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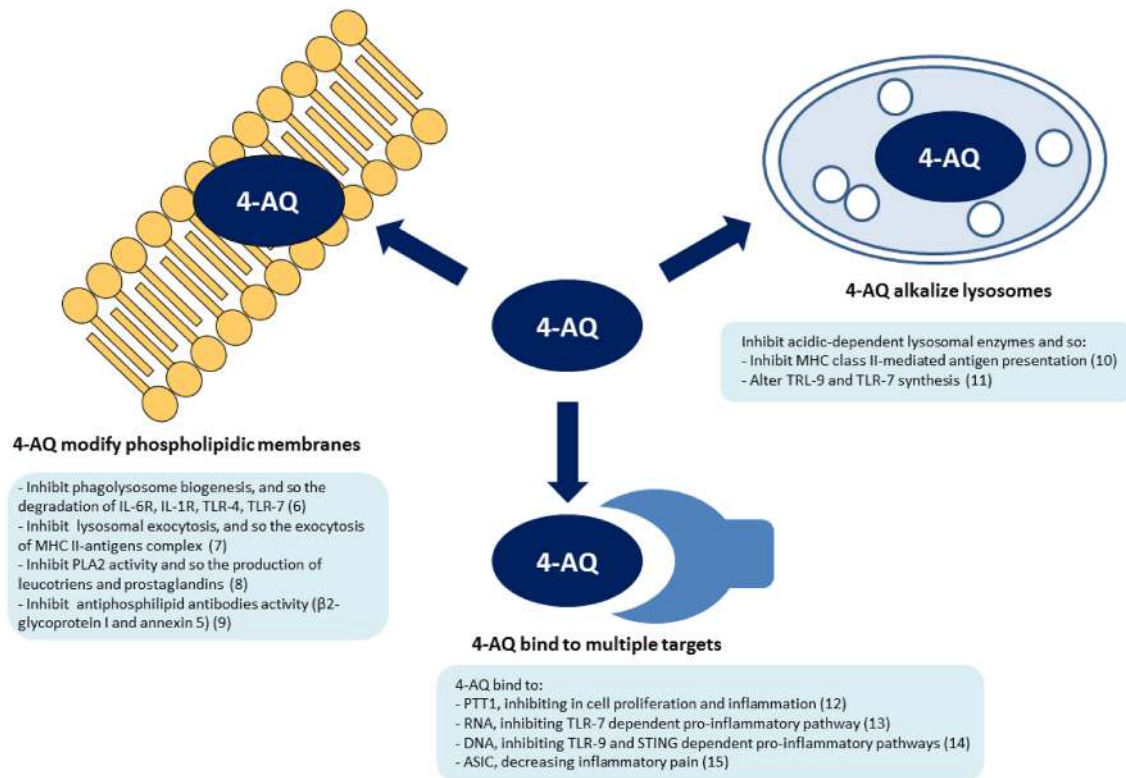
Legend: 4-AQ alkalize lysosomes, modify phospholipidic membranes properties and bind to numerous targets, thus widely regulating the immune system.

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

Declarations

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