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REVIEW ARTICLE

Safety of Hydroxychloroquine: What a Dermatologist Should Know

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Abstract

The unique immunomodulatory properties of hydroxychloroquine (HCQ) have attracted considerable interest beyond its use for malaria and rheumatological diseases, including a variety of dermatological conditions. Over recent years, especially after the coronavirus disease 2019 (COVID-19) pandemic, the prescription of HCQ has also significantly expanded, sometimes inappropriately, thus posing additional challenges on its optimal use, due to emerging safety issues. In this review, we provide dermatologists with the latest advancements on selected clinically relevant toxicities, namely retinopathy, pro-arrhythmia, cutaneous reactions, and neuropsychiatric effects. It is hoped this update can assist dermatologists to identify high-risk patients for tailored monitoring, screening, and risk minimization strategies, thus supporting safer HCQ prescribing.

Key Points

Hydroxychloroquine's use has revealed safety concerns, including retinopathy, cardiac toxicity, and psychiatric effects, especially after its widespread COVID-19 use.

Safe prescribing requires adherence to dosing guidelines, regular monitoring, and individualized risk mitigation to prevent severe toxicities.

1 Introduction

Hydroxychloroquine (HCQ) and chloroquine, both 4-aminoquinoline drugs, were originally developed for malaria treatment [1]. While chloroquine inhibits DNA and RNA polymerase, blocking *Plasmodium*'s use of hemoglobin [2], HCQ increases the pH in parasitic vacuoles, disrupting hemoglobin degradation [2]. The key pharmacological properties of HCQ are summarized in Table 1 [3–13]. HCQ is widely used to treat rheumatological conditions like systemic lupus erythematosus (SLE) and rheumatoid arthritis, by virtue of their immunomodulatory properties [2]. HCQ's lower cost, favorable safety profile compared to other immunomodulators [14], demonstrated effectiveness as a modifying agent, and survival benefits in SLE [15] have increased its use in developed countries. Unlike chloroquine, HCQ rarely causes retinal toxicity over similar treatment periods, contributing to its widespread use [1]. Particularly for the treatment of SLE according to current guidelines, HCQ dosages of 5 mg/kg per day or less are recommended to reduce the risk of toxicity, but this may lead to increased flare-ups. It is the clinician's responsibility to balance the right dosage to suit the individual patient [16]. HCQ is also used in dermatological conditions, such as cutaneous lupus erythematosus, cutaneous and mucosal lichen planus, cicatricial alopecias, dermatomyositis, and porphyria cutanea tarda [17–33]. Table 2 summarizes the indications, relevant posology, and clinical benefit for the main dermatological conditions. Except for porphyria cutanea tarda, generally, for

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Table 1 Key pharmacological properties of HCQ

Pharmacological feature	Key data	Notes
Mechanism of action	Inhibition of lysosomal activity and autophagy, pro-inflammatory cytokines (IL-1, IFNα, TNF), interference with TLR7, TLR9 signaling pathways, cGAS activity	Inhibition of terminal glycosylation of ACE2 and raised pH in endosomes may explain the antiviral activity against SARS-CoV-2 (COVID-19)
Off-target effect	hERG K^+ blockade in the heart (rapidly activating delayed rectifier potassium channel I_{Kr}, implicated in cardiac repolarization)	Main mechanism responsible for QT prolongation and pro-arrhythmia (TdP)
Bioavailability	70–80%	Administer with food or milk
Volume of distribution	44,257 L	Large distribution across tissues
Protein bound	50% (64% for *S*-enantiomer, mainly to albumin and alpha-1-acid glycoprotein)	Low potential for DDIs by protein displacement
Metabolism	CYP3A4 (substrate), CYP2D6 (substrate and inhibition), and CYP2C8 (substrate)	Potential PK interactions with strong CYP3A4 inhibitors/inducers (victim) and CYP2D6 substrates (perpetrator)
Elimination	Renal (16–30% unchanged)	No dose adjustment in renal impairment, but renal damage may occur (in patients with connective tissue disorders)
Terminal $t_{½}$	123–180 h (5–7 days)	Slow onset of action and prolonged effects after drug discontinuation
Use in pregnancy	HCQ should be avoided, except when, in the judgement of the physician, the individual potential benefits outweigh the potential hazards. If treatment with HCQ is necessary during pregnancy, the lowest effective dose should be used[a]	HCQ readily crosses the placenta (cord blood levels corresponding to maternal plasma levels)
Warnings and precautions	Cardiomyopathy and ventricular arrhythmias, retinal toxicity, serious skin reactions, worsening of psoriasis, hepatotoxicity (when used in porphyria), hemolytic anemia (G6PD deficiency), myopathy/neuropathy, neuropsychiatric reactions including suicidality, hypoglycemia, and renal toxicity	Ventricular arrhythmias and retinal toxicity represent key serious safety issues that can be prevented, for which risk factors have been identified

There is a large interindividual variability in the PK, with tissue-specific absorption, distribution, metabolism, excretion, and lysosome-specific sequestration. Data have been derived from US prescribing information [3], Drug Bank [4], Paludetto et al. (2023) [5], Schrezenmeier and Dörner (2020) [6], Collins et al. (2018) [7], and Munster et al. (2002) [8]

ACE angiotensin-converting enzyme, *cGAS* cyclic GMP-AMP synthase, *COVID-19* coronavirus disease 2019, *CYP* cytochrome P450, *DDI* drug–drug interactions, *G6PD* glucose-6-phosphate dehydrogenase, *hERG* human ether-a-go-go–related gene, *HCQ* hydroxychloroquine, PK pharmacokinetic, *IL-1* Interleukin-1, *IFNα* Interferon-alpha, *SARS-CoV-2* Severe Acute Respiratory Syndrome Coronavirus 2, *TdP* torsade de pointes, *TLR* Toll-like receptor, *TNF* Tumor Necrosis Factor, $t_{½}$ half-Life

[a]This is the official statement from the European summary of product characteristics. The vast majority of the evidence suggests that HCQ does not cause congenital malformations [9, 10]. The background information on data in "300–1000 prospective pregnancies from observational studies, as well as a meta-analysis of pregnancy exposure (mainly in women with autoimmune disease)," at doses ranging from 200 mg to 400 mg, "which did not show a statistically significant increase of congenital malformations or feto/neonatal toxicity related to hydroxychloroquine use in pregnancy," was replaced by text citing a recent US cohort study, which found a small increase in risk of congenital malformations from 35.3/1000 in women not taking HCQ to 44.1/1000 in those taking HCQ in the first trimester (all indications), with a statistically significant increase in risk only with daily doses > 400 mg [11]. These recommendations by the European Medicines Agency were criticized and led to global counterstatements [12, 13]

Table 2 Main therapeutic indications of HCQ in dermatology

Dermatological disease	Dosing	Clinical benefits
Cutaneous lupus erythematosus [17–21]	5–6.5 mg/kg/day Reducing or stopping HCQ could be considered after remission, at least in a subset of patients, considering the risk of potential relapse	HCQ can prevent the formation of new lesions and can promote the healing of existing ones. In the long term, it prevents skin recurrences and makes the skin less sensitive to sunlight
Cutaneous and mucosal lichen planus [22–24]	Variable dosage of 200 and 400 mg per day, depending on body weight and patient tolerance. HCQ is used as second-line treatment in extensive, chronic, and/or severe forms refractory to topical or systemic treatment with corticosteroids or steroid-sparing drugs	In the cutaneous form, it leads to a decrease in itching and lesions present. In the mucous form, pain relief and reduction of erythema is observed after 1–2 months of therapy; in contrast, erosive forms require up to 3–6 months of treatment. As a result, quality of life may improve. The clinical response is slower than with the other drugs used, but it is a safer long-term alternative to systemic corticosteroids
Cicatricial alopecias [25–29]	Variable dosage of 200 and 400 mg per day, depending on body weight and patient tolerance. HCQ generally represents maintenance therapy. Topical, intramuscular, or intralesional corticosteroids and topical calcineurin inhibitors represent the first choice of therapy in the inflammatory phases of the disease	HCQ reduces inflammation in hair follicles, preventing the formation of new scars and slowing down the progression of the disease, although it cannot restore already destroyed follicles
Dermatomyositis [30, 31]	Dosage of 5 mg/kg/day. HCQ is used as an adjuvant when disease control is not adequate with other systemic agents (methotrexate, mycophenolate mofetil, rituximab, intravenous immunoglobulins)	HCQ is effective in treating skin manifestations (heliotrope rash, Gottron's papules, itching). It reduces skin reactivity to ultraviolet rays; it reduces the likelihood of recurrence of skin lesions and helps maintain remission of the disease
Porphyria cutanea tarda [32, 33]	Dosage of 100 mg twice a week, to be discontinued once clinical remission is reached. HCQ is first-line therapy together with phlebotomy	HCQ binds porphyrins within hepatocytes and consequently promotes their urinary excretion, in addition to its anti-inflammatory properties in the skin

HCQ hydroxychloroquine

dermatological diseases, the dosage of HCQ used is 5 mg/kg/day, administered in clinical practice with a flat dose of 200 mg twice a day, and based on clinical response, doses may be decreased.

However, HCQ can cause side effects like gastrointestinal discomfort, hypersensitivity reactions, heart issues, neuropsychiatric and muscular toxicity, cytopenias, skin disorders, and serious ocular effects such as retinopathy [34, 35].

Due to its antiviral and anti-inflammatory properties, HCQ was also tested during the coronavirus disease 2019 (COVID-19) pandemic [15, 34], thereby increasing the emergence of rare but life-threatening cases of toxicity, such as pro-arrhythmia possibly leading to sudden cardiac death. By searching the term “hydroxychloroquine” in the PubMed database (as of September 22nd, 2024), an increasing number of published articles can be observed, with a significant peak during the pandemic years. Specifically, the number of results increased from 490 in 2019 to 2698 in 2020 and to 2045 in 2021. This increase has led to better documentation of HCQ-associated toxicities.

Given its broad expanding usage, healthcare providers should be aware of these potential toxicities and their management. A comprehensive search was conducted using PubMed, Scopus, Web of Science, EMBASE, and the Cochrane Library, focusing on studies related to HCQ toxicity and safety in dermatological practice. The search was performed on September 1st, and included terms such as "hydroxychloroquine" OR "HCQ" AND "toxicity" OR "safety" AND "dermatology" OR "cutaneous diseases" OR “ophthalmology” OR “retinal toxicity” OR “psychiatric” OR “cardiotoxicity” OR “QT prolongation,” with filters applied for English language. No specific criteria were used for study design; systematic reviews, meta-analyses, randomized controlled trials, cohort studies, and case reports/series were included.

This state-of-the-art review aims to provide dermatologists with the latest advancements on the safety profile of HCQ. Specifically, the focus will be on toxicities of special interest that can have the greatest impact on patients' health and quality of life, and for which risk minimization strategies can be implemented by dermatologists, such as ocular, cardiac, cutaneous, and psychiatric ones.

2 Ophthalmological Toxicities

Previously, HCQ retinopathy was thought to be rare because it was typically detected only in advanced stages [1]. Earlier studies reported a 0.38% incidence of retinal toxicity among 526 patients in 2003, and 0.68% in 2010 for those using HCQ for 5–7 years [36, 37]. This led the American Academy of Ophthalmology to update screening guidelines in 2011 [38]. In a 2014 study, Melles and Marmor assessed 2361 patients who had used HCQ for over 5 years, identifying a 7.5% prevalence of retinopathy, which increased to 20–50% after 20 years of use. This study's higher toxicity estimates were due to more sensitive detection methods like spectral-domain optical coherence tomography (SD-OCT), long-term HCQ use (mean 15 years), and high doses prescribed before safer dosing guidelines were established [39].

HCQ binds to melanin in the retinal pigment epithelium (RPE), causing damage to macular cones outside the fovea. It inhibits lysosomal activity, leading to reduced phagocytosis of photoreceptor outer segments, which then accumulate. This triggers pigment-containing RPE cells to migrate into the outer retina layers, resulting in photoreceptor loss and RPE atrophy [40]. HCQ toxicity has traditionally been characterized as a bullseye maculopathy, featuring a parafoveal ring of RPE degeneration while sparing the foveal center, typically in patients experiencing central vision loss [1]. Early signs include macular edema and/or bilateral granular depigmentation of the macular RPE. The *"flying saucer" sign*, visible on optical coherence tomography (OCT), shows preservation of outer retinal layers under the fovea with perifoveal loss of the ellipsoid zone. Defects in the ganglion cell complex and peripapillary retinal nerve fiber layer are also observed [1, 2, 35, 40, 41]. As HCQ exposure continues, this can progress to an atrophic bullseye maculopathy, marked by concentric rings of hypopigmentation and hyperpigmentation around the fovea [35, 41]. In Asian patients, these changes may appear in the peripheral macula near the arcades [42]. Prolonged drug exposure can lead to widespread retinal atrophy, arteriolar attenuation, and optic disc pallor [43]. HCQ retinal toxicity is classified by severity: early (patchy photoreceptor defects without RPE involvement), moderate (a partial or full ring of photoreceptor damage without RPE involvement), and severe (combined RPE damage) [1]. In early stages, patients are often asymptomatic but may experience color vision deficits, particularly with red objects, central vision loss, reading difficulty, blurred vision, glare, flashing lights, and metamorphopsia, typically affecting both eyes [35, 40, 41].

The primary risk factors for HCQ-induced retinal toxicity include daily dosage, duration of use, renal impairment (estimated Glomerular Filtration Rate (eGFR) < 60 mL/min/1.73 m^2), tamoxifen usage, and existing ocular diseases [1]. The risk is minimized with a daily dose of less than 5 mg/kg actual body weight [35]. The American College of Rheumatology and other professional institutions recommend careful communication between doctors, patients, and eye care providers to ensure HCQ's safe use, particularly adhering to dosing limits [1, 44]. The risk of retinal toxicity is relatively low (< 1%) in the first 5 years and remains under 2% up to 10 years. However, it increases significantly to nearly 20% after 20 years. Notably, if a patient has not developed toxicity after 20 years, the risk for the subsequent year drops to 4% [35]. Other risk factors include female sex,

older age at initiation, and genetic polymorphisms, which can either increase susceptibility (e.g., polymorphisms in the cytochrome P450 (CYP) gene, which may increase blood concentrations) or offer some protection against toxicity (e.g., non-pathogenic ABCA4 polymorphisms) [35, 45]. Concomitant retinal conditions may also elevate the risk due to pre-existing cellular damage [35, 46].

Modern retinal imaging has revolutionized the detection, dosing recommendations, and screening procedures for HCQ toxicity. Techniques like OCT can identify early parafoveal damage in asymptomatic individuals, characterized by outer retinal changes or localized sensitivity loss on visual field testing [1]. This early detection allows for the cessation of HCQ treatment before the disease progresses to irreversible visual loss [1]. In early toxicity, visual field tests often show a paracentral scotoma, with potential variations depending on the test used (e.g., 24-2, 30-2, or 10-2 fields). For non-Asian patients, the risk zone on a 10-2 Humphrey visual field is typically 2°–6° from the center, though variations exist. Additionally, fundus autofluorescence (FAF) can detect early photoreceptor damage, initially appearing as hyper-autofluorescence, which may later turn hypo-auto fluorescent as RPE atrophy sets in [38, 47]. Multifocal electroretinography (mf-ERG) can also reveal early depression in the parafoveal or extramacular areas [1, 2, 35, 40, 41]. It is always important to differentiate HCQ maculopathy from other conditions with similar features, such as age-related macular degeneration, cone dystrophy, rod-cone dystrophy, Stargardt's disease, neuronal ceroid lipofuscinosis, and fenestrated sheen macular dystrophy [40].

To minimize the risk of visual loss from toxic retinopathy in HCQ users, screening is now recommended to detect early disease changes [1]. The American Academy of Ophthalmology issued guidelines in 2002, 2011, and 2016 for screening patients on chloroquine and HCQ therapy [35, 38, 48]. Furthermore, different collaborative recommendations are also present in the literature [44, 49, 50]. These guidelines suggest baseline testing within the first year of therapy, including a dilated fundus exam to identify pre-existing retinal conditions. Although not mandatory, automated visual field testing and SD-OCT are often conducted at this visit.

The guidelines recommend a 10-2 threshold visual field test for most patients, but a 24-2 or 30-2 visual field protocol for Asian patients, due to the higher incidence of retinopathy outside the central 20°. Other recommended tests include SD-OCT, FAF, and mf-ERG, the last being the most sensitive but less commonly available. For Asian patients, wide-field SD-OCT and FAF are advised. The guidelines no longer recommend baseline retinal photography, time-domain OCT, full-field ERG, electro-oculography, fluorescein angiography, color vision tests, or Amsler grid tests [51]. Annual screening should begin after 5 years of therapy unless additional risk factors, such as small stature, obesity, liver or kidney disease, and pre-existing retinal disease, necessitate earlier annual testing. The suggested protocol involves initial use of SD-OCT/FAF and visual field tests, with mf-ERG introduced if these tests indicate potential retinopathy. It is recommended not to discontinue HCQ based on uncertain findings, but rather on convincing evidence of chronic toxicity, which should involve consultation with the prescribing physician [44]. Due to HCQ's long half-life, retinopathy can progress for over 6 months, and changes may continue up to 20 years after stopping the drug [52]. Early detection of retinal toxicity is crucial, as untreated progression can lead to paracentral vision loss, central vision loss, and night blindness, even after discontinuation of therapy.

HCQ can also negatively impact the cornea and ciliary body. Cornea verticillata, or vortex keratopathy, is a common side effect of chloroquine use and involves intraepithelial corneal deposits composed of the unchanged drug. These deposits bind to cellular lipids and settle in the basal epithelial layer, forming patterns like whirls, linear opacities, or punctate lesions [40, 53]. Typically, these deposits disappear over time after discontinuation of the drug [2]. This condition usually appears after 2–3 weeks to a few months of drug use and presents as diffuse punctate deposits or in a vortex pattern. Most patients do not experience visual symptoms, though some may report halos around lights and photophobia [54]. Vortex keratopathy is rare in patients taking HCQ, possibly due to chloroquine's greater accumulation in non-pigmented tissues, independent of melanin. The condition's symptoms, like increasing halos and blurred vision, are reversible once therapy is stopped.

Lastly, ciliary body involvement can occur with chloroquine, leading to accommodative dysfunction, but this side effect has not been observed in HCQ users. Patients may report difficulty with activities requiring accommodation, such as reading. Unlike toxic retinopathy, these non-retinal effects are generally reversible [2, 55].

3 Cardiac Toxicity

Drug-induced QT prolongation is a recognized surrogate marker of cardiotoxicity, potentially leading to the so-called torsade de pointes (TdP), a potentially life-threatening peculiar form of tachyarrhythmia, which may ultimately result in ventricular fibrillation and sudden cardiac death [56]. Drug-induced TdP is still a research and clinical priority, especially after the COVID-19 pandemic. Although it is currently believed that myocardial damage might represent a main driver of enhanced arrhythmic risk in COVID-19 patients, different proarrhythmic factors (including concomitant pharmacological treatments) may synergize with pre-existing arrhythmogenic substrates and high-grade systemic

inflammatory state to reduce the repolarization reserve in the myocardium, with ultimate TdP onset [57]. Different agents were used "off-label" to counteract virus invasion/replication; this was especially the case of (controversial) prophylactic use of HCQ in combination with azithromycin.

There are plenty of data on the pro-arrhythmic potential of HCQ, which is a well-known agent blocking the human ether-a-go-go–related gene (hERG) potassium channel, the most important and widely accepted mechanism of drug-induced QT prolongation [58–62]. In the vast majority of cases, clinically significant QT prolongation was rarely observed during on-label uses of the drug, and in patients with documented risk factors [63]. During the COVID-19 pandemic, a number of pharmacovigilance studies using individual case safety reports from large databases found a considerable number (and increase) of cardiovascular events, including TdP and cardiomyopathy [64–68].

With regard to dermatological uses, a recent systematic review examined ten articles (389 patients with cicatricial alopecia; eight retrospective chart reviews) and found that only one patient with multiple cardiovascular comorbidities and exposed to diuretics developed non-sustained ventricular tachycardia 17 months after starting HCQ 400 mg daily [69]. Notably, a recent retrospective chart review on 55 patients with cutaneous sarcoidosis found a prolonged QT interval only in 5.4% of patients (vs 12.1% in 116 controls), with a non-significant increase in mean QT length (+ 6 ms) in a sub-analysis of 22 patients [70]. Another retrospective chart review of 131 patients with cicatricial alopecia who were prescribed HCQ in a specialty alopecia clinic found no significant QT prolongation during regular electrocardiograms (ECGs) despite 22% of patients being exposed to drugs with known TdP potential, especially antidepressants [71].

Minimizing the risk for QT prolongation is important for patient safety, particularly since TdP can be fatal. Although there is general agreement on general discontinuation rules (e.g., QT interval, corrected for cardiac frequency, > 500 ms, and increases > 60 ms), the need for baseline QT assessment and timing for electrocardiographic re-assessment may vary depending on the drug, as well as underlying expected susceptibility. General warnings and monitoring guidance are reported in the European summary of product characteristics and US prescribing information, commenting on risk of cardiomyopathy and conduction abnormalities, as well as on the QT prolongation and risk of TdP. However, ECG monitoring is not part of the current standard practice when HCQ is prescribed for the treatment of rheumatological or dermatological conditions, and there is currently insufficient evidence on which to base specific monitoring recommendations.

The "American College of Rheumatology White Paper on Antimalarial Cardiac Toxicity" provided practice considerations on obtaining a baseline ECG in patients with additional risk factors for QT prolongation and avoidance (or deprescribing) additional drugs with known QT-prolonging potential [72]. In this regard, the interactive website crediblemeds.org (and relevant apps) provided updated lists of drugs categorized by their potential to cause QT prolongation and/or TdP (with links to US label and PubMed articles), and additional features such as a list of clinical risk factors associated with QT/TdP risk, also in terms of quality of the evidence (e.g., bradycardia is a strong risk factor for TdP, with high quality of the evidence). For HCQ, ECG monitoring could be considered after 3–4 days of therapy initiation in patients with different patient-, drug- and disease-related risk factors (Figure 1): frail patients with severe renal/liver impairment, cancer, cardiovascular comorbidities (including COVID-19), uncorrected hypokalemia/hypomagnesemia (e.g., due to diuretics or gastrointestinal diseases/malabsorption), and exposure to multiple drugs that can interact via pharmacokinetic (e.g., strong CYP and P-glycoprotein inhibitors such as verapamil, azithromycin) and/or pharmacodynamic (potent hERG blockers such as haloperidol) mechanisms. A synopsis of key drugs with QT-prolonging potential and TdP liability is provided in Table 3. Patients should be also educated and involved in shared decision-making about the potential for HCQ cardiac effects as well as the effect of other medications that prolong the QT interval.

Most institutions utilize clinical decision support systems alerting healthcare providers on potential harm of QTc prolonging drug–drug interactions of medications being ordered for a patient [56]. Specifically, the Tisdale risk score calculator was designed as a new risk advisory tool to help guide decision making when managing patients at risk of TdP. The Tisdale risk score, validated in 2013 from a prospective observational study used to predict QTc prolongation in hospitalized patients, combined the aforementioned clinical risk factors to estimate the TdP risk when managing patients in and out-of-hospital settings, with suggestions for obtaining ECG and implementing medication review [73, 74].

4 Cutaneous Toxicity

HCQ is widely prescribed in various dermatoses, especially autoimmune disorders, due to its clinical benefits, including increased long-term survival, reduced cumulative steroid doses, and benefits in improving cardiovascular risk profile, whereas lupus erythematosus and rheumatoid arthritis patients are both associated with elevated cardiovascular risk [63, 75].

On the other hand, various cutaneous adverse events have been reported (Table 4), mostly in women over 50 years of age [76]. For most reported adverse effects, discontinuation of HCQ typically results in spontaneous resolution within

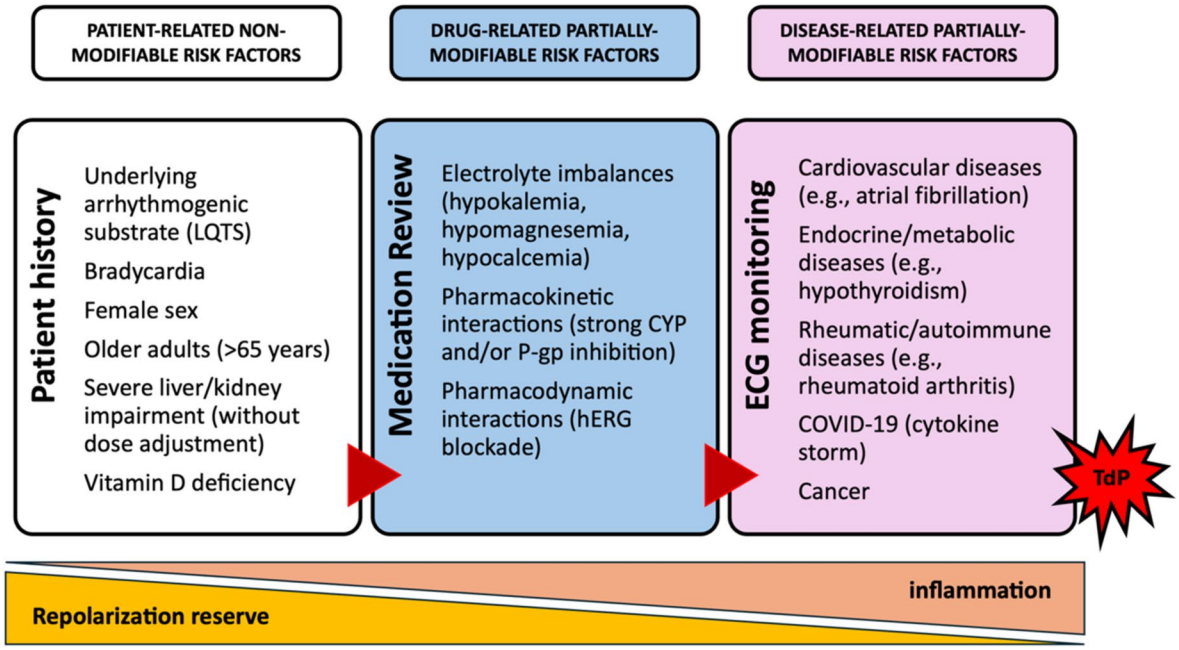

Fig. 1 The concept of reduced repolarization reserve caused by a synergy among clinical risk factors, and leading to TdP. *COVID-19* coronavirus disease 2019, *CYP* cytochrome P450, *ECG* electrocardiography, *hERG* human ether-a-go-go–related gene channel, *LQTS* long QT syndrome, *P-gp* P-glycoprotein, *TdP* torsade de pointes

weeks to a few months, with or without topical corticosteroids, which are the most common treatment [77].

Cutaneous rash and pruritus are the most common skin reactions in up to 10% of patients receiving HCQ [76–80]. The typical presentations are maculopapular, erythematous, or urticarial rashes, usually occurring within 4 weeks of treatment [76, 77, 81]. Sometimes pruritus may be presenting as isolated, unresponsive to antihistamine therapy [76, 79, 82]. Acute generalized exanthematous pustulosis (AGEP) is an acute adverse skin reaction to drugs, characterized by the development of edema and erythema followed by the eruption of multiple punctiform, non-follicular, sterile pustules, predominantly in intertriginous areas, associated with fever and leukocytosis. AGEP has been rarely described in association with HCQ [83–85]. It occurs rapidly and has prompt resolution within a few weeks. Sometimes AGEP and Stevens-Johnson syndrome (SJS) may occur simultaneously (overlapping), with a potentially severe mucosal involvement [86–88]. SJS and toxic epidermal necrolysis (TEN) are highly life-threatening adverse drug reactions characterized by the local detachment of the epidermis and mucous membranes, with possible involvement of internal organs. The main drugs implicated are allopurinol, carbamazepine, different antibiotics, and also HCQ [77, 89, 90]. SJS and TEN typically occur when the average cumulative dose exceeds 100 mg [77]. The condition starts with fever and flu-like symptoms lasting 1–3 days, followed by photophobia, conjunctival itching, dysphagia, and skin pain. It manifests with atypical targetoid skin lesions characterized by a central opaque or dark erythematous maculo-papular component, indicative of epidermal necrosis, which evolve into vesicles or blisters within 1–3 days, causing skin detachment. Involvement with intermediate extension is termed SJS/TEN overlap [91]. In most cases, erosions of the mucous membranes (oropharynx, eyes, and genitals) usually appear a few days before the skin lesions [76]. Supportive therapy is recommended for the treatment of SJS/TEN, which may include systemic corticosteroids, intravenous immunoglobulins, cyclosporine, and Tumor Necrosis Factor-alpha (TNF-α) antagonists [90, 92]. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe T cell-mediated delayed-type adverse reaction. It presents with fever, diffuse morbilliform rash, facial edema, lymphadenopathy, organ involvement, and hematological abnormalities (eosinophilia and lymphocytosis with atypical lymphocytes). Human herpesvirus 6 reactivation plays a role in the pathogenesis of DRESS [20]. The mortality rate is up to 10% [94]. It represents a rare HCQ adverse event, with a delayed onset [89, 93, 95, 96].

Hyperpigmentation of skin and mucosae may occur in 10–30% after a prolonged period, with an average of 6.1 years, improving within several months after discontinuation [63, 89, 97]. It is characterized by blue-grey discoloration due to pigment deposition of melanin and iron into the basal and dermal layers, typically occurring on the face, extremities, oral mucosa, and nails. Mucosal pigmentation

Table 3 Selected medications with QT-prolonging potential and TdP liability that dermatologists need to know. For details, please refer to crediblemeds.org

Pharmacological class	TdP category	Active substance	Notes
Antipsychotics	Known risk	Haloperidol	First-generation antipsychotics carry a higher TdP risk as compared to second- and third-generation agents
	Possible risk	Aripiprazole	
	Conditional risk/not classified	Olanzapine	
Antidepressants	Known risk	Citalopram	Selective serotonin reuptake inhibitors carry a higher TdP risk as compared to tricyclic antidepressants
	Possible risk	Mirtazapine, venlafaxine	
	Conditional risk/not classified	Amitriptyline, fluoxetine	
Antimicrobials	Known risk	Azithromycin, moxifloxacin	Macrolides and fluoroquinolones carry a higher TdP risk as compared to penicillins/cephalosporins
	Possible risk	lopinavir/ritonavir	
	Conditional risk/not classified	Amoxicillin, ketoconazole, metronidazole	
Antiemetics and/or prokinetics	Known risk	Domperidone, ondansetron	First-generation 5-HT3 antagonists carry a higher TdP potential Domperidone use was restricted in pediatrics
	Possible risk	Granisetron	
	Conditional risk/not classified	Metoclopramide	
Analgesics	Known risk	Methadone	Methadone is known to cause TdP
	Possible risk	Morphine, buprenorphine, tramadol	
	Conditional risk/not classified	Paracetamol	
Anticancer drugs	Known risk	Vandetanib	Tyrosine kinase inhibitors carry a higher TdP risk as compared to monoclonal antibodies
	Possible risk	Osimertinib, ribociclib	
	Conditional risk/not classified	Abiraterone	
Cardiovascular drugs	Known risk	Amiodarone	Amiodarone causes significant QT prolongation but only rarely TdP due to multiple compensatory actions on sodium and calcium channels
	Possible risk	Alfuzosin, nicardipine	
	Conditional risk/not classified	Furosemide, omeprazole	

Known risk of TdP: These drugs prolong the QT interval *AND* are clearly associated with a known risk of TdP, even when taken as recommended. HCQ is classified as known risk for TdP

Possible risk of TdP: These drugs can cause QT prolongation *BUT* currently lack evidence for a risk of TdP when taken as recommended

Conditional risk of TdP: These drugs are associated with TdP *BUT* only under certain conditions of their use (e.g., excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) *OR* by creating conditions that facilitate or induce TdP (e.g., by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP)

5-HT3 5-hydroxytryptamine 3, *HCQ* hydroxychloroquine, *TdP* torsade de pointes

Table 4 Cutaneous toxicity with HCQ

Toxicity	Frequency	Significance
Mucocutaneous hyperpigmentation	10–30%	Chronic use (several months or years)
Cutaneous rash (maculopapular, urticarial)	10%	Within 4 weeks of treatment
AGEP, SJS/TEN, DRESS	Rare (< 1/100)	Often associated to extra-cutaneous events
Photosensitivity	Rare	HCQ is used for its photoprotective properties in the treatment of various photodermatoses
Psoriasis/psoriasiform dermatitis	Rare	Some case reports exist, but a systematic review found no causal relationship [99]

AGEP acute generalized exanthematous pustulosis, *DRESS* drug reaction with eosinophilia and systemic symptoms, *HCQ* hydroxychloroquine, *SJS/TEN* Stevens-Johnson syndrome/toxic epidermal necrolysis

involves the hard palate, gingiva, and lips. Melanonychia striata is a rare adverse event associated with HCQ. It may be associated with skin hyperpigmentation. All patients, especially those on long-term HCQ, should be informed of this side effect. An ophthalmological examination is recommended for patients who develop HCQ-induced hyperpigmentation, due to the increased risk of retinopathy [98].

Although HCQ is used to treat photodermatoses (e.g., benign summer light eruption, polymorphic light eruption, and porphyria cutanea tarda), photosensitivity, including photoallergic and phototoxic reactions, has been reported but is very rare [63, 76, 79, 89].

Psoriasis or psoriasiform dermatoses exacerbation during HCQ therapy have been described [77, 89]. HCQ can induce different forms of psoriasis, including inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis [76]. A systematic review showed a lack of high-quality evidence to support a causal relationship [99].

5 Psychiatric Toxicity

The first description of psychiatric effects with HCQ is dated back to 1962, when a case series described psychological symptoms and depression in patients treated for rheumatoid diseases [100]. Thereafter, several reports of mood disorders (including suicidal behavior), suicide, and psychotic disorders were published [101–103]. While several pharmacodynamic mechanisms were hypothesized, including inhibition of serotonin transporter and acetylcholinesterase, prostaglandin E antagonism, the accumulation of toxic metabolites of HCQ in the lysosome, and down-regulation of glycoprotein-P in the blood–brain barrier, no clear explanation could be identified [101]. Notably, HCQ has the ability to cross the blood–brain barrier, reaching concentrations in the brain that are 10–20 times higher than those in peripheral blood plasma. A recent systematic review of 14 population studies and 12 individual case reports described psychiatric effects associated with HCQ [104]. Anxiety was the most commonly reported symptom, followed by psychotic symptoms and insomnia [105–113]. Additional effects included suicidal thoughts, self-harm, confusion, attention problems, emotional instability, depression, nervousness, and irritability [105–113]. Case reports highlighted auditory hallucinations, increased psychomotor activity, irritability, and visual hallucinations as frequent side effects [114–116]. Symptoms typically appeared within 5 days, but the onset ranged from 3 h to 48 weeks. The median dose was 551 mg, with a range from 100 to 4700 mg, and there was no clear correlation between dosage and adverse effects [104], although higher than recommended dosage due to therapeutic error, misuse, abuse, or overdose could be a predictor for HCQ-induced neuropsychiatric adverse events. Generally, symptoms resolved within a week, although the resolution time varied from a few hours to 5 months (owing to the long half-life of HCQ), sometimes with or without antipsychotic or antidepressant treatment [104]. Higher-risk groups for psychiatric side effects include individuals with a family history of psychiatric disorders, females, older adults, and those who are overweight [104]. Co-administration of CYP3A4 inhibitors and low-dose corticosteroids represent additional drug-related risk factors. Importantly, rheumatic diseases represent per se a risk factor for neuropsychiatric disorders. Although, at present, only a few cases of neuropsychiatric reactions have been described during dermatological use of HCQ [117–120], clinicians should closely monitor these patients, especially during the first week of treatment, consider discontinuing the medication in case serious psychiatric events occur, and implement interprofessional management with a psychiatrist to discuss antipsychotic or antidepressant options. Finally, it is important to state that none of the abovementioned cases of psychiatric toxicities are related to dosages normally used in dermatology [104].

6 The Role of Therapeutic Drug Monitoring

In the recent past, a vast amount of literature has been published on the potential role of therapeutic drug monitoring (TDM), namely monitoring of HCQ plasma levels, to assess patient adherence to therapy, or detect toxicities in situations of potential drug accumulation (e.g., severe renal or hepatic impairment). Of note, all studies have been carried out in SLE cohorts, thus limiting generalizability to dermatology.

On one hand, low blood concentrations of HCQ were found to be predictive of subsequent flares and thrombotic events in patients with SLE [121, 122], with non-adherence to HCQ being a major cause of flares in these patients [123]. On the other hand, Petri et al. (2020) demonstrated the usefulness of measuring blood levels of HCQ (median seven measurements) to predict the risk of retinopathy, with older age, higher body mass index, and longer duration of HCQ intake associated with a higher risk of toxicity [124].

However, results from a case–control study by Lenfant et al. (2020) are conflicting and failed to identify high HCQ blood levels as an independent risk factor [125], while confirming longer HCQ intake and high cumulative dose as key determinants [39]. Therefore, although reducing daily dose in patients with persistently high blood levels could be logical, the actual cost-utility and cost-effectiveness implications of TDM in dermatology remain uncertain.

7 What a Dermatologist Should Know

We have witnessed a notable surge in prescriptions of HCQ in recent years, not only for dermatological conditions but also for non-dermatological uses, particularly during the COVID-19 pandemic. This increased use has brought greater attention to its associated toxicities, such as ocular, cardiac, cutaneous, and psychiatric effects, thus underscoring the importance of regular monitoring and tailored risk management strategies including TDM,

Table 5 Key considerations for dermatologists when prescribing HCQ

Toxicity	Pre-treatment Screening	Monitoring during Treatment
Ophthalmological (retinopathy)	Perform baseline ophthalmological evaluation to rule out pre-existing retinopathy (dilated fundus exam, SD-OCT, and visual field testing) within the first year Use 24-2 or 30-2 visual field testing for Asian patients	Begin annual screening after 5 years of use unless risk factors (e.g., high dose[a], renal impairment, tamoxifen use) are present Regular monitoring with SD-OCT and visual field tests; use mf-ERG if early toxicity signs are suspected
Cardiac (QT prolongation, TdP)	Baseline ECG in patients with risk factors (e.g., renal/liver impairment, concurrent QT-prolonging drugs). Review co-medications with QT-prolonging potential and consult cardiologist in frail poly-medicated patients.	ECG monitoring after 3–4 days of therapy in patients with multiple risk factors Educate patients about symptoms of cardiac toxicity (e.g., tachycardia)
Cutaneous (rashes, SJS, TEN)	Inform patients about potential for skin reactions, especially in women over 50 Educate patients about signs of serious cutaneous reactions (e.g., SJS, TEN)	Advise patients to report any new rashes or skin discolorations Discontinue HCQ if severe reactions like SJS or TEN occur
Psychiatric (anxiety, psychosis)	Assess psychiatric history for risk of psychiatric symptoms	Monitor closely during the first week for symptoms such as anxiety, insomnia, or mood changes Discontinue if serious psychiatric symptoms appear and refer to a psychiatrist for management

ECG electrocardiography, *HCQ* hydroxychloroquine, *mf-ERG* multifocal electroretinography, *SD-OCT* spectral-domain optical coherence tomography, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *TdP* torsade de pointes

[a]Optimal patient dosing is ≤ 5.0 mg/kg of actual (real) body weight (≤ 6.5 mg/kg of ideal body weight) or 400 mg daily, whichever is lower, in most patients. Ideal dosing is unclear for obese patients

whenever feasible and cost-effective. However, aside from patients with pre-existing conditions that may predispose them to higher toxicity risks, HCQ remains a safe and valuable therapeutic option. This focused review provides an update on these selected toxicities. Table 5 provides a comprehensive summary of the key considerations for dermatologists when prescribing HCQ, including the identification of susceptible patients, thus supporting its safer prescribing. Dermatologists, in particular, should consider HCQ as a reliable alternative when managing chronic cutaneous conditions since, with personalized risk management, it continues to offer significant benefits in dermatological care.

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