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DRUG SAFETY EVALUATION

# Hydroxychloroquine in systemic lupus erythematosus (SLE)

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**ABSTRACT**

**Introduction**: Hydroxychloroquine (HCQ) is an alkalinizing lysosomatropic drug that accumulates in lysosomes where it inhibits some important functions by increasing the pH. HCQ has proved to be effective in a number of autoimmune diseases including systemic lupus erythematosus (SLE).

**Areas covered**: In this review the mechanisms of action, the efficacy, and the safety of HCQ in the management of patients with SLE have been reviewed. HCQ may reduce the risk of flares, allow the reduction of the dosage of steroids, reduce organ damage, and prevent the thrombotic effects of antiphospholipid antibodies. The drug is generally safe and may be prescribed to pregnant women. However, some cautions are needed to prevent retinopathy, a rare but serious complication of the prolonged use of HCQ.

**Expert opinion**: HCQ may offer several advantages not only in patients with mild SLE but can also exert important beneficial effects in lupus patients with organ involvement and in pregnant women. The drug has a low cost and few side effects. These characteristics should encourage a larger use of HCQ, also in lupus patients with organ involvement.

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**KEYWORDS**
Systemic lupus erythematosus; hydroxychloroquine; antimalarial agents; retinopathy; lupus flares; cutaneous lupus; lupus nephritis

## 1. Introduction

Hydroxychloroquine (HCQ) sulfate is the hydroxylated analog of chloroquine. The drug has been initially used as an antimalarial agent, since it may inhibit the plasmodial heme polymerase. However, a number of experimental and clinical observations also outlined the efficacy of HCQ in a wide array of conditions, including diabetes mellitus, dyslipidemias, coagulopathies, infectious diseases, malignancies, as well as in a number of autoimmune diseases, including Sjogren's syndrome, rheumatoid arthritis, and systemic lupus erythematosus (SLE) [1].

Following a systematic review of the literature on Entrez-PubMed, we have provided an overview of the main mechanisms of action, the pharmacological and clinical data, and the safety of HCQ in the management of SLE.

## 2. Efficacy and safety

### 2.1. Mechanisms of action

HCQ is a lipophylic, lysosomotropic drug that can easily pass through cell membranes. In the cytoplasm, the free base form of HCQ accumulates in lysosomes (Table 1). Lysosomes are spherical vesicles that contain an array of hydrolytic enzymes which are activated by the highly acidic pH. Lysosomes generate and maintain their pH gradients by using the activity of a proton-pumping V-type ATPase, which uses metabolic energy in the form of ATP to pump protons into the lysosome lumen. The high concentrations of the alkalinizing HCQ in lysosomes increase their pH from the normal levels of 4.7–4.8 to 6 [2]. The alkalinization caused by HCQ results in expansion and vacuolization of lysosomes and inhibition of their functions, including enzyme release, receptor recycling, plasma membrane repair, cell signaling, and energy metabolism [3–5]. Since these changes can interfere with the function of the immunocompetent cells (see below), HCQ can contribute with other drugs in downregulating the immune response against autoantigenic peptides, a property that can be exploited in the treatment of SLE (Box 1).

SLE is an autoimmune disease, characterized by the inability of the immune system to discriminate between certain self-antigens and foreign ones. The loss of self-tolerance is induced by the interaction of susceptibility genes and environment risk factors which eventually lead to dysregulation of innate and adaptive immunity. In SLE, genetic factors, including polygenic and monogenic factors, as well as epigenetic influences [6], operate in the setting of environmental triggers such as ultraviolet light [7], Epstein–Barr virus infections [8], and smoking [9]. The final result is the abnormal production of pathogenic autoantibodies directed against nucleic acids and their binding proteins. Several steps are involved in the pathogenesis of SLE. The disease is initiated by accelerated cell death combined with defective clearance of dying cells. Normally, dying cells express signals that are recognized by the receptors of professional phagocytes which remove dying cells and their debris from tissues so that they cannot elicit inflammation or immune responses [10]. In SLE, an accelerated cell death combined with a clearance deficiency may lead to the accumulation in blood and tissues of debris from fragmented dying cells

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Table 1. Main mechanisms of action of hydroxychloroquine (HCQ).

HCQ can easily pass through the cell membrane

↓

It accumulates in the acidic lysosomes

↓

The high concentration of alkaline HCQ increases the pH in lysosomes

↓

The increased pH inhibits lysosomes functions interfering with metabolic and immune pathways

BOX Drug summary.

| | |
|---|---|
| Drug name (generic) | Plaquenil |
| Phase (for indication under discussion) | Approved by US Food and Drug Administration to treat lupus |
| Indication (specific to discussion) | Systemic lupus erythematosus |
| Pharmacology description/ mechanism of action | Hydroxychloroquine (HCQ) is an alkalinizing lysosomotropic drug that can accumulate in lysosomes where it increases the pH from the normal levels of 4.7–4.8 to 6.0. The alkalinization results in expansion and vacuolization of lysosomes and inhibition of their functions, including enzyme release, receptor recycling, plasma membrane repair, cell signaling, and energy metabolism. HCQ can contribute with other drugs in downregulating the immune response against auto-antigenic peptides. |
| Route of administration | By mouth |
| Chemical structure | HCQ sulfate |
| Pivotal trial(s) | [50,68,69] |

[11]. There is also an overproduction of interferon which increases cell death and further accumulation of nucleic material [12]. The levels of circulating DNA are further increased by debris extruded from polymorphonuclear cells dying in the neutrophil extracellular traps (NETs), which lead to accumulation of nucleic acid containing immune complexes and ribonucleoproteins [13]. The extracellular extrusion of endogenous molecules alarm toll-like receptors (TLRs), the sentinels of the innate immunity. Among them, an important role in SLE is played by TLR7 and TLR9 [14], which recognize the nucleic fragments as antigens and activate the innate immunity by inducing inflammatory cytokines. In the inflammatory environment, the dendritic cells (DCs) intercept the autoantigens, become mature, and produce large amounts of type I interferon [15]. This cytokine further primes additional neutrophils for NETosis and aids DC maturation with subsequent autoreactive T-cell activation [16]. Mature DCs and macrophages present the autoantigens to immune competent T cells that interact with B cells and induce their production of plasmacytes and autoantibodies in predisposed hosts. A critical role in promoting activation and survival of autoreactive B cells is played by the increased production of effector TH1 and TH17 cells [17,18], which enhance B cell receptor [19] and B cell activating-factor (BAFF) receptor [20]. Recently, a pivotal role in the development of SLE has been attributed to autophagy. This is a catabolic process through which cytoplasmic constituents can be degraded in lysosome and reused. There are three forms of autophagy: macroautophagy (which is the main pathway and is also called autophagy), microautophagy and chaperone-mediated autophagy. To remove damaged organelles the canonical process of autophagy involves the formation of hierarchically ordered double-membrane vesicles (autophagosomes) about the organelle marked for destruction. Autophagosomes, which are formed by 15 proteins, migrate to lysosomes where they are degraded by acidic lysosomial hydrolases. There is also a noncanonical autophagy, in which the formation of the double-membraned autophagosome does not require the hierarchical order, moreover double membranes do not necessarily elongate from a single source, and only a subset of autophagic proteins can be recruited [21]. Autophagy is regulated precisely and plays a vital role in maintaining cell homeostasis. The process of autophagic degradation has an important role in activating innate and adaptive immunity. It can direct nucleic acids to TLRs, can degrade antigens and deliver them to T cells, and can regulate survival, differentiation, and proliferation of T cells, B cells, and plasmablasts [22]. In parallel autophagic proteins can trigger specific responses that limit detrimental, uncontrolled immune activation and inflammation. In the presence of normal autophagy, the immune and inflammatory responses are balanced, but if autophagy is imbalanced the self-cannibalistic or, paradoxically, even the prosurvival functions of autophagy may be deleterious, resulting in cell death [23]. Alterations to the regulation of autophagy may contribute to the progression of various rheumatic diseases, including SLE. Patients with lupus have a high number of autophagocytic vacuoles in T cells, suggesting that deregulated autophagy may promote survival of autoreactive T cells [24]; an enhanced autophagy has been demonstrated in murine and human lupus B cells [25]; and deficiency of a form of noncanonical autophagy (LC3-associated phagogytosis) has been shown to be associated to a loss of self-tolerance and development of SLE-like features in a mice model [26].

In SLE, HCQ can interfere with the immune response at different levels (Figure 1). The drug can interfere with the activation of the innate immunity by inhibiting TLR7 and 9 signaling. These receptors are located intracellularly on endosomal membranes, and their ligands must be taken up into the endosome to result in activation [27]. Theoretically HCQ might interfere with TLR7 and TLR9 by inhibiting the endosomal acidification. However, it is more likely that HCQ directly binds to inhibitors to nucleic acids masking their TLR-binding epitope [28]. HCQ accumulation in the lysosomes of antigen-presenting cells (DCs, macrophages, B cells) can inhibit the presentation of the major histocompatibility complex peptides to T cells, since acidic cytoplasmic components are needed for the antigen to be digested and for binding to assemble to the α and β chains of the MHC type II [29]. This effect can be enhanced by the co-administration of minocycline [30]. HCQ

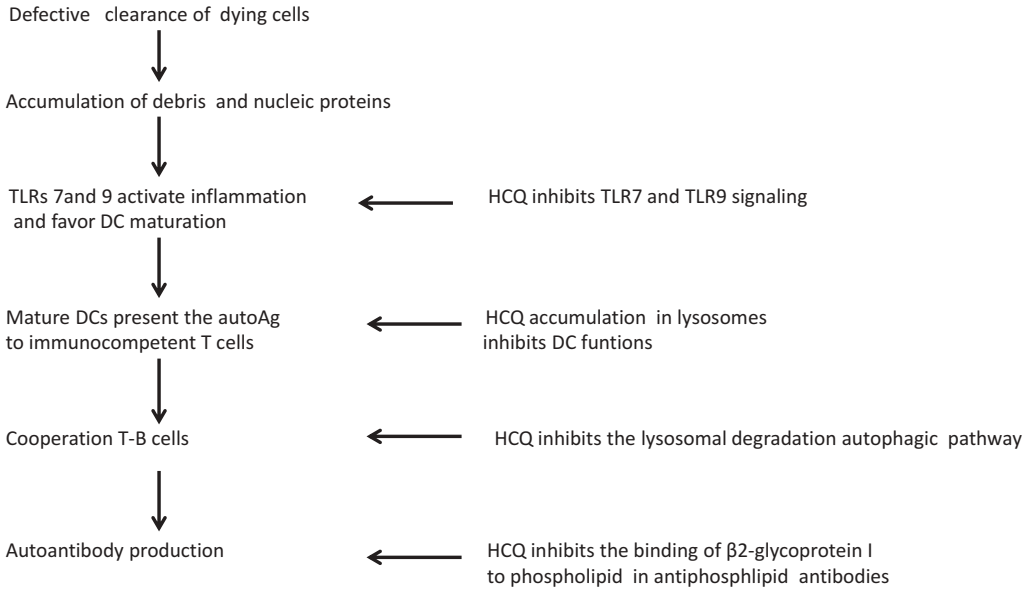


**Figure 1.** A very short outline of pathogenesis of SLE (left) and possible pathways of interference of hydroxychloroquine (right). SLE is initiated by a defective clearance of dying cells. This leads to accumulation in the blood of endogenous debris and nucleic proteins. These molecular patterns are recognized as antigens by toll like receptors (TLRs) 7 and 9. Adapter molecules recruited by TLRs activate kinases that transmit the amplified signal to nuclear factors that encode the genes regulating the inflammatory response. In the inflammatory milieu, dendritic cells (DCs) capture the antigen become mature and migrate to the lymphatic system where they present the antigen to quiescent T cells. Activated T cells can cooperate with B cells favoring their production of plasmacytes and antibodies. In SLE, deregulated autophagic pathways play a key role in antigen processing presentation and in lymphocyte development, survival, and proliferation. Hydroxychloroquine (HCQ) can interfere with different steps of these mechanisms. It can inhibit the TLR signaling, can inhibit the accumulations of nucleic fragments in the lysosomes, can inhibit the autophagic protein degradation by rising lysosomal pH, and can prevent the production of antiphospholipid antibodies by inhibiting the binding of β2-glycoprotein I to phospholipids.

can inhibit the proinflammatory cytokines IL-6, IL-1β tumor necrosis factor-α (TNF-α) [31], and can block T cell activation by disrupting the T cell receptor dependent calcium signaling [32]. Moreover, HCQ is a powerful inhibitor of lysosome-dependent autophagy. By preventing the acidification of lysosomal compartment HCQ can impair autophagic protein degradation, which is a critical step for activating innate and acquired immunity. This effect is currently investigated by oncologists, who are using combination of HCQ with anticancer treatments in different types of malignancy [33]. Finally, treatment with HCQ has been associated with reduced risk of thrombosis in antiphospholipid syndrome. By using techniques of ellipsometry and atomic force microscopy, Rand et al. demonstrated that HCQ can inhibit the binding of antiphospholipid antibody – β2-glycoprotein I complexes to phospholipid bilayers [34]. HCQ can also exert another mechanism of protection against antiphospholipid syndrome. Annexin A5 is a protein that crystallizes over phospholipid bilayers. Antiphospholipid antibodies disrupt the annexin A5 binding, so inhibiting the activity of this potent anticoagulant protein. HCQ can reverse the effect of antiphospholipid antibodies on annexin 5 and restore annexin A5 binding to phospholipid bilayers, so protecting the annexin A5 anticoagulant activity from disruption by antiphospholipid antibodies [35].

### 2.2. Pharmacological data

HCQ sulfate is a weak base that is completely absorbed from the gastrointestinal tract. The drug has a good bioavailability (about 0.74) and is metabolized in the liver by cytochrome P450 enzymes to *N*-desethylhydroxychloroquine, desethylchloroquine, and bisdesethylchloroquine. It is mainly excreted via the kidneys with a long half-life of elimination, approximately 40–60 days [36]. The drug is extensively sequestered in the tissues. The slow accumulation can account for its delay in achieving steady-state concentrations and elimination. Variable concentrations may arise after standard administered doses because of inter-individual pharmacokinetic variability. These factors are likely to contribute to the delayed therapeutic response and the variable response, respectively. Pharmacokinetic interaction studies are limited. Potentially important kinetic interactions have been documented for D-penicillamine and cimetidine but have not been found for aspirin, ranitidine, or imipramine [37]. Drugs that induce cytochrome P450 enzymes (such as isoniazide or anticonvulsivant agents) may reduce the blood levels of HCQ while inhibitors of cytochrome P450 (such as nondihydropyridinic calcium channel blockers) may increase the blood levels. HCQ improves both beta cell function and insulin sensitivity in non-diabetic individuals. These metabolic effects may explain why HCQ treatment is associated with a lower risk of type 2 diabetes [38]. However, dose altering is recommended in patients taking insulin to prevent severe hypoglycemia. In SLE patients, the initial dosage of HCQ is 400 mg orally once or twice a day. Therapeutic effect may appear after several weeks or months. The maintenance dose ranges between 200 and 400 mg per day. There is controversy about the best dose of this medication, with some advocating dosing based on actual body weight, whilst others are in favor of calculating the daily dose based on ideal body weight.

HCQ concentration in the blood displays a great variability among patients under treatment and even in healthy volunteers and adherent patients [39]. Low HCQ blood levels can be associated with development of flares in patients with inactive SLE. In unselected patients with SLE who were receiving HCQ at a dose of 400 mg per day for at least 6 months, the mean blood levels of HCQ were significantly lower (mean 694 ng/ml) in those with active disease than in those with inactive disease (mean 1079 ng/ml). A multivariate logistic regression showed that the HCQ concentration was the only predictor of exacerbation [40]. In another study on SLE patients, it was shown that the blood levels of HCQ were similar regardless of height and ideal body weight. There was a trend toward higher disease activity with lower HCQ levels. The authors concluded that a dose of 6.5 mg/kg of actual body weight (maximum 400 mg daily) is appropriate. Accordingly, the daily dose should be reduced below 400 mg per day for those weighing less than 61 kg [41].

### 2.3. Efficacy in SLE

The first reports on the use of HCQ in SLE were published more than 50 years ago [42]. For some decades, the drug was mainly used in patients with cutaneous lupus, often in association with other antimalarial agents. Retrospective reviews of large series reported good results in different categories of skin lupus treated with HCQ, either alone or in combination with other antimalarial agents, particularly when blood concentrations of HCQ were monitored [43–45]. Today, the benefit of antimalarials in the treatment of cutaneous SLE is well established. However, about 50% of patients with cutaneous SLE fail to respond to HCQ. In these patients, a progressive increase of HCQ doses to reach blood concentrations greater than 750 ng/ml may obtain response in 81% of cases. Thus, it has been suggested to increase HCQ doses to reach blood concentrations greater than 750 ng/ml before addition of other treatments in refractory skin lupus [46]. In patients who do not respond to adequate dosage of HCQ, additional treatments can be proposed [47]. These may include synthetic drugs (such as glucocorticoids, cyclophosphamide, azathioprine, mycophenolate, cyclosporine, and tacrolimus) and biologic agents (such as, belimumab and intravenous immunoglobulins)

There is growing evidence of the beneficial effects of HCQ to treat mild symptoms of systemic lupus- such as arthralgia, fatigue, fever, rash – and to prevent disease flares[48–51]. As pointed out earlier, HCQ can also decrease the risk of thromboembolism in patients with antiphospholipid antibodies [52–55]. Although HCQ passes through the placenta, the available studies showed that it is neither teratogenic nor harmful for the baby and can allow for the reduction of the average dose of glucocorticoids during pregnancy [56–60].

A main advantage of HCQ consists in its potential prevention of some severe complications. Osteoporosis is frequent in patients with SLE, particularly in women receiving prolonged steroid treatment. The use of HCQ may increase the spine bone mineral density in women with SLE [61]. Accelerated atherosclerosis and its long-term sequelae are a major cause of late morbidity and mortality among patients with SLE. HCQ can interfere with some risk factors of atherogenesis by reducing the incidence of thrombotic events, lowering total cholesterol in patients receiving steroids, and lowering fasting blood glucose concentration [62,63]. Murine models also suggested other cardioprotective mechanisms of HCQ. By enhancing phosphorylation of the pro-survival kinase ERK1/2, HCQ can exert protection in a myocardial ischemia-reperfusion injury model [64]. In a model of SLE with endothelial damage caused by reactive oxygen species, an early administration of HCQ could exert vascular protection, via an anti-oxidant effect [65]. In NZBWF1 lupus mice, chronic HCQ treatment reduced hypertension, endothelial dysfunction, and organ damage, despite the persistent elevation of anti-double-stranded DNA [66]. Thus, although atherosclerotic complications are caused by multiple factors, clinical and experimental studies would suggest the possibility of reducing the burden of cardiovascular diseases in lupus patients [67].

To assess whether HCQ influenced survival in SLE patients, a multiethnic case-control study, called Lumina, was performed. In Lumina study, 61 deceased patients (cases) were matched for disease duration (within 6 months) with 547 living patients (controls) in a proportion of 3:1. Propensity scores were derived by logistic regression to adjust for confounding by indication as patients with SLE with milder disease manifestations are more likely to be prescribed HCQ. HCQ was well tolerated and demonstrated a protective effect on survival, which was evident even after taking into consideration the factors associated with treatment decisions [68]. In another study, the group of Toronto evaluated whether HCQ may prevent organ damage in SLE. The authors conducted a nested case-control study embedded in an inception cohort of patients with lupus. Patients with Systemic Lupus International Collaborating Clinics Damage Index (SDI) >0 at 3 years were considered cases and patients with SDI = 0 were controls. Among 481 patients who had 3 or more years of follow-up 151 cases were matched with 151 controls. Univariate analysis identified age, the use of any immunosuppressive drugs, HCQ, and cumulative dose of steroids as significant covariates associated with damage accrual. In multivariate analysis, the use of HCQ remained significantly associated with less damage (odds ratio [OR] = 0.34) while age (OR = 1.05) and a variable combining SLE activity and steroid dose (OR = 1.73) were associated with damage at 3 years. The investigators acknowledged that there were limitations to their analysis but concluded that HCQ use was associated with less damage at 3 years after diagnosis of SLE when attention was given and adjustment done for disease activity and steroid dose, duration of disease, and calendar year of diagnosis [69]. A systematic review of the English literature between 1982 and 2007 reported that there was a high level of evidence that chloroquine and HCQ can prevent lupus flares and increase long-term survival of patients with SLE; there was moderate evidence of protection against irreversible organ damage, thrombosis and bone mass loss. Toxicity of these drugs was infrequent, mild and

usually reversible, with HCQ having a safer profile. By contrast, evidence supporting an effect on severe lupus activity, lipid levels, and subclinical atherosclerosis was weak [70].

In summary, there is evidence that HCQ may exert a number of potential benefits not only in patients with mild forms of SLE but also in patients with organ involvement. In prescribing the dose, the physician should take into account that HCQ is a slow-acting drug, its benefit may often manifest after 6 months. Therefore, in acute phases of SLE should be used in combination with other therapeutic agents which could later be reduced when the antimalarial effect becomes manifest

When using HCQ in patients with lupus nephritis is preferable not to check proteinuria by dipstick. In fact, the analytical interference of HCQ with standard dipstick test may lead to a high rate of false positive results [71]. Although many authorities believe that HCQ should be given to most patients with SLE during the whole course of the disease, irrespective of its severity, the percentage of lupus patients taking HCQ remains lower than expected [72].

### 2.4. Safety evaluation

HCQ is considered to be a safe drug. However, as any other medicament HCQ can be responsible of a number of adverse events. HCQ side effects are usually dose-dependent and many adverse events reflect intentional or unintentional over-dosage. Patients with allergy, psoriasis, porphyria, and alcoholism are more susceptible to cutaneous side effects. Children are particularly vulnerable to side effects for even small over-dosage of chloroquine. There is limited data on pediatric HCQ overdoses and no reports of toxicity from 1 to 2 pills, but given its similarity to chloroquine, HCQ should also be considered potentially toxic at small doses in the pediatric population [73]. As a general rule, monitoring side effects should be continued throughout the time patients are taking HCQ long term.

Here, we report the most serious side effects of HCQ, taking into account that not all the reported complications occurred in patients without SLE.

#### 2.4.1. Ocular complications

About 10% of patients receiving HCQ may develop corneal deposits. These changes are dose-dependent, transient, and reversible [74]. The most worrying ocular complication is retinopathy. It is characterized by edema, atrophy, loss of foveal reflex, increased macular recovery time following exposure to a bright light, and elevated retinal threshold to red light in macular, paramacular, and peripheral retinal areas. Visual field defects have included pericentral or paracentral scotoma, central scotoma with decreased visual acuity, rarely field constriction, and abnormal color vision. The most common visual symptoms attributed to retinopathy are reading and vision difficulties (words, letters, or parts of objects missing), photophobia, blurred distance vision, missing or blacked out areas in the central or peripheral visual field, and light flashes and streaks. High dose and long duration of use are the most significant risks of developing retinopathy. The risk dramatically increases with cumulative doses higher than 1000 g of HCQ [75]. At recommended doses of 6.5 mg/kg, the risk of retinal toxicity up to 5 years is under 1% and up to 10 years is under 2%, but it rises to almost 20% after 20 years. However, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year [76]. In most cases, retinopathy is not reversible, and there is no present therapy. Recognition at an early stage is important to prevent central visual loss. The American Academy of Ophthalmology recommends that patients and prescribing physicians should be informed about risk of toxicity, and the importance of regular annual screening. A maximal daily HCQ use of ≤5 mg/kg real body weight is recommended. The primary screening tests are automated visual fields plus spectral-domain optical coherence tomography. These should look beyond the central macula in Asian patients. The multifocal electroretinogram can provide objective corroboration for visual fields, and fundus autofluorescence can show damage topographically. Modern screening should detect retinopathy before it is visible in the fundus [76].

#### 2.4.2. Cardiovascular side effects

Cardiotoxicity is a rare but serious complication of HCQ. Cardiotoxicity commonly manifests clinically as a restrictive or dilated cardiomyopathy or with conduction system abnormalities including atrioventricular block and bundle branch block. However, non-specific chest discomfort may be a presenting feature [77]. Risk factors for the development of HCQ-induced cardiotoxicity include older age, female gender, longer duration of therapy (>10 years), elevated per-kilogram daily dose, pre-existing cardiac disease, and renal insufficiency [78,79]. The pathogenetic role of HCQ has been questioned, but it is possible that the lysosomal dysfunction caused by HCQ can lead to endomyocardial accumulation of pathologic metabolic products [80]. The diagnosis may be difficult and often requires endomyocardial biopsy that may reveal myocyte vacuolization at optic microscopy and pathognomonic sarcoplasmic myelinoid and curvilinear bodies on electron microscopy [81]. Prognosis in HCQ cardiotoxicity can vary from death to cardiac transplantation to partial or complete improvement [77,82].

#### 2.4.3. Cutaneous complications

Dermatologic adverse events have included nonlight-sensitive psoriasis, bleaching of hair, alopecia, pruritus, skin and mucosal pigmentation, photosensitivity, and skin eruptions. These side effects are often caused by allergic reactions [83]. Exceptional cases of life-threatening epidermal necrolysis [84–86] have been reported. HCQ in the skin can be detected in some patients with mucocutaneous hyperpigmentation. It may be attributed to the strong binding of HCQ to melanin HCQ in the skin can be detected in some patients with mucocutaneous hyperpigmentation [87].

#### 2.4.4. Neurologic and psychiatric complications

Nervous system side effects include headache, dizziness, vertigo, tinnitus, and difficulty in seeing to read. Rare cases of convulsions have been reported [88]. Peripheral neuropathy

may be associated with a bilateral progressive proximal weakness of the lower extremities with variable polyneuropathy, especially in patients with worsening renal function [89]. HCQ may also cause myopathy that may be so severe to cause respiratory failure [90]. HCQ-related neuromyopathy may be underdiagnosed because its signs, symptoms, and laboratory results are similar to other chronic diseases [91]. Therapeutic doses of HCQ sometimes cause psychosis, delirium, personality change, and depression [92].

#### 2.4.5. Liver complications

Hepatic side effects include isolated cases of abnormal liver function and fulminant hepatic failure [93–95].

#### 2.4.6. Gastrointestinal complications

Diarrhea, loss of appetite, nausea, or vomiting and stomach cramps may occur in these patients. These troubles may be caused by microbiota modifications induced by HCQ [96]. To prevent gastric discomfort a tablet of HCQ may be taken once or twice a day with a glass of milk or a meal to decrease nausea. Antacids should not be prescribed as they can impair gastrointestinal absorption. Gastrointestinal side effects may be reversed by adjusting the dose or by withdrawing the drug for a short period.

## 3. Conclusions

The available data show that the use of HCQ in patients with SLE is effective and safe. HCQ can be used for treatment of constitutional symptoms of lupus, such as joint pain and swelling, rashes, and fatigue. However, the drug may also be given along with steroids and immunosuppressive drugs to improve the life expectancy of patients with SLE and in reducing lupus flares and organ damage accrual. Of great importance, HCQ may prevent the thrombotic complications in patients with antiphospholipid syndrome and may be used safely during pregnancy. Further benefits may include protection against osteoporosis and atherosclerosis.

HCQ is generally considered to be a safe drug. However, its long-term use may be rarely complicated by some serious side effects, particularly retinopathy. To minimize the risk of ocular complications some precautions are needed. These include a fundus oculi evaluation before prescribing the drug and an annual ophthalmologic control thereafter. Retinopathy and other side effects are usually related to the cumulative dosage of HCQ. In adults, the daily dose should not exceed 400 mg. Overdose is particularly dangerous in children.

## 4. Expert opinion

SLE is a chronic autoimmune disease that mainly affects women in childbearing age and certain racial groups. The disease has protean manifestations and follows a relapsing and remitting course. Many organs and tissues are involved in SLE, such as the kidneys, the heart, and the brain as well as the skin, the joints, the pleura, and the pericardium. The prognosis of SLE was ominous until few years ago, particularly for patients with organ involvement and frequent flares. Today, the life expectancy is considerably improved [97]. Even in lupus nephritis, the most severe form of SLE, the patient survival at 20 years ranges around 95% [98]. A better understanding of the disease, an earlier diagnosis and a more refined treatment in comparison with the recent past accounted for these improved results. Yet, SLE is still a challenge for physicians. Most patients with lupus need a continuous treatment with glucocorticoids and/or immunosuppressive agents which have significant side effects. This iatrogenic morbidity can impair the quality of life and the long-term prognosis. Biological agents may allow to reduce the dosage of synthetic drugs but the long-term safety and efficacy of the available monoclonal antibodies are still poorly defined [99,100] while their high cost is a main limitation to their extensive use in lupus patients, particularly in those with poor socioeconomic status.

In this complicated setting, the use of HCQ may offer several advantages. It may control constitutional symptoms, spare the use of glucocorticoids, decrease the risk of flares and organ damage, and increase the life expectancy of SLE patients. HCQ can also reduce the risk of antiphospholipid syndrome complications and can be used safely in pregnant women. Importantly, HCQ has a low cost and few side effects. These characteristics should encourage a larger use of HCQ not only in patients with mild SLE but also in those with organ involvement.

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## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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