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Comparison of flares in 85 patients with SLE who maintained, discontinued or reduced dose of hydroxychloroquine during a prospective study of ophthalmological screening for retinopathy (PERFOCTAPS Study)

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ABSTRACT

Objective Little is known about the risk of SLE flares associated with hydroxychloroquine (HCQ) reduction or cessation, especially after ophthalmological screening. We analysed the risk of SLE flares after HCQ reduction or discontinuation after detection of early ophthalmological toxicity.

Methods This study includes all patients with SLE among the 109 included in the prospective PERFOCTAPS Study and treated with HCQ for at least 5 years. Patients were divided into 3 groups: HCQ maintenance, reduction and discontinuation after intensive ophthalmological screening. Flare occurrence (SELENA-SLEDAI Flare Index) was assessed for 2 years after HCQ reduction or discontinuation or after inclusion in the maintenance group.

Results This study included 85 patients (98% women, mean age 40.0 years, and mean durations of SLE and HCQ treatment 14.4±7.7 years and 12.9±7.2 years, respectively). The PERFOCTAPS Study identified ophthalmological abnormalities in 25 patients (29.4%); these led to dose reduction in 20 patients and discontinuation in 5. Flares occurred in 29 patients (34.1%): 17 (28.3%) in the maintenance group, 10 (50%) in the reduction group and 2 (40%) in the discontinuation group. After adjustment for potential confounders, HCQ reduction was independently associated with the risk of flare (adjusted HR 2.26; 95% CI 1.03 to 4.97). The same trend was observed in the discontinuation group, but was no longer statistically significant (adjusted HR 2.13; 95% CI 0.44 to 10.27).

Conclusion In this prospective study, HCQ reduction due to early suspicion of retinal toxicity was associated with a statistically significantly increased risk of disease flare.

Trial registration number NCT02719002.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hydroxychloroquine (HCQ) is one of the most valuable treatments in SLE, but the optimal dose for balancing its benefits and its risk of toxicity is highly controversial.

⇒ Most recent guidelines recommend 5 mg/kg/day of HCQ, but the optimal dose of HCQ is not yet determined.

WHAT THIS STUDY ADDS

⇒ Our study aimed to know the impact of HCQ dose modification on SLE flares in patients included in the PERFOCTAPS Study. It is the first study to evaluate the occurrence of SLE flares due to modification of HCQ dose after detection of signs of early retinal toxicity.

⇒ We showed that HCQ dose reduction was associated with a statistically significant increased risk of SLE flare. Patients who discontinued HCQ showed the same trend (although not statistically significant).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The risk of SLE flares after reducing HCQ dose should lead to tighter follow-up and treatment adjustment.

⇒ More studies are needed to determine the best dose of HCQ regarding its benefits and risks.

INTRODUCTION

The use of hydroxychloroquine (HCQ) in SLE has several beneficial effects, including the prevention of flares and the improvement in survival, and its use is supported by every recent SLE international guideline, regardless of disease severity.[1–7]

It is, however, associated with long-term side effects, mainly ophthalmological, with toxicity related to duration, cumulative dose, chronic kidney disease and pre-existing retinal or macular disease.[8–10] Ophthalmological

screening is thus recommended at baseline and then annually after 5 years of HCQ treatment to search for early retinal changes (so-called premaculopathy). This screening makes it possible to avoid advanced macular disease (clinical maculopathy), which is usually irreversible.

The optimal daily HCQ dose for an appropriate balance between the ophthalmological risk of HCQ and its benefits has been the object of intense controversy in recent years.[11–13] For a long period, the dose of 6.5 mg/kg/day of HCQ was recommended. In 2014, a study reported an increased risk of ophthalmological toxicity associated with a daily used dose greater than 5.0 mg/kg.[14] Following this, the 2019 European Alliance of Associations for Rheumatology (EULAR) guidelines recommended prescribing no more than 5 mg/kg of HCQ per day.[15] However, this recommendation was considered by some as due to a misinterpretation of the ophthalmological study, and also as risky as it did not take into consideration the potential risks of reduction.[11–13 16–18]

Indeed, little is known about the risk of reducing HCQ dose. Recently, three observational studies showed a higher risk of SLE flare after HCQ discontinuation or dose reduction,[16–18] while a smaller one performed in a population of older patients with stable SLE did not find such a risk.[19] A fifth study found a linear dose–response relationship between HCQ/chloroquine dose and survival of patients with SLE, with better survival with doses above 5 mg/kg/day.[20] However, all these studies but one[19] did not report who decided to reduce or stop the treatment (the patients because of non-adherence or the physicians) or why (toxicity, non-adherence, prolonged SLE inactivity or other causes) which could induce biases.[16–18]

We recently published the results of a prospective ophthalmological study that used the results of automated visual fields associated with spectral-domain optical coherence tomography and multifocal electroretinography performed every 6 months for 2 years to detect early signs of retinal disease (PERFOCTAPS Study, Clinicaltrials.gov: NCT02719002).[21] Since HCQ was reduced or stopped in patients with abnormalities during this intense screening, we used this unique opportunity to analyse the impact of unbiased discontinuation or dose reduction of HCQ on SLE flares.

METHODS

Study population

The PERFOCTAPS Study included patients from August 2016 through February 2021. The committees for the protection of people approved this study, which adhered to the Declaration of Helsinki, on 15 December 2015. In addition to the PERFOCTAPS inclusion criteria (age older than 18 years, HCQ intake for at least 5 years), inclusion in this study required a diagnosis of SLE according to the Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria. Exclusion criteria were the same as for the PERFOCTAPS Study: presence of media opacities (dense cataract, corneal opacity), amblyopia, high myopia or hyperopia (>8 dioptres) or history of retinal surgery.

As previously described, the PERFOCTAPS inclusion criteria required patients to be screened regularly for two consecutive years at the Rothschild Foundation Hospital where they underwent a complete ophthalmological examination on five visits (at inclusion=time zero (T0), then at 6, 12, 18 and 24 months) to assess HCQ toxicity.[21] At the same time, the patients continued regular follow-up with the physician caring for their SLE (routine visits every 6 months when SLE is quiescent and every 3 months otherwise with follow-up of proteinuria every 3 months). Patients were seen rapidly if they had any clinical sign of flare.

Public involvement

Patients were included in the study by the physician caring for their lupus if they met the inclusion criteria. The study was explained to all patients, but they were not involved in the design, or conduct, or reporting, or dissemination plans of the research.

Data collection and outcomes

Demographic, clinical, laboratory and treatment data were obtained from electronic medical records. Data collected at inclusion included demographics and SLE characteristics, including disease activity, flares versus remission or lupus low disease activity state (LLDAS), and past and present treatment. Data regarding HCQ treatment were collected as daily dose in milligrams (mg) per day and as mg per kilogram. We used actual body weight and not ideal body weight according to Melles and Marmor.[14] Disease activity was scored by the SLE Disease Activity Index-2000 (SLEDAI-2K),[22] SLE flares were defined according to the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI Flare Index, which classifies flares as mild/moderate or severe,[23] remission was defined according to the definition of remission in SLE,[24] and LLDAS according to Franklyn *et al*.[25]

The patients were divided into three groups: a maintenance group of patients with no ophthalmological alterations who thus continued HCQ treatment at the same dose; a reduction group composed of patients with mild ophthalmological alterations that led to HCQ dose reduction; and the discontinuation group of patients with retinal abnormalities for which they discontinued HCQ. Information about SLE flares, disease remission and treatment was collected for patients in the maintenance group for the 2 years after inclusion in the PERFOCTCAPS Study (Clinicaltrial.gov NCT02719002) (=T0), and for the reduction and discontinuation groups, for the 2 years after reduction/discontinuation of the HCQ dose (=T0).

Statistical analysis

Descriptive analyses are presented as counts (percentages) for categorical variables and medians (IQRs) or

means (SD) for continuous variables. We used logistic regressions and analyses of variance to compare patient characteristics at inclusion by group (maintenance, reduction or discontinuation).

The associations between HCQ maintenance, reduction or discontinuation, and SLE flare risk were assessed by survival analysis. Patients contributed person-time from T0 (inclusion date for the maintenance group and date of HCQ reduction or discontinuation for the other two) until the first flare, or 2 years after T0. Associations were assessed with Cox proportional hazard models and further adjusted for potential confounders (duration of HCQ treatment in years, immunosuppressant use and variables associated with a value of p<0.1 in univariate analyses). In a sensitivity analysis, we assessed the association between HCQ maintenance, reduction or discontinuation, and the SLE flare risk in the 6 months after T0. For this analysis, patients contributed person-time from T0 until the first flare, or for 6 months after T0. Q-values were calculated using the false discovery rate correction or multiple testing.

A value of p<0.05 was considered statistically significant. All analyses were performed with R V.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics at inclusion

Of the 109 patients included in the PERFOCTAPS Study, 85 patients with SLE were included in this study. Most patients were women (n=83; 98%) with a mean±SD age of 40.0±12.9 years. Mean duration of disease since SLE diagnosis was 14.4±7.7 years, and mean duration of treatment with HCQ was 12.9±7.2 years. Mean daily dose per kilogram of real weight of prescribed HCQ at study inclusion was 5.6±1.8 mg/kg/day (table 1). At T0, mean SLEDAI was 1.3±2.4, with 59 patients (69.4%) in remission and 69 (81.2%) in LLDAS.

Ophthalmological screening identified abnormalities in 25 patients (29.4%). Depending on the specific abnormality, 20 patients reduced their HCQ dose, and 5 patients discontinued this medication. Therefore, the maintenance, reduction and discontinuation groups included 60, 20 and 5 patients, respectively. Table 1 summarises the characteristics of the population in each group at T0.

The maintenance and reduction groups were very similar at T0 for sex, age, SLE duration, manifestations and disease activity. More patients were prescribed prednisone in the reduction group (75% vs 40% in the maintenance group; p=0.014), but their daily prednisone doses were roughly similar (4.23 mg/day vs 6.37 mg/day; p=0.15). Patients in the discontinuation group were significantly older, with longer durations of SLE and of HCQ treatment than patients in the other groups, with low doses of prednisone, and only one patient taking another immunosuppressant. HCQ doses (mg/kg/day) at inclusion did not differ significantly between the three groups, but there was a trend towards fewer patients with an HCQ dose >6.5 mg/kg/day at inclusion in the maintenance group (31.7%) versus the groups with identification of retinal abnormalities (55.0% in the reduction group and 60% in the discontinuation group (p=0.060)). After treatment modification, the mean prescribed HCQ dose in the reduction group fell from 6.0±2.1 mg/kg/day to 3.4±1.5 mg/kg/day (p<0.001), corresponding to a mean HCQ reduction of 45%±9%. After reduction, the proportion of patients with an HCQ dose less than 5 mg/kg/day in the reduction group was significantly higher than in the maintenance group (85% vs 35%, p<0.001).

SLE flares

During the 2 years of follow-up, 29 patients (34.1%) had SLE flares: 17 (28.3%) in the maintenance group, 10 (50%) in the reduction group and 2 (40%) in the discontinuation group (p=0.20). Detailed information on manifestations of flare is included in online supplemental table 1. When the analyses were restricted to the first 6 months, flares occurred in 8 (13.3%) patients in the maintenance group, 6 (30%) in the reduction group and 2 (40%) in the discontinuation group. In the reduction group, the HCQ doses after reduction did not differ between patients with and without flares.

Flares were severe in 6 patients (10%) in the maintenance group, 4 (20%) in the reduction group and none (0%) in the discontinuation group.

Comparison of patients with and without flares showed a significantly lower mean HCQ dose among patients with a flare (4.3 vs 5.3 mg/kg/day, p=0.025, table 2). Although not statistically significant, among those with a flare, 55.2% had an HCQ dose <5 mg/kg/day vs 39.3% among those without flares. Finally, lupus flares led to treatment modification in 26/29 patients (89.7%): 19 patients (65.5%) were prescribed higher prednisone doses and 20 (69%) were prescribed a new immunosuppressant (table 2). The three patients with no treatment modification had mild flares, which spontaneously resolved. Detailed information about the maximum dose of prednisolone and treatment duration can be found on online supplemental table 2.

Table 3 summarises the associations of both the groups and characteristics at inclusion with the flare risk. In the univariate analysis, HCQ reduction, compared with maintenance, was associated with this risk (HR 2.21; 95% CI 1.01 to 4.83) (figure 1). The same trend was observed in the discontinuation group, but did not reach statistical significance, likely because of the small sample (adjusted HR 1.78; 95% CI 0.41 to 7.71). SLEDAI-2K at inclusion was also associated with the flare risk (table 3). In the multivariate analyses, after adjustments for duration of HCQ treatment, immunosuppressant use, history of renal involvement, SLEDAI-2K at inclusion, HCQ reduction was still associated with the flare risk (adjusted HR 2.26; 95% CI 1.03 to 4.97), and the same trend was observed with HCQ discontinuation (adjusted HR 2.13; 95% CI 0.44 to 10.27). Of note, the use of immunosuppressant treatment was not associated with the risk of flare.

Table 1 Characteristics at inclusion of patients whose hydroxychloroquine prescription was maintained, reduced or discontinued (N=85)

	Overall (N=85)	Maintenance (N=60)	Reduction (N=20)	Discontinuation (N=5)	P value	Q value
Clinical characteristics						
Female sex	83 (97.6)	59 (98.3)	19 (95.0)	5 (100.0)	0.653	0.7
Age at inclusion, years	40.0 (12.9)	38.5 (11.7)	37.50 (9.2)	68.0 (5.2)	<0.001	0.007
Duration of SLE, years	14.4 (7.7)	13.2 (6.7)	15.4 (7.4)	24.0 (13.7)	0.008	0.2
SLE renal involvement	35 (41.2)	25 (41.7)	9 (45.0)	1 (20.0)	0.591	0.8
HCQ treatments						
Duration of HCQ treatment	12.9 (7.2)	11.9 (5.8)	13.4 (7.3)	23.8 (13.4)	0.001	0.2
HCQ dose (mg/kg/day) at inclusion, mean (SD)	5.65 (1.81)	5.52 (1.67)	6.03 (2.09)	5.65 (2.36)	0.553	0.8
HCQ dose (mg/kg/day) at inclusion, by categories					0.060	0.14
<5 mg/kg/day	31 (36.5)	21 (35.0)	8 (40.0)	2 (40.0)		
5–6.5 mg/kg day	21 (24.7)	20 (33.3)	1 (5.0)	0 (0.0)		
>6.5 mg/kg day	33 (38.8)	19 (31.7)	11 (55.0)	3 (60.0)		
HCQ dose (mg/kg/day) after reduction, mean (SD)	4.98 (1.86)	5.52 (1.67)	3.38 (1.46)	0	<0.001	<0.001
HCQ dose (mg/kg/day) after reduction, by categories					<0.001	0.003
<5 mg/kg/day	38 (47.5)	21 (35.0)	17 (85.0)	NA		
5–6.5 mg/kg day	22 (27.5)	20 (33.3)	2 (10.0)	NA		
>6.5 mg/kg day	20 (25.0)	19 (31.7)	1 (5.0)	NA		
Other treatments						
Concomitant prednisone use	42 (49.4)	24 (40.0)	15 (75.0)	3 (60.0)	0.022	0.074
Prednisone dose, mg per day (n=42)	5.47 (4.1)	6.37 (5.1)	4.23 (1.6)	4.00 (1.0)	0.271	0.4
Immunosuppressants	30 (35.3)	20 (33.3)	9 (45.0)	1 (20.0)	0.649	0.7
Azathioprine	8 (9.4)	5 (8.3)	3 (15.0)	0 (0.0)		
Mycophenolate mofetil	8 (9.4)	5 (8.3)	2 (10.0)	1 (20.0)		
Methotrexate	10 (11.8)	6 (10.0)	4 (20.0)	0 (0.0)		
Tacrolimus	4 (4.7)	3 (5.0)	1 (5.0)	0 (0.0)		
SLE activity at inclusion						
SLEDAI-2K	1.3 (2.4)	1.3 (2.3)	1.1 (2.4)	1.6 (3.6)	0.908	0.8
Remission (DORIS)	59 (69.4)	40 (66.7)	15 (75.0)	4 (80.0)	0.680	0.8
LLDAS	69 (81.2)	47 (78.3)	18 (90.0)	4 (80.0)	0.511	0.7
SLE flare during the 6-month follow-up	16 (18.8)	8 (13.3)	6 (30.0)	2 (40.0)	0.117	0.2
SLE flare during the 2-year follow-up	29 (34.1)	17 (28.3)	10 (50.0)	2 (40.0)	0.200	0.4

Results are expressed as N (%) for categorical variables and means (SD) for continuous variables. Groups were compared by logistic regression for categorical variables and analyses of variance for continuous variables.
Q values were calculated using the false discovery rate correction or multiple testing.
DORIS, definition of remission in SLE; HCQ, hydroxychloroquine; LLDAS, lupus low disease activity state; mg, milligrams; SLEDAI-2K, SLE Disease Activity Index-2000.

When we restricted our multivariate analyses to the flares in the 6 months after T0, HCQ reduction was still associated with the flare risk (adjusted HR 3.00; 95% CI 1.00 to 8.97) and the same trend was observed with HCQ withdrawal (adjusted HR 5.32; 95% CI 0.89 to 31.92).

DISCUSSION

Our prospective study is the first to analyse the consequences of reducing or discontinuing HCQ after the early detection of abnormalities during intensive ophthalmological monitoring. We found that 29.4% of our patients with SLE had such abnormalities after HCQ treatment for a mean duration of 14.4±7.7 years. Reducing their HCQ dose after these findings was associated with a statistically significantly increased risk of SLE flare, and HCQ discontinuation with an increased risk of SLE flare in the same range but not statistically significant. The flares in the reduction and discontinuation groups mostly occurred

Table 2 Treatment characteristics of patients according to SLE flare (N=85)

	Overall (N=85)	No flare (N=56)	SLE flare (N=29)	P value
Treatment group				0.200
Maintained HCQ	60 (70.6)	43 (76.8)	17 (58.6)	
Reduced HCQ dose	20 (23.5)	10 (17.9)	10 (34.5)	
Discontinued HCQ	5 (5.9)	3 (5.4)	2 (6.9)	
HCQ at inclusion (n=80*)				
HCQ dose (mg/kg/day), mean (SD)	5.0 (1.0)	5.3 (1.8)	4.3 (1.9)	0.025
HCQ dose (mg/kg/day), by categories				0.233
<5 mg/kg/day	38 (44.7)	22 (39.3)	16 (55.2)	
5–6.5 mg/kg day	22 (25.9)	15 (26.8)	7 (24.1)	
>6.5 mg/kg day	20 (23.5)	16 (28.6)	4 (13.8)	
Treatment modification after flare (N=29)	–	–	26 (89.7)	
Increased prednisone dose	–	–	19 (65.5)	
New immunosuppressant	–	–	20 (69)	
Azathioprine	–	–	1 (3.4)	
Mycophenolate mofetil	–	–	5 (17.2)	
Methotrexate	–	–	10 (34.5)	
Tacrolimus	–	–	2 (6.9)	
Rituximab	–	–	2 (6.9)	

Results are expressed as N (%) for categorical variables and means (SD) for continuous variables. Comparisons were made with logistic regression for categorical variables and analyses of variance for continuous variables.
*Comparisons were made after exclusion of patients who discontinued HCQ.
HCQ, hydroxychloroquine; mg, milligrams.

in the first 6 months after dose modification, timing that supports the role of HCQ in controlling SLE activity. The occurrence of flares led to increases in the corticosteroid doses or other immunosuppressants in 90% of patients with flares.

Although not significant, due to a probable lack of power, the association of SLE flares with HCQ discontinuation (adjusted HR 2.13) was close to what was observed in the well-known small double-blind randomised trial published in the *New England Journal of Medicine* in 1991 that showed a risk of flare in patients who discontinued the treatment 2.5 times higher than in those who continued it.[6] It should be noted that the retinal abnormalities compatible with HCQ toxicity that led to discontinuation of treatment in our study were seen in an older population (mean age 68.0 years) who had been taking HCQ for a much longer period (mean 23.8±13.4 years) and at higher doses (6.1±2.8 mg/kg/day) than those in

Table 3 HRs (95% CIs) for the risk of SLE flare in the 2 years after time zero (N=85)

		Risk of SLE flare		
	Overall N=85	N events (%) or mean (SD)	Univariate HR (95% CI)	Multivariate HR (95% CI)
HCQ groups				
Maintained HCQ	60 (70.6)	17 (28.3)	Reference	Reference
Reduced HCQ dose	20 (23.5)	10 (50.0)	2.21 (1.01 to 4.83)	2.26 (1.03 to 4.97)
Discontinued HCQ	5 (5.9)	2 (40.0)	1.78 (0.41 to 7.71)	2.13 (0.44 to 10.27)
Duration of HCQ treatment, years	12.9 (7.7)	13.1 (8.7)	1.01 (0.95 to 1.06)	1.01 (0.95 to 1.07)
Immunosuppressant use	30 (35.3)	13 (43.3)	1.76 (0.85 to 3.66)	1.64 (0.78 to 3.47)
Renal involvement	35 (41.2)	16 (45.7)	1.94 (0.93 to 4.03)	1.60 (0.72 to 3.55)
SLEDAI 2 K at inclusion	1.3 (2.4)	2.0 (3.1)	1.19 (1.05 to 1.36)	1.14 (0.99 to 1.32)

Results are expressed as N (%) for categorical variables and means (SD) for continuous variables.
HCQ, hydroxychloroquine; mg, milligrams; SLEDAI-2K, SLE Disease Activity Index-2000.

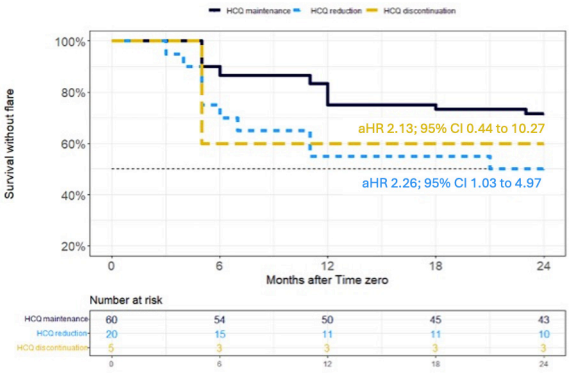

Figure 1 Kaplan-Meier curves for the risk of flare in patients whose HCQ prescription was maintained, reduced or discontinued (N=85). The multivariate models included the following variables: duration of HCQ treatment, immunosuppressant use, history of renal involvement and SLEDAI-2K at inclusion. aHR, adjusted HR; HCQ, hydroxychloroquine; SLEDAI-2K, SLE Disease Activity Index-2000.

the other groups. This finding is also concordant with the literature. Importantly, since SLE tends to be less active over the years, the older age of the patients in our discontinuation group should have been protective against the risk of flares, reinforcing our findings.

HCQ reduction was associated with the risk of flare in the univariate analysis (HR 2.21; 95% CI 1.01 to 4.83, with the maintenance group as the reference). This association persisted in the multivariate analysis and when considering only the flares that occurred within 6 months after T0. This finding is concordant with three recent studies in this field also reporting higher flare risk in patients taking reduced HCQ doses.[16 17] In a population of 1460 patients included in the SLICC cohort, the authors identified a higher risk of first SLE flare in the reduction and discontinuation groups (adjusted HR 1.20, 95% CI 1.04 to 1.38 and 1.56, 95% CI 1.31 to 1.86, respectively), but provided no information about the reasons for discontinuation.[17] In the retrospective case-crossover study by Jorge *et al* of 342 patients, a daily dose of HCQ ≤5 mg/kg was associated with a higher risk of SLE flares, especially moderate or severe, while the adjusted OR for lupus flare associated with a lower HCQ dose was 1.98 (95% CI 1.03 to 3.79) and for moderate or severe flares only 6.04 (95% CI 1.71 to 21.30).[16] However, the authors did not report either the reason for dose reduction (application of published guidelines or SLE activity) or any other recent dosage change. The study conducted by Kisaoglu *et al* found an increased risk of flare for children on daily HCQ dose <5 mg/kg during remission with OR 5.8 in multivariable analysis (95% CI 1.3 to 69.5, p=0.023), again with no information on the reason for dose reduction.[18] The only negative study was performed by Fernandez-Ruiz *et al* and analysed an older population of 58 patients. It found a not statistically significant trend towards higher flare risk in the withdrawal group (HR 1.28; 95% CI 0.31 to 5.30; p=0.73).[19] Our study also supports the importance of HCQ dose in the occurrence of flares, with lower dose in patients that flared, with most patients with HCQ dose <5 mg/kg/day although this was not statistically significant.

What distinguishes our study is that the need to discontinue or reduce HCQ was not motivated by the patient's or physician's preference but by abnormalities found in the ophthalmology examination. Our study focused on an SLE population undergoing close ophthalmological surveillance (due to their inclusion in the PERFOCTAPS Study) that identified subclinical abnormalities in 29.4% of them. This percentage is substantially higher than the reported incidence of HCQ clinical retinal toxicity of 1.0 per 1000 person-years reported in a recent multinational study[10] and 1 in 1207 patients in another multicentre study.[26] With the improved sensitivity of ophthalmological screening, the probability of finding subclinical abnormalities has markedly increased over the years. Even though our patients were treated with HCQ for a relatively long period, the high incidence of these subclinical abnormalities calls into question the importance to be attributed to such findings, especially balanced against the higher risk of SLE flares and the ensuing higher risk of use of other treatments with potentially severe side effects, such as corticosteroids and immunosuppressive drugs. Moreover, the increasing gap between the incidence of subclinical (increasingly frequent) and clinical retinopathy (historically rare) raises questions about whether these abnormalities should be considered signs of HCQ impregnation rather than toxicity and should lead to closer follow-up but not necessarily to reduction of treatment.

Finally, our study raises the practical question of what to do when a patient presents with ophthalmological abnormalities. From our empirical point of view, the first step is to confirm these abnormalities by an expert ophthalmologist and, if possible, to measure blood HCQ levels, since if they are high, it is easy to reduce the daily dose without risk.[11 27–29] If it is necessary to reduce or discontinue the HCQ dose, the patient should be followed more closely, including for proteinuria, and treatment should be optimised if possible. This may include optimising adherence to remaining treatments, adjusting their doses, or even discussing the addition of other immunosuppressants that could include biotherapy. And since prevention is the best treatment, optimising HCQ treatment by using therapeutic drug monitoring as soon as HCQ is prescribed could avoid part of the toxicity.[28–30]

We acknowledge some limitations to our study. First, our sample size was limited, with especially a small number of patients in the discontinuation group, which might be responsible for a lack of power in the results. Second, T0 corresponded to the inclusion date in the maintenance group and to the date of HCQ reduction or discontinuation during the first 2 years after inclusion for the other groups, respectively; this difference might have introduced a bias. However, this bias would have favoured the reduction or discontinuation groups since classically, SLE tends to be less active over the years. The

same remark applies to the older age of the patients in our discontinuation group. These points are thus unlikely to have biased our results. In addition, HCQ blood levels were not systematically collected in the study. Of note, their results would have been complicated to interpret since some patients had reduction of daily doses or even cessation of treatment, and this would have introduced a differential bias when taking this into account. Also, we did not collect SLE flares in the year preceding the inclusion, precluding us from seeing if the patients with recent flares were more likely to flare in the setting of lowering HCQ. Regardless, this would not have changed the results and conclusion of our study. Finally, we were not able to assess the frequency of flares, which would require a longer-term study.

In conclusion, we found a higher risk of SLE flare in patients whose HCQ dosages were reduced after abnormal findings during their close ophthalmological surveillance. This adds data to what may be a return of the pendulum on the subject of HCQ dose reduction: we must always balance the potential benefits of tapering or discontinuing HCQ with the risk of SLE flare and subsequent need to increase or start other drugs, especially corticosteroids or immunosuppressors that have well-known adverse effects.

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