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Review Article

Ophthalmology Section

Screening for Hydroxychloroquine-Associated Retinopathy: A Review

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ABSTRACT

Hydroxychloroquine (HCQ) is a well-known medication, which is approved for a number of medical disorders. However, the HCQ-associated retinal toxicity is also a very well known complication, which may result in irreversible toxic maculopathy and severe visual loss, if not diagnosed in the early phase. Although some authorities argue about the role of screening, the American Academy of Ophthalmology recommends regular patient evaluations and prescription of HCQ in the recommended dose of less than 5 mg/kg real body weight. High dose, long duration of use and high cumulative dose, renal disease, and some drug interactions are major risk factors. Among various subjective and objective methods proposed for screening HCQ toxicity, visual field evaluation and optical coherence tomography have been recommended as the first line.

In this article, we outlined the current published literature concerning the various aspects of HCQ retinopathy. It is recommended that patients be screened for this complication at appropriate intervals in order to detect earliest signs of damage and discontinue the drug in order to prohibit further damage.

Keywords: Macular toxicity, Risk factors, Toxic retinopathy

INTRODUCTION

It is now more than 60 years since the first introduction of the antimalarial drugs Chloroquine (CQ) and Hydroxychloroquine (HCQ) into the management of diseases other than endemic malaria infection. The medication has gained popularity because these agents were observed to be effective against various dermatologic and arthropathic manifestations of rheumatologic disorders, namely, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjogren's disease, Dermatomyositis, and so forth. Despite its old history, the drug is still in the market with possible newer indications such as diabetes mellitus, cardiovascular diseases, hematologic malignancies, solid tumours, and antiphospholipid antibody syndrome, as either sole or additive agent [1-5]. The promising applications of these agents make them drugs of future, not past.

Along with increased use of antimalarial agents in rheumatology, a dreadful side effect presented itself; irreversible loss of vision that was first described in the literature by Hobbs and colleagues in 1959 [6]. However, despite concerns regarding the CQ- and HCQ-associated retinopathy, their application in the medical practice has expanded. Hence, appropriate guidelines are needed to address concerns regarding the side effects because the number of patients taking them is growing. This is especially the case for HCQ, which has, superseded CQ in current medical practice.

HCQ is a 4-aminoquinolone antimalarial agent with avidity for pigmented tissues due to binding to melanosomes. Its action is accomplished via unknown mechanisms. Nonetheless, the drug activity is thought to interfere with antigen presentation, cytokine production, and Toll-like receptor signaling via increasing lysosomal pH, which in turn has been linked to reduced proteolytic activity of this intracellular organelle. It seems that the acidic environment of lysosomes is crucial for protonating the HCQ, which is followed by osmotic swelling of lysosomes and increased membrane permeability. The release of enzymes into cytoplasm induces apoptosis which may play an important role in the observed immunomodulatory characteristics of HCQ [7-10]. HCQ has also been categorised as an autophagy inhibitor with new insights in the molecular mechanisms of cancer development, metabolic, and neurodegenerative disorders [11-13].

The goal of this article was to review the effects of HCQ on retina and screening for avoiding its side effects, based on the latest published literature.

ARTICLE SEARCH METHODOLOGY

In order to prepare this review, authors conducted a search on PubMed for the registered literature. No time filter was applied to our search. Titles were looked containing exact phrases of "hydroxychloroquine" and one of the following words: "toxicity", "retinopathy", "mechanism", and "screening". The search yielded 95 articles in total, of which, 81 articles were determined relevant to the present work based on their abstracts. Then, authors studied the relevant articles in full and organised the current review according to 58 out of 81 (since the rest of the articles were irrelivent to the topic or were in non english language) which are referenced at the end of this paper.

REVIEW OF LITERATURE

Retinal Toxicity

As mentioned above, the most important complication associated with use of HCQ is irreversible retinopathy, though the drug may affect anterior segment structures of the eye in a non-vision-threatening manner. While variable results have been reported in different studies, the HCQ-associated retinal toxicity is estimated to occur in 0.5 to 7.5 percent of patients [14-16]. This wide range is reflective, to some extent, of the difference in the duration of consumption among population studies. Older reports had included patients on short-term treatment while recent reports focused on long-term regimens [15,17]. Nevertheless, the new screening proposals and widespread availability of screening modalities may alter the epidemiological characteristics of HCQ-associated retinal toxicity mostly because more and more patients are screened and diagnosed at an earlier stage.

Presentation

HCQ retinopathy typically presents as retinal atrophy predominantly affecting the macular area. The so-called "bull's eye maculopathy" is a textbook figure which is neither sensitive nor specific for HCQ retinopathy. It is now only occasionally seen due to increased awareness of the risk and increased screening. Although not fully elucidated, it appears that the damage inflicts mainly the retinal photoreceptor layer with propagation to the Retinal pigment epithelium (RPE). The clinical signs mainly begin in the inferotemporal retina which corresponds to the superonasal visual field [18] and occasional reports of scotomas in very alert patients. On the other hand, recent evidence supports extramacular involvement at least in the Asian population [19,20] which is a challenge to the current screening protocols. We discuss these issues further in the following sections.

Risk Factors

Risk factors associated with the occurrence of CQ/HCQ retinopathy are summarised in [Table/Fig-1] [21]. In general, the role of major risk factors is proven; yet, the participatory role of minor risk factors is not foolproof.

Major risk factors
Overdosing medication above 5 mg/kg (real body weight) per day Above 5-years consumption Kidney disease with reduced GFR Tamoxifen consumption Macular disease
Minor risk factors
Old age Liver disease Genetic predisposition
Possible protective factors
ABCA4 gene variants Smoking Alpha-TTP

[Table/Fig-1]: Risk and protective factors for HCQ toxic retinopathy.
HCQ: Hydroxychloroquine; alpha-TTP: Alpha-tocopherol transfer protein

Total Daily Dose

Among major risk factors, total daily dose exerts the greatest effect on the occurrence of retinopathy. It appears that the greater the daily dose, the greater the incidence of retinal damage [22,23]. It is noteworthy that the previous recommendation of maximum prescription doses (6.5 and 3 mg/kg/d for HCQ and CQ, respectively) [15,24] according to ideal body weight, is better replaced by dosing adjusted for real body weight, not only due to ease of calculation, but also due to reduced chance of toxicity observed among thin patients [21,25]. One should not forget that this amount of daily dose only refers to the level below which severe retinal toxicity is less probable. No consensus is present as to the exact safe dose below which the retinal toxicity is precluded [26].

Cumulative Dose

The concept of cumulative dose combines the duration of consumption and the total daily dose parameters into a single predictive factor. If the duration of use is a sole concern, given the safe dose is not violated, the risk is negligible if the drug has been taken for less than 5 years; however, the risk is increased afterwards significantly to 1 percent and reaches to 2 percent after 10 years [25]. According to Melles RB et al., patients taking HCQ above 5 mg/kg/d had 4-fold increased risk of retinopathy after 20 years relative to the risk after 10 years (40 versus 10 percent). In doses between 4-5 mg/kg/d the risk after 20 years of consumption increased 10-fold relative to the risk after 10 years (20 versus 2 percent) [25]. These findings demonstrate that the effects of daily dose should be considered along with the duration of consumption when the probability of retinopathy is being evaluated. Previously, the cumulative dose of 1000 g HCQ and 460 g CQ were considered to correlate with retinopathy. Some authors propose that the cumulative dose concept should be corrected as duration of consumption in relation to daily dose per real body weight.

Renal Function

Renal function should be considered as an important factor while monitoring patients on HCQ. There is a case report of retinal toxicity in renal dysfunction while maintaining even safe-doses [27]. The fact is that about half the metabolism and excretion of HCQ is performed by kidneys, thence, the regular evaluation and proper adjustment of the daily dose should not be undermined [28,29].

Concurrent tamoxifen use: Tamoxifen-associated retinal toxicity has been described first in 1978 by Kaiser-kupfer and Lippman [30]. However, only recently has the synergistic effect of tamoxifen and HCQ retinopathy been reported [31]. The results of a recent study demonstrated a 5-fold increase in the rate of retinal toxicity if both tamoxifen and HCQ were administered simultaneously [25].

Concomitant retinal disease: Another issue that must be contemplated while evaluating HCQ retinopathy is the presence of concomitant retinal diseases. Though the effect of preexisting retinal diseases on HCQ retinopathy has not been evaluated in a well-designed study, it has been proposed that addition of a potentially toxic agent to a vulnerable retina may increase the risk of damage [15]. Additionally, interpretation of screening results is confounded if the retina is previously compromised [25].

Other factors: To a lesser extent, the role of age, liver disease, and genetic polymorphisms has been implicated, though without a clear-cut association [21,24].

PROTECTIVE FACTORS

There is no proven protective factor against HCQ retinopathy. However, there are few associations advocated in literature that might provide some protection against toxic effects of HCQ.

Genetic polymorphisms: While earlier investigations of mutations in the ABCA4 gene were suggestive of a predisposing role, a recently published study attributed a protective role for common variants of this gene. Nevertheless, all of these studies are deficient first, by limited number of cases and controls, and second, by only assessing patients taking CQ [32,33].

Smoking: The observation that SLE patients who smoke cigarette are less prone to disease modifying effects of HCQ is interesting [34-36]. It is suggested that smoking interferes with accumulation of HCQ in the lysosomes (a proposed mechanism necessary for antimalarial action) and also induces the metabolic pathway (possibly P450), thus leading to decreased efficacy of HCQ and CQ. Unfortunately, the drug interactions with cigarette smoking may have numerous confounding factors and there is no conclusive data about HCQ-associated retinopathy and smoking [37-39].

Alpha-TTP: Alpha-tocopherol transfer protein (alpha-TTP) is located in all retinal layers. In animal models, it has been demonstrated that the absence of alpha-TTP causes severe CQ retinal toxicity irrespective of vitamin E level status [40].

SCREENING

In case of HCQ retinopathy, there is no screening method that can detect retinopathy before it is established (stage 1 prevention). One may reckon that appropriate screening would only assist in limiting progressive damage (stage 2 prevention). According to current literature, the sooner the diagnosis is made, the better the outcome in terms of foveal functional loss, if the drug is discontinued in a timely manner [41]. On the other hand, a systematic approach to patients with suspected HCQ-induced retinopathy through properly devised guidelines, not only serves to support withdrawal of the causative agent in case of definite damage, but also prohibits inappropriate discontinuation of the drug in those who need it to control their extra-

ocular disease. Furthermore, it may omit unnecessary variations and suboptimal care observed by some investigators [42-44].

In contrast to proponents of universal screening, this approach is criticised by some authorities. Any subject of recommendation for universal screening should encompass the following virtues: first, the cause and effect relationship should be fulfilled; second, there should be (an) available screening method(s) that detect(s) damage at a reversible level or at least at a level that the damage course could be stopped; third, withdrawal of the cause should prevent further damage; fourth, there should be no risk superimposed on the patient by the screening procedures. Addressing the HCQ retinopathy, the first and the last features are agreed. However, it is postulated that by the time screening reveals discernible signs of toxicity, the damage may have gone too far beyond the stage of reversibility. For unknown reasons, the damage at Retinal pigment epithelium (RPE) level may ensue even after the drug has been stopped [45,46]. However, it seems logical that if the diagnosis is made early enough, at least debilitating retinopathy is preventable [41,47]. On the other hand, the cost effectiveness of universal screening is highly debated, when the high prevalence of HCQ use and the relatively low incidence of retinal toxicity are taken into account [44]. It is necessary to consider such issues while selecting groups of patients for screening.

SCREENING TOOLS

[Table/Fig-2] summarises all techniques available for screening HCQ retinopathy [21]. Here, we describe the screening methods according to their current status of recommendation.

Comparison of the Recommended Tools

Deciding on which test is the best for screening is difficult and may be unnecessary, given the combination approach that is currently recommended. It appears that sensitivity and specificity of both spectral domain optical coherent tomography (SD OCT) and 10-2 Visual field (VF) perimetry are favourably high enough to be used as screening techniques and, in combination, the resulting sensitivity reaches 89 percent [48,49]. According to Browning DJ et al., the sensitivity of multifocal electroretinography (mfERG) was highest, though least specific, in comparison to other tests, whereas SD OCT acquired the highest specificity with lowest sensitivity [49]. They also reported superiority of adding either SD OCT or 10-2 VF to mfERG instead of combining SD OCT and 10-2 VF. In 2006, Lai TY et al., reported similar sensitivity results for 10-2 VF and mfERG [50]. Kellner U et al., reported a similar efficacy of SD OCT, mfERG, and Fundus autofluorescence (FAF) at detection of early stage HCQ toxicity [51]. In another study, all the recommended screening tools were compared on 10 patients with early, moderate, and severe HCQ retinopathy with quite comparable results in detecting retinal abnormalities, though the mfERG demonstrated better sensitivity at diagnosis of early retinopathy [18]. Cukras C et al., divided 57 patients according to mfERG criteria into two groups of affected and unaffected patients. They provided the population with SD OCT, VF, FAF, and fundus photograph, and reported SD OCT and 10-2 VF to be most specific and most sensitive with reference to the mfERG findings [48].

The following recommendations not only are advocated in the literature, but also take into account the availability and utility in the field of general ophthalmology.

PRIMARY RECOMMENDED TECHNIQUES

Visual Field Test and OCT

Previously, the white target 10-2 VF testing were described as the single primary screening tool for detection of central and paracentral scotomas in patients on HCQ treatment [52]. Although quite sensitive, the subjective nature and reliability issues inherent with the visual field testing may complicate the interpretation of the results. Subtle changes should not be rejected simply as “insignificant” or “unremarkable” or “nonspecific” and repeat test should be considered in order to detect reproducible changes [24].

Until recently, larger test patterns of 24-2 and 30-2 were regarded ineffective for screening HCQ toxicity due to insufficient central targets [24]. However, in light of current evidence, this recommendation may need revision. Care must be taken not to discard the possibility of HCQ toxicity merely based on 10-2 visual field testing especially among the non-European ancestry. The recent attention to extramacular pattern of toxicity in the Asian population should prompt the ophthalmologist to also look for paracentral scotomas within the 24 or 30 degrees’ visual field, in the non-European descent, until enough epidemiological data regarding ethnical variations in pattern and extent of retinal damage becomes available [19,20].

Although generally less sensitive in comparison to visual field testing, SD OCT is highly specific and its objective time-saving nature makes it an invaluable tool for primary screening [49]. The possible racial variations mentioned above should be considered for the OCT examinations as well, and wider field images could be helpful if clinically relevant. The main feature associated with toxic retinopathy is disruption of the parafoveal photoreceptor layer (the so-called ellipsoid zone) with reduced thickness especially in the inner inferior subfield [18,48]. If possible (considering availability, local policies, and financial concerns) both the visual field and SD-OCT tests should be ordered as primary screening techniques.

SECONDARY RECOMMENDED TECHNIQUES

Both mfERG and FAF imaging are useful in confirming the diagnosis of HCQ toxicity. They can be used in conjunction with OCT or VF tests, or as second line modalities if the results of primary screening techniques are borderline.

Multifocal ERG

This is an objective tool that evaluates the localised retinal function with sensitivity profiles at least comparable to that of automated VF [50]. Multifocal ERG results may be used to confirm the equivocal field losses observed in routine VF test and the results are expected to be enhanced if the ring ratio

Subjective	Objective		Recommended		Not recommended	Not clinically widespread
Functional	**Structural**	**Functional**	**Primary**	**Secondary**		Microperimetry
Automated VF	SD OCT	mfERG	VF	mfERG	Fundus examination	Adaptive optics retinal imaging
Microperimetry	FAF		SD OCT	FAF	Fundus photography	
	Adaptive optics retinal imaging				TD OCT	
					FA	
					Full-field ERG	
					Amsler grid	
					Color vision testing	
					EOG	

[Table/Fig-2]: Screening methods for detection of HCQ retinopathy.
VF: Visual field; SD OCT: Spectral-domain OCT; FAF: Fundus autofluorescence; mfERG: Multifocal electroretinogram; TD OCT: Time-domain OCT; FA: Fluorescein angiography; EOG: Electro-oculogram

analysis is added [21,31]. Some authorities have reported greatest sensitivity in diagnosing early HCQ-induced retinopathy by mfERG [18,53,54]. It has also been postulated that the mfERG correlates well with the progressive nature of the HCQ-induced toxicity [50]. In a recent systematic review published in 2015, this modality was found to be of greatest sensitivity (90%) and variable specificity [55]. It is efficient at localising subtle changes in the central and paracentral macula, with reduced amplitudes and increased implicit times illustrating the greatest specificity for HCQ retinopathy [47]. Based on a recent study, if the defects are visible on SD OCT, they are already appreciable on mfERG [18]. However, some authors believe that the mfERG is not objective. There is high subjective variation in interpretation with no agreement upon standards for toxicity.

Despite invaluable features that make mfERG gold standard of diagnosis, its limited availability in line with unfamiliarity of primary care ophthalmologists for interpretation of results and cost of the procedure, impose great drawback on its adoption as the primary screening method [43].

Fundus Autofluorescence

This is a gem technique for objectively detecting structural changes in the photoreceptor and RPE layers. Early on, the insult is confined to the photoreceptor layer which appears as a paracentral rim of increased autofluorescence. With progression of the damage and RPE involvement, a prominent change into decreased autofluorescence becomes apparent [56].

NOT RECOMMENDED TECHNIQUES

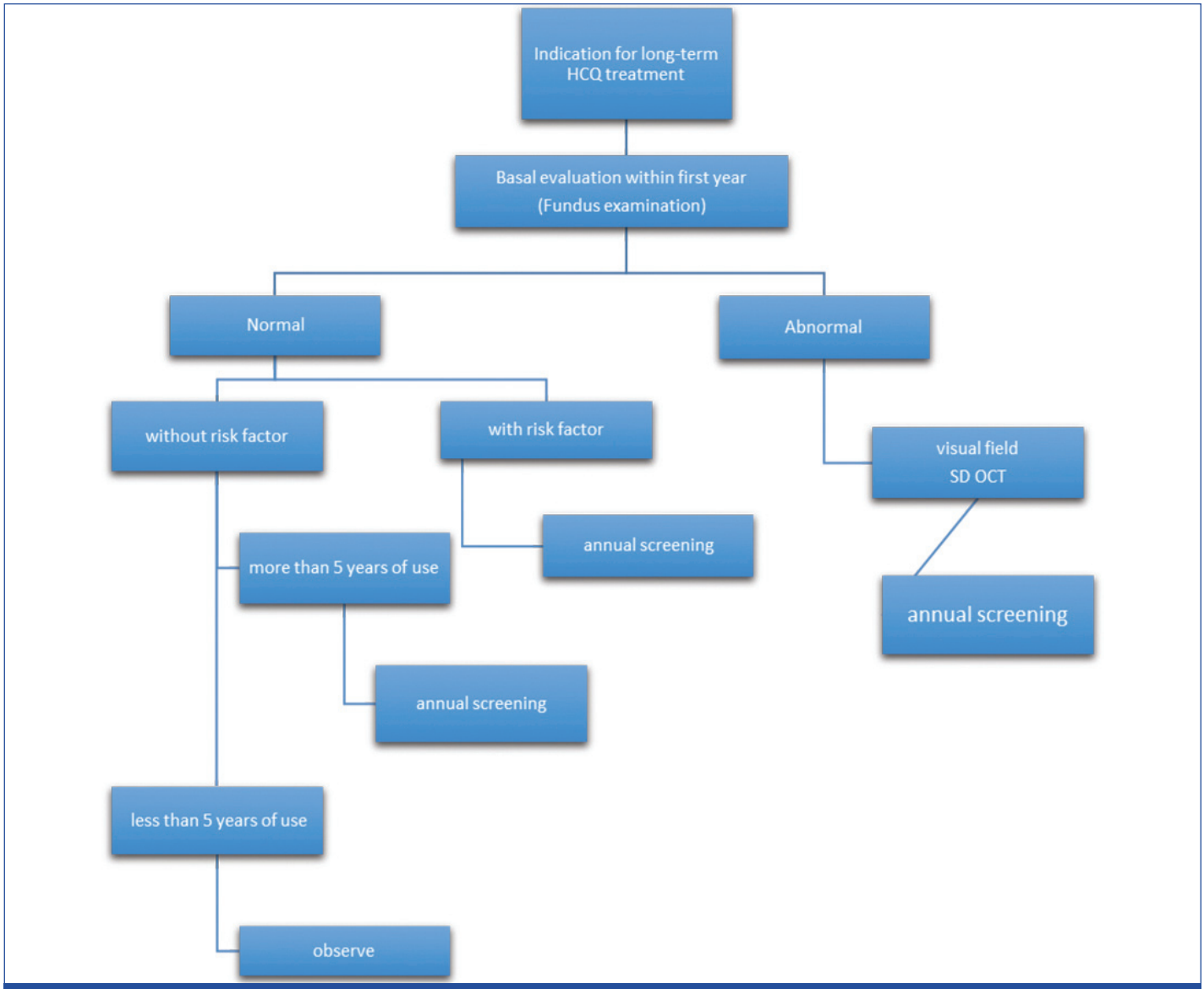
[Table/Fig-2] lists a number of techniques that are not recommended for screening HCQ toxicity. It is worth mentioning that indirect ophthalmoscopy, as a part of routine ophthalmologic exam, should not be undermined. In fact, basal evaluation of uncomplicated patients starts solely with fundus examination. However, because retinal examination, either by indirect ophthalmoscopy or by serial fundus photographs, remains normal until late in the disease course, and the published data reported nearly one-third normal look retina in patients with established retinopathy, the clinical examination should not be considered as a screening method on the yearly basis [48]. The classic appearance of bull's eye maculopathy is a manifestation of advanced RPE loss when discontinuing medications may not protect against further injury.

Very recent screening methods, namely, adaptive optics retinal imaging and microperimetry have been proposed but there is still limited data regarding their clinical utility and they are very rarely available. The former can objectively assess the damaged cone structures in early disease. The latter is a very good localising modality of visual field defects, however, similar to automated perimetry, it is hindered by its time consuming and subjective nature.

DISCUSSION

Screening Approach

The screening for HCQ retinopathy may be classified as baseline evaluation and continued evaluation [Table/Fig-3]. A uniform



[Table/Fig-3]: The flowchart of screening for HCQ retinopathy.

guideline for the screening schedule would reduce the variability in the recommendations presented to patients that may lead to suboptimal care reported by some investigators [42,43]. It also may help better acceptance and liaison by the patient's part.

Baseline evaluation: Current recommendation by the American Academy of Ophthalmology (AAO) states that all patient candidates for initiation of a prolonged HCQ treatment plan should visit an ophthalmologist within the first year of treatment, to detect and appropriately document preexisting retinal conditions. If the examination proves normal at the baseline evaluation, the choice for routine VF or OCT testing depends on the preferences of the patient and physician. Yet, any abnormal finding must be investigated, preferentially, by both VF and SD OCT. This approach benefits both patients and physicians to make proper adjustments in the dosing regimen, or, in decision making as to whether the choice of treatment should be altered to other retinal sparing drugs at first instance. It also provides a valuable basis for comparison of the future screening results and may help avoid falsely attributing abnormal screening findings to HCQ-related retinal toxicity.

Continued Evaluation

Due to negligible rate of incidence of HCQ toxicity in the first 5 years of treatment, especially with safe dose regimens, it is recommended to postpone the annual screening until 5 years has passed since the initiation of therapy. This is both cost effective and safe for those who have undertaken basal evaluation and have not been complicated by simultaneous retinal or renal disease. However, the screening threshold should be low if any of the aforementioned major risk factors listed in table 1 are present as they justify annual screening started within 5 years of consumption.

Also, the patient and the prescribing physician should be informed properly so as to any change in the dosing or medical conditions (such as weight loss, kidney disease, liver function abnormality, etc.,) or addition of retinopathic agents such as tamoxifen that may predispose to increased risk of retinal toxicity be reported to the ophthalmologist accordingly if timely steps are to be taken to detect early retinopathy.

CONCLUSION

Timely screening is invaluable and may be sight saving. If it is possible, the screening plan should be individualised based on the patient's status and the ophthalmologist's preferences, considering expertise, local policies, availability of various techniques and their cost, making sure that none of the patient's interests would be compromised. On the other hand, a uniform guideline for baseline and continued evaluation would reduce the variability in the recommendations and the suboptimal care.

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