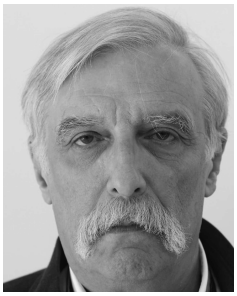
Editorial





Routine Hydroxychloroquine Blood Concentration Measurement in Systemic Lupus Erythematosus Reaches Adulthood

The benefits of hydroxychloroquine (HCQ) treatment in patients with systemic lupus erythematosus (SLE) are now clearly recognized and it has been highly recommended that all patients with SLE should be prescribed this drug[1]. One less well-known benefit of HCQ is related to its pharmacokinetic properties (i.e., its long half-life) and to the availability of a blood assay to measure its blood concentration. Indeed, HCQ and its metabolite levels can be quantified by high performance liquid chromatography, which is available in many centers because this type of equipment is required to monitor other drugs (antidepressants, tyrosine kinase inhibitors, antibiotics, etc.). Methods of dosage may vary slightly, but for reasons of sensitivity and reproducibility, blood HCQ concentrations ([HCQ]) should be measured in whole blood (minimum 1 ml blood sampled in EDTA or in lithium heparinate tubs).

In the 1980s, Tett, *et al* first described this method and studied the importance of [HCQ] measurement in patients with rheumatoid arthritis (RA). They first showed that there was a great variability in [HCQ] among individuals, including in healthy volunteers and adherent patients[2,3]. They also found a significant, although weak, correlation between [HCQ] and clinical efficacy in RA [corresponding to the so-called pharmacokinetic/pharmacodynamic (PK-PD) effect][3,4]. These data were later confirmed by Munster, *et al*[5].

When this blood measurement became available in our center in 2000, we decided to evaluate the PK-PD relationship of HCQ in patients with SLE. Among 143 unselected patients with SLE who were all receiving 400 mg/day of HCQ, the mean [HCQ] on day 0 was 1017 ± 532 ng/ml with more than a 10-fold range of drug concentrations found after similar doses[6]. We observed that low [HCQ] were associated with increased disease activity, and that low baseline [HCQ] in patients with inactive SLE were strongly associated with risk of developing SLE flares during the subsequent 6 months: among the 120 patients who had inactive disease at baseline, the mean [HCQ] at baseline in the 14 (12%) who had disease exacerbations during followup was significantly lower than that in the patients whose disease remained inactive (703 ± 534 vs 1128 ± 507 ng/ml; $p = 0.006$). Using receiver-operating characteristic (ROC) curve analysis to determine the [HCQ] associated with the lowest risk of SLE flare in the subsequent 6 months, we found that a threshold value of 1000 ng/ml provided the best tradeoff between sensitivity and specificity, as well as a high negative predictive value for SLE flares (96%). We therefore proposed 1000 ng/ml as the target [HCQ] in patients with SLE[6]. These results were later confirmed in 300 patients with cutaneous lupus[7].

This PK-PD relationship questioned the need for individualized dosing to obtain [HCQ] associated with optimal outcomes. A French randomized, double-blinded, placebo-controlled, multicenter trial that included 573 patients with SLE (Plaquenil LUpus Systemic: PLUS study) was set up to answer this question[8]. However, even if this study confirmed the PK-PD relationship, we did not confirm the importance of adapting the daily HCQ dose to its blood level in terms of efficacy because patients in the "adaptation" group had the same probability of flare as those with stable daily dose. The simplest explanation for this negative result is that higher HCQ doses do not have an added therapeutic effect, especially in patients who are doing quite well. An alternative explanation could be that low [HCQ] is a marker of poor adherence to other medications, especially steroids, or is a marker of specific poor metabolism that also affects other drugs. In such cases, correcting only [HCQ] could be insufficient. Thus, this negative result can probably be explained — at least partially — by nonadherence issues[8].

This leads us to the most interesting aspect of this measurement. If we go back to our first PK/PD study

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performed between 2000 and 2004, the included patients had all received explanations about the PK/PD study before signing informed consent. When we received the results, however, we found a substantial number of patients with undetectable blood HCQ levels. Because HCQ half-life is at least 5 days[9], such patients had undoubtedly not taken HCQ for quite a long time (and not just forgotten their last tablets). This prompted us to retrospectively interview the patients: we found that 7% were severely nonadherent to treatment and had a mean [HCQ] of 26 ± 46 ng/ml, range (0–129 ng/ml). Even more strikingly, using [HCQ] lower than 100 ng/ml, Ting, *et al* found that 29% of adolescents and young adults with SLE were nonadherent to HCQ treatment[10]. In that study, medication adherence estimated using [HCQ] correlated very well with adherence rates as measured using pharmacy refill information[10].

In this issue of *The Journal*, in their report on 686 patients, and using a level < 15 ng/ml, Durcan, *et al* found that 88 patients (13%) were completely nonadherent[11]. The authors also demonstrated that counseling patients with low [HCQ] led to an increase of these concentrations: only 56% of the patients had levels above 500 ng/ml at their first [HCQ] measurement, versus 80% at last followup in those who attended 3 visits or more.

In retrospect, we believe that our knowledge about nonadherence through HCQ measurement has led us to significantly modify our daily practice. This measurement is relevant in 2 situations: during routine clinics or in case of flare. Regarding the routine clinics, a patient with a very low level (undetectable, < 100 ng/ml, or < 200 ng/ml) can definitely be considered as both nonadherent and at risk of flare. Such result is sometimes completely unexpected according to the physician's evaluation, particularly in very nice patients, who never miss a medical appointment and who conform perfectly to ophthalmological followup for HCQ. It is then of utmost importance to explain the benefit/risk ratio of HCQ, to discuss this result with the patient in a nonjudgmental way, bearing in mind how difficult it is to follow treatment over the long term, and how common nonadherence is[12]. Diagnosing nonadherence can then be considered as the first step to find solutions with the patients. When the blood level is intermediate, the patient may have poor adherence as well as having a specific metabolism (i.e., cytochrome P450 2D6 polymorphism)[13]. In the first case, just by informing him/her that the level is quite low, an increase may be observed in the following months as shown by Durcan, *et al*[11]. In the second case, given the negative results of the PLUS study, we do not recommend increasing the daily dose of HCQ.

The second situation in which this measurement can be done is in SLE flares. In such a situation, blood HCQ levels help distinguish flares due to a lack of response to treatment (indication to change treatment) from those due to poor adherence to treatment (indication for education, etc.). As a consequence, such laboratory tests may avoid unnecessary or even dangerous regimen escalation[12]. Of note, results of an ongoing international study evaluating the extent of nonadherence in patients with SLE may emphasize the importance of this blood measurement (ClinicalTrials.gov: NCT01509989).

Some limitations or unmet needs of this measurement should be noted. (1) The determinants of variations of [HCQ] are not fully understood[9]. (2) Even if it is written almost everywhere that HCQ half-life is around 40 days, this value refers to the terminal half-life. By contrast, the mean elimination half-life of HCQ was 123 ± 45 h in another study[5]. Accordingly, we have shown that some patients may reach high levels of [HCQ] within only a few days[9], showing that while specific, low [HCQ] are probably not highly sensitive to diagnose nonadherence, and that even if rates of nonadherence as high as 29% have been found in patients with SLE, this is likely only the "tip of the iceberg." (3) The respective importance of measurement of HCQ versus its metabolites has not been fully addressed. (4) The significance of high [HCQ] has not been studied. (5) Little is known regarding the links between [HCQ] and HCQ toxicity. High [HCQ] have been associated with an increased risk of adverse gastrointestinal reactions[5]. In another study, [HCQ] in HCQ-induced pigmentation cases were significantly higher than in controls, but differences were small and thought not to be clinically relevant given the wide range of distribution in [HCQ][14]. (6) Lastly, no data have been published regarding high [HCQ] and ophthalmological toxicity, but some personal data suggest that the link is very similar to the one observed with cutaneous toxicity (significant, but not relevant), which is not surprising, given that cumulative dose is probably the most important risk factor of ophthalmological toxicity[15].

The increasing use of this laboratory test by recognized teams in the United States[11], Australia[16], Canada[10], and the United Kingdom[17], to name but a few, should provide some answers to these questions.

NATHALIE COSTEDOAT-CHALUMEAU, MD, PhD,
AP-HP, Hôpital Cochin,
Centre de référence maladies auto-immunes et systémiques rares;
Université Paris Descartes-Sorbonne Paris Cité,
Paris, France;
VÉRONIQUE LE GUERN, MD,
AP-HP, Hôpital Cochin,
Centre de référence maladies auto-immunes et systémiques rares,
Paris, France;
JEAN-CHARLES PIETTE, MD,
AP-HP, Hôpital Pitié-Salpêtrière,
Centre de référence maladies auto-immunes et systémiques rares,
Paris, France.
Address correspondence to Dr. N. Costedoat-Chalumeau, Hôpital Cochin, 75014, Paris, France. E-mail: nathalie.costedoat@gmail.com

REFERENCES

1. van Vollenhoven RF, Mosca M, Bertsias G, Isenberg D, Kuhn A, Lerstrom K, et al. Treat-to-target in systemic lupus erythematosus:

recommendations from an international task force. Ann Rheum Dis 2014;73:958-67.
2. Tett S, Day R, Cutler D. Hydroxychloroquine relative bioavailability: within subject reproducibility. Br J Clin Pharmacol 1996;41:244-6.
3. Tett SE, Cutler DJ, Beck C, Day RO. Concentration-effect relationship of hydroxychloroquine in patients with rheumatoid arthritis—a prospective, dose ranging study. J Rheumatol 2000;27:1656-60.
4. Tett SE, Day RO, Cutler DJ. Concentration-effect relationship of hydroxychloroquine in rheumatoid arthritis—a cross sectional study. J Rheumatol 1993;20:1874-9.
5. Munster T, Gibbs JP, Shen D, Baethge BA, Botstein GR, Caldwell J, et al. Hydroxychloroquine concentration-response relationships in patients with rheumatoid arthritis. Arthritis Rheum 2002;46:1460-9.
6. Costedoat-Chalumeau N, Amoura Z, Hulot JS, Hammoud HA, Aymard G, Cacoub P, et al. Low blood concentration of hydroxychloroquine is a marker for and predictor of disease exacerbations in patients with systemic lupus erythematosus. Arthritis Rheum 2006;54:3284-90.
7. Frances C, Cosnes A, Duhaut P, Zahr N, Soutou B, Ingen-Housz-Oro S, et al. Low blood concentration of hydroxychloroquine in patients with refractory cutaneous lupus erythematosus: a French multicenter prospective study. Arch Dermatol 2012;148:479-84.
8. Costedoat-Chalumeau N, Galicier L, Aumaitre O, Frances C, Le Guern V, Liote F, et al. Hydroxychloroquine in systemic lupus erythematosus: results of a French multicentre controlled trial (PLUS Study). Ann Rheum Dis 2013;72:1786-92.
9. Jallouli M, Galicier L, Zahr N, Aumaitre O, Frances C, Le Guern V, et al. Determinants of hydroxychloroquine blood concentration variations in systemic lupus erythematosus. Arthritis Rheumatol 2015;67:2176-84.
10. Ting TV, Kudalkar D, Nelson S, Cortina S, Pendl J, Budhani S, et al. Usefulness of cellular text messaging for improving adherence among adolescents and young adults with systemic lupus erythematosus. J Rheumatol 2012;39:174-9.
11. Durcan L, Clarke WA, Magder LS, Petri M. Hydroxychloroquine blood levels in SLE: Clarifying dosing controversies and improving adherence. J Rheumatol 2015;42:2092-7.
12. Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, Le Guern V, Leroux G, Marra D, et al. Adherence to treatment in systemic lupus erythematosus patients. Best Pract Res Clin Rheumatol 2013;27:329-40.
13. Lee JY, Vinayagamoorthy N, Han K, Kwok SK, Ju JH, Park KS, et al. Polymorphisms of cytochrome P450 2D6 are associated with blood hydroxychloroquine levels in patients with systemic lupus erythematosus. Arthritis Rheumatol 2015 Aug 28 (E-pub ahead of print).
14. Jallouli M, Frances C, Piette JC, Huong DL, Moguelet P, Factor C, et al. Hydroxychloroquine-induced pigmentation in patients with systemic lupus erythematosus: a case-control study. JAMA Dermatol 2013;149:935-40.
15. Costedoat-Chalumeau N, Dunogue B, Leroux G, Morel N, Jallouli M, Le Guern V, et al. A critical review of the effects of hydroxychloroquine and chloroquine on the eye. Clin Rev Allergy Immunol 2015 Feb 12 (E-pub ahead of print).
16. Croyle L, Morand EF. Optimizing the use of existing therapies in lupus. Int J Rheum Dis 2015;18:129-37.
17. Alexander S, Chusney G, Chusney VD, Lee J, Cairns T, Lightstone L. The achilles heel of lupus nephritis treatment- identifying non adherence using hydroxychloroquine blood levels (abstract PO06). J Am Soc Nephrol 2013;24:790A.

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