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A Prospective International Study on Adherence to Treatment in 305 Patients With Flaring SLE: Assessment by Drug Levels and Self-Administered Questionnaires

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Abstract

Nonadherence to treatment is a major cause of lupus flares. Hydroxychloroquine (HCQ), a major medication in systemic lupus erythematosus, has a long half-life and can be quantified by high-performance liquid chromatography. This international study evaluated nonadherence in 305 lupus patients with flares using drug levels (HCQ <200 ng/ml or undetectable desethylchloroquine), and self-administered questionnaires (MASRI <80%). Drug levels defined 18.4% of the patients as severely nonadherent. In multivariate analyses, younger age, nonuse of steroids, higher body mass index, and unemployment were associated with nonadherence by drug level. Questionnaires classified 23.4% of patients as nonadherent. Correlations between adherence measured by questionnaires, drug level, and physician assessment were moderate. Both methods probably measured two different patterns of nonadherence: self-administered questionnaires mostly captured relatively infrequently missed tablets, while drug levels identified severe nonadherence (i.e., interruption or erratic tablet intake). The frequency with which physicians miss nonadherence, together with underreporting by patients, suggests that therapeutic drug monitoring is useful in this setting. (Trial registration: ClinicalTrials.gov: NCT01509989.)

Therapeutic management of systemic lupus erythematosus (SLE), a systemic autoimmune disorder with significant morbidity and mortality, may include nonsteroidal antiinflammatory drugs, hydroxychloroquine (HCQ), low to high doses of corticosteroids, and immunosuppressive agents, as well as biotherapies.[1] As in many other chronic diseases, the effectiveness of these treatments (at least for self-administered medication) is impaired by nonadherence to treatment, reported to vary between 3% and 76% in SLE depending on the study and assessment method used, and all have limitations.[2]

HCQ has been recognized as the cornerstone of SLE treatment; among its other beneficial effects, it reduces SLE flares.[3-7] HCQ is rapidly absorbed after oral administration (2–4 h) and is relatively unaffected by concomitant food. HCQ protein binding is about 50% to both albumin and alpha glycoprotein. The volume of distribution is very large due to extensive sequestration of the drug by tissues.[4, 8] From 21–70% of HCQ is excreted without metabolism, while the rest is mostly metabolized via cytochrome P450 2D6 (the main isoform involved in a population of Korean lupus patients),[9] 3A4, 3A5, and 2C8 isoforms.[9] Approximately half of unchanged HCQ and metabolites are excreted through the kidneys.[4, 10]

HCQ and desethylchloroquine (DCQ), its main metabolite, can be quantified by high-performance liquid chromatography (HPLC). A pharmacokinetic/pharmacodynamic (PK/PD) relation for HCQ has been found in rheumatoid arthritis,[11, 12] cutaneous lupus,[13] and SLE; a low blood HCQ level is a marker and predictor of SLE exacerbation.[14] Although the large French multicenter randomized prospective study PLUS did not confirm the interest of adapting daily HCQ dosage to its blood level in terms of efficacy, it did confirm the correlation between HCQ levels and efficacy.[15] Possibly most important, since the blood half-life of HCQ is at least 5 days, and the terminal half-life of HCQ is 43 days,[8] very low blood HCQ levels objectively indicate severe nonadherence (i.e., identify patients who have not taken HCQ for a significant period and not those who miss a few tablets).[2, 16-24]

Here we studied the frequency and determinants of nonadherence in SLE flaring patients treated with HCQ by assessing nonadherence by two different methods: blood drug assays (HCQ and DCQ levels), and patient questionnaires (Medication Adherence Self-Report Inventory scale (MASRI)). We correlated the results of these two methods with physician evaluations of nonadherence.

RESULTS

Study population

The study included 305 patients (288 women; mean (±SD) age 37.7 ± 11.6 years): 304 had blood HCQ levels assessed at inclusion and 299 completed the adherence questionnaire. Ethnic groups included 153 whites (50.2%), 83 blacks (27.2%), and 69 others (22.6%). The daily dose of HCQ was 400 mg for 219 patients (71.8%), 200 mg for 47 (15.4%), and another dose (always >200 mg) for 39 (12.8%).

Median (interquartile ranges: Q1–Q3) disease duration was 10.0 (5.0–15.0) years, and the median duration of HCQ treatment was 7.5 (3.6–12.1) years (one missing value). All patients had positive tests for antinuclear antibodies, 109 (35.7%) a history of renal involvement, and 32 (10.5%) an associated antiphospholipid syndrome (one missing value).

At inclusion, the median SLEDAI (Q1–Q3) was 8.0 (6.0–10.0). According to the SELENA-SLEDAI composite flare index, flares were mild or moderate in 173 patients (56.7%) and severe in 132 (43.3%). Flares were renal in 67 (22%), and neurological in only three (1%). They resulted in the hospitalization of 74 patients (24.3%) and an increased steroid dose for 210 (68.9%).

Nonadherence by drug levels

Among the 304 patients with drug level measurements, mean blood HCQ was 812 ± 618 ng/ml, and mean blood DCQ 122 ± 95 ng/ml. HCQ levels were very low (<200 ng/ml) in 44 (14.5%) patients, and undetectable in 22 (7.2%). DCQ was undetectable in 48 (15.8%) patients. Overall, 56 (18.4%) patients were nonadherent, as defined by a blood HCQ level below 200 ng/ml and/or undetectable blood DCQ. The proportion of nonadherent patients by drug level was 15.2% (7/46) in patients with a prescribed HCQ dose of 200 mg/d and 18.3% (40/219) in those with a 400 mg/d dose.

Univariate analyses (**Table** 1) showed that the 56 patients classified as nonadherent by drug level differed from the other patients only for age at SLE diagnosis (23.1 ± 8.9 vs. 28.0 ± 11.3; $P = 0.003$), frequency of unemployment (46.3% (25/54) vs. 30.9% (75/243), $P = 0.030$), and prescription of a steroid treatment (60.7% (34/56) vs. 79.8% (198/248), $P = 0.002$). Drug level assessment at inclusion was more often their first drug measurement (83.9% (47/56) vs. 70.9% (175/247), $P = 0.046$).

The multivariate analyses showed that younger age at diagnosis ($P < 0.001$; odds ratio (OR) per 5 years 0.71 (95% confidence interval (CI): 0.59–0.85)), nonuse of steroids ($P < 0.001$; OR 3.73 (95% CI: 1.84–7.56)), higher body mass index (BMI) ($P = 0.017$; OR per 5 kg/m^2 1.35 (95% CI: 1.06–1.72)), and unemployment ($P = 0.010$; OR 2.38 (95% CI: 1.23–4.61)) were associated with nonadherence by drug level (**Table** 2).

Effect of previous blood HCQ measurement

As part of their routine clinical management, 81/303 patients (26.7%) had undergone at least one blood HCQ measurement in the months or years preceding inclusion in the current study, and poor adherence had been diagnosed at least once for 36.8%.

At inclusion, median HCQ levels of patients with a previous blood HCQ measurement was 839 (600–1,140) vs. 637 (316–1,045) in those not previously tested. Nine of the 81 patients (11.1%) with a previous HCQ measurement were nonadherent by drug level vs. 47 of the 222 (21.2%) never tested ($P = 0.046$).

Nonadherence by self-administered questionnaires

The MASRI score for HCQ averaged 85.8 ± 20.5 (six missing values) and was <80 for 70/299 patients (23.4%). Accordingly, questionnaires classified 23.4% of the patients as nonadherent.

In the univariate analyses (**Table** 1), the 70 patients classified as nonadherent by questionnaires differed from the other patients for age at inclusion (33.3 ± 9.8 vs. 39.0 ± 11.8; $P < 0.001$) and at SLE diagnosis (23.3 ± 9.0 vs. 28.1 ± 11.4; $P < 0.001$), race (white: 38.6% (27/70) vs. 54.6% (125/229); black: 37.1% (26/70) vs. 24.5% (56/229); and other ethnicity: 24.3% (17/70) vs. 20.9% (48/229), $P = 0.0468$), and frequency of smoking (24.3% (17/70) vs. 11.9% (27/227), $P = 0.0107$).

Current hospitalization in nonadherent patients was 40.0% (28/70) vs. 19.7% (45/229) in the others (P <0.001). We note that 82.2% of whites self-reported that they were adherent vs. 68.3% of blacks and 73.8% of others (P = 0.0468).

Table 1. Characteristics of patients according to their adherence defined by blood drug measurements or by questionnaires

Patient characteristics	Total (*n* = 305)	Blood drug levels (*n* = 304)*			Questionnaires (*n* = 299)**		
		Nonadherent patients (*n* = 56)	Other patients (n = 248)	*P*	Nonadherent patients (*n* = 70)	Other patients (n = 229)	*P*
Mean Age (± SD) (yr)a	37.7 (11.6)	35.4 (10.8)	38.2 (11.7)	0.09	33.3 (9.8)	39.0 (11.8)	0.0003
Sex, female (%)	288 (94.4)	55 (98.2)	232 (93.5)	0.33	68 (97.1)	216 (94.3)	0.53
Ethnicity (%)				0.15			0.0468
White	153 (50.2)	23 (41.1)	129 (52.0)		27 (38.6)	125 (54.6)	
Black	83 (27.2)	21 (37.5)	62 (25.0)		26 (37.1)	56 (24.5)	
Other	69 (22.6)	12 (21.4)	57 (23.0)		17 (24.3)	48 (20.9)	
Highest educational level (%) (*n* = 296)				0.97			0.67
Before high school	46 (15.5)	8 (14.8)	38 (15.8)		13 (18.9)	32 (14.5)	
High school level	79 (26.7)	14 (25.9)	64 (26.6)		17 (24.6)	60 (27.1)	
After high school	171 (57.8)	32 (59.3)	139 (57.7)		39 (56.5)	129 (58.4)	

Employment status (*n* = 298)				0.03			0.59
Unemployed	100 (33.6)	25 (46.3)	75 (30.9)		25 (36.2)	73 (32.7)	
Employed or in training	198 (66.4)	29 (53.7)	168 (69.1)		44 (63.8)	150 (67.3)	
Insurance status (%) (*n* = 299)	279 (93.3)	52 (96.3)	226 (92.6)	0.55	67 (97.1)	209 (93.3)	0.38
Active smokers (%) (*n* = 303)	44 (14.5)	10 (18.2)	34 (13.8)	0.64	17 (24.3)	27 (11.9)	0.0107
History of SLE glomerulonephritis (%)	109 (35.7)	17 (30.4)	92 (37.1)	0.34	26 (37.1)	80 (34.9)	0.74
Mean age at diagnosis (± SD) (yr)	27.0 (11.0)	23.1 (8.9)	28.0 (11.3)	0.0025	23.3 (9.0)	28.1 (11.4)	0.0004
Median disease duration [Q1–Q3] (yr)	10.0 [5.0–15.0]	11.0 [7.0–17.0]	9.0 [5.0–14.0]	0.06	9.0 [5.0–13.0]	10.0 [5.0–15.0]	0.57
Median duration of HCQ use [Q1–Q3] (yr) (*n* = 304)	7.5 [3.6–12.1]	6.1 [3.9–11.0]	7.9 [3.3–12.3]	0.50	6.2 [3.7–10.5]	7.6 [3.6–12.7]	0.21
Previous blood HCQ level determination (%) (*n* = 303)	81 (26.7)	9 (16.1)	72 (29.1)	0.046	20 (28.6)	60 (26.4)	0.72

Median BMI [Q1–Q3] (*n* = 295)a	23.1 [21.2–28.0]	24.1 [21.9–29.7]	23.0 [21.1–27.8]	0.06	23.2 [20.7–28.3]	23.0 [21.2–27.9]	0.80
Median creatinine [Q1–Q3] (*n* = 297)	63 [54–76]	60 [53–70]	64 [54–79]	0.94	61 [54–76]	63 [53–76]	0.99
Median creatinine clearance [Q1–Q3] (*n* = 297)	111 [87–132]	126 [96–153]	107 [86–125]	0.005	118 [85–143]	108 [87–126]	0.18
Current steroid use (%)	233 (76.4)	34 (60.7)	198 (79.8)	0.005	50 (71.4)	178 (77.7)	0.28
Current use of immunosuppressive drug or biotherapy (%)	141 (46.2)	23 (41.1)	117 (47.2)	0.46	34 (48.6)	106 (46.3)	0.82
Severe Lupus flare (%)	132 (43.3)	20 (35.7)	112 (45.2)	0.20	36 (51.4)	92 (40.2)	0.10
Current hospitalization (%)	74 (24.3)	11 (19.6)	63 (25.4)	0.36	28 (40.0)	45 (19.7)	0.0005
Median HADS anxiety score [Q1–Q3] (*n* = 299)	8.0 [4.0–11.0]	8.0 [3.0–10.5]	8.0 [5.0–11.0]	0.30	8.0 [4.0–11.0]	8.0 [5.0–11.0]	0.99
Median HADS depression score [Q1–Q3] (*n* = 293)	6.0 [3.0–8.0]	5.5 [4.0–9.0]	6.0 [3.0–8.0]	0.38	6.0 [3.5–8.0]	6.0 [3.0–9.0]	0.45
Median VAS HCQ adherence by physician on a 0–100 scale [Q1–Q3]	85 [68–94]	75 [43–90]	87 [70–95]	$< 10^{-4}$	57 [35–85]	89 [74–95]	$< 10^{-4}$

***							
No. of patients with physician evaluation of HCQ adherence < 80 (%)***	182 (59.7)	32 (57.1)	91 (36.7)	0.005	50 (71.4)	69 (30.1)	$< 10^{-4}$
No. of patients with physician evaluation of HCQ adherence < 20 (%)***	293 (96.1)	8 (14.3)	4 (1.6)	0.0002	8 (11.4)	4 (1.7)	0.0003
Nonadherent patients with MASRI HCQ (< 80%) (*n* = 299)***	70 (23.4)	32 (57.1)	38 (15.7)	<0.001	NA	NA)	NA
Median VAS of adherence to steroid treatment by physician on a 0–100 scale [Q1–Q3] (*n* = 231)***	90 [79–97]	83 [69–90]	91 [80–99]	0.003	75 [51–90]	92 [81–99]	$< 10^{-4}$
Median blood HCQ level [range] (*n* = 304)***	717 [370–1099]	121 [0–343]	820 [220–3727]	NA	284 [127–698]	810 [525–1233]	$< 10^{-4}$
Median blood DCQ level [Q1–Q3] (*n* = 301)***	109 [60–173]	0 [0–58]	128 [34–586]	NA	52 [0–98]	124 [80–186]	$< 10^{-4}$

The number of available data is specified in the first column when data are missing.

MASRI is a self-questionnaire assessing adherence from the patient's point of view. A MASRI ≥ 80% is considered good adherence to treatment.

Patients not classified as nonadherent by drug level or questionnaire are characterized as “other” rather than adherent patients: although some may have been adherent, others may have taken only part of their HCQ treatment but not been diagnosable by HCQ measurements or might not have admitted their nonadherence.

Nonadherence by drug levels was defined by blood HCQ level <200ng/ml and/or undetectable level of DCQ. Nonadherence by questionnaires was defined by MASRI <80%. “Others” included patients perfectly adherent as well as less adherent patients with a blood level of HCQ >200ng/ml and a measurable DCQ (for drug levels) or MASRI ≥ 80% (for questionnaires).

BMI, body mass index; HCQ, hydroxychloroquine; SLE, systemic lupus erythematosus; DCQ, desethylchloroquine; HADS, Hospital Anxiety and Depression Scale; MASRI, Medication Adherence Self–report Inventory scale; SD, standard deviation; Q1–Q3, quartile 1-quartile 3; yr, year; No., number; VAS, Visual Analogue Scale.

*: 1 missing data regarding blood HCQ and DCQ levels; ** 6 patients did not complete adherence questionnaire.

***Variable not eligible for multivariate analysis.

Table 2. Multivariate analysis of predictors of nonadherence defined by blood drug measurements

	Odds ratio	95% confidence interval	*P*
Younger age at diagnosis (per 5 years)	0.71	0.59–0.85	<0.001
Absence of steroids	3.73	1.84–7.56	<0.001
Higher BMI (per 5 kg/m^2)	1.35	1.06–1.72	0.017
Being unemployed	2.38	1.23–4.61	0.010

BMI, body mass index.

According to the multivariate analyses, only younger age at diagnosis (*P* =0.002; OR per 5 years 0.79 (95% CI: 0.67–0.92)), current hospitalization (*P* = 0.001; OR 2.65 (95% CI: 1.46–4.83), and active smoking (*P* = 0.025; OR 2.26 (95% CI: 1.11–4.59)) were associated with nonadherence by questionnaire (**Table** 3).

Table 3. Multivariate analysis of predictors of nonadherence defined by questionnaires

	Odds ratio	95% confidence interval	*P*
Age at diagnosis (per 5 years)	0.79	0.67–0.92	=0.002
Current hospitalization (%)	2.65	1.46–4.83	0.001
Active smokers (%)	2.26	1.11–4.59	0.025

Overall nonadherence

In all, 94/298 patients (31.5%) were considered nonadherent to HCQ treatment by at least one criterion (drug levels or questionnaires), and 32/298 (10.7%) by both methods. Interestingly, 24 (43%) of the nonadherent patients by blood drug level (including patients with both HCQ and DCQ undetectable) would have been classified as adherent based on questionnaire.

Physicians' assessment of nonadherence

Median adherence (Q1–Q3) to HCQ treatment in the previous month was evaluated by physicians at 85 (68–94) on a visual analog scale (VAS) from 0 (complete nonadherence) to 100 (full adherence). Physicians estimated that 123/305 patients (40.3%) took less than 80% of their HCQ treatment in the previous month and that only 12/305 (3.9%) took less than 20% (**Figure** 1).

Among the 56 patients nonadherent by drug level, physician's median adherence assessment was 75.1 (42.7–89.6) vs. 87.0 (70.0–95.1) for the other patients ($P < 0.0001$). Physicians estimated that 32/56 (57.1%) of the patients nonadherent by drug level took less than 80% of their treatment and that only 8/56 (14.3%) took less than 20%.

Correlation between adherence by drug level, by questionnaire, and by physician assessment

The correlation between adherence by drug level and by questionnaire was moderate (**Table** 4), with a Spearman rank correlation (r_s) of 0.37. Correlation between adherence by questionnaire and physician assessment was also moderate, with an r_s of 0.43. The correlation between adherence by drug level and physician assessment was weaker, with an r_s of 0.19 and even worse when patients with a previous blood HCQ measurement were excluded ($r_s = 0.16$). This did not affect the other correlations, however.

Table 4. Spearman correlation coefficient between blood drug levels, lupus activity, HADS, questionnaires, and physician adherence evaluation

	DCQ levels	SLEDAI score	HADS Anxiety	HADS Depression	MASRI HCQ score			HCQ physician VAS	Steroid physician VAS
HCQ levels	0.90	−0.06	0.07	−0.04	0.37			0.19	0.21
DCQ levels		−0.05	0.13	−0.01	0.36			0.19	0.23
SLEDAI score			−0.08	0.02	0.04			0.10	−0.02
HADS Anxiety				0.63	0.00			−0.06	−0.05
HADS Depression					−0.06			−0.03	0.01
MASRI HCQ score								0.43	0.41
HCQ physician VAS									0.77

HCQ, hydroxychloroquine; SLE, systemic lupus erythematosus; DCQ, desethylchloroquine; HADS, Hospital Anxiety and Depression Scale; MASRI, Medication Adherence Self-report Inventory scale.

Nonadherence to prednisone and immunosuppressive drugs

In addition to HCQ, 233/305 patients (76.4%) were treated with prednisone, and 141/305 patients (46.2%) with immunosuppressive drugs or biotherapies at inclusion. Physicians evaluated median adherence (Q1–Q3) to HCQ and steroids in the previous month at 84.6 (68.0–94.3) and 90.3 (79.1–97.1), respectively. **Table** 4 shows a strong correlation between evaluation of nonadherence to HCQ and evaluation of nonadherence to other SLE medications.

DISCUSSION

This prospective international study of flaring SLE patients showed nonadherence rates to HCQ treatment of 18.4% by drug level, 23.4% by questionnaire, and 31.5% overall. Nonadherence to other SLE treatments (especially steroids) could not be objectively measured but physician-estimated adherence to HCQ and to steroids correlated well.

Evaluating nonadherence is difficult: methods vary widely and do not capture the same patterns of nonadherence.[2, 16, 18, 20, 25-41] Studies using self-administered questionnaires report that 17–30%[2, 40] of patients take less than 80% of their treatment. Consistently, only 23.4% of our patients admitted HCQ adherence below 80% with the MASRI. Given that <80% is a high threshold for nonadherence, such small numbers (for the MASRI) are very encouraging. Nonetheless, these questionnaires, based on what patients are willing to admit, are not objective and underestimate nonadherence.[2] More objective methods report strikingly higher nonadherence rates. Using electronic monitoring over a 2-year period, Marengo *et al*. showed that 76% of the 78 participating patients had an adherence rate below 80%.[35] In a recent large study using pharmacy refill information from US Medicaid data, Feldman *et al*. found that 79% of 9,600 new users of HCQ had an adherence rate <80%.[42] These objective nonadherence rates are much higher than the 23.4% self-reported nonadherence rate (with MASRI score) and the 40.3% physician-estimated nonadherence rate in our study, which are probably highly optimistic, especially as we assessed flaring patients, known to be at higher risk of nonadherence.[42]

Few studies have assessed adherence by blood HCQ measurements. We previously reported that 14 of 203 patients (7%) had HCQ levels lower than 200 ng/ml and thereafter admitted severe nonadherence.[20] Ting *et al*., defining nonadherence by a blood HCQ level less than 100 ng/ml, found that 12 of 41 adolescents and young adults with SLE (29%) were nonadherent.[16] Moreover, adherence estimated with blood HCQ correlated well with that measured by pharmacy refill information.[16] Recently, Iudici *et al*., using the same cutoff of 100 ng/ml, found that 24 of 83 SLE patients (29%) in remission were nonadherent.[24] Using a level below 15 ng/ml, Durcan *et al*. found that 88 of 686 patients (13%) were severely nonadherent.[21] Here we found a nonadherence rate of 14.5% with HCQ levels only and 18.4% when we also considered undetectable DCQ levels. These percentages are in keeping with the 5–10% of patients who completely stopped or frequently interrupted tablet ingestion in studies using electronic monitoring.[43, 44] Blood drug level measurements can objectively detect only severe nonadherence (i.e., absence of any treatment or intake of only a few tablets), since high HCQ levels may be reached within days after treatment resumes[19] due especially to flares or simply the "white-coat" compliance effect.[2] Accordingly, rates of nonadherence by drug levels are likely to reveal only the tip of the iceberg. It is nonetheless worth knowing, both because of its deleterious consequences, and because physicians are frequently unaware of it.

The lack of overlap between questionnaires and drug levels, which probably measure different patterns of nonadherence, is reflected by the moderate correlation between these methods. Thus, two separate and independent patterns of nonadherence have been described[43]: 1) tablets missed relatively infrequently (but more than 20%), and 2) tablet intake completely stopped or frequently interrupted and erratic. Interestingly, some patients with undetectable levels of both HCQ and DCQ (i.e., who had not taken any treatment for some time) had MASRI scores greater than 80%. This observation suggests that some patients are very reluctant to admit severe nonadherence, perhaps even to themselves. We may hypothesize that questionnaires can capture the first pattern, while very low blood drug levels identify only the latter. These methods may thus be regarded as complementary.

The factors associated with nonadherence by drug level by multivariate analyses were age (younger) at diagnosis, nonuse of steroids, BMI, and unemployment, whereas those associated with nonadherence by questionnaire were age at diagnosis, current hospitalization, and active smoking. The absence of steroid prescriptions may reflect milder disease, whereas younger age at diagnosis, BMI, unemployment and active smoking are standard factors of nonadherence.

Improving treatment adherence is very difficult. Studies have used different methods, often complex and time-consuming, but have found inconstant and only small effects on adherence.[2] By contrast, Durcan *et al*.[21] showed in a large cohort that routine measurement of HCQ levels usually led to adherence improvement over time. Our study confirms the potential value of repeated assays to improve adherence: patients with at least one previous HCQ measurement were less likely to be nonadherent by drug level. Our experience is that physicians are sometimes very surprised to discover nonadherence by drug level, particularly in patients who never miss medical appointments and who regularly perform ophthalmological tests to detect HCQ toxicity. Consistently, we found a poor correlation between nonadherence by drug level and by physician assessment. This is not surprising, as clinical judgment of adherence has been found wanting in almost every relevant study.[45] A more pessimistic interpretation of our result (and those of Durcan *et al*.[21]), however, is that some patients may briefly improve HCQ adherence because they suspect they might be tested at their next clinical visit.[19] In this setting, undetectable levels of DCQ might be particularly interesting, since unmasking nonadherence is the first step in trying to improve it.

Our study has some limitations. First, there is no gold standard method for measuring nonadherence. We used a previously validated HCQ cutoff,[20] but other cutoffs could have been used.[16, 21, 24] Although our clinical experience since our first publication[20] confirms the clinical relevance of this cutoff (200 ng/ml), no large study has conducted retrospective interviews of patients to confirm nonadherence. Second, multiple corticosteroids have been found to induce higher levels of expression of the CYP (2D6) that metabolizes HCQ.[46] The high doses of corticosteroids that flaring lupus patients may receive could serve as a confounding factor that lowers their HCQ levels and thus results in overestimation of nonadherence by therapeutic drug monitoring. However, CYP metabolism is not the major route of elimination for HCQ; the 2D6 isoform may not be the main isoform involved in non-Korean populations; the drug is sequestered in tissues; our definition used for severe nonadherence was relatively stringent; and most of our patients had undetectable DCQ levels. These facts make it unlikely that this mechanism could have significantly altered our results. Third, although it is logical from a pharmacological perspective to look for undetectable DCQ levels, its use requires further validation. Fourth, we were unable to

objectively assess nonadherence to steroids and immunosuppressive drugs by assays, because of their much shorter half-life. Furthermore, our inclusion of only flaring patients precludes the generalization of our figures to all lupus cohorts: flares could have led to an overestimation of nonadherence given the inverse association between adherence and lupus activity, but also to an underestimation since patients might have resumed their treatment between the onset of the flare and the inclusion in the study. Similarly, since some of our centers routinely use drug levels to assess adherence (a quarter of our patients had previously been assessed for HCQ level, before inclusion), nonadherence might have been underestimated. Finally, because this study took place mainly in expert SLE centers and was aimed at detecting nonadherence, participation necessarily increased clinicians' awareness of this issue. In real life, the poor correlation between physician evaluation and confirmed nonadherence might be even worse.

In conclusion, almost a third of our patients were nonadherent and 20% were objectively severely nonadherent, often without their physicians' knowledge. Questionnaires and drug levels captured different patterns of nonadherence and seem complementary. Questionnaires are simple and inexpensive but underestimate nonadherence and are rarely used for practical reasons. Blood drug measurements are easier to implement in a routine clinical setting, but detect only severe nonadherence. Finally, given the pivotal importance of keeping steroid use as low as possible in SLE patients[6] and considering that the steroid dose had to be increased in 68.9% of these flaring patients, unmasking nonadherence in this subset of patients is really useful, for it may avoid unnecessary treatment escalation. We thus recommend routinely measuring HCQ drug levels and using questionnaires as tools to assess nonadherence in SLE patients on HCQ.

METHODS

Patients

The study was an international, prospective, observational multicenter study conducted from January 2013 through June 2015 in 19 centers in 10 countries. Patients were included if they fulfilled the following inclusion criteria 1) diagnosis of SLE according to the SLICC classification criteria[47]; 2) HCQ treatment for at least 2 months with a stable daily HCQ dosage of at least 200 mg; and 3) SLE flare, as defined by the SELENA-SLEDAI flare composite score.[48] This score defines mild-to-moderate and severe flares and includes three elements: the SELENA-SLEDAI score; an assessment of new or worsening disease activity, medication changes, and hospitalizations not captured by the SLEDAI alone; and physician's global assessment (PGA) on a VAS (from 0 to 3).[48]

Patients were excluded if they were unable to take oral medications or had received chloroquine in the past 2 months (because it interferes with blood HCQ measurements).

At inclusion, patients underwent a complete physical examination and local laboratory testing including a complement assay and antidouble-stranded DNA antibody assays. Whole-blood HCQ and DCQ levels were measured in a centralized laboratory (Paris, France) by HPLC with fluorometric detection.[14] The patient's physician scored all components of the flare composite index and estimated adherence to HCQ treatment (and to other SLE treatments when relevant) in the past month on a VAS ranging from 0 (complete nonadherence) to 100 (full adherence). Patients

completed self-administered questionnaires: one dealing with treatment adherence (described below), and the Hospital Anxiety and Depression Scale (HADS),[49] which measures anxiety and depression.[49] It is a 14-item scale (7 relating to anxiety and 7 to depression) with a 4-point (0–3) response category, so that both anxiety and depression scores can range from 0 to 21. A score of 0 to 7 for each subscale is interpreted as within the normal range, a score of 11 or higher as indicating a probable mood disorder, and a score of 8 to 10 as suggestive of it.[50]

Evaluation and definition of nonadherence

Adherence was evaluated by drug levels and by one questionnaire: part A of the Medication Adherence Self-Report Inventory scale (MASRI)[33].

The MASRI is a self-administered questionnaire assessing adherence from the patient's point of view. An MASRI ≥80% is considered good adherence to treatment. Part A consists of five 4-point scale items and one VAS item. The latter asks patients how much medication they have taken in the past month on a scale from 0% to 100% and is the only item used to estimate adherence quantitatively. The other five items simply assist patients in estimating their adherence.

Nonadherence was defined in three ways: by drug levels, by questionnaires, and by overall nonadherence. Nonadherence by drug level was defined by blood HCQ level <200 ng/ml as previously validated, or by undetectable blood DCQ, indicating either the complete absence of HCQ treatment (when HCQ levels are also undetectable) or very recent treatment resumption (when very low HCQ levels are detected). Nonadherence by questionnaires was defined as MASRI <80%. Overall nonadherence was defined as nonadherence by either criterion.

Study oversight

The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. A French ethics committee (Saint-Louis Hospital) and the local Institutional Review Boards for each center approved the study protocol. All participants provided written informed consent.

Statistical analysis

Qualitative variables are described by proportions and percentages, and quantitative variables by means and standard deviations (SDs) or medians and interquartile ranges (Q1–Q3). The chi-square test (or Fisher's test, as appropriate) and Student's *t*-test (or the Mann–Whitney *U*-test) tested differences between nonadherent and other patients. Multiple logistic regressions were used to identify the variables independently associated with nonadherence. Every variable with $P < 0.15$ by univariate analysis was included in the multivariable regression model, except for age, to avoid multicollinearity between age and age at diagnosis. Similarly, because creatinine was not associated with nonadherence by drug level, creatinine clearance was excluded to avoid multicollinearity with BMI. We performed stepwise selection after performing 1,000 bootstrap resamplings to assess the consistency of variable selection across randomly resampled datasets. Variables that appeared in at least 60% of the models were retained. Results are expressed as odds ratios with their 95% CIs. Spearman rank correlations were used to assess the relations between adherence by drug level, by questionnaire, and by physician assessment. Statistical significance was defined by $P < 0.05$. The statistical analysis used SAS 9.3 (SAS Institute, Cary, NC).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

N.C.-C. wrote the article; N.C.-C., J.-C.P., M.P., and D.I. designed the research; N.C.-C., F.H., P.I., V.L., S.N., M.J., G.R.-I., G.B., E.H., N.A.-L., Y.S., F.D., J.B., C.D., R.C., E.L., H.B., G.L., N.M., J.-F.V., C.P., L.G., R.v.V., A.T., H.N., G.G., J.P., J.-C.P., M.P., and D.I. performed the research; N.C.-C. and G.B. analyzed the data; N.Z. contributed new reagents/analytical tools. The last two authors contributed equally to this work.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Nonadherence to treatment in SLE varies widely depending on the study and assessment method used. Frequency of nonadherence in SLE patients with flares, who are thereby candidates for treatment escalation or may enter pharmaceutical trials, is unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ For the first time, we evaluated nonadherence to HCQ treatment in SLE patients with flares using drug levels and self-questionnaires.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ Drug levels objectively identified that one patient in five was severely nonadherent, often without the physician's knowledge.

HCQ levels and self-administered questionnaires measured two different patterns of nonadherence: questionnaires mostly captured relatively infrequently missed tablets, while very low blood drug levels identified complete interruption or erratic tablet intake.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

☑ The frequency with which physicians miss nonadherence, together with underreporting by patients, suggest that therapeutic drug monitoring is useful in real life and should be a prerequisite to inclusion in pharmaceutical trials.

Figure Legend

Figure 1: Adherence as estimated by physicians. In the histograms, the dark gray rectangles represent nonadherent patients by drug levels, and the light gray rectangles the others. The patient's physician scored all components of the flare composite index and estimated adherence to HCQ treatment in the past month on a VAS ranging from 0 (patient took no treatment) to 100 (patient took all treatment). Physicians estimated that 123/305 patients (40.3%) took less than 80% of their HCQ treatment in the previous month and that only 12/305 (3.9%) took less than 20% of it. Physicians considered many of the nonadherent patients by drug levels to be adherent (circle).

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