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Review

Hydroxychloroquine: From Pharmacological Profile to Neglected Adverse Reactions

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ABSTRACT

The effectiveness of **hydroxychloroquine (HCQ)** has been increasingly recognized in nearly all major fields of medicine. This ancient but still indispensable drug has a high bioavailability and a very long half-life due to its large volume of distribution. Although HCQ is generally considered a safe and well-tolerated drug, it can sometimes cause mild and reversible reactions that do not require treatment interruption such as gastrointestinal discomfort, photosensitivity and cutaneous findings. However, long-term treatment and high cumulative doses of HCQ may rarely lead to severe adverse reactions (including retinal, neuromuscular, cardiac and auditory toxicities) which are considered serious and require drug discontinuation but unfortunately not always reversible. The interaction of HCQ with other drugs (and vice versa) is also an important clinical issue. It has been emphasized that caution should be used in prescribing medications concurrently with HCQ, such as drugs that prolong QT interval and other arrhythmogenic drugs, drugs known to induce retinal toxicity, insulin or other antidiabetics, digoxin, cyclosporine, drugs used to treat myasthenia gravis and drugs known to lower the convulsive threshold. In this article, the pharmacological properties, clinically significant drug interactions as well as frequent and rare adverse reactions of HCQ have been reviewed in detail.

Keywords: hydroxychloroquine, antimalarial, pharmacokinetic, drug interaction, adverse reaction

INTRODUCTION

Hydroxychloroquine (HCQ), which was initially used to prevent or treat malaria, is a multi-functional drug due to its lysosomotropic, immunomodulatory, anti-inflammatory, anti-infective, anti-thrombotic, anti-tumoral (pronounced effects on autophagy and apoptosis processes) and beneficial metabolic (improved lipid profiles, decreased insulin resistance) properties. Owing to all these positive effects, it has been used successfully in the treatment of many autoimmune, rheumatological (e.g., systemic lupus erythematosus, rheumatoid arthritis), dermatological (e.g., discoid lupus erythematosus, porphyria cutanea tarda, lichen planus) and infectious diseases (e.g., human immunodeficiency virus, dengue virus) (1–6). In addition, there are still ongoing in vitro or in vivo investigations through various clinical, animal and/or laboratory studies to evaluate its effectiveness in some clinical situations particularly in the fields of oncology (as an adjuvant agent in advanced/metastatic tumors) and neurology (in multiple sclerosis, Alzheimer's disease) (6, 7). In recent times, this former drug has entered the spotlight again owing to the fact that it has been shown to be effective promisingly in the global coronavirus disease 2019 (COVID-19) pandemic (8).

HCQ (Plaquenil® tablet containing 200 mg HCQ sulphate) is considered a safe drug because its common adverse reactions are mild and include gastrointestinal discomfort, photosensitivity and skin rashes. Rarely seen but serious adverse events (such as retinal damage) are usually reversible, if detected early and HCQ treatment is discontinued. However, the use of high dose HCQ in some neurological and oncological diseases in recent phase studies has raised concerns in terms of significant acute toxic and sometimes irreversible reactions such as cardiotoxic and neuromuscular adverse events (9–12).

In this article, the pharmacological properties, clinically significant drug interactions as well as frequent and rare adverse reactions of HCQ were evaluated with a comprehensive literature review. The Medline literature database was searched through PubMed using the key words, individually and in combination: 'hydroxychloroquine', 'chloroquine', 'antimalarial', 'pharmacological properties', 'pharmacokinetics', 'drug interactions', 'safety', 'tolerability', 'medicine', 'adverse reaction' and 'toxic effect'. Only articles available in original or translated English were taken into account.

Pharmacological properties of HCQ

Pharmacokinetics

Chloroquine (C18H26ClN3) and HCQ (C18H26ClN3O), the most commonly used antimalarials, are organic compounds called aminoquinoline-derived drugs because they contain an amino group bound to the quinoline ring. HCQ has been produced by the addition of a β-hydroxy chain to the original chloroquine (CQ) molecule, and as a result it is more reliable and less toxic alternative agent than CQ. Although both drug molecules are dissolved in water, HCQ having a hydroxyl group is much more soluble (1). HCQ is administered perorally as a sulphate salt and is generally absorbed in the upper intestinal tract. After being absorbed almost completely and rapidly from the gastrointestinal tract with approximately 75% bioavailability, it is partially bound to plasma proteins and partially metabolised by cytochrome P450 (CYP) enzymes in the liver. The ultimate availability of the desired target effector molecule depends on the complex interaction between absorption, distribution, metabolism and excretion due to the wide distribution volume and long half-life of this drug. However, available data on the pharmacokinetics of HCQ are largely based on the studies of healthy individuals (6, 7).

HCQ is metabolised to N-desethylhydroxychloroquine, the main metabolite, through N-desethylation with CYP enzymes CYP2D6, CYP2C8, CYP3A4 and CYP3A5. There has been shown to be a relationship between blood N-desethylhydroxychloroquine levels and the effectiveness of HCQ treatment (7). The delay time between oral absorption of HCQ sulphate and its measurement in the blood has been reported to be about 0–0.85 hours (average 0.43 hours). It can distribute to aqueous cellular and intercellular compartments, resulting in long mean residence times (~1.300 hours, a long half-life of approximately 50 days). HCQ binds strongly to melanin and can deposit in melanin containing tissues such as the skin and the eyes, which might explain HCQ-induced pigmentation and HCQ retinopathy. It can also cross the blood-brain barrier. HCQ is excreted by the kidney and liver, and partly by feces. Only small amounts are excreted through the biliary and secretory system (by sweat and saliva). Since the renal elimination is the main excretion route and the drug is a weak base, its excretion from the body can be enhanced by the acidification of urine (6). HCQ, which accumulates in the tissues especially in long-term treatments, tends to reach higher concentrations in the brain, muscle, skin, heart and liver than in the blood. Therefore, it has been suggested that tissue concentrations rather than blood concentrations may be related to the efficacy and adverse reactions of this drug (7).

Drug interactions with HCQ

The interaction of antimalarial drugs with other drugs (and vice versa) is also an important clinical issue. Both CQ and HCQ can interfere with other medications because they are substrates of CYP450 enzymes, which are responsible for the metabolism of multiple drugs. In other words, CQ/HCQ can alter the pharmacokinetic properties of other drugs, thereby causing an increase or decrease in their bio-availabilities, efficacies and adverse effects. It has also been showed that other drugs may affect antimalarial drug pharmacokinetics (7, 12).

Most drug interactions have been observed with the structurally related CQ use, but cannot be ruled out for HCQ. It is important to remember that some medicinal products create a serious threat and others require special attention, as opposed to the common view that HCQ has lower toxicity and fewer drug-drug interactions compared to CQ. In this context, currently existing literature data on HCQ and other drug interactions are very limited; however, they have been listed together in most publications as drug interactions associated with CQ/HCQ (7,11–15). Similarly, in this review, significant drug interactions with CQ/HCQ have been presented in Table 1. Based on this table, caution should be used in prescribing medications concurrently with HCQ, such as drugs that prolong QT interval and other arrhythmogenic drugs, drugs known to induce retinal toxicity, insulin or other antidiabetics, digoxin, cyclosporine, drugs used to treat myasthenia gravis and drugs known to lower the convulsive threshold (11–15).

Although it has been suggested that smoking interferes with the bioavailability of HCQ in many studies, a recent study did not find a relationship between smoking status and the efficacy and plasma levels of HCQ (16, 17). There are no contraindications or specific warnings with regard to live vaccines because of the fact that HCQ is not an immunosuppressive drug. Similarly, inactivated vaccines show no restrictions in effectiveness (11). However, if a rabies vaccine is required, it has been recommended to stop or discontinue HCQ due to the possibility of decreased antibody response (12).

Safety and possible adverse reactions of HCQ

In addition to the lack of clear definitions regarding the minimum dose required for clinical efficacy and which doses are toxic in HCQ treatment, unknown dose-response relationships of this drug can create difficulties in clinical practice. However, the CQ and HCQ compounds, which have been in clinical use over the past six decades, have shown excellent safety profile with long-term good tolerance, not only in the general population but also in some special conditions including kidney failure and pregnancy (6). Although reduced drug clearance in chronic kidney disease leads to increased (and potentially toxic) concentrations of HCQ, current guidelines do not include a recommendation to reduce the dosage of HCQ in patients with chronic kidney disease (18, 19). However, in SLE patients with renal dysfunctions, the consensus group recommends a readjustment of HCQ doses only for a GFR of <30 mL/min (11). In general, HCQ is considered safe to use during pregnancy and lactation. Despite the initial concerns about HCQ crossing the placenta and the presence of drug-related pigmentations in fetal tissue, this compound is not considered to have any significant toxic effects on the fetus (20–22). Current guidelines strongly recommend continuing HCQ treatment during pregnancy in patients with autoimmune disease. Continuing HCQ treatment after delivery also has the advantage of preventing disease exacerbations in mothers (23). It has been demonstrated that the use of HCQ during pregnancy reduces the risk of preterm delivery and neonatal congenital heart block, especially in the presence of anti-Ro antibodies (24, 25). In a systematic review and meta-analysis evaluating reproductive outcomes following HCQ use, Kaplan et al. found

Table 1. Significant interactions of chloroquine/hydroxychloroquine with other medications

Drugs interacting with CQ/HCQ	Major interactions	Results/Recommendations
Digoxin (7,10,12,13)	HCQ inhibits digoxin metabolism, increasing its plasma levels by fourfold.	Increased bioavailability of digoxin and high risk of toxicity Serum digoxin concentrations should be closely monitored during CQ/HCQ treatment.
Metoprolol (7,10,13)	HCQ influences the levels of metoprolol by competing for the same CYP2D6 enzyme and prevention of its metabolism.	Increased plasma concentrations and the bioavailability of metoprolol
Anticonvulsants (11,12)	CQ/HCQ can disrupt the activity of anticonvulsant drugs and lower the convulsive threshold.	CQ/HCQ interferes with neuromuscular transmission and therefore should not be used in patients with disruption of neuromuscular transmission via predisposing conditions or secondary to medications.
Mefloquine/other drugs known to lower the convulsive threshold (13)	HCQ can increase the proconvulsant activity of other drugs that lower the convulsive threshold	HCQ can lower the convulsive threshold Co-administration of HCQ with these drugs may increase the risk of convulsions
Neostigmine/Pyridostigmine (11,12)	HCQ weakens the action of neostigmine/pyridostigmine	These drug interactions may considerably complicate the therapy of myasthenia gravis with a significant intensification of symptoms.
Drugs that prolong QT interval and other arrhythmogenic drugs (7,12,14)	HCQ prolongs the QT interval and should not be administered with other drugs that have the potential to induce cardiac arrhythmias. There may be an increased risk of inducing ventricular arrhythmias if HCQ is used concomitantly with other arrhythmogenic drugs, such as amiodarone, azithromycin or moxifloxacin.	Especially concurrent use of HCQ and amiodarone is absolutely contraindicated due to a high risk of severe cardiac rhythm disturbances.
Tamoxifen (7,15)	Concomitant use of tamoxifen with HCQ increases the risk of eye toxicity due to the synergistic inhibition of lysosomal enzymes in retinal epithelial cells.	Concomitant use of HCQ with drugs known to induce retinal toxicity such as tamoxifen is not recommended. According to the ophthalmology recommendations, the combined use of tamoxifen with CQ/HCQ should be limited to six months.
Insulin/other antidiabetics (11,12)	HCQ may enhance the effects of a hypoglycemic treatment.	Total daily dose of insulin or other antidiabetic drugs may need to be reduced to prevent severe hypoglycemia.
Ampicillin (12,13)	HCQ significantly reduces the bioavailability of ampicillin.	An interval of at least two hours between intake of ampicillin and HCQ should be observed.
Methotrexate (7,10)	HCQ can reduce the gastrointestinal absorption of methotrexate through local pH changes.	HCQ reduces the bioavailability of methotrexate. This effect may also reduce the risk of acute hepatotoxicity associated with methotrexate.
Cyclosporine (7,10,11).	HCQ can cause a sudden increase in serum cyclosporine level	HCQ increases the risk of side effects of cyclosporine, especially with concurrent increased nephrotoxicity. Close monitoring of serum cyclosporine level is recommended and, if necessary, HCQ should be discontinued.
Antacids (PPI, etc.), kaolin/ pectin, cholestyramine (7,10,13)	Some agents that increase the pH of the gastric acid may also reduce the oral absorption and oral bioavailability of CQ/HCQ.	The intake of these medications should not be within four hours of CQ/HCQ treatment.
Cimetidine (13)	Cimetidine can inhibit the metabolism of CQ/HCQ, increasing its plasma level.	Bioavailability of CQ/HCQ is enhanced by cimetidine. Concomitant use of cimetidine with CQ/HCQ should be avoided.

CQ: chloroquine; **HCQ:** hydroxychloroquine; **PPI:** proton pump inhibitors

that prenatal exposure to HCQ for autoimmune diseases did not appear to increase the risk of adverse pregnancy outcomes except spontaneous abortion rate, which result might be associated with the underlying disease activity (26).

HCQ, which is generally well tolerated drug, can sometimes cause reactions that are not serious and do not require treatment interruption (e.g., gastrointestinal reactions, cutaneous findings). However, it can rarely lead to severe adverse reactions (such as retinal, neuromuscular and cardiac toxicities) which are considered serious and require drug discontinuation but unfortunately not always reversible (9, 11, 18). Among them, the risk of retinopathy with prominent irreversible pigmented change is the most obvious adverse effect and is the main limiting factor for chronic use of HCQ (6, 12, 15).

Among the adverse reactions associated with HCQ, the most common and early symptoms are gastrointestinal effects such as nausea, vomiting, stomach pain, diarrhea, anorexia and weight loss. Less often, patients may experience anorexia, heartburn,

abdominal distension and high transaminases. Although case reports related to HCQ-induced hepatotoxicity are very rare, care should be taken in the case of pre-existing liver disease. No specific hepatic dose adjustment guidelines are available, but it has been generally recommended to use a more conservative dose in the presence of liver disease (11, 27). It should be remembered that there is a risk of acute hepatitis, even at recommended dosages of antimalarial drugs, in patients with pre-existing porphyria cutanea tarda (12, 13).

Skin rashes associated with HCQ are generally rare and have been reported in about 10% of patients treated (27, 28). In a systematic review characterizing the adverse dermatologic effects of HCQ, it has been mentioned that 94.4% of those are cutaneous reactions (most often morbilliform drug eruptions, followed by hyperpigmentation and pruritus) (29). Less frequently, some changes associated with skin appendages and mucous membranes (such as hair loss, stomatitis and melanonychia) may also be seen (29–33). Although it is not common in clinical practice, HCQ may exacerbate the pre-existing psoriasis. Moreover, the use of HCQ has rarely been associated with various cutaneous reactions such as urticaria, eczematous eruptions, photosensitivity, erythema multiforme, erythema annulare centrifugum, exfoliative dermatitis, and widespread severe reactions (widespread acute generalized exanthematous pustulosis, erythroderma, drug rash with eosinophilia and systemic symptoms, Stevens-Johnson syndrome/toxic epidermal necrolysis) (27, 29, 34, 35). Cutaneous hypersensitivity reactions associated with HCQ have been reported more frequently in patients with dermatomyositis (27, 29). It is known that the detection of HCQ activity is relatively slow, typically within 2 or 3 months. Sometimes, it can take several months to achieve maximum effectiveness. Therefore, it may be difficult to determine whether early skin rashes that occur after the onset of oral HCQ are linked to HCQ treatment or an exacerbation of the pre-existing disease. Dermatologists should distinguish these conditions and make an appropriate decision in terms of the treatment (30). Mild skin rashes may regress without stopping the drug, or in some cases, HCQ may be restarted slowly after a temporary cessation (27). If early skin rashes are not severe and no reaction has been observed in other organs, oral HCQ can be continued under careful monitoring. In the presence of widespread severe reactions, widespread skin rash and/or severe irritation, HCQ should be stopped completely and alternative medication should be considered. The decision to stop and then restart HCQ treatment, except for severe reactions, should depend entirely on the patient's symptoms (30). Recently, Tal et al. reported that prolonged HCQ oral desensitization is an effective method (>90%) for overcoming mild to moderate late hypersensitivity reactions and this protocol enables safe re-introduction of a highly recommended treatment (28).

HCQ-induced hyperpigmentation of the skin and/or mucosa is uncommon and appears within 3 months to 22 years following the initiation of treatment (33). It has been primarily described in patients with SLE and in approximately 7% of them. Discrete or diffuse areas of brown or blue-gray discoloration generally affect the face, forearm and lower legs, and sometimes the palate, gingiva and nails (27, 31). Unfortunately, cutaneous hyperpigmentation may also persist permanently, similar to retinopathy. Spontaneous healing is usually slow or inadequate, and the Q-switched laser used in its treatment can only be partially effective (27). The exact reason underlying increased tendency to bruising and/or insufficient pigment absorption with the use of HCQ is unclear. When both hemosiderin and melanin are present in the dermis, bruising can facilitate the hypermelanosis process (32). A recent study by Bahloul et al. supported the hypothesis that ecchymosis, the use of platelet antiaggregants and oral anticoagulants may be the main predisposing factors to HCQ-induced pigmentation (31).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a contraindication for antimalarial treatment according to expert information, since hemolytic anemia has been reported in those with genetic G6PD deficiency in the literature (11). However, Mohammad et al. mentioned that there was no episodes of haemolysis among patients with G6PD deficiency when under HCQ treatment, suggesting that G6PD testing may not be required prior to treatment (36). Although the benefit of routinely controlling the G6PD status is uncertain and not recommended, a previous blood test in susceptible individuals may prevent this concern. Rare hematological adverse reactions such as agranulocytosis, aplastic anemia, leukopenia and thrombocytopenia have also been reported in association with HCQ (6, 10).

It is well known that the absolute contraindication for the use of antimalarials is retinopathy (11–13,15). The incidence of retinopathy increases with the cumulative dose of HCQ and the duration of treatment. According to a recent analysis of a large clinical database, it has been demonstrated that at doses of 4–5 mg/kg/day of the actual body weight, the risk of retinopathy with 10 years of treatment is less than 2% and increases to over 20% if the exposure lengthens to 20 years (37). The American Academy of Ophthalmology recently revised its guidelines and recommended limiting chronic HCQ treatment at doses of <5 mg/kg/day actual body weight or <400 mg/day (whichever is lower) to reduce the risk of retinopathy (15). When comparing with the previous daily limit of 6.5 mg/kg ideal body weight, it has now been demonstrated that the use of actual body weight is superior to ideal body weight when estimating toxicity risk. Various factors such as a drug dose of >5 mg/kg actual body weight per day, prolonged use of the drug (10–25 years), a high cumulative dose (above 600–1000 gram), stage 3–5 chronic kidney disease (GFR <60 ml/min; 50% drop in renal function increases risk of retinopathy by two-fold), history of retinopathy/maculopathy and co-medication with tamoxifen (>6 months) have been thought to increase the risk of developing retinopathy during HCQ treatment (38).

The risk of retinal toxicity associated with HCQ use may not be as low as previously thought. In literature, it has been reported that HCQ-related macular toxicity ranges from 0.1% to 9.4% (18). Unfortunately, it can cause permanent vision loss, which may continue to progress even after HCQ is stopped (39). Early damage is asymptomatic and indicates the necessity of screening at regular intervals. Changes in colour perception, reading difficulties, flashing lights or blurred and reduced vision should

immediately lead to further examinations. The pathophysiology of retinopathy induced by CQ derivatives involves binding of the drug to melanin in the pigmented epithelial layer, and then damage to the rods and cones. Less frequently, ocular toxicity of HCQ affects cornea and ciliary body (15). Multifocal electroretinogram, spectral field optical coherence tomography and fundus autofluorescence methods, which are used in the monitoring of retinopathy, have been shown to have better sensitivity than classical visual field examination. These tests have facilitated the detection of uncertain early changes of retinal pathologies such as thinning of the foveal photoreceptor outer segment, thickening of the retinal pigment epithelium, and loss of the macular ganglion cell-inner plexiform layer (6, 40). The current guidelines recommend combination of automated visual fields with at least one of these procedures (15). However, with the advent of such sensitive screening techniques, it has not yet been established whether there are significant improvements in clinical outcomes. We know that the risk of retinopathy is minimal when detected early, but it has been frequently emphasized that the prognosis worsens significantly after a decrease in central foveal thickness and prominence in the classic bull's eye lesion (38–41). According to the recommendations, basic fundus examination should be performed to exclude pre-existing maculopathy, and those who have been under treatment for more than five years (even on acceptable HCQ doses and without concomitant risk factors) should be screened annually with an automatic visual field test and retinal examination. However, screening should be performed earlier and more frequently (once a year) if risk factors are present (15).

Although most of the studies related to inflammatory diseases indicate that HCQ plays a vascular protective role, long-term HCQ treatment has been reported to induce serious cardiac disorders. Cardiotoxicity is rarely observed in the patients taking HCQ, but when it occurs it may be irreversible and life-threatening. This is a major concern in certain situations that require high doses and/or long-term treatment, but it is extremely rare to occur with chronic low-dose treatment (11, 14). Long-term treatment and high cumulative doses with HCQ trigger dysfunction of lysosomal enzymes, causing disruption in intracellular degradation processes and subsequent accumulation of metabolic products (glycogen and phospholipids). In the literature, HCQ-related cardiac disorders such as congestive heart failure, conduction disorders and cardiomyopathy (with hypertrophy and often restrictive physiology) have been reported. Third-degree atrioventricular block can be diagnosed many years before clinical signs of congestive heart failure (14). Demir et al. reported an unusual case of immune thrombocytopenia associated with HCQ use in the late period following open heart surgery (42). In case of acute toxicity developing with high dose administration of HCQ, ST segment depression, T wave inversion, QT interval prolongation, sick sinus syndrome and malignant ventricular arrhythmias can be observed in relation to blockade in sodium, calcium and potassium channels (14, 43). Discontinuation of the HCQ is sometimes insufficient to correct the toxicity and therefore a heart transplant may be the most suitable option in selected cases (44). Similar to recommendations for screening toxic retinopathy, clinicians should be aware of the potential iatrogenic effects and should perform electrocardiograms periodically to detect conduction disorders related to HCQ. Cardiotoxicity may occur even if the HCQ plasma dose is within therapeutic standards; therefore, detecting the plasma dose can not help diagnosis of possible cardiac disorders related to HCQ. It should be remembered that the diagnosis of cardiac toxicity associated with HCQ can be quite difficult, especially because underlying diseases such as systemic lupus erythematosus and rheumatoid arthritis often occur with cardiovascular symptoms. In the clinical diagnosis of HCQ-related cardiac toxicity, clinical history, cardiac biomarkers in serum (such as B-natriuretic peptide or troponin), electrocardiography, echocardiography and magnetic resonance imaging can help, but in the presence of multiple confounding factors, definitive evidence of cardiac toxicity can sometimes only be obtained with an endomyocardial biopsy (10, 11, 14).

Peripheral neuropathy-associated myopathy is a rare but possible adverse effect of long-term HCQ treatment. Although it resolves with discontinuation of the drug, recovery usually takes weeks due to the long-term elimination half-life of HCQ. Caucasian race and concomitant kidney failure are risk factors for the development of myopathy. HCQ-induced myopathy usually involves proximal muscles and may be associated with cardiac myotoxicity. The diagnosis is usually confirmed by electromyography and muscle biopsy. Muscle fiber atrophy is observed in skeletal muscles with characteristic bioptic features and vacuolar changes with curvilinear bodies (45). It has been mentioned by Tselios et al. that chronic use of antimalarials in patients with systemic lupus erythematosus may lead to an increase in creatinine kinase levels. This condition may continue asymptomatically in approximately two-thirds of patients but clinical myopathy can also develop in 2.5% of them (46). In the follow-up of HCQ-induced myopathies, basal serum creatinine kinase and lactate dehydrogenase levels are recommended to be repeated at intervals of 3–6 months (11). Although central and peripheral nervous system effects (e.g., diplopia, paresthesia/dysesthesia, dyskinesia, headaches, seizures, myasthenic syndrome) can be observed, psychological changes such as mood changes, irritability, nightmares, psychoses and confusion have often been identified with higher treatment doses of antimalarials than standard doses (10, 27). These psychiatric side effects usually occur within a few days after the beginning of treatment and improve after cessation of treatment. It has been emphasized that antimalarials should be used with caution in patients with psychotic disorders, as well as in patients with documented neuromuscular disorders such as myasthenia gravis (11, 12).

Rarely reported ototoxicity related to HCQ is characterized by temporary (reversible after discontinuation of the treatment) or permanent disturbance in auditory and/or vestibular function, mainly manifested by tinnitus, sensorineural hearing loss, and vertigo symptoms. Although its exact mechanism is yet not well established, ototoxicity has been suggested to be associated with the destruction of the cochlear sensory hair cells in varying degrees, a decline in neuronal population, change in supporting structures as well occurrence of atrophy of the stria vascularis as a

possible result of ischemia (47, 48). Antimalarial accumulation and long-term involvement in the melanocytes of the inner ear may also explain the late onset of the lesions (following several years of HCQ treatment) and their relationship with high cumulative doses (47). However, in only a few patients, HCQ-related ototoxicity has been reported to occur after relatively short periods of use (just a few months) and even at low doses. Therefore, physicians have been advised to inform patients about the ototoxic potential of HCQ, as well as to detect eventual ototoxic changes early and avoid possible irreversible damage by a long and regular periodic audiology evaluation (48).

According to observations in cancer studies, prescribed HCQ doses can reach up to 1200 mg per day. Despite high doses and even combination with other oculotoxic agents, no HCQ-associated serious adverse effects have been reported in these studies (5, 49). However, the treatment durations of oncological conditions are generally much shorter than rheumatic diseases, and therefore it should not be overlooked that the cumulative dose is generally lower in cancer patients than in rheumatic patients. Concerns about gastrointestinal, hemodynamic and cardiac adverse reactions are still ongoing and increasing gradually due to the high bioavailability and long elimination half-life of HCQ, which is generally used at higher doses in oncology applications. Therefore, the use of nanoparticle-based targeted drug delivery methods have been proposed recently to increase the delivery of the drug to the desired tissues and reduce the potential toxicity (5).

Recently, it has been suggested that the effect of autophagy, which plays an important role in cell development, differentiation, normal growth and immunity, is interestingly a double-edged sword for cancer cells (5). It prevents the accumulation of damaged proteins and organelles as a tumor suppressor, while also as a tumor promotor it facilitates tumor growth and aggressiveness by surviving microenvironmental stress. Fortunately, in a nationwide population-based cohort study, Mao et al. showed that the use of HCQ was not associated with an increased risk of cancer in patients with autoimmune diseases (50). Nevertheless, it is obvious that further investigations in well-designed studies and large well-defined cohorts are required before more clear conclusions can be drawn.

In summary, the effectiveness of HCQ has been increasingly recognized in nearly all major fields of medicine, including rheumatology, dermatology, haematology, oncology, cardiology and severe infectious diseases. Recent and ongoing clinical trials testing HCQ on new indications and challenging diseases are still receiving great attention. This safe and well-tolerated drug may sometimes cause mild and reversible reactions such as gastrointestinal and dermatological adverse events. However, long-term treatment and high cumulative doses of HCQ may rarely lead to serious adverse effects such as retinal, neuromuscular, cardiac and auditory toxicities which require drug discontinuation but unfortunately not always reversible. Therefore, clinicians should be aware of the pharmacological profiles, drug interactions and potential adverse reactions of this ancient well-known drug. In this context, the dosage and duration of HCQ treatment should be adjusted according to the clinical indication and adverse drug reaction profile.

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