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An Update on the Benefits and Safety Profile of Hydroxychloroquine

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Hydroxychloroquine, an antimalarial drug developed in 1950, has been used for decades in the management of various systemic autoimmune rheumatic diseases. By targeting both the innate and adaptive immune systems, it exerts widespread immunomodulatory effects to attenuate the inflammatory response and exert antirheumatic effects. Its favourable safety profile, coupled with proven benefits in improving disease activity and decreasing morbidity and mortality, especially in patients with systemic lupus erythematosus and rheumatoid arthritis, has solidified its place in the long-term management of patients with rheumatic diseases. Recently, therapeutic drug level monitoring has been used to predict the risks of disease flares and prevent treatment-related toxicity. This review article briefly reviews the benefits of using hydroxychloroquine in the management of systemic autoimmune rheumatic diseases, its common and serious adverse effect profile, and the role of drug blood level monitoring in improving patient-related health outcomes.

Introduction

Hydroxychloroquine, an antimalarial drug that was first synthesized in 1950 and approved by the Food and Drug Administration in 1955, is an immunomodulatory agent that is widely used in Rheumatology to manage a number of systemic autoimmune rheumatic diseases.[1-8] Hydroxychloroquine is considered the anchor drug in the management of systemic lupus erythematosus (SLE). The European Alliance of Associations for Rheumatology (EULAR) recommends hydroxychloroquine treatment for all patients with SLE, barring those with contraindications or drug intolerances.[2] Both the American College of Rheumatology (ACR) and EULAR extend this recommendation further to include pregnant SLE patients, advising that they take hydroxychloroquine during pregnancy considering its benefits for maternal health and in pregnancy.[3,4] Furthermore, the ACR suggests using hydroxychloroquine, along with Aspirin and heparin, for managing pregnant patients with thrombotic or obstetric antiphospholipid

antibody syndrome (APS).[3] In rheumatoid arthritis, hydroxychloroquine can be used as a monotherapy for patients with low disease activity, or, alternatively, as part of combination therapy with other disease-modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine to achieve disease remission.[5,6] Additionally, hydroxychloroquine has been used as an adjunct therapy for managing patients with obstetric APS who have had recurrent pregnancy losses to improve live birth rates and prevent pregnancy complications.[3,7-9] Finally, an exploratory clinical trial demonstrated that hydroxychloroquine could reduce the recurrence of congenital heart block (CHB) in a select group of patients with positive anti-SSA antibodies (Ro60 or Ro52 or both) who had had previous pregnancies complicated by CHB.[10] Another trial, the Study of Anti-Malarials in Incomplete Lupus Erythematosus (NCT03030118), is currently underway to evaluate the effects of HCQ on clinical progression of symptoms in patients with incomplete lupus erythematosus, and aims to quantify both patient-reported outcomes and assess changes to their immunologic profile with therapy[11]. These benefits, coupled with its relative safety and favourable tolerability profile, has solidified the ubiquitous use of hydroxychloroquine in Rheumatology practice.

In this review article, I will briefly summarize hydroxychloroquine's proposed mechanisms of action, discuss its benefits in managing various systemic autoimmune rheumatic diseases, and review its safety profile, including common and serious adverse side effects. I will outline the recent advances in using drug blood level monitoring to improve treatment outcomes and decrease drug-associated toxicity and conclude with a reflection on future directions in the field of hydroxychloroquine research.

Mechanisms of action

Despite decades of use, the precise mechanisms by which hydroxychloroquine modulates the immune response *in vivo* remain largely unclear, with multiple mechanisms hypothesized to play a role in attenuating inflammation. As a weak base, hydroxychloroquine is thought to accumulate in lysosomes, disrupting their participation in cellular autophagy and phagocytosis, thereby impairing lysosome-mediated cellular recycling, the processing of phagocytosed substrates, and antigen processing.[12,13] This, coupled with its disruption of toll-like receptor (TLR) 7 and 9 signalling, and cyclic GMP-AMP synthase activation, ultimately interferes with the activation of both innate and adaptive immune systems.[12,13] It impacts antigen presentation through class II major histocompatibility complexes to effector immune cells, and decreases the downstream production of important cytokines, including interleukin (IL)-1, IL-6, tumour necrosis factor, interferon a and interferon g.[12,13] These pleiotropic effects are thought to play a key role in its immunomodulatory and antirheumatic effects.[12,13]

The Use of Hydroxychloroquine for Managing Systemic Autoimmune Rheumatic Diseases

Hydroxychloroquine is an anchor drug in the management of SLE.[2] Multiple studies have demonstrated that its sustained use is associated with better health outcomes, including preventing disease flares, decreasing the accrual of disease-mediated organ damage, decreasing the risk of thrombosis, enhancing the cardiovascular risk profile and providing steroid-sparing benefits; it is the only drug used in the treatment of SLE with proven mortality benefit.[14-21] In a pivotal Canadian clinical trial, withdrawal of hydroxychloroquine therapy in patients with clinically stable SLE was associated with a 2.5 fold increased risk of disease flare, shorter time to disease flare and a 6.1 fold increased risk of severe disease flare necessitating withdrawal from the study.[14] Considering these benefits, it is recommended that all patients with SLE be treated with hydroxychloroquine in the absence of contraindications.[2] This recommendation includes pregnant patients with SLE, in whom continued treatment with hydroxychloroquine is recommended due to the risk of precipitating disease flares with drug discontinuation.[2,4,20] In addition, a substantial body of literature that supports its beneficial effects on maternal and fetal outcomes.[2,4,20]

In rheumatoid arthritis, hydroxychloroquine treatment is indicated for managing patients with mild disease, or as part of a combination strategy with other conventional synthetic DMARDs such as methotrexate and sulfasalazine, to target disease remission and improve clinical outcomes.[5,6,22,23] In both rheumatoid arthritis and SLE, hydroxychloroquine treatment is associated with improved glycemic control and a decreased risk of incident diabetes mellitus, likely by its role in preventing insulin degradation and improving

peripheral insulin sensitivity.[24-26] Moreover, hydroxychloroquine treatment improves lipid profiles, with decreases noted in the levels of low-density lipoprotein, triglycerides, and total cholesterol, while increasing high-density lipoprotein levels.[21,24,27,28] Furthermore, hydroxychloroquine use is associated with a decreased risk of thrombosis in SLE and a reduced risk of cardiovascular disease morbidity and mortality in rheumatoid arthritis.[21,24,29,30]

An exploratory clinical trial has shown that hydroxychloroquine can reduce the recurrence of CHB by more than 50% in a select group of pregnant patients with positive anti-SSA (Ro60 and Ro52/TRIM) antibodies who had prior pregnancies complicated by CHB.[10] Furthermore, the use of hydroxychloroquine as adjunct therapy for managing pregnant patients with thrombotic or obstetric antiphospholipid antibody syndrome has been suggested, with prior studies demonstrating a net benefit in improving live birth rates and preventing pregnancy complications including preterm delivery, pre-eclampsia and intrauterine growth restriction.[3,7-9]

Considering its myriad proven benefits in improving disease activity and decreasing patient morbidity and mortality, especially in patients with SLE and rheumatoid arthritis, hydroxychloroquine has solidified its pivotal role in the long-term management of patients with systemic autoimmune rheumatic diseases.

Safety profile and select adverse effects

Treatment with hydroxychloroquine is generally well-tolerated and relatively safe; nonetheless, a multitude of adverse effects have been reported in the literature which may limit its use. ([12,13,20,21,31,32] and references therein). Reassuringly, most of these side effects are mild and generally resolve with cessation of the drug.[12,13,21,31] HCQ desensitization protocols have been described in the literature in patients with HCQ-induced rash and hypersensitivity skin reactions with good effect; this can be considered in patients with bothersome cutaneous eruptions to facilitate continued therapy.[32-33] In cases where treatment with HCQ is not tolerated or contraindicated, chloroquine may be used in its stead or alternatively, quinacrine may also be considered for treatment of cutaneous lupus erythematosus.[2]

In this section, I will discuss some of the common and serious adverse events associated with hydroxychloroquine use.

a) Cutaneous Adverse Effects

Cutaneous adverse effects have been reported to occur in about 10–25% of patients and range from mild maculopapular eruptions, pruritis, urticaria, and drug-induced psoriasis, to more serious drug reactions such as acute generalized exanthematous pustulosis, drug rash with eosinophilia and systemic symptoms, and Stevens-Johnson syndrome/toxic epidermal necrolysis.[13,20,21,31,34] In addition, hyperpigmentation of the skin, nails, and the mucosal surfaces has been reported, as has stomatitis and hair changes including hair loss, hyperpigmentation, and bleaching.[13,20,34] While most resolve with cessation of the drug, more symptomatic and severe cutaneous adverse effects can be treated with topical and/or systemic corticosteroids, desensitization to HCQ, or in case of HCQ-induced hyperpigmentation, use of laser therapy.[51]

b) Gastrointestinal Adverse Effects

Gastrointestinal side effects are common, reported in 10–37% of patients treated with hydroxychloroquine, with nausea, vomiting, abdominal pain, and diarrhea frequently reported.[12,13,21,31] As with cutaneous reactions, these tend to improve with cessation of drug. [12,13,21,31] Rarely, changes in taste and severe liver toxicity have also been reported.[13,31,35,36]

c) Drug-Drug Interactions

Treatment with hydroxychloroquine has been associated with QTc prolongation in some studies, thought to be mediated via its blockade of potassium efflux channels, with reported incidence rates of <1% in the literature.[13,52,53] Concerns about QTc prolongation and the risk of conduction abnormalities and fatal arrhythmias, especially when used in conjunction with other QT-prolonging medications such as antimicrobials, prompted both the Canadian Rheumatology Association and the ACR to publish position statements and white papers on HCQ safety and risk of cardiotoxicity, respectively.[12,13,31,52,54] Considering the conflicting data in the literature on the effect of treatment with HCQ on cardiac conduction, there remains uncertainty about whether routine monitoring for QTc prolongation is warranted in patients treated

with HCQ but clinicians may elect to obtain a routine baseline electrocardiogram (ECG) prior to initiation of therapy.[31,52,54] Moreover, care must be taken when prescribing hydroxychloroquine in combination with other drugs that are also metabolized by cytochromes P450 and 3A4, because these interactions can alter *in vivo* drug levels and lead to treatment-related toxicity and morbidity.[12,13,31]

d) Cardiac Adverse Effects

While rare, more serious cardiotoxic adverse effects, including cardiomyopathy and conduction system abnormalities, ranging from QTc prolongation to complete atrioventricular block and Torsades de Pointes have been reported with hydroxychloroquine use, especially with higher doses and long-term treatment duration.[12,13,20,21,31,37] The prevalence of HCQ-related cardiomyopathy and arrhythmias in patients is estimated to be about 3%, as reported in a pharmacovigilance database, with a higher incidence of conduction system abnormalities, of about 15.7%, noted on ECG of patients with SLE treated with HCQ from the Toronto Lupus Cohort.[12,13,20,21,31,37,52,53] HCQ can result in restrictive, dilated, or hypertrophic cardiomyopathy, and patients may present with signs and symptoms of congestive heart failure or syncope/presyncope, with endomyocardial biopsy showing classic findings of curvilinear bodies, vacuoles, and lysosomal bodies.[41,52] While conduction abnormalities are generally permanent, cardiomyopathy may improve with drug cessation, with a case series from the Toronto Lupus Clinic describing regression of hypertrophy and improvement in cardiac biomarkers with drug cessation.[31,37,52]

e) Ocular Adverse effects

The most feared complication with hydroxychloroquine use is ocular toxicity, specifically, retinopathy.[12,13,20,21,31,38] Ocular adverse effects range from reversible corneal deposits and paracentral scotoma to loss of visual acuity, of night vision, and of peripheral vision in advanced cases.[13,20,21,31,38]

Prevalence of retinopathy amongst patients treated with HCQ has been reported to be anywhere between 4 and 13% in the literature, with an estimated risk of retinopathy <1% of patients in the first 5 years of therapy, <2% of patients in the first 10 years, ~12% and up to 20% of patients after 20 years of therapy.[38,39,41,55] Risk factors for development of retinopathy include treatment with doses of hydroxychloroquine that exceed 5 mg/kg of actual body weight, concomitant chronic kidney disease or tamoxifen use, prolonged duration of therapy, high cumulative dose, older age, patients from the sub-Saharan African and West Indies regions, and patients with pre-existing retinal disease.[12,13,20,21,31,38-40] Recently, a study by Petri *et al.* showed that higher hydroxychloroquine blood levels were also associated with the development of later retinal toxicity, although a smaller study published around the same time did not confirm this association.[39,40]

Ocular toxicity may be reversible if HCQ is stopped when early signs of toxicity are detected during routine screening examinations.[13,38,41] However, HCQ-related retinopathy is thought to be irreversible, and can even progress after the drug is discontinued, making early detection crucial to prevent permanent visual loss.[13,38,41] Considering its significant morbidity and risk of patient harm, the American Academy of Ophthalmology recommends baseline screening retinal examinations to assess for pre-existing macular disease. For patients without major risk factors for the development of retinopathy, annual screening eye exams, including automated visual fields and optical coherence tomography, are recommended after 5 years of therapy.[38] Patients with major risk factors for retinopathy should receive individualized screening regimens.[38]

f) Rare Adverse Effects

A number of other adverse effects have been reported in the literature. These include neurologic adverse events such as headache, reported in about 10% of patients, and tinnitus, dizziness, ataxia, and seizures, all of which are less common and reported in <1%.[13,41] Neuropsychiatric effects including depressive mood, anxiety, irritability, hallucination, mania, psychosis, and suicidality have been reported with HCQ use but are thought to be generally mild, self-limited, and rare with estimated prevalence rates of 1–5% in one systematic review.[13,31,41,42]

Finally, myotoxicity has been reported in the literature. [21,31,41,43] This is usually signalled by elevated muscle enzymes and skeletal muscle weakness, with muscle biopsy demonstrating evidence of vacuoles and curvilinear and lamellar bodies, which typically improves with discontinuation of hydroxychloroquine.[21,31,41,43]

The Role of Hydroxychloroquine Blood Drug Level Monitoring

Hydroxychloroquine drug levels can be measured in either patient serum or whole blood using liquid chromatography, mass spectrometry, or both.[44-46] For the last two decades, hydroxychloroquine drug level monitoring has been used to establish therapy non-adherence and its negative consequences, such as increases in disease activity and flare rates. On the one hand, multiple studies have validated this approach, and have also established the protective effects of therapeutic, stable hydroxychloroquine blood levels (defined in one study to be 750–1200 ng/mL) against disease flares and acute healthcare utilization.[44-47] On the other hand, severely subtherapeutic levels, signalling likely therapy non-adherence, were associated with an increased risk of disease flares, accrual of early damage, and mortality.[44,48] Conversely, supratherapeutic drug levels may be associated with hydroxychloroquine-related toxicity, such as gastrointestinal side effects and skin hyperpigmentation, or signal the development of later drug-related toxicity, such as retinopathy.[39,49,50]

While hydroxychloroquine drug level monitoring has been in use for almost two decades, it is still not widely used in clinical practice, perhaps due to a perceived lack of access, although it is listed as an available send-out test through a national medical laboratory (DynaCare) as well as through LabCorp and through specialized research laboratories.[30,39,45,46,47,56,57] The lack of equitable access and difficulties with scalability and reliable blood sampling has impeded its widespread use in clinical practice and clinical guidelines have not outlined recommendations for its use in routine practice apart from recommending that HCQ drug levels be used to guide drug dose adjustments and assess for treatment adherence.[2] Clinically, it may prove useful to measure HCQ drug levels periodically, for instance, within several months of treatment initiation or modification to assure treatment adherence and assess for supratherapeutic drug levels, allowing for tailored drug dosing for individual patients. Additionally, it may be worthwhile to check drug levels during disease flares or in patients with persistent disease activity, to assess for treatment non-adherence and allow for targeted patient-centered interventions to improve treatment uptake. Indeed, patients may be more motivated to maintain treatment with HCQ if drug levels were routinely monitored, improving their disease activity and overall trajectory. I suspect that we will be routinely measuring hydroxychloroquine levels as part of clinical care within the next several years.

Conclusions and Future Directions

In summary, hydroxychloroquine has been effectively used for the last several decades for managing a number of systemic autoimmune rheumatic diseases with proven benefits in improving disease activity, decreasing the risks of disease flares and development of damage, and improving clinical outcomes and survival. In addition to its antirheumatic and immunomodulatory effects, hydroxychloroquine has also been shown to modulate glycemic control and lipid metabolism, thereby improving cardiovascular risk profiles in patients with rheumatic diseases and further decreasing their associated morbidity and mortality. It is a generally well-tolerated medication with a largely favourable side effect profile. Although the risk of retinal toxicity increases with prolonged use and higher cumulative doses, established screening guidelines to routinely monitor patients for the development of retinal toxicity can help detect early changes before irreversible damage occurs. In addition, more widespread use of hydroxychloroquine drug level monitoring may help identify patients who are at an increased risk of developing drug-related toxicities in the future prior to the accrual of treatment-related damage.

While significant strides in research have been made to date, including in the last year, I propose that future research efforts can address several unmet needs. Historically, prior studies with higher doses of hydroxychloroquine were used for inducing and maintaining disease remission. However, subsequent to the publication of the American Academy of Ophthalmology 2016 guidelines on hydroxychloroquine-related ocular toxicity, treatment recommendations

have evolved to recommend that doses should not exceed 5 mg/kg of actual body weight.[2,38] It remains unclear whether these reduced doses are sufficient to induce long-term disease remission, reduce the risk of disease flares, and prevent the accrual of disease-related damage and associated morbidity and mortality. Moreover, considering the increased risk of retinal toxicity in patients with chronic kidney disease, it is unclear whether these patients may require further dose adjustments to prevent drug accumulation and reduce the risk of drug-mediated toxicity. Furthermore, despite decades of experience with this drug, the exact mechanisms by which it exerts its antirheumatic and immunomodulatory effects remains unknown. Further research efforts may help identify new drug targets that similarly modulate the immune response without resulting in significant immunosuppression. Finally, with the advent in the use of hydroxychloroquine blood drug levels, and their association with disease activity and flare rates, there is a need to scale up measurement techniques. This would allow for their widespread adoption and incorporation into routine clinical practice, to improve treatment adherence, decrease the risks of drug-related toxicity, and improve patient-related health outcomes.

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Financial Disclosures

None declared.

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