Review Article

What is new in Recommendations on Ophthalmological Screening in Patients Treated with Chloroquine and Hydroxychloroquine? Update and Literature Review

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ABSTRACT

Based on the present literature, in March 2016, new recommendations of the American Academy of Ophthalmology for ophthalmic screening tests in patients treated with chloroquine and hydroxychloroquine were published. These recommendations emphasized the fact that toxicity is related to the dose calculated by real weight. The recommended hydroxychloroquine and chloroquine doses have been limited. It is no longer recommended to calculate the cumulative dose of chloroquine to establish the risk of toxicity. Kidney failure and the use of tamoxifen are proven risk factors of ocular complications in these patients. The screening agenda was established and available diagnostic methods were evaluated. Screening in patients treated with chloroquine derivatives may prevent an irreversible complication-toxic retinopathy. The present recommendations warn against making premature decision on medicine withdrawal, especially in the light of the most recent studies on their beneficial systemic influence. This paper systematizes the information on ophthalmological screening in chloroquine derivatives users.

KEYWORDS: *Chloroquine, hydroxychloroquine, hydroxychloroquine retinopathy, screening, recommendations*

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Chloroquine (CQ) and its analogue hydroxychloroquine (HCQ) belong to the group of antimalarial drugs (AMs) with anti-inflammatory, immunomodulating, and inhibiting cell proliferation activities. CQ is used in some developing countries as antimalarial prophylaxis in fever. This drug is available in such countries without prescription, which leads to its frequent use without medical consultations. This played a role in the development of chloroquine-resistant *Plasmodium falciparum* in countries such as Nigeria.[1,2] In developed countries, both drugs are commonly used in patients with autoimmune diseases and in connective tissue disorders such as systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, Sjögren's syndrome, psoriatic arthritis, and dermatomyositis.[3] The use of HCQ is also considered in the treatment of diabetes, heart diseases, and as an adjuvant therapy in patients with neoplasms.[4] This is associated with antithrombotic activity of AMs, which also improve blood rheology, inhibit erythrocyte and thrombocyte aggregation through decrease of thromboxane A_2 production, and inhibition of the process activated by antiphospholipid antibodies. AMs also improve glycemia control, decrease glycated hemoglobin concentration, and reduce tissue insulin resistance.[5] Furthermore, they decrease concentrations of triglycerides, total cholesterol, and low and very low density lipoproteins (LDL and VDL fractions); while on the other hand, they increase high density cardiovascular system-protective lipoprotein concentration (HDL

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fraction) in the blood.[5] Influence on bone tissue density increase, measured within the spinal and hip bones, is also possible. Despite the expected permeation of the medicine through the placenta and into mother's milk, HCQ is a commonly used drug during pregnancy and lactation. So far, neither a teratogenous activity of HCQ nor increased risk of congenital fetal defects have been proven.[5,6]

A wide range of AM distribution, ease of penetration through cell membrane by medicine particles, and its accumulation in lysosomes and endosomes may contribute to multiorgan adverse effects of the therapy with these medicines. Starting with nausea, vomiting, photophobia, and skin lesions through depression, psychoses and myositis, and ending up with sudden heart block.[1,5,6] The most frequent complications resulting from AMs withdrawal are indeed ophthalmic complications. It was measured that CQ avidity in retinal cells containing melatonin exceeds by 100–200 times the concentration of this medicine in plasma.[5]

Ophthalmological side effects of AMs can be divided into reversible and irreversible. Patients may complain of transient accommodation disturbances in the form of deteriorated near vision and diplopia. In approximately 90% of the persons receiving CQ and in approximately 5% treated with HCQ, deposits of AMs within cornea can be observed.[5] The course of this complication may be asymptomatic or may manifest by vision deterioration with a halo effect around light sources. One of the irreversible adverse effects of therapy with AMs includes retinopathy. Diagnosing retinopathy can be the reason for cessation of treatment with AMs or dose reduction. A "bull's eye" image of the retina is observed in the advanced stage of toxic retinal impairment. This is an area of retinal hypopigmentation in the perimacular region, matching the atrophy of the retinal pigment epithelium (RPE) cells. The CQ deposits are stored in the RPE, which leads to an irreversible degeneration of photoreceptors. Most cases of retinopathy run without decrease of visual acuity which may be the reason why patients seek ophthalmic help in the late stage of disease advancement. If toxic impairment affects the fovea, there may be a decrease in visual acuity or deterioration in night vision. On the other hand, damage of the macular area may be reflected in narrowing of the peripheral field vision or presence of paracentral scotomas. RPE destruction may also progress after withdrawal of the medicine. This is probably associated with already initiated process of degeneration and not with the time of flushing the drug out of the organism, although the concentration of AMs in the blood may persist for many months after their withdrawal. Therefore, the CQ/HCQ retinopathy is an irreversible, slowly progressing process, and early detection of lesions may limit visual organ damage. Owing to effective management schemes in patients treated with AMs in developed countries, a classic form of "bull's eye" with depigmentation in the RPE perimacular region is almost no longer observed. In Caucasian patients, the most common changes affect the parafoveal region, while in the yellow race, they are located extramacularly and may manifest as narrowing of the peripheral field of vision. Moreover, changes in the posterior pole may involve thinning of retinal vessels, a pale optic disc (nerve II), and even symptoms of pseudoretinitis pigmentosa. CQ may lead to decrease in visual acuity, or in extreme cases, complete vision loss (blindness). Severe intoxication might result in slower pupillary reaction to light, pupillary asymmetry, or afferent pupillary defect.[1,5,7,8] The only proven factor limiting toxic retinopathy development in the course of treatment with AMs is medicine withdrawal. Use of lutein and zeaxanthin dietary supplements has no proven protective effect in these patients.[4] It may, however, be recommended in comorbid degenerative macular changes.

Although HCQ differs chemically from CQ only by the presence of a hydroxyl group in the lateral chain, it is well known that the use of CQ is associated with a significantly higher incidence of ocular complications compared to its analogue – HCQ.[5,9] In some countries, access to HCQ is still limited. Introduction of HCQ to the Polish market by the Drug Policy and Pharmacy Department of the Ministry of Health in 2015 helped to limit the toxicity of AMs.[10] However, many years of both CQ and HQ administration requires regular ophthalmic follow-up consultations.

In March 2016, the American Academy of Ophthalmology (AAO) published updated recommendations on screening for retinopathy in patients treated with CQ and HCQ.[4] So far, these have been the only recommendations describing in detail the management of patients treated with AMs relying on evidence-based medicine (EBM). The current AAO recommendations are already the fourth version of management guidelines in the prophylaxis of ocular complications in patients using AMs. Modifications in the previous management were introduced after analysis of up-to-date literature on the condition of the visual organ in patients taking AMs for many years.[11]

The present recommendations maintained the standpoint that the risk of toxicity of AMs rises along with an increase in the dose and duration of treatment. An important change is, however, resigning from calculating medicine dose on the basis of ideal body weight, which

was in the previous AAO recommendations from 2011.[12] This method of calculation was related to a lower concentration of the medicine in muscle and adipose tissue while retaining it in the liver, kidneys, and melanin-containing tissues. Applying this conversion could result in overestimation in patients with lower real body weight, increasing the risk of toxic influence of AMs. The maximum daily dose of HCQ was set at ≤5.0 mg/kg real body weight. There is no current data for CQ, however, the literature tells that 5 mg/kg HCQ is equivalent to 2.3 mg/kg CQ. Based on the above, the recommended daily dose of CQ was set at ≤2.3 mg/kg real body weight.[4] The 2011 recommendations suggested a significant relation between a cumulative dose of AMs and a risk of toxic retinopathy. At present, a cumulative dose is no longer a recommended risk factor. Currently, a combined assessment of duration of taking the medicine and daily dose calculated as a real body weight of the patient is recommended.[4,11] A limiting factor for adjusting the dose to individual patient needs may be availability of AMs in the form of single dose tablets – 200 mg HCQ and 250 mg CQ. A possible solution might be splitting the tablets or skipping doses on certain days of the week. AMs might be administered for 5 days with a weekend break in the drug intake in chronic usage.

Marmor *et al.*,[4] report incidence of toxic ocular effects in less than 1% of patients treated with AMs below 5 years. This percentage increases to 2% if the medicine was used under 10 years and to almost 20% for treatment over 20 years. Then, this risk increases annually by 4%. Duration of treatment and the dose most strongly correlate with an increase in the risk of ocular complications in the course of use of AMs.

The factors which may have influence on the ophthalmic condition in recipients of AMs comprise [Table 1]: concomitant macular disorders-considerable RPE loss is a contraindication for the therapy whereas isolated deposits or retinal drusen in macular region without visual acuity decrease or visual field deficiencies may only impede the assessment of toxic changes in accessory examinations. In concomitant macular disorders, additional tests might be necessary to clarify the etiology of pathology;- renal function disturbances-the drug is eliminated in 45-50% by the kidneys.[5] Disturbed functioning of this organ may result from increased concentration of the medicine in systemic blood, and thus, increase the risk of toxicity;- receiving tamoxifen-the medicine used in women with hormone-sensitive breast cancer which causes a five-fold higher risk of toxicity.[4] No relation for newer medicines from this group has been shown.

Table 1: Risk factors for chloroquine toxic retinopathy[4]

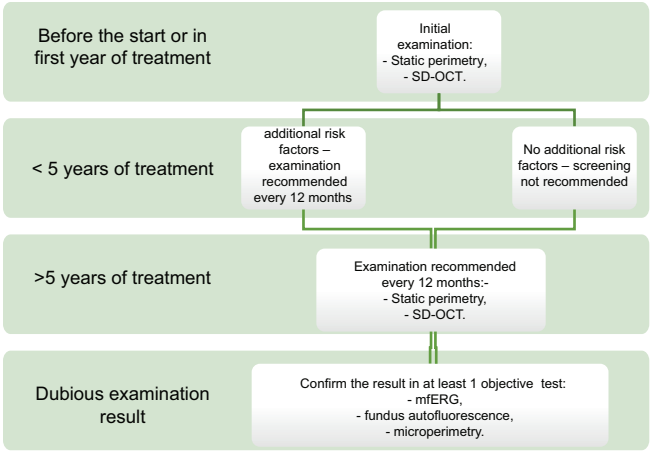
HCQ daily dose	>5.0 mg/kg real weight
CQ	>2.3 mg/kg real weight
Duration of therapy	>5 years (after exclusion of additional risk factors)
Renal function disturbances	GFR decrease, prolongation of drug elimination
Additional medications	tamoxifen
Macular disorders	might impede the assessment of toxic changes in accessory examinations

Abbreviations: HCQ, hydroxychloroquine; CQ, chloroquine; GFR, Glomerular Filtration Rate

Neither the patient's age nor liver function disturbances were found to influence the risk of toxicity of AMs. There is also no definitive evidence for the influence of both the patient's age and for cytochrome P450 gene polymorphism.[4]

The 2016 AAO recommendations emphasize an individual approach to the frequency of ophthalmic follow-up examinations in patients receiving AMs as well as the choice of accessory tests. Based on studies on a large group of patients (n = 2361[11]) it was decided that a consultation is necessary in the first year of treatment, with eye fundus evaluation and in the presence of macular disturbances-expanding the diagnostics with visual field test or the Spectral Domain Optical Coherence Tomography (SD-OCT). Initial examination prior to medicine initiation is especially recommended in individuals with comorbidities such as macular disorders or ocular diseases such as glaucoma. They may affect control test results or hinder their interpretation. Ophthalmological examination is strongly advised before the end of the first year of medicine use to rule out concomitant eye fundus disturbances. Initial

Table 2: Ophthalmological screening agenda in patients treated with chloroquine and hydroxychloroquine[4]



Abbreviations: SD-OCT, Spectral Domain Optical Coherence Tomography; mfERG, multifocal electroretinogram

test may be useful for risk assessment of treatment complications or for deciding on the recommended dose. Current screening recommendations in patients treated with AMs is presented in Table 2.

Annual follow-up is recommended in patients using AMs longer than 5 years. If any of the abovementioned additional risk factors for the development of ocular complications occurs, earlier regular follow up is suggested.

Examinations recommended by the AAO for assessment of ocular complications in patients treated with AMs is presented in Table 3:[4,13]- static perimetry-the most sensitive method, recommended as an initial examination. Cooperation with the patient may limit test outcome; therefore, a dubious result should be confirmed with an objective examination. In the Caucasian race, it is recommended to perform a 10-2 central visual field examination evaluated according to an individualized pattern deviation map. In the yellow race, a 24-2 or 30-2 peripheral visual filed examination is recommended. The earliest changes are observed in the inferior temporal and superior nasal areas. Dubious results should be confirmed with repeat examination or with an objective method-mfERG, FAF, SD-OCT;- SD-OCT-there may be observed a reduction in the thickness of the retina in the perifoveal region in the Caucasian race or near vascular arcades in the yellow race. These areas are the toxicity markers of AMs. This method is now widely available;- multifocal electroretinogram (mfERG)-objective test that may show functional disturbances. In the initial phase of retinopathy, decreased response of the perifoveal area is found. The authors report a test sensitivity comparable to static perimetry.[4] However, The use of this method requires specialist equipment and qualified personnel;- fundus autofluorescence (FAF)-the area of early damage is seen as a field of increased autofluorescence. Disturbances found in FAF may precede lesions seen in SD OCT. Advanced changes are observed as dark non-fluorescent fields;- microperimetry-a method that combines visual field examination with eye-fundus tomography. The possibility of following bulbar movements in real time allows to project a light marker direct on the retina in the area decided by the examiner. There is a reduced influence of cooperation with the patient on test outcome and on central fixation disturbances which at present may be assessed in the course of maculopathy. However, a long time of examination may lead to patient's exhaustion giving a falsified result.

Examinations not recommended by the AAO for assessment of ocular complications in patients treated with AMs [Table 3]:[4,13]- eye-fundus examination-too low test sensitivity. Only advanced changes can be detected while the aim of screening is to find changes on the structural level of RPE, which may be determined with the use of more sensitive methods;- Amsler Grid-may not be used for early detection of scotomas in the visual field;- color vision testing-too low test sensitivity and specificity;- Electrooculography (EOG)-was not confirmed to be a reliable screening method for patients using AMs;- full-field multifocal electroretinogram (full-field ERG)-shows retinal disturbances evaluated globally. It allows for detection of late-stage toxic impairment;- fluorescein angiography-may only detect advanced changes in RPE. The use of this method can be limited to patients with primary nephropathy;- time domain optical coherence tomography (TD-OCT)-not sufficient test resolution.

Table 3: Recommended and not recommended examinations in toxic retinopathy screening in patients treated with chloroquine and hydroxychloroquine[4]

Recommended examinations by AAO	Examinations not recommended by AAO
static perimetry	eye-fundus examination
SD-OCT	Amsler Grid
mfERG	color vision testing
fundus autofluorescence	EOG
microperimetry	full-field ERG
	fluorescein angiography

Abbreviations: AAO, American Academy of Ophthalmology; EOG, Electrooculography; mfERG, multifocal electroretinogram; SD-OCT, Spectral Domain Optical Coherence Tomography; TD-OCT, Time Domain Optical Coherence Tomography

Conclusions

A patient treated with AMs should be informed by the doctor on ocular adverse effects of treatment. Baseline examination is recommended in the first year of treatment at the latest to rule out additional risk factors for the development of retinopathy. Annual ophthalmic follow up is recommended in patients receiving AMs longer than 5 years, with visual acuity and eye-fundus examination, accompanied by one of the following tests: static perimetry, spectral-domain optical coherence tomography, and multifocal electroretinogram. Earlier screening is advised in individuals with additional risk factors, especially with concomitant macular disturbances, renal failure, or persons receiving tamoxifen. The evaluation of risk factors for ocular complications should consider the duration of treatment with AMs and the dose of the medicine calculated by real weight of the patient. The lack of regular ophthalmic follow-up in patients treated

with CQ or HCQ may result in ocular complications. The present AAO recommendations emphasize the role of a gain-and-loss account for continuation of AMs and warn against too early withdrawal of the medicine. In the case of dubious test outcomes, it is recommended to repeat the examinations or to perform one objective test to confirm retinopathy. Management of patients treated with AMs should be carried out in close cooperation of an internal medicine doctor or infectious medicine specialist with an ophthalmologist.

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Conflicts of interest

There are no conflicts of interest.

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