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Hydroxychloroquine: A multifaceted treatment in lupus

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Summary

The efficacy of antimalarials, especially hydroxychloroquine (HCQ), in preventing systemic lupus erythematosus (SLE) flares is well demonstrated. However, many studies show that the percentage of SLE patients treated with HCQ remains low. By blocking the toll-like receptor 7 and 9 in plasmacytoid dendritic cells, HCQ inhibits interferon-alpha production which plays a crucial role in SLE pathogenesis. In addition to reducing damage accrual in SLE patients, HCQ appears to protect against the occurrence of diabetes, thrombotic events, and dyslipidemia. As a consequence, some studies have suggested that HCQ, which is inexpensive, has a protective effect on survival in SLE patients. Thanks to the pharmacokinetic properties of HCQ (long half-life) and to the availability of its blood assay, very low or undetectable blood HCQ concentrations are a valuable marker of non-adherence to treatment, thus adding a new benefit to HCQ prescriptions. The main side effect of HCQ is retinal toxicity. This complication is very rare, but may be potentially severe, thus requiring regular screening. Retinal toxicity remains the only absolute contra-indication of HCQ in adult SLE patients. Other contra-indications are few and rare. During pregnancy and breast-feeding, HCQ continuation is not only allowed but recommended. In conclusion, the risk/benefit ratio of HCQ is excellent. Many now believe that all SLE patients should be offered this treatment.

Hydroxychloroquine (HCQ), a drug which has been used for more than 50 years in the treatment of SLE, has long been considered a relatively minor component in the treatment of systemic lupus erythematosus (SLE). However, increasing evidence shows that HCQ is an important medication for this disease [1]. After briefly reviewing the mechanisms of action

of HCQ, we will discuss the risk/benefit ratio, the contra-indications of HCQ, and the benefits of measuring its blood concentration. In conclusion, we will review for which SLE patients this treatment is most adequate.

Mechanisms of action

Antimalarials have been used for many years in inflammatory rheumatism, but their numerous and complex mechanisms of action remain controversial. It is generally accepted that these molecules, which are weak bases, interfere with the function of phagocytosis through an increase of pH in intracellular compartments, leading to a disruption of the selective presentation of self-antigens (which are of low affinity), while respecting that of exogenous antigens [2].

Besides altering the process of antigen presentation, chloroquine (CQ) and HCQ may also block the proliferative responses of T-cells after stimulation by mitogens or alloantigens [3–7]. Except in one study on interleukin (IL)-1 [8], the experimental data have constantly shown an inhibition of the production of cytokines (IL-1, IL-2, IL-6, IL-17, IL-22, interferon [IFN] alpha and gamma and/or Tumor Necrosis Factor [TNF] alpha) [3,6,9–16]. The data concerning the relationship between HCQ and apoptosis are conflicting: HCQ has been shown to induce apoptosis in peripheral blood lymphocytes [8,17–21] but some experimental results have found that HCQ exhibits an anti-apoptotic action on lymphocytes. In SLE patients, this anti-apoptotic effect seems to be linked with its interference with antigen processing in macrophages and other antigen-presenting cells [22]. Other mechanisms of action involve the inhibition of DNA polymerases [23] or the inhibition of the activity of phospholipases A2 [24].

More recent data strongly support the notion that the key activity of HCQ in SLE could be an inhibition of the Toll-like receptor (TLR) activation. TLRs are receptors involved in innate immunity that seem to have a particularly important role in autoimmune diseases including SLE [25]. TLRs have been first known for their ability to discriminate microbial macromolecules from host tissue and thereby rapidly activate the innate immune system. However, it has become increasingly apparent in recent years that certain specific host molecules, especially nucleic acids, can serve as endogenous TLR ligands, perhaps promoting responses to damaged tissue [25]. The acidic lysosomal environment is favorable for the binding of nucleic acids to intracellular TLRs. As previously seen, HCQ inhibits endosomal acidification, on which signaling of the intracellularly located TLRs, such as TLRs 3, 7, 8, and 9, depend [25]. The inhibitory action of CQ and HCQ on TLRs interaction with nucleic acid ligands has been confirmed in the past decade [25–27]. Leadbetter et al. have demonstrated in a transgenic mouse model that the production of rheumatoid factors by activated B-lymphocytes requires activation of TLR 9 [28]. In this study, CQ was able to block the production of rheumatoid factors by

inhibiting TLR 9 in the endosomes. Brentano et al. [26] showed that HCQ, used in vitro as an anti-TLR, inhibits the production of cytokines and chemokines by fibroblasts that have been stimulated by cells from necrotic synovial fluid from patients with rheumatoid arthritis [26]. Sacré et al. showed that plasmacytoid dendritic cells from SLE patients receiving HCQ were unable to produce IFN-α and TNF-α upon stimulation with TLR-9 and TLR-7 agonists (TLR-9 and TLR-7 being constitutively expressed by these cells) [15]. Finally, as emphasized by Lafyatis et al. [25], it is notable that the in vivo concentrations (above 1000 ng/mL) which are associated with a decreased frequency of subsequent SLE flares [29] were in the same range as those able to block intracellular TLRs in vitro [28].

Benefits of hydroxychloroquine

The benefits of HCQ result both from its direct effects on SLE activity and from its indirect effects, such as its antithrombotic properties and its ability to protect against diabetes or hyperlipidemia which may contribute to reduce the high cardiovascular risk of SLE patients.

Direct effects on SLE activity

Overall efficacy

First of all, HCQ is effective in SLE as demonstrated by a randomized, double-blinded, placebo-controlled study from the Canadian Hydroxychloroquine Study Group [30,31]. This study included 47 SLE patients on stable doses of HCQ. Patients were randomized to continue drug therapy (n = 25) or to be changed to a placebo (n = 22). During the six-month period after HCQ discontinuation the risk of clinical SLE flares increased by 2.5 (95% CI: 1.08 to 5.58; P = 0.02): 9 flares out of 25 patients in the HCQ group versus 16 out of 22 in the placebo group. The relative risk of severe SLE exacerbations including vasculitis, transverse myelitis, and lupus nephritis was 6.1 times higher (95% CI: 0.72 to 52.44) in the group of patients who discontinued HCQ (1 flare out of 25 patients versus 5 out of 22), but this result did not reach statistical significance (P = 0.06) [30]. In the follow-up study of the Canadian Hydroxychloroquine Study Group, in which randomization and blinding were not maintained, nephritis flare incidence was reduced by 74% among those continued on HCQ, but this result did not reach statistical significance (P = 0.25) [31]. Similar results have been found in pregnant patients [32]. A 12-month double-blind, placebo-controlled trial of CQ (250 mg daily) similarly showed that CQ improved non-major organ manifestations, reduced steroid requirements, and prevented disease exacerbations [33].

Efficacy on renal manifestations

Several studies have shown that HCQ is useful in patients with SLE glomerulonephritis [34]. A study including 450 SLE patients demonstrated that HCQ use was protective against renal

insufficiency: 64% of patients treated with HCQ achieved remission within a year, as compared to 22% of patients without HCQ ($P = 0.036$ on the basis of a log-rank test) [35]. HCQ is also an independent predictor of complete renal remission in SLE patients treated with mycophenolate mofetil for membranous lupus nephritis [36]. In that study, patients treated with mycophenolate mofetil and HCQ had a remission rate 5.2 times higher than those treated with mycophenolate mofetil alone (95% CI: 1.2 to 22.2; $P = 0.026$). Finally, as we will see below, renal damage may be delayed by HCQ [37].

In their guidelines for the management of SLE nephritis, both the American College of Rheumatology (ACR) [38] and the European League Against Rheumatism (EULAR) [39] have recommended the use of HCQ as an adjunctive therapy in SLE nephritis.

Efficacy to delay SLE

Early HCQ use was associated with delayed SLE onset in a retrospective study of a cohort of 130 US military personnel who later met ACR SLE criteria [40]. The authors studied patients who had initially less than 4 criteria of the ACR SLE classification. Those treated with HCQ at the onset of symptoms ($n = 26$) had a longer time between the first clinical symptom and the ''diagnosis'' of SLE according to the ACR SLE classification (i.e. presence of 4 or more items; median: 1.08 versus 0.29 years, $P = 0.018$). The 4 classification criteria were also fulfilled more slowly in patients treated with prednisone before diagnosis ($P = 0.011$). No difference was found according to nonsteroidal anti-inflammatory drug (NSAID) use. Patients treated with HCQ had a lower rate of autoantibodies and a decreased number of autoantibody specificities at the time and after diagnosis of SLE [40].

Indirect beneficial effects of HCQ

The beneficial effects of antimalarials largely exceed their direct effect on SLE activity, especially in this setting of patients exposed to treatment side effects and to atherothrombosis.

Effects on thrombosis

Antimalarials, especially HCQ, reduce platelet aggregation. This effect is strong enough for HCQ to have been proposed, a few decades ago, as an agent for deep vein thrombosis prophylaxis in patients undergoing hip replacements. The antithrombotic properties of HCQ have been demonstrated in an animal model: after a standardized thrombogenic injury, by injection of purified immunoglobulin G from a patient with antiphospholipid syndrome, mice showed significantly smaller thrombi, that persisted for a shorter period of time, if they were fed with HCQ, as compared to placebo [41].

Petri et al. reported in 1996 that HCQ use was protective against future thrombosis in SLE patients included in the Johns Hopkins Lupus Cohort [42]. These results have been confirmed in Chinese patients with an odds ratio (OR) of thrombotic complications of 0.17 (95% CI: 0.07 to 0.44; $P < 0.0001$) in patients taking HCQ [43]. Ruiz-Irastorza et al. found similar results with a hazard ratio (HR) of 0.28 (95% CI: 0.08 to 0.90) [44]. In 442 SLE patients from the multi-ethnic LUMINA cohort, HCQ was protective against thrombotic events only in the univariate analysis [45]. In a cohort of Greek SLE patients, the duration of HCQ use was protective against thrombosis both in SLE patients with ($n = 144$) and without ($n = 144$) antiphospholipid antibodies [46].

In 2009, Kaiser et al. analyzed risk factors for thrombosis in a large ($n = 1930$) multi-ethnic SLE cohort [47]. After adjusting for disease severity and incorporating propensity scores, HCQ use was significantly protective against thrombosis (OR 0.62, $P < 0.001$) [47].

Jung et al. published in 2010 a nested case-control study embedded in an inception cohort of patients with SLE: 54 cases of thrombotic events were matched with 108 control SLE subjects. After accounting for the effects of disease severity, disease duration and calendar year, antimalarial drugs were associated with a 68% reduction in the risk of all thrombotic events, with a range of risk reduction of at least 26% up to as high as 86% [48].

Broder et al. studied the association between HCQ use and persistent antiphospholipid antibodies and/or lupus anticoagulant (LA) in SLE [49]. Among 90 patients included in the study, after adjustment, HCQ was associated with significantly lower odds of having persistent LA and/or antiphospholipid antibodies (OR 0.21, 95% CI: 0.05 to 0.79, $P = 0.02$) [49].

As a consequence, the AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION), an international research network will launch a randomized controlled trial evaluating HCQ in the primary prevention of thrombosis in persistently aPL-positive but thrombosis-free patients without other systemic autoimmune diseases [50].

The observed reduction of thrombosis in human and experimental antiphospholipid syndrome by HCQ may be explained by a reversible reduction in the formation of antiphospholipid-β2-glycoprotein complexes to phospholipid surfaces and monocytes, as demonstrated by Rand et al. [51]. Interestingly, using the techniques of ellipsometry and atomic force microscopy, the authors showed that this effect was observed for HCQ concentrations of 1000 ng/mL and greater [51], which is consistent with the target blood HCQ concentration in SLE patients that we have defined [29].

Effects on glycemia

Hypoglycemia is a well-recognized adverse effect of treatment with antimalarials [52]. In vitro and animal studies show that antimalarials improve insulin secretion and peripheral insulin sensitivity. During an intensive outpatient intervention including 38 decompensated patients with type 2 diabetes resistant to treatment, those treated with HCQ (200 mg, 3 times per day

during 6 months) had an absolute reduction in glycated hemo-globin A1c level of 3.3% (95% CI: −3.9 to −2.7; P = 0.001), while no significant changes were seen in patients on placebo. The daily insulin dose in patients treated with HCQ was reduced in average by 30% [53].

In a large prospective, multicenter observational study of 4905 adults with rheumatoid arthritis and no diabetes, Wasko et al. [54] showed that the use of HCQ was associated with a reduced risk of diabetes during the 21.5 years of follow-up. The hazard ratio for incident diabetes among patients who had taken HCQ (n = 1808) was 0.62 (95% CI: 0.42 to 0.92) compared with those who had not taken HCQ (n = 3097) [54]. Risk reduction increased with duration of HCQ exposure: the adjusted relative risk of developing diabetes among patients who had taken HCQ for more than 4 years (n = 384) was 0.23 (95% CI: 0.11 to 0.50; $P < 0.001$).

More recent studies have confirmed that HCQ may be beneficial for improving glycemic control in SLE patients [55], and for preventing diabetes [56].

Effects on lipid profile

Antimalarials have a beneficial effect on lipid profile of patients with rheumatoid arthritis and SLE, especially those treated with steroids [57–62].

Concordant studies show reduced total cholesterol levels in patients taking antimalarials. Petri et al. [58] studied 264 SLE patients of the John Hopkins Lupus Cohort. In the longitudinal regression analysis, HCQ was associated with lower serum cholesterol levels whatever the HCQ dose (200 or 400 mg/day). The authors calculated that HCQ was able to ''balance'' the adverse effect of 10 mg of prednisone on cholesterol level. Rahman et al. [57] studied 815 SLE patients. Initiation of antimalarials without steroids reduced the baseline total cho-lesterol by 4.1% at 3 months (P = 0.02) and by 0.6% at 6 months (P = NS), while initiation of antimalarials on a stable dose of steroids reduced the total cholesterol by 11.3% at 3 months (P = 0.0002) and 9.4% at 6 months (P = 0.004). The cessation of antimalarials increased the total cholesterol levels by 3.6% at 3 months (P = NS) and 5.4% at 6 months (P = NS). In 181 patients taking both steroids and antimalarials, the mean total cholesterol level was 11% lower than that of 201 patients receiving a comparable dose of steroids alone (P = 0.0023). Others have found similar results [62].

In addition to confirming the reduction in total cholesterol level, some studies have focused on lipid profile. Results are concor-dant except for the effect on high-density lipoprotein (HDL) levels, which were found unchanged [60,62,63], decreased [59] or increased [61,64].

The mechanism of cholesterol-lowering by antimalarials remains unclear but may involve an overall reduction in hepatic cholesterol synthesis, as demonstrated in animal studies [65]. This could be explained by the inhibition of lysosomal function by antimalarials, which leads to an accumulation of LDL in the lysosome. Indeed, CQ is known to block cholesterol transport out of the lysosome and is used for these properties in in vitro models studying cholesterol metabolism [66]. Moreover, by using a radioactive cholesterol-rich nanoemulsion that mimics the LDL structure, it has been demonstrated in vivo that plasma LDL removal by LDL receptor was increased in SLE patients taking CQ with a consequent beneficial decrease in LDL levels [67].

In conclusion, antimalarials, alone or added to steroids, appear to have a beneficial effect on dyslipidemia. This suggests that antimalarials, especially HCQ, may have a role in reducing the key risk factors for atherosclerosis in SLE, namely platelet aggregation, diabetes and dyslipidemia. Accordingly, despite high rates of use of HCQ in their study, Roman et al. found a significant negative relation between the use of HCQ and the presence of atherosclerosis (carotid plaques) in 197 SLE patients [68].

Effects on bone mineral density

Two studies have analyzed the relationship between the bone mineral density and antimalarial use in SLE patients. The first one [69] studied dual X-ray absorptiometry in 34 postmeno-pausal SLE patients who had received a long-term steroid therapy. By multivariate analysis, the use of HCQ, either current or past, was associated with a higher spinal bone mineral density. The second one [70] studied dual X-ray absorptiometry in 92 consecutive SLE patients (98% had received prednisone, 68% had received HCQ and 51% were postmenopausal). In the multivariate analysis, the use of HCQ was the only factor associated with higher bone mineral density of the hip and spine. By contrast, in a recent study, the use of antimalarials at baseline was associated with bone mineral density loss [71].

Effects on cancer

There is data showing that CQ may play a role in the treatment of some cancers, especially glioblastoma. Indeed, in a small randomized, double-blind, placebo-controlled study of 30 patients, CQ, added to conventional treatment, improved sur-vival in patients with glioblastoma multiforme [72]. If confir-med, this effect could be due to protective properties of antimalarials against DNA damage. Antimalarials are weak bases that concentrate in lysosomes and are strong DNA-intercalating agents that prevent mutations in cells [72]. CQ has shown an inhibitory action on telomerase, which is involved in the unlimited replication of tumorous cells. CQ improves cellular mechanisms of DNA repair after damage caused by alkylating therapy [72]. Rahim et al. [73] found that the growth of human breast cancer cell lines in vitro was inhibited by CQ and HCQ via a regulation of protein acetylation events. HCQ has an anti-autophagic effect that might be useful in treated patients with cancer or lymphoma. Many clinical trials are ongoing to confirm or not the benefit of HCQ as an adjuvant

therapy in different cancers (more than half of the studies on HCQ registered in clinicaltrial.gov are currently focusing on cancer or lymphoma; see www.clinicaltrials.gov).

Regarding SLE patients, an observational prospective cohort study of 235 SLE patients has found that antimalarials may have a protective effect against cancer [74]. The adjusted hazard ratio for cancer among patients who received antimalarials at any time compared with patients never treated with these treatments was 0.15 (95% CI: 0.02 to 0.99; P = 0.049). As emphasized by the authors, these results should be confirmed in larger multicenter studies.

Anti-infectious effects

In addition to their antimalarial properties, CQ and HCQ have antibacterial, antifungal, and antiviral actions [75,76]. Doxycycline in association with HCQ is already the recommended treatment of chronic Q fever [76] and Whipple's disease [77]. Preliminary *in vivo* clinical trials suggest that CQ alone or in combination with antiretroviral drugs might be an interesting way to treat human immunodeficiency virus (HIV) infection [76], although the first clinical trial was not very convincing [78]. The clinical consequences of these effects in SLE patients are unknown.

One must note that HCQ is not effective against CQ-resistant strains of *Plasmodium falciparum* and is not active against the exo-erythrocytic forms of *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium malariae*. Therefore HCQ neither prevents infection due to these organisms when given prophylactically, nor prevents relapse of infection.

Effects on damage accrual

Several studies have assessed the relationship between HCQ use and the risk of overall damage accrual in SLE patients [79–81].

Molad et al. included 151 SLE patients from Israel [79]. After a mean follow-up of 45 months, treatment with HCQ was associated with a higher damage-free survival (P < 0.0001).

The LUMINA study group [80] followed up annually on 518 SLE patients with less than 5 years of disease duration at inclusion. At study entry, 291 (56%) were treated with HCQ. At the end of the follow-up period, untreated patients on enrolment had higher Systemic Lupus Activity Measure (SLAM) and Systemic Lupus International Collaborating Clinics damage index (SDI) scores, and were significantly more likely to have major organ involvement such as renal disease (P < 0.0001) or central nervous system disease (P < 0.0025), and to accrue damage (HR = 0.68; 95% CI: 0.53 to 0.93; P < 0.014). After adjustment for the propensity scores for differences in treatment assignment, HCQ use was still associated with a reduced risk of developing new damage (HR = 0.73; 95% CI: 0.52 to 1.00; P = 0.05). This benefit was demonstrated only in patients who had no damage at study entry (HR = 0.55; 95% CI: 0.34 to 0.87; P = 0.011).

In 2009, the LUMINA study group specifically assessed whether HCQ can delay renal damage occurrence in 203 lupus nephritis patients with no renal damage (using the SLICC Damage Index) at baseline (79.3% of which were treated with HCQ) [37]. Sixty-three (31%) of the 203 patients developed renal damage (mostly proteinuria) over a mean disease duration of 5.2 ± 3.5 years. After adjusting for possible confounding factors, HCQ delayed renal damage development in full (HR = 0.12; 95% CI: 0.02 to 0.97; P = 0.046) and reduced (HR = 0.29; 95% CI: 0.13 to 0.68; P = 0.004) models [37].

The same group found a similar protective effect of HCQ on the occurrence of integument damage in SLE (scarring alopecia, extensive skin scarring, and skin ulcers lasting at least 6 months) [82].

Akhavan et al. conducted a nested case-control study embedded in an inception cohort of 481 SLE patients who were followed for at least 3 years [81]. They matched 151 cases with 151 controls. In multivariate analysis, the use of HCQ was significantly associated with less damage (OR 0.34, 95% CI 0.132–0.867; P = 0.02), while age (OR = 1.05; 95% CI 1.027 to 1.078; P < 0.0001) and a variable combining SLE activity and steroid dose (OR = 1.73; 95% CI 1.306 to 2.295; P = 0.0001) were associated with damage at 3 years [81].

Petri et al. have studied organ damage predictors among 2054 SLE patients of the Hopkins lupus cohort. During follow-up, the risk of damage was higher for those who were older, had more disease activity, had low complement levels, were positive for anti-double-stranded DNA, satisfied more ACR criteria for SLE or were receiving corticosteroids. A lower risk was observed among patients receiving HCQ. After adjustment for other variables, age, hypertension, and corticosteroid use emerged as the most important predictors of damage accrual, whereas HCQ use seemed protective (P = 0.060) [83].

Effects on survival

In consequence of their numerous beneficial effects, antimalarials appear to have a protective effect on survival in SLE patients [44,84,85].

Ruiz-Irastorza et al. [44] reported an observational prospective cohort study of 232 SLE patients, including 150 patients (64%) who received antimalarials. Among the 23 patients who died, 19 (83%) had never received antimalarials. No patient treated with antimalarials died of cardiovascular complications. Cumulative 15-year survival rates were 0.68 for patients who had never received HCQ compared to 0.95 for those who had received HCQ (P < 0.001). Antimalarial use remained protective on survival even after adjusting for patient characteristics [44].

Alarcon et al. [84] have performed a case-control study among 608 SLE patients from the LUMINA cohort. Sixty-one deceased patients (cases) were matched for disease duration with living patients (controls) in a 3 to 1 proportion. Propensity scores

were derived by logistic regression to adjust for confounding by indication (since SLE patients with milder disease manifestations were more likely to be prescribed HCQ). The authors found that HCQ had a protective effect on survival (OR = 0.128; 95% CI: 0.054 to 0.301 for HCQ alone, and OR = 0.319; 95% CI: 0.118 to 0.864 after adding the propensity score) [84].

In 2010, Shinjo et al. evaluated the beneficial effect of antimalarial treatment on survival in the Grupo Latino Americano de Estudio del Lupus Eritematoso (GLADEL) cohort [85]. Among the 1480 patients included in the GLADEL cohort, 1141 (77%) had been treated at least for 6 consecutive months with antimalarials and were considered antimalarial users, with a mean duration of drug exposure of 48.5 months (range 6–98 months). Death occurred in 89 patients (6.0%). A lower mortality rate was observed in antimalarial users compared with non-users (4.4% versus 11.5%; $P < 0.001$). After adjustment for potential confounders in a Cox regression model, antimalarial use was associated with a 38% reduction in the mortality rate (HR = 0.62, 95% CI 0.39–0.99). This protective effect on SLE survival seemed to be time-dependent.

Finally, Zengh et al. studied the predictors of survival in 491 Chinese patients with lupus nephritis [86]. In the multivariate analysis, increased creatinine (HR = 2.041; 95% CI: 1.134 to 3.672; $P = 0.017$) and proteinuria $\geq 3.5g/24$ hours (HR = 1.716; 95% CI: 1.104 to 2.666; $P = 0.016$) were independent risk factors of mortality whereas the use of steroids (HR = 0.457; 95% CI: 0.252 to 0.828; $P = 0.01$) and HCQ (HR = 0.197; 95% CI: 0.047 to 0.820; $P = 0.026$) were independent protective factors [86].

Miscellaneous effect: prevention of recurrence of cardiac neonatal lupus

Anti-SSA/Ro-positive patients with or without SLE have a 1 to 2% risk of having a child with congenital heart block (CHB, the main manifestation of neonatal lupus) [87]. When a mother has had an affected fetus or child, the risk of recurrence increases to around 18% [87].

A case-control study first suggested a benefit of HCQ in lowering the risk of CHB in pregnancies of anti-SSA/Ro-positive patients with SLE [88]. A following study identified a total of 257 pregnancies subsequent to the birth of a child with cardiac neonatal lupus (NL) from 3 different databases [89]. The recurrence rate of cardiac-NL in fetuses exposed to HCQ was 7.5% (3 of 40) compared with 21.2% (46 of 217) in the unexposed group ($P = 0.050$). In a multivariable analysis that adjusted for database source, maternal race/ethnicity, and anti-SSB/La status, HCQ use remained significantly associated with a decreased risk of cardiac-NL (OR = 0.23; 95% CI, 0.06–0.92; $P = 0.037$). Similar results were obtained with propensity score analysis [89]. A prospective study is under way (ClinicalTrials.gov Identifier: NCT01379573), to confirm or not these preliminary results.

Synthesis

In 2008, using the GRADE system to analyze the quality of the evidence, Ruiz-Irastorza et al. extensively reviewed the clinical efficacy and side effects of antimalarials in SLE [90]. The authors concluded that there is:
- high evidence that antimalarials prevent SLE flares (including during pregnancy), and increased long-term survival of SLE patients;
- moderate evidence that antimalarials protect against irreversible organ damage, thrombosis and bone mass loss;
- low evidence that antimalarials have an effect on severe lupus activity, lipid levels and subclinical atherosclerosis.

As we have seen, more recent published articles support or reinforce these conclusions. In addition, it is important to remember that HCQ is inexpensive, especially compared with more recent treatments, and that it is widely available, even in developing countries.

Toxicity

In general, antimalarials are well tolerated and rarely need to be discontinued for an adverse reaction. Two types of side effects may be encountered. The first includes gastrointestinal intolerance, aquagenic pruritus [91] and other cutaneous manifestations [92,93]. These manifestations are not rare, usually disappear with dose reduction, and rarely require withdrawal of the treatment (except for the interruption of HCQ for esthetical reasons in case of skin coloration). The second type of toxicity is rare but potentially severe and involves various combinations of retinal, neuromuscular and cardiac manifestations. Discontinuation of the treatment is usually required and is generally associated with a slow and sometimes incomplete resolution of the symptoms.

In their review of clinical efficacy and side effects of antimalarials in SLE using the GRADE system, Ruiz-Irastorza et al. found high evidence supporting the global safety of antimalarials, both HCQ and CQ, as well as moderate grade of evidence that HCQ offers a safer profile than CQ [90]. In their review, reported adverse effects were rare, involved mainly gastrointestinal and cutaneous manifestations, and were usually mild. They pointed out only one study comparing the toxicity of HCQ and CQ [94]. In this large series of 940 patients (including 178 with SLE) there was a higher frequency of adverse effects in patients treated with CQ compared with those receiving HCQ (28.4% vs 14.7%, $P = 0.001$). Overall, 15% of patients discontinued antimalarials due to toxicity. Patients receiving HCQ were less likely to discontinue the drug due to side effects than those taking CQ (OR = 0.62; 95% CI: 0.40 to 0.96) [94].

Ophthalmological toxicity

Much of the concerns regarding antimalarials have focused on potential ocular toxicity. Deposition of the drug in the cornea may be associated with complaints of blurred vision,

photophobia, focusing difficulties and visual halos. These side effects are most commonly seen within the first several weeks of treatment and typically resolve despite the continuation of therapy. To our knowledge, this is not associated with further retinal toxicity.

In the retina, antimalarials bind to the melanin of the pigmented epithelial layer and may damage rods and cones. Early retinal changes (so-called premaculopathy) are typically first detected in the macula with findings of macular edema, increased pigmentation and granularity, and loss of the foveal reflex. Although patients with premaculopathy generally have no visual complaints, a paracentral scotoma to a red test object may be detected on testing. These types of retinal changes are considered reversible upon discontinuation of the antimalarial drug.

Advance macular disease (maculopathy) is characterized by a central area of patchy depigmentation of the macula surrounded by a concentric ring of pigmentation (bull's eye lesion). If drug exposure continues, the pigment epithelial atrophy and functional disturbance may gradually spread over the entire fundus. Advanced cases show widespread pigment epithelial and retinal atrophy with loss of visual acuity, peripheral vision and night vision. Patients may be initially entirely asymptomatic or may complain of nyctalopia and scotomatous vision with field defects of paracentral, pericentral ring types, and typical temporal scotoma. When a maculopathy is present, even after cessation of the drug, there is little if any visual recovery, and sometimes a progression of visual loss [95]. Of note, symptoms or fundus changes that are unilateral are generally not considered sufficient to implicate drug toxicity [95].

Incidence of retinopathy in clinical practice is very small and studies of several large series of patients with rheumatic disease report little or no toxicity among thousands of subjects [90,95,96]. The incidence of this toxicity seems lower for HCQ, as demonstrated by Ruiz-Irastorza et al. [90]. In 4 studies including 647 patients treated with CQ for a mean of > 10 years, 16 (2.5%) patients were diagnosed with definite retinal toxicity [90]. In comparison, only 2 (0.1%) of 2043 patients taking HCQ for a similar period included in 6 studies (OR = 25.88; 95% CI: 6.05 to 232.28; $P < 0.001$) had a retinopathy [90]. When patients classified as having probable retinal toxicity were added, 17/647 (2.6%) of CQ users and 6/2,043 (0.3%) of HCQ users had a toxicity (OR = 9.16; 95% CI: 3.42 to 28.47; $P < 0.001$) [90].

Historical studies have linked toxic retinopathy to the daily dosage of HCQ with a cut-off of 6.5 mg/kg/day. More recent studies did not confirm this and found that retinopathy was associated with cumulative dose, and longer duration of use [97].

Ophthalmological screening recommendations

Even if retinal toxicity from HCQ is rare, its potential permanence and severity make it imperative that physicians take measures to minimize its occurrence and effects. The goal is to detect premaculopathy in order to stop the treatment before the occurrence of irreversible damage. However, there is no universally-accepted method for screening or for judging risks [97].

The American Academy of Ophthalmology updated their recommendations on screening for HCQ retinopathy in 2011 [97]. It is now recommended that all individuals starting HCQ or CQ have a complete baseline ophthalmologic screening within the first year of treatment. This should include both a complete ophthalmologic examination (visual acuity and dilated examination of the cornea and retina), and a central field testing (with Humphrey 10-2 fields). Whenever it is possible, it is recommended that at least one of the following procedures be also used for routine screening: multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF). Amsler grid and color testing are no longer recommended.

Thereafter, annual screening should begin after 5 years of treatment or sooner if there are unusual risk factors. These risk factors are a cumulative dose greater than 1000 grams, a daily dose of HCQ greater than 400 mg/day (or > 6.5 mg/kg ideal body weight for short individuals), old age, kidney or liver dysfunction, and retinal disease or maculopathy.

Cardiac toxicity

Cardiotoxicity includes both heart conduction disturbances and congestive heart failure. These cardiac toxic effects described either singly or in combination, have been reported with CQ and much less frequently with HCQ alone [98].

In a thorough review published in 2007, congestive heart failure was found in 25 patients leading to death in 11 cases (46%) and to transplantation in 2 cases. Heart conduction disorders were associated in 16 cases (64%). Patients were treated with CQ ($n = 16$; 64%), HCQ ($n = 7$; 28%), or both ($n = 2$; 8%). Duration of antimalarial use varied widely, ranging from 3 months to 27 years (mean: 10 years) with a similarly wide range of cumulative doses of antimalarial drugs (0.270–9.125 kg). Associated toxicity was found in 15 patients and included myopathy ($n = 12$; 48%), retinopathy ($n = 6$; 24%), neuropathy ($n = 5$; 20%), and/or skin coloration ($n = 3$; 12%). It should be noted that these manifestations might have been under-diagnosed since they were not systematically assessed. Clinical and echocardiographic presentations often included a restrictive pattern and biventricular hypertrophy that can mimic amyloidosis.

Heart conduction disturbances secondary to antimalarial long-term treatment were found in 45 patients [98] and included bundle-branch block and atrioventricular block. Only 2 of these 45 patients had been treated with HCQ only.

Histological findings are essential to confirm the diagnosis and to exclude differential diagnoses, such as lupus-related

myocarditis, viral myocarditis, and ischemic heart disease. Light microscopy discloses enlarged and vacuolated cardiocytes, whereas electron microscopy shows the presence of curvilinear bodies in cardiac myocytes. When myocardial biopsy is contraindicated, a muscle biopsy may help to establish the diagnosis, since lesions of antimalarial myopathy and cardiopathy are usually very similar [98]. After withdrawal of antimalarials, improvement of myocardial involvement has been more frequently reported than regression of heart conduction disorders.

By contrast with what is proposed for ophthalmologic assessment, there is no recommendation concerning electrocardiographic screening and survey of patients with prolonged treatment with antimalarials [92]. Cardiac assessment with baseline and annual ECG could be discussed for patients treated with CQ, for those with other manifestations of toxicity, and for those with a high daily dose and/or a prolonged duration of treatment.

Neuromyotoxicity

Antimalarials can cause a marked neuromyopathy, characterized by slowly progressive weakness of insidious onset. This adverse effect is rare. A review published in 2000 [99] found 12 reported cases of neuromyotoxicity related to HCQ, including 3 occurring in SLE patients.

This weakness usually affects the proximal muscles of the legs first and may be associated with peripheral neuropathy. Myasthenia-like syndromes including ptosis related to CQ [99,100], and respiratory failure due to paresis of respiratory muscles related to HCQ have also been reported [101]. Reflexes are usually diminished symmetrically. Creatinine kinase levels are often normal. Electromyogram shows both neuropathic and myopathic changes. Muscle biopsy reveals a vacuolar myopathy including curvilinear bodies and type 1 and type 2 muscle fiber atrophy. These histological findings are very similar to those found in cardiac toxicity. Nerve biopsy may show axonal degeneration and rarely demyelination [99]. Other manifestations of antimalarial toxicity may be associated. Slow partial to complete recovery has been reported on cessation of antimalarials [99]. Few patients have been rechallenged with antimalarials at a lower dose without ill effect whereas others have shown recurrence of symptoms [99].

Gastrointestinal toxicity

Common gastrointestinal symptoms include nausea, vomiting, and diarrhea. Other symptoms including anorexia, heartburn, abdominal distension, and elevated transaminases are rare. Gastrointestinal manifestations are generally seen during the first weeks of treatment. They are associated with a higher dosage of HCQ and generally resolve with time, either by decreasing the dosage or by administering HCQ twice a day,

during meals. They are probably related to high blood HCQ levels [102].

Cutaneous toxicity

Cutaneous pigmentation

The majority of cases reported in the literature relate to CQ [103], and to our knowledge, only 9 cases of hyperpigmentation to HCQ had been reported before our recent case-control study comparing 24 SLE patients with HCQ-induced pigmentation to 517 SLE controls [93]. Skin pigmentation predominated on the anterior side of the shins (pretibial), and appeared after a median HCQ treatment duration of 6.1 years (range: 3 months–22 years). Twenty-two patients (92%) reported that the appearance of pigmented lesions was preceded by the occurrence of ecchymotic areas, which gave way to a localized blue-gray or brown persisting pigmentation. Twenty-three patients (96%) had at least 1 condition predisposing them to easy bruising. Skin biopsies confirmed the very high concentration of iron in biopsy specimens of pigmented lesions. Treatment with HCQ was discontinued definitively because of skin pigmentation in 2 patients who reported a gradual incomplete fading of hyperpigmentation. Among patients who continued HCQ treatment (n = 22), an improvement in pigmented lesions was reported in 6 despite the maintenance of a similar daily dose of HCQ. Pigmentation remained stable in the other patients.

Pigmentary changes due to antimalarials have also been reported in the face, hard palate, forearms, nail bed (with transversal bands or diffuse pigmentation), and in deeper structures such as joint tissue, trachea, and cartilage of the nose and ears.

Apart from pigmentation, antimalarials, mainly CQ, may also give rise to hypopigmentation. Vitiligo has been reported to occur in African patients with dark skin. Similarly, the roots of the hair can become bleached or blond (so-called ''acquired poliosis'') [104]. This hypochromia generally disappears within a few months after interruption of the drug.

Pruritus

Pruritus may occur in patients taking antimalarials [105]. Jimenez-Alonso et al. studied 105 SLE patients and 31 patients with cutaneous lupus, of whom 104 had taken HCQ or CQ [91]. They observed that 44.2% of the patients in the antimalarial group versus 5.6% of those not receiving these treatments had pruritus ($P < 0.01$). Six patients were classified as having probable or definite pruritus related to antimalarials. They all had an aquagenic or postwetness type of generalized pruritus which started 1 to 3 weeks after initiation of antimalarials. The withdrawal of antimalarials was necessary in 4 cases and a reintroduction was possible in 2 cases [91].

Psoriasis exacerbation

In contrast to other treatments such as lithium and beta-blockers, antimalarials do not induce de novo psoriasis, although some data have suggested that HCQ may trigger already existing psoriasis [106]. However, in 2006, a systematic review analyzed 31 case series and case reports (since no randomized trial was found) and concluded that there was no strong evidence to either refute or support a role of anti-malarials in the exacerbation of psoriasis [107].

Other cutaneous manifestations, including hypersensitivity skin eruptions

Other cutaneous reported manifestations are rare and include morbilliform eruptions, exfoliative dermatitis, urticaria, ecze-matous lesions, photosensitivity, erythroderma, acute genera-lized exanthematous pustulosis and erythema annular centrifugum [108].

Some of these manifestations appear in the first days or weeks of treatment, and are indicative of hypersensitivity rash, which is considered a contra-indication to further use of these treat-ments. The frequency of this side effect is difficult to evaluate and is, in our experience, extremely rare in patients treated with HCQ. Success of slow oral desensitization has been repor-ted in patients with hypersensitivity skin eruption due to HCQ [109,110].

Hematological toxicity

To our knowledge, agranulocytosis and aplastic anemia have been observed in only 2 patients treated with HCQ, both before 1969 [111,112]. There is some concern that antimalarials could cause hemolysis in patients with glucose-6-phosphate dehy-drogenase (G6PD) deficiency. To our knowledge, no cases have been reported in SLE patients or in patients treated with HCQ.

Other

Nightmares, headaches, irritability, nervousness, psychosis, seizures, hyperexcitability, dizziness, hearing loss, constitutio-nal complaints and hypoglycemia have been rarely reported with CQ and HCQ [1].

Pregnancies and breast-feeding

Pregnancies

Even if HCQ crosses the placenta, with cord blood concentra-tions nearly identical to those found in maternal blood [113], numerous studies have reported the safety and in some cases the efficacy of HCQ during pregnancy [32,114–121].

Ophthalmic examinations of the offspring have been done in some studies, and results were reassuring [32,116,117,122–124]. Only one small study found electroretinogram abnorma-lities in some infants exposed to HCQ in utero [125] but the methodology used, especially tests in mesopic conditions, and the absence of an adequate control group, were highly

debatable [126]. A recent review of the literature concluded that even if larger follow-up studies were needed, current evidence suggested no fetal ocular toxicity of antimalarial medications during pregnancy [127].

Breast-feeding

By measuring the concentration of HCQ in a few maternal milk samples [113,123,128], it has been calculated that HCQ inges-tion by infants is no more than 0.2 mg/kg/day, a very low dosage compared with the daily recommended dosage of 6.5 mg/kg in adults.

Synthesis

In 2004, during the 4th International Conference « Sex Hormo-nes, Pregnancy and the Rheumatic Diseases », international experts concluded:
- that when indicated, antimalarials should be continued during pregnancy and lactation (evidence level II, according to the classification by Miyakis et al.);
- that HCQ is the antimalarial of choice in fertile women in need of treatment (evidence level IV);
- that both CQ and HCQ are compatible with breast-feeding (evidence level IV) [129].

Contra-indications

Absolute contra-indications

According to the Physician desk reference (PDR) and to Micro-medex, the absolute contra-indications of antimalarials are rare and include:
- retinal or visual field changes attributable to any 4-aminoquinoline compound;
- known hypersensitivity to any 4-aminoquinoline compound;
- long-term use in children [92,130].

Since desensitization may be effective for patients with hyper-sensitivity [109,110], retinal toxicity remains the only absolute contra-indication in adult SLE patients.

Relative contra-indications

The PDR and/or Micromedex state that caution should be used in patients with documented psychotic disorders, epilepsy or pre-existing auditory damage, in patients with liver disease, alcoholism, psoriasis, G6PD deficiency, porphyria cutanea tarda (PCT) and neuromuscular disorders including myasthenia gra-vis, and in case of concurrent administration of known hepa-totoxic drugs or of drugs with tendency to produce dermatitis [92,130].

Not all of these contra-indications are supported by facts. As discussed above, we believe that HCQ can be used cautiously in SLE patients with psoriasis or G6PD deficiency. Even if concerns regarding the use of antimalarials in patients with known myasthenia gravis have been raised by some cases of rever-sible myasthenia-like symptoms following CQ use, HCQ is

usually well tolerated by patients with both SLE and myasthenia gravis [131].

The co-existence of SLE and PCT poses therapeutic challenges, since the relationships between antimalarials and PCT are complex. First, cases of antimalarial drug-induced PCT (or porphyria unmasked by antimalarials) have been reported. Second, some patients with PCT who receive HCQ or CQ may present with an acute exacerbation of hepatic disease followed by a long-term clinical remission after recovery from the acute exacerbation [108]. This observation has led to use antimalarials at a very low dosage as treatment for PCT [132,133]. In patients with coexisting PCT and SLE, it is usually recommended to initiate antimalarials cautiously either at a very low dosage to prevent an acute exacerbation (i.e. 100 mg of HCQ twice weekly) or, more rarely, at a higher dosage in hospitalized patients with close hepatic monitoring. In some cases, patients may also be pre-treated with phlebotomies [108].

It should be noted that, since both G6PD deficiency and PCT are rare, routine testing for these conditions are not recommended before initiating HCQ treatment.

Measurement of blood HCQ concentrations

Other benefits in favor of HCQ prescription are related to its pharmacokinetic properties (long half-life) and to the availability of its blood concentration measurement, which have emerged in the recent years as particular assets in the field of adherence evaluation [134] (see below). Indeed, HCQ and its metabolite levels can be quantified by high performance liquid chromatography (HPLC). For reasons of sensitivity and reproducibility, HCQ concentrations should be measured in whole-blood [102]. There is a great interindividual variability in blood HCQ concentrations, leading to the question of the relationship between concentrations and efficacy, and raising the need for individualized dosing in order to obtain HCQ concentrations associated with optimal outcomes. Indeed, except in one study concerning SLE patients [135], a relationship between whole-blood concentrations of HCQ and clinical efficacy has been repeatedly reported in patients with rheumatoid arthritis [102,136,137], SLE [29,138] and cutaneous lupus [139].

The PLUS study, a French multicenter randomized prospective study, failed to demonstrate the benefits of individualized HCQ dosing schedules aimed at maintaining the blood HCQ concentration above 1000 ng/mL, despite the fact that at baseline, patients with higher blood HCQ concentrations had less frequently active SLE, and also despite the fact that patients within the therapeutic target throughout follow-up tended to have fewer SLE flares than those with low blood HCQ concentrations (20.5% vs 35.1%, $P = 0.12$) [138].

One of the main appeals for this blood HCQ assay remains that it is a simple, objective and reliable marker of non-adherence to medications [134,140–142]. Indeed, since HCQ has a long terminal elimination half-life, patients who have undetectable blood HCQ concentrations have undoubtedly not taken HCQ for a long time. In our experience, regular drug assays (available within a few days in our center), help physicians detect non-adherence and can serve as the basis for counselling and supporting patients with poor adherence to therapeutic regimens. Additionally, we strongly believe that in case of an SLE flare, blood HCQ levels should be assessed in order to distinguish flares due to a lack of response to treatment from those due to a poor adherence to treatment, thus avoiding unnecessary or even dangerous regimen escalation [134].

Practical hint when prescribing HCQ

When initiating a treatment with HCQ, it is important to keep in mind that HCQ is characterized by a long delay in the onset of action because of its long half-life. As a result, patients may incorrectly interpret this delay as a lack of efficacy of the treatment, and may become poorly adherent to treatment [140]. Thus, when prescribing these drugs, the physician should explain to the patient that efficacy might take 2 to 8 weeks to be achieved.

Children are especially sensitive to the 4-aminoquinoline compounds, with a number of fatalities reported following accidental ingestion of only a few tablets of CQ. There are limited data on pediatric HCQ overdoses, but given its similarity to CQ, HCQ is considered potentially toxic at small doses [143]. As a consequence, patients should be strongly warned to keep these drugs out of children's reach.

Conclusion

In conclusion, given its very favorable risk/benefit ratio, we believe that all SLE patients should be treated with HCQ, unless they have an antimalarial related retinopathy. Although many colleagues agree with this statement [84,144,145], the percentage of SLE patients receiving HCQ remains surprisingly low. A recent study performed in a US diverse community-based cohort of SLE patients has found for instance a prevalence of HCQ use of only 55 per 100 person-years [146]. Additionally, the rate of patients treated with HCQ in recent randomized clinical trials for new drugs ranged from 44 to 72%, although by nature, these trials involved selected patients and experienced clinicians [147–149]. We believe that the management of SLE patients could be easily improved with a more systematic use of this old and inexpensive treatment.

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