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REVIEW

How toxic is an old friend? A review of the safety of hydroxychloroquine in clinical practice

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Abstract

Hydroxychloroquine (HCQ) and its close relative chloroquine (CQ) were initially used as antimalarial agents but are now widely prescribed in rheumatology, dermatology and immunology for the management of autoimmune diseases. HCQ is considered to have a better long-term safety profile than CQ and is therefore more commonly used. HCQ has a key role in the treatment of connective tissue diseases including systemic lupus erythematosus (SLE), where it provides beneficial immunomodulation without clinically significant immunosuppression. HCQ can also assist in managing inflammatory arthritis, including rheumatoid arthritis (RA). Debate around toxicity of HCQ in COVID-19 has challenged those who regularly prescribe HCQ to discuss its potential toxicities. Accordingly, we have reviewed the adverse effect profile of HCQ to provide guidance about this therapeutic agent in clinical practice.

Introduction

Hydroxychloroquine (HCQ) plays an important role in the treatment of connective tissue diseases (CTDs), particularly systemic lupus erythematosus (SLE),[1–3] and in rheumatoid arthritis (RA).[4] HCQ is a derivative of chloroquine (CQ); both were used initially as antimalarial agents as they interfere with the parasite's ability to degrade and detoxify host haemoglobin, and thus parasite replication.[5] HCQ has a better side effect profile and so is more widely prescribed than CQ. Most patients with SLE take HCQ at some stage, typically for around 6–7 years.[6] In SLE, HCQ confers well-documented clinical benefits including increased long-term survival, reduced cumulative steroid doses, protection against accrual of organ damage, reduction in thrombosis and pregnancy complications,[2,3,7] as well as less risk of developing polyautoimmunity.[8] HCQ may also improve cardiovascular risk profile – an important consideration in RA and SLE which are both associated with elevated cardiovascular risk.

The sometimes heated public debate around HCQ's toxicity in the context of potential treatment for coronavirus disease 2019 (COVID-19) provides an opportune moment to reflect on conventional views about its safety and tolerability. Accordingly, we summarise the evidence and provide clinical practice suggestions based on the experience of relevant specialty practitioners (Table 1).

Mechanism of action

Both HCQ and CQ have a long *in vivo* half-life (around 50 days),[9] reaching steady-state levels after 3 to 6 months.[10] Surprisingly, the mechanism of action of antimalarials in autoimmune disease is still incompletely understood,[9] but involves effects on both innate and adaptive immunity. HCQ can interfere with intracellular signalling downstream of toll-like receptors, including cytokine production and modulation of co-stimulatory molecule expression.[9] HCQ has been shown to inhibit the production of multiple cytokines including

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Table 1 Summary of frequency of reported adverse events with HCQ

Toxicity	Estimated frequency	Significance
GI disturbance: nausea, vomiting, diarrhoea or loose stool	7–37%	Inform patients. Usually does not require cessation and improves with time
Cutaneous hyperpigmentation	10–25%	Inform patient. Usually improves with discontinuation; depends on patient preference
Myopathy	1.3–12.6% Clinically significant disease uncommon	Infrequently requires cessation
Retinopathy	0.29–7.5% after 5 years Increasing risk with longer duration of therapy Transient diplopia may also occur on initiation	Usually requires cessation Consult with ophthalmologist, ideally retinal specialist Rare, consult with ophthalmologist
Conduction defects including QT prolongation and torsades de pontes	Rare; case report data	Consider QT monitoring in patients with known LQT or other risk factors (renal impairment, co-prescription of other QT-prolonging medications); consider baseline ECG for reassurance
Cardiomyopathy	Rare; case report data	Case-by-case
Neuropsychiatric symptoms	Rare; case report data	Case-by-case
Hypoglycaemia	Rare; case report data	Consider informing patients at risk of hypoglycaemia (e.g. insulin-dependent diabetes)
Serious cutaneous eruptions	Rare; case report data	Case-by-case
Oxidative haemolysis	Rare; no episodes in recent review of G6PD-deficient patients	N/A
Cytopenias	Rare; not with current dosing regimens	N/A
LFT derangement	Rare; case report data	Case-by-case

G6PD, glucose-6-phosphate dehydrogenase; HCQ, hydroxychloroquine; LFT, liver function; LQT, long QT interval; N/A, not applicable.

interleukin (IL)-1, IL-6, and IL-17, interferon alpha and gamma, and tumour necrosis factor alpha.[4,11,12] HCQ and CQ are weak bases and therefore raise intracellular pH, which can inhibit the formation of peptide–major histocompatibility complex protein complexes in cytoplasmic compartments, thus reducing stimulation of T cells by antigen-presenting cells.[13]

Ocular toxicity

HCQ can cause retinal damage. The classical pattern of advanced HCQ retinal toxicity is irreversible 'bull's eye' (central) maculopathy. The estimated prevalence of retinal toxicity varies significantly depending on diagnostic criteria, from 0.29[14] to 7.5% after 5 years of therapy[15] (Table S1). The most important risk factors are daily HCQ dose and duration of therapy (especially longer than 5 years).[14,15] HCQ is significantly renally excreted[16,17] and retinopathy is more frequent in those with impaired renal function.[15] HCQ blood levels may also be higher in those with renal impairment.[18] Tamoxifen therapy has also been associated with increased risk[15]; while tamoxifen can itself cause retinopathy, the reason for its potential synergism with HCQ is unknown. Underlying retinal or macular disease may confer increased risk,[19] or preclude adequate monitoring because of pre-existing retinal abnormalities.[20] Cumulative total doses of 800 g or higher confer increased risk,[14] though less accurate than an assessment based on weight-based daily dose and duration of use.[19] Guidelines aimed at preventing retinal toxicity recommend using less than 5 milligrams of HCQ per kilogram (mg/kg) of actual body weight per day[20] or less than 6.5 mg/kg/day of ideal body weight (typically, actual body weight is 25–30% higher than ideal body weight).[15] Actual body weight dosing at 5 mg/kg/day has been shown to reduce excess HCQ dosing, particularly in obese patients, in comparison to dosing based on ideal body weight at 6.5 mg/kg/day.[21] Age does not appear to significantly increase the risk of retinopathy independent of treatment duration.[14,15] Monitoring HCQ blood levels may help predict the risk of retinopathy[22] but is not routinely available.

The mechanism of retinal toxicity may have a genetic component[23] or reflect HCQ-induced alterations in photoreceptor metabolism.[14,19] Nonvisually significant corneal deposition can also occur.[24] In early retinal toxicity, patients can develop paracentral scotomata.[14,19] However, subtle early changes are often asymptomatic and only revealed by visual field testing.[19] Location of initial

retinal damage may vary between racial groups[25] – parafoveal distribution is more common in Caucasian patients, compared with a peripheral extramacular distribution (near the arcades) in Asian patients.[25] African American and Hispanic patients can develop a mixed pattern.[25]

Physicians who prescribe HCQ long term should refer the patient for ocular monitoring.[20] While the American Academy of Ophthalmology (AAO; USA) recommends a baseline eye examination within 1 year of commencing therapy,[19] this is not recommended in the most recent Royal College of Ophthalmologists (RCO; UK) guidelines.[20] The RCO cites two reasons for this change: first, only 4% of patients discontinue HCQ because of abnormal baseline eye testing, and second, many patients do not continue HCQ for 5 years and thus never reach a higher risk threshold for toxicity.[20] In contrast, the AAO recommends a baseline ophthalmologic examination within 1 year, including visual acuity, corneal/retinal examination with a dilated pupil and (optionally) colour vision testing (to detect preexisting colour-blindness).[19] The AAO does not recommend baseline visual field testing or spectral-domain optical coherence tomography (SD-OCT).[19]

Patients taking <5 mg HCQ/kg and without other risk factors (tamoxifen therapy, renal impairment or CQ use) are considered 'low risk' and age-appropriate ophthalmologic examinations are sufficient during the first 5 years of therapy, but patients with risk factors should be screened annually from commencement.[19,20] After 5 years of therapy with HCQ, all patients should be screened annually.[19,20] Screening aims to detect potentially reversible HCQ toxicity early, before any visual acuity is lost.[19] Automated visual field testing is a subjective, functional test that is widely available and recommended for all patients, although its accuracy depends on patient reliability. SD-OCT is also routinely recommended by both the AAO and RCO[1920]; it provides detailed imaging of the retina and can demonstrate thinning of photoreceptor layers. Widefield fundus autofluorescence (FAF) may detect early retinal pigment epithelial cell damage, prior to abnormality on SD-OCT. Multifocal electroretinography may be useful in those with persistent visual field defects but no structural defects on SD-OCT or FAF.[20]

Cardiac toxicity and QT prolongation

Clinically significant QT prolongation and cardiotoxicity with antimalarials are rarely seen in rheumatology practice.[26] Case reports describe conduction disorders (prolonged QT interval, AV block, intraventricular conduction delays), left ventricular hypertrophy (LVH) and heart failure,[26] as well as QT interval prolongation and subsequent torsade de pointes (TdP).[27,28] These findings have not been reproduced in prospective studies.[29]

There has been an explosion of concern regarding the risk of QT prolongation with the combination of high-dose HCQ (600-800 mg/day) and azithromycin for COVID-19.[30] Population-based studies suggest that a prolonged QT interval may occur in up to 8.7% of individuals over time in the setting of acute illness, electrolyte disturbance or QT-prolonging medications.[31] The frequency of clinically significant complications from QT prolongation in these clinical settings is unclear. In COVID-19 patients taking high-dose HCQ and azithromycin, very low/no incidence of ventricular arrhythmias or TdP has been described.[30] Prolonged QT can also occur with many commonly used medications, such as antiarrhythmics, some antimicrobials (e.g. macrolides including azithromycin, fluoroquinolones, antifungals and some antivirals), antidepressants, methadone, tamoxifen and antipsychotic medications.[32] Other risk factors include electrolyte abnormalities, renal failure, heart failure or ischemic heart disease. We could not find evidence that baseline or interval QT monitoring is recommended routinely when prescribing these medications, although caution is emphasised with known long QT syndrome. In a study of 681 patients with RA and SLE without clinical cardiovascular disease, HCQ did not predict prolonged QTc.[29] Nine of 681 patients taking HCQ had a QTc greater than 500 ms, with no arrhythmias or deaths.[29] A longer QTc in patients taking antipsychotic agents and HCQ was seen compared with HCQ alone (441 ms vs 432 ms), but no significant associations were seen with other QT-prolonging medications.[29]

LVH and cardiomyopathy can rarely occur with HCQ, possibly attributable to impaired lysosomal enzyme function and accumulation of pathologic metabolites (such as phospholipid and glycogen), disturbing membrane stability and signal transduction in cardiac myocytes.[33,34] Decreased myocardial contractility may occur with higher doses or longer duration of therapy (especially >10 years)[33]; other risk factors may include older age, female sex, renal failure and preexisting cardiac disease.[34] Both HCQ-induced cardiac failure and arrhythmias are considered reversible with drug cessation.[10] Retrospective data suggest HCQ use in SLE is in fact protective against incident atrial fibrillation despite the significant prevalence of AF risk factors in these HCQ users.[35]

In summary, recent prospective data and longstanding clinical experience with HCQ in rheumatology would not suggest that prolonged QT is a clinically significant problem. Firm evidence is lacking, and no guidelines

from specialty societies exist. A 12-lead ECG to exclude baseline QT prolongation can be considered in people with other risk factors (e.g. renal failure, significant history of cardiovascular disease or QT-prolonging medications).

Gastrointestinal side effects

Gastrointestinal (GI) disturbance is relatively common with commencing HCQ (7–37%),[6,36] especially nausea/vomiting and diarrhoea/loose stool. The prevalence of these symptoms increases with higher doses but often reduces over time.[36] Although occasionally severe enough to warrant discontinuation, at doses of 400 mg/day or less this is uncommon.[36] To ameliorate GI upset, HCQ can be taken with food, the dose can be divided, or liquid formulation may be trialled.

Deranged liver function tests may infrequently occur with HCQ, especially in those patients with underlying liver disease; however, overt drug-induced hepatitis is rare.[37]

Cutaneous reactions

Mucocutaneous blue-grey hyperpigmentation can occur in up to 25% of patients taking long-term antimalarials.[38] Hyperpigmentation typically occurs on the face, distal extremities, oral mucosa, nails or within scars.[38,39] The pathogenesis of mucocutaneous hyperpigmentation is poorly understood, but CQ has affinity for melanin.[38] Mucocutaneous hyperpigmentation may be a marker of ocular toxicity.[39] Skin pigmentation can cause cosmetic concern and patients taking long-term HCQ should be informed about it. Improvement can sometimes occur without drug discontinuation.[39]

Pruritic morbilliform drug eruptions can occur, which are typically mild and resolve after cessation.[40,41] Reintroduction of low-dose HCQ or alternative antimalarials using desensitisation protocols may be successful.[41] Acute cutaneous reactions tend to occur within the first 4 weeks of commencing treatment,[42] and may include acute generalised exanthematous pustulosis, drug eruption with eosinophilia and systemic symptoms syndrome, erythema multiforme, Stevens–Johnson syndrome or toxic epidermal necrolysis. Some rheumatological diseases may confer a higher risk for acute cutaneous reactions, such as dermatomyositis.[41] Severe acute cutaneous reactions are rare and can recur with rechallenge, so in these cases antimalarials should be avoided.[42]

Photosensitivity with HCQ is reported but is very uncommon.[43] Because of its impact on keratinisation, HCQ may induce psoriasiform hyperplasia.[41] Literature supporting the risk of HCQ-induced exacerbation of psoriasis is mixed; observational data suggest up to 31% of patients with psoriasis experience a flare caused by HCQ, but a recent systemic review highlighted a lack of high-quality evidence to support a causal relationship.[41]

Neuromuscular toxicities

Estimates of the prevalence of neuromuscular disease with HCQ vary widely, from 1.3%[6] to 12.6%.[44] Risk factors may include Caucasian background, renal dysfunction and coadministration of other myotoxic drugs.[45] Myotoxicity is characterised by weakness and abnormal muscle enzymes (e.g. creatinine kinase, lactate dehydrogenase or aldolase). There are similar histological features between HCQ-induced cardiomyopathy and skeletal myopathy.[34] Mechanistically, myopathy may relate to accumulation of intracellular debris in autophagic vacuoles[44] and lysosomal damage.[46] HCQ-induced muscle weakness is not always present even with abnormal muscle enzymes,[44] but, rarely, it may be severe, including respiratory involvement.[46] Myopathy is considered reversible on cessation of HCQ.[44]

Neuropsychiatric symptoms have been attributed to HCQ although are rarely encountered in rheumatology practice. Case reports include psychomotor agitation/aggression,[47] psychosis,[48] mood disorders and suicidality.[49] Possible predisposing factors include low body weight, family history, concomitant prednisolone therapy, alcohol and drug interactions including CYP3A4 inhibitors (which can increase HCQ levels) and p-glycoprotein inhibitors (which may increase blood–brain barrier permeability to HCQ).[50]

Metabolic and haematological considerations

HCQ can reduce haemoglobin A1c and blood glucose in patients with RA[51] and thus reduce the risk of type 2 diabetes mellitus (DM). This effect may be mediated by increased pancreatic insulin production and secretion, or decreased insulin clearance.[51] The anti-inflammatory effects of antimalarials may also contribute to lowering of glucose and lipid levels, and thus improve cardiovascular risk profiles in at-risk populations.[52] Clinically significant hypoglycaemia may rarely occur with[53] or without underlying DM.[54] HCQ may reduce insulin requirements in patients with insulin-dependent DM by up to 30%,[53] with concomitant reduction in haemoglobin A1c levels (1–3%).[55] Those with difficult to control diabetes should be informed of this when commencing HCQ.

The largest review to date of HCQ in rheumatology patients found no episodes of haemolysis in G6PD-deficient patients.[56] Leukopenia and aplastic anaemia are extremely rare with modern dosing regimens.[57]

The bigger picture

Outside of retinal toxicity, treatment-limiting toxicity with HCQ is rare in clinical practice. In SLE, HCQ remains the only agent with a demonstrable mortality benefit.[1] HCQ is not only safe but encouraged in pregnancy and breastfeeding, improving pregnancy outcomes in SLE[2] and the risk of thrombosis and pregnancy loss in the antiphospholipid syndrome.[3] HCQ reduces the risk of neonatal lupus and congenital heart block by more than 50% in anti-SSA/Ro positive women with a history of a previously affected pregnancy.[58] Current dosing recommendations of 5 mg/kg/day were developed to mitigate the risk of retinal toxicity rather than to maximise efficacy.[59] The European League Against Rheumatism recommends dose-reducing patients with long-standing stable disease[59] with some data suggesting no increased risk of flare when reducing from 6.5 to 5 mg/kg/day.[60] However, recent data raise the question of whether body weight dosing is the ideal method of HCQ dosing. HCQ blood levels are not widely available, but may assist in stratifying the risk of retinal toxicity as well as assessing adherence[22] and predicting flares, with data demonstrating a higher risk of disease flare in those with lower HCQ blood levels.[61,62] Furthermore, recent data suggest lower efficacy and a significantly higher risk of thrombotic events in SLE patients with lower HCQ blood levels.[63]

Conclusion

HCQ continues to play a pivotal role in managing rheumatic diseases. Despite widespread media debate in the context of COVID, it is an effective, inexpensive and comparatively safe disease-modifying therapy in SLE, providing beneficial immunomodulation without clinically significant immunosuppression. As an adjunctive to disease-modifying agents in RA, HCQ has potential added benefits for improving metabolic syndrome and cardiovascular risk profile. Retinal toxicity is a recognised side effect, with continually evolving guidelines for monitoring this risk, but other toxicities appear to be rare. Systematic assessment of the potential nonretinal toxicities of HCQ as prescribed in typical clinical practice would be helpful, particularly of the significance of QT prolongation. However, while endorsing the need for continual refinements to optimise the safe prescribing of HCQ, we believe it is also important to allay anxieties about what most clinicians would regard as a tried and trusted drug.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1 Summary of the frequency and variation of reported ocular toxicity of HCQ