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A prospective international study on adherence to treatment in 305 patients with flaring SLE: assessment by drug levels and by 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 HPLC.

This international study evaluated nonadherence in 305 lupus patients with flares using drug levels (HCQ<200ng/ml or undetectable desethylchloroquine), and self-administered questionnaires (MASRI<80% or MMAS-8<6).

Drug levels defined 18.4% of the patients as severely nonadherent. In multivariate analyses, younger age, non-use of steroids, higher BMI and unemployment were associated with nonadherence by drug level. Questionnaires classified 39.9% 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 under-reporting by patients, suggests that therapeutic drug monitoring is useful in this setting.

Trial registration: [ClinicalTrials.gov: NCT01509989](https://clinicaltrials.gov/ct2/show/study/NCT01509989)

Keywords

Hydroxychloroquine; blood concentration; blood levels; systemic lupus erythematosus; adherence; desethylchloroquine

Therapeutic management of systemic lupus erythematosus (SLE), a systemic autoimmune disorder with significant morbidity and mortality, may include nonsteroidal anti-inflammatory 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

Hydroxychloroquine 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 to 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 importantly, 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 2 different methods: blood drug assays (HCQ and DCQ levels), and patient questionnaires (Medication Adherence Self-Report Inventory scale (MASRI) and the Morisky Medication Adherence Scale (MMAS-8)). We correlated the results of these two methods with physician evaluations of nonadherence.

RESULTS

Study population

The study included 305 patients (288 women; mean ($\pm$ SD) age 37.7 $\pm$ 11.6 years): 304 had blood HCQ levels assessed at inclusion and 303 completed at least 1 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 (1 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 (1 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 3 (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 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 versus 28.0 ± 11.3 ; $P=0.003$), frequency of unemployment (46.3% (25/54) versus 30.9% (75/243), $P=0.030$), and prescription of a steroid treatment (60.7% (34/56) versus 79.8% (198/248), $P=0.002$). Drug level assessment at inclusion was more often their first drug measurement (83.9% (47/56) versus 70.9% (175/247), $P=0.046$).

The multivariate analyses showed that younger age at diagnosis ($P<0.001$; OR per 5 years 0.71 [95% CI: 0.59–0.85]), non-use of steroids ($P<0.001$; OR 3.73 [95% CI: 1.84–7.56]), higher BMI ($P=0.017$; OR per 5 kg/m² 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 [600–1140] versus 637 [316–1045] in those not previously tested. Nine of the 81 patients (11.1%) with a previous HCQ measurement were nonadherent by drug level versus 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 (6 missing values) and was <80 for 70/299 patients (23.4%); the MMAS-8 score for HCQ averaged 6.1 ± 2.0 (4 missing values) and was <6 for 112/301 patients (37.2%). Accordingly, questionnaires classified 121/303 patients (39.9%) as nonadherent.

In the univariate analyses (Table 1), the 121 patients classified as nonadherent by questionnaires differed from the other patients for age at inclusion (34.7 ± 10.0 versus 39.7 ± 12.2 ; $P < 0.001$) and at SLE diagnosis (24.2 ± 8.8 vs 29.0 ± 12.0 ; $P = 0.001$), race (white: 37.2% [45/121] vs 59.3% [108/182]; black: 34.7% [42/121] vs 22.5% [41/182]; and other ethnicity: 28.1% [34/121] vs 18.1% [33/182], $P = 0.0008$) and frequency of steroid treatment (68.6% [83/121] vs 81.3% [148/182], $P = 0.011$). Current hospitalization in nonadherent patients was 29.8% (36/121) versus 20.3% (37/182) in the others ($P = 0.060$). We note that 70.6% of whites self-reported that they were adherent versus 49.4% of blacks and 49.3% of others ($P = 0.0008$).

According to the multivariate analyses, only younger age at diagnosis ($P < 0.001$; OR per 5 years 0.79 [95% CI: 0.70–0.90]), race (black versus white: $p = 0.015$; OR 2.03 [95% CI: 1.15–3.61]), and another ethnicity versus white: $p = 0.012$; OR 2.19 [95% CI: 1.19–4.06]), and non-use of steroids ($P = 0.005$; OR 2.29 [95% CI: 1.28–4.10]) were associated with nonadherence by questionnaire (Table 3).

Overall nonadherence

In all, 137/302 patients (45.4%) were considered nonadherent to HCQ treatment by at least one criterion (drug levels or questionnaires), and 40/302 (13.2%) 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 at least one of the two questionnaires.

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 for the MASRI HCQ and of 0.31 for the MMAS-8 HCQ. Correlation between adherence by questionnaire and physician assessment was also moderate with an r_s of 0.43 for the MASRI HCQ and 0.36 for the MMAS-8 HCQ. 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.

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, regardless of mode of evaluation.

DISCUSSION

This prospective international study of flaring SLE patients showed nonadherence rates to HCQ treatment of 18.4% by drug level, 39.9% by questionnaire, and 44.9% overall. Nonadherence to other SLE treatments (especially steroids) could not be objectively measured but self-reported nonadherence to HCQ and to other treatments as well as 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 two-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 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, Ludici *et al.*, using the same cut-off 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 resumes¹⁹

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 (a) tablets missed relatively infrequently (but more than 20%) and (b) 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, non-use of steroids, BMI, and unemployment whereas those associated with nonadherence by questionnaire were age at diagnosis, steroid non-use, and race (black or another ethnicity, versus white). The absence of steroid prescriptions may reflect milder disease, whereas younger age at diagnosis, BMI, and unemployment are standard factors of nonadherence. Nonwhite patients reported nonadherence by questionnaire more frequently, but drug levels did not differentiate severe nonadherence according to ethnicity.

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.* 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 cut-off,²⁰ but other cut-offs could have been used.^{16, 21, 24} Although our clinical experience since our first publication²⁰ confirms the clinical relevance of this cut-off (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 half of 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 routine clinical setting, but detect only severe nonadherence. Finally, given the pivotal importance of keeping steroid use as low as possible in SLE patients⁶ 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.

PATIENTS AND 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 3

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 anti-double-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 3 self-administered questionnaires: 2 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 2 questionnaires: part A of the Medication Adherence Self-Report Inventory scale (MASRI)³³ and the Morisky Medication Adherence Scale (MMAS-8). Patients treated with other SLE medication completed separate MASRI and MMAS-8 forms for "other SLE medication," which included (in the same questionnaires) steroids, immunosuppressive drugs, and biotherapies.

The MASRI is a self-administered questionnaire assessing adherence from the patient's point of view. A 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 5 items simply assist patients in estimating their adherence. The MMAS-8 is an 8-item questionnaire that produces scores ranging from 0 to 8; higher scores indicate higher adherence.

Nonadherence was defined in 3 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% and/or MMAS-8 <6. 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 (SD) 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 multiple-variable 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 body mass index (BMI). We performed stepwise selection after performing 1000 bootstrap re-samplings to assess the consistency of variable selection across randomly resampled data sets. Variables that appeared in at least 60% of the models were retained. Results are expressed as odds ratios with their 95% confidence intervals (95%CI). Spearman rank correlations were used to assess the relations between adherence by drug level, by questionnaire, and by physician assessment. Receiver operating characteristics (ROC) analysis was used to evaluate the ability of MASRI and MMAS-8 values to discriminate between adherence and nonadherence, with nonadherence by drug level as the reference standard. Youden's index [(sensitivity + specificity) – 1] was used to identify the cut-off points for MASRI and MMAS-8 that optimized sensitivity and specificity. Statistical significance was defined by $P < 0.05$. The statistical analysis used SAS 9.3 (SAS Inst. Inc., Cary, NC, USA).

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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 1 patient in 5 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 under-reporting by patients, suggest that therapeutic drug monitoring is useful in real life and should be a prerequisite to inclusion in pharmaceutical trials.

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).

Table 1

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

Patient characteristics	Blood drug levels (n=304)*				Questionnaires (n=303)**		
	Total (n=305)	Non-adherent patients (n=56)	Other patients (n = 248)	P	Non-adherent patients (n=121)	Other patients (n = 182)	P
Mean Age (± SD) (yr) ***	37.7 (11.6)	35.4 (10.8)	38.2 (11.7)	0.09	34.7 (10.0)	39.7 (12.2)	0.0002
Sex, female (%)	288 (94.4)	55 (98.2)	232 (93.5)	0.33	117 (96.7)	170 (93.4)	0.21
Ethnicity (%)							
- White	153 (50.2)	23 (41.1)	129 (52.0)	0.15	45 (37.2)	108 (59.3)	0.0008
- Black	83 (27.2)	21 (37.5)	62 (25.0)		42 (34.7)	41 (22.5)	
- Other	69 (22.6)	12 (21.4)	57 (23.0)		34 (28.1)	33 (18.1)	
Highest educational level (%) (n=296)							
- Before high school	46 (15.5)	8 (14.8)	38 (15.8)	0.97	20 (17.1)	26 (14.7)	0.78
- High school level	79 (26.7)	14 (25.9)	64 (26.6)		29 (24.8)	49 (27.7)	
- After high school	171 (57.8)	32 (59.3)	139 (57.7)		68 (58.1)	102 (57.6)	
Employment status (n=298)							
- Unemployed	100 (33.6)	25 (46.3)	75 (30.9)	0.03	36 (30.8)	63 (35.2)	0.43
- Employed or in training	205 (66.4)	29 (53.7)	168 (69.1)		81 (69.2)	116 (64.8)	
Insurance status (%) (n=299)	279 (93.3)	52 (96.3)	226 (92.6)	0.55	111 (93.3)	167 (93.8)	0.85
Active smokers (%) (n=303)	44 (14.5)	10 (18.2)	34 (13.8)	0.64	22 (18.3)	22 (12.2)	0.12
History of SLE glomerulonephritis (%)	101 (33.1)	17 (30.4)	92 (37.1)	0.34	42 (34.7)	65 (35.7)	0.86
Mean age at diagnosis (± SD) (yr)	27.0 (11.0)	23.1 (8.9)	28.0 (11.3)	0.0025	24.2 (8.8)	29.0 (12.0)	0.001
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 [5.0–15.0]	10.0 [5.0–15.0]	0.74
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	6.8 [4.0–11.5]	7.6 [3.1–12.7]	0.82
Previous blood HCQ level determination (%) (n=303)	81 (26.7)	9 (16.1)	72 (29.1)	0.046	30 (24.8)	50 (27.8)	0.57
Median BMI [Q1–Q3] (n=295) ***	23.1 [21.2–28.0]	24.1 [21.9–29.7]	23.0 [21.1–27.8]	0.06	23.1 [20.6–28.3]	23.1 [21.3–27.9]	0.95
Median creatinine [Q1–Q3] (n=297)	63 [54–76]	60 [53–70]	64 [54–79]	0.94	63 [54–76]	63 [53–75]	0.23
Median creatinine clearance [Q1–Q3] (n=297)	111 [87–132]	126 [96–153]	107 [86–125]	0.005	108 [86–134]	112 [88–129]	0.89
Current steroid use (%)	233 (76.4)	34 (60.7)	198 (79.8)	0.005	83 (68.6)	148 (81.3)	0.02
Current use of immunosuppressive drug or biotherapy (%)	141 (46.2)	23 (41.1)	117 (47.2)	0.46	53 (43.8)	87 (47.8)	0.73

Patient characteristics	Blood drug levels (n=304)*			Questionnaires (n=303)**		
	Total (n=305)	Non-adherent patients (n=56)	Other patients (n=248)	P	Non-adherent patients (n=121)	Other patients (n=182)
Severe Lupus flare (%)	132 (43.3)	20 (35.7)	112 (45.2)	0.20	56 (46.3)	74 (40.7)
Current hospitalisation (%)	74 (24.3)	11 (19.6)	63 (25.4)	0.36	36 (29.8)	37 (20.3)
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	7.5 [4.5–10.0]	8.0 [4.0–11.0]
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 [3.0–8.0]	6.0 [2.0–9.0]
Median VAS HCQ adherence by physician on a 0–100 scale [Q1–Q3] ***	85 [68–94]	75 [43–90]	87 [70–95]	< 10 ⁻⁴	75 [50–89]	90 [74–96]
No. of patients with physician evaluation of HCQ adherence < 80 (%) ***	182 (59.7)	32 (57.1)	91 (36.7)	0.005	63 (52.1)	59 (32.4)
No. of patients with physician evaluation of HCQ adherence < 20 (%) ***	293 (96.1)	8 (14.3)	4 (1.6)	0.0002	11 (9.1)	1 (0.5)
Non-adherent patients with MASRI HCQ (< 80%) (n=298) ***	70 (23.4)	32 (57.1)	38 (15.7)	< 0.001	70 (58.3)	0 (0.0)
Non-adherence to HCQ by self-questionnaires (MASRI < 80 OR MMAS-8 < 6) (n=302) (%) ***	121 (39.9)	40 (71.4)	81 (32.9)	< 10 ⁻⁴	121 (100)	0 (0.0)
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	80 [65–93]	94 [85–99]
Median blood HCQ level [range] (n=304) ***	717 [370–1099]	121 [0–343]	820 [220–3727]	NA	556 [186–899]	800 [526–1221]
Median blood DCQ level [Q1–Q3] (n=301) ***	109 [60–173]	0 [0–58]	128 [34–586]	NA	80 [0–153]	123 [82–185]

Legends: 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; MMAS-8: Morisky Medication Adherence Scale. SD: standard deviation; Q1–Q3: quartile 1–quartile 3; yr: year; No.: number. VAS: Visual Analogue Scale. 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.

The MMAS-8 is an 8-item questionnaire, producing scores ranging from 0 to 8; higher scores indicate higher adherence.

Patients not classified as non-adherent by drug level or questionnaire are characterised 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 non-adherence.

Non-adherence by drug levels was defined by blood HCQ level < 200 ng/ml and/or undetectable level of DCQ. Non-adherence by questionnaires was defined by MASRI < 80% and/or MMAS-8 < 6. “Others” included patients perfectly adherent as well as less adherent patients with a blood level of HCQ > 200 ng/ml and a measurable DCQ (for drug levels) or either MASRI 80% or MMAS-8 6 (for questionnaires).

* : 1 missing data regarding blood HCQ and DCQ levels;

** 2 patients did not complete any adherence questionnaire.

*** Variable not eligible for multivariate analysis.

Table 2

Multivariate analysis of predictors of non-adherence 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

Legends: BMI: body mass index.

Table 3

Multivariate analysis of predictors of non-adherence defined by questionnaires.

	Odds ratio	95% confidence interval	p
Age at diagnosis (per 5 years)	0.79	0.70–0.90	<0.001
Absence of steroids	2.29	1.28–4.10	0.005
Ethnicity			
Black vs white	2.03	1.15–3.61	0.015
Other vs white	2.19	1.19–4.06	0.012

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	MMAS-8 @HCQ @score	MMAS-8 @other @medication @score	HCQ @physician @VAS	Steroid @physician @VAS
HCQ levels	0.90	-0.06	0.07	-0.04	0.37	0.31	0.20	0.19	0.21
DCQ levels		-0.05	0.13	-0.01	0.36	0.30	0.20	0.19	0.23
SLEDAI score			-0.08	0.02	0.04	0.03	-0.03	0.10	-0.02
HADS Anxiety				0.63	0.00	0.01	-0.13	-0.06	-0.05
HADS Depression					-0.06	-0.01	-0.18	-0.03	0.01
MASRIHCQ score						0.75	0.63	0.43	0.41
MMAS-8 HCQ score							0.83	0.36	0.38
MMAS-8other medication score								0.30	0.33
HCQ physician VAS									0.77

Legends: HCQ Hydroxychloroquine; SLE: Systemic lupus erythematosus; DCQ: desethylchloroquine; HADS: Hospital Anxiety and Depression Scale; MASRI: Medication Adherence Self-report Inventory scale; MMAS-8: Morisky Medication Adherence Scale.