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Review article

Advancements on the impact of hydroxychloroquine in systemic lupus erythematosus

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ABSTRACT

Hydroxychloroquine (HCQ) has gained significant attention as a therapeutic option for systemic lupus erythematosus (SLE) because of its multifaceted mechanism of action. It is a lipophilic, lysosomotropic drug, that easily traverses cell membranes and accumulates in lysosomes. Once accumulated, HCQ alkalizes lysosomes within the cytoplasm, thereby disrupting their function and interfering with processes like antigen presentation. Additionally, HCQ has shown potential in modulating T-cell responses, inhibiting cytokine production, and influencing Toll-like receptor signaling. Its immunomodulatory effects have generated interest in its application for autoimmune disorders. Despite its established efficacy, uncertainties persist regarding the optimal therapeutic concentrations and their correlation with adverse effects such as retinal toxicity. Therefore, standardized dosing and monitoring guidelines are crucial. In this study, we provide a comprehensive review of the mechanisms, efficacy, dosing variations, and retinal toxicity profiles of HCQ, which are essential to optimize SLE treatment protocols and ensure patient safety.

1. Introduction

Systemic lupus erythematosus (SLE) is a diffuse connective tissue disease mediated by autoimmunity and fundamentally pathologically characterized by vasculitis as its fundamental pathological manifestation. Nevertheless, its pathogenesis remains unclear. SLE primarily manifests with a variety of autoantibodies and involves multiple systems, characterized by recurrent disease episodes. Without proper management, it can lead to irreversible damage to the affected organs, ultimately resulting in patient mortality. A multicenter study conducted in Europe involving 1000 patients revealed [1] that the overall 10-year survival rate of patients with SLE was 92 %. However, this rate decreased to 88 % when kidney involvement was present. Active SLE, thrombosis, and infections were identified as the most common causes of death among SLE patients.

Hydroxychloroquine (HCQ) is a structural derivative of the antimalarial drug chloroquine. It is characterized by the addition of a hydroxyl group to the side chain of chloroquine, resulting in comparatively fewer adverse reactions. In the 1950s, it gained recognition as an immunomodulator and was employed in the treatment of SLE due to its improved safety profile. Given its excellent safety record, HCQ is widely used to treat autoimmune diseases. Numerous studies have confirmed its ability to reduce SLE disease activity, prevent disease flares, decrease the need for prolonged steroid use, and provide benefits during pregnancy. Moreover, HCQ exhibits diverse therapeutic effects including anti-thrombotic, cardiovascular risk reduction, glucose regulation, lipid level improvement, and

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photoprotection [2]. Undoubtedly, the pharmacology and clinical applications of HCQ in the treatment of SLE remain an active area of research. Therefore, providing a comprehensive overview of the mechanisms, therapeutic effects, correlation with blood drug concentrations, and toxicity risks of HCQ in the treatment of SLE holds significant importance and reference value for relevant clinicians and patients.

A systematic search was conducted in PubMed data up to June 30, 2023. We created a strategy based on Medical Subject Headings (MeSH), popular keywords, and their thorough combination in order to boost the search's sensitivity. Hydroxychloroquine, Hydroxychloroquine Sulfate, Oxychlorochin, Oxychloroquine, Hydroxychlorochin, Plaquenil, Systemic Lupus Erythematosus, Lupus Erythematosus Disseminatus, Lupus were among the MeSH and common keywords that were included. By haphazardly putting together relevant keywords and MeSH terminology, the most comprehensive set of data was gathered. Titles and abstracts were evaluated based on the inclusion and exclusion criteria separately by two researchers. Finally, by reading the entire text, studies unrelated to HCQ and SLE were excluded.

The purpose of this study was to comprehensively analyze the research progress on HCQ blood concentrations in the treatment of SLE and its impact on side effects through a systematic review.

2. Pharmacology of HCQ

Commonly used in clinical practice are tablet formulations of HCQ sulfate, with a strength of 100 mg per tablet. The dosage of HCQ varies according to its indications. The American Academy of Ophthalmology recommends [3] a dosage in SLE not exceeding 5 mg/kg/day based on the actual body weight, with a maximum daily dose of 400 mg, to reduce the occurrence of retinal complications. HCQ is typically administered orally, absorbed in the intestinal lumen, and transported to the liver, where it undergoes first-pass metabolism. Subsequently, it is distributed to other parts of the body and eventually excreted by the kidneys. After oral administration, HCQ is well absorbed with an approximate bioavailability of 80 %, reaching peak concentrations within 3–4 h [4].

HCQ has an elimination half-life of 20–60 days, and its metabolites can be detected in the urine for months after administration.

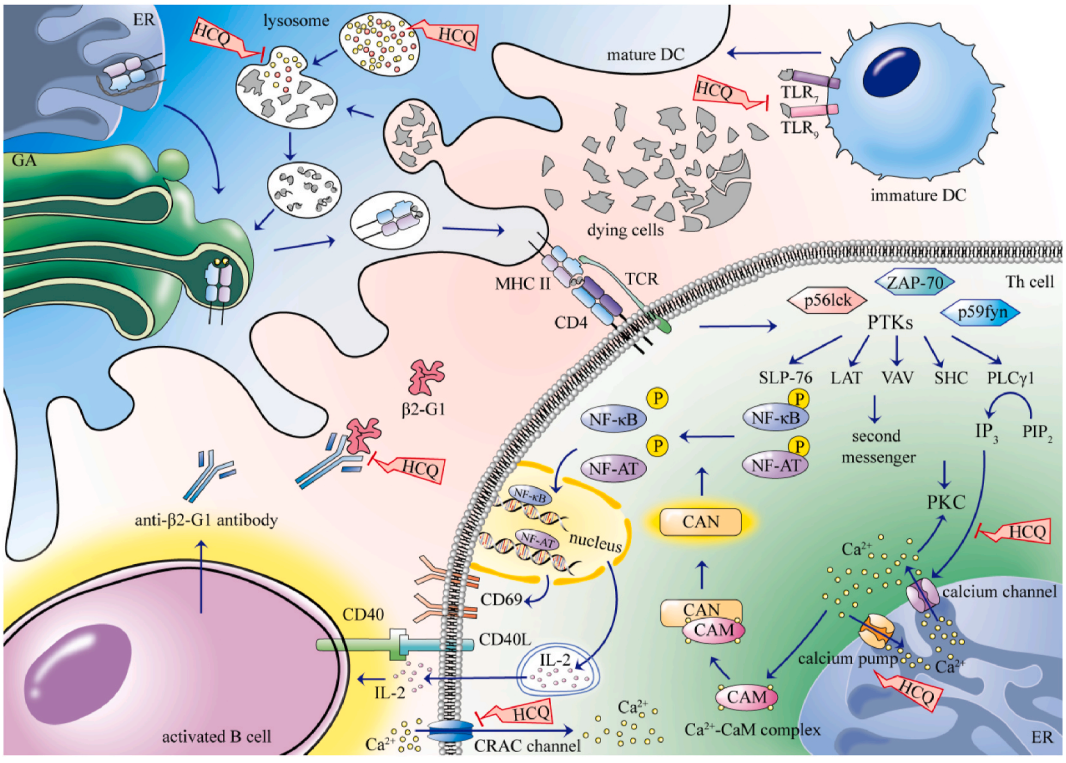

Fig. 1. Mode of action of hydroxychloroquine on immune response. Several signaling pathways have been identified: the up-regulation of CD69 and IL-2 expression through the regulation of CAM, CAN, NF-AT, NF-κB, and other downstream signaling molecules induced by intracellular free Ca^{2+}. HCQ hinders the release of calcium ions from the Ca^{2+} reservoir by inhibiting the calcium channel of the IP3 receptor, while promoting the entry of Ca^{2+} into the Ca^{2+} reservoir through the stimulation of Ca^{2+} pumps. Therefore, HCQ inhibits TCR-mediated intracellular calcium flux, CD69 expression on the surface of Th cells, and IL-2 secretion. Dead cell fragments can induce the maturation of immature DCs by interacting with TLR7 and TLR9. HCQ is known to inhibit the signaling pathways of TLR7 and TLR9. Once accumulated in lysosomes, HCQ can also inhibit the functions of mature DCs. In addition, HCQ is capable of hindering the lysosomal degradation pathway, a key process in autophagy. Finally, HCQ inhibits the binding of β2-G1 to phospholipid in antiphospholipid antibodies. Abbreviations: DC, dendritic cell; CAM, calmodulin; CAN, calcineurin; CRAC channel, Ca2+ release activated Ca2+ channel; β2-G1, β2-glycoprotein 1; TLR, toll-like receptor; ER, endoplasmic reticulum; GA, golgi apparatus.

Steady-state concentrations were achieved after approximately 6 months of administration, with relatively minor fluctuations during treatment. Following administration, hepatic cytochrome P450 enzymes swiftly dealkylate HCQ, generating pharmacologically active demethylated HCQ, desethylchloroquine, and bidesethylchloroquine. Up to 60 % of HCQ is primarily excreted by the kidneys in unchanged or metabolized forms, whereas the remaining 40 % is typically cleared or stored in other body tissues through routes such as hepatic metabolism, fecal excretion, and deposition in the skin [5,6].

3. Mechanisms of action

HCQ, a lipophilic lysosomotropic agent, readily permeates cell membranes. In the cytoplasm, the unprotonated form of HCQ accumulates within the lysosomes. Lysosomes are spherical vesicles containing various hydrolytic enzymes that become active in highly acidic pH conditions. Lysosomes generate and maintain their pH gradient through the activity of the vacuolar-type ATPase (v-ATPase), utilizing metabolic energy in the form of ATP to pump protons into the lysosomal lumen. The elevated concentration of alkaline HCQ in lysosomes increases their pH from the usual 4.7–4.8 range to 6 [7]. HCQ-induced alkalinization results in lysosomal swelling and vacuolation, which impairs lysosomal functionality. This encompasses enzyme release, receptor recycling, plasma membrane repair, cell signaling, and energy metabolism [8–10]. As these changes can perturb the functions of immune-competent cells, HCQ can synergize with other agents to downregulate immune responses against self-antigenic peptides. This property has previously been used to treat SLE.

Currently, the effects of HCQ on T lymphocytes and B lymphocytes have also garnered significant attention. Research has shown that HCQ can rebalance the immune response mediated by Th17/Treg and improve SLE [11]. HCQ primarily affects T cell lipid metabolism, thereby promoting the differentiation and function of Tregs [12]. Additionally, HCQ can inhibit the proliferation of T cells

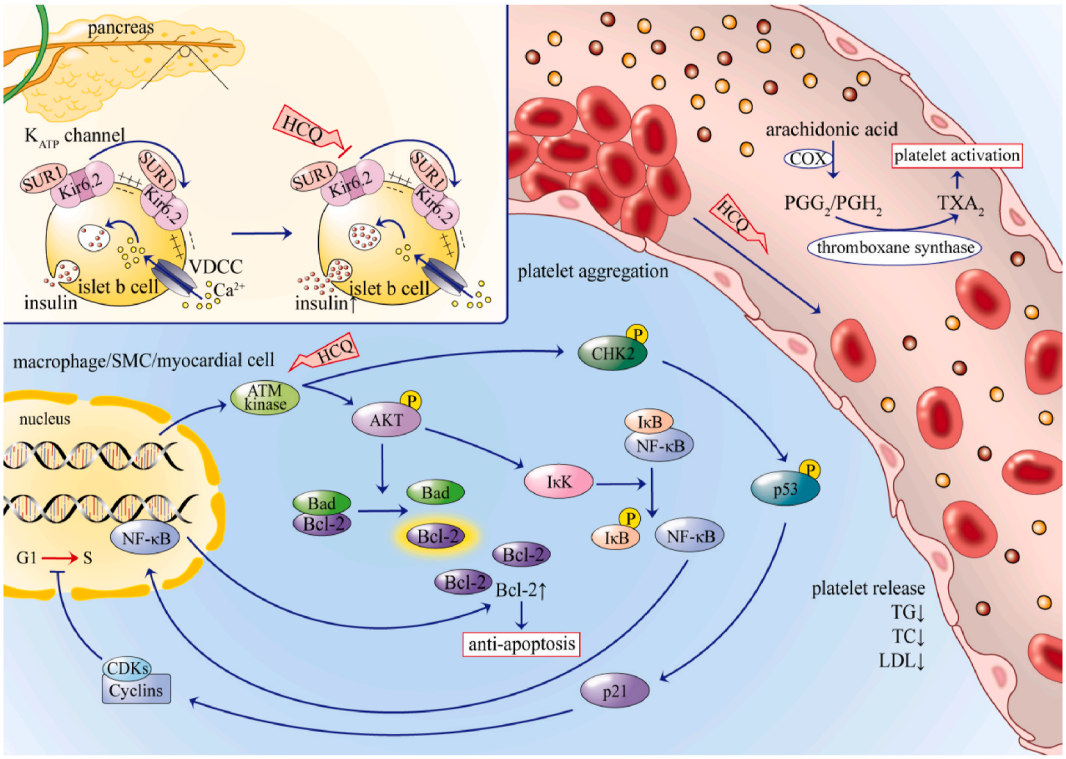

Fig. 2. The antithrombotic, cardiovascular disease risk reduction, hypoglycemic and hypolipidemic effects of HCQ. (1) HCQ blocks platelet aggregation by interfering with the release of arachidonic acid and reduces the size of thrombus. (2) The ATM-Akt pathway plays a crucial role in cell survival, particularly in the context of myocardial infarction, through two main mechanisms: Akt phosphorylation leads to enhanced Bcl-2 expression via IκK activation and NF-κB dimer dissociation, and to increased Bcl-2 activity through Bad activation. Additionally, ATM lowers cardiovascular disease risk by inhibiting cell cycle transition from G1 to S phase via CHK2. (3) HCQ inhibits inwardly rectifying potassium channel subunit Kir6.2 in islet B cell, leading to a change in cell membrane potential. This change results in a decreased calcium inflow into cells through VDCCs, which subsequently enhances insulin secretion in pancreatic beta cells and leads to a reduction in blood sugar levels. (4) Treatment with HCQ has also been shown to reduce the levels of TG, TC, and LDL, thereby contributing to a decrease in blood lipid levels. Abbreviations: COX, cyclooxygenase; PGG_2, prostacycline$_2$; PGH_2, prostaglandin$_2$; TXA_2, thromboxane; ATM, ataxia telangiectasia mutated; Akt, protein kinase B; IκK,1-Kappa-B kinase; IκB, 1-Kappa-B; NF-κB, Nuclear factor κB; Bcl-2 , B-cell lymphoma gene 2; Bad, BCL2-Associated d; VDCC, voltage-dependent Ca2+ channel; CHK2, checkpoint kinase 2; CDKs, cyclin dependent kinases; SUR1, sulfonylurea receptor 1; TG, total cholesterol; TC, total cholesterol; LDL, low density lipoprotein.

and B cells, leading to reduced production of T follicular helper (Tfh)-related cytokines CXCL13, type I and type II interferons, and immunoglobulins [13].

The mechanism of HCQ action in patients with SLE involves numerous molecular pathways. HCQ, a weakly basic agent, accumulates within lysosomes, elevating their pH levels. This interference with phagocytosis and disruption of self-antigen presentation can be achieved by increasing the lysosomal pH in antigen-presenting cells [14]. Furthermore, HCQ can alter T-cell responses and inhibit the production of various cytokines (e.g., IL-1, IL-6, IL-17, IL-22, and TNF-α) [15–17]. Particularly noteworthy is HCQ's potential to inhibit Toll-like receptor activation. The weakly basic hydroxychloroquine interferes with Toll-like receptor signaling, reducing signal transductions of 7 and 9 [18]. Consequently, decreased Toll-like receptor signaling leads to reduced dendritic cell activation and diminished interferon production [19]. In vitro experiments have shown that HCQ induces apoptosis of peripheral blood mononuclear cells, while also reducing the secretion of IL-17 factors in the peripheral blood [20] (Fig. 1).

4. The role of HCQ in SLE

4.1. Antithrombotic effects of HCQ

Antiphospholipid antibody (aPL)-positive status, disease activity, and various factors collectively contribute to thrombosis, which remains the leading cause of mortality in SLE. Thrombosis in SLE, specifically antiphospholipid syndrome, results from multifaceted interactions. Jung et al. conducted a nested case-control study, revealing that antimalarial drugs exhibit thromboprotective properties, correlating with a remarkable 68 % reduction in the risk of all thrombovascular events [21]. Numerous retrospective and prospective studies have consistently shown that HCQ has a protective effect against thrombosis in SLE patients, resulting in a decreased risk of both arterial and venous thrombosis [22–24]. The latest study found that for every 200 ng/ml increase in HCQ blood levels, thrombosis rates were reduced by 13 % [25]. HCQ has long been acknowledged as an antiplatelet agent [26], due to its ability to interfere with arachidonic acid release, leading to the inhibition of platelet aggregation and reduction in thrombus size [27]. Furthermore, studies have demonstrated that HCQ can reverse the thrombotic characteristics induced by aPL antibodies in mice [28] (Fig. 2).

4.2. HCQ in reducing cardiovascular disease risk

Patients treated with glucocorticoids can induce or exacerbate hyperlipidemia, disrupt vascular endothelial function, and lead to luminal narrowing [29,30]. These factors contribute to the development of atherosclerosis in SLE patients, leading to changes in both cardiac structure and function, and ultimately resulting in left ventricular remodeling. Research suggests that HCQ can activate the ataxia-telangiectasia mutated (ATM) pathway [31], which, in turn, can modulate the expression and activity of cardiac protein kinase B, a downstream signaling molecule [32]. This modulation may potentially mitigate the development of atherosclerosis. However, Subo Dey's research [33] has indicated that prolonged administration and high dosages of HCQ have been associated with cardiotoxic effects such as bradycardia, tachycardia, QT prolongation, atrioventricular block, and cardiomyopathy, highlighting the need for further investigation to confirm HCQ's impact on improving ventricular structure (Fig. 2).

4.3. HCQ in regulating glycemic homeostasis

Various factors contribute to elevated blood glucose levels in SLE patients beyond the presence of coexisting diabetes. Long-term high-dose steroid treatment disrupts endogenous glycemic control, consequently raising the risk of developing diabetes in patients with SLE. Recent studies have confirmed that patients with SLE undergoing HCQ treatment exhibit improvements in blood glucose, lipid levels, and serum insulin concentrations. A previous study by Emami [34] provided evidence from animal experiments that HCQ reduces blood glucose levels and increases serum insulin concentrations in diabetic rats, with the benefits showing dependency on HCQ blood concentrations. A study from Taiwan analyzing the relationship between HCQ use and the risk of diabetes in patients with SLE indicated an association between HCQ use and lower diabetes event risks [35]. Wasko et al. conducted a randomized, double-blind trial to investigate the impact of HCQ on insulin sensitivity and β-cell function. The results demonstrated that HCQ improves β-cell function and improves insulin sensitivity in non-diabetic patients [36]. The hypoglycemic mechanism of HCQ may be attributed to its inhibition of Kir6.2 [37]. (Kir6.2 is an adenosine triphosphate-sensitive potassium channel expressed in pancreatic cells like β-cells.) Downregulation of Kir6.2 is associated with increased insulin secretion in pancreatic β-cells [38]. Therefore, by interacting with the Kir6.2 channel in pancreatic β-cells, HCQ has the potential to enhance insulin secretion and reduce blood glucose levels (Fig. 2).

4.4. HCQ in regulating lipid homeostasis

Dyslipidemia is highly prevalent in patients with SLE, primarily characterized by decreased levels of high-density lipoprotein (HDL) and elevated levels of triglycerides (TG) [39]. HCQ use may be associated with decreased serum lipid levels in patients with SLE, particularly those on glucocorticoid treatment. Chenyang et al. [40] conducted a systematic review and meta-analysis on whether antimalarial drugs affect serum lipid levels in patients with SLE, and the results demonstrated that HCQ treatment leads to reductions in TG, total cholesterol (TC), and low-density lipoprotein (LDL) levels. Additionally, Cairoli et al. conducted a longitudinal assessment to examine the effects of HCQ on LDL cholesterol levels in patients with SLE. The study involved measuring fasting levels of TG, TC, HDL, and LDL in patients at baseline and after 3 months of HCQ treatment. The results revealed significant reductions in TC and LDL levels after three months of HCQ treatment [41]. However, a study conducted by Lizhi et al. [42] in China found no significant impact

of HCQ on the serum lipid profile of Chinese patients with SLE. This lack of effect could be attributed to the relatively mild or inactive lupus status of the participants, who might have been using lower doses of glucocorticoids. Based on current clinical research both domestically and internationally, HCQ appears to improve lipid metabolism in patients with SLE; however, further exploration into the specific molecular mechanisms through additional fundamental experiments is warranted (Fig. 2).

The multifaceted impacts of HCQ extend to several disease states, which highlights its broad therapeutic potential. Considering HCQ's wide-ranging impacts, the key findings from numerous studies, highlighting HCQ's role in disease modulation, its therapeutic benefits, and potential adverse effects were summarized in Table 1.

4.5. HCQ in reducing disease activity and preventing disease flare

Some cohort studies have indicated that high blood levels of HCQ are correlated with reduced disease activity in SLE [43]. Specifically, maintaining the therapeutic concentration of HCQ has been shown to decrease the odds of flares by 26 % [44]. Moreover, HCQ has demonstrated substantial efficacy in patients with SLE and lupus nephritis (LN), including improved outcomes in children with proliferative LN [45].

4.6. HCQ in ensuring protection for both patients and fetuses during pregnancy

SLE affects women of childbearing age and results in various adverse pregnancy outcomes (APOs). Pregnant women with SLE are at heightened risk for complications such as disease flare, preterm birth, intrauterine growth restriction (IUGR), spontaneous abortion, thromboembolic disease, and post-partum infection [46,51]. The incidence of flare is notably higher during pregnancy and the first three months postpartum[47]. In a mouse model of obstetric antiphospholipid syndrome, Liu et al. observed that HCQ treatment could partially reverse the process of aPL antibodies reducing trophoblastic invasion and migration, This improvement in placental function helps prevent fetal death and reduces the incidence of pathological pregnancies [52]. Clinical data further suggest that the degree of lupus activity during pregnancy is significantly lower in women who continue HCQ treatment [53]. Continuing HCQ also appears to mitigate the risk of flare during and after pregnancy [47].

Table 1
The summary of HCQ efficacy.

HCQ efficacy	Species	Modulated molecule	Regulation	References
Antithrombotic Effects of HCQ				
Thrombosis inhibition	Human	arachidonic acid	Interference with arachidonic acid release; Inhibition of the platelet aggregation; Reduction in the thrombus size	[22–27]
HCQ in Reducing Cardiovascular Disease Risk				
Atherosclerosis releasement	Human	ATM-Akt	Reduction in the propensity for cardiovascular disease	[31,32]
Cardiotoxic efficacy	Human	–	Induction of bradycardia, tachycardia, QT prolongation, atrioventricular block, and cardiomyopathy	[33]
HCQ in Regulating Glycemic Homeostasis				
Blood glucose levels reduction	Rat	–	Reduction in blood glucose levels; increases serum insulin concentrations	[34]
Blood glucose levels reduction	Human	Kir6.2	increases insulin secretion in pancreatic β-cells	[36–38]
HCQ in Regulating Lipid Homeostasis				
Blood lipid levels reduction	Human	–	Reduction in total cholesterol and low-density lipoprotein levels	[40,41]
Blood lipid levels no significant change	Human	–	The effect of HCQ on lipid levels may be related to HCQ concentration	[42]
HCQ in Reducing disease activity and Preventing disease flare				
disease activity reduction	Human	–	–	[43,44]
HCQ in Ensuring protection for both patients and fetuses during pregnancy				
The prevention of fetal death and the reduction in the incidence of pathological pregnancies.	Rat	aPL	–	[45]
lower disease activity during pregnancy	Human	–	the benefit of HCQ during pregnancy is more symptom relief than an alteration in the underlying pregnancy pathology associated with SLE.	[46]
The prevention of fetal death and the reduction in the incidence of pathological pregnancies.	Human	–	–	[47]
HCQ in Autophagy and Metabolism				
Impede autophagy	Human	–	affecting autophagosome formation, maturation, and lysosomal degradation	[48,49]
45modulate metabolic pathways	Human	–	regulating autophagy, glucose metabolism, and lipid metabolism.	[36–38, 40–42,50]

4.7. HCQ in autophagy and metabolism

HCQ has garnered widespread attention for its ability to inhibit autophagy, which is a cellular process crucial for maintaining homeostasis. This antimalarial drug is recognized for its multifaceted effects on the autophagic pathway, affecting autophagosome formation, maturation, and lysosomal degradation [48,49]. Studies have suggested that HCQ modulates autophagy by inhibiting lysosomal function, thereby impeding the fusion of autophagosomes with lysosomes [54]. This interference leads to the accumulation of autophagic vesicles, contributing to altered cellular processes. Beyond its canonical role, HCQ's impact on autophagy extends to various signaling pathways involved in cell survival and death [55,56].

More importantly, HCQ plays a pivotal role in modulating various metabolic pathways, including energy metabolism and nutrient absorption. This is achieved through autophagy process, ensuring normal physiological functions of the body [50]. Meanwhile, HCQ is intricately linked to glucose and lipid metabolism, suggesting its potential to alleviate metabolic disruptions [36–38,40–42]. These findings offer broad prospects for the future clinical application of HCQ.

5. Blood concentrations of HCQ and disease outcomes in SLE

5.1. HCQ blood concentrations: variability and influencing factors

Currently, our understanding of the dose-exposure/response relationship associated with HCQ remains limited. Despite taking the same dose of medication, there are considerable variations in HCQ blood concentrations among individuals [57]. Chinese patients receive an average HCQ dose of 305.66 ± 77.00 mg/day exhibit a median blood concentration of 541.82 ng/mL, ranging from a minimum of 205.99 ng/mL to a maximum of 1936.46 ng/mL [58]. Blood concentrations of 1017 ± 532 ng/mL were measured in SLE patients who received a 400 mg/day dose of HCQ by Costedoat-Chalumeau et al. [59]. A study on the population pharmacokinetics of HCQ in patients with cutaneous and systemic lupus erythematosus conducted by Japanese researchers showed that different doses (200–400 mg/day) resulted in whole-blood concentrations of 462.0–942.7 ng/mL. Furthermore, the data for HCQ in plasma showed greater variability compared to whole-blood data, and measuring HCQ concentrations in whole blood rather than plasma is a better choice [60]. Likewise, a study evaluating HCQ concentrations in the whole blood, plasma, and serum of patients with SLE found that whole-blood monitoring provided higher accuracy [61], supporting the viewpoint of Japanese researchers. Moreover, a key factor influencing individual concentration differences may be the genetic polymorphism of HCQ-metabolizing enzymes. HCQ is primarily deacetylated by hepatic cytochrome P450 enzymes [62], and studies by Chinese scholars have shown that genetic polymorphisms of CYP3A5*3, CYP3A4*18B, and CYP2D6*10 in patients with SLE are associated with HCQ blood concentrations [63], explainingthe fluctuations in blood concentrations among patients taking different doses of HCQ.

5.2. Correlation between HCQ blood concentrations and disease activity

Multiple domestic and international studies have consistently demonstrated a positive association between the effectiveness of HCQ and its blood concentration in the treatment of SLE. Inadequate HCQ concentration is associated with higher SLE disease activity and serves as a strong predictor of disease worsening [59]. Patients who reduce or discontinue HCQ treatment are at an increased risk of disease flare-ups compared to those who maintain HCQ therapy [64]. An effective reference range for HCQ blood levels, 750–1200 ng/mL, was associated with 71 % lower odds of active lupus [44]. Among childhood-onset SLE patients with HCQ blood concentration ≥750 ng/mL, 87.6 % had inactive SLE [65]. We reckon the HCQ blood concentration higher than 750 ng/mL can effectively reduce SLE activity. However, in a prospective study, the blood concentration limit for HCQ to cause damage to other organs was 500 ng/mL. Compared with the therapeutic group (≥500 ng/mL), the subtherapeutic HCQ concentration (<500 ng/mL) was associated with the development of new-onset LN and had significant associations with disease activity and cumulative organ damage in SLE patients over time [66]. However, high blood concentrations of HCQ may lead to other toxicities, which are discussed later. Therefore, the correlation between blood concentration and disease activity and complications still needs to be further explored.

5.3. Adherence, therapeutic thresholds, and disease outcomes

Foreign researchers have suggested that HCQ levels below 500 ng/ml could be defined as poor compliance, as patients below this baseline demonstrate significantly increased lupus activity [66]. Durcan et al., on the other hand, propose that an HCQ blood concentration above 500 ng/mL can be considered a critical threshold for effectiveness and reflects better patient compliance [67]. In a 6-month follow-up study of 143 patients with SLE, Costedoat et al. demonstrated that HCQ concentration was the sole predictive indicator for acute exacerbation (OR = 0.4, 95%CI = 0.18–0.85, P = 0.01). Additionally, according to the receiver operating characteristic curve, a HCQ concentration of 1000 ng/ml corresponded to a negative predictive value of 96 % for the absence of lupus flares [59]. For patients with LN, maintaining a HCQ level above 600 ng/mL as a target may reduce the probability of kidney disease recurrence [68]. Based on these studies, some scholars have proposed that the threshold of 1000 ng/mL provides an optimal balance between sensitivity and specificity, suggesting the use of 1000 ng/mL as the target HCQ concentration for patients with SLE [69].

Importantly, Costedoat-Chalumeau et al., modified the HCQ dosage for patients who failed to attain a blood concentration of 1000 ng/mL to achieve the desired target concentration based on their own research. They continued to follow these patients for seven months and found that throughout the follow-up period, adjusting the HCQ dosage did not reduce SLE flare-ups [70]. This implies that the 1000 ng/mL threshold may not accurately reflect the therapeutic concentration of HCQ. Currently, there is considerable debate

surrounding the optimal concentration for HCQ treatment, and clinical monitoring of HCQ blood levels is conducted frequently. Consequently, it is imperative to conduct more comprehensive large-scale prospective studies to furnish substantial evidence for evidence-based medicine. In Table 2, we summarize the relationship between HCQ blood concentration and disease outcomes in SLE patients.

6. HCQ side effects

Although HCQ is generally regarded as safe, several adverse reactions have been reported. Gastrointestinal discomfort was the most common, while allergic reactions were rare. Rarer adverse reactions include cardiomyopathy, cardiac conduction defects, neurotoxicity, hematologic suppression, and excessive skin pigmentation [72]. Ocular adverse effects are the most relevant and concerning among all HCQ adverse reactions associated with HCQ in clinical practice. The primary manifestation of HCQ is retinal toxicity, which clinically presents as central vision loss, peripheral vision disturbances, later-stage night vision blurriness, and partial loss. The main mechanism of HCQ retinal toxicity could be attributed to its binding with melanin in the retinal pigment epithelium (RPE), causing damage to the extrafoveal cone cells. It inhibits lysosomal activity in the RPE, reduces the phagocytic activity of shed outer photoreceptor segments, and leads to the accumulation of outer segment fragments. In response, pigmented RPE cells migrate to the outer nuclear and outer plexiform layers of the retina, resulting in irreversible photoreceptor loss and RPE atrophy [73].

A meta-analysis conducted by Yam and Kwok on HCQ ocular toxicity studies published between 1960 and 2005 revealed that retinal changes caused by HCQ were exceedingly rare, with only 12 out of 4415 patients developing retinal lesions [73]. The introduction of more accurate screening techniques in contemporary clinical research has led to a gradual increase in the reporting rate of ocular toxicity. Melles et al. conducted a retrospective case-control study on 2361 patients who had been continuously using HCQ for at least 4 years. Retinal evaluations were performed through visual field testing or spectral-domain optical coherence tomography. The final data indicated an overall incidence rate of 7.5 % for HCQ retinal toxicity. However, during the initial 2 years of usage, the incidence rate of retinal toxicity remained below 10 %, which increased to nearly 20 % after 20 years of use. This increase in the incidence rate was correlated with both the dosage and duration of HCQ administration [74]. Based on this study, the American Academy of Ophthalmology revised its dosage recommendations in 2016, lowering the maximum daily dose of HCQ from 6.5 mg/kg/d (as of 2011) to less than 5.0 mg/kg/d [75].

However, the association between the blood concentration of HCQ and retinal toxicity remains a controversial and ongoing debate. A previous study [76] confirmed that higher blood concentrations of HCQ could serve as a predictor of subsequent retinal damage caused by HCQ. However, research by Lenfant et al. [77] indicated, through both univariate and multivariate analyses, no association between blood concentration and retinal toxicity. These discrepant findings may arise from the lack of consensus on the definition of retinal lesions. Further research is necessary to investigate the relationship between HCQ blood concentration and retinal toxicity.

In addition to retinal toxicity, HCQ can lead to other severe side effects, including myopathy [78]. Casado et al. conducted a prospective study involving patients receiving CQ and HCQ. Muscle biopsy was conducted in cases where patients exhibited elevated levels of creatine kinase, lactate dehydrogenase, or aldolase. The observed prevalence of antimalarial-induced myopathy was 12.6 % [79]. The specific mechanisms underlying HCQ-induced myopathy are not yet fully elucidated. Lysosomal impairment is a critical mechanism involved. HCQ penetrates lysosomes and various intracellular vacuoles, which accumulates in its cationic form. This accumulation leads to a change in contraction, elevating the intravacuolar pH, thereby inhibites lysosomal enzyme activity. Consequently, this disruption hampers protein degradation, macromolecules assembly, and post-translational modifications, results in the accumulation of numerous vesicles filled with lipid and other cytoplasmic degradation products [80]. In contrast to the treatment of inflammatory myositis, the management of HCQ-induced myopathy involves discontinuation of the drug. Therefore, early detection and definitive diagnosis of HCQ-induced myopathy are crucial in clinical practice. For clinicians, vigilance is paramount when treating patients with a history of HCQ usage, especially in cases when muscle pain or elevated muscle enzyme levels are observed. Conducting a muscle biopsy can be a critical diagnostic tool in assessing the progression of the condition and providing valuable insights.

Table 2
The summary of the Blood Concentrations of HCQ and Disease Outcomes in SLE.

HCQ efficacy	HCQ Blood Concentrations	Study type	Sample size	References
71 % lower odds of active lupus	750–1200 ng/ml	Longitudinal cohort study	158	[44]
87.6 % inactive childhood-onset systemic lupus erythematosus	≥750 ng/ml	Prospective observational study	55	[65]
A higher incidence of newly developed lupus nephritis (LN)	<500 ng/ml	Longitudinal cohort study	338	[71]
Poor compliance, increased lupus activity	<500 ng/ml	Longitudinal cohort study	108	[66]
Better patient compliance	>500 ng/ml	Longitudinal cohort study	686	[67]
HCQ concentration was the sole predictive indicator for acute exacerbation; a negative predictive value of 96 % for the absence of lupus flares	= 1000 ng/ml	Follow-up study	143	[59]
The probability of kidney disease recurrence reduction	>600 ng/ml	Retrospective observational study.	171	[68]
Adjusting the HCQ dosage did not reduce SLE flare-ups	<1000 ng/ml	Prospective randomized, double-blind, placebo-controlled, multicenter study	573	[70]

7. Conclusion

The therapeutic efficacy of HCQ in the treatment of SLE is well-established. However, confirmation of the relationship between the HCQ treatment concentration and retinal toxicity requires larger prospective studies. Currently, there is a lack of uniformity in HCQ dosages and treatment durations across different regions of China, and clinical monitoring of hydroxychloroquine concentrations is infrequent. Therefore, conducting extensive clinical trials to establish a standardized and appropriate treatment regimen for the Chinese population. Building upon domestic and international literature as well as previous research, this study aims to investigate the impact of HCQ concentration on SLE disease outcomes, explore the safe and effective blood concentrations of HCQ in SLE treatment, and assess the correlation between hydroxychloroquine and retinal toxicity.

8. Limitations of the study

While the therapeutic potential of HCQ for SLE is compelling, there are still several potential factors of concern that may impact the interpretation and application of these findings. Firstly, the precise mechanisms of HCQ's action, particularly its immunomodulatory effects, are not fully understood, which may limit the predictability and optimization of HCQ's therapeutic effects. Secondly, there is an ongoing debate regarding the optimal therapeutic concentrations of HCQ. Variations in individual patient responses, potential drug interactions, and differing disease states may affect the optimal dosage, adding another layer of complexity to the clinical application of HCQ. Lastly, the potential for retinal toxicity presents a significant concern. Although HCQ has established efficacy in treating SLE, its correlation with retinal toxicity is still under investigation. The long-term effects of HCQ use, particularly at high doses or over extended periods, are not yet entirely known. Further research is needed to better understand these effects and mitigate potential risks.

These limitations underline the necessity of continuing investigation into the therapeutic potential of HCQ. To maximize its therapeutic potential while maintaining patient safety, a deeper comprehension of its mechanisms of action, ideal dosing approaches, and long-term safety profile will be essential.

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This article does not contain any studies with human participants or animals performed by any of the authors.

Data availability statement

Data supporting article results reported in the article is in the published articles.

CRediT authorship contribution statement

Liu Peng-Cheng: Writing – original draft, Visualization, Software, Formal analysis, Conceptualization. **Lv Meng-Na:** Writing – original draft, Methodology, Formal analysis, Conceptualization. **Li Jian-Bin:** Visualization, Software, Methodology, Data curation. **Yu Shu-Jiao:** Visualization, Conceptualization. **Rui Wu:** Writing – review & editing, Visualization, Software, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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