Hydroxychloroquine in Dermatology and Beyond: Recent Update

Abstract

Hydroxychloroquine is one of the most frequently used drugs in dermatology with a wide variety of uses due to its immunomodulatory, anti-inflammatory, photoprotective, and metabolic actions and low side effect profile. Demonstration of its antiviral action *in vitro* has led to renewed interest by physicians worldwide during the ongoing coronavirus disease of 2019 (COVID-19) pandemic. Like its immunomodulatory action, its antiviral activity is also due to its ability to alkalinize the intracytoplasmic milieu, leading to disordered viral entry/fusion and deranged viral protein synthesis. However, randomized controlled trials are the need of the hour to conclusively determine its clinical efficacy in such infections. A review of the multitude of mechanisms of action, updated screening and monitoring guidelines, drug interactions, side effects, and its use in special populations is described.

Keywords: *arrhythmias, cardiotoxicity, COVID-19, dermatology, hydroxychloroquine, lupus, mechanism, retinopat*hy, side effects, uses

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Introduction

Although Payne is credited with the first use of quinine for the treatment of discoid lupus erythematosus (DLE), the formal efficacy of the drug has been ascribed to Page who used quinacrine (mepacrine) in DLE, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA).[1] We will focus on hydroxychloroquine (HCQ) in this article.

HCQ has been used successfully to treat a number of dermatological disorders, and new uses continue to be found even today, most notably, its antiviral effect has been rediscovered, making it a much sought after drug by governments worldwide. We seek to review its effects and safety profile while detailing its relevance in the current coronavirus disease of 2019 (COVID-19) pandemic.

History of Antimalarials in Dermatology

All the antimalarials used in LE and RA are quinine derivatives and have a common 4-aminoquinoline radical.

Some of the quinine derivatives used in Dermatology are listed in Table 1.

Cinchona bark was serendipitously discovered to be effective in treatment of malaria in 1634. It took almost 200 years for quinine to be identified as the main antimalarial component in cinchona bark in 1820 by Pelletier and Caventou.

The history of the use of antimalarials in LE and RA is deeply intertwined with world history. Chloroquine (CQ) was synthesized in 1930s by German Hans Andersag (*Resochin* in 1934 and *Sontochin* in 1936).[2] But after Germany's defeat in World War II, this compound was taken to and "re-introduced" in the United States as CQ, and was seen to be substantially more potent than quinine due to the chlorine atom at C7 position, following which it became famous worldwide owing to its potency, stability, low toxicity, and low cost.

Also, during the war, antimalarials had been administered to the soldiers as malaria prophylaxis. However, at the end of the war, British physicians realized that they had led to improvement of the soldiers' skin rashes and inflammatory arthritis as well![3] This led to quinacrine, and later CQ, being tried in LE and RA. Payne, a physician in London, had described the successful use of quinine to treat DLE[4] much earlier in 1894. However, it was Page who, apparently unaware of the Payne's publication, published a series of 20 patients with LE and RA treated successfully with quinacrine in 1951 in *Lancet*, which led to extensive

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use of quinacrine and later other antimalarials in LE and RA worldwide.[5]

In 1946, HCQ was introduced as the hydroxylated analog of CQ. It was shown to be approximately 40% less toxic than CQ in animal studies.[6] It was first used for SLE and RA in 1955 and received U.S. Food and Drug Administration (U.S. FDA) approval soon afterward in 1956 especially for skin and joint symptoms of SLE and RA.

Pharmacokinetics

Between 75% and 100% of oral HCQ is absorbed, and 50% is eventually bound to serum proteins. The drug is excreted in a rapid phase followed by a slower phase. The half-life of the drug in rapid phase is 3 days and 40–50 days in the slower phase.[7] Forty-five percent of HCQ is excreted through the kidney, 20% via the gastrointestinal tract, 5% via the skin. And around 25–45 % is stored in lean body tissues. Acidification of the urine increases the renal excretion of HCQ. Steady-state plasma levels are reached after 6 months of therapy.[8]

It is preferentially stored in the adrenal and pituitary glands, melanin-rich tissues, liver, spleen, and leukocytes. The epidermal levels are 100–200 times the plasma concentrations, but the main dermatological effect seems to be via its effect on the immune system and its anti-inflammatory action.

Mechanisms of Action[9]

Apart from its antimalarial activity, HCQ has antiproliferative, anti-inflammatory, photoprotective, and immunomodulatory effects. Among its varied actions [Table 2], there is a renewed interest in its antiviral action against HIV, influenza, and coronavirus.

Immunomodulatory effects (Inhibition of antigen presentation and apoptosis)

HCQ is an amphiphilic molecule (lipophilic ring structure and hydrophilic side chain) and preferential localizes to interphases such as phospholipid membranes. Being a weakly basic molecule, it can pass through the cell membranes and is protonated in the acidic milieu of the cytoplasm. It then loses its ability to pass through the membrane, and thus accumulates in the cell primarily in macrophages and lysosomes (100–1000 times higher). This leads to an increase in the vesicle pH from approximately 4.0 to 6.0, which interferes with the acid-dependent subcellular functions.[7]

The acidic cytoplasmic compartments are required for the antigen peptide processing and presentation. An essential initial step is the uptake and processing of antigen by the antigen-presenting cells (APCs) followed by expression of antigen-major histocompatibility complex (MHC) protein to the helper T lymphocytes (CD4+). The process of association of antigen peptide with MHC is pH sensitive. The antigen is digested by proteases and the peptides need to assemble with the α and β chains of MHC class II proteins. In the normal acidic environment, the digested peptides compete with the invariant (I_i) chains to form the complex of peptide-MCH that will be transported to the surface of the cell membrane to interact with CD+ T cells.[7] The intracellular raised pH secondary to HCQ decreases the affinity of the peptides and prevents the displacement of the α-I_i and β-I_i, and thus decreases the antigen presentation [Figure 1].

The increased pH leads to immunoregulatory effects, including stabilization of lysosomal membranes, attenuation of antigen processing and presentation, and inhibition of

Table 1: List of common quinine derivatives

Class of drug	Examples
4-aminoquinalines*	Chloroquine, hydroxychloroquine, amodiaquine, and pyronaridine
Acridine compounds (4-aminoquinolines with benzene ring)*	Quinacrine (mepacrine)
Cinchona alkaloids*	Quinine, quinidine
8-aminoquinolines	Primaquine, tafenoquine, and bulaquine
Quinolone methanol	Mefloquine

*Quinine derivatives that have been or are used in Dermatology

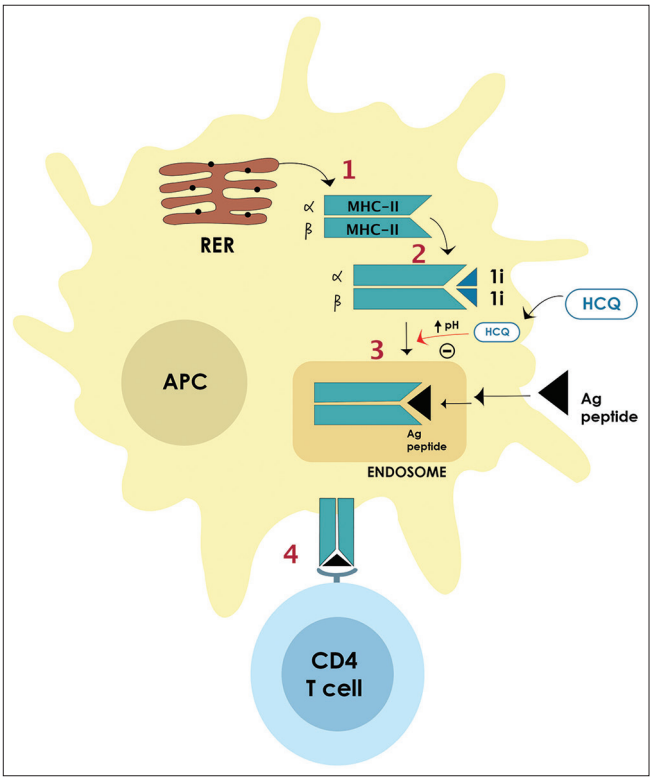

Figure 1: 1. *α&β* chains of the MHC-II proteins are synthesized on the RER. 2. They bind to 1i (invariant) chain, forming *α*-1i and *β*-1i complexes. 3. After entering acidic endosomes→acid hydrolases lead to dissociation of 1i chains from *α&β* chains→bind to peptide antigens (Ags) →MHC-Ag peptide complex expresses at the cell membrane. 4. The antigen presenting cell interacts with the T cell via the T-cell receptor (TCR) that binds to the MHC-Ag. HCQ increases the pH of endosomes→inhibits the dissociation of the *α*-1*i* and *β*-1*i*→leads to decreased binding of the MHC-II to Ags→ineffective presentation of antigens to T cells

Table 2: Overview of Mode of action[9]

Effect	Mechanism of action
Anti-infectious	Antimicrobial effects on HIV, coronavirus, influenza viruses.
Anti-inflammatory effects	Inhibition of phospholipase A2 and C.
	Inhibition of formation of IL1β, TNF-α.
	Inhibition of mast cells.
	Inhibition of Toll-like receptor 9 signal pathway.
Antiproliferative	Inhibits protein synthesis
	Promote chemo sensitization.
	Inhibit cell growth or cell death or both.
	Prevent mutations in cells with high mitotic rates.
Effect on coagulation	Inhibit platelet aggregation and adhesion.
	Inhibit formation of antiphospholipid antibody-β2-glycoprotein 1 complexes.
	Prevent antiphospholipid antibody binding of annexin-5
Immunological	Inhibits autoantigen processing (MHCII).
Response	Reduced stimulation of autoreactive CD4+ T cells
	Reduced cytokine production:
	Reduces serum interleukin (IL)-1β, IL-6, IL-18, and tumor necrosis factor-alpha (TNF-α)(takes 3 months)[10]
	IL-18 is the interferon gamma (IFN-γ)-inducing factor, thus its reduction affects the adaptive immunity.[11]
	CQ inhibits macrophage TNF- α mRNA transcription and endotoxin induced secretion of TNF- α, IL-1, and IL-6.
	Binding to DNA and thus competitive inhibition of anti-DNA antibodies.
	Block of activation of innate and adaptive immunity process mediated by Toll-like receptors.[12]
Metabolic	Decreased hydroxylation of Vitamin D
	Lowered levels of LDL, Triglycerides and cholesterol.
	Increased excretion of porphyrin due to complex formation of HCQ with porphyrin
Photoprotective	Increased UV filtration? (Questionable relevance). It can cause spectral shift due to accumulation in melanin and increase in epidermal concentrations
	Inhibition of UV-induced inflammatory reactions

cell-mediated cytotoxicity.[13] Furthermore, it inhibits the intracellular Toll-like receptors (TLRs), particularly TLR9. TLR3, TLR7, TLR8, and TLR9 specifically recognize nucleic acid motifs and are also distinct from other TLRs in that they are expressed not on the plasma membrane but intracellularly.[14]

HCQ does not consistently inhibit tumor necrosis factor (TNF-α), but blocks interleukin 1 (IL-1), IL-6, and IFN-α production.[15] HCQ-related clinical improvement has been correlated with reduction in IFN-α levels, which corroborate its clinical effects in SLE.[16]

The effect of HCQ is delayed due to its slow process of altering the pH of the antigen processing cells. Also, cryptic autoantigens are characterized by their low affinity for self-MHC. The selective uptake of exogenous peptides and selective sparing of self-peptides is facilitated by an increased pH in the endoplasmic reticulum loading compartment which explains why no increase in infections would occur with HCQ.

Anti-inflammatory properties

The anti-inflammatory effects of HCQ result from downregulation of the components of the arachidonic acid pathway, namely phospholipase A2 and C, which contribute to the production of pro-inflammatory prostaglandins and lipid peroxidation.[17] Lipid peroxidation is thought to play a role in apoptosis, particularly in response to ultraviolet A and ultraviolet B irradiation.[18] HCQ also has antioxidant properties and may protect against tissue damage from free radicals.[19]

Photoprotective action

In the skin, HCQ absorbs ultraviolet (UV) light in a concentration-dependent manner. It has been proposed that the beneficial effect of the HCQ in various photodermatoses may result from its ability to enhance the protective early limb of the UV response. It also binds to cellular deoxyribonucleic acid (DNA) by intercalation between base pairs, thus stabilizing the DNA and regulates ribonucleic acid (RNA) transcription; thus, subsequent RNA translation is inhibited.[9]

A more relevant mode of action is described by Wozniacka *et al*.,[20] who showed that HCQ reduces the expression of pro-inflammatory cytokines in the irradiated skin of patients with SLE, and also causes a reduction of human leukocyte antigen (HLA)–DR+ and CD1a+ cell numbers

in both unirradiated and UV-irradiated skin. This is the plausible explanation of its use in skin lupus.

Anti-infective action

HCQ increases the pH of intracellular organelles leading to reduced survival of intracellular bacteria and fungi and viruses in lysosomes and endosomes, and a disordered posttranslational modification of synthesized proteins (such as viral envelope glycoproteins) in infected cells.[21] In rheumatological literature, multiple studies have shown a reduction in the risk of major infections which account for its real-life proof of this action[22,23] and a renewed interest has been generated in the COVID-19 epidemic.

Anti-bacterial

In Q fever (*Coxiella burnetii)* and Whipple's disease (*Tropheryma whipplei*), its action is via alkalinization of intracellular phagosomes (where the bacteria live), thus inhibiting their growth and multiplication and restoring the intracellular activity of antibiotics. This is the basis of successfully combining doxycycline and HCQ.[24]

Antiviral

There are many probable mechanisms for its antiviral activity:[21]

- Increase in pH
  - Inhibition of low-pH-dependent changes responsible for fusion, penetration, or uncoating of viruses within endosomes (influenza virus, hepatitis A virus [HAV], and hepatitis C virus [HCV])
  - Inhibition of posttranslational modification of viral proteins (such as gp120 in HIV) and inhibition of sialic acid production[25] (present in HIV-1 glycoproteins and severe acute respiratory syndrome coronavirus 2 [SARS-Cov-2] receptor angiotensin-converting enzyme 2 [ACE2])
- Immunomodulatory and anti-inflammatory: HIV and SARC-CoV-2
- Decreased cellular iron: HIV

CQ and HCQ have been reported to interfere with flavivirus infections *in vitro*, Japanese encephalitis virus internalization, Yellow fever virus replication, and Dengue virus penetration and maturation. However, in a randomized controlled trial (RCT), CQ failed to significantly reduce viremia in dengue patients.[26] Thus, *in vitro* activity of HCQ does not always translate to clinical efficacy.

COVID-19

- Though studies are still on, HCQ probably interferes with the glycosylation of ACE2 (the cellular receptor of SARS-CoV-2) and blocks viral fusion with the host cell.[27] Due to diminished glycosylation of ACE2, there occurs inefficient binding between SARS-CoV spike (S) viral protein and ACE2 on host cells[28] Also, the S-protein uses sialic acid linked to host cell surface ganglioside for entry. HCQ binds to sialic acid and gangliosides and the viral S-protein is unable to bind the ganglioside further interfering with viral entry[29]
- In addition, HCQ has been shown to block the transport of SARS-CoV-2 from early endosomes to endolysosomes, which is needed to release the viral genome[25,30,31]
- The anti-inflammatory effects of HCQ [Table 2] may probably partially combat the cytokine storm seen in critically ill COVID-19 patients as high concentration of cytokines have been seen in their plasma.[32] However, it remains to be seen whether this effect is clinically relevant or not.

Other actions

HCQ inhibits platelet adhesion and aggregation leading to an antithrombotic effect and has a favorable effect on lipid profile (reduced cholesterol, triglycerides [TG], very-low-density lipoprotein [VLDL], low-density lipoprotein [LDL])[33] particularly in patients on concomitant corticosteroid therapy. Thus, HCQ may be a useful drug in patients with comorbid cardiovascular disease, diabetes, and dyslipidemia due to its metabolic benefits.[34,35]

Indications

HCQ is often used as adjunctive therapy in combination regimens for RA and LE and is the most common disease-modifying agent used in rheumatology [Table 3].

LE

Chronic Cutaneous Lupus Erythematosus

When antimalarial therapy is initiated, 85% of lesions show resolution but the onset of action varies from 1 to 3 months.[36] Significant scalp involvement with alopecia in addition to disseminated discoid, annular, or papulosquamous subacute cutaneous LE skin lesions also respond to antimalarials. Verrucous and hypertrophic plaques do not respond well to antimalarial therapy. Due to the delay in achieving consistent plasma concentrations, it is recommended that therapy be administered for at least 2 months before switching to another drug. Smokers have been shown to have a poorer response to treatment.

SLE

HCQ is useful for arthritis, pleuritis, pericarditis, and lethargy.[37] In case the patient is not responsive, HCQ may be switched to CQ, but the two should not be used together because of the greater risk of ophthalmologic toxicity.[38] HCQ can inhibit exacerbations in longstanding SLE and prolong patient survival.[39] In addition, the drug has a protective effect against irreversible organ damage, thrombosis, and loss of bone mass. It is also known to cause reduction in blood lipids, protection against osteonecrosis, remission of lupus-related nephritis, delayed development of systemic lupus, and protective effects against developing cancer. Additional symptoms such as fatigue, weakness, arthralgia, myalgia, serositis, and mucous

Table 3: Approved and unapproved uses of HCQ[9]

FDA approved	**Lupus erythematosus Rheumatoid arthritis Malaria**
Off label	
Photosensitivity disorders	PCT, PMLE, solar urticaria, chronic actinic dermatitis, and hydroa vacciniforme
Granulomatous disorders	Sarcoidosis, granuloma annulare, LMDF, and granulomatous cheilitis
CT disorders	Dermatomyositis, scleredema, and LE
Disorders with Lymphocytic Infiltrate	Jessner's infiltrate and lymphocytoma cutis
Panniculitis	Lupus panniculitis and erythema nodosum
Miscellaneous	Alopecia areata Atopic dermatitis Eosinophilic fasciitis Follicular mucinosis Lichen nitidus Lichen planus Morphea Psoriatic arthritis Ulcerative stomatitis Urticarial vasculitis
Infections	HIV, influenza, SARS-CoV, and SARS-CoV2 (COVID-19)

membrane ulcers improve in patients with SLE.[40] Also early HCQ use is associated with delayed onset of SLE.[41]

An overview of its use in LE in given in Box 1.

PMLE

Its efficacy is based on its inhibitory effect on IL-1, IL-6, and IL-8, which play a role in the inflammatory process.[42] HCQ in a dose of 400 mg daily for 1 month, and 200 mg daily for 2 months, was superior to placebo in preventing development of the rash.[43]

Porphyria Cutanea Tarda

In this disorder, either twice weekly 125 mg CQ or 100 mg HCQ is given. In patients with elevated plasma iron levels, combination therapy, that is, beginning with bloodletting—500 mL every 4 weeks—plus CQ 250 mg/weekly (HCQ 200 mg/weekly) is recommended.[44,45]

Pseudolymphoma

A dose of HCQ of 200 mg/day initially, increased to 400 mg/day, has been noted to be effective.[46]

Jessner's Lymphocytic Infiltrate

Both CQ sulfate and HCQ sulfate have been found to be useful but in different dosages as compared to DLE. HCQ 200 mg once or twice a day, or CQ 200 mg daily can be used.[47]

Sarcoidosis

HCQ, similar to corticosteroids, tends to suppress the disease rather than cure it. Indications for administering CQ or HCQ in patients with sarcoidosis include chronic disfiguring skin lesions, progressive extracutaneous lesions in patients in whom steroid therapy is contraindicated, adjuvant therapy with steroid treatment, and neurosarcoidosis with steroid failure.[48] Hypercalcemia in sarcoidosis, but not in B-cell lymphoma, has shown improvement after HCQ therapy.

Box 1: Overview of antimalarials in LE[9]

Dose: Hydroxychloroquine initially at 200 mg twice daily, reducing to 200 mg/day, once a response is achieved
Onset of action: 6 weeks (4-8 weeks)
Duration: 6 months
Tapering: Reduce by 25% every 3-6 months, maintain with 1-2 tablets/week
Efficacy: 60%-75% of patients respond; subacute LE (60%-75%): tumid LE (90%)
Relapse: 50% relapse within 6 months

Granuloma Annulare

HCQ has been used in generalized granuloma annulare with a dose of 9 mg/kg/day for 2 months, tapered down to 6 mg/day for 1 month and 2 mg/kg/day for another 1 month.[49]

Lichen planus

- Lichen planus (mucosal)[50]
  Oral lichen planus can improve on therapy. Pain and redness improve after 1–2 months, whereas it takes 3–6 months for erosions to heal.
- Actinic lichen planus[51]
  It appears that HCQ therapy is highly effective in this indication.[52]

COVID-19

The Centers for Disease Control and Prevention (CDC) stated that in the absence of any approved drug for COVID-19, the U.S. FDA has granted "emergency authorization" in March 2020 for the use of CQ and HCQ in hospitalized

COVID-19 patients. The U.S. FDA has also given its nod to Phase III clinical trials with approximately 440 patients in the USA to evaluate the use of HCQ in a randomized, double-blind, placebo-controlled manner.

In India, the Indian Council of Medical Research National Taskforce for COVID-19 has advocated extended HCQ prophylaxis for healthcare workers and household contacts as follows:

Eligible individuals and dose (for prophylaxis):[53]

- Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks
- Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks.

However, currently there is a severe dearth of firm and high-quality reproducible scientific evidence of clinical efficacy of this drug in COVID-19.[53]

Wang *et al*.[54] had first reported the efficacy of CQ in an *in vitro* study in China. Soon afterwards, the same group reported that HCQ was a safer and equally effective option as CQ.[55] An open-label nonrandomized trial of 20 COVID-19 patients given HCQ with/without azithromycin concluded that HCQ significantly reduced nasopharyngeal viral carriage 6 days after start of treatment vis-à-vis untreated controls. Azithromycin added to the efficacy of HCQ and all patients treated with the combination tested negative after 6 days.[56] However, the study had major limitations of a painfully small sample size and non-randomization.

Another study from France had contrasting results with the same treatment regimen. Of 11 patients, repeat nasopharyngeal swabs were done on 10 (1 expired) and 8 were found to be still positive at 6 days after HCQ and azithromycin.[57] A retrospective study from France reported no difference in the primary outcome (ICU transfer or death due to any cause within 1 week) between hospitalized COVID-19 patients who received HCQ and those who did not.[58]

In China too, Chen *et al*.[59] showed no difference between HCQ and control groups in the clinical outcome or negative conversion rate of nasopharyngeal samples.

Alhazzani *et al*.[60], in their guidelines on critically ill patients with COVID-19, concluded that in the absence of any randomized published trials on HCQ, there is insufficient evidence to issue a recommendation on the use of CQ or HCQ.

At present, most reports have small sample sizes (hence underpowered) and have short or no follow-ups. Only well-formulated prospective, randomized, placebo-controlled clinical studies with long follow-up periods may give more definitive results. In addition, it seems obvious that progress to unsalvageable ARDS depends more on the cytokine storm than the high viral load and moreover HCQ is not by itself a powerful antiviral agent. In fact, in some of these critically ill patients, physicians might need to stop the antimalarials in view of their ineffectiveness or potential adverse effects.[61]

There have been safety concerns with HCQ, mainly with regard to cardiac toxicity, more so when it is combined with azithromycin. HCQ may cause QT interval prolongation and ventricular arrhythmia, which may be difficult to identify and manage especially in the setting of either pre-existing cardiac disease or myocarditis due to COVID-19.

Notably recent study by ICMR on side effects of prophylactic doses of HCQ in healthcare workers observed abdominal pain in 10%, nausea in 6%, and hypoglycemia in 1.3%.

Dosage

Adults: HCQ sulfate tablets contain 200 mg HCQ sulfate, equivalent to 155 mg base, used for oral administration. Usual starting dose for HCQ is between 200 and 400 mg/day.

The minimum effective dose should be used. This dose should not exceed 6.5 mg/kg/day (calculated from ideal body weight). However, in clinical practice, a dose of HCQ at 5 mg/kg per day (unadjusted or real weight) is used.

Earlier, it was believed that irreversible retinopathy depends on whether the maximum daily dosage based on ideal body weight is exceeded or not. However, it has recently been shown that real body weight is a better predictor of risk of retinopathy than ideal body weight, perhaps because of the increasing variance of real body weight in the population and due to reduced chance of toxicity observed among thin patients. If the maximum dosages are observed, retinopathy is not a concern, even with therapy lasting for several years.[62]

Smoking leads to a decreased efficacy of HCQ and other antimalarials, possibly due to reduced absorption, enhanced metabolic turnover and by inhibiting lysosomal uptake.[63]

These effects of smoking could be additional reasons to encourage smoking cessation.

Blood levels of HCQ also determine the effects and low drug levels (<750 ng/mL) will necessitate a higher dosage to reach adequate levels and improve response in smokers.

Children: HCQ is used at a dose of 3 –5 mg/kg/day, typically to a maximum of 400 mg/day. The 200 mg tablet is therefore not suitable for use in children with an ideal body weight of less than 30 kg. To achieve this dosing in younger children using the 200-mg tablets, the drug can be dosed every other day.

Choice of Antimalarials: HCQ, CQ, or Quinacrine?

HCQ has certain advantages over CQ in the form of almost equal clinical efficacy, better tolerability, and favorable side effect profile. It has been shown to be threefold less toxic[64] than CQ, especially in terms of retinopathy. Also keratopathy is seen 40 times more frequently with high doses of CQ than with HCQ.[65] Patients who are unable to take CQ are often seen to tolerate HCQ well.

Quinacrine has certain unique adverse effects—it is contraindicated in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals due to the risk of hemolysis and is also known to cause aplastic anemia on occasion. It does not deposit in the retina and hence does not cause retinopathy but its cutaneous side effects are responsible for it not being a popular choice among dermatologists and rheumatologists. It causes deep lemon yellow pigmentation of the skin, nails, sclera, sweat, and lacrimal secretions. The typical bluish-gray pigmentation on the shins, face, and palate seen with CQ and HCQ are infrequent with quinacrine.

The equivalent doses of HCQ, CQ, and quinacrine are 400, 250, and 100 mg, respectively.

Combination of Antimalarials

Quinacrine can be added to HCQ or CQ when there is lack of or suboptimal clinical response in LE. Cavazzana *et al*.[66] and Tanenbaum *et al*.[67] have shown reduction in CLASI activity scores and initiation of response in recalcitrant cases with combination of HCQ and Quinacrine.

Workup and Monitoring

The drug is safe and in usual doses and indications nothing else is needed besides ophthamic monitoring.[68]

Ophthalmic examination

- The American Academy of Ophthalmology (AAO) recommends that patients on long-term HCQ should visit an ophthalmologist within the first year of treatment for fundus examination. They have found that the risk of toxicity increases toward 1% after 5–7 years of use or a cumulative dose of 1000 g or 460 g of HCQ or CQ, respectively
- The testing of the central visual field (VF) sensitivity by an automated field tester (Humphrey 10-2) is done alone with fundus examination and if normal with no risk factors, annual screening tests should start after 5 years while if there are any risk factors, they should start within 5 years. If the baseline fundus examination is abnormal screening tests should be performed annually[69]
- The screening tests are automated VFs and spectral-domain optical coherence tomography (SD OCT). These should look beyond the central macula in Asian patients
- Risk factors for retinopathy include dose >5 mg/kg (real body weight) per day, duration >5 years, preexisting renal disease with decreased GFR, Tamoxifen treatment, and preexisting macular disease.

Cardiac evaluation

- Screen for digoxin use and history of cardiomyopathy or severe heart failure. In such cases electrocardiogram (ECG) during therapy is warranted and watch for depression of ST segment, T-wave inversion and QT interval prolongation[70]
- A baseline ECG should be done if a combination with azithromycin is considered. Other drugs that may increase the QT interval (see later) should be avoided and serum electrolytes should be checked periodically
- Determination of creatine kinase (CK) and lactate dehydrogenase (LDH) in blood is appropriate to screen for myopathy and cardiomyopathy and should be checked before starting the treatment and then every 3 months.

Liver studies

Aspartate transaminase (AST), alanine transaminase (ALT), and bilirubin if patient is receiving long-term treatment.

Hematological

- Complete blood count (CBC) and platelets; white blood cell (WBC), red blood cell (RBC), and platelets may be decreased; if severe, product should be discontinued; assess for malaise, fever, bruising, and bleeding (rare)
- G6PD levels *do not* need to be routinely screened, unless patient is on another drug that may cause methemoglobinemia.[71]

Cutaneous reactions

- New-onset pruritus, rash, urticaria, and mucositis (acute generalized exanthematous pustulosis [AGEP] and drug reaction with eosinophilia and systemic symptoms [DRESS] can.

Ototoxicity (tinnitus, vertigo, and change in hearing)

- Audiometric testing should be done before and after treatment.

Safety Profile

- HCQ is a well-tolerated drug and,except for GIT side effects, discontinuation of the drug is rarely required [Box 2].

Ocular

Melles and Marmor[62] reported that the prevalence of HCQ-induced retinopathy was 7.5% and varied with the dose (odds ratio, 5.67; for >5.0 mg/kg) and with duration of use (odds ratio, 3.22; for >10 years). At doses of 4–5 mg/kg, it

Box 2: Overview of side effects with Antimalarial Drugs

GIT: Nausea, vomiting, anorexia, diarrhea, cramps
Eye & ENT: Blurred vision (dose dependent), corneal changes, retinal changes, difficulty focusing, tinnitus, vertigo, deafness, photophobia, corneal edema
Blood: Thrombocytopenia, agranulocytosis, leukopenia, aplastic anemia
Skin: Pruritus, pigmentation changes, skin eruptions, lichen-planus-like eruptions, eczema, exfoliative dermatitis, alopecia, Stevens-Johnson syndrome, photosensitivity
CNS: Headache, stimulation, fatigue, irritability, seizures, bad dreams, dizziness, confusion, psychosis, decreased reflexes
CVS: Hypotension, heart block, asystole with syncope
Psychiatric: Can affect lability
Hypoglycemia: Hydroxychloroquine has been shown to cause severe hypoglycemia including loss of consciousness that could be life threatening in patients treated with and without antidiabetic medication
Neuromyotoxicity- insidious-onset proximal weakness with a normal CPK, peripheral neuropathy and cardiac myotoxicity.

*Those underlined are commonly seen

was <2% within the first 10 years of use but rose to almost 20% after 20 years of use; however, even after 20 years, a patient without toxicity has only a 4% risk of converting in the subsequent year.[72]

Common: Blurring of vision due to a disturbance of accommodation is dose dependent and reversible accommodation defects are seen in those taking higher dosages >500 mg/day of CQ.

Uncommon: Retinopathy and VF defects can occur, but appear to be uncommon if the recommended daily dose (5 mg/kg/day) is not exceeded.[62,72] Retinopathy, which can lead to impaired vision, appears to be extremely rare, especially in the first 5 years of therapy. The early form of retinopathy secondary to HCQ is reversible if the drug is discontinued.[73] However if it is allowed to develop, there is risk of progression regardless of drug cessation.

Initial presentation of retinal involvement can be asymptomatic or can present as paracentral, temporal, pericentral ring type scotomas along with color vision anomalies. The pathognomonic finding is bull's eye maculopathy characterized by involvement of retinal pigment epithelial cell layer leading to depigmentation of central macula and relative sparing of the macular fovea.

However, bull's eye maculopathy is now merely a textbook term which is hardly seen clinically due to increased screening. Retinopathy starts in the inferotemporal retina (corresponding to the superonasal VF). Recent evidence has shown extramacular involvement, especially in the Asian population which can be missed during standard screening as pericentral retinopathy spares the macula.[69] Hence, screening tests (VF and OCT) should be extended in fields beyond the macula.

Corneal changes including edema and opacities have been reported. They are either asymptomatic or may cause visual disturbances such as haloes, blurring of vision, or photophobia. They may be transient and are reversible on stopping treatment.

Dermatological Effects

a. Pigmentation: A bluish-gray to black hyperpigmentation may occur in 10%–30% of patients treated for 4 months or longer with any of the drugs. The pigmentation typically affects the shins (resembling ecchymoses), face, palate (with a sharp line demarcating the hard and soft palate), and nailbeds (as transverse bands). The pigmentation may take months to fade after discontinuation of therapy

b. Progressive bleaching of the hair roots of the scalp, the face, and the body is another unusual pigmentary disturbance that may appear in as many as 10% of patients taking HCQ. This pigmentary phenomenon is also reversible. It has been suggested that taking CQ/HCQ for 3 weeks out of 4 weeks can help prevent this side effect[74]

c. The incidence of pruritus and various cutaneous eruptions associated with antimalarial use has been reported to be 10%–20%. Pelle and Callen[75] have reported that roughly 25% of all dermatomyositis patients experience hypersensitivity drug eruptions (mostly morbilliform, occasionally AGEP or DRESS) during antimalarial therapy

d. Antimalarial drugs are known to occasionally exacerbate existing psoriasis. However, psoriasis is not a contraindication for CQ therapy.

e. Uncommon side effects

- Bullous eruptions including erythema multiforme
- Drug rash with eosinophilia and systemic symptoms (DRESS syndrome)
- Stevens–Johnson syndrome and toxic epidermal necrolysis
- Photosensitivity.

Patients should be advised to use sunglasses in bright sunlight to decrease photophobia and to wear protective clothing while on HCQ.

Cardiac effects

The side effects reported include conduction disturbances, sick sinus syndrome, torsades de pointes, malignant ventricular arrhythmias, congestive heart failure, and cardiomyopathy (hypertrophic and restrictive). Immediate withdrawal of HCQ is essential if toxicity is suspected because of the early reversibility of cardiomyopathy. Cardiac toxicity due to HCQ needs to be differentiated from that due to LE/RA in patients. With regard to conduction defects, Chatre *et al*.[76] reported that nearly 85% patients had conduction disorders after a median of 7 years and a high cumulative dose (median 1235 g HCQ).

Myopathy

Proximal muscle myopathy may be associated with cardiac myotoxicity. Risk factors include Caucasian race and renal failure.

Haematological

G6PD screening is no longer considered essential before starting HCQ. Youngster *et al*.[77] concluded that there was no effect of HCQ on RBC lifespan G6PD-deficient patients. However, caution should be exercised when combining the drug with other agents with possible hemolytic effects.

Gastrointestinal

Gastrointestinal adverse effects are some of the most common causes of drug discontinuation. The most frequent symptoms are anorexia, heartburn, nausea, vomiting, diarrhea, and abdominal distention. These symptoms are usually transient and promptly disappear after the drug is stopped or the dose is lowered.

Drug Interactions

The salient interactions are listed in Table 4.

Coadministration with azithromycin: Monitoring of the QTc interval (baseline and daily for the duration of treatment) is strongly advised, when both drugs are co-prescribed.[78] However, azithromycin is not as strong an inhibitor of CYP450 (cf. erythromycin) and thus may have less drug interactions.

Use In Special Populations

- **Children:** Safe in children with juvenile idiopathic arthritis (JIA) and LE. However, no appropriate dosage forms of HCQ are available for children <30kg. Capsules or tablets need to be pulverized and mixed with jam, jelly, or honey to mask the bitter taste
- **Pregnancy and lactation:** Pregnancy category C. As HCQ has a long $t_{1/2}$, even discontinuation at the time of pregnancy cannot avoid fetal exposure. Although it can cross the placenta, it does not have teratogenic or fetopathic effects.[79]

There are numerous studies in rheumatology that substantiate the use of this drug in lupus in pregnancy and it has been shown that HCQ use is associated with decreased disease activity scores and lower prednisone doses at delivery,[80] whereas discontinuation is associated with disease flares. There are no reports of toxicity or developmental disabilities in the children born to mothers with a history of intake of HCQ during pregnancy or lactation.[81] Therefore, maternal HCQ use is considered safe during pregnancy and breast feeding.[82]

Conclusion

HCQ has been used for many decades in Dermatology and in the light of its varied actions and favorable safety profile; it finds wide use in Rheumatology and varied off-label indications. However, the risk of retinopathy and cardiac adverse effects should never be neglected and physicians should adhere to the prescribed guidelines at all times. Although its use has been renewed due to its purported antiviral action, it must be remembered that this has not been conclusively proven as of date and the final word on this is still awaited.

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Table 4: Drug interactions of HCQ

Interaction	Mechanism	Drugs
Drugs that decrease the effect of HCQ		Antacids, kaolin, magnesium and trisilicate
Drugs that increase the effect of HCQ		Cyclosporine and digoxin
Drugs whose level is increased by HCQ	Inhibition of P-glycoprotein (P-gp) efflux transporter	Cyclosporine and digoxin (substrates of P-gp)
	CYP2D6 inhibition by HCQ	Metoprolol
Drugs that increase level of HCQ	CYP450 inhibition	Cimetidine
	CYP2C8 inhibition	Gemfibrozil and clopidogrel
	CYP3A4/5	Verapamil, diltiazem, azoles, macrolides, and quinolones
Additive toxicity with HCQ	QT prolongation, arrhythmias	Methadone, amiodarone, quinolones, clarithromycin, azithromycin, moxifloxacin, pimozide, tricyclic antidepressants, and antiemetics (promethazine, ondansetron)
	Seizures	Tramadol, bupropion
	Methemoglobinemia	Benzocaine and prilocaine
Increased antibody titer		Anti-rabies vaccine
Decreased effect of		live virus vaccines and botulinum toxoids

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Conflicts of interest

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