundation Research Institute (CN-14-2069-H).

RESULTS

The study population included 1956 patients with SLE (Figure 1). The MPR was estimated from a full 2 years of observation in 76% of patients, while the mean length of observation to calculate adherence was 21.4 months. Only 58% of patients achieved ≥ 80% HCQ adherence. Among those with adherence ≥ 80%, the mean adherence was 96%, while among those with adherence < 80%, the mean adherence was 51%.

The study population comprised 90% women, and mean age was 47 years (SD 15). Median household income at the level of the census block group averaged $78,710 among adherent and $77,425 among nonadherent patients. None of the 4 variables measuring socioeconomic status differed between adherent and nonadherent patients (Table 1). The adherent group was slightly older than the nonadherent group ($p < 0.001$) and was disproportionately white ($p < 0.0001$). Sex and language were not associated with adherence in unadjusted analyses.

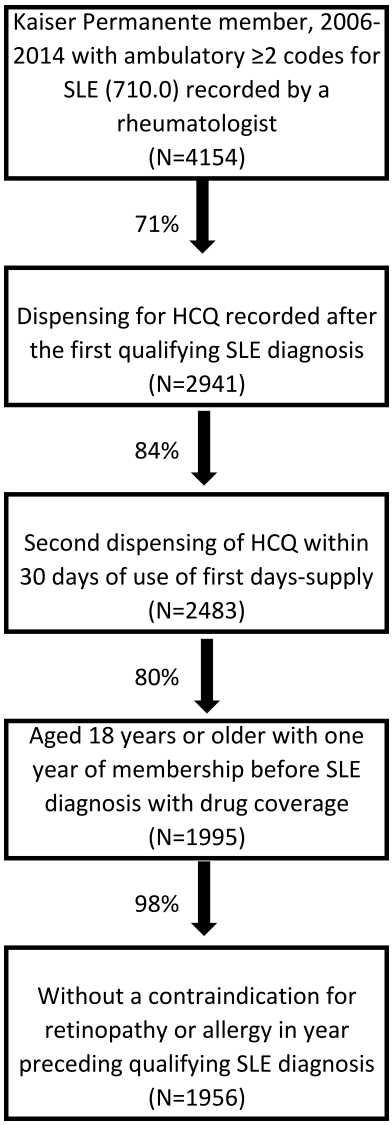

Figure 1. Cohort enrollment. SLE: systemic lupus erythematosus; HCQ: hydroxychloroquine.

We assessed 4 variables that reflect the patient's condition: Charlson comorbidity index, eGFR, number of rheumatology visits, and history of hospitalization for any cause in the year before the index date. A larger number of rheumatology visits and eGFR of 60–89 (vs ≥ 90) ml/min/1.73 m^2 were associated with better adherence. The Charlson index and a history of hospitalization were not associated with adherence to a significant degree. Regarding therapy, only 3 patients used CYC, and therefore we did not further consider this drug. Mycophenolate mofetil was somewhat inversely associated with the odds of adherence (OR 0.81, 95% CI 0.64–1.03). The use of prednisone and ACE inhibitor were not associated with adherence. Regarding healthcare system factors, compared to the average medical center, the odds of adherence ≥ 80% at the medical center with the best adherence were 1.13 (95% CI 0.91–1.86), while at the medical center with the worst adherence, the odds were 0.84 (95% CI 0.67–1.17; $p > 0.05$). The rheumatologist was not associated with adherence ($p > 0.05$).

The adjusted analysis included age, race/ethnicity, and the number of rheumatology visits (Table 2). Increasing age (65–89 yrs compared with ≤ 39 yrs: OR 1.44, 95% CI 1.07–1.93), white race ($p < 0.05$), and the number of rheumatology visits in the year before baseline (≥ 3 compared with 0 or 1: OR 1.47, 95% CI 1.18–1.83) were associated with higher adherence ≥ 80%. Compared to white patients, the OR for ≥ 80% adherence was 0.74 (95% CI 0.56–0.97) for African American patients, 0.76 (95% CI 0.59–0.99) for Asian/Pacific Islander patients, and 0.59 (95% CI 0.44–0.77) for Hispanic patients. We also compared adjusted analyses with and without eGFR, which ultimately was removed from the adjusted model because it was not significantly associated with adherence after accounting for age, race, and the number of rheumatology visits. Finally, we assessed whether the random effects of rheumatologist and medical center improved the fit of the adjusted model, but they did not (both $p > 0.05$).

DISCUSSION

In a community-based population with insurance coverage, relatively low drug copayments, and a high level of care coordination, only 58% of patients with SLE had ≥ 80% adherence to HCQ. Factors associated with adherence included age, race/ethnicity, and the number of rheumatology visits in the previous year, a marker of SLE severity. Our findings are consistent with previous studies that showed that age, race, and SLE severity were associated with medication adherence[1,2,6,7,13].

The study included patients who differed broadly in their

Table 1. Crude OR and 95% CI for associations of 4 WHO dimensions of adherence with adherence ≥ 80% in 1956 Kaiser Permanente patients with SLE and 2 recent prior fills of hydroxychloroquine, Northern California, 2006–14.

Characteristics	Adherence ≥ 80%, n = 1132	Adherence < 80%, n = 824	Crude OR	95% CI	p
Socioeconomic status (block-group)					
Median household income, thousands					
15–54	26.9	28.7	1.00	Ref.	
55–74	23.1	23.7	1.21	0.94–1.56	0.13
75–99	24.7	25.3	1.04	0.81–1.33	0.75
100–250	25.3	22.3	1.04	0.81–1.34	0.74
Percent household income below poverty level					
0–3.0	24.5	25.5	1.00	Ref.	
3.1–6.5	25.9	23.5	1.03	0.80–1.33	0.80
6.6–12.7	24.7	25.9	0.99	0.77–1.28	0.96
12.8–100	24.9	25.1	1.15	0.89–1.48	0.30
Percent unemployed					
0–3.7	26.2	24.8	1.00	Ref.	
3.8–5.4	25.0	25.6	0.90	0.70–1.15	0.40
5.5–7.2	23.6	23.2	0.97	0.75–1.25	0.79
7.3–22	25.2	26.4	0.92	0.72–1.19	0.54
Percent high school graduate					
0–13	26.3	25.0	1.00	Ref.	
14–19	21.7	23.5	1.06	0.81–1.38	0.68
20–28	30.1	31.8	0.90	0.71–1.14	0.37
29–59	21.9	19.7	0.87	0.67–1.13	0.30
Patient-related factors					
Age, yrs					
≤ 39	29.4	34.2	1.00	Ref.	
40–49	21.0	26.6	0.92	0.72–1.17	0.50
50–64	32.0	25.8	1.44	1.14–1.82	0.00
65–89	17.6	13.4	1.53	1.16–2.03	0.00
Sex					
Male	10.5	9.0	1.00	Ref.	
Female	89.5	91.0	0.84	0.62–1.14	0.26
Race/ethnicity					
African American	15.2	16.9	0.68	0.52–0.89	< 0.01
Asian/Pacific Islander	19.7	21.2	0.70	0.54–0.90	< 0.01
Hispanic	14.1	19.2	0.55	0.42–0.72	< 0.0001
White	41.0	30.8	1.00	Ref.	
Other/unknown*	2.2	3.2	0.63	0.46–0.86	< 0.001
Language					
English	93.0	92.3	1.00	Ref.	
Other	7.0	7.7	0.91	0.64–1.28	0.57
Condition-related factors in the year before index					
Charlson comorbidity index					
0	83.6	84.5	1.00	Ref.	
1	9.2	6.9	1.34	0.96–1.88	0.09
≥ 2	7.2	8.6	0.85	0.61–1.18	0.34
Rheumatology visits					
0–1	24.0	29.6	1.00	Ref.	
2	26.3	25.1	1.29	1.01–1.65	0.04
≥ 3	49.7	45.3	1.35	1.09–1.68	0.01
Hospitalization for any cause					
No	81.6	82.0	1.00	Ref.	
Yes	18.4	18.0	1.03	0.81–1.30	0.82
eGFR,** ml/min/1.73 m^2					
30–59	0.7	1.5	0.53	0.22–1.32	0.17
60–89	29.1	21.1	1.52	1.23–1.89	0.0001
≥ 90	70.2	77.4	1.00	Ref.	
Therapy-related factors in the year before index					
Medications (yes vs no)					
Prednisone	58.0	56.9	1.05	0.87–1.26	0.62
Mycophenolate mofetil	15.6	18.5	0.81	0.64–1.03	0.09
Azathioprine	11.8	11.5	1.03	0.78–1.36	0.83
ACE inhibitor	20.1	18.3	1.12	0.89–1.41	0.32

Values are % unless otherwise specified. * Includes multiracial, Native American, and unknown. ** Missing for 65 patients. WHO: World Health Organization; SLE: systemic lupus erythematosus; eGFR: estimated glomerular filtration rate; ACE: angiotensin-converting enzyme.

Table 2. Adjusted OR and 95% CI for associations of patient- and condition-related factors* with adherence ≥ 80% in 1956 Kaiser Permanente patients with SLE and 2 recent prior fills of hydroxychloroquine, Northern California, 2006–14.

Variables	Adjusted OR	95% CI	p
Age, yrs			
≤ 39	1.00	Ref.	
40–49	0.92	0.72–1.18	0.51
50–64	1.39	1.09–1.76	0.01
65–89	1.44	1.07–1.93	0.02
Race			
African American	0.74	0.56–0.97	0.03
Asian/Pacific Islander	0.76	0.59–0.99	0.04
Hispanic	0.59	0.44–0.77	< 0.001
White	1.00	Ref.	
Other/unknown	0.67	0.49–0.92	0.01
No. rheumatology visits			
0–1	1.00	Ref.	
2	1.30	1.01–1.67	0.04
≥ 3	1.47	1.18–1.83	< 0.001

* Other factors in Table 1 were not associated with adherence to a significant degree in the adjusted model. The rheumatologist and the medical center also were not associated with adherence to a significant degree in the adjusted model. SLE: systemic lupus erythematosus.

socioeconomic status, but in this population with health insurance, socioeconomic status was not an important predictor of adherence. This likely reflects adequate access to medication in our integrated healthcare system. In an integrated healthcare system, patients have increased physical access to medication because clinics are in close proximity to pharmacies, and refills can be mailed directly to patients. In contrast, Feldman and colleagues' study of Medicaid patients with SLE found that patients who were nonadherent to HCQ had lower socioeconomic status than adherent patients[2]. One important socioeconomic factor is the ability to pay for medications. In our patient population, financial barriers are likely limited given that the average copay for medication is < $20 for the majority of the patients. In a quasi-experimental study of Veteran's Administration patients, Doshi and colleagues observed that co-pay was inversely related to adherence[14]. Notwithstanding, among patients with a zero copayment, 40% were nonadherent[14]. HCQ is one of the less expensive medications used in rheumatology, yet adherence to HCQ is lower than adherence to biologic agents, which are costlier[15]. Interventions for improving medication adherence must expand beyond increasing financial accessibility.

HCQ is a medication with mild side effects that takes effect over several weeks. This may mislead patients to believe that the medication is not effective. A patient's belief in the efficacy of medication has been shown to be integral to adherence, and patients who do not experience an immediate clinical effect from a drug may not take it, regardless of other factors. Patients who have more frequent followup visits with their rheumatologists are more likely to be adherent to HCQ. Close followup provides an opportunity for providers to forge a therapeutic alliance with their patients and reinforce the importance of medication adherence. Though our study did not record remote encounters, there is some evidence that online interactions through Web-based education modules and social media group participation may improve HCQ adherence, particularly in younger patient populations[16]. In one study, cellular text messaging helped improved adherence to office visits but not HCQ adherence in patients with pediatric-onset SLE[17]. FaceTime has also been used successfully to enforce directly observed therapy remotely, increasing adherence to mycophenolate mofetil in pediatric patients with SLE[18]. Studies are under way to explore the use of mobile health technologies in other chronic diseases such as hypertension[19,20,21], diabetes[20,22], cancer treatment[23], and human immunodeficiency virus[24], and the findings of these studies may be applicable to the SLE population in enhancing medication adherence.

Patients who are sicker are more likely to be adherent. The patients in our community-based study have relatively few comorbidities and intact renal function, and one reason for the relatively low adherence that we observed may be the low severity or activity of SLE. Neurologic manifestations of SLE often include depression and cognitive impairment, which are not measured by the Charlson comorbidity index alone. Severity of depression in patients with SLE has been shown to strongly affect adherence[25]. Although not within the scope of our study, it would have been interesting to examine the effect of specific SLE disease activity on adherence.

A limitation of the study was the use of the MPR in place of more direct measures such as pill count, electronic lid monitoring, or blood level of HCQ. While MPR and other measures such as proportion of days covered (PDC) are often used to measure medication adherence based on claims data, they preclude the evaluation of primary medication adherence because they can only be calculated if at least 2 prescriptions have been filled. In one study, Tamblyn and colleagues found that up to one-third of patients in the primary care setting do not fill their new prescription, highlighting the need to understand primary as well as secondary adherence[26]. MPR and PDC also exclude patients who filled their first prescription, but then failed to fill their second prescription, which will likely underestimate the rate of secondary medication adherence. More recent studies have demonstrated the utility of HCQ blood level to monitor medication adherence and correlation with SLE flare[27,28,29]. Future studies on medication adherence in HCQ can be strengthened by measuring blood level rather than using MPR.

Our study also did not examine the dosing schedule of HCQ as related to adherence, which can vary by weight and renal function. Although it is well known that increasing dosing frequency impairs adherence[30], our analysis would have been complicated by changes in dosing schedule during

the study period. The strengths of our study included access to comprehensive information, the integrated setting in which certain sources of variation were minimized, and the large and diverse study population. Despite the integrated setting, we found a high level of nonadherence with HCQ therapy.

Medication adherence is a major public health problem in the management of SLE and other chronic illnesses and is thought to cost the US healthcare system an excess of $100 billion to $300 billion a year[31]. Given this burden, it is critical to determine contributing causes and to develop and create evidence for tailored interventions to improve adherence[32]. Research is needed to better understand the role of patient beliefs and attitudes, the patient-physician relationship and communication, and health literacy. We recommend mixed method and qualitative approaches to learn why patients are not taking their medications.

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