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REVIEW

Systemic toxicity of chloroquine and hydroxychloroquine: prevalence, mechanisms, risk factors, prognostic and screening possibilities

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Abstract

Chloroquine (CQ) and its hydroxylated analog, hydroxychloroquine (HCQ), are 4-aminoquinoline initially used as an antimalarial treatment. CQ and HCQ (4-aminoquinoline, 4-AQ) are today used in rheumatology, especially to treat rheumatoid arthritis and systemic lupus erythematosus. Their mechanism of action revolves around a singular triptych: 4-AQ acts as alkalizing agents, ionized amphiphilic molecules, and by binding to numerous targets. 4-AQ have so pleiotropic and original mechanisms of action, providing them an effect at the heart of the regulation of several physiological functions. However, this broad spectrum of action is also at the origin of various and original side effects, notably a remarkable chronic systemic toxicity. We describe here the 4-AQ-induced lesions on the eye, the heart, muscle, the nerves, the inner ear, and the kidney. We also describe their prevalence, their pathophysiological mechanisms, their risk factors, their potential severity, and the means to detect them early. Most of these side effects are reversible if treatment is stopped promptly. This 4-AQ-induced toxicity must be known to prescribing physicians, to closely monitor its appearance and stop treatment in time if necessary.

Keywords Hydroxychloroquine · Iatrogenesis

Introduction

Chloroquine (CQ) and its hydroxylated analog, hydroxychloroquine (HCQ), are 4-aminoquinoline initially used as an antimalarial treatment. The fields of application of these molecules have increased considerably in recent years. Indeed, CQ and HCQ (anti-malarial drugs, 4-AQ) are today commonly used in rheumatology [1–3], especially for the treatment of systemic lupus erythematosus. Their mechanism of action revolves around a singular triptych: 4-AQ acts as alkalizing agents, in particular in lysosomes, but also as ionized amphiphilic molecules, modifying phospholipidic membranes properties, and finally by binding to numerous targets whose list is constantly increasing. 4-AQ are conventional synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs), which modulate innate and adaptive immunity by acting on several key points of immune regulation (Fig. 1). Indeed, 4-AQ inhibits the recognition of nucleic acids by TLRs (Toll-Like Receptor), the MHC (Major Histocompatibility Complex) class II-mediated antigen presentation, inflammation-induced cell proliferation, and antiphospholipid antibodies activity, which are major aspects of the pathophysiology of systemic lupus erythematosus for example [4–13]. But their action is not limited to the regulation of immunity: 4-AQ acts at the heart of the regulation of other primordial physiological functions, such as lipid and glucose metabolism, hemostasis, vasoactivity, and tumor control. This broad spectrum of action could lead to a wide range of undesirable effects, but 4-AQ are overall well-tolerated treatments. Many randomized clinical trials have studied 4-AQ, without highlighting any major risk associated with taking these drugs [14–18]. The most common side effects were headache and nausea, which could affect around 10% of patients. However, due to their limited size and duration, these studies cannot take into account the rare and late effects of these treatments. Yet, 4-AQ has a cumulative toxic effect on many organs.

Here we describe the systemic toxic effects associated with chronic 4-AQ intake apart from any overdose.

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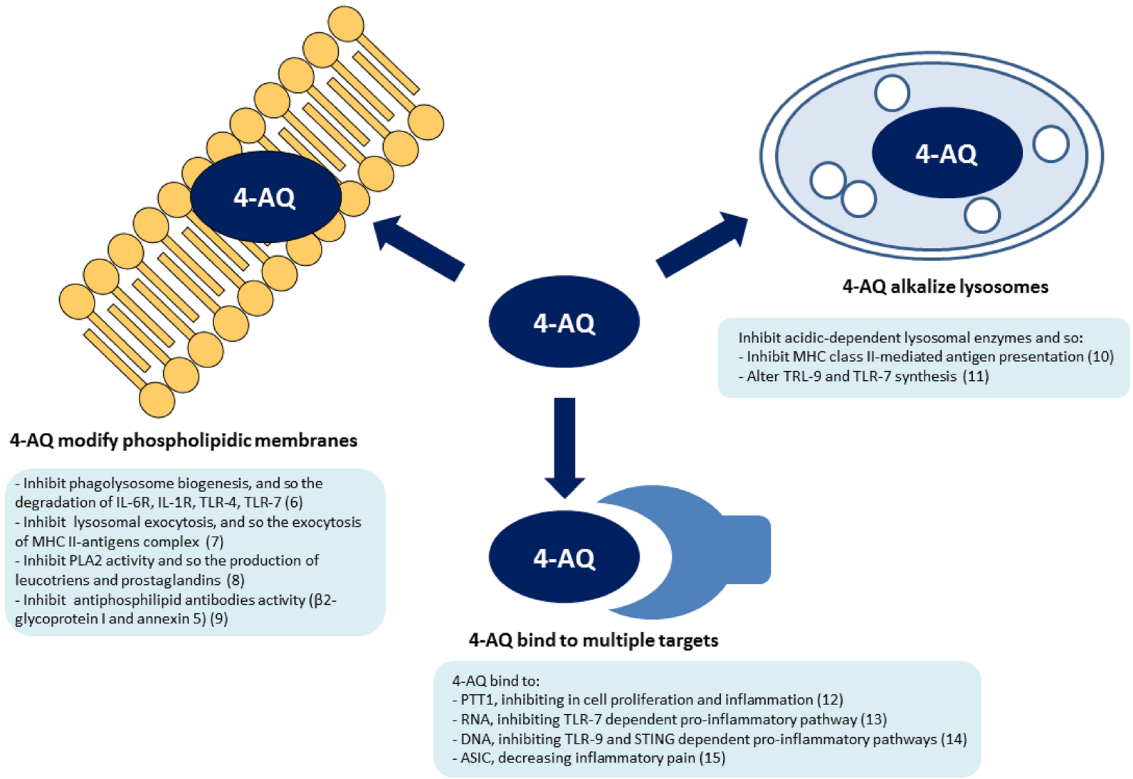

Legend: 4-AQ alkalize lysosomes, modify phospholipidic membranes properties and bind to numerous targets, thus widely regulating the immune system.

ASIC: Acid-Sensing Ion Channels inhibitors , MHC: major histocompatibility complex , PLA2: phospholipase A2, PTT1: Palmitoyl-protein

Fig. 1 4-AQ modulate innate and adaptive immunity by acting on several key points of immune regulation

Ocular toxicity

Ocular toxicity is the best known and most studied of the toxicities of 4-AQ. Among the ophthalmic disorders, retinal involvement is both the most frequent and the most likely to have serious functional repercussions [19].

Retinal toxicity

Induced lesions

The toxicity of 4-AQ is characterized by a progressive perifoveolar degeneration of the photoreceptors and cells of the pigment epithelium [20]. This degeneration is usually classified into 4 stages: a first "preclinical" phase corresponding to an eye fundus and normal visual acuity, followed by a "clinical" maculopathy corresponding to anomalies in the eye fundus or acuity visual, then by the stage of Bull's-eye maculopathy and finally blindness.

Prevalence

The exact prevalence of these retinal lesions is difficult to determine. Indeed, the progress made in recent years in screening methods has shown the presence of signs of early-onset retinal toxicity and therefore has led to an increase in its prevalence [21]. Thus, the prevalence of retinal toxicity assessed by visual acuity, fundoscopy, an Amsler grid, and/or color, vision assessments is estimated between 0.5 and 2% [22]. This toxicity is correlated with the duration of use of the treatment [23]. Retinopathy occurs only very rarely in the first 5 years of treatment for doses lower than 6.5 mg/kg/day, and in only 1% in the first 10 years [21]. However, it affects 3.1% of patients treated

for more than 20 years. The prevalence of retinal toxicity assessed by more modern and sensitive methods such as spectral-domain optical coherence tomography (SD-OCT) and 10-2 visual field analyser (VFA)is much higher, estimated at 7.5% [24, 25]. More precisely, this toxicity is estimated at less than 2% within the first 10 years of use but at almost 20% after 20 years of use [24]. The daily dose of 4-AQ plays a major role since patients treated with more than 5 mg/kg/day have 5–7 times more toxicity [24, 25].

Mechanisms

The eye is a prime target for 4-AQ toxicity, probably due to the high concentration of this molecule in the ocular tissue [26]. This particularly high concentration could be linked to the ability of 4-AQ to bind to melanin [27], which is particularly abundant in the retina. The mechanism of vision loss due to the toxicity of 4-AQ has been attributed to changes in the retinal pigment epithelium, which causes accumulation of lipofuscin and loss of photoreceptors [28]. Indeed, the accumulation of lipofuscin is implicated in many degenerative diseases of the retina, in particular in the degeneration of photoreceptors [29], and 4-AQ inhibit the autophagy of the cells of the pigment epithelium, inhibiting the lysosomal storage mechanisms of lipofuscin, so resulting in its intracellular accumulation [30]. In addition, 4-AQ are alkalizing agents, which inhibit the pH-dependent activity of organic anion transporting polypeptide 1A2 (OATP1A2) [31]. This inhibition prevents the recycling of all-trans-retinol in the cells of the pigment epithelium [32]. This accumulation of all-trans-retinol again leads to an accumulation of lipofuscin. However, several studies have suggested that the initial retinal damage does not occur in the retinal pigment epithelium but in the ganglion cells and that the other retinal layers are only affected until after [33, 34]. Indeed, experimental studies in rats and monkeys have shown degeneration of ganglion cells preceding CQ maculopathy [35]. In addition, patients without any clinical sign of 4-AQ maculopathy, and without any degeneration of the cells of the pigment epithelium have significantly lower retinal nerve fiber layer (RNFL) thickness measurements [36], indicating early loss of ganglion cells [37]. The mechanism of this toxicity is not precisely known to date. 4-AQ also seems to be able to permeabilize the blood-retinal barrier [38], and have direct toxicity to photoreceptors [39], without the mechanism being known.

Risk factors

The main risk factors known to date correspond to the dose of 4-AQ administered. First, the daily dose of 4-AQ administered, related to the patient's weight, is a risk factor [40]. Two different methods of calculation of this weight have been proposed [41]. Ideal body weight (IBW) is the oldest method, based on the fact that 4-AQ accumulates mainly in hydrophilic tissues and little in adipose tissue [42]. A daily dose > 6.5 mg/kg IBW constitutes a major risk factor of retinopathy. Nevertheless, "actual" body weight (ABW) appeared to be more efficient than IBW in a 2014 study [24], where a daily dose > 5 mg/kg ABW was the main risk factor. This superiority of ABW over IBW was not confirmed in a study carried out in 2016 on 565 patients [43]. Note that these estimates exclude the patient compliance rate. Some data suggest that the determination of plasma HCQ, which is correlated with compliance, is a good predictor of retinal toxicity [44]. The total duration of treatment is also a risk factor, especially after 5 years of treatment [45]. The cumulative dose, dependent on the daily dose and the duration of treatment, is so logically correlated with the occurrence of retinopathy [22]. A cumulative dose greater than 600 g seems to be particularly at risk [46]. Chronic kidney disease and tamoxifen [47] also appear to be risk factors. Older age, female gender, high body mass index, and genetic predisposition are discussed factor risks [21, 44, 48]. The toxicity of HCQ appears to be lower than that of CQ [49].

Prognosis

4-AQ-induced retinopathy can have significant functional implications. The first consequences on vision are the appearance of a peri-foveal annular scotoma [50], which gradually spreads, and can lead to significant loss of visual acuity or even blindness [51]. The classic late-stage finding of 4-AQ retinopathy, seen as a ring of retinal depigmentation in the parafoveal region is called Bull's-eye maculopathy [52]. In practice, stopping 4-AQ breaks the progression of lesions in the vast majority of cases, even if some rare cases of irremediable progression are reported [53]. Early stopping of 4-AQ is a major prognostic factor [54]: advanced lesions are irreversible and never regress, whereas cessation of 4-AQ before involvement of the external limiting membrane may be associated with regeneration of the photoreceptor layer and with potential functional visual improvement [55].

Screening

Recognition of retinopathy at an early stage, before any retinal pigment epithelium loss, is essential to prevent loss of visual acuity. The latest recommendations suggest

initial screening in the first year of treatment but can be done within 5 years [56–58]. This first screening must determine the existence of previous retinal lesions. All patients should receive baseline examination including fundus photography. The realization in addition of a systematic SD-OCT is recommended by The Royal College of Ophthalmologists [56]. The rest of the follow-up includes VFA plus SD-OCT. Systematic realization of widefield fundus autofluorescence is recommended by The Royal College of Ophthalmologists [56], whereas this exam is optional according to the American Academy of Ophthalmology [57]. Established retinal toxicity is defined by two test results with abnormalities typical of 4-AQ retinopathy, and should lead to stop the treatment. Patients with one abnormal test result on retinal imaging but normal visual fields should continue to be monitored annually.

Other ocular toxicity

4-AQ accumulates in the cornea [59], causing vortex keratinopathy [60]. These corneal deposits can be symptomatic and cause haloes and glare. These deposits are generally gradually reversible when the treatment is stopped. Concomitant use of amiodarone could be a risk factor [61].

Chronic intake of 4-AQ is also associated with a thinning of the choroid, associated with a signal void area on the choriocapillaris in the areas of the retinal pigment epithelium defect [62]. These anomalies are probably secondary to retinal toxicity since only observed in the context of toxic retinopathies, but direct choroid toxicity of 4-AQ is not excluded [63].

Rare cases of diplopia are reported, induced by the neuromuscular toxicity of CQ [64].

Cardiac toxicity

Induced lesions

The cardiac toxicity of 4-AQ is polymorphic [65]. Long-term use of 4-AQ is associated with the development of conduction disorders, structural heart disease, sick sinus syndrome [66], QT prolongation, elevation of cardiac biomarkers [67] and heart failure [68].

Prevalence

The exact prevalence of 4-AQ cardiotoxicity is difficult to estimate. Indeed, firstly, this cardiac involvement is polymorphic, secondly, it is influenced by the cumulative dose of 4-AQ, and thirdly the estimates fluctuate between studies. Thus, QT prolongation is observed in 1–10% of patients under 4-AQ, as highlighted by the numerous trials conducted with these treatments in COVID-19 [69, 70]. This prolongation usually appears between the 3rd and 5th day of treatment [71]. Secondary torsades de pointes are rare [72], but may occur up to several years after initiation of treatment if it is maintained [73]. Conduction abnormalities have rarely been observed in the context of COVID-19 [69, 70], but seem more frequent in the context of systemic lupus erythematosus, affecting nearly 16% of patients in a study of 453 patients with a cumulative median dose of 1200 g [74]. The conductive anomalies reported are mainly atrioventricular blocks, followed by bundle branch blocks [75] and appear to be more frequent in the short term than after prolonged treatment [74]. Structural anomalies are estimated at almost 12% of patients in this same study. These are mainly ventricular enlargements, more rarely restrictive heart disease. Ventricular hypokinesias are also reported. Valvular and pulmonary artery wall hypertrophy abnormalities seem very rare.

Mechanisms

4-AQ has several effects on the heart. First, 4-AQ alkalizes the cardiomyocyte lysosomes, which cause structural heart disease [76]. Indeed, endomyocardial biopsies reveal an accumulation of polysaccharides in cardiomyocytes, probably due to the inhibition of the activity of alpha-galactosidase A, beta-galactosidase, and arylsulfatase, which is reversible after 4-AQ cessation [77]. The pathophysiology of ventricular thickening induced by 4-AQ therefore closely resembles that of Fabry disease, a genetic deficit in alpha-galactosidase A [78]. Ventricular hypertrophy is common to these two pathologies, and, histologically, only the presence of curvilinear bodies in electron microscopy, specific to the toxicity of 4-AQ can make the difference with fabry disease [79]. 4-AQ also exert a "quinine-like" effect due to its common chemical structure with quinidine drugs [80]. Therefore, they are a class 1a antiarrhythmic drug, which, at a physiological dose, can be responsible for a flattening of electrocardiographic T wave, QT prolongation, and cardiac arrhythmia [81].

Risk factors

Risk factors for the development of 4-AQ-induced cardiotoxicity include advanced age, female gender, long duration of treatment with a high cumulative dose, and renal failure [76, 82]. The presence of retinopathy and clinical signs of myopathy are also correlated with cardiac involvement

[75]. Finally, genetic susceptibility is discussed [83], and Fabry disease seems to constitute a genetic predisposition to the cardiac toxicity of 4-AQ [84]. Arrhythmia, QT prolongation and conduction disorders are more frequent using CQ versus HCQ [85], and more frequent at the initiation of treatment than after several years. Other risk factors for the appearance of arrhythmia or conduction disorders include the co-prescription of anti-arrhythmic drugs or treatments that prolong QT [86].

Prognosis

Prognosis in 4-AQ cardiotoxicity can vary from complete improvement in cardiac function to death or cardiac transplantation [87]. According to two studies published in 2018 using data from 42 [88] and 78 [84] patients, treatment withdrawal resulted in complete recovery of heart function in 20–45% of patients but did not prevent the death of 15–45% of them. Meanwhile, regression of conduction disease appears to be rare.

Screening

Performing an electrocardiogram (ECG) before then daily for 5 days after starting 4-AQ is recommended to detect conduction disorder or prolonged QT [89, 90]. However, there is no clinical trial demonstrating the relevance of systematic screening for chronic myocardial toxicity. In the context of chronic treatment, Chatre et al. [75] recommend performing an ECG and an echocardiography every 2 years during treatment for screening cardiac structural and conduction disorders. Tselios et al. [67] suggest the evaluation of cardiac biomarkers (troponin, brain natriuretic peptide: BNP) as a screening test for patients using 4-AQ for longer than 5 years. In case of an abnormality in this screeing, the realization of a heart RMI, endomyocardial biopsy or genetic Fabry disease screening are sometimes necessary to confirm the diagnosis of 4-AQ toxicity.

Neuromuscular toxicity

Induced lesions

Neuromuscular toxicity of 4-AQ is polymorphic [91]. 4-AQ may be responsible for bilateral proximal symmetric muscle deficits, and polyneuropathies [92].

Prevalence

The prevalence of muscle toxicity has been studied in several studies. Casado et al. [93] defined this toxicity by the association of increased creatinine kinase level and a compatible histological pattern in a study of 119 patients, reporting a prevalence of toxic myopathy induced by 4-AQ at almost 10%, corresponding to an annual incidence of 1%. Avina-Zubieta et al. focused on the clinical assessment of this toxicity, that is to say, the occurrence of muscle deficit, affecting approximately 1 in 100 patient-years treatment in their study [94].

The prevalence of central and peripheral neuronal damage is unknown but appears to be rare [95].

Mechanisms

The mechanism of lesions induced by 4-AQ on rhabdomyocytes seems similar to that of lesions induced on cardiomyocytes. The lysosomal alkalinization and the ensuing enzymatic inhibition causes an accumulation of membrane phospholipids and glycogen and subsequently curvilinear bodies and lamellar structures [96]. The histological aspect can highlight acid phosphatase-positive granules and vacuoles, as in the context of the Pompe disease, a glycogenosis due to deficiency of lysosomal acid α-glucosidase [97]. Analysis by light microscopy is however most often normal [93]. Electron microscopy reveals curvilinear bodies and myeloid bodies, membranous whorls, and autophagic structures. These cytoplasmic complex lipid bodies constitute the characteristic features of antimalarial myopathy. Only ceroid lipofuscinosis, a rare lipid storage disease, can show a similar pattern [98]. CQ also inhibits cytokine production, resulting in fiber digestion and distinctive cytosome formation with curvilinear profiles and lipofuscin on histopathological findings [99]. Alteration of antioxidant enzymes and alteration of regulation of oxidative metabolites such as nitric oxide (NO) also plays an important role in increasing lipid peroxidation in nerve and muscle tissue [100]. In addition, in vitro, 4-AQ has the property of inhibiting neuromuscular transmission, without the mechanism of action being known [101]. Nerve damage appears to be linked to perineural and Schwann cell damage [102]. Nerve biopsies indeed reveal demyelination associated with cytoplasmic inclusions within Schwan cells [103].

Risk factors

Risk factors for 4-AQ-induced neuromyotoxicity are not well known. Caucasians and kidney failure are likely risk factors [96]. Concomitant use of other myotoxic drugs, such as statins, proton pump inhibitors or corticosteroids has been reported as a possible risk factor [104]. The duration of treatment is probably a risk factor since treatment has been taken for more than a year in the majority of the cases reported [105]. The presence of cardiac toxicity is correlated with the

existence of peripheral muscular toxicity [84]. HCQ probably has less muscle toxicity than CQ [106].

Prognosis

The neuromuscular toxicity of 4-AQ is generally moderate [105]. Only a few serious cases with life-threatening effects are described [107, 108]. Stopping treatment most often allows almost complete recovery [105, 109].

Screening

There is no clinical trial demonstrating the relevance of systematic screening for chronic neuromuscular toxicity. A complete clinical examination and an annual evaluation of muscular enzymes level is recommended by Casado et al., which has the advantage of being non-invasive and simple to perform, despite an imperfect sensitivity [93].

Cutaneous toxicity

Induced lesions

In addition to acute skin manifestations probably of allergic origin and non-specific, 4-AQ are associated with chronic pruritus [110] and skin pigmentation disorders: both hyperpigmented macules [111], which predominates on the anterior side of the shins, and depigmentation of the skin, nails and hair [112].

Prevalence

The prevalence of CQ-induced pruritus has been estimated up to 50% of patients in several studies [113], while recently the prevalence of HCQ-induced pruritus has been estimated to be less than 10% [114]. The prevalence of HCQ-induced hyperpigmentation can affect between 10 and 20% of the patients according to recent studies [115, 116]. 4-AQ induced hypopigmentation seems to be rare.

Mechanisms

Concerning pruritus, CQ can bind to and activate the mas-related G protein-coupled receptors MrgprA3/MrgprX, which can be coupled to PLC-b3 or TRPA1 and so initiate pruritus [117]. The activation of this receptor is the main known mechanism of CQ-induced pruritus and even constitutes an animal model of itch [118]. More, opiate receptor, serotonin receptor, *N*-methyl-D-aspartate receptors, and gastrin-releasing peptide receptor are probably involved in this iatrogen itch, but exact mechanisms are unknown [119]. 4-AQ-induced hyperpigmentation has been studied through histological studies, describing melanin granules and hemosiderin deposits in the dermis corresponding to bruises [120]. The main physiopathological hypothesis to date is that these hyperpigmentations are initially triggered by real bruising. Indeed, bruises "which do not disappear" are reported, as well as post-traumatic hyperpigmentations [115]. 4-AQ-induced immunosuppression, including decreased phagocytic function, inhibition of lysosomal function, and decreased secretion of pro-inflammatory cytokines, may inhibits clearance of skin deposits from hemosiderins and decreases the elimination of melanin [121]. Accumulation within the dermis of these deposits can locally stimulate melanogenesis, explaining the localized skin hyperpigmentation [120]. This hypothesis is consistent with the fact that the main known risk factor for these hyperpigmented macules is the taking of antiaggregant or anticoagulant treatment [115, 116]. Concerning the depigmentation of integuments, mechanisms of 4-AQ-induced poliosis and vitiligo remain unclear; the main hypothesis is that 4-AQ bind to eumelanin and pheomelanin and so disturb melanogenesis [122].

Risk factors

Renal failure is associated with skin adverse effect [117]. Itching is more frequent with HCQ than with CQ. Acute pruritus and skin depigmentation exhibit a racial predilection, rather occurring in black subjects [123]. The duration of treatment is correlated with the appearance of hyperpigmented lesions [115]. Thus, their prevalence is multiplied by 3 after 5 years of treatment. Platelet antiaggregants and oral anticoagulants are also predisposing factors to 4-AQ-induced pigmentation [115, 116].

Prognosis

Adverse skin effects are rarely life-threatening [124]. However, these lesions can have a strong aesthetic impact, in particular when they touch the face or the hair. Hair or nail coloring disorders and pruritus completely regress when treatment is stopped [110, 112]. Nevertheless, the regression of hyper and hypo-pigmented macules is only partial after stopping 4-AQ. Q-switched ruby laser could provide regression of lesions [125].

Screening

The patient's skin should be regularly examined [116]. Black patients and those taking treatment which facilitate bruising

should be warned of the respective risks of depigmentation and hyperpigmentation of integuments.

Ear nose and throat (ENT) toxicity

Induced lesions

4-AQ-induced taste and odor changes are described [126]. Acute and chronic audiovestibular manifestations are also reported [127] including tinnitus, vertigo, hearing loss and deafness [128, 129]. 4-AQ can also cause dysphagia, due to its muscle toxicity [130].

Prevalence

Prevalence of 4-AQ-induced taste and odor changes is unknown. Acute and transient audiovestibular disorders are reported in 10% of patients when initiating HCQ [131]. Audiovestibular manifestations also correspond to almost 3% of the adverse effects of 4-AQ reported to French pharmacovigilance centers [132].

Mechanisms

The inner ear is an organ rich in melanocytes, the loss of which is responsible for audiovestibular dysfunction [133]. Thus, it has been suggested that, as in the context of skin depigmentation induced by 4-AQ, the binding of 4-AQ to pheomelanin is harmful to the melanocyte and provokes progressive dysfunction of the inner ear [134]. The decrease in melanin could in particular lead to an accumulation of reactive oxygen species toxic to cochlear hair cells [135]. This chronic toxicity could explain that prolonged treatment with CQ leads to progressive impairment of auditory evoked potentials (AEP) [136]. Sudden deafness occurring after years of treatment with 4-AQ could be of ischemic origin. Indeed, several histological studies have reported the destruction of cochlear sensory hair cells, of neuronal population, and support structures, associated with vasoconstriction of the capillaries suggesting an underlying ischemic mechanism [137]. The mechanisms of taste and odor alteration remain unclear.

Risk factors

4-AQ-induced audiovestibular complication can appear from the first administration of 4-AQ [138], but are more frequent after 1 year of treatment [132]. A prolonged exposure time and high cumulative doses are so probably risk factors [139]. Acoustic trauma could also represent a risk factor [135].

Prognostic

4-AQ-induced taste and odor changes are reversible after interruption of treatment [126]. Acute and mild audiovisual disorders occurring at the start of treatment are often transient without sequelae [131, 140]. Conversely, sudden deafness occurring during 4-AQ treatment, suspected of being of ischemic origin, is most often irreversible [141], even if rare cases with a favorable outcome after stopping treatment and prescribing corticosteroids are reported [142]. 4-AQ-induced chronic and progressive audiovestibular toxicity, suspected of being secondary to the decrease in melanin, appear to be reversible when treatment is stopped early, that is to say when the signs of toxicity appear on the hearing evoked potentials, before any hearing loss on the audiogram [136].

Screening

No screening strategy has proven effective to date. Sudden deafness of vascular origin seems unpredictable. Chronic audiovisual dysfunction can be detected by auditory evoked potentials, which are much more sensitive than the audiogram.

Kidney toxicity

Induced lesions

Taking 4-AQ is associated with the onset of chronic renal failure [78, 143]. 4-AQ-induced polyuria is also described [144].

Prevalence

Prevalence of kidney toxicity is unknown, but seems to be extremely rare since only a few case reports are described.

Mechanisms

In case of kidney failure, biopsies reveal renal phospholipidosis, characterized by Zebra bodies and myelin figures at electron microscopy [145, 146]. These aspects are in favor of an accumulation of polysaccharides induced by the alkalinization of lysosomes caused by 4-AQ. Impairment of autophagy flux is also harmful to glomerular and tubular cells [147]. This nephropathy closely resembles that of Fabry disease, all the more so in the event of 4-AQ-induced cardiac toxicity associated [148–150]. 4-AQ-induced polyuria is multifactorial. On the one hand, 4-AQ downregulates the water channel aquaporin-2 and

Table 1 Systemic toxicity of 4-AQ

Involved organ	4-AQ-induced lesion	Estimated prevalence	Suspected mechanisms	Suspected risk factors	Prognosis	Proposed screening
Retina	Perifoveolar degeneration of the photoreceptors	Assessment by AVF and SD OCT: Less than 2% within the first 10 years but almost 20% after 20 years of use [24]	Accumulation of lipofuscin Alteration of ganglion cells	Daily dose of 4-AQ > 6.5 mg/kg IBW Daily dose of 4-AQ > 5 mg/kg ABW Duration of treatment by 4-AQ > 5 years Cumulative dose of 4-AQ > 600 g CQ more toxic than HCQ Chronic kidney disease, tamoxifen, older age, female gender, high body mass index, some genetic predispositions	Blindness if continued treatment Reversible lesions if early cessation	Control at baseline, and then again after 5 years, including AVF and SD OCT Then, AVF and SD OCT each year [56, 57]
Heart	Conduction and rhythm disorders	1–15% of the patients [74]	Quinine-like effect	Co-prescription of: Anti-arrhythmic drugs Treatments that prolong QT Initiation of the treatment	Reversible after cessation	ECG before and daily for a few days after starting 4-AQ [89] Then,ECG every 2 years [75]
	Structural heart disease	10% of the patients [75]	Lysosomal dysfunction and accumulation of polysaccharides, Fabry-like disease	Cumulative dose of 4-AQ Advanced age, female gender, kidney failure, toxic retinopathy, toxic myopathy, some genetic dispositions	After cessation 50% complete recovery 35% of sequelae 15% of death	Echocardiography every 2 years [75] and annual evaluation of cardiac biomarkers [67]
Neuromuscular	Chronic myopathy	1% of the patients per year [93]	Lysosomal dysfunction, Pompe-like disease	Cumulative dose of 4-AQ HCQ more toxic than CQ	Reversible after cessation	Annual examination and evaluation of muscular enzymes [93]
	Chronic polyneuropathy	Unknown but rare	Demyelination, Schwan cell dysfunction	Cardiac toxicity, Caucasian origin, kidney failure, concomitant statin, proton pump inhibitors or corticosteroids		
Skin	Pruritus	50% of the patients [113]	Activation of MrgprA3/MrgprX	African origin, kidney failure, CQ more than HCQ	Reversible after cessation	Regular skin exam [116]
	Hyperpigmented macules	10–50% of the patients [116]	Inhibition of clearance of hemosiderins	Extended duration of treatment Platelet antiaggregants Oral anticoagulants	Partial regression after cessation	
	Depigmentation	Unknown but rare	Binding to melanin and disturbing melanogenesis	African origin, kidney failure	Partial regression after cessation	

Table 1 (continued)

Involved organ	4-AQ-induced lesion	Estimated prevalence	Suspected mechanisms	Suspected risk factors	Prognosis	Proposed screening
Inner ear	Chronic audiovestibular dysfunction	Unknown	Binding to melanin and disturbing melanogenesis	Duration of the treatment > 1 year Cumulative dose of 4-AQ, acoustic trauma	Reversible lesions if early cessation	No validate screening Discuss AEP [136]
	Acute audiovestibular dysfunction	Unknown	Ischemic lesions	Acoustic trauma	Sometimes reversible	No screening
Kidney	Chronic renal failure	Extremely rare	Lysosomal dysfunction, Fabry-like disease	Extended duration of the treatment	Reversible after cessation	Annual creatinine testing

the Na^+-K^+-$2Cl^-$-cotransporter (NKCC), causing urinary sodium loss and an increase in diuresis [144]. On the other hand, it is showed that CQ modulates the synthesis of plasma arginine vasopressin [151, 152] and its effect on the kidney [153], disrupting the urine concentration mechanisms.

Risk factors

Kidney toxicity is associated with prolonged treatment and a cumulative dose of 4-AQ [146].

Prognostic

4-AQ-induced kidney toxicity appears to be reversible upon discontinuation of 4-AQ [146].

Screening

There is no validated strategy for monitoring the kidney toxicity of 4-AQ. However, given the very progressive onset of kidney failure, annual creatinine testing seems both effective and minimally invasive.

Conclusion

4-AQ have pleiotropic and original mechanisms of action, acting at the heart of the regulation of immunity, lipid and glucose metabolism, hemostasis, vasoactivity, and tumor control. However, this broad spectrum of action is also at the origin of various and original side effects, notably including ocular, cardiac, neuromuscular or cutaneous toxicity (Table 1). Most of these side effects are reversible if treatment is stopped early, but can have serious consequences if stopped too late. The pathophysiology and risk factors of these toxicities are becoming better known, allowing identifying the riskiest situations (Table 2), and proposing risk reduction strategies (Table 3). For instance, prescribing HCQ instead of CQ seems to reduce retinal, cutaneous, and neuromuscular toxicity, and regular monitoring of muscle enzymes appears to be effective in detecting neuromuscular toxicity. This 4-AQ-induced toxicity most often occurs after chronic treatment and must be known to prescribing physicians. It is important to closely monitor its appearance and, if necessary, to stop the treatment before the benefit-risk balance becomes unfavorable.

Table 2 Situations particularly at risk of 4-AQ related systemic toxicity

	Risk factors	Involved organs
4-AQ-related risk factors	High daily dose	Retina
	Short duration of treatment	Conduction disorders
	Long duration of treatment	Retina, inner ear
	CQ more toxic than HCQ	Retina, neuromuscular, pruritus
	High cumulative dose of treatment	Retina, heart, neuromuscular, skin, inner ear, kidney
Patient-related risk factors	Chronic kidney disease,	Retina, heart, skin
	Advanced age	Retina, heart
	Female gender,	Retina, heart
	high body mass index	Retina
	Caucasian origin	Neuromuscular
	African origin	Skin
	Genetic predispositions	Retina, heart
	Acoustic trauma	Inner ear
Drug co-prescription	Anti-arrhythmic drugs	Heart
	Treatments that prolong QT	Heart
	Tamoxifen,	Retina
	Statin	Neuromuscular
	Proton pump inhibitors	Neuromuscular
	Corticosteroids	Neuromuscular
	Platelet antiaggregants	Skin
	Oral anticoagulants	Skin

Table 3 Proposed screening for 4-AQ-induced toxicity [56, 57, 67, 75, 89, 93, 116]

Screening	Periodicity
AVF and SD OCT	Control at baseline, and then each year after 5 years of treatment
ECG	Before treatment, then daily for a few days after starting 4-AQ, and finally every 2 years [75, 90]
Echocardiography	Every 2 years
Evaluation of cardiac biomarkers	Annual
Evaluation of muscular enzymes	Annual
Evaluation of creatinine	Annual

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Declarations

Conflict of interest The author(s) declare that they have no competing interests.

References

1. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, Khamashta MA (2010) Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. Ann Rheum Dis 69(1):20–28
2. Raghu G, Berman JS, Govender P (2018) Treatment of sarcoidosis. Am J Respir Crit Care Med 197(6):P9-10
3. Smolen JS, Landewé R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M et al (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 76(6):960–977
4. Lübow C, Bockstiegel J, Weindl G (2020) Lysosomotropic drugs enhance pro-inflammatory responses to IL-1β in macrophages by inhibiting internalization of the IL-1 receptor. Biochem Pharmacol 20(175):113864
5. Lapaquette P, Nguyen HTT, Faure M (2017) L'autophagie garante de l'immunité et de l'inflammation—Tout est bien, tout va bien, tout va pour le mieux qu'il soit possible. Méd Sci 33(3):305–311
6. Europe PMC (Internet) (2020) Antimalarial drugs inhibit phospholipase A2 activation and induction of interleukin 1beta and tumor necrosis factor alpha in macrophages: implications for their mode of action in rheumatoid arthritis. Abstract (cited 2020 Mar 25). Available from: https://europepmc.org/article/med/9510087. Accessed 25 Mar 2020
7. Rand JH, Wu X-X, Quinn AS, Ashton AW, Chen PP, Hathcock JJ et al (2010) Hydroxychloroquine protects the annexin A5 anticoagulant shield from disruption by antiphospholipid antibodies:

evidence for a novel effect for an old antimalarial drug. Blood 115(11):2292–2299
8. Ewald SE, Lee BL, Lau L, Wickliffe KE, Shi G-P, Chapman HA et al (2008) The ectodomain of toll-like receptor 9 is cleaved to generate a functional receptor. Nature 456(7222):658–662
9. Hsing LC, Rudensky AY (2005) The lysosomal cysteine proteases in MHC class II antigen presentation. Immunol Rev 207:229–241
10. Rebecca VW, Nicastri MC, Fennelly C, Chude CI, Barber-Rotenberg JS, Ronghe A et al (2019) PPT1 promotes tumor growth and is the molecular target of chloroquine derivatives in cancer. Cancer Discov 9(2):220–229
11. Vollmer J, Tluk S, Schmitz C, Hamm S, Jurk M, Forsbach A et al (2005) Immune stimulation mediated by autoantigen binding sites within small nuclear RNAs involves toll-like receptors 7 and 8. J Exp Med 202(11):1575–1585
12. An J, Woodward JJ, Sasaki T, Minie M, Elkon KB (2015) Cutting edge: antimalarial drugs inhibit IFN-β production through blockade of cyclic GMP-AMP synthase–DNA interaction. J Immunol (Internet) (cited 2020 Mar 25). Available from: https://www.jimmunol.org/content/early/2015/03/27/jimmunol.1402793. Accessed 25 Mar 2020
13. Roy DN (2018) Acid sensing ion channels (ASICS): potential targets for the discovery of novel therapeutics in disease management. Int J Clin Biomed Res 4:62–68
14. Paton NI, Lee L, Xu Y, Ooi EE, Cheung YB, Archuleta S et al (2011) Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. Lancet Infect Dis 11(9):677–683
15. Gottenberg J-E, Ravaud P, Puéchal X, Le Guern V, Sibilia J, Goeb V et al (2014) Effects of hydroxychloroquine on symptomatic improvement in primary Sjögren syndrome: the JOQUER randomized clinical trial. JAMA 312(3):249–258
16. Pareek A, Khopkar U, Sacchidanand S, Chandurkar N, Naik GS (2008) Comparative study of efficacy and safety of hydroxychloroquine and chloroquine in polymorphic light eruption: a randomized, double-blind, multicentric study. Indian J Dermatol Venereol Leprol 74(1):18–22
17. Yokogawa N, Eto H, Tanikawa A, Ikeda T, Yamamoto K, Takahashi T et al (2017) Effects of hydroxychloroquine in patients with cutaneous lupus erythematosus: a multicenter, double-blind, randomized. Parallel-Group Trial Arthritis Rheumatol Hoboken NJ 69(4):791–799
18. Divala TH, Mungwira RG, Mawindo PM, Nyirenda OM, Kanjala M, Ndaferankhande M et al (2018) Chloroquine as weekly chemoprophylaxis or intermittent treatment to prevent malaria in pregnancy in Malawi: a randomised controlled trial. Lancet Infect Dis 18(10):1097–1107
19. Aylward JM (1993) Hydroxychloroquine and chloroquine: assessing the risk of retinal toxicity. J Am Optom Assoc 64(11):787–797
20. Tehrani R, Ostrowski RA, Hariman R, Jay WM (2008) Ocular toxicity of hydroxychloroquine. Semin Ophthalmol 23(3):201–209
21. Jorge A, Ung C, Young LH, Melles RB, Choi HK (2018) Hydroxychloroquine retinopathy—implications of research advances for rheumatology care. Nat Rev Rheumatol 14(12):693–703
22. Wolfe F, Marmor MF (2010) Rates and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Care Res 62(6):775–784
23. Mavrikakis I, Sfikakis PP, Mavrikakis E, Rougas K, Nikolaou A, Kostopoulos C et al (2003) The incidence of irreversible retinal toxicity in patients treated with hydroxychloroquine: a reappraisal. Ophthalmology 110(7):1321–1326
24. Melles RB, Marmor MF (2014) The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. JAMA Ophthalmol 132(12):1453–1460
25. Browning DJ, Lee C (2018) Somatotype, the risk of hydroxychloroquine retinopathy, and safe daily dosing guidelines. Clin Ophthalmol Auckl NZ 3(12):811–818
26. McChesney EW, Banks WF, Fabian RJ (1967) Tissue distribution of chloroquine, hydroxychloroquine, and desethylchloroquine in the rat. Toxicol Appl Pharmacol 10(3):501–513
27. Ings RM (1984) The melanin binding of drugs and its implications. Drug Metab Rev 15(5–6):1183–1212
28. Sundelin SP, Terman A (2002) Different effects of chloroquine and hydroxychloroquine on lysosomal function in cultured retinal pigment epithelial cells. APMIS Acta Pathol Microbiol Immunol Scand 110(6):481–489
29. Blasiak J (2020) Senescence in the pathogenesis of age-related macular degeneration. Cell Mol Life Sci CMLS 77(5):789–805
30. Lei L, Tzekov R, Li H, McDowell JH, Gao G, Smith WC et al (2017) Inhibition or stimulation of autophagy affects early formation of lipofuscin-like autofluorescence in the retinal pigment epithelium cell. Int J Mol Sci (Internet) (cited 2020 Mar 30) 18(4). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5412314/. Accessed 30 Mar 2020
31. Morita T, Akiyoshi T, Sato R, Katayama K, Yajima K, Kataoka H et al (2019) pH-dependent transport kinetics of the human organic anion-transporting polypeptide 1A2. Drug Metab Pharmacokinet (Internet) (cited 2020 Mar 30). Available from: http://www.sciencedirect.com/science/article/pii/S1347436719302423. Accessed 30 Mar 2020
32. Maeda A, Maeda T, Golczak M, Palczewski K (2008) Retinopathy in mice induced by disrupted all-trans-retinal clearance. J Biol Chem 283(39):26684–26693
33. Ivanina TA, Zueva MV, Lebedeva MN, Bogoslovsky AI, Bunin AJ (1983) Ultrastructural alterations in rat and cat retina and pigment epithelium induced by chloroquine. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol 220(1):32–38
34. Ramsey MS, Fine BS (1972) Chloroquine toxicity in the human eye. Histopathologic observations by electron microscopy. Am J Ophthalmol 73(2):229–35
35. Yoshida T, Fukatsu R, Tsuzuki K, Aizawa Y, Hayashi Y, Sasaki N et al (1997) Amyloid precursor protein, a beta and amyloid-associated proteins involved in chloroquine retinopathy in rats—immunopathological studies. Brain Res 764(1–2):283–288
36. Bonanomi MT, Dantas NC, Medeiros FA (2006) Retinal nerve fibre layer thickness measurements in patients using chloroquine. Clin Exp Ophthalmol 34(2):130–136
37. Brandao LM, Palmowski-Wolfe AM (2016) A possible early sign of hydroxychloroquine macular toxicity. Doc Ophthalmol Adv Ophthalmol 132(1):75–81
38. Korthagen NM, Bastiaans J, van Meurs JC, van Bilsen K, van Hagen PM, Dik WA (2015) Chloroquine and hydroxychloroquine increase retinal pigment epithelial layer permeability. J Biochem Mol Toxicol 29(7):299–304
39. Pasadhika S, Fishman GA, Choi D, Shahidi M (2010) Selective thinning of the perifoveal inner retina as an early sign of hydroxychloroquine retinal toxicity. Eye Lond Engl 24(5):756–762 (**quiz 763**)
40. Levy GD, Munz SJ, Paschal J, Cohen HB, Pince KJ, Peterson T (1997) Incidence of hydroxychloroquine retinopathy in 1,207 patients in a large multicenter outpatient practice. Arthritis Rheum 40(8):1482–1486
41. Marmor MF (2017) Hydroxychloroquine screening alert: change is in the wind. Ophthalmic Surg Lasers Imaging Retina 48(2):96–8

42. Furst DE (1996) Pharmacokinetics of hydroxychloroquine and chloroquine during treatment of rheumatic diseases. Lupus. 5(1):11–15
43. Melles RB, Marmor MF (2016) The prevalence of hydroxychloroquine retinopathy and toxic dosing, and the role of the ophthalmologist in reducing both. Am J Ophthalmol 170:240
44. Petri M, Elkhalifa M, Li J, Magder LS, Goldman DW (2020) Hydroxychloroquine blood levels predict hydroxychloroquine retinopathy. Arthritis Rheumatol 72(3):448–453
45. Eo D, Lee MG, Ham D-I, Kang SW, Lee J, Cha HS et al (2017) Frequency and clinical characteristics of hydroxychloroquine retinopathy in korean patients with rheumatologic diseases. J Korean Med Sci 32(3):522–527
46. Mills PV, Beck M, Power BJ (1981) Assessment of the retinal toxicity of hydroxychloroquine. Trans Ophthalmol Soc UK 101(1):109–113
47. Hambly R, Lally A (2017) Hydroxychloroquine toxicity and aromatase inhibitors. Br J Dermatol 177(3):882–882
48. Katsman D, Sanfilippo C, Sarraf D (2017) Panretinal degeneration associated with long-term hydroxychloroquine use and heterozygous USH2A mutation. Retin Cases Brief Rep 11(1):S77–S80
49. Finbloom DS, Silver K, Newsome DA, Gunkel R (1985) Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. J Rheumatol 12(4):692–694
50. Browning DJ, Lee C (2015) Scotoma analysis of 10-2 visual field testing with a white target in screening for hydroxychloroquine retinopathy. Clin Ophthalmol Auckl NZ 9:943–952
51. Ingster-Moati I, Quoc EB, Crochet M, Orssaud C, Dufier J-L, Roche O (2008) Intoxication rétinienne sévère aux antipaludéens de synthèse. /data/revues/01815512/00290006/642/ (Internet) (cited 2020 Mar 30). Available from: https://www.em-consulte.com/en/article/113253. Accessed 30 Mar 2020
52. Modi YS, Singh RP (2019) Bull's-eye maculopathy associated with hydroxychloroquine. N Engl J Med (Internet) (cited 2020 Mar 30). Available from: https://www.nejm.org/doi/10.1056/NEJMicm1412167?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dwww.ncbi.nlm.nih.gov. Accessed 30 Mar 2020
53. Kellner S, Weinitz S, Farmand G, Kellner U (2014) Cystoid macular oedema and epiretinal membrane formation during progression of chloroquine retinopathy after drug cessation. Br J Ophthalmol 98(2):200–206
54. Marmor MF, Hu J (2014) Effect of disease stage on progression of hydroxychloroquine retinopathy. JAMA Ophthalmol 132(9):1105–1112
55. Mititelu M, Wong BJ, Brenner M, Bryar PJ, Jampol LM, Fawzi AA (2013) Progression of hydroxychloroquine toxic effects after drug therapy cessation: new evidence from multimodal imaging. JAMA Ophthalmol 131(9):1187–1197
56. The Royal College of Ophthalmologists (2020) Opthalmologists TRC of clinical guidelines (Internet) (cited 2020 Mar 30). Available from: https://www.rcophth.ac.uk/standards-publications-research/clinical-guidelines/. Accessed 30 Mar 2020
57. Marmor MF, Kellner U, Lai TYY, Melles RB, Mieler WF, American Academy of Ophthalmology (2016) Recommendations on screening for chloroquine and hydroxychloroquine retinopathy (2016 revision). Ophthalmology 123(6):1386–1394
58. Rosenbaum JT, Costenbader KH, Desmarais J, Ginzler EM, Fett N, Goodman SM et al (2021) ACR, AAD, RDS, and AAO 2020 joint statement on hydroxychloroquine use with respect to retinal toxicity. Arthritis Rheumatol Hoboken NJ. https://doi.org/10.1002/art.41683
59. Stokkermans TJ, Trichonas G (2020) Chloroquine and hydroxychloroquine toxicity. StatPearls Publishing (Internet), Treasure Island (FL) (cited 2020 Mar 30). Available from: http://www.ncbi.nlm.nih.gov/books/NBK537086/. Accessed 30 Mar 2020
60. Dosso A, Rungger-Brändle E (2007) In vivo confocal microscopy in hydroxychloroquine-induced keratopathy. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol 245(2):318–320
61. D'Amico DJ, Kenyon KR, Ruskin JN (1981) Amiodarone keratopathy: drug-induced lipid storage disease. Arch Ophthalmol Chic Ill 1960 99(2):257–261
62. Ahn SJ, Ryu SJ, Joung JY, Lee BR (2017) Choroidal thinning associated with hydroxychloroquine retinopathy. Am J Ophthalmol 183:56–64
63. Ahn SJ, Ryu SJ, Lim HW, Lee BR (2019) Toxic effects of hydroxychloroquine on the choroid: evidence from multimodal imaging. Retina 39(5):1016–1026
64. Rubin ML, Thomas WC (1970) Diplopia and loss of accommodation due to chloroquine. Arthritis Rheum 13(1):75–82
65. Tönnesmann E, Kandolf R, Lewalter T (2013) Chloroquine cardiomyopathy—a review of the literature. Immunopharmacol Immunotoxicol 35(3):434–442
66. Cairoli E, Danese N, Teliz M, Bruzzone MJ, Ferreira J, Rebella M et al (2015) Cumulative dose of hydroxychloroquine is associated with a decrease of resting heart rate in patients with systemic lupus erythematosus: a pilot study. Lupus 24(11):1204–1209
67. Tselios K, Gladman DD, Harvey P, Akhtari S, Su J, Urowitz MB (2019) Abnormal cardiac biomarkers in patients with systemic lupus erythematosus and no prior heart disease: a consequence of antimalarials? J Rheumatol 46(1):64–69
68. Hartmann M, Meek IL, van Houwelingen GK, Lambregts HPCM, Toes GJ, van der Wal AC et al (2011) Acute left ventricular failure in a patient with hydroxychloroquine-induced cardiomyopathy. Neth Heart J 19(11):482–485
69. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A et al (2020) Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. N Engl J Med 383(21):2041–2052
70. Lagier J-C, Million M, Gautret P, Colson P, Cortaredona S, Giraud-Gatineau A et al (2020) Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: a retrospective analysis. Travel Med Infect Dis 36:101791
71. Padilla S, Telenti G, Guillén L, García JA, García-Abellán J, Ding C et al (2020) Predictive factors for cardiac conduction abnormalities with hydroxychloroquine-containing combinations for COVID-19. Int J Antimicrob Agents 56(4):106142
72. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N et al (2020) Effect of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med 383(21):2030–2040
73. O'Laughlin JP, Mehta PH, Wong BC (2016) Life threatening severe QTc prolongation in patient with systemic lupus erythematosus due to hydroxychloroquine. Case Rep Cardiol 2016:4626279
74. McGhie TK, Harvey P, Su J, Anderson N, Tomlinson G, Touma Z (2018) Electrocardiogram abnormalities related to antimalarials in systemic lupus erythematosus. Clin Exp Rheumatol 36(4):545–551
75. Chatre C, Roubille F, Vernhet H, Jorgensen C, Pers Y-M (2018) Cardiac complications attributed to chloroquine and hydroxychloroquine: a systematic review of the literature. Drug Saf 41(10):919–931
76. Joyce E, Fabre A, Mahon N (2013) Hydroxychloroquine cardiotoxicity presenting as a rapidly evolving biventricular cardiomyopathy: key diagnostic features and literature review. Eur Heart J Acute Cardiovasc Care 2(1):77–83

77. Frustaci A, Morgante E, Antuzzi D, Russo MA, Chimenti C (2012) Inhibition of cardiomyocyte lysosomal activity in hydroxychloroquine cardiomyopathy. Int J Cardiol 157(1):117–119
78. Navratil M, Ivković JI (2017) Chloroquine toxicity misdiagnosed as fabry disease associated with systemic lupus erythematosus and hashimoto thyroiditis. J Rheumatol 44(12):1940
79. Hanneman K, Alberdi HV, Karur GR, Tselios K, Harvey PJ, Gladman DD et al (2020) Antimalarial-induced cardiomyopathy resembles fabry disease on cardiac MRI. JACC Cardiovasc Imaging 13(3):879–881
80. White NJ (2007) Cardiotoxicity of antimalarial drugs. Lancet Infect Dis 7(8):549–558
81. Traebert M, Dumotier B (2005) Antimalarial drugs: QT prolongation and cardiac arrhythmias. Expert Opin Drug Saf 4(3):421–431
82. Nord JE, Shah PK, Rinaldi RZ, Weisman MH (2004) Hydroxychloroquine cardiotoxicity in systemic lupus erythematosus: a report of 2 cases and review of the literature. Semin Arthritis Rheum 33(5):336–351
83. Zhao H, Wald J, Palmer M, Han Y (2018) Hydroxychloroquine-induced cardiomyopathy and heart failure in twins. J Thorac Dis 10(1):E70–E73
84. Chatre C, Filippi N, Roubille F, Pers Y-M (2016) Heart involvement in a woman treated with hydroxychloroquine for systemic lupus erythematosus revealing fabry disease. J Rheumatol 43(5):997–998
85. Jordan P, Brookes JG, Nikolic G, Le Couteur DG (1999) Hydroxychloroquine overdose: toxicokinetics and management. J Toxicol Clin Toxicol 37(7):861–864
86. Nguyen LS, Dolladille C, Drici MD, Fenioux C, Alexandre J, Mira JP, Moslehi JJ, Roden DM, Funck-Brentano C, Salem JE (2020) Cardiovascular toxicities associated with hydroxychloroquine and azithromycin. Circulation 142(3):303–305
87. Costedoat-Chalumeau N, Hulot J-S, Amoura Z, Delcourt A, Maisonobe T, Dorent R et al (2007) Cardiomyopathy related to antimalarial therapy with illustrative case report. Cardiology 107(2):73–80
88. Tselios K, Deeb M, Gladman DD, Harvey P, Urowitz MB (2018) Antimalarial-induced cardiomyopathy: a systematic review of the literature. Lupus 27(4):591–599
89. Notice patient—PLAQUENIL 200 mg, comprimé pelliculé—base de données publique des médicaments (Internet) (cited 2020 Apr 1). Available from: http://base-donnees-publique.medicaments.gouv.fr/affichageDoc.php?specid=67767535&typedoc=N. Accessed 01 Apr 2020
90. Cipriani A, Zorzi A, Ceccato D, Capone F, Parolin M, Donato F et al (2020) Arrhythmic profile and 24-hour QT interval variability in COVID-19 patients treated with hydroxychloroquine and azithromycin. Int J Cardiol 1(316):280–284
91. Hydroxychloroquine neuromyotoxicity. Abstract—Europe PMC (Internet) (cited 2020 Apr 2). Available from: https://europepmc.org/article/med/11128688. Accessed 02 Apr 2020
92. Karasic TB, O'Hara MH, Loaiza-Bonilla A, Reiss KA, Teitelbaum UR, Borazanci E et al (2019) Effect of gemcitabine and nab-paclitaxel with or without hydroxychloroquine on patients with advanced pancreatic cancer: a phase 2 randomized clinical trial. JAMA Oncol 5(7):993–998
93. Casado E, Gratacós J, Tolosa C, Martínez JM, Ojanguren I, Ariza A et al (2006) Antimalarial myopathy: an underdiagnosed complication? Prospective longitudinal study of 119 patients. Ann Rheum Dis 65(3):385–390
94. Avina-Zubieta JA, Johnson ES, Suarez-Almazor ME, Russell AS (1995) Incidence of myopathy in patients treated with antimalarials A report of three cases and a review of the literature. Br J Rheumatol 34(2):166–170
95. Loftus LR (1963) Peripheral neuropathy following chloroquine therapy. Can Med Assoc J 89(18):917–920
96. Khosa S, Khanlou N, Khosa GS, Mishra SK (2018) Hydroxychloroquine-induced autophagic vacuolar myopathy with mitochondrial abnormalities. Neuropathol Off J Jpn Soc Neuropathol 38(6):646–652
97. Shukla S, Gultekin SH, Saporta M (2019) Pearls & Oysters: hydroxychloroquine-induced toxic myopathy mimics Pompe disease: critical role of genetic test. Neurology 92(7):e742–e745
98. Neville HE, Maunder-Sewry CA, McDougall J, Sewell JR, Dubowitz V (1979) Chloroquine-induced cytosomes with curvilinear profiles in muscle. Muscle Nerve 2(5):376–381
99. Al-Bari MAA (2015) Chloroquine analogues in drug discovery: new directions of uses, mechanisms of actions and toxic manifestations from malaria to multifarious diseases. J Antimicrob Chemother 70(6):1608–1621
100. Uzar E, Ozay R, Evliyaoglu O, Aktas A, Ulkay MB, Uyar ME et al (2012) Hydroxychloroquine-induced oxidative stress on sciatic nerve and muscle tissue of rats: a stereological and biochemical study. Hum Exp Toxicol 31(10):1066–1073
101. Simpson LL (1982) The interaction between aminoquinolines and presynaptically acting neurotoxins. J Pharmacol Exp Ther 222(1):43–48
102. Léger JM, Puifoulloux H, Dancea S, Hauw JJ, Bouche P, Rougemont D et al (1986) Chloroquine neuromyopathies: 4 cases during antimalarial prevention. Rev Neurol (Paris) 142(10):746–752
103. Pagès M, Pagès AM (1984) Peripheral nerve lesions in chloroquine-induced neuromyopathies. Ann Pathol 4(4):289–295
104. Clark DWJ, Strandell J (2006) Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors? Eur J Clin Pharmacol 62(6):473–479
105. Stein M, Bell MJ, Ang LC (2000) Hydroxychloroquine neuromyotoxicity. J Rheumatol 27(12):2927–2931
106. Estes ML, Ewing-Wilson D, Chou SM, Mitsumoto H, Hanson M, Shirey E et al (1987) Chloroquine neuromyotoxicity. Clinical and pathologic perspective. Am J Med. 82(3):447–455
107. Ak S, Si H, Km W, Kr E, Ls E (2007) Hydroxychloroquine-induced toxic myopathy causing respiratory failure. Chest 131(2):588–590
108. Abdel-Hamid H, Oddis CV, Lacomis D (2008) Severe hydroxychloroquine myopathy. Muscle Nerve 38(3):1206–1210
109. Jafri K, Zahed H, Wysham KD, Patterson S, Nolan AL, Bucknor MD et al (2017) Antimalarial myopathy in a systemic lupus erythematosus patient with quadriparesis and seizures: a case-based review. Clin Rheumatol 36(6):1437–1444
110. Gül U, Cakmak SK, Kiliç A, Gönül M, Bilgili S (2006) A case of hydroxychloroquine induced pruritus. Eur J Dermatol EJD 16(5):586–587
111. Puri PK, Lountzis NI, Tyler W, Ferringer T (2008) Hydroxychloroquine-induced hyperpigmentation: the staining pattern. J Cutan Pathol 35(12):1134–1137
112. Meller S, Gerber PA, Homey B (2008) Clinical image: blonde by prescription. Arthritis Rheum 58(8):2286
113. Adebayo RA, Sofowora GG, Onayemi O, Udoh SJ, Ajayi AA (1997) Chloroquine-induced pruritus in malaria fever: contribution of malaria parasitaemia and the effects of prednisolone, niacin, and their combination, compared with antihistamine. Br J Clin Pharmacol 44(2):157–161
114. Lipner SR, Wang Y (2020) Retrospective analysis of dermatologic adverse events associated with hydroxychloroquine reported to the US Food and Drug Administration. J Am Acad Dermatol 83(5):1527–1529
115. Jallouli M, Francès C, Piette J-C, Huong DLT, Moguelet P, Factor C et al (2013) Hydroxychloroquine-induced pigmentation in

patients with systemic lupus erythematosus: a case-control study. JAMA Dermatol 149(8):935–940
116. Bahloul E, Jallouli M, Garbaa S, Marzouk S, Masmoudi A, Turki H et al (2017) Hydroxychloroquine-induced hyperpigmentation in systemic diseases: prevalence, clinical features and risk factors: a cross-sectional study of 41 cases. Lupus (Internet) (cited 2020 Apr 3). Available from: https://journals.sagepub.com/doi/10.1177/0961203317700486. Accessed 03 Apr 2020
117. Ajayi AAL (2019) Itching, chloroquine, and malaria: a review of recent molecular and neuroscience advances and their contribution to mechanistic understanding and therapeutics of chronic non-histaminergic pruritus. Int J Dermatol 58(8):880–891
118. Blubaugh A, Denley T, Banovic F (2020) Characterization of a chloroquine-induced canine model of pruritus and skin inflammation. Vet Dermatol 31(2):128–133
119. Haddadi N-S, Foroutan A, Ostadhadi S, Azimi E, Rahimi N, Nateghpour M et al (2017) Peripheral NMDA receptor/NO system blockage inhibits itch responses induced by chloroquine in mice. Acta Derm Venereol 97(5):571–577
120. Granstein RD, Sober AJ (1981) Drug- and heavy metal–induced hyperpigmentation. J Am Acad Dermatol 5(1):1–18
121. Murase D, Hachiya A, Takano K, Hicks R, Visscher MO, Kitahara T et al (2013) Autophagy has a significant role in determining skin color by regulating melanosome degradation in keratinocytes. J Invest Dermatol 133(10):2416–2424
122. Giacomo TD, Valente NYS, Nico MMS (2009) Chloroquine—induced hair depigmentation. Lupus (Internet) (cited 2020 Apr 3). Available from: https://journals.sagepub.com/doi/10.1177/0961203308097473. Accessed 03 Apr 2020
123. Coulombe J, Boccara O (2017) Hydroxychloroquine-related skin discoloration. CMAJ Can Med Assoc J 189(5):E212
124. Murphy M, Carmichael AJ (2001) Fatal toxic epidermal necrolysis associated with hydroxychloroquine. Clin Exp Dermatol 26(5):457–458
125. Becker-Wegerich PM, Kuhn A, Malek L, Lehmann P, Megahed M, Ruzicka T (2000) Treatment of nonmelanotic hyperpigmentation with the Q-switched ruby laser. J Am Acad Dermatol 43(2 Pt 1):272–274
126. Weber JC, Alt M, Blaison G, Welsch M, Martin T, Pasquali JL (1996) Changes in taste and smell caused by hydroxychloroquine. Presse Med Paris Fr 1983 25(5):213
127. Seçkin U, Ozoran K, Ikinciogullari A, Borman P, Bostan EE (2000) Hydroxychloroquine ototoxicity in a patient with rheumatoid arthritis. Rheumatol Int 19(5):203–204
128. Hart CW, Naunton RF (1964) The ototoxicity of chloroquine phosphate. Arch Otolaryngol 80(4):407–412
129. Matz GJ, Naunton RF (1968) Ototoxicity of chloroquine. Arch Otolaryngol 88(4):370–372
130. Gyorffy JB, Marowske J, Gancayco J (2018) A rare cause of dysphagia and weight loss. Case Rep Gastroenterol 12(3):640–645
131. Paton NI, Goodall RL, Dunn DT, Franzen S, Collaco-Moraes Y, Gazzard BG et al (2012) Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: a randomized controlled trial. JAMA 308(4):353–361
132. Jourde-Chiche N, Mancini J, Dagher N, Taugourdeau S, Thomas G, Brunet C et al (2012) Antimalarial ototoxicity: an underdiagnosed complication? A study of spontaneous reports to the French Pharmacovigilance Network. Ann Rheum Dis 71(9):1586
133. Bonnet C, Daudin J-B, Monnet D, Brézin A (2017) Vogt-Koyanagi-Harada disease. J Fr Ophtalmol 40(6):512–519
134. Barrenäs ML, Holgers KM (2000) Ototoxic interaction between noise and pheomelanin: distortion product otoacoustic emissions after acoustical trauma in chloroquine-treated red, black, and albino guinea pigs. Audiol Off Organ Int Soc Audiol 39(5):238–246
135. Barrenäs ML (1997) Hair cell loss from acoustic trauma in chloroquine-treated red, black and albino guinea pigs. Audiol Off Organ Int Soc Audiol 36(4):187–201
136. Bernard P (1985) Alterations of auditory evoked potentials during the course of chloroquine treatment. Acta Otolaryngol (Stockh) 99(3–4):387–392
137. Ruedi L, Furrer W, Luthy F, Nager G, Tschirren B (1952) Further observations concerning the toxic effects of streptomycin and quinine on the auditory organ of guinea pigs. Laryngoscope 62(4):333–351
138. Hadi U, Nuwayhid N, Hasbini AS (1996) Chloroquine ototoxicity: an idiosyncratic phenomenon. Otolaryngol-Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg 114(3):491–493
139. Scherbel AL, Harrison JW, Atdjian M (1958) Further observations on the use of 4-aminoquinoline compounds in patients with rheumatoid arthritis or related diseases. Cleve Clin Q 25(2):95–111
140. Nielsen-Abbring FW, Perenboom RM, van der Hulst RJ (1990) Quinine-induced hearing loss. ORL J Oto-Rhino-Laryngol Its Relat Spec 52(1):65–68
141. Obiako MN (1985) Chloroquine ototoxicity: an iatrogenic problem. Mater Medica Pol Pol J Med Pharm 17(3):195–197
142. Mukherjee DK (1979) Chloroquine ototoxicity–a reversible phenomenon? J Laryngol Otol 93(8):809–815
143. Albay D, Adler SG, Philipose J, Calescibetta CC, Romansky SG, Cohen AH (2005) Chloroquine-induced lipidosis mimicking Fabry disease. Mod Pathol Off J US Can Acad Pathol Inc 18(5):733–738
144. von Bergen TN, Blount MA (2012) Chronic use of chloroquine disrupts the urine concentration mechanism by lowering cAMP levels in the inner medulla. Am J Physiol Renal Physiol 303(6):F900-905
145. Costa RM, Martul EV, Reboredo JM, Cigarran S (2013) Curvilinear bodies in hydroxychloroquine-induced renal phospholipidosis resembling Fabry disease. Clin Kidney J 6(5):533–536
146. de Menezes Neves PDM, Machado JR, Custódio FB, Dos Reis Monteiro MLG, Iwamoto S, Freire M et al (2017) Ultrastructural deposits appearing as "zebra bodies" in renal biopsy: Fabry disease?- comparative case reports. BMC Nephrol 18(1):157
147. Wang B, Guo H, Ling L, Ji J, Niu J, Gu Y (2020) The chronic adverse effect of chloroquine on kidney in rats through an autophagy dependent and independent pathways. Nephron 144(2):96–108
148. Wu S-Z, Liang X, Geng J, Zhang M-B, Xie N, Su X-Y (2019) Hydroxychloroquine-induced renal phospholipidosis resembling Fabry disease in undifferentiated connective tissue disease: a case report. World J Clin Cases 7(24):4377–4383
149. Sperati CJ, Rosenberg AZ (2018) Hydroxychloroquine-induced mimic of renal Fabry disease. Kidney Int 94(3):634
150. Bracamonte ER, Kowalewska J, Starr J, Gitomer J, Alpers CE (2006) Iatrogenic phospholipidosis mimicking Fabry disease. Am J Kidney Dis Off J Natl Kidney Found 48(5):844–850
151. Musabayane CT, Wargent ET, Balment RJ (2000) Chloroquine inhibits arginine vasopressin production in isolated rat inner medullary segments induced cAMP collecting duct. Ren Fail 22(1):27–37
152. Musabayane CT, Windle RJ, Forsling ML, Balment RJ (1996) Arginine vasopressin mediates the chloroquine induced increase in renal sodium excretion. Trop Med Int Health TM IH 1(4):542–550
153. Ahmed MH, Ashton N, Balment RJ (2003) The effect of chloroquine on renal function and vasopressin secretion: a nitric oxide-dependent effect. J Pharmacol Exp Ther 304(1):156–161