Hydroxychloroquine Blood Levels in Systemic Lupus Erythematosus: Clarifying Dosing Controversies and Improving Adherence

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ABSTRACT. ***Objective.*** Hydroxychloroquine (HCQ) is used for its effect on systemic lupus erythematosus (SLE) disease activity and longterm benefits. This can be limited by adherence. One way to assess adherence is to measure blood levels. Conflicting data exist regarding blood levels and disease activity. There is disagreement about dosing; rheumatologists recommend weight-based dosing while some other specialists advocate height-based "ideal body weight" dosing.

Methods. Patients were prescribed HCQ not exceeding 6.5 mg/kg (max 400 mg/day). In hemodialysis, the dose was 200 mg after each session, and in renal insufficiency it was 200 mg/day. Levels were measured at each visit with a therapeutic range of 500–2000 ng/ml. Patients were divided according to baseline blood level. To assess the effect of measurement and counseling on adherence, we compared the proportion of patients with a level of 500 ng/ml or higher based on the number of prior assessments.

Results. The proportion of patients with HCQ levels in the therapeutic range differed significantly by age, sex, and Vitamin D level. There was a trend toward lower levels with renal failure. Blood levels were similar regardless of height and ideal body weight. Comparing those with undetectable, subtherapeutic, and therapeutic levels, disease activity decreased (SLE Disease Activity Index 2.92, 2.36, and 2.20, $p = 0.04$ for trend). At first, 56% were therapeutic, and by the third measurement this increased to 80% ($p \leq 0.0001$).

Conclusion. There was a trend toward higher disease activity with lower HCQ levels. Renal failure dosing led to suboptimum levels. We show that weight-based dosing (max 400 mg daily) is appropriate and that height does not appear to influence levels. Measurement, counseling, and repeated testing can increase adherence rates. (First Release October 1 2015; J Rheumatol 2015;42:2092–7; doi:10.3899/jrheum.150379)

Key Indexing Terms:
HYDROXYCHLOROQUINE SLE DISEASE ACTIVITY ADHERENCE

Hydroxychloroquine (HCQ) is the cornerstone of medical management of systemic lupus erythematosus (SLE). It has been shown to prevent flares[1], decrease thrombosis[2,3,4,5], improve lipid levels[6], and decrease insulin resistance[7,8,9]. In terms of its specific effects on SLE, it is an effective means of treating cutaneous manifestations[10] and arthritis[11]. It has been shown to enhance response to other treatments in those with renal involvement[12]. It is associated with improved survival[3,13] and decreased organ damage[14].

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Medication nonadherence predicts poor outcomes in chronic diseases, including SLE[15]. The nonadherence rates in patients with SLE range from 3 to 76%, depending on the methods used[16,17,18,19,20]. Self-reported rates of nonadherence are between 7 and 45%[17,18,20,21,22]. Koneru, *et al* based their analysis on pharmacy refill information and found that 51% of individuals were nonadherent to their HCQ at least 80% of the time[19]. Ting, *et al*[23] found that 29% of adolescents and young adults with SLE had undetectable HCQ levels, which correlated with refill rates obtained from pharmacies. SLE medication regimens are often changed and intensified in response to disease activity without knowing whether patients have been adherent to first-line therapy. In this setting, any opportunity to gain knowledge regarding HCQ adherence is likely to have clinical use. It is unknown whether knowledge of a patient's blood levels of HCQ coupled with counseling when the levels are low improves the rate of adherence.

Regarding HCQ levels and SLE activity, Costedoat-Chalumeau, *et al*[24] measured whole blood levels in 143 individuals taking a standard dose of 400 mg per day and found a lower HCQ level in those with active disease and

that lower baseline levels were predictive of disease flare. Francès, *et al*[25] evaluated HCQ levels in chronic discoid lupus and found that median blood HCQ concentration was significantly higher in patients with complete remission compared with partial remission and treatment failure. However, even if a relationship between blood levels and flare was found, in a subsequent clinical trial, no reduction of flare was obtained when levels were increased to a target level of ≥ 1000 ng/ml[26].

It is possible to measure plasma, serum, and whole blood HCQ levels. The measurement of whole blood rather than plasma HCQ is important. Whole blood concentrations are about 5 times the plasma concentrations, are more precise, and are favored for pharmacokinetic measurements[27].

Here we report on the use of blood HCQ levels in clinical practice, their relationship to disease activity, and other variables such as body mass index (BMI), height, renal function, and ethnicity, and the effect of measurement and counseling on subsequent blood levels.

MATERIALS AND METHODS

As described[28], the Hopkins Lupus Cohort was a prospective study of predictors of flare, atherosclerosis, and health status in SLE. The study cohort included all patients at the Hopkins Lupus Center who had a clinical diagnosis of SLE and gave informed consent to participate in the study. Enrolled subjects were followed quarterly, or more frequently if clinically necessary. The clinical history, laboratory testing, and damage accrual data were recorded at the time of entry into the cohort and were updated at subsequent visits. The Hopkins Lupus Cohort has been approved by the Johns Hopkins University School of Medicine Institutional Review Board and complies with the Health Insurance Portability and Accountability Act.

HCQ blood levels were measured by liquid chromatography-tandem mass spectrometry as described by Füzéry, *et al*[29]. The therapeutic range was 500–2000 ng/ml. Our assay had been shown to have acceptable precision over the range 15.7–2000 ng/ml. This was chosen as our therapeutic range based on a review of the available literature. Costedoat-Chalumeau, *et al* reported a mean level of 1017 ± 432 ng/ml, and in a second work by the same author, the mean concentration was 1079 ng/ml with a range of 0–2629 ng/ml. There are interindividual variations in HCQ bioavailability that are considered secondary to pharmacokinetic and pharmacodynamics factors, which are as yet poorly understood. Levels were taken on the day of clinic assessment and were untimed relative to the last dose of HCQ. Given the long half-life of HCQ and the previously documented within-day variations of < 8%, this was considered appropriate[24]. All patients in the cohort were prescribed HCQ not exceeding a dose of 6.5 mg/kg. The maximum daily dose prescribed was 400 mg. In those who were receiving hemodialysis, 200 mg was prescribed after each dialysis session. In those with renal insufficiency, the dose was 200 mg daily.

Starting in January of 2013, blood levels of HCQ were measured at each visit for cohort patients who had been prescribed HCQ (85% of the cohort). For those in whom a subtherapeutic level was detected, the patient was counseled to improve compliance. An e-mail was sent on receipt of a low HCQ blood level asking that the patient not miss any doses. At their next encounter, the low level was highlighted in the chart for discussion.

SLE disease activity was measured using the physician's global assessment (PGA) and the Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA) revision of the SELENA–SLE Disease Activity Index (SLEDAI) instrument score[30] at each visit. The PGA is a well-validated tool that has been used in a large number of rheumatic diseases. It is composed of a visual analog on a 0–3 scale, with 0 = no activity, 1 = mild, 2 = moderate, and 3 = most severe. The SELENA-SLEDAI measures SLE disease activity within the last 10 days. It includes 24 clinical and laboratory variables that are weighted by organ system. Disease activity can range from 0–105[30].

At each clinic visit, 25-hydroxy Vitamin D [25(OH)D] was also measured, with a target level above 40 ng/ml, as described[31]. Patients were prescribed 50,000 IU of Vitamin D (1.25 mg ergocalciferol) weekly if levels were subtherapeutic.

For statistical analysis, the patients were divided according to their blood level. Levels below 15 ng/ml were considered consistent with complete nonadherence. Levels of 15–500 ng/ml were considered partially adherent (although it was possible that in this group, there may be individuals who, because of variations in their metabolism, were adherent but achieved lower blood concentrations), between 500–2000 ng/ml were therapeutic, and above 2000 ng/ml were considered supratherapeutic. Ideal body weight was calculated as 45.5 kg + 2.3 kg per 2.5 cm over 152 cm for women, and 50 kg + 2.3 kg per 2.5 cm over 152 cm for men. We then compared demographic and clinical subgroups with respect to the proportion in each HCQ group at their first blood level ("baseline"). Statistical significance of differences was determined based on a Pearson chi-square test.

We also compared the HCQ groups with respect to mean disease activity levels at baseline and assessed significance using ANOVA. In addition, we performed a within-person analysis by calculating, for each person, their mean activity level during visits when blood levels of HCQ were > 500 ng/ml and comparing that with their mean activity level during visits when blood levels were < 500 ng/ml. The statistical significance of average differences was assessed using a paired Student t test. Finally, to assess the effect of measurement and counseling on HCQ adherence, we compared the proportion of patients with an HCQ level of 500 ng/ml or higher based on the number of prior assessments of HCQ.

RESULTS

The demographics of the group at their baseline measurement are outlined in Table 1. Our analysis included 686 patients studied over 2400 visits. One hundred thirty-eight individuals (20%) had a single blood level taken. The remainder were evaluated on multiple occasions: 357 (52%) had between 2 and 4 visits, and 191 (28%) were seen on 5 to 12 occasions. The patients were for the most part women (n = 633, 92%). They were 49% white, 42% African American, and 9% "other" ethnicity (mostly Asian and Hispanic patients).

At baseline, 304 patients (44%) had subtherapeutic levels. Of these, 88 (13%) had levels of HCQ in their blood < 15 ng/ml, indicative of complete nonadherence. Despite appropriate weight-based dosing, 16 individuals (2%) were above the therapeutic range.

There were some statistically significant differences seen when demographic groups were compared with respect to the proportion in each HCQ group (Table 1). Men were more likely to be in the therapeutic range than women (71% compared with 52%, p = 0.050). There were significant differences by age group (p = 0.0018 with those under 30 yrs old, and those over 60 yrs more likely to be in the therapeutic range). Education and family income did not distinguish any differences in HCQ level.

Renal failure (creatinine of over 5 mg/ml) was present in 6 individuals (0.8%). Only 1 of these had HCQ blood levels in the therapeutic range. In those who had renal impairment (creatinine 1.4–4.9 mg/ml, n = 15), 60% were subtherapeutic. There was 1 individual with a level of over 2000 in the setting

Table 1. Various levels of HCQ at the first HCQ assessment by patient characteristics. Values are n (%) unless otherwise specified.

Characteristics	HCQ < 15 ng/ml	HCQ 15–500 ng/ml	HCQ 500–2000 ng/ml	HCQ ≥ 2000 ng/ml	p
All, n = 686	88 (13)	216 (31)	366 (53)	16 (2)	
Sex					0.050
Female, n = 633	84 (13)	206 (33)	329 (52)	15 (2)	
Male, n = 53	4 (8)	10 (19)	38 (71)	1 (2)	
Ethnicity					0.41
White, n = 333	37 (11)	104 (31)	182 (55)	10 (3)	
African American, n = 287	43 (15)	86 (30)	154 (54)	4 (1)	
Other, n = 66	8 (12)	26 (39)	30 (45)	2 (3)	
Age, yrs					0.0018
≤ 30, n = 89	10 (11)	18 (20)	59 (66)	2 (2)	
30–44, n = 244	28 (11)	98 (40)	114 (47)	4 (2)	
45–59, n = 230	36 (16)	75 (33)	114 (49)	6 (3)	
60+, n = 123	14 (11)	25 (20)	80 (65)	4 (3)	
Education					0.12
Less than high school, n = 51	5 (10)	18 (35)	25 (49)	3 (6)	
High school, n = 160	30 (19)	49 (31)	78 (49)	3 (2)	
Some college, n = 465	52 (11)	144 (31)	259 (56)	10 (2)	
Family income (US$)					0.54
≤ 30,000, n = 195	29 (15)	59 (30)	103 (53)	4 (2)	
30,000–60,000, n = 160	26 (16)	47 (29)	84 (53)	3 (2)	
Over 60,000, n = 316	32 (10)	105 (33)	170 (54)	9 (3)	
BMI					0.26
< 20, n = 66	9 (14)	20 (30)	34 (52)	3 (5)	
20–24.99, n = 203	25 (12)	57 (28)	114 (56)	7 (3)	
25–25.99, n = 185	30 (16)	55 (30)	97 (52)	3 (2)	
30+, n = 215	19 (9)	79 (37)	114 (53)	3 (1)	
SLEDAI					0.38
0, n = 267	27 (10)	83 (31)	150 (52)	7 (3)	
1–3, n = 217	32 (15)	71 (33)	112 (52)	2 (1)	
4+, n = 202	29 (14)	62 (31)	104 (51)	7 (3)	
PGA					0.37
0, n = 193	15 (8)	59 (31)	114 (59)	5 (3)	
> 0–0.99, n = 301	42 (14)	98 (33)	157 (52)	4 (1)	
1.00–1.49, n = 80	14 (18)	23 (29)	40 (50)	3 (4)	
1.50–1.99, n = 56	6 (11)	19 (34)	29 (52)	2 (4)	
2.00+, n = 48	9 (19)	16 (33)	21 (44)	2 (4)	
Vitamin D					0.011
< 40 ng/ml, n = 359	55 (15)	125 (35)	170 (47)	9 (3)	
40+ ng/ml, n = 321	33 (10)	89 (28)	192 (60)	7 (2)	
Creatinine, mg/ml					0.029
< 1.4, n = 618	76 (12)	195 (32)	334 (54)	13 (2)	
1.4–4.9, n = 15	5 (33)	4 (27)	6 (40)	0 (0)	
5.0+, n = 6	1 (17)	3 (50)	1 (17)	1 (17)	
Height, inches					0.31
< 60, n = 20	5 (25)	3 (15)	11 (55)	1 (5)	
60–62.5, n = 221	22 (10)	78 (35)	113 (51)	8 (4)	
63–67.9, n = 320	44 (14)	97 (30)	174 (54)	5 (2)	
68+, n = 113	15 (13)	33 (29)	63 (56)	2 (2)	
Ideal body weight					0.82
Less than, n = 95	14 (15)	28 (29)	50 (53)	3 (3)	
Greater than, n = 574	69 (12)	183 (32)	309 (54)	13 (2)	

HCQ: hydroxychloroquine; BMI: body mass index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; PGA: physician's global assessment.

of renal failure. When analyzed by height and ideal body weight across the groups of HCQ concentrations, we did not see any significant differences.

Our target for Vitamin D was above 40 ng/ml. It is our standard practice that those with levels < 40 ng/ml are prescribed 50,000 IU of Vitamin D per week. The majority of our patients were below target (n = 359, 52%). Those with Vitamin D levels below our target generally had lower levels of HCQ (p = 0.011). There was a correlation between blood levels of Vitamin D and HCQ levels (correlation coefficient

0.12, p < 0.0022). It was also possible that some of this increase in Vitamin D was because of the effect of HCQ on the conversion of 25(OH)– to 1,25(OH)2-D.

There were no differences seen in the distribution of blood levels of HCQ by BMI or disease activity as measured by either the SLEDAI or PGA. However, the p value for trend for decreasing SLEDAI with increasing blood levels was statistically significant (p = 0.04; Table 2). Considering those patients who had at least 1 visit with an HCQ blood level of 500 ng/ml or higher, and at least 1 visit in the subtherapeutic range, there was not a statistically significant improvement in disease activity when a therapeutic HCQ level was achieved (Table 3).

At their first HCQ measure, only 56% of the patients had levels above 500 ng/ml consistent with adherence. This proportion increased with each visit, to 80% in those who had 3 visits or more (p < 0.0001; Table 4).

DISCUSSION

Our work demonstrates that prior to instituting routine testing, up to 44% of our patients with SLE did not take their most important medication as prescribed. This is similar to the reported literature in SLE and in other chronic diseases. In SLE, pharmacy refills have shown that 51%[19] are nonadherent to their HCQ. In other chronic diseases, studies have consistently shown that 20–30% of medication prescriptions are never filled and that about 50% of medications for chronic disease are not taken as prescribed[32,33]. In our study, neither income nor education predicted adherence.

In SLE, nonadherence to medication is associated with poor outcomes. Julian, *et al*[22] reported more outpatient visits and emergency room use in those who had adherence issues. Bruce, *et al*[34] reported that patient factors were deemed the main reason for renal impairment in 5/17 (29%) individuals with SLE who went on to develop chronic renal insufficiency. In our cohort, poor PGA of compliance and patient attendance at routine outpatient appointments were associated with bad outcomes in renal disease[15]. Thus, we think that HCQ blood monitoring will be cost-effective.

Importantly, our work demonstrates that with repeated measurement and patient counseling, adherence can be significantly improved upon. In our study, it increased to 80%. Undoubtedly, there is interindividual variation in HCQ blood levels. The fact that 80% of patients achieved a level > 500 ng/ml on repeated testing suggests that a level > 500 can be considered adherent. In other chronic diseases, education and behavioral support have been shown to be effective interventions. This has been shown in renal transplantation[35], hypertension (HTN)[36,37,38], and diabetes[39,40]. In the renal transplantation literature, medication adherence has been shown to improve with multidimensional interventions[41]. These conditions are notable in that they all have measurable indications of adherence. In transplant patients, drug levels are routinely monitored. In HTN, the blood pressure can be easily followed, and in diabetes, decisions are guided by the glycosylated hemoglobin level. To date, in rheumatology we have not made routine use of any measurable indication of adherence. Further, the effect of measurement and counseling on patient adherence has not been previously reported in rheumatology. There is a probable Hawthorne effect to be taken into consideration. However, it could be argued that any change in behavior in response to an individual being monitored is the Hawthorne effect. This does not diminish the likely benefits of an intervention.

We do not know whether nonadherence to HCQ can be considered an indicator for total medication nonadherence.

Table 2. Disease activity at the first HCQ assessment by HCQ level. Values are mean (SD) unless otherwise specified.

Variables	HCQ < 15 ng/ml, n = 88	HCQ 15–500 ng/ml, n = 216	HCQ 500+ ng/ml, n = 382	p
SLEDAI	2.92 (3.62)	2.36 (2.89)	2.20 (2.64)	0.10*
PGA	0.75 (0.68)	0.63 (0.63)	0.60 (0.63)	0.14
Vitamin D	37.5 (19.75)	38.40 (16.87)	45.52 (15.56)	0.0021

* P = 0.04 for trend. HCQ: hydroxychloroquine; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; PGA: physician's global assessment.

Table 3. SLEDAI and PGA values for patients who experienced at least 1 visit in compliance (HCQ 500+ ng/ml) and 1 visit out of compliance (HCQ < 500 ng/ml). Values are mean (SD) unless otherwise specified.

Measure	Visits in Therapeutic Range	Visits Below Therapeutic Range	Difference	p*
SLEDAI, n = 246	2.37 (2.56)	2.51 (3.02)	0.14 (2.35)	0.34
PGA, n = 244	0.65 (0.59)	0.68 (0.64)	0.03 (0.43)	0.30

* P value testing whether difference is significantly different from 0. SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; PGA: physician's global assessment.

Table 4. Proportion of patients in compliance (blood level HCQ 500+) by number of previous HCQ blood level assessments.

No. Prior Visits with an HCQ Assessment	Proportion (%) with Blood Levels of 500 or More*
0	382/686 (56)
1	379/548 (69)
2	347/452 (77)
3 or more	569/714 (80)

* The p value for the trend toward higher rates as the visit number increased was < 0.0001. HCQ: hydroxychloroquine.

This is difficult to demonstrate because blood levels of most of our medications are not available. We used Vitamin D levels as a surrogate marker for other medications (although HCQ can influence Vitamin D metabolism[42,43]). There was a strong correlation between increasing Vitamin D levels and blood HCQ levels over time and a statistically significant difference when patients were compared according to their baseline HCQ level. This is in contrast to a recent work by Schoindre, *et al*[44], but there are significant differences in the dosing regimens prescribed (800–1000 IU per day vs 50,000 IU per week). Our work suggests that improved HCQ adherence may be considered a marker for other medication adherence. Although there is a suggestion in the literature that HCQ can decrease Vitamin D, it is likely that our relatively high-dose replacement therapy means that this is not the case in our work.

There was a statistically significant trend toward higher disease activity in those who had low HCQ blood levels. This was in keeping with the work by Costedoat-Chalumeau, *et al*[24] showing that lower levels were associated with higher disease activity. However, individual analysis over time did not demonstrate improvement in disease activity when therapeutic levels were attained. Similarly, when HCQ levels were increased to target, a clinical trial did not demonstrate flare reduction with the attainment of therapeutic levels[26]. The lack of improvement in disease activity with HCQ is disappointing, but does not negate the longterm benefits of HCQ. The clinical benefit of HCQ may lie more in the longterm prevention of flares and thromboses. However, HCQ did not reduce severe flares in the belimumab trials[45]. Given the accumulation of HCQ in tissues over time, it is possible that tissue levels may grant us better understanding of the relationship between the drug and its mechanisms of action, and disease activity. A limitation in our work is the lack of a time on HCQ therapy analysis.

All patients in our study were dosed based on weight (and in some cases, renal function) with a maximum dose of 400 mg per day. Despite this, a small proportion (2%) had high blood levels. It is unclear whether this supratherapeutic group may represent those who received an extra HCQ, whether it is influenced by their dosing on the day of testing or whether it may relate to decreased clearance. There is current interest in genomic variants that may affect HCQ metabolism, but we did not have access to these tests. There were no differences in HCQ levels when both height and ideal body weight were compared across the different blood concentrations. This suggests that we are correctly dosing patients based on actual rather than ideal body weight (not exceeding a dose of 400 mg per day) and indicated that dosing based on height is unnecessary. In particular, we found that many of our patients with renal insufficiency or failure appeared to be underdosed based on HCQ blood levels using our current dosing regimen.

Monitoring HCQ levels represents an important opportunity to improve medication adherence in patients with SLE. Serial monitoring and dedicated followup with clinical counseling improved medication adherence. Given the low toxicity (in particular when compared with immunosuppressives and corticosteroids) and improved longterm prognosis with HCQ therapy, strategies to maximize adherence are essential. This may have broader applicability to other rheumatological diseases.

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