Hydroxychloroquine in systemic lupus erythematosus: overview of current knowledge

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Abstract: The antimalarial hydroxychloroquine (HCQ) has demonstrated several crucial properties for the treatment of systemic lupus erythematosus (SLE). Herein, we reviewed the main HCQ pharmacologic features, detailed its mechanism of action, and summarized the existing guidelines and recommendations for HCQ use in rheumatology with a systematic literature search for the randomized controlled trials focused on lupus. HCQ has been shown to decrease SLE activity, especially in mild and moderate disease, to prevent disease flare and to lower the long-term glucocorticoid need. The numerous benefits of HCQ are extended to pregnancy and breastfeeding period. Based on cohort studies, antithrombotic and metabolic HCQ's effects were shown, including lipid-lowering properties, which might contribute to an improved cardiovascular risk. Moreover, early HCQ use in antinuclear antibodies positive individuals might delay the progression to SLE. Finally, HCQ has a significant favorable impact on long-term outcomes such as damage accrual and mortality in SLE. Based on these multiple benefits, HCQ is now the mainstay long-term treatment in SLE, recommended by current guidelines in all patients unless contraindications or side effects. The daily dose associated with the best compromise between efficacy and safety is matter of debate. The concern regarding retinal toxicity rather than proper efficacy data is the one that dictated the daily dosage of ≤5 mg/kg/day actual body weight currently agreed upon.

Keywords: antimalarials, cutaneous lupus erythematosus, hydroxychloroquine, immunomodulatory, lupus nephritis, systemic lupus erythematosus

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Background

Hydroxychloroquine (HCQ) is an antimalarial drug used initially for the treatment of *Plasmodium* parasitic infection, from where the name of the drug class came from. Beyond its initial indication as antimalarial, HCQ has been used in auto-immune and infectious diseases, as well as in metabolic or neoplastic disorders.[1] But, as recently reviewed,[2] clear benefits were reported mainly in systemic lupus erythematosus (SLE).

Thus, HCQ is now one of the most valuable therapies in SLE, showing multiple benefits over several outcomes associated with the disease itself,

but also to its related comorbidities. HCQ is an inexpensive, generally available, well-tolerated immunomodulator.[3] For more than a decade, different authors emphasized that all patients with SLE should be given HCQ[4–7] and the latest guidelines' recommendations also stated the HCQ importance in SLE unless there are contraindications or side effects.[8–11]

The history of HCQ is supposed to start *circa* 1600 with the Incas in Chile, from whom the cinchona bark properties were learned by the Jesuits. The main alkaloids of quinine and cinchonine were isolated in 1820 and subsequently

chloroquine (CQ) was obtained much later in 1934.[12] HCQ sulfate is the hydroxylated analogue of CQ, synthesized in 1946. Due to a better safety profile, HCQ was given since 1955 as an alternative to CQ.[12,13]

For SLE, the first report of the antimalarials use dates back to 1894, regarding the improvement of cutaneous lupus lesions with quinine.[14,15] In the United States, HCQ was approved for SLE in 1955 for symptoms like fatigue, rashes, joint pain, and mouth sores[16] and, with specific approval and license characteristics for each country, is now among the main drugs used for SLE treatment worldwide.

Pharmacology of hydroxychloroquine

Molecular structure
The knowledge about the pharmacokinetics of antimalarials is not completely understood and still debated. These pharmacokinetic characteristics are complex[17–19] due to the large volume of distribution,[19,20] significant tissue binding,[20–22] and long terminal elimination half-life.[18,19,23,24] Indeed, important differences have been observed between HCQ pharmacokinetic parameters as evidenced recently by its use in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19).[25] Historically, terminal elimination half-lives were considered very long, 40–50 days for HCQ[18,23] and up to 60 days for CQ.[19,24] More recent studies suggest a shorter half-life of about 5 days.[25,26] A long HCQ half-life can be attributed to extensive tissue uptake rather than to an intrinsic inability to clear the drug. The expected delay in the attainment of steady-state concentrations (3–4 months) may be in part responsible for the slow therapeutic response observed with HCQ.[27] Renal clearance is an important consideration for both drugs as reduced clearance increases the bioavailability[28] and subsequently the related side effects.[19,20,24] Finally, dose–response relationships and toxicity thresholds have not yet been fully defined. The main pharmacodynamic properties of antimalarials are shown in Table 1.

Galenic and commercial presentations
HCQ is commercialized as 200 mg HCQ sulfate tablets corresponding to 155 mg HCQ base for each tablet.[29] The daily dosage of HCQ varies accordingly to its indication,[29] with the American Academy of Ophthalmology (2016-AAO) recommending no more than 5 mg/kg/day of real body weight in SLE to decrease retinopathy occurrence,[30] recommendation that has been recently reinforced by agreement of four medical societies.[31] The indication is based on an ophthalmological study by Melles and Marmor[32] of nearly 2500 patients in whom daily HCQ intake below 5 mg/kg/day of regular body weight was associated with a low risk of toxicity, <2% within the first 10 years of use. However, some authors highlighted that in that study, the dose of HCQ was based on pharmacy refill information and not on prescribed dose.[33]
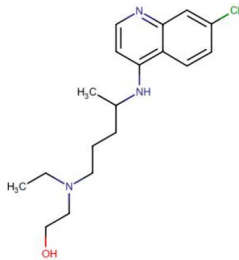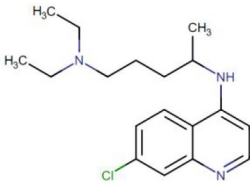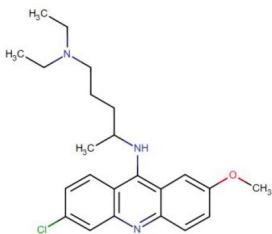
Dose adjustments with 50% reduction of posology are needed for patients with renal impairment and lower than 30 ml/min filtration rate.[34] For patients weighting more than 80 kg, a maximum daily dose of 400 mg is recommended in SLE. Doses for CQ were established only from extrapolation of HCQ and those lower than 2.3 mg/kg/day were considered safe.[30,35]

As the terminal elimination half time is not short,[36] dosing can be adjusted by alternate day regimens, such as 200 mg on the first day and 400 mg on the second day, yielding a mean dose equivalent to 300 mg per day.[32] Based on recent surveys, the most common daily dosage for HCQ is 400 mg daily.[37,38]

Mechanism of action
The mechanisms of action for HCQ are complex and still not completely understood (see Table 2 and Figure 1). Because of its high lipophilicity, lysosomotropism, and pH,[39,40] HCQ can pass through cell membranes and accumulate into lysosomes[40] where it disrupts key important cellular functions via the inhibition of the Toll-like receptors (TLRs)[41–43] and of the Cyclic GMP-AMP synthase–Stimulator of Interferon Genes (cGAS-STING) pathway.[44] The main effects include the inhibition of enzyme and cytokine release,[45–47] receptor recycling, plasma membrane repair, cell signaling, apoptosis,[48–50] autophagy,[39,51] antigen presentation,[52] T-cell polarization,[53–56] inhibition of the natural killer (NK) cells,[57,58] energy metabolism,[40] and increases photoprotection against ultraviolet (UV)-A and B.[59–65]

Table 1. Main pharmacodynamic properties of antimalarials.

	Hydroxychloroquine (HCQ)	Chloroquine (CQ)	Quinacrine
Chemical structure			
Chemical formula	$C_{18}H_{26}ClN_3O$	$C_{18}H_{26}ClN_3$	$C_{23}H_{30}ClN_3O$
Way of administration	Oral intake		
Absorption	In upper intestinal tract after a 200 mg oral dose, HCQ reached a C_{max} of 129.6 ng/ml with a T_{max} of 3.26 h in the blood[18]	In upper intestinal tract oral CQ reaches a C_{max} of 65–128 µg/L with a T_{max} of 0.5 h[19]	In upper intestinal tract more details not available
Bioavailability	67–74%[20]	67–100%[19]	Not available
Volume of distribution	5522 liters from blood and 44,257 liters from plasma[20]	200–800 L/kg[19]	Not available
Protein binding	50%[20]	46–74%[21]	80–90%[22]
Metabolism	In the liver, N-dealkylated by CYP3A4 to the active metabolite desethylhydroxychloroquine, as well as the inactive metabolites desethylchloroquine and bidesethylchloroquine[17,18]	In the liver, N-dealkylated primarily by CYP2 C8 and CYP3A4 to N-desethylchloroquine N-dealkylated to a lesser extent by CYP3A5, CYP2D6, and to an ever lesser extent by CYP1A1[19]	Not available
Elimination	40–50% of HCQ is excreted renally, while only 16–21% of a dose is excreted in the urine as unchanged drug 5% of a dose is sloughed off in skin and 24–25% is eliminated through the feces[19,20]	Predominantly eliminated in the urine, renal excretion: 65–70%.[24] 50% of a dose is recovered in the urine as unchanged CQ, with 10% of the dose recovered in the urine as desethylchloroquine[19]	Less than 11% is eliminated in the urine daily[28]
Elimination half-life	Historically, 40–50 days (chronic use) A 200 mg oral dose of HCQ: 537 h to 50 days (blood) or 32 days or 123 days in plasma[18,23] Maybe shorter, about 5 days, according to more recent studies[25,26]	6–60 days (mean of 20 days)[19,24]	5–14 days

Efficacy in systemic lupus erythematosus

Systematic search of randomized controlled trials regarding hydroxychloroquine in systemic lupus erythematosus

A systematic search for randomized controlled trials (RCTs) regarding HCQ treatment in SLE was performed using the medical subject headings (MeSH) terms 'Hydroxychloroquine' AND 'Lupus Erythematosus, Systemic' AND 'Clinical Trials, Randomized'. The search was performed on Excerpta Medica/EMBASE, MEDLINE via PubMed, Cochrane Library, and Thomson Reuters' Web of Science Core Collection using the same combination of relevant keywords (see Supplemental File 1). The four databases were systematically searched from inception to 1 February 2021, without any language, geographic, or type of article restrictions. The references and citations of the articles identified were also screened.

Reports not referring to HCQ or CQ use in SLE, not involving human subjects, not including adult cases, and presenting other types of studies than

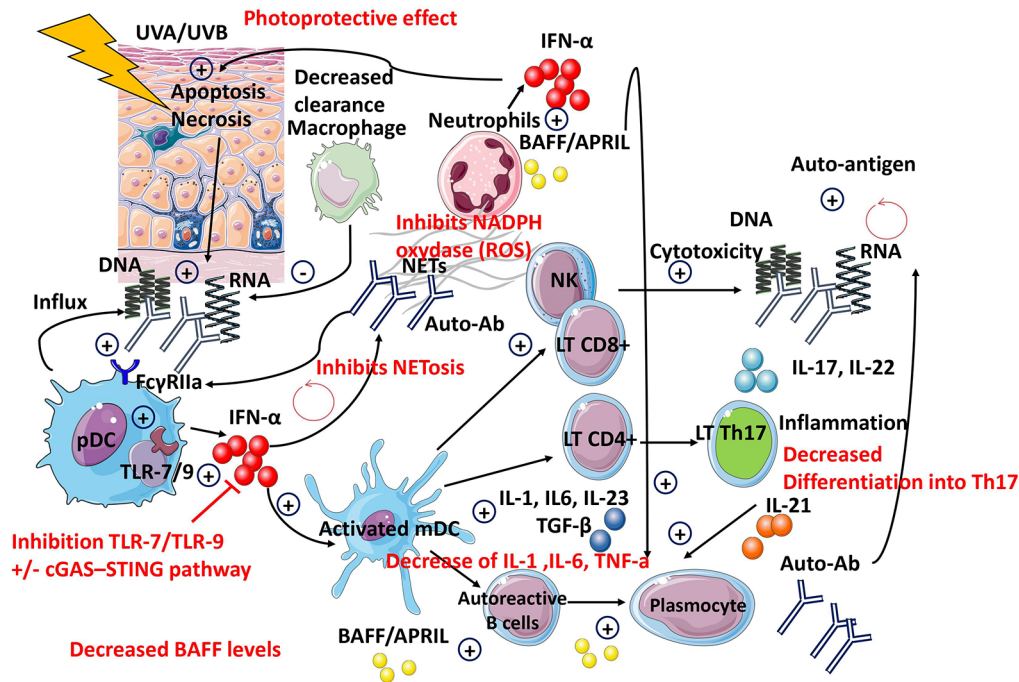**Table 2.** Mechanisms of action of hydroxychloroquine.

HCQ/CQ Mechanisms of action	Molecular mechanism(s) demonstrated	Potential consequence(s) in SLE pathogenesis	References
Inhibition of TLR-7 and TLR-9	Suppression of endosomal TLR activation direct binding of antimalarials to nucleic acids rather than inhibition of endosomal acidification	Inhibition of IFN-I production by pDC	Lamphier et al.[41] Kužnik et al.[42] Gardet et al.[43]
Inhibition of cyclic GMP-AMP synthase (cGAS) activity	Inhibition of (cGAS)-STING pathway	Inhibition of IFN-I production	An et al.[44]
Inhibition of autophagy	Blockade of autophagosome fusion with the lysosome	Inhibition of MHC class II-mediated autoantigen presentation by antigen-presenting cells to CD4+ T cells	Levy et al.[51] Schrezenmeier and Dörner[39]
Inhibition of antigen presentation	CQ has been shown to inhibit presentation of antigen *in vitro* by affecting invariant chain dissociation from MHC class II	Inhibition of MHC class II-mediated autoantigen presentation by antigen-presenting cells to CD4+ T cells	Humbert et al.[52]
Inhibition of inflammatory cytokine production and angiogenesis	Decrease mRNA expression of IL-1β, IL-6, and TNF-α in CLE skin lesions Decrease VEGF expression in CLE skin lesion	Decrease of local inflammation Decrease of mononuclear cellular infiltrate in the skin Inhibition of angiogenesis	Wozniacka et al.[45] Lesiak et al.[46] Zeidi et al.[47]
Photoprotection against UVA and UVB	Increase of c-Jun mRNA expression Decrease mRNA expression of IL-1β, IL-6, and TNF-α in CLE skin lesions Decrease UV-induced ICAM-1 expression in keratinocytes CQ inhibits lipid peroxidation and decrease UVB and induces phospholipase A2 activity in skin Decrease of the number of cutaneous HLA-DR+ and CD1a+ cells after UVB irradiation	Decrease of local inflammation, apoptosis, and necrosis of keratinocytes Decrease of the release of skin nucleic acids Decrease of the mononuclear cellular infiltrate in the skin	Nguyen et al.[65] Sjolin-Forsberg et al.[59] Wozniacka et al.[64] Wozniacka et al.[60] Bondeson and Sundler[61] el Tahir et al.[62] Segal-Eiras et al.[63]
Decrease NET formation and circulating DNA	HCQ inhibits NETs formation *in vitro* Circulating DNA significantly decreases after CQ treatment	Decrease of circulating nucleic acids Inhibition of IFN-I production Decrease of LL37 formation and inflammasome activation Decrease of MMP-9 and reduced endothelial cell death	Smith et al.[48] Smith and Kaplan[49] Cepika et al.[50]
Change in T-cell polarization	HCQ decreases Th17-related cytokines HCQ decreases Th22-related cytokines HCQ blood concentrations correlate negatively with the percentage of CD45RO+ CD4+ cells	Decrease of mononuclear cellular infiltrate in the skin Decrease of survival and proliferation of human B cells as well as the differentiation of B cells into antibody-producing cells Recruitment and activation of inflammatory cells with tissue damage Inhibition of angiogenesis	Silva et al.[53] Zhao et al.[54] Shin et al.[55] Sailler et al.[56]
Inhibition of NK cells	Decrease proliferation, cytotoxicity, and cytokine production of NK cells	Possible deleterious effects of NK cells in SLE: tissue infiltration, proinflammatory cytokine production: IFNγ, IL-15	Spada et al.[57] Fox[58]

cGAS, cyclic GMP-AMP synthase; CLE, cutaneous lupus erythematosus; CQ, chloroquine; DC, dendritic cells; HCQ, hydroxychloroquine; ICAM, intercellular adhesion molecule-1; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NETs, neutrophil extracellular traps; NK, natural killer; SLE, systemic lupus erythematosus; STING, stimulator of interferon genes; Th, T helper; TLRs, Toll-like receptors; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

RCTs were excluded. A total of eight RCTs were identified in the initial search with one more identified after the references and citations screen (see Supplemental Figure 1–Flowchart Diagram, Supplemental Table 1). For each RCT included, the following information was extracted: study design, drug posology, time of follow-up, study's endpoints, proven efficacy, and side effects noted (as presented in Supplemental Table 2a, 2b).

To the best of our knowledge, the first RCT involving antimalarial therapy in SLE was

Figure 1. Hydroxychloroquine's mechanisms of action.

published in 1991 by Canadian Hydroxy-chloroquine Study Group[66] and reported a 2.5-fold increase in the risk of mild flare after HCQ withdrawal in the placebo group.[66] In 1998, Tsakonas *et al.*[67] presented an extension phase in 1991 and evaluated the risk of major flare after HCQ withdrawal.[67] The endpoint considered, namely flare, subtype of flare, and hospitalization, were all improved under long-term HCQ therapy; however, the results did not reach statistical significance most probably due to the small sample size.[67]

Other RCTs have also demonstrated improvement of arthralgia[14] even if without a significant impact over arthritis,[68] prevention of SLE flares and reduction of the corticosteroids dose,[14] improvement of lipid metabolism[69] with decrease in total cholesterol and triglycerides, while increase in HDL-cholesterol,[70] and a safety profile of administration during pregnancy.[71] Also, the PLUS (Plaquenil LUpus Systemic) failed to demonstrate that adjusted HCQ dosing schedules targeting [HCQ] ≥1000 ng/ml might reduce the occurrence of SLE flares.[72] Most recently, Zanetti *et al.*[73] tested the efficacy of lower HCQ doses (2–3 mg/ kg/day)[30] and found similar 6- and 12-month flare rates between groups.[73]

For cutaneous lupus erythematosus (CLE), the first RCT by Kraak *et al.*[74] in 1965 tested HCQ up to a maximum posology of 1200 mg daily. Furthermore, the efficacy of antimalarials has been tested in RCTs against placebo,[75] acitre-cin,[76] or clofazimine[77] in RCTs showing proven efficacy in RCT with better safety profile than clofazimine or acitrecin.

Observational data for hydroxychloroquine in systemic lupus erythematosus

Currently published RCTs do not cover the whole spectrum of SLE features. Many of the data regarding HCQ benefits are from prospective SLE cohorts, such as the Hopkins Lupus Cohort,[78–83] LUMINA (Lupus in Minorities: Nature *versus* Nurture) Cohort,[84–89] Toronto Lupus Cohort,[90,91] or GLADEL (multinational Latin American lupus) Cohort[92–94] (see Table 3; Supplemental Table 3).

Antimalarials: chloroquine diphosphate (CDP) or hydroxychloroquine sulfate (HCQ). The most significant HCQ effect is the control of SLE disease activity itself, which implies amelioration of active clinical involvements, decrease in serum markers, decrease in activity scores, prevention of disease flares, and sustained remission on long-term use.

Table 3. Research for antimalarials in systemic lupus erythematosus.

Effects	Randomized controlled trials	Observational studies	Systematic reviews
Decrease of disease severity		Prospective study, 25 patients[95] Prospective LUMINA Cohort, 256 patients[84] Cross-sectional study, 57 patients[96] Longitudinal study, LUMINA cohort, 35 patients[85] Prospective study, 41 SLE patients[97] Observational study, 28 SLE pregnant women[98] Retrospective study, 165 SLE patients[99] Retrospective study, 101 SLE patients[100] Prospective Hopkins Lupus Cohort, 916 patients[101]	Databases: Medline and Embase[13]
Prevent of disease flare	RCT, NCT03122431: 73 stable LN patients[73] RCT, NCT00413361: 573 patients[72] RCT, 24 SLE patients stable disease[14] RCT, 47 clinically stable SLE patients[66] RCT, 20 patients lupus pregnancy[71]	Retrospective, matched with themselves, 43/209 patients[102] Retrospective, matched with themselves, 43 patients, 76 matched years[103] Prospective, Padua Lupus Cohort, 319 SLE patients[104] Retrospective study, 101 SLE patients[100] Prospective, Hopkins Lupus Cohort, 2512 patients[78] Longitudinal, 143 SLE patients[105]	Databases: Medline and Embase[13]
Cutaneous lupus	RCT, NCT01551069: 103 patients Cutaneous Lupus[75] RCT, 20 patients lupus pregnancy[71]	Retrospective, matched with themselves, 43/209 patients[102] Prospective, 17/27 patients SLE[106] Prospective, 300 patients subacute or chronic CLE[107] Retrospective cohort, 200 patients DLE[108] Cross-sectional study, 1002 patients CLE[109] Prospective cohort, 218 CLE and SLE patients[110] Retrospective, 36 LE tumidus[111] Retrospective, 61 DLE and SCLE patients[112] Prospective, 34 CLE patients[113]	Databases: Medline, Embase, Scopus, Cochrane[114]
Adjuvant for lupus nephritis remission		Prospective, Hopkins Lupus Cohort, 29 patients[79] Retrospective study, 35 patients[115] Retrospective study, 206 patients lupus nephritis[116] Prospective LUMINA Cohort, 256 patients[84] Retrospective study, 90 patients with lupus nephritis[117]	Databases: Medline and Embase[13]
Improvement of articular complaints	RCT, 71 SLE patients mild SLE[68] RCT, 24 SLE patients stable disease[14]		Databases: Medline and Embase[13]
Decrease disease activity/ prevent flare during pregnancy	RCT, 20 patients lupus pregnancy[71]	Prospective study, 60 patients – 103 pregnancies[118] Prospective, Hopkins Lupus Pregnancy Cohort, 282 (163 + 56 + 68) pregnancies[80] Retrospective study, 176 patients – 396 pregnancies[119] Retrospective study, 179 pregnancies[120]	Databases: Medline and Embase[3] Databases: Medline and Embase[13]
Protection against preeclampsia		Retrospective cohort, 151 pregnancies[121] Prospective cohort, 316 pregnancies[122] 114 HCQ-exposed pregnancies[123]	
Prevention of fetal growth restriction and prematurity		Observational study, 28 SLE pregnant women[98]	

(Continued)

Table 3. (Continued)

Effects	Randomized controlled trials	Observational studies	Systematic reviews
Reducing antiphospholipid antibodies persistence		Retrospective study, 90 patients – 17 patients with persistent LA[124]	
Reduce the risk of thrombosis		Prospective cohort, 92 patients[125] Retrospective study, 272 patients[126] Prospective cohort, 232 patients[127] Prospective cohort, 67 SLE-aPL patients[128] Retrospective study, 206 patients lupus nephritis[116] Longitudinal, cross-sectional, 144 patients[129] Prospective, Tromso Lupus cohort, 158 patients[130] Retrospective study, 1930 patients[131] Nested case–control study, 54 SLE cases *versus* 108 controls[132] Prospective Hopkins Cohort, 1795 SLE patients, 193 thrombotic events, 10,508 person-years[133] Prospective study, 189 SLE patients[134] Prospective Hopkins Cohort, 739 patients[135]	Databases: Medline and Embase[3] Databases: Medline and Embase[13]
Lower fasting glucose/ diabetes mellitus protection		Cross-sectional study, 149 SLE patients[136] Population-based cohort study, 221 with diabetes mellitus out of 8628 SLE patients[137]	
Improving lipidic profile	RCT, 72 SLE patients[69] RCT, 17/19 SLE female patients[70]	Cross-sectional, 155 patients (SLE + AR)[138] Case-control, 18 SLE patients[139] Longitudinal Cohort – John Hopkins, 264 patients[81] Retrospective study, 382 patients[140] Cross-sectional study, 123 patients[141] Cross-sectional study, 90 subjects – 60 SLE patients[142] Cross-sectional study, 86 patients[143] Prospective study, 30 subjects – 20 SLE patients[144] Cross-sectional study, 185 outpatients[145] Prospective – Toronto Lupus Cohort – 1260 patients[90] Case-control, 100 lupus nephritis patients[146] Cross-sectional study, 24 patients[147] Prospective Hopkins Cohort, 51 patients, over 229 visits[82] Cross-sectional study, 48 patients[148]	Databases: PubMed, Embase, Cochrane[149] Databases: PubMed, Embase, Web of Science, Medline/Ovid, Google Scholar, CINAHL, Cochrane[150] Databases: Medline and Embase[3] Databases: Medline and Embase[13]
Reduction of atherosclerosis		Pittsburgh Lupus Registry, 220 women[151] Prospective study, 41 SLE patients and 96 controls[152]	Databases: Medline and Embase[153]
Decrease the risk of infections		Retrospective study, 206 patients lupus nephritis[116] A nested case–control study, Lupus-Cruces cohort, 83/166 patients[154] Prospective cohort, Northern California, 3030 patients[155] Retrospective study, Spanish Rheumatology Society Lupus Registry (RELESSER), 3658 patients[156] Case–control study, 65 SLE patients *versus* 130 controls[157] Prospective RELES Cohort, 282 SLE patients[158] Retrospective study, 339 patients[159] Inception cohort study GLADEL, 1243 patients[92] Population-based study, 24343 SLE patients[160]	Databases: PubMed, Embase, Cochrane[161]

(Continued)

Table 3. (Continued)

Effects	Randomized controlled trials	Observational studies	Systematic reviews
Improvement of bone mineral density		Prospective study, 92 patients[162] Prospective study, 34 SLE patients[163]	Databases: Medline and Embase[13]
Protection against osteonecrosis		Nested matched case–control study, LUMINA cohort[86]	Databases: Medline and Embase[13]
Decrease the corticosteroids need	RCT, 20 patients lupus pregnancy[71]	Retrospective, matched with themselves, 43 patients, 76 matched years[103] Prospective LUMINA Cohort, 256 patients[84] Prospective study, 257 pregnancies[80]	
Protection against accrual damage		Prospective Israeli Cohort, 151 patients[164] Prospective LUMINA Cohort, 632 patients[88] Prospective LUMINA Cohort, 256 lupus nephritis[84] Prospective LUMINA Cohort, 580 patients[89] Prospective Hopkins Cohort, 2054 patients[83] Nested case-control, Inception cohort – Toronto Lupus Cohort, 685 patients: 174/307 patients[3] SLICC Inception Cohort Study, 1722 patients[165] Retrospective inception cohort, 476 subjects, 26 years[166] Early Lupus Project, Prospective Inception Cohort, 230 patients[167]	Databases: Medline and Embase[3]
Protection against neoplasia		Prospective cohort, 235 patients[168]	
Reducing SLE-related hospitalization		Retrospective study, 339 patients[159] Retrospective study, 526 patients[169] Retrospective registry-based, 40,381 patients[170]	
Improvement of survival		Case-control, 76 matched pairs[171] Prospective cohort, 232 patients[127] Case-control study – LUMINA L cohort, 608 patients[87] Retrospective study, 206 patients lupus nephritis[116] Prospective University of Toronto Lupus Clinic, 1241 patients[91] Prospective GLADEL cohort, 1480 patients[93] Retrospective, 1956 SLE inpatients[172] Retrospective, 42 patients lupus nephritis[173] Retrospective study, 491 patients with lupus nephritis[174] Prospective cohort, 803 SLE patients[175] Longitudinal cohort, 345 lupus nephritis patients[176] Prospective cohort, 914 SLE patients[177] Retrospective study, 6241 patients[178]	Databases: Medline and Embase[3] Databases: Medline and Embase[13]
Delays the evolution to SLE		Retrospective study, 130 military personal[179] Nested case–control study, GLADEL cohort, 265/530 patients[94]	Databases: Medline and Embase[13]

CC, case-control; CLE, cutaneous lupus erythematosus; CS, cross-sectional; DLE, discoid lupus erythematosus; DS, descriptive studies; GLADEL, Grupo Latino Americano de Estudio del Lupus; HCQ, hydroxychloroquine; LAC, lupus anticoagulant; LN, lupus nephritis; LUMINA, Lupus in Minorities: Nature vs Nurture; PC, prospective cohort; RA, retrospective analysis; RC, retrospective cohort; RCT, randomized controlled trial; SCLE, subacute cutaneous lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics.

Therefore, decrease in disease activity,[84,85,95–101] prevention of disease flares,[78,100,103–105] and improvement of proinflammatory cytokine profiles[85,95,97,104,180,181] have been highlighted with HCQ.

Moreover, delay of the immune clinical spectrum to overt SLE was described in antinuclear antibodies (ANA)-positive patients.[94,179] A recent study showed that HCQ might suppress early mediators like the B cell activating factor (BAFF) and interferon (IFN), lowering the IFN-γ-induced protein 10 (IP-10) levels in incomplete or new-onset SLE, supporting the hypothesis that HCQ could influence disease progression.[182]

In observational studies, HCQ has been shown beneficial for cutaneous lupus,[95,102,106–112] musculoskeletal involvement,[99] and various other key manifestations of SLE. The management of lupus nephritis (LN) remains suboptimal[183] and HCQ is adjuvant therapy to the immunosuppressive regimens in obtaining remission.[79,84,115–117]

HCQ decreases disease activity and prevents SLE flare during pregnancy,[80,118,119,122] and furthermore, there are reports sustaining a possible protective role for preeclampsia,[120–123] fetal growth restriction, and prematurity.[98] Current data regarding HCQ efficacy during pregnancy are conclusive, however for other outcomes the results are contradictory. Thus, there are reports that did not found the impact of HCQ on pregnancy loss, preterm delivery or intrauterine growth retardation,[119] or upon miscarriage, stillbirth, pregnancy loss, or congenital abnormality rates.[80]

For neonatal lupus, one retrospective study that analyzed data of a historical cohort counting more than 200 pregnancies in SLE patients with positive anti-Ro/SS-A antibodies found HCQ benefits over recurrence and outcome of the neonatal lupus.[184] In another research, HCQ was not identified as independent protective factor for neonatal lupus after adjusting for confounders like age, race, antibodies status, corticosteroids, and prior cardiac-neonatal lupus risk, even if the neonatal lupus cases were less frequent in pregnancies treated by HCQ (14% *versus* 37%).[185]

Despite potential benefits of HCQ during pregnancy, adherence seems to be low. A population-based registry identified 376 pregnancies in which discontinuation of antimalarials occurred in 16.7% of cases in the year prior to pregnancy, 29.8% in the first trimester, 9.7% in the second, and 26.0% in the third.[186]

Importantly, HCQ passes the placenta and has fetal serum concentrations equal to those measured in the maternal blood. However, HCQ use during pregnancy[80,119,120,123,187–189] and breastfeeding is considered safe.[5,190] During lactation, HCQ passes in the maternal milk, but with lower concentrations than in maternal blood, estimated to be 0.2 mg/kg/day.[5]

There are reports of CQ overdose in children and, by parallel, cautions are related to HCQ. Antimalarials might be toxic in children in relatively small doses and patients should be counseled to keep these drugs out of children.[5]

SLE disease itself is a risk factor for thrombosis. Also, about 20% of patients with SLE have antiphospholipid syndrome (APS).[191] Antimalarials might reduce the antiphospholipid antibodies titers[124] and the risk of thrombosis,[116,125–135] but not all published studies reported a protective effect over thrombosis.[192–194]

HCQ has also some metabolic effects by lowering fasting glucose,[136] yielding protection against diabetes,[137] and improvement of the lipids profile in most[81,90,138–147] but not all[195,196] studies. However, the efficacy of HCQ upon atherosclerosis is more controversial.[151,152,197,198]

It is to remember that smoking might inhibit HCQ effects[7,109,110,112] and determine a twofold lower response of cutaneous involvement under HCQ;[199] counseling for smoking cessation is therefore important. Possible anti-neoplastic properties of HCQ have been poorly assessed in SLE.[168]

HCQ might inhibit the conversion of 25-(OH)-vitamin D to 1,25-(OH)2-vitamin D.[200] However, data regarding the impact of HCQ on bone metabolism in SLE remain controversial.[86,162,163,201,202] Many data suggest that HCQ has a protective role against infections[92,116,154–160] and severe events included[92,154–156] in SLE.

Corticosteroids are widely prescribed, but also important determinants of cardiovascular, gastrointestinal, and metabolic comorbidities as well as of accrual damage and impaired quality of life in SLE. Thus, another important role for HCQ in

SLE is that of corticosteroid-sparing agent.[80,84,103] However, as for other outcomes, there are also studies with negative results.[102]

SLE is a severe disease with survival rates at 5 years of only 50% in early studies, which now exceed 90%.[203] While mortality in early stages is usually related to severe organ involvement and SLE disease activity itself, in late, long-standing SLE, accrual damage, and cardiovascular risk are the main determinants. In spite of some contrary results,[204] many studies reported HCQ protective effects for accrual damage[3,83,84,87–89,164–167] and HCQ has also been associated with shorter SLE-related hospitalization length.[159,169,170] And last, but not least, HCQ is one of the few treatments that has been shown to improve survival rates in SLE.[87,91,93,116,127,171–178]

Therefore, based on its wide spectrum of effects, HCQ should probably be considered a possible confounder in all research involving patients with SLE.

Systematic reviews and meta-analyses on hydroxychloroquine use in systemic lupus erythematosus

The first systematic review regarding HCQ in SLE included a total of 95 studies published between 1982 and 2007.[13] All studies which considered disease activity as the main outcome (11 articles) found positive results, with more than 50% reduction in disease activity in most reports and a decrease in corticosteroid needs in three studies;[13] however, the risk of severe SLE flare was reduced only with borderline significance.[13] Also, the HCQ benefits as adjuvant therapy for LN was also confirmed.[13] The potential benefits upon accrual damage and survival were reported in a limited number of studies.[13] This systematic review was continued by another one using a similar methodology for the 2007–2012 period.[3] The authors reported further evidence thrombosis prevention, increased survival, control of disease activity, lipid profile improvement, and prevention of damage accrual[3] (see Supplemental Table 4).

The protective effect of HCQ against infections was further confirmed in two systematic reviews and meta-analysis.[153,161] Also, two meta-analyses reported improvement of the lipid profile under HCQ in SLE.[149,150] For cutaneous involvement, Fairley *et al.*[114] reported in one systematic review only moderate HCQ efficacy.

A 2018 meta-analysis of observational data failed to identify any significant beneficial effect of HCQ over fetal growth restriction and prematurity. However, the authors mentioned that these results should be regarded with caution due to lack of RCTs, high heterogeneity among reported data, and of numerous missing data like those on the antiphospholipid antibodies status.[205]

Overview of guidelines

We reviewed here systematically the European League against Rheumatism (EULAR) recommendations referring to the use of HCQ. We identified all EULAR guidelines (www.eular.org) for the last 5 years and searched for HCQ-related paragraphs using the terms 'Hydroxychloroquine' and the respective abbreviation 'HCQ'. All paragraphs found were extracted (see Supplemental Table 5) and data were further analyzed and summarized (see Supplemental Figure 2).

From the total 30 EULAR management guidelines published since 2016, 10 referring to HCQ were identified, and main indications were noted (see Supplemental Table 6). Recommendations addressing specifically to HCQ were found in seven guidelines[8,34,206–210] while in others, HCQ was included as part of Disease Modifying AntiRheumatic Drugs (DMARDs).[211–213] The EULAR Guidelines recommendations referring mainly to SLE and related conditions are summarized in Figure 2.

Tunnicliffe *et al.*[214] and Tamirou *et al.*[215] reviewed SLE recommendations published up to 2014 and between 2004 and 2017, respectively, and identified not least than 14 and 23, respectively, original clinical guidelines or original statements with focus on SLE.

The 2020 American College of Rheumatology (ACR) Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases[190] advise for HCQ use during pregnancy and breastfeeding, in cases with positive anti-Ro/SS-A and anti-La/SS-B antibodies as well as additional or alternative therapy in SLE women with refractory obstetric APS. HCQ continuation is strongly recommended in men who are planning to father a pregnancy.[190] The 2012 ACR Guidelines for Screening, Treatment, and Management of Lupus Nephritis specifies that all SLE patients with nephritis should be treated with HCQ as background therapy.[9]

Systemic Lupus Erythematosus 2019	HCQ is recommended in all SLE patients, when no contraindication	LoE 1b	GoR A	LoA 9.6
	Posology of maximum 5 mg/kg/day	LoE 3b	GoR C	
	Ophthalmological screening for HCQ surveillance: at baseline, after 5 years, and yearly thereafter	LoE 2b	GoR B	LoA 9.7
	Addition of immuno-modulating/suppressive treatment is considered in patients non-responding to HCQ +/- corticosteroids			LoA 9.8
	HCQ and quinacrine are part of first line treatment for skin disease	LoE 1a	GoR A	LoA 10
Lupus Nephritis 2020	Co-administration of HCQ maximum 5 mg/kg/day adjusted to GFR	LoE 2b LoE 3b	GoR B GoR C	LoA 9.2
	Long term use of HCQ in patients with lupus nephritis	LoE 2b	GoR C	LoA 9.4
	Compatible during pregnancy and lactation	LoE 1b	GoR B	LoA 9.7
Antiphospholipid Syndrome 2019	HCQ addition is considered in women with obstetric antiphospholipid syndrome and recurrent pregnancy complications under LDA and prophylactic heparin	LoE 4	GoR D	LoA 8.7
Pregnancy 2017	HCQ is one of the drugs considered for the prevention and treatment of lupus flares during pregnancy	LoE 1	GoR B	LoA 9.7
	HCQ is recommended preconceptionally and throughout pregnancy	LoE 2	GoR B	LoA 9.8

Figure 2. Recommendations for hydroxychloroquine (HCQ) use according to the European League against Rheumatism (EULAR) guidelines.

The 2018 British Society for Rheumatology guideline for the management of SLE in adults[10] identified 45 studies to sustain the recommendation of antimalarial use (<6.5 mg/kg/day) for mild disease, prevention of flare in all patients, prevention of damage, and as steroid-sparing agent (overall SIGN level of evidence 1+++ and grade A of recommendation).[10]

Finally, the Latin American Group for the Study of Lupus (GLADEL, Grupo Latino Americano de Estudio del Lupus)–Pan-American League of Associations of Rheumatology (PANLAR) stated also that antimalarials should be used in all SLE patients with exception of those who refuse or who have absolute contraindications, as first line for musculoskeletal or cutaneous involvement as well as associated with immunosuppressive treatments for other SLE organ involvements.[11]

Hydroxychloroquine safety profile

A wide range of side effects such as cardiovascular, dermatological, digestive, hematological, metabolic, ophthalmologic, as well as other rare side effects were reported to be associated with HCQ use.[4,13,30,31,32,35,216–238] The main side effects of HCQ are summarized in Table 4.

Reviewing the antimalarials' safety profile in SLE, Ruiz-Irastorza *et al.*[13] noted low prevalence of antimalarials' toxicity, mainly mild gastrointestinal and cutaneous side effects. These were significantly more frequent under CQ when compared with HCQ, results parallel by higher discontinuation rates for CQ. Overall, the HCQ global safety was rated as high.[13] Eljaaly *et al.*[236] published recently a meta-analysis for the HCQ safety when administrated for different pathologies (chronic urticaria, RA, SLE, osteoarthritis, IgA nephropathy, asymptomatic HIV infection, Alzheimer disease, cutaneous lupus) in daily doses of 200–400 mg and presented also encouraging results. Besides significant more frequent occurrence of skin pigmentation under HCQ, no other side effect reached a significant difference (rash, gastrointestinal complaints, headache, fatigue, visual troubles) and also no cardiac toxicity was reported.[236]

Thus, for long-term HCQ use, medium uptake duration of 32 months,[35] the skin hyperpigmentation is not rarely reported and might be favored

Table 4. Side effects of hydroxychloroquine.

System	HCQ's side effects		
	Short term	**Long term**	**References**
Cardiovascular	Hours-days: prolonged QT [a](attention to the association with other drugs that affect the QT interval) Overdose: cardiovascular shock, collapse	Weeks-months: Conduction troubles, cardiomyopathy, vacuolar myopathy, valvular disorders[a]	Costedoat-Chalumeau et al.;[4] Doyno et al.;[216] Nishiyama et al.;[217] Ruiz-Irastorza et al.;[13] Chatre et al.;[218] Zhao et al.;[219] Fiehn et al.[35]
Dermatologic	Days-weeks: pruritus, rashes, urticaria, exanthematous pustulosis, toxic epidermal necrolysis, Stevens–Johnson syndrome[a]	Years: hyperpigmentation	Costedoat-Chalumeau et al.;[4] Ruiz-Irastorza et al.;[13] Chatre et al.;[218] Fiehn et al.[35]
Digestive intolerance	Days: nausea, vomiting, diarrhea, bloating		Costedoat-Chalumeau et al.;[4] Ruiz-Irastorza et al.;[13] Chatre et al.;[218] Fiehn et al.[35]
Hematological	Days to weeks: bone marrow toxicity, cytopenia (neutropenia)[a]	Weeks-months: bone marrow toxicity, cytopenia (neutropenia)[a]	Sames et al.;[220] Chatre et al.;[218] Fiehn et al.[35]
Metabolic	Days: hypoglycemia[a]		El-Solia et al.;[221] Cansu and Korkmaz;[222] Ruiz-Irastorza et al.;[13] Chatre et al.;[218] Fiehn et al.[35]
Neuropsychiatric	One-two days: confusion, disorientation, hallucination Overdose: psychosis, seizure[a,b]	Weeks-months: agitation, bradyphrenia, delirium, disorientation, drowsiness, confusion, pseudo-parkinsonism[a,b]	Mascolo et al.;[225] Chatre et al.;[218] Fiehn et al.[35]
Neuromuscular	Days: increase of creatine kinase[a]	Months: myositis, muscle weakness[a]	Ruiz-Irastorza et al.;[13] Chatre et al.;[218] Stein et al.;[223] Fiehn et al.;[35] Siddiqui et al.[224]
Ophthalmologic	Days-weeks: eye accommodation troubles	Months–years (5–20 years): retinopathy (maculopathy)	Marmor et al.;[30] Rosenbaum et al.;[31] Fiehn et al.;[35] Petri et al.;[226] Xie and Zhang;[227] Marmor et al.;[30] Melles and Marmor;[32] Wolfe and Marmor;[228] Ruiz-Irastorza et al.[13]
Otorhinolaryngology	Days-weeks: ototoxicity, tinnitus[a]		Chatre et al.;[218] Fiehn et al.[35]
Only case reports	Fulminant hepatic failure; toxic myopathy with respiratory failure; podocytopathy mimicking Fabry disease; rare cutaneous side effects (erythroderma, dark rash, gray skin, erythema multiforme)		Chatre et al.;[218] Makin et al.;[229] Abou Assalie et al.;[239] Koumaki et al.;[230] Pai et al.;[231] Pelechas and Drosos;[232] Ivo et al.;[233] Serre et al.;[234] Wu et al.[235]

HCQ, hydroxychloroquine.
The HCQ-related side effects, in terms of frequency and severity, are related to daily posology, treatment duration, concomitant therapies, and associated comorbidities.
[a]Only rare reported.
[b]Association not confirmed yet.

by factors like ecchymosis, bruising, platelet antiaggregant, and oral anticoagulants. Beside hyperpigmentation, all other HCQ-related side effects are only rarely encountered.

On short-term use, the digestive intolerance is the most frequently encountered side effect, with occurrence possible since first HCQ administration.[237,238]

A wide range of mild neuropsychiatric manifestations, but also psychosis, was reported in relation to HCQ use, especially in elderly. However, this relation remains controversial as other concomitant

factors like concomitant drugs, alcohol intake, use of glucocorticoids, or background disease itself could originate the neuropsychiatric manifestations occurrence in patients with SLE under HCQ.[225]

Retinopathy occurrence remains the most discussed and studied HCQ's side effect in SLE. The main risk factors for HCQ-related retinopathy are the treatment duration, daily and cumulative dose, chronic kidney disease, as well as pre-existent retinal disease.[34] Ophthalmologic screening is mandatory, yearly from baseline if there are known risk factors or at baseline, after 5 years on HCQ, and yearly therefore in patients without retinopathy risk factors.[8,30,31,34] The current 2020 Joint Statement on HCQ[31] reinforced the old recommendations[8,30,34,32] of the need of sensitive testing modalities such as optical coherence tomography (OCT) and automated visual fields that could detect early toxicity.[31] When available, quinacrine (mepacrine) might be considered as an alternative in SLE patients with HCQ-related ocular or cutaneous side effects.

As the eye side effects are dose-related, not only the duration of use but also the blood levels are predictors of retinopathy development with a statistical association in patients with [HCQ] blood levels >1200 ng/ml.[226,227] However, association between HCQ blood concentration and retinopathy has not been confirmed in another study.[240] For non-rheumatic diseases, doses of up to 1000 mg daily (up to 20 mg/kg daily) showed eye toxicity within 2 years in 25–40% of the patients exposed,[30] while for the doses up to 5 mg/kg of real body weight, the risk of retinopathy within 10 years was 2%.[32] For lifetime HCQ users, definite or probable toxicity was documented in only 0.65% even if 6.5% patients discontinued therapy because of eye-related side effects.[228] One longitudinal study showed ophthalmological alterations confirmed by ophthalmological examination in 5.5% of cases.[241]

When compared with HCQ, the risk of retinopathy related to CQ seems to be much higher, hence CQ is not recommended as the first-line antimalarial for the SLE treatment. One systematic review including four studies for CQ *versus* six studies for HCQ found definite retinal toxicity in 2.5% *versus* 0.1% and probable retinopathy in 2.6% *versus* 0.3% patients.[13] A recent report from the Hopkins cohort showed a higher overall frequency of retinopathy of 4.3%, but the risk

increased significantly after 15 years of HCQ use,[226] namely 1% in the first 5 years, 1.8% for 6–10 years, 3.3% for 11–15 years, and 11.5% for 16–20 years.[226]

For antimalarials cardiac toxicity, the results of 86 articles were systematically reviewed and a total of 127 patients (65.4% female) were identified, of which about 60% had taken CQ, while the rest HCQ.[218] The most frequent cardiac side effects reported were conduction disorders (85%), followed by cardiac hypertrophy (22%), hypokinesia (9.4%), cardiac failure (26.8%), pulmonary arterial hypertension (3.9%), and valvular dysfunction (7.1%). Less than half of the patients (44.9%) recovered normal heart function after the antimalarial drug withdrawal.[218]

Disparate cases of HCQ-related neuromyopathy, particularly manifested as insidious onset of proximal myopathy that may be later associated with peripheral neuropathy and cardiac myotoxicity, are reported. The frequency of HCQ-related myopathies is not known, but is probably extremely rare.[35] Early recognition is important as the recovery after the drug withdrawal might be incomplete.[223]

Different case reports presented rare and very rare sides effects attributable to HCQ in the absence of other identifiable causes, like early fulminant hepatic failure,[229] toxic myopathy with respiratory failure,[224] and rare cutaneous lesions.[230–235,239]

Hydroxychloroquine blood level monitoring and withdrawal

Even if the HCQ role in SLE is acknowledged, less than half of the patients are taking HCQ as prescribed.[242] Measurement of HCQ in whole blood was proposed to monitor both response and adherence to treatment, but an appropriate cut-off for defining efficient HCQ's blood levels remains under debate. For CLE, one prospective multicenter study found significantly higher median blood [HCQ] levels in patients with complete remission (910 ng/ml in remission *versus* 692 ng/ml when partial remission and 569 ng/ml in treatment failure, $p = 0.007$).[107] In a prospective study, improvement of cutaneous lesions was observed when [HCQ] blood levels higher than 750 ng/ml were reached.[113] Also, one study defined subtherapeutic [HCQ] levels, associated with trend of

more disease flares, as less than 500 ng/ml.[243] A recent report showed that low [HCQ] blood levels are associated with thrombotic events (720 ng/ml *versus* 935 ng/ml; $p = 0.025$).[135]

On one hand, a decrease in the flare rate was not observed when [HCQ] level was maintained over 1000 ng/ml.[72] On the other hand, decrease to 2–3 mg/kg/day did not modify serum [HCQ] levels significantly at 3 and 6 months, but only at 12 months.[73]

One of the main reasons for using [HCQ] blood levels in daily practice is the great interindividual variability, of which determinants are not completely characterized.[5] [HCQ] levels were found to be related to its major metabolite, N-desethylhydroxychloroquine (DHCQ), to HCQ weight-adjusted oral dose and also to the time since last dose taken.[243,244]

Analyzing a longitudinal cohort, Mok *et al.*[243] found that the majority of SLE patients screened had mainly [HCQ] subtherapeutic levels: <10 ng/ml (defined as total non-adherence) in 11%, 10–500 ng/ml (subtherapeutic levels) in 77%, and >500 ng/ml (therapeutic levels) in only 12% patients. Levels correlated with the dose prescribed[243] and, importantly, higher [HCQ] levels were associated with less SLE flare occurrence over time.[243]

Monitoring HCQ levels might allow identification of early nonadherence[243] and improve nonadherence.[72] HCQ levels measurement might help in counseling before the treatment change in regard to lack of adherence *versus* lack of treatment efficacy.[5]

Finally, considering the HCQ's side effects related to long-term use, one important question is how to identify the appropriate moment for stopping the treatment. The first RCT designed for HCQ[66,67] showed efficacy of long-term HCQ use in sustaining remission. In this RCT, the average HCQ total treatment duration before withdrawal was about 3 years.[66,67] A more recent retrospective study showed that HCQ discontinuation in patients older than 55 years with quiescent SLE and more than 5 years treatment, due to retinal toxicity, patient's preference, cardiac toxicity, or other suspected adverse effects, did not result in significant increase in flare occurrence.[245] Finally, a recent survey across large international sample of physicians has shown that in case of sustained remission, 49.7% maintained the same dose indefinitely, 48.3% reduced the dose, while only 2.0% discontinued antimalarials.[37]

Conclusion

In summary, HCQ is indicated in all patients with SLE in the absence of any contraindications or side effects, with high grade evidence in case of LN, cutaneous involvement, or during pregnancy and breastfeeding. However, there is a relatively small effect size for the prevention of severe flares in SLE. Monitoring HCQ blood levels might help to overcome adherence issues, which are quite common in SLE and adjust the daily dosage based on individual pharmacokinetic variability. Still, there is a need for additional research focused on defining the optimal conditions for HCQ withdrawal.

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