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Lupus (S Manzi, Section Editor)

Anti-malarials: Are There Benefits Beyond Mild Disease?

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Opinion statement

Therapeutic applications for hydroxychloroquine, a quinine compound originally used as an anti-malarial, have evolved and expanded over the years to include the treatment of autoimmune rheumatic diseases. In systemic lupus erythematosus (SLE), hydroxychloroquine has emerged as a cornerstone medication for not only mild disease but also severe disease as adjunctive therapy. With the advent of highly effective biologic disease-modifying agents over the last two decades for treatment of rheumatoid arthritis (RA), hydroxychloroquine's future in RA is less clear. However, hydroxychloroquine's pleiotropic benefits in rheumatic diseases have been increasingly recognized, supporting its place in the therapeutic armamentarium. These benefits include but are not limited to its beneficial impact on glycemic and lipid profiles and its anti-thrombotic effects. These are of major significance in light of the great burden of cardiovascular morbidity and mortality in patients with lupus and RA. This relatively safe, inexpensive, and generally well-tolerated medication's uncommon but serious risk is retinal toxicity which can be minimized by following screening and monitoring guidelines and using appropriate weight-based dosage. In this review article, we present an overview of hydroxychloroquine's potential role beyond its anti-rheumatic benefits.

Introduction

First developed in Central America in the 1700s as a quinine compound from cinchona bark extract, this agent's first use was as a weapon against malaria. Its rheumatologic debut began as a synthetic compound called quinacrine. During World War II, allied soldiers noticed improvement in their rashes and inflammatory arthritis after utilizing quinacrine for long-term malaria prophylaxis [1]. Since 1953, its modern synthetic

quinine derivatives, namely chloroquine and hydroxychloroquine, have been most widely used. Hydroxychloroquine, a refined version of chloroquine, is known to have a lower risk of retinopathy, hence its preferential use in lieu of chloroquine in the USA.

Hydroxychloroquine contains a hydroxyl group side chain in addition to the two carbon rings of chloroquine. Chloroquine and hydroxychloroquine increase pH within intracellular lysosomes leading to diminished proteolysis, intracellular processing, glycosylation, and protein secretion [2, 3]. Its anti-inflammatory properties are recently proposed to be due to interference with antigen processing in macrophages and other antigen presenting cells, potentially via the Toll-like receptor 9 pathway [4].

Today, hydroxychloroquine remains an integral standard of care for cutaneous and arthritic manifestations of systemic lupus erythematosus (SLE) and in mild rheumatoid arthritis (RA). It is frequently combined with other anti-rheumatic drugs in more aggressive disease. The pleiotropic effects of this cost effective and relatively well-tolerated medication have been studied in relation to glucose, lipids, and thrombosis in RA and SLE where cardiovascular disease is a major cause of death. The potential therapeutic role of hydroxychloroquine in multiple medical disciplines beyond RA and SLE has also been extensively studied.

In this clinical review, we report the benefits of hydroxychloroquine beyond its use in mild rheumatic disease.

Current use in RA and SLE

Hydroxychloroquine is known to be moderately efficacious with low toxicity in the treatment of RA [5–8]. Its use in RA beyond mild disease has been endorsed by the American College of Rheumatology in the 2012 Update of Recommendations for Use of DMARDs in Treatment of RA [9]. Specifically, use of hydroxychloroquine has been recommended as part of the disease-modifying anti-rheumatic drug (DMARD) combination therapy (including double and triple therapy combinations with methotrexate and sulfasalazine) in RA with moderate to high disease activity or RA unresponsive to DMARD monotherapy. Triple therapy has been shown to be superior to DMARD monotherapy [10, 11] and, in some studies, comparable to the addition of biologics to methotrexate in those that are unresponsive to methotrexate monotherapy [12, 13].

In SLE, hydroxychloroquine has emerged as a cornerstone therapy that is given to all patients with cutaneous and arthritic symptoms. It is also considered part of the regimen for severe lupus. The first randomized control trial of efficacy of hydroxychloroquine in SLE was the Canadian Hydroxychloroquine Study Group which showed a lower rate of SLE flares and lower rate of severe flares in the hydroxychloroquine users [14••]. This was subsequently confirmed in other randomized controlled trials and observational studies [15–17]. In lupus nephritis, its use has been associated with a higher rate of sustained remission [18], a higher rate of membranous lupus nephritis remission [19], and a lower prevalence of new renal disease [20]. It has been studied in lupus during pregnancy and associated with a lower lupus activity [21–23]. Some studies have shown decreased end-organ damage [24, 25] and enhanced survival [20, 26, 27] with its use in SLE. Hydroxychloroquine is also used as adjunctive treatment in Sjogren's syndrome and is a part of the European League Against Rheumatism (EULAR) recommendations for use as adjunctive treatment for chronic calcium pyrophosphate deposition (CPPD) arthropathy [28].

Effects on lipid profile

In RA and SLE, cardiovascular disease is a leading cause of death, and DMARDs have been studied in an effort to mitigate this cardiovascular risk, with attention to its favorable effect on individual cardiovascular risk factors. Hydroxychloroquine use has been associated with a more favorable lipid profile in several cross-sectional studies. One of the earliest studies was by Wallace et al. in 1990, who studied the effects of hydroxychloroquine on lipids in RA and lupus and found its use to be associated with low levels of triglycerides, low density lipoproteins (LDL), and total cholesterol irrespective of concomitant steroid use [29]. In a longitudinal observational study, Morris et al. found hydroxychloroquine use in their RA cohort of 706 patients to be independently associated with a significant decrease in LDL, total cholesterol, LDL/HDL, and total cholesterol/HDL [30••]. Hydroxychloroquine users had LDL levels that were 7.55 mg/dl lower than non-hydroxychloroquine users, adjusted for multiple variables known to affect lipids, including use of steroids and statins. In a 16-week randomized blinded cross-over trial of 23 RA patients, Solomon and colleagues subsequently showed that hydroxychloroquine reduced total and LDL cholesterol by 12.7 and 12.4 mg/dl, respectively [31]. These changes were small but statistically significant, and the hydroxychloroquine benefit was not sustained during an 8-week crossover to placebo. Similar changes have been observed in the Veterans Affairs RA patient cohort; hydroxychloroquine use of at least 3 months' duration was associated with better lipid profiles irrespective of disease activity or statin use [32]. Studies on the effects of hydroxychloroquine on lipids are summarized in Table 1.

Table 1. Effects of hydroxychloroquine on lipids

Reference	Type of study	Outcomes	Findings
Wallace et al.[29]	Cross-sectional study of RA or SLE patients ($n = 155$)	Levels of cholesterol, triglycerides, HDL, and LDL	Patients treated with HCQ had significantly lower levels of cholesterol, triglycerides, and LDL
Morris et al. [30]	Observational cohort of RA ($n = 706$)	Levels of total cholesterol, LDL, HDL, and triglycerides	Significant decrease in LDL, total cholesterol, LDL/HDL, and total cholesterol/HDL with HCQ use
Solomon et al. [31]	16-week randomized blinded cross-over trial of RA patients ($n = 23$)	Insulin sensitivity index (ISI) and total cholesterol, HDL, calculated LDL, and triglycerides	HCQ reduced total and LDL cholesterol by 12.7 and 12.4 mg/dl, respectively
Kerr et al. [32]	Observational Veterans Affairs Rheumatoid Arthritis cohort ($n = 788$)	Direct comparisons of lipid values in HCQ users and non-users	HCQ use of at least 3 months' duration was associated with better lipid profiles (total cholesterol:HDL and HDL:LDL ratios)

RA rheumatoid arthritis, *SLE* systemic lupus erythematosus, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *HCQ* hydroxychloroquine

These observations support hydroxychloroquine's potential to favorably affect lipid profiles and ultimately diminish cardiovascular risk in patients with rheumatic diseases.

Effects on glucose

Type 2 diabetes mellitus (T2DM) has approached epidemic proportions in the USA. The tremendous burden of T2DM and associated atherosclerosis in the general population has sparked keen interest in studying effective glucose control and cardiovascular risk reduction in rheumatic diseases as well. Wasko et al. were the first to report a protective relationship between hydroxychloroquine and incident diabetes in the Arthritis, Rheumatism, and Aging Medical Information Systems (ARAMIS) adult RA cohort [33••]. In this 21.5 year observational study, long-term use (>4 years) of hydroxychloroquine is associated with a 77 % reduction in the risk of developing diabetes in patients with RA. In RA and lupus patients with established diabetes, initiation of hydroxychloroquine at a dose typically based on ideal body weight (<6.5 mg/kg/day, or 400 mg daily) is associated with a mean reduction in HbA1c of 0.66 % [34].

Hydroxychloroquine's glycemic benefits have also been studied in the general population. Two small double-blind placebo-controlled trials lasting 6 and 18 months report use of high dose hydroxychloroquine (600 mg daily) as a useful adjunct therapy in patients with T2DM [35••, 36]. Subsequently, a 6-week open-label study of 13 obese non-diabetic patients receiving hydroxychloroquine 6.5 mg/kg/day reported a statistically significant improvement in insulin sensitivity [37]. Studies on the effects of hydroxychloroquine on glycemic profile are summarized in Table 2.

Collectively, these observational studies suggest that hydroxychloroquine attenuates the risk of diabetes and may improve diabetic glycemic control in patients with rheumatic diseases. It is a relatively safe, generically available treatment option that also affects cardiovascular risk factors like dyslipidemia, thereby reducing the risk of microvascular complications of T2DM.

Concerns about retinal toxicity of hydroxychloroquine in diabetes, a disease complicated by microvascular retinopathy in patients with poor glycemic control, have prevented it from becoming a mainstream anti-diabetic agent. Of note, this toxicity is a cumulative effect of dose and duration, particularly use of hydroxychloroquine at higher than recommended doses [i.e., >6.5 mg/kg of ideal body weight] and can be minimized by following screening and monitoring guidelines. No increase in risk of retinal toxicity with hydroxychloroquine has been noted in diabetic patients taking this medication.

Effects on thrombosis

Assessment of the effect of hydroxychloroquine on platelet aggregation was studied in vitro in the early 1960s by Madow who reported that hydroxychloroquine decreased red blood cell "sludging" [38] and then by Born and Cross who reported a statistically significant reduction in platelet aggregation using adenosine diphosphate as the initiating agent [39]. Subsequently, clinical studies in the 1970s indicated that in perioperative general surgery and

Table 2. Effects of hydroxychloroquine on glycemic profile

Reference	Type of study	Outcomes	Findings
Quatraro et al. [36]	Prospective, randomized, placebo, double-blind trial of HCQ in decompensated, treatment-refractory diabetes ($n = 38$)	Changes in glucose profile and HbA1c over 6 months	HCQ group had a glucose profile decrease of 11.7 mmol/l and HbA1c decrease of 3.3 %
Gerstein et al. [35]	Randomized controlled trial of HCQ in sulfonylurea-refractory patients with poorly controlled diabetes ($n = 135$)	Changes in HbA1c over 18 months	HCQ decreased HbA1c by 1.02 % and improved glucose tolerance
Wasko et al. [33]	Arthritis, Rheumatism, and Aging Medical Information Systems (ARAMIS) adult RA observational cohort ($n = 4905$) over 21.5 years	Incident diabetes (self-reported or hypoglycemic medication use)	Long-term use (>4 years) of HCQ was associated with a 77 % reduction in the risk of developing diabetes
Rekedal et al. [34]	Observational study of patients with pre-existing diabetes and rheumatic illness starting HCQ ($n = 45$)	Changes in HbA1c within 12 months	HCQ use associated with a mean reduction in HbA1c of 0.66 %
Mercer et al. [37]	6-week open-label longitudinal study of obese non-diabetic patients ($n = 13$)	Insulin sensitivity index, insulin resistance, and insulin secretion	HCQ use for 6 weeks associated with significant increase in insulin sensitivity and trends toward reduced insulin resistance

HbA1c glycated hemoglobin, *HCQ* hydroxychloroquine, *RA* rheumatoid arthritis

hip arthroplasty patients, hydroxychloroquine reduced the risk of venous thromboembolic events [40, 41]. The daily dosage (600–1200 mg) studied was too high to be considered as a long-term prophylaxis option due to the concern of retinopathy. Based on hydroxychloroquine's postulated antiplatelet effects, and aspirin's impact on reducing cardiovascular risk, a similar benefit has been the subject of speculation in rheumatic disease patients.

Observational studies of hydroxychloroquine in lupus [42••, 43] and in lupus with anti-phospholipid syndrome (APS) reported that hydroxychloroquine conferred a protective effect against arterial and venous thrombosis, plaque development, and vascular remodeling [44, 45]. In those with primary APS, hydroxychloroquine conferred protection against arterial and venous thrombosis [46]. Studies on the effects of hydroxychloroquine on thrombosis are summarized in Table 3.

The mechanism of this effect on thrombosis has also been studied. Hydroxychloroquine treatment appears to reduce blood viscosity, red blood cell sludging, and platelet aggregation [47–49], all of which may contribute to the observed anti-thrombotic effects. In vitro experiments have shown that chloroquine, the parental molecule of hydroxychloroquine, inhibits aggregation and release of arachidonic acid from platelets stimulated with agonists [50, 51]. Animal studies have shown that hydroxychloroquine decreases the size of thrombus induced by anti-phospholipid antibodies (aPL) in mice [52]. Hydroxychloroquine can also reverse platelet activation induced by aPL in the

Table 3. Effects of hydroxychloroquine on thrombosis

Reference	Type of study	Outcomes	Findings
Carter et al. [40]	Randomized controlled series of patients having major surgery ($n = 565$ and $n = 52$)	Post-operative DVT and PE observed clinically (1st series) and by phlebography (2nd series)	Reduced incidence of post-operative DVT and PE with use of HCQ
Johnson et al. [41]	Observational study patients undergoing total hip arthroplasty ($n = 2144$)	Post-operative clinical diagnosis of PE	Incidence of fatal and non-fatal post-operative PE with prophylactic HCQ use was 0.28 and 4.15 %
Wallace [43]	Observational cohort of SLE patients ($n = 92$)	Thromboembolic events (DVT and PE)	Thromboembolic events had an inverse association with hydroxychloroquine use
Petri [45]	Hopkins lupus cohort, a longitudinal cohort study of over 2000 SLE patients (35 % on HCQ)	Prospective arterial and venous thrombotic events	HCQ use associated with reduced thrombosis
Erkan et al. [46]	Cross-sectional study of asymptomatic aPL positive patients ($n = 56$)	Vascular thrombosis events	HCQ use is protective against arterial and venous thrombosis
Jung et al. [42••]	Nested case–control study embedded in an inception cohort of patients with SLE ($n = 162$)	Arterial and venous thrombovascular events	Anti-malarial use associated with a 68 % reduction in the risk of all thrombovascular events

DVT deep venous thrombosis, *PE* pulmonary embolism, *HCQ* hydroxychloroquine, *aPL* anti-phospholipid antibody, *SLE* systemic lupus erythematosus

presence of suboptimal levels of a thrombin agonist [53]. Inhibition of GPIIb/IIIa expression, a marker of platelet activation, by hydroxychloroquine prevents platelet-to-platelet aggregation through fibrinogen. Additionally, hydroxychloroquine has been found to reduce the binding of aPL-β2GPI complex to phospholipid surfaces [54] and thus protect against the disruption of the anticoagulant shield of Annexin A5 [55], thereby decreasing the thrombogenicity of platelets and vascular endothelial cells.

Miscellaneous effects

The anti-cancer effects of anti-malarials have been thought to stem from their ability to suppress autophagy—a cancer survival pathway involved in recycling byproducts of rapid turnover and allowing tumors to continue rapidly dividing. By inhibiting autophagosome fusion and degradation [56, 57] and manipulating the autophagy pathway, hydroxychloroquine may help potentiate the effects of other antineoplastic agents and improve clinical outcomes in treatment of cancer. The utility of hydroxychloroquine in an antineoplastic setting is the current topic of investigation in over 30 phase I and II clinical trials [https://clinicaltrials.gov/]. In one randomized, double-blind, placebo-controlled trial, there was a median 11 to 24 months

increased survival in patients with glioblastoma multiforme when chloroquine was added to standard chemotherapy [58]. In an ongoing investigation, imatinib with hydroxychloroquine is better at reducing the number of residual leukemia cells than imatinib alone [59]. In an observational prospective study of 235 lupus patients, Ruiz et al. raised the hypothesis of a protective action of anti-malarials against cancer by reporting a lower adjusted hazard ratio for cancer among anti-malarial users [60]. Other malignancies where anti-malarials are being studied include prostate, Burkitt's lymphoma, breast, and chronic lymphoid leukemia. In comparison to standard dosing for rheumatoid patients (approximately 400 mg daily), antineoplastic trials have utilized dosages above 600 mg daily, raising the concern for potential retinal toxicity which requires close monitoring.

Beyond anti-malarial properties, hydroxychloroquine has been found to have additional antimicrobial effects. This is of particular interest in the treatment of rheumatic disease as disease-modifying agents and glucocorticoids are well known to increase risk of infection. Prior use of hydroxychloroquine in 206 patients diagnosed with lupus nephritis was shown to result in significantly fewer infections (11 vs 29 %, $p = 0.006$) compared to those not on hydroxychloroquine, with no significant difference in oral steroid or cyclophosphamide use [61]. Several studies have documented the effectiveness of hydroxychloroquine in the treatment of HIV, likely stemming from its ability to regulate the immune response through disruption of post-translational glycosylation thus decreasing infectivity [62–64].

Additional benefit of hydroxychloroquine can be seen in a wide array of dermatologic conditions often as first and second line therapies. By blocking ultraviolet light, use of hydroxychloroquine can help protect against skin lesions as first line treatment in SLE patients. In patients with porphyria cutanea tarda where phlebotomy is ineffective, hydroxychloroquine has been studied and found to be a useful adjunct [65–67]. Improvement of skin manifestations in dermatomyositis [68, 69] and sarcoidosis [70, 71] can be seen with hydroxychloroquine. Dermatologists continue to explore the role of hydroxychloroquine in polymorphous light eruption, lichen planus, and disseminated granuloma annulare.

Toxicity, monitoring, and safety

Hydroxychloroquine is generally well tolerated and considered relatively safe. Gastrointestinal intolerance, nightmares, and headaches may be a reason for discontinuation in occasional patients. Skin hyperpigmentation, usually at sites of prior trauma such as the shins, is a cosmetic issue noted commonly with long-term use. Rare cases of neuromyopathy have been reported. Other less common adverse effects include cytopenias and hepatotoxicity.

The retinal toxicity associated with hydroxychloroquine is recognized as a side effect associated with long-term use and daily dosage >6.5 mg/kg of ideal body weight (IBW) [72–74]. The exact mechanism of toxicity has not been elucidated. Affinity for melanin-containing structures may explain its retinal toxicity properties. Continuous exposure to the drug may lead to ganglion cell degeneration and retinal pigmented epithelial atrophy,

resulting in parafoveal thinning and loss of visual acuity, peripheral vision, and/or night vision [75]. The characteristic bull's eye maculopathy on retinal exam is evident only in advanced cases of hydroxychloroquine retinopathy and is typically associated with central vision loss, which is often preceded by a loss of acuity, peripheral vision, and night vision. Early on, a rare patient may note a paracentral scotoma that causes trouble with reading as well as diminished color vision. Other rare ocular complications include corneal deposits and posterior subcapsular cataracts reported with chloroquine use. Differential diagnosis considered by an ophthalmologist for bull's eye maculopathy, especially if unilateral, are age-related macular degeneration, benign concentric annular dystrophy, central areolar choroidal dystrophy, chronic macular hole, cone and cone-rod dystrophies, and Stargardt disease. Nevertheless, hydroxychloroquine must be stopped when there is a suspicion of bull's eye maculopathy.

Historical literature indicates that the risk of hydroxychloroquine retinal toxicity is low in rheumatic disease patients when using relatively insensitive screening tools. The largest study ever published to address the frequency of hydroxychloroquine-related retinal complications is reassuring, indicating a toxicity rate of <1 % in over 1200 patients followed longitudinally [72]. However, toxicity detection was based solely on Humphrey 10–2 visual fields for retinal function and dilated retinal exams. These tools are less sensitive than newer methods to reliably detect early toxicity, before central vision becomes impaired. In subsequent observational studies of rheumatic disease patients by Marmor et al., the rate of hydroxychloroquine retinal toxicity was found to be more common than previously recognized [76••, 77].

While visual field testing may suggest early toxicity, it can be challenging to interpret because of variations in subject reliability and variability in interpretation of results. More sensitive, objective screening tools are essential to detect earlier pathology before central vision loss occurs if hydroxychloroquine-related visual impairment is to be avoided. The 2011 American Academy of Ophthalmology (AAO) screening guidelines for hydroxychloroquine retinal toxicity recommend baseline assessment with Spectral Domain Optical Coherence Tomography (SD-OCT), multi-focal electroretinography (mfERG) or fundus autofluorescence (FAF), plus visual fields and a complete eye examination [78••]. These sensitive tools have become more widely available in recent years and enhanced the ophthalmologist's ability to detect early signs of retinal toxicity. In the absence of unusual risk factors for toxicity, annual exams are advised after 5 years in individuals with normal baseline evaluations. Factors associated with retinal toxicity other than higher cumulative and daily dose include age above 60 years, use for more than 5 years, underlying retinal disease, and renal or hepatic impairment. Daily 400 mg dosing is ideal in individuals with height >160 cm and IBW >60 kg, in whom dosing of <6.5 mg/kg/day based on IBW is deemed preferable to minimize risk.

In pregnancy, hydroxychloroquine has been studied and found to be safe and to have a beneficial effect on lupus activity [21–23]. It has been found to reduce the risk of fetal cardiac abnormalities in mothers positive for SSA/SSB autoantibodies [79, 80]. It is regarded as safe for women to continue during pregnancy and lactation [81].

Conclusions

In summary, hydroxychloroquine has been studied and shown to have several benefits beyond its traditional use in mild rheumatic diseases. In light of the pleiotropic benefits outlined above, we hope to re-establish hydroxychloroquine as a cornerstone medication to benefit rheumatic disease patients. These benefits include, but are not limited to, a favorable glycemic profile, a less atherogenic lipid profile, and anti-thrombotic properties. It is thus conceivable that hydroxychloroquine could potentially help lower cardiovascular risk in rheumatic disease patients, a population with known high cardiovascular morbidity and mortality. This subject is of particular interest and is being studied by the authors. Given the relative safety, low cost, and the biologic plausibility of beneficial effect on cardiovascular risk factors reviewed in this article, investigation of this agent in a randomized study for prophylaxis against cardiovascular disease is conceivable. While acknowledging and further exploring these benefits, the risk of hydroxychloroquine-induced retinopathy can and should be minimized by following appropriate screening guidelines.

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Compliance with Ethics Guidelines

Conflict of Interest
Tarun S. Sharma declares that he has no conflict of interest. Erika Joyce declares that she has no conflict of interest. Mary Chester M. Wasko declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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