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Adherence to treatment in systemic lupus erythematosus patients

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A B S T R A C T

Adherence is defined as "the extent to which a person's behaviour coincides with medical or health advice." Poor adherence to therapeutic regimens is a common and expensive problem in patients with chronic diseases including systemic lupus erythematosus (SLE) and is associated with a higher risk of flares, morbidity, hospitalisations and poor renal outcome. Non-adherence to the treatment is multifactorial for most patients and varies according to unintentional or intentional patterns. The rates of non-adherence in SLE patients range from 3% to 76% depending on the assessment methods, which are all subject to limitations. Indeed, poor adherence to therapeutic regimens is difficult to evaluate. Two studies have shown that undetectable blood hydroxychloroquine (HCQ) concentration may be a simple, objective and reliable marker of

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non-adherence in SLE patients. The accurate diagnosis of non-adherence may prevent one from incorrectly interpreting disease manifestations as a lack of response. It may then avoid an unnecessary or even dangerous treatment escalation.

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A. Definitions of adherence

The therapeutic management of systemic lupus erythematosus (SLE) is based on the type and severity of organ involvement and includes non-steroidal anti-inflammatory drugs, corticosteroids, hydroxychloroquine (HCQ) and immunosuppressive agents. The recent availability of new biological treatments, especially monoclonal antibodies, will modify this classic therapeutic approach. These new biologics are mostly targeted at patients with active disease [1]. However, one of the main causes of persistent SLE activity despite treatment may be the lack of adherence to the treatment since "drugs don't work in patients who don't take them." [2] To avoid unnecessary treatment escalation, physicians should recognise non-adherent patients as accurately as possible, even if we acknowledge that this task is quite challenging. In this review, we first define adherence, and then we successively analyse the literature regarding the tools to assess non-adherence, the adherence rate in the general population and, specifically in SLE patients, the consequences of non-adherence, its determinants (also referred to as the barriers to adherence) and the actions that can be implemented to (try to) improve adherence.

Adherence or compliance, terms that differ mainly with regard to the patient's active involvement (or lack thereof), is defined as "the extent to which a person's behaviour (taking medication, following a diet programme, or modifying her/his lifestyle), corresponds with agreed recommendations from a health care provider." [3,4]. The term 'adherence' is preferred by many health-care providers. Indeed, 'compliance' suggests that the patient is passively following the doctor's advice and that the treatment plan is not based on a therapeutic alliance or contract established between the patient and her/his physician. The notion of persistence refers to the ability of the patient to continue to take her/his treatment for the duration of the prescription.

The rate of adherence is usually reported as the percentage of the prescribed doses of the medication actually taken by the patient over a specified period of time. No consensual standard defines the adequate adherence. Most of the studies consider that rates $>80\%$ are acceptable, but in some conditions (e.g., infection with the human immunodeficiency virus), rates $>95\%$ may be required. By contrast, rates $<20\%$ are generally used to define non-adherence. However, it is not always possible to distinguish between non-adherent and adherent patients since there is a continuum from 0 to $>100\%$ (a few patients may take more than the prescribed amount of a drug).

The behaviour of non-adherent patients may vary widely. Consequently, non-adherence can be total or partial, continuous or intermittent, intentional or unintentional and recognised by the patient or not.

B. Available tools to assess non-adherence

Poor adherence to therapeutic regimens is difficult to evaluate [2], partly "because it is a task-specific behaviour rather than a personality trait." [5] Several methods can be used. Patient self-reports, clinician's assessments and keeping appointments are disputable. Non-adherence may be under-reported by patients, the physician global assessment is highly subjective and inaccurate (including in our experience), and failure to attend scheduled visits is not easy to assess routinely and not necessarily correlated with poor adherence to treatment. The pill count, refilling approach and use of electronic monitoring devices are three methods of the direct measure of adherence based on the treatment intake. The pill count means that a physician or another person counts the pills the patient has brought back. The refilling approach needs a closed pharmacy system that allows counting how many tablets the patient had filled in the pharmacy, to compare the result to the theoretical number of tablets prescribed by the physician. Electronic monitoring devices record the opening of the pill container. The mean proportion of days covered (often referred to as PDC) is then calculated. These

methods are not routinely applicable except for the rate of refilling prescription in some specific areas using electronic medical records and a closed pharmacy system (e.g., Canada). These methods are also subject to limitations, the most important being that adherence may be overestimated as the patient may not have ingested the pills that are missing/have been filled/have been removed from the pill container. However, while patients may occasionally open their bottles without taking their medications, such behaviour over several months would require a very unusual 'routine trickery'. Then, provided they are used for a sufficient period of time to allow the patient to behave 'normally', it is usually considered that electronic monitoring devices are the gold standard for assessing adherence, only surpassed by direct intake observation, which is impractical for daily oral therapies.

Other methods use clinical or biological markers of non-adherence. For example, the absence of bradycardia in patients treated with beta-blockers or of 'Cushing-like' appearance in patients treated with high-dose corticosteroids may raise suspicion of non-adherence. When available, biological markers may be helpful as hyperuricaemia in patients treated with pyrazinamide for tuberculosis. Similarly, measuring the international normalised ratio (INR) provides some evidence of adherence in patients treated with traditional oral anticoagulants.

Finally, objective direct methods, such as unscheduled blood or urine samples for measuring the concentration of a drug, may be attractive. However, these 'dosing' methods are often limited by the unavailability or the cost of sensitive assays, the frequent need for repeated sampling (due to short drug half-life) and their inability to identify overall poor adherence in patients whose adherence improves shortly before the doctors' appointment (the 'white-coat compliance' effect) [2,6].

Because of its long terminal elimination half-life (7–40 days), these limitations do not apply to blood hydroxychloroquine (HCQ) assays: undetectable blood HCQ concentration necessarily means that the patient has not taken HCQ for a long time (not that she/he has just forgotten her/his recent dose). Moreover, the white-coat compliance effect in a patient with poor long-term non-adherence would not increase HCQ blood concentration to the usual concentration.

C. Rates of non-adherence

Adherence rates are typically lower among patients with chronic conditions, as compared with those with acute conditions, the persistence among patients with chronic conditions decreasing drastically after the first 6 months of therapy. For example, in a pharmacy refill prescription study of long-term persistence with statin therapy in 34,501 American patients who were 65 years of age and older, the mean PDC by a statin was 79% in the first 3 months of treatment, 56% between 3 and 6 months and 42% after 120 months. Only one patient in four maintained a PDC of at least 80% after 5 years [7]. In another study of 167,907 patients newly treated with at least one of six drug classes (prostaglandin analogues, statins, bisphosphonates, oral antidiabetics, angiotensin II receptor blockers and antimuscarinics indicated for overactive bladder), the mean 12-month adherence rates (based on PDC calculations) ranged from 35% to 72% depending on the drug class [8]. At 1 year, with the application of a 60-day refill grace period, the persistence rates had dropped to 18–54% [8]. The authors found that the risk of non-persistence decreased with increasing age [8].

The non-adherence rates in patients with SLE ranged from 3% to 76% depending on the methods used and on the drug studied [9–28]. Table 1 summarises the main studies on adherence to treatment in SLE patients and emphasises the heterogeneity of the methods that were used to measure it.

The first studies assessed non-adherence by patient self-reports, physician's judgement, visit attendance and counts of tablets, but as we have previously emphasised, these methods are debatable [2]. Indeed, it is interesting to note that the reported adherence rates were higher when self-questionnaires were used, especially in postal surveys. Recently and for the first time, Marengo et al. quantitatively measured the adherence to oral therapies in patients with SLE using electronic monitoring over a 2-year period [20]. They showed that in a population of 78 patients (mostly from ethnic minorities receiving care at publicly funded clinics), only 24% had an adherence rate of at least 80%. Interestingly, this is very similar to the results that were reported in other chronic diseases [7]. The adherence was 62% for all drugs combined and did not differ significantly for individual medications. Polypharmacy and depression were associated with a lower adherence [20].

Table 1
Summary of the main studies on adherence to treatment in patients with systemic lupus erythematosus (SLE).

	Patients	Number of patients	Methods used	Rate of non-adherence	Treatment evaluated	Factors associated with non-adherence
Costedoat-Chalumeau et al. [21]	Cohort of SLE patients	203	[HCQ] followed by interviews	7%[a] severely non-adherent	HCQ	- Higher SLE activity, - Fear of side-effects
Mosley-Williams et al. [11]	Cohort of SLE women (68 African American/ 54 White)	122	Self report: 5-point scale (1: never failed to take SLE treatment during the past year, 5: failed all the time), missed clinic visits	9.2% of African Americans and 10.6% of Whites reported failing to take their medication "all the time", 27.4% of African Americans and 42.6% of Whites missed visits	Not specified	- Ethnicity, - For African–Americans: increased depression, poorer short-term memory, fear of side-effects, need for child or elder care, increased symptoms, fewer comorbid conditions, - For Whites: perceiving treatment as having less efficacy - Missed visits: depression, having less trust in one's physician
Oliveira-Santos et al. [15]	Cohort of SLE women	246	Self report: MMAS	68.3% of the patients reported an adherence $<100\%$	All medications	- Lower education, - No family support, - Illegibility of the medical prescription, - Adverse drug reaction, - No haematological manifestations, - Mucocutaneous and joint manifestations,
Sailler et al. [23]	Cohort of SLE patients	58	Self-report: VAS from 0 to 10 (0: no treatment taken, 10: 100% of the treatment taken)	20.7% of the patients reported a poor adherence (score <8)	HCQ	- None (neither duration of the disease, nor smoking habits)
Ward et al. [24]	Cohort of SLE women	100	Pill counts	Percentage of prescribed pills taken: 70.6 ± 25.8	Not specified	Not specified
Julian et al. [25]	Prospective cohort of SLE patients included in the Lupus Outcome Study	834	Self report: 4-point scale (never a problem, sometimes a problem, a problem most of the time, a problem all of the time)	45.6% reported forgetting to take medications at least some of the time	Not specified	- Severity of depression, - Disease activity, - Disease duration
Daleboudt et al. [26]	SLE patients receiving at least one immuno-suppressive agent	106	Self report: MASRI, missed clinic visits	Mean self-reported adherence rate: $86.7 \pm 18.0\%$ 5.2% of missed visits.	Immunosuppressive drugs	- Cognitive dysfunction, - Fear of side-effects, - Younger age

Marengo et al. [20]	SLE patients attending rheumatology clinics	78	Electronic monitoring[b] for 2 years, Self report: CQR	76% took less than 80% of their doses (no difference between treatments)	All medications	- Polypharmacy, - Depression
Garcia-Gonzalez et al. [27]	SLE patients attending rheumatology clinics in US	32	Self report: CQR	Mean self-reported adherence rate: 68.0 ± 8.3%	All medications	- Ethnic minority, - Lower education, - Side effects
Ting et al. [18]	Adolescents and young adults with SLE	41	Undetectable [HCQ], Pharmacy refill information, Self report: MASRI	29% undetectable [HCQ], 68% refilled less than 80% of their doses, mean self-reported adherence rate: 80 ± 20%	HCQ	/
Chambers et al. [19]	Cohort of SLE patients in London	199	Self report: VAS from 0 (non-adherence) to 10 (perfect adherence) (postal survey)	Median self-reported adherence rate: 9.7 (8.8–10)	All medications	- Fear of side-effects
Chambers et al. [48]	Cohort of SLE patients in Jamaica	75	Self report: questionnaire, interview for 20 patients	44% reported an adherence <85%	All medications	- High cost of medications - Poor availability of medications - Side-effects - Perceived mild severity of SLE
Koneru et al. [17]	Cohort of SLE patients	55 (41 on prednisone and 37 on HCQ)	Self report: MASRI, Pill count, Physician's evaluation, Pharmacy refill information	39% refilled less than 80% of their prednisone doses, 51% refilled less than 80% of their HCQ doses, adherence rate of 100% for prednisone: 27% with refilled information versus 49% with MASRI. Only 51% brought their medications for pill count	HCQ and corticosteroids	Not specified

Table 1 (*continued*)

	Patients	Number of patients	Methods used	Rate of non-adherence	Treatment evaluated	Factors associated with non-adherence
Rojas-Serrano et al. [14]	SLE patients visiting the emergency department	180	Self report: VAS from 0 to 10	Mean self-reported adherence rate: 8.3 ± 2.2	All medications	- Risk of hospitalisation
Lee et al. [28]	Cohort of SLE patients	30	[HCQ]	10% had undetectable concentration (severely non-adherent)	HCQ	Not specified
Pétri et al. [9]	Cohort of SLE patients	198	Physician's evaluation, missed clinic visits	47% of the patients were considered non-adherent	All medications	- Younger age and non-White ethnicity - Severe renal disease
Bruce et al. [22]	SLE patients with renal insufficiency	17	Physician's evaluation	30% of renal insufficiency were attributed to non-adherence	All medications	- Ethnic minority, - Fear of side effects, - Cost of medications, - Preference for alternative therapies
Duvdevany et al. [16]	37 SLE outpatient and 63 participants recruited through an SLE forum website	100	Self report: 5-point scale (1: almost never; 5: almost every day).	Mean self-reported adherence score: 4.53 ± 1.17	All medications	

–MMAS: Morisky Medication Adherence Scale is a self-report measure of medication-taking behaviour. The reliability and validity of this scale were originally established as a 4-item questionnaire. Advantages of the MMAS include simplicity of the questions and ease of scoring. It has recently been expanded with 4 additional items addressing the circumstances surrounding adherence behaviour. The updated version of the MMAS (MMAS-8) has better psychometric properties than the original 4-item version. Scores obtained from this scale range from 0 to 8, where higher scores indicate higher adherence.

–MASRI: Medication Adherence Self-report Inventory scale is a self-reported questionnaire. The MASRI has been shown to be a reliable and valid measure of medication adherence in SLE patients. Part A of the MASRI is 87% sensitive and 86% specific for identifying patients who were non-adherent [17]. Part A consists of five 4-point scale items and one visual analogue scale (VAS) item. The VAS item asks patients to indicate how much medication they have taken in the past month on a scale from 0% to 100%. Only the VAS item is used to get a numerical estimate of the adherence level. The other 5 items are added to help patients develop this adherence estimate.

–CQR: Compliance Questionnaire Rheumatology. The CQR is a 19-item measure specifically developed for patients with rheumatic diseases, which has been tested and validated with electronic monitoring in patients with rheumatic diseases. Items are scored on a 4-point Likert response scale ranging from 1 (do not agree at all) to 4 (agree very much). The score for this measure ranges from 0 (complete noncompliance) to 100 (perfect compliance) [50].

–UV: ultraviolet; [HCQ]: hydroxychloroquine blood level.

[a] The rate of severe non-adherence was 23% in patients with SLEDAI $\geq$6 and 30% in patients with SLEDAI $\geq$12.

[b] The authors used the Medication Events Monitoring System (MEMS; AARDEX Group, Sion, Switzerland) that consists of a microchip placed in the cap of the medicine bottle which records the date and time of every opening.

Since electronic monitoring cannot be used in daily practice, a simple, objective and reliable marker of non-adherence to medications in patients with SLE was needed. Used for more than 50 years, HCQ is an essential medication for SLE with a high efficacy/toxicity ratio [29,30]. HCQ can be reliably quantified by high-performance liquid chromatography (HPLC). For reasons of sensitivity and reproducibility, the HCQ level has to be measured in whole blood [31]. The interindividual variability of the blood HCQ level (meaning the variability from one patient to another) is important with more than a 10-fold range of drug concentrations found after similar dose administrations. This has been observed in supposedly adherent patients with rheumatoid arthritis [31–33], SLE [34] and in healthy volunteers [35,36]. A relationship between blood concentrations of HCQ and clinical efficacy has been reported in patients with rheumatoid arthritis [31–33], cutaneous lupus [37] and SLE [34,38]. In a study including 143 SLE patients, we found that several patients had undetectable blood HCQ concentrations [38]. As HCQ has a long terminal elimination half-life, this finding implied that these patients had not taken HCQ for a long time. This result prompted us to evaluate the interest of very low blood HCQ concentrations as a marker of poor adherence to treatment. Briefly, HCQ concentrations were determined in 203 unselected patients with SLE. At the end of the study, the patients were informed of the results and retrospectively interviewed about their adherence to treatment [21]. Fourteen patients (7%) confirmed their non-adherence when confronted with their blood HCQ levels, explaining that they did not take HCQ treatment at all or took it no more than once or twice a week. This percentage is consistent with the 5–10% of patients who completely stopped or frequently interrupted tablet ingestion in studies using electronic monitoring [39,40]. The treating physicians of nine of these 14 patients (64%) did not suspect non-adherence. This is not surprising as clinical judgement has been found to be inaccurate in most of the studies in which it has been used [2]. The remaining five patients denied non-adherence until faced with their blood test result. This finding suggests that interviews without blood HCQ results may be insufficient for diagnosing non-adherence.

The mean HCQ concentration in these 14 patients was very low: 26 ng ml^{-1} (range: 0–129). By contrast, the remaining patients had a mean HCQ concentration of 1079 ng ml^{-1} (range: 205–2629) [21]. We then proposed 200 ng ml^{-1} as a cut-off value for definite non-adherence. It should be emphasised that two distinct independent patterns of non-adherence have been described [39]: (a) relatively infrequently missed medication and (b) complete stopping or frequently interrupted and erratic tablet intake. Very low blood HCQ concentrations can identify only the latter; patients who missed some medication had blood HCQ concentrations above 200 ng ml^{-1} and were thus indistinguishable from those who had good adherence.

In this study, the non-adherent patients were at a higher risk of SLE flares. Interestingly (this point was not detailed in our previous article), the definite non-adherence rate (defined as blood HCQ concentration lower than 200 ng ml^{-1}) was higher in patients with active disease: eight out of 35 (23%) in patients with a systemic lupus erythematosus disease activity index (SLEDAI) $\geq$6 and six out of 20 (30%) in patients with SLEDAI $\geq$12. Therefore, a high activity of SLE should raise suspicion regarding non-adherence.

Similarly, Ting et al. assessed the non-adherence in a cohort of patients with childhood-onset SLE to determine the baseline adherence to medications and visits [18]. They found that 29% of adolescents and young adults with SLE were non-adherent as defined by undetectable blood HCQ concentration, and that medication adherence estimates using blood HCQ concentration correlated with adherence rates as measured using pharmacy refill information (Pearson correlation coefficient $r = 0.50$, $p < 0.0001$). [18]

D. Consequences of non-adherence

In general, failure to adhere to a regular treatment results in poor disease control, increasing morbidity and mortality and decreasing quality of life. Non-adherence also results in a significant economic burden, such as increased hospitalisation and emergency department visits, resulting in unnecessarily high costs of health care [41]. This has been shown for many chronic disorders or conditions including asthma, hypertension, diabetes, myocardial infarction, human immunodeficiency virus (HIV) infection, tuberculosis, depression, epilepsy or organ transplantations [41]. Interestingly, a

low adherence to treatments has been associated with poor outcomes, even when the treatment was a placebo [42]. This observation can be explained in part by the 'adherer effect' theory, which states that these patients are also more adherent to other recommendations (diet and exercise) and have healthier lifestyles.

Similarly, non-adherence in SLE patients is a major concern, as it has been associated with a higher risk of flares, morbidity, hospitalisation and poor renal outcome [9,21,22,43].

E. Determinants of non-adherence

Non-adherence to treatment is multifactorial for most patients and varies according to the unintentional or intentional pattern of non-adherence. The World Health Organization (WHO) has identified health-care systems, provider relationships, disease, treatment, patient characteristics and socioeconomic characteristics to be factors affecting adherence [41]. Regarding some of these factors:

- Pill or prescription burden, also referred to as polypharmacy, appears to be an important predictor of non-adherence, as well as the number of times per day (or times per week) of dosing, once a day being associated with the highest level of adherence [44]. Interestingly, a recent study addressed the consequence of the generic prescription on adherence to treatment. This nested case-control study in patients with epilepsy included 11,472 non-adherent patients, and 50,050 controls showed that the sole change in pill colour was significantly associated with non-persistence [45]. It may then be very important not to change the appearance of each drug in a given patient.
- Low socioeconomic and educational status has been associated with poor adherence, but it is not clear whether these findings represent mostly unintentional (system barriers) or intentional non-adherence (specific beliefs and attitudes). Adherence is also associated with patient knowledge and beliefs about the treatments, including their beliefs on side-effects and effectiveness [44]. This has been confirmed in some studies on SLE patients.
- Depression and other psychosocial characteristics have been associated with poor adherence, whereas social support may improve adherence.
- The relationship between disease severity, organ damage and poor adherence is likely to be bidirectional: low adherence may cause deleterious outcomes, and on the other hand, patients with increased disease severity may be less likely to maintain their scheduled visits and be adherent to their medications, since they may lose confidence in health care. In the same way, we have observed that some patients stopped HCQ after observing that the forgetting of HCQ but not of steroids for a few days is not associated with the relapse of symptoms. This is explained by the long half-life of HCQ, which must be explained to the patients.
- The quality of the patient–doctor relationship, and then the patient involvement in the decision to take medication, has been associated with patient adherence to recommendations. [44]

In contrast to intentional non-adherence, unintentional non-adherence is thought to be the result of a passive process that is less strongly associated with individuals' beliefs and perceptions [46]. Unintentional non-adherence can be related to issues with the health system, such as financial costs, pharmacy processes, opening hours and accessibility and language barriers [44]. Patients from disadvantaged populations are at a higher risk of non-adherence due to the barriers imposed by the system itself [41].

Regarding SLE, the reported results are often conflicting (see Table 1). From a practical point of view, since the fear of the medication's side effects may be an important barrier to adherence [11,19,21,27,47,48], physicians should consider this by talking about this specific aspect with their patients.

In our study, we were unable to identify any marker non-adherence except for ongoing SLE flares [21]. However, when the non-adherence diagnosis was confirmed using very low blood HCQ concentration, the interviews of the patients showed that the main barriers to adherence were due to HCQ treatment characteristics including the patients' fear of side effects.

F. Actions that can be taken to improve adherence

The WHO has emphasised the importance of improving adherence and stated that "effective ways to help people follow medical treatments could have far larger effects on health than any treatment itself." [41] The WHO also considers that the 'state-of-the-art' adherence interventions should target the patient, the provider and the health-care system [41].

The research on interventions to promote adherence has mainly focussed on modifying patient behaviour. No single intervention targeting patient behaviour was effective, and the most promising methods to improve adherence behaviour used combined strategies: patient education, behavioural skills, self-rewards, social support and telephone-call follow-up [41,42,49]. Only few randomised controlled trials targeting patient adherence behaviour have been reported [41,49].

In their Cochrane literature review, Haynes et al. concluded that improving short-term adherence was relatively successful with a variety of simple interventions. By contrast, even if some combinations of these techniques increased adherence, they had no substantial effects on adherence behaviour over the long term despite the amount of effort and required resources [41,49]. Indeed, there is no evidence that low adherence can be 'cured', and efforts to improve adherence must be maintained for as long as the treatment is needed [42,49]. This supports the utility of innovative, modified health-care system teams in addressing the problem [41].

In SLE, Daleboudt et al. suggested that given the high prevalence of unintentional non-adherence and its association with missing clinic visits, a primary focus on reducing unintentional non-adherence would greatly improve treatment adherence [26]. Additionally, reducing the number of dosings might be useful: for example administering HCQ once a day (given its long half-life) might increase adherence. However, all these measures that look logical have not been evaluated so far.

In our experience, one of the most difficult tasks is to recognise poor adherence. Once the diagnosis is made with blood HCQ concentration, we can talk to the patients and respond to their specific concerns. For example, we may re-explain the high benefit/risk ratio for HCQ treatment to patients with fear of side effects. In our study on adherence in SLE patients, two were lost to follow-up after being diagnosed with non-adherence. The remaining 12 underwent a second unscheduled blood HCQ assay, 13 $\pm$ 7 months later. The mean blood HCQ concentration increased significantly, from 30 $\pm$ 49 to 636 $\pm$ 354 ng ml^{-1} [0–1157 ng ml^{-1}] ($p = 0.0005$), but remained significantly lower than that of the entire cohort ($p = 0.01$). Two patients remained non-adherent with follow-up HCQ concentrations of 0 and 56 ng ml^{-1}, because of persistent side effects in one and persistent concerns about ophthalmologic risks in the other. These results have since been verified in our daily experience, confirming that the physicians' awareness of non-adherence is an essential prerequisite for improving adherence [21].

In conclusion, SLE, similarly to other chronic diseases, depicts a high rate of non-adherence, leading to major clinical consequences. Diagnosing non-adherence should be a major goal in our daily practice, especially in patients with active SLE despite treatment. Unscheduled, regular assays of HCQ levels in whole blood may help physicians to screen non-adherent SLE patients: undetectable or unexpectedly low HCQ concentration should prompt a non-judgemental discussion with the patient to assess the adherence to HCQ and other drugs. This may prevent one from incorrectly interpreting poor adherence as a lack of response and leading to unnecessary and dangerous regimen escalation.

An international prospective study enrolling consecutive patients with an SLE flare despite a treatment regimen that includes HCQ is ongoing (ClinicalTrials.gov: NCT01509989). This very simple study consists of sampling one tube of whole blood for the dosage of HCQ. Adherence self-questionnaires have to be completed by the patients and the physicians. The hypothesis is that a significant proportion of patients in whom therapeutic escalation would be considered are in fact non-adherent to their current treatment. It might further demonstrate the interest of HCQ concentration monitoring, both in 'real life' and in pharmaceutical clinical studies in SLE. Finally, since patients with non-adherence are at a higher risk of flares, the clinical implications of our study, including the patient's quality of life, might be essential.

Practice points

- Poor adherence to therapeutic regimens is a common and costly issue in patients with chronic diseases and is difficult to diagnose.
- The rate of non-adherence in SLE patients is high.
- Unscheduled, regular assays of HCQ levels in whole blood are a reliable, simple and objective method for identifying severely non-adherent SLE patients.

Research agenda

- An international prospective study enrolling consecutive patients with an SLE flare despite a treatment regimen that includes HCQ is ongoing.
- Future research should focus on interventional studies to improve adherence in SLE patients.

Summary

One of the main causes of persistent SLE activity despite treatment may be the lack of adherence to treatment. To avoid unnecessary treatment escalation in patients with active SLE, it is therefore important that physicians recognise non-adherent patients as accurately as possible. However, this is very challenging. Several methods can be used: patient self-reports, clinician's assessments, keeping appointments, pill count, refilling approach, electronic monitoring devices, clinical or biological markers of non-adherence and objective direct methods, such as unscheduled blood or urine drug sampling. All these methods have limitations, but due to its long half-life, undetectable (or very low) blood HCQ concentrations may be the most reliable tool to assess non-adherence in SLE patients treated with this essential medication. In two separate studies, such low levels have been found in 29% of adolescents and young adults with SLE and in 30% of patients with high SLE activity.

An international prospective study enrolling consecutive patients with an SLE flare despite a treatment regimen that includes HCQ is ongoing to assess the utility of blood HCQ concentration measurement. If it confirms that the rate of non-adherent patients is high, the future research will focus on interventional studies to improve adherence in SLE patients.

Conflicts of interest

The authors had no potential conflicts of interest to be disclosed.

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