Hydroxychloroquine: A double-edged sword (Review)

RONGXIU HUO*, CHENGCHENG WEI*, YANTING YANG*, JINYING LIN and XINXIANG HUANG

Department of Rheumatology and Immunology, Guangxi Academy of Medical Sciences, The People's Hospital of Guangxi Zhuang Autonomous Region, Nanning, Guangxi Zhuang Autonomous Region 530016, P.R. China

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Abstract. Hydroxychloroquine (HCQ) is an antimalarial drug that has historically been used to treat and prevent malaria. However, its mechanism of action has not yet been fully elucidated. HCQ affects various cellular and molecular pathways through different mechanisms. HCQ has also been shown to be a disease-improving agent for the treatment of rheumatic diseases, including systemic lupus erythematosus, antiphospholipid syndrome, rheumatoid arthritis and primary Sjögren's syndrome. Although generally considered safe, adverse reactions have been reported with the use of HCQ and clinicians should carefully monitor patients with rheumatism when prescribing these drugs. The purpose of the present review is to strengthen the clinical use of HCQ for autoimmune diseases while highlighting the adverse effects that may occur during treatment.

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Correspondence to: Dr Xinxiang Huang or Dr Chengcheng Wei, Department of Rheumatology and Immunology, Guangxi Academy of Medical Sciences, The People's Hospital of Guangxi Zhuang Autonomous Region, 6 Taoyuan Road, Qingxiu, Nanning, Guangxi Zhuang Autonomous Region 530016, P.R. China
E-mail: nnhxx_china@163.com
E-mail: wcc2399571052@163.com

*Contributed equally

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1. Introduction

The antimalarial drug chloroquine was the drug of choice for the treatment of malaria in the first half of the 20th century (1). Its derivative, hydroxychloroquine (HCQ), is widely used for the treatment of rheumatic diseases, especially immune-mediated systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis (RA) and primary Sjögren's syndrome (pSS), among others (2-5). HCQ has been used as an immunomodulatory drug to induce remission in autoimmune diseases. It also reduces adverse reactions caused by high-dose corticosteroids and other synthetic disease-modifying antirheumatic drugs (DMARDs). Therefore, HCQ is considered a steroid-sparing agent (6). HCQ is generally well-tolerated. After its clinical use as an antimalarial drug and DMARD, certain safety data have accumulated, but some adverse reactions may still occur. Reflecting on its positive and negative aspects and keeping these potential adverse effects in mind can help clinicians manage HCQ-related adverse effects more effectively.

2. Pharmacological characteristics of HCQ

HCQ is a hydroxylated analog of chloroquine with antimalarial and anti-inflammatory activities (Fig. 1). HCQ enters the cell in a protonated form and its concentration is inversely proportional to pH. Therefore, it accumulates in acidic organelles, including endosomes, lysosomes and Golgi vesicles, thereby increasing their pH (7). HCQ is administered in its sulfate form and has excellent oral absorption and bioavailability. HCQ is a weak base with a large distribution volume and long mean residence time (1,300 h). Of drug metabolites, ~62% undergo unmodified renal clearance, compared with 21% that undergo modified renal clearance. When HCQ passes through the liver, it is metabolized by cytochrome P450. After metabolism, 18% of HCQ is converted to desethyl chloroquine and 16% to desethyl HCQ. The final half-life is 45±15 days (7).

3. Relevant mechanisms of HCQ

The exact mechanism of action of HCQ in the treatment of rheumatic diseases is not fully understood. The possible mechanisms involved are as follows (Fig. 2): HCQ can block Toll-like receptors 7 and 9 in dendritic cells and inhibit lysosomes to increase intracellular pH, which facilitates appropriate antigen presentation (7). HCQ can also inhibit the

overactivation of B cells and reduce antibody production (8), thus inhibiting the overactivation of the classical complement pathway and reducing the production of the proinflammatory complement fragments C3a and C5a. In addition, it inhibits T cell overactivation and blocks T cell responses, reducing the production of proinflammatory cytokines, such as IFN-γ, TNF-α, IL-1 and IL-2 (9). HCQ can inhibit the binding of C5a to the C5a receptor on neutrophils, thus inhibiting the excessive activation of neutrophils and neutrophil extracellular traps (NETs) (10). In addition, HCQ inhibits platelet aggregation and reduces arachidonic acid production by activated platelets (7), thus reducing the incidence of thrombosis. These results indicate that HCQ has immunomodulatory and antithrombotic effects.

4. Application of HCQ in rheumatic diseases

HCQ can be used to treat various rheumatic diseases (Fig. 3) and has demonstrated substantial benefits. The present review referred to the recommendations of the European League Against Rheumatism (EULAR) guidelines for different autoimmune diseases to classify evidence as low, medium, or high (5).

Evidence for advanced levels of SLE and APS. According to EULAR, HCQ therapy is recommended for all patients with SLE, with a target dose of 5 mg/kg of actual body weight per day. HCQ is recommended for APS secondary to SLE and early use of HCQ is suggested for patients with recurrent miscarriages (11,12).

RA and Sjögren's syndrome (SS) as evidence of intermediate levels. In RA, as per EULAR guidelines, methotrexate (MTX) is usually the drug of choice. However, in cases of poor efficacy, traditional triple therapy [MTX + sulfasalazine (SSZ) + HCQ] and leflunomide (LEF) + SSZ + HCQ are more effective than monotherapy, highlighting the importance of HCQ (13). Regarding SS, the use of HCQ is recommended for the management of the central triad of symptoms (dryness, fatigue and pain) and for the management of systemic diseases, based on moderate evidence (14).

Dermatomyositis (DM) and osteoarthritis (OA) as low-level evidence. HCQ use is not recommended for these two diseases as per EULAR guidelines and the use of HCQ has been reported mainly in sporadic studies. In particular, in DM, HCQ use may be associated with an increased risk of HCQ-related rash (15).

HCQ and SLE. SLE is a chronic autoimmune disease that affects multiple organs and systems with varying incidence rates. In a systematic review of the global incidence of SLE from 2013 to 2016, the incidence ranged from 0.3-23.2 per 100,000 person-years (16). It mainly affects young women between the ages of 15 and 45. Thus, HCQ can be effectively used to treat SLE. It accumulates in lysosomes, where it normalizes the acidic environment by increasing pH levels. This interferes with antigen loading and presentation by class II major histocompatibility complex proteins. In addition, it partially interferes with the activation of Toll-like receptors by deoxyribonucleic acid and ribonucleic acid (7).

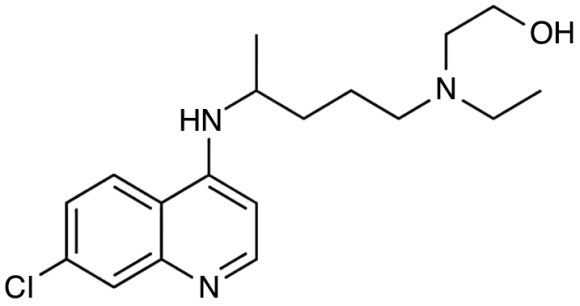

Figure 1. Chemical structure of hydroxychloroquine.

HCQ is associated with a reduced risk of thrombotic events in patients with SLE. Jung *et al* (17) compared 54 patients with SLE with previous thrombosis to 108 patients with SLE without thrombosis and found that HCQ was associated with a lower risk of thrombotic events. In a retrospective study of 1,946 patients with SLE in Taiwan, the authors found that patients with SLE who used HCQ in the first year of treatment experienced a small reduction in the risk of vascular events over an average follow-up period of 7.4 years [hazard ratio, 0.91, 95% confidence interval (CI) 0.71-1.15] compared with those who did not use HCQ during the same period (18). HCQ also offers preventive benefits. The risk of severe disease activity in patients with quiescent SLE is reduced by 57% after the use of HCQ (19) and disease activity and clinical symptoms worsen after drug withdrawal (20).

HCQ has advantages for the treatment of patients with SLE during pregnancy and lactation (21). Various autoantibodies are present in patients with SLE, such as anti-Ro/SSA and anti-La/SSB antibodies, which can cross the placental barrier and are associated with congenital atrioventricular blockade. Particularly, when the mother has a history of fetal involvement, the recurrence rate may increase from 13-18%. HCQ can reduce the incidence of SLE-related antibody involvement in neonatal hearts (22). Additionally, patients with SLE who continue to receive HCQ treatment have a lower risk of developing endometriosis (23).

Other studies enrolled 826 patients with SLE treated with HCQ. After >1 year of follow-up, 795 patients remained in the study (24). After adjusting for chronic comorbidities, long-term HCQ treatment was associated with a reduced risk of coronary artery disease in patients with SLE who had used HCQ for ≥318 days. HCQ not only provided cardiovascular protection but also reduced the risk of coronary artery disease (24,25). It did not increase the risk of arrhythmias or ventricular arrhythmias (26,27). In addition to reducing the risk of cardiovascular disease, HCQ also mitigates the risk of chronic kidney disease in patients (28).

HCQ is also associated with reduced mortality because of SLE. Shinjo *et al* (29) analyzed 1,480 patients with SLE and found that the longer HCQ was used, the more substantial the reduction in mortality. The mortality rate was 3.85 (95% CI 1.41-8.37) after 6-11 months of use. From 12-24 months, the mortality rate decreased to 2.7 (95% CI 1.41-4.76). After 24 months, the mortality was 0.54 (95% CI 0.37-0.77). For non-users, the mortality rate was 3.07 (95% CI 2.18-4.20). After adjusting for potential confounders, HCQ was associated

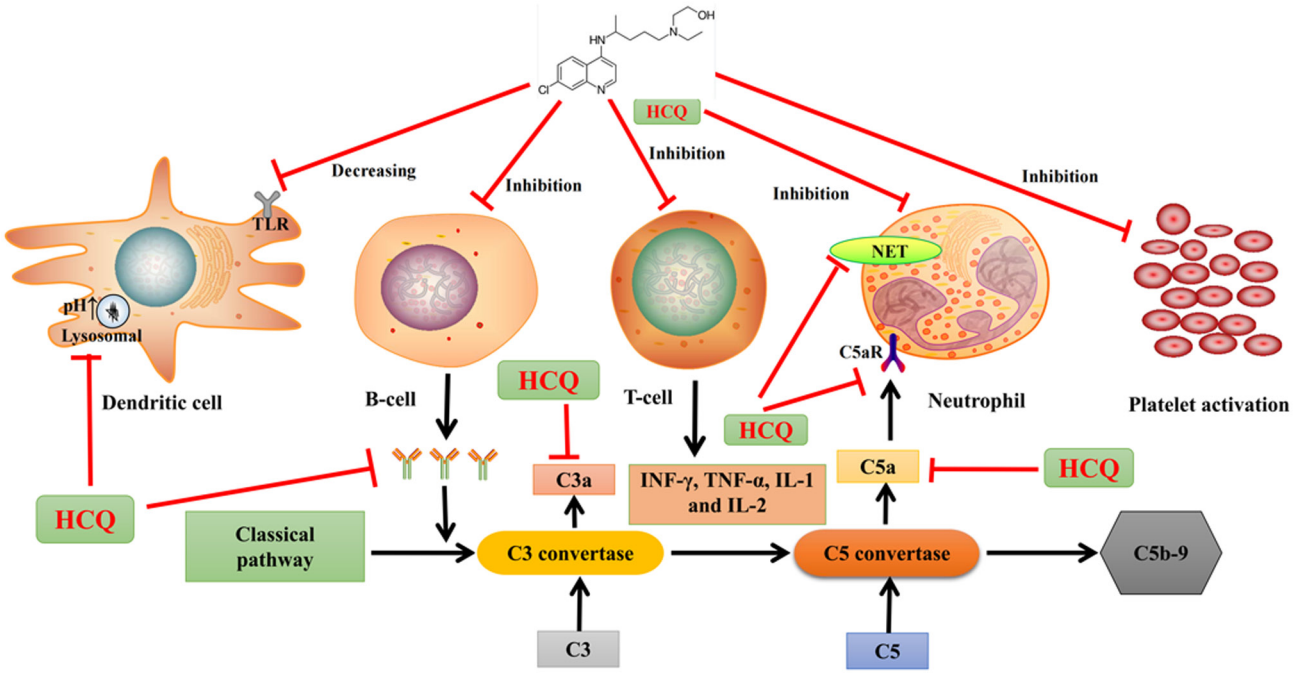

Figure 2. Proposed mechanisms of action of HCQ. HCQ, hydroxychloroquine; TLR, toll-like receptor; NET, neutrophil extracellular trap; C3, complement 3; C5, complement 5; IFN, interferon; TNF, tumor necrosis factor; C5aR, complement 5a receptor; pH, potential of hydrogen; IL, interleukin; C5b-9; membrane attack complex.

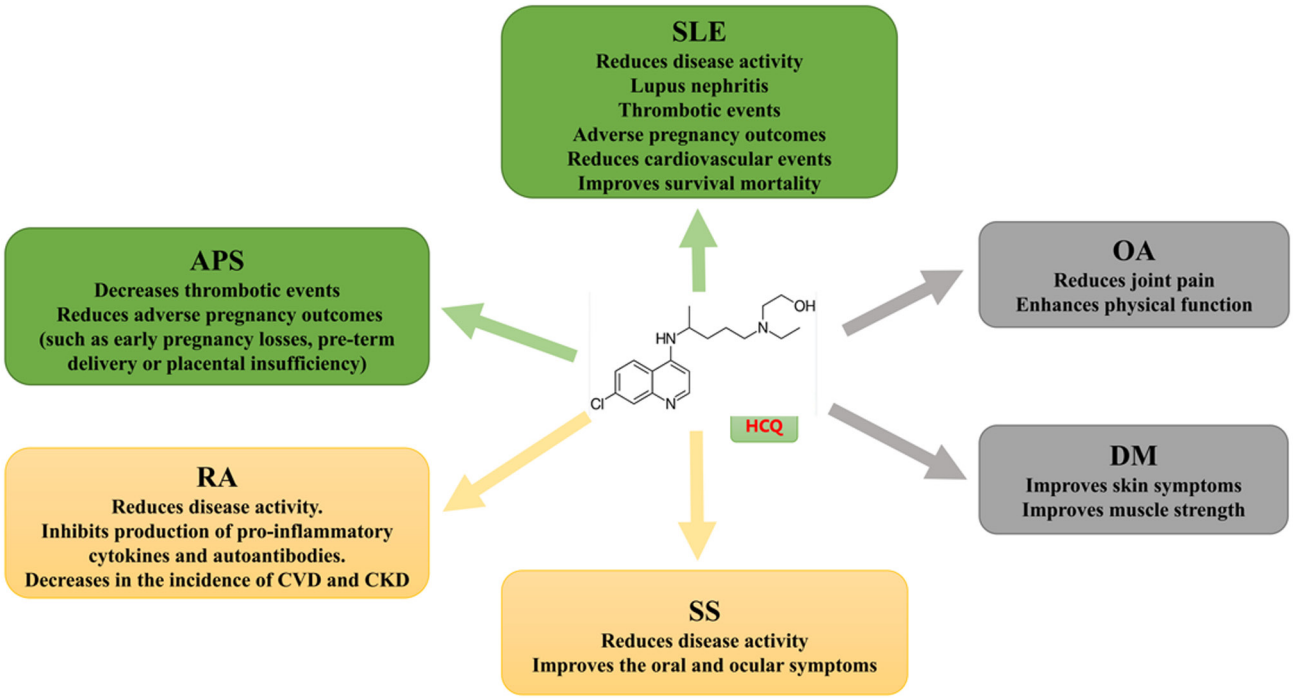

Figure 3. Application of HCQ in rheumatism. Different color codes are used depending on the level of evidence supporting the use of HCQ for each condition. Green; high level of evidence, yellow; moderate level of evidence, grey; low level of evidence. HCQ, hydroxychloroquine; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; OA, osteoarthritis; DM, dermatomyositis; RA, rheumatoid arthritis; SS, Sjögren's syndrome.

with a 38% reduction in mortality (hazard ratio, 0.62; 95% CI 0.39-0.99).

In a study conducted in the United States involving 30,086 patients diagnosed with SLE, HCQ was the most commonly used treatment (30). Corticosteroids, although effective, are associated with complications, such as high blood pressure and infections. In patients with SLE, regardless of background therapy, the addition of HCQ to immunosuppressants (such as mycophenolate, tacrolimus, cyclosporine, MTX and azathioprine) not only reduces disease activity but also allows for the gradual tapering of corticosteroid doses (31), thereby reducing the occurrence of adverse reactions.

HCQ and APS. APS is an autoimmune disease characterized by arterial and/or venous thrombosis, pathological pregnancies and persistently positive antiphospholipid antibodies (aPL). It usually affects young adults, most commonly those between the ages of 15 and 50 years. Primary and secondary APS are more common in women than in men, with a male-to-female ratio of ~1:3.5 for primary APS and 1:7 for secondary APS (32). The prevalence of catastrophic APS is low, accounting for less than 1% of all APS cases (33).

HCQ has demonstrated efficacy in APS and can play an antithrombotic role while reducing pathological pregnancy rates by inhibiting aPL-induced immune cell activation, platelet activation and complement hyperactivation. In mouse models of APS, HCQ reduces thrombosis, vascular inflammation and endothelial dysfunction (34). For the treatment of thrombotic APS, guidelines recommend that HCQ be used as an adjuvant therapy for APS-related thrombosis (35). Schreiber *et al* (36) treated 22 aPL-positive patients with HCQ for 3 months and found that soluble tissue factor levels decreased. However, there were no significant differences in other markers of thrombotic potential, such as annexin 5 activity and complement activation. However, HCQ can reduce C3a and C5a levels in the blood of patients with APS (37). HCQ can significantly reduce the percentage of NET-positive neutrophils and NET release by inhibiting autophagosome-lysosome fusion (38). Moreover, HCQ directly inhibits platelet activation and aggregation. The inhibition of NETs reduces platelet aggregation and significantly lowers circulating tissue factor levels (39), so as to prevent and treat APS related thrombus.

HCQ is increasingly regarded as an adjunct treatment in APS pregnancy. The EULAR guidelines recommend increasing heparin to therapeutic doses in patients with recurrent pregnancy complications, with HCQ considered during the first trimester (40). In a retrospective cohort study of 170 pregnancies involving 96 women, the live birth rates were 57% in the HCQ-untreated group and 67% in the HCQ-treated group, indicating an association with higher live birth rates (41). A multicenter trial spanning several European countries is currently evaluating the role of HCQ in patients with APS or persistent aPL. The trial aims to assess the effects of HCQ initiated before pregnancy and continued for 9 months on adverse pregnancy outcomes associated with aPL, including early pregnancy loss, preterm birth (<34 weeks) and placental insufficiency (42). Mar *et al* (43) reported a patient with a history of catastrophic APS who experienced fetal growth restriction in the sixth week of gestation, despite receiving therapeutic doses of aspirin and enoxaparin before pregnancy. After adding HCQ and intravenous immunoglobulin therapy, the pregnancy was carried to term successfully. These findings suggest that HCQ, in combination with other therapies, can prevent catastrophic APS and improve pregnancy outcomes.

HCQ and RA. RA is a common chronic autoimmune disease that mainly affects individuals aged 20-50 years and was estimated to affect >1.3 million individuals in the United States alone prior to 2016, leading to decreased quality of life and increased mortality (44). HCQ can be used as an adjunct therapy to DMARDs to control the progression of RA and achieve disease activity remission.

High levels of proinflammatory cytokines are associated with RA pathogenesis. HCQ can inhibit the stimulatory cytokines involved in RA pathogenesis, such as IL-1, IL-6, IL-12, IL-15, IL-17, IL-23 and B-cell activating factor. It also inhibits the production of proinflammatory cytokines and autoantibodies (8). Schapink *et al* (45) studied the efficacy of HCQ-MTX combination therapy compared with MTX monotherapy in 325 patients with early RA. After 6 months, disease activity and clinical symptoms improved more significantly in the MTX-HCQ combination therapy group. The use of HCQ for treating RA-related cardiovascular complications is beneficial for patients with RA. A large retrospective cohort study conducted over 12 years showed a 72% reduction in the incidence of cardiovascular diseases in patients taking HCQ (46). Recently, it was found that HCQ treatment for RA does not increase the risk of arrhythmias or ventricular arrhythmias (26). Additionally, the use of HCQ in patients with RA has been associated with improved renal function outcomes. A recent large observational cohort study showed a 36% reduction in the incidence of chronic kidney disease in patients with RA treated with HCQ compared with those not treated with HCQ (47). These benefits are observed in both the short and long term.

Currently, MTX is considered the first-line treatment for most patients with RA. However, not all patients respond well to MTX monotherapy, necessitating combination therapy with other drugs (48). In a study comparing the efficacy of patients with RA receiving MTX + HCQ and MTX + LEF (97 patients in each group), the remission rate in the MTX + HCQ group was higher than that in the MTX + LEF group (70.1 vs. 56.7%; P=0.048) (49). The median response times were 11 and 16 months, respectively. At the endpoint, more patients in the HCQ group achieved remission (46.8 vs. 32.5%; P=0.063) and maintained sustained low disease activity (53.2 vs. 38.6%; P=0.062) compared with those in the LEF group. Furthermore, more patients in the HCQ group were able to withdraw glucocorticoids (32 vs. 16.7%; P=0.053). The incremental cost-effectiveness ratio was also improved in the HCQ group (49). There was no significant difference in safety between the groups (49). This indicates that the efficacy and cost-effectiveness of HCQ combination therapy is improved compared with that of LEF. Regarding HCQ and biologics, studies comparing disease activity and other outcomes in patients with RA receiving MTX + HCQ + SSZ and those receiving MTX + etanercept for 48 weeks showed no significant differences in outcomes, such as disease activity, imaging progression, pain, health-related quality of life, or major drug-related adverse events, between the groups (50,51). Moreover, MTX + etanercept was found to be less cost-effective than triple DMARD therapy (51). Concerning other biologics, a randomized, blinded investigator-initiated study showed higher clinical response rates at week 48 for abatacept and peficitinib but not for tocilizumab compared with traditional regimens containing HCQ (52). Radiological progression was low and similar across treatment groups (52). Although the therapeutic effect of biologics may be improved compared with that of HCQ-containing regimens, they are relatively expensive, whereas HCQ-containing regimens are more economical (53). Additionally, Janus kinase inhibitors (JAKi) play an important role in the treatment of refractory active RA.

JAKi improves the signs and symptoms of RA in patients with an inadequate response to MTX, enhances physical function and inhibits imaging progression at week 12. However, JAKi has been found to be less effective than adalimumab (54). The use of JAKi increases the risk of infection, whereas the addition of HCQ reduces the incidence of serious adverse events (including severe infections and impaired liver function) and overall adverse events, thus extending survival (55). This indicates that HCQ plays an important role in RA treatment when combined with other drugs, enhancing efficacy and reducing adverse reactions.

HCQ and SS. PSS, with an estimated prevalence of 0.06% worldwide (56), is a chronic and systemic autoimmune disease characterized by focal lymphocytic infiltration of the exocrine glands, leading to dryness of the mouth and eyes, fatigue and pain. More than 80% of patients experience these symptoms, which can seriously affect their work and life (57). At the cellular level, the inhibition of autophagy by HCQ prevents the immune activation of different cell types. This inhibition reduces cytokine production and regulates CD154 expression in T cells, which may be an important mechanism in the treatment of SS (7).

HCQ treatment for pSS significantly improves ocular symptoms and prevents systemic damage (58,59). However, a randomized trial demonstrated that HCQ did not significantly improve symptoms compared with placebo during 24 weeks of treatment in patients with pSS (60). A meta-analysis by Wang *et al* (61) showed that in patients with pSS, there were no significant differences in dry mouth or dry eyes between the HCQ-treated and placebo groups. A recent meta-analysis revealed that HCQ significantly improved oral symptoms and related measures, including reductions in C-reactive protein, erythrocyte sedimentation rate and IgM and IgA levels. However, other clinical features, including ocular involvement, fatigue, joint lesions, pulmonary symptoms, neurological symptoms, lymphoid hyperplasia, renal dysfunction and experimental parameters, were not significantly improved (62). HCQ treatment for SS does not increase the risk of arrhythmias or ventricular arrhythmias (26). Currently, there are no drugs that can cure pSS. Relieving symptoms and preventing complications remain crucial. Therefore, rheumatologists must design and identify potential immunosuppressive therapeutic agents for the treatment of pSS.

HCQ and other rheumatic diseases. HCQ seems to improve skin manifestations in DM and reduce the use of corticosteroids for treating skin inflammation in DM (63). HCQ is beneficial not only for skin manifestations but also for systemic manifestations in patients with DM. In a retrospective case series, nine patients with youth-onset DM who had a poor response to previous systemic corticosteroid treatments showed improved skin rashes and significant improvements in proximal and abdominal muscle strength after 3 months of HCQ treatment (64). However, HCQ may aggravate inflammatory skin manifestations in juvenile DM (65).

In a randomized controlled trial of knee OA, the HCQ group (200 mg twice daily) showed reduced knee pain and improved physical function at the end of 24 weeks compared with the placebo group (66). However, a recent meta-analysis revealed that HCQ had only a small and statistically insignificant effect on reducing knee and hand OA pain and a modest effect on improving dysfunction compared with placebo. No improvement in quality of life was observed for hand OA (67). Therefore, HCQ should be administered to patients with DM and OA based on their specific conditions.

5. Major adverse events related to HCQ

There is some debate in the literature regarding the recommended HCQ doses. Generally, a dose of ≤6.5 mg/kg of ideal body weight is considered safe, provided that the HCQ dose is converted to the correct weight for height (68). This view was developed based on clinical trials showing that, owing to the low accumulation of HCQ in adipose tissue, it is often overprescribed in obese individuals, leading to a greater risk of side effects (68,69). In recent years, based on the actual body weight of patients, the preferred dose has been adjusted to ≤5 mg/kg (69). There is a risk of adverse reactions with long-term (usually refers to >1 year) use of HCQ, which is largely dependent on the daily dose relative to body weight (70). Recently, guidelines in the US and UK revised the recommended HCQ dose from 6.5 mg/kg per day to 5 mg/kg per day (71).

Although HCQ is generally effective, safe and well-tolerated, some adverse events have been reported (Fig. 4). The most common adverse events are gastrointestinal disorders, such as abdominal pain, nausea, vomiting and diarrhea. These problems may be related to HCQ-induced microbiota modifications (72). HCQ tablets can be ingested once or twice daily along with a glass of milk or a meal to reduce nausea. However, antacids should not be used as they impair absorption in the gastrointestinal tract. Gastrointestinal side effects are often reversible by adjusting the dosage or stopping the drug for a short time (73).

Cardiotoxicity. Cardiotoxicity is a serious adverse effect. Long-term HCQ use can lead to conduction disorders, structural heart disease, sick sinus syndrome, prolonged QT intervals, elevated cardiac biomarkers and heart failure (74-76). A systematic review of 127 patients, most of whom had SLE (n=49) or RA (n=28), was conducted. Of these patients, 39.4% received HCQ. Most patients were treated for a prolonged period (median 7 years, range 3 days to 35 years) with a median cumulative dose of 803 g and higher cumulative dose of 1,235 g. Conduction dysfunction was the main side effect in 85% of the patients. Other nonspecific adverse cardiac events included ventricular hypertrophy, hypokinesia, heart failure, pulmonary hypertension and valve dysfunction (77). When patients show symptoms of myocardial toxicity, screening and evaluation of cardiac biomarkers (including troponin and brain natriuretic peptide), cardiac MRI and endomyocardial biopsy are performed when necessary (60) to confirm the diagnosis of HCQ toxicity and guide treatment. Patients with autoimmune diseases should be screened for heart disease before initiating HCQ therapy. Standard tests, such as electrocardiograms and cardiac ultrasounds, are performed to rule out heart-related conditions. If a serious conduction block is detected, HCQ is not recommended. If cardiac disease develops during treatment, it is recommended to stop HCQ immediately. However,

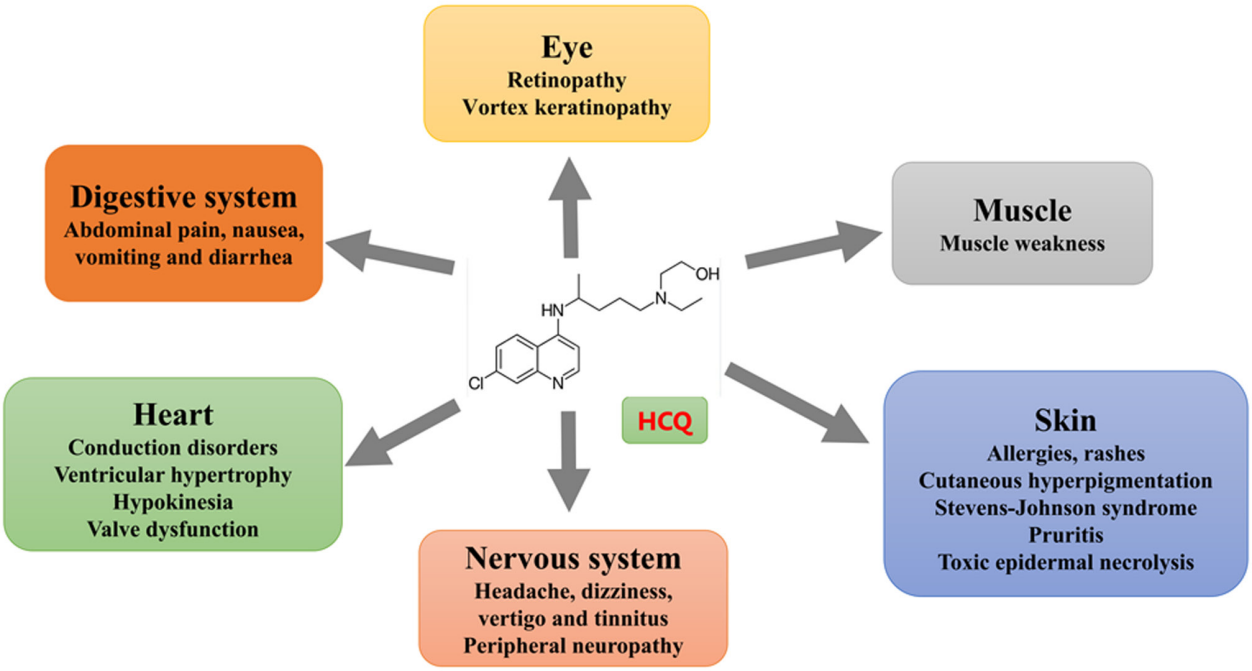

Figure 4. Adverse reactions related to HCQ. HCQ, hydroxychloroquine.

only 45% of patients recover fully after discontinuation (77). If the condition does not improve, additional cardiac evaluations should be conducted and appropriate medications prescribed if necessary (78). Therefore, cardiac monitoring is essential for patients treated with HCQ for rheumatic diseases.

Eye toxicity. HCQ can accumulate in the eye, damaging photoreceptor cells in the retinal pigment epithelium and causing progressive perifoveal degeneration, leading to retinopathy (79). This toxicity is associated with the duration of treatment. The 5-, 10- and 20-year toxicity risks for retinopathy at recommended doses were found to be <1, 2 and 20%, respectively. The risk of toxicity in individuals beyond 20 years of use increases by 4% annually (80). When the daily dose of HCQ exceeds 5 mg/kg/d, the risk of toxicity increases five to sevenfold (81). The earliest manifestation of this toxicity is the appearance of annular dark spots around the fovea (82), which gradually spread and may lead to severe vision loss or blindness. Typically, late-stage HCQ retinopathy is characterized by a ring of retinal depigmentation in the parafoveal region, commonly referred to as bull's-eye maculopathy (83).

Patients receiving daily doses of ≤1,000 mg (20 mg/kg) exhibit a 25-40% incidence of eye toxicity within 2 years, whereas patients on ≤5 mg/kg/d have a 2% risk of retinopathy over 10 years (84). For patients using HCQ over a lifetime, even although 6.5% discontinued treatment because of eye-related side effects, only 0.65% experienced confirmed retinal toxicity (85). A longitudinal study confirmed retinal changes in 5.5% of cases through eye examinations (86). In clinical practice, stopping HCQ is often necessary when toxicity is detected. However, even after discontinuation, retinal damage may progress in cases of moderate or severe retinopathy, possibly because of prior retinal pigment epithelial cell damage causing photoreceptor loss (87). Baseline retinal assessments are recommended before initiating HCQ therapy. Annual screening should begin after 5 years of therapy in the absence of major risk factors. If risk factors, such as advanced age or liver dysfunction, are present, annual screening should start earlier. Recommended tests include automated visual field assessment and spectral-domain optical coherence tomography. In some cases, additional tests, such as multifocal electroretinography, which provides objective information about the visual field, may be required, particularly for Asian patients (80).

Cutaneous toxicity. HCQ use may cause adverse dermatological effects of varying severity. Acute skin reactions, such as drug eruptions or rashes, may arise from allergies or nonspecific origins (88). Long-term use can cause pruritus and hyperpigmentation of the skin and oral mucosa. The prevalence of HCQ-induced pruritus is estimated to be <10%, whereas hyperpigmentation occurs in 10-20% of patients (89). A systematic review of HCQ's dermatological adverse effects, which included 94 articles, revealed that most cases involved patients with SLE (72%) or RA (14%). Adverse skin reactions were observed with cumulative doses ranging from 3 to 2,500 g. The most common dermatological side effects included drug eruptions or rashes (358 cases), hyperpigmentation (116 cases), pruritus (62 cases), acute generalized exanthematous pustulosis (27 cases), Stevens-Johnson syndrome or toxic epidermal necrolysis (26 cases), alopecia (12 cases) and stomatitis (11 cases) (74). Notably, acute pruritus and dermal depigmentation show racial preferences, primarily occurring in Black patients (90). Pruritus typically resolves completely upon discontinuation of HCQ (76,77), whereas hyperpigmentation may only partially resolve. If an allergic reaction occurs, the drug should be discontinued immediately. Regular skin assessments, including dermoscopy and skin biopsies, if necessary, are recommended during HCQ therapy to monitor for dermatological complications.

Neurotoxicity. Central nervous system toxicities include headache, dizziness, vertigo and tinnitus. A few cases of epilepsy associated with a reduced seizure threshold and psychosis have been reported, especially when HCQ is combined with cortisol (91). Nerve damage appears to be associated with perineural and Schwann cell damage (92). Pagès and Pagès (93) revealed demyelination associated with cytoplasmic inclusions within Schwann cells through nerve biopsies. Neurotoxicity is rare and pseudo-Parkinsonism has rarely been reported (94). Clinical trials have not demonstrated the relevance of systematic screening for chronic neuromuscular toxicity. However, if a patient exhibits nervous system changes, it is recommended that the peripheral nerves be properly examined using electromyography to determine whether there is a transmission disorder. Additionally, brain CT, MRI, or EEG can be performed to rule out central nervous system abnormalities.

Muscle toxicity. Studies have reported muscular toxicity associated with HCQ, which is defined by increased creatine kinase levels and compatible histological patterns (95,96). Patients with myopathy present with proximal muscle weakness without myalgia or elevated enzyme levels; respiratory failure may occur in severe cases (96). These conditions often improve upon drug discontinuation (97). Muscular toxicity is rare, with few reports of myositis, myasthenia, or limb weakness (94). During HCQ use, if muscular toxicity is suspected, it is recommended to confirm the diagnosis of HCQ-induced myopathy through electromyography and muscle biopsy. Additionally, dynamic monitoring of muscle enzyme levels should be conducted.

6. HCQ and coronavirus disease 2019 (COVID-19)

At the onset of the COVID-19 pandemic, the disease posed a deadly threat to humans and caused a health crisis via respiratory transmission among patients in Wuhan, China. On February 11, 2020, the virus was officially named COVID-19, caused by severe acute respiratory syndrome coronavirus 2, by the WHO (98). In addition to antiviral drugs, such as Remdesivir and Lopinavir/ritonavir, HCQ inhibits viral development (99). *In vitro* studies have shown that HCQ can inhibit viral entry, replication and glycosylation of the viral surface receptor angiotensin-converting enzyme 2 by increasing the pH of intracellular endosomes (100,101). The early stages of COVID-19 are mainly characterized by inflammation and cytokine storms can occur in severe cases, negatively affecting patient prognosis (102). Through its immunomodulatory and anti-inflammatory properties, as well as its ability to regulate proinflammatory cytokines, such as TNF, IL-1 and IL-6, HCQ may have beneficial effects in patients with COVID-19 (103). In a clinical trial in France, 20 patients with COVID-19 who received 600 mg/d of HCQ were compared with patients who did not receive HCQ. Nasopharyngeal swabs were tested daily for viral load. The authors found that 57.1% of patients treated with HCQ alone were virus-free, compared with only 12.5% of those not treated with HCQ ($P<0.001$), suggesting that HCQ monotherapy may reduce viral exposure (104). In another study, 80 patients with COVID-19 received HCQ (600 mg/d for 10 days), along with azithromycin (500 mg on day 1, followed by 250 mg daily for the next 4 days). On day 7, no virus was detected in the nasopharyngeal samples of 83% of patients. By day 5, 97.5% of respiratory samples tested negative for viral cultures (105). These results suggest that HCQ may have a virus-reducing effect. However, this study lacked a comparison with HCQ monotherapy. In a prospective randomized cohort study, patients were divided into two groups based on treatment regimen: 56 in the tocilizumab-HCQ group and 52 in the tocilizumab-remdesivir group. C-reactive protein was significantly decreased and the PaO_2/FiO_2 ratio was significantly increased in both groups after treatment (106). Ferritin, low-density lipoprotein and D-dimer levels were significantly decreased in the tocilizumab-HCQ group (106). Complications, including secondary bacterial infections (42.3%), myocarditis (15.4%) and pulmonary embolism (7.7%), occurred only after tocilizumab treatment (106). These findings suggest that HCQ combined with other drugs may be effective and safe for treating COVID-19. By contrast, in patients with severe COVID-19, adding HCQ to standard care led to marked clinical deterioration, an increased risk of renal insufficiency and a greater need for invasive mechanical ventilation (107). In patients hospitalized with mild-to-moderate COVID-19, HCQ alone or in combination with azithromycin did not improve clinical status over 15 days and was associated with prolonged QT intervals and elevated liver enzyme levels compared with standard care (108). Additionally, a multicenter open-label randomized controlled trial reported similar numbers of negative viral tests after 28 days in both the HCQ and non-HCQ groups (109). In summary, although some small studies suggest that HCQ is associated with shorter recovery times in COVID-19, several factors contribute to conflicting results, including small sample sizes, lack of randomized and placebo-controlled trials, single-center designs, low-quality methods, differing baseline characteristics and potential biases (110). Evidence regarding the effects of HCQ on all-cause mortality, disease progression, symptom resolution and viral load remains inconclusive and insufficient (111). The widespread use of HCQ exposes some patients to potential adverse effects, such as hematological complications and cardiotoxicity (including QT prolongation, ventricular arrhythmias and cardiac arrest) (112). Therefore, HCQ should be used to treat COVID-19 only in accordance with national, regional, or local treatment guidelines and patients should be closely monitored during therapy.

7. Conclusion

Further studies on the molecular and cellular mechanisms of HCQ have shown that it plays an immunomodulatory role by regulating molecular processes and cellular responses. These effects are achieved through direct or indirect suppression of inflammatory responses. HCQ is widely used in the treatment of rheumatic diseases and significantly improves quality of life in patients. In general, HCQ is considered safe. Although the incidence of side effects is low, they can still occur and negatively affect lives of patients. Most adverse effects are associated with prolonged use and extensive dose accumulation. Monitoring relevant indicators and conducting appropriate examinations are essential during HCQ therapy and timely intervention should be implemented to manage adverse reactions. HCQ has also been explored for treating

COVID-19 because of its antiviral and immunomodulatory properties. Initial data from small studies generated enthusiasm for its use. However, questions about HCQ's efficacy and safety have arisen, with some adverse effects being highlighted. The efficacy and safety of HCQ in treating COVID-19 should continue to be evaluated under appropriate supervision.

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Authors' contributions

RH, CW and YY wrote the manuscript. RH, CW and YY acquired and interpreted the data. RH conceptualized and designed the study. JL and XH reviewed the manuscript for intellectual content. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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