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Screening and Diagnosis of Hydroxychloroquine Toxicity: Advances and Controversies

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Introduction

Hydroxychloroquine (HCQ) is a widely-used medication. Although classically associated with the treatment of malaria and systemic lupus erythematosus (SLE), the potential spectrum of HCQ utility is actually quite expansive, and may come to include more common diseases and disorders [1]. Although generally considered a safe medication in the medical community, the adverse effect profile of HCQ is distinguished by irreversible retinal toxicity, with a reported prevalence between 0.5% and 7.5% [2,3]. Primary prevention is a key for these patients, because the retinal damage is considered largely irreversible. However, the means of primary prevention, i.e. screening, has been at the center of controversy in the ophthalmology community for several years.

The most recent guidelines for the screening and treatment of HCQ retinopathy were published in 2011 [2]. These guidelines cover issues ranging from initial dosing methods, variables for classifying risk, and frequency and modalities of screening. However, there have been substantial additions to our understanding of HCQ retinopathy epidemiology and pathophysiology and the armamentarium of diagnostic modalities since their publication. As a result, current practice in HCQ retinopathy screening and management is heterogeneous, and it is unclear what exactly constitutes best practice.

Current Guidelines and Practice

The mechanism of HCQ retinopathy is tied directly to the toxic effects of the HCQ molecule itself. The HCQ molecule is a weak base and becomes ionized in the acidic environment of the retinal pigment epithelial cell lysosomes [4]. Not only does this trap the HCQ molecule in the lysosome, it raises the pH; this disrupts lysosome function and impairs RPE cell function, leading to accumulation of photoreceptor waste and breakdown products [5]. Genetic variants have also been implicated in HCQ retinopathy, particularly the photoreceptor specific ATP-binding cassette transporter ABCA4 (coded for by the ABCR gene). Certain variants of this gene have been identified as either significantly decreasing [6] or increasing [7] the risk for retinopathy. While this association supports the utility of incorporating genetically-determined risk into future screening tools, the dominant opinion is that the directly toxic effects of the HCQ molecule are the major causative factor in the development of HCQ retinopathy. As a result, current preventative strategies are aimed at limiting HCQ exposure and ensuring regular screening.

The 2011 screening guidelines recommend a baseline exam within the first year of starting HCQ in order to record fundus appearance and function, as well as to counsel the patient on risks of HCQ and the importance of regular exams. This initial exam should include slit lamp biomicroscopy, 10-2 Humphrey visual field central 10-2 white-on-white pattern (HVF), and at least one of three objective tests (fundus autofluorescence, spectral domain optical coherence tomography (SD-OCT), or multi-focal electroretinogram (mfERG)). Patients are stratified into average or high-risk groups. Patients at average risk should then be followed with annual screenings beginning 5 years after initial exam. Patients with high-risk features should be followed annually starting with the initial exam. High-risk features include high dose (cumulative dose >1000 g, daily dose >400 mg/day, or daily dose >6.5 mg/kg of ideal body weight for short individuals), renal or liver disease, or pre-existing retinal disease. At each annual screening appointment, it is recommended that both average and high-risk patients be screened with slit lamp biomicroscopy, 10-2 HVF, and at least one of fundus autofluorescence, SD-OCT, or mfERG [8].

New Advances

Since the implementation of these guidelines, there have been significant advances in the ability to detect HCQ retinopathy at increasingly early stages. The capabilities of SD-OCT have markedly improved, and functional techniques, such as mfERG, have become more sensitive. Moreover, novel imaging techniques, such as adaptive optics, and advanced tools for testing retina function, such as microperimetry, have enabled the detection of retinopathy prior to symptom onset and offered significant insight into the anatomic and physiologic changes that occur from HCQ exposure [9].

Notably, SD-OCT has been growing in both popularity and capability. Modern SD-OCT has provided incredible insight into the anatomic changes in HCQ retinal toxicity by offering increasingly refined levels of anatomic detail. These capabilities are clinically important because changes on SD-OCT not only tend to occur in a stereotyped fashion8, but have been found in asymptomatic patients9. Moreover, certain anatomic features, such as an intact external limiting membrane, are associated with an improved prognosis [10]. Accordingly, SD-OCT may indeed by useful for both early diagnosis and determining prognosis.

Functional testing modalities have also emerged as highly sensitive means to test for HCQ retinopathy. The multifocal electroretinogram (mfERG) is considered the gold standard for defining and diagnosing HCQ retinopathy. It is an excellent confirmatory test and has up to 90% sensitivity for detecting HCQ retinopathy [11]. Such sensitivity has clinical importance because functional impairment may precede anatomic change on SD-OCT. A recent study using microperimtery reported a series of 16 patients taking HCQ who had abnormal microperimetry despite normal 10-2 HVF, FAF, mfERG, and SD-OCT [12]. A different study of 34 patients identified a subset that had abnormal mfERG and/or HVF despite having completely normal SD-OCTs [13]. Functional change may indeed precede anatomic change; this study also failed to find patients with abnormal SD-OCT who also had normal functional tests [13].

Completely new techniques have also emerged as potentially useful additions to the screening armamentarium. Adaptive optics scanning ophthalmoscopy has been shown to identify early toxicity in preclinical stages by monitoring for changes in cone density patterns [14,15]. As of 2016, investigators have been using brand new multispectral imaging devices to further investigate HCQ retinal toxicity [16].

Taken together, these studies suggest that functional testing may be superior to anatomic testing for detecting early disease. However, the data is by no means that clear. For example, one prospective study of 57 patients found that careful application of SD-OCT, with special attention to subtle anatomic changes, when combined with visual fields, was just as sensitive and specific as mfERG for detecting HCQ retinopathy [17].

The evidence for functional vs. anatomic approaches to screening is at best mixed. Moreover, early damage is not uniformly detectable by one modality of screening due to high inter-individual variability [8]. The best use of these modalities is most likely in a combined approach in which the strengths and weaknesses of each technique complement each other. In a critical study of 10 patients, Marmor concludes that each test has its own strengths and weakness, so using of more than one modality is the most appropriate [8]. This observation is based on sound data, but the scope of evidence comparing diagnostic techniques is regrettably restricted to comparative studies with small sample sizes and non-inferiority studies aimed at validating new techniques. As a result, expert opinion and clinical experience tend to drive practice patterns, resulting in heterogeneous practice and controversy.

Controversies and Future Directions

The 2011 guidelines have faced their fair share of controversies. Patient safety is of the utmost importance, but this is inevitably weighed against the therapeutic benefits of HCQ in progressively debilitating and life-threatening diseases such as SLE. Dosing the medication correctly and implementing an efficacious and cost-effective uniform screening practice are therefore paramount to ensuring the responsible use of HCQ. The use of weight-based dosing and the overall cost-effectiveness of the guidelines have been two points of controversy that have dominated the debate since 2011.

The relationship of body weight to dosing of HCQ and risk for retinopathy is a key piece of evidence needed to strike an acceptable balance between the therapeutic efficacy of HCQ and its retinal toxicity. The 2011 guidelines reasoned that because HCQ is not stored in fatty tissues, dosing based on actual body weight may result overdosage for short or obese individuals [2]. Therefore, the recommendation is to dose obese individuals based on height and dose short individuals based on ideal body weight [2]. Although this reasoning is sound, this method of dosing is not uniformly practiced; in two retrospective studies, ideal bodyweight was used to re-calculate HCQ dose and found that approximately half of these patients were overdosed [18,19]. Moreover, the specific method of determining ideal body weight can also impact risk of overdosage and subsequent dose adjustment [20]. However, it is important to note that this recommendation was based on the above reasoning and importance of primary prevention, and on data from such large-scale observational studies as exist available today.

Observational data published since 2011 has not uniformly supported the hypothesis that ideal body weight is a superior predictor of risk of HCQ retinopathy. In fact, the preponderance of evidence supports the use of actual body weight to dose HCQ. A prospective study of 300 patients taking HCQ found that actual body weight strongly correlated with blood levels of HCQ [21], as did a recent study in the rheumatology literature examining the effects of monitoring on compliance [22]. Moreover, a recent retrospective study of 2361 patients taking HCQ found that actual body weight correlated with risk of retinopathy whereas ideal body weight did not [3]. Therefore, actual weight, as a better predictor of both blood levels and risk for retinopathy, may be superior to ideal weight for determining safe weight-based doses of HCQ.

Focusing on weight-based dosing to classify risk becomes increasingly important over the duration of treatment; damage to the retina by HCQ is cumulative, and cumulative dose is a highly-predictive risk factor. The importance of cumulative dose is stressed by the 2011 guidelines (recommending <1000 g) [2]. Although the guidelines mainly cite both the pathophysiology and a single retrospective study that found a five-fold increase in the incidence of HCQ retinopathy after 7 years or 1000 g of HCQ [2], further evidence continues to support cumulative dose as an important prognostic factor. In their 2014 observational study, Melles and Marmor also found a significant increase in odds ratio for retinopathy with cumulative doses over 20 g/kg, duration of therapy over 10 years and high daily dose (over 5 mg/kg) [3]. More broadly, these findings imply that a cumulative dose should exist over which the risk for retinopathy becomes unacceptably high. While Melles and Marmor offer evidence that this dose may hover around 20 g/kg, the process of determining this "threshold risk dose", and the cost-effectiveness of screening at different risk levels, intimately depends on the screening methods used.

To this end, one important criticism of the 2011 guidelines is that they rely too heavily on objective testing that is difficult, costly, and of questionable additional utility. While decreased screening ostensibly leads to decreased diagnosis, a 2013 study compared incidence of HCQ retinopathy diagnosis in 176 returning patients before and after the addition of mfERG and SD-OCT, and examined 36 new patients with the full 2011 screening method. However, they failed to identify any additional cases of HCQ with the addition of mfERG or SD-OCT, concluding that the addition of these tests raised costs without providing additional venefit [23]. The importance of these objective tests, such as the mfERG, fundus autofluorescence, and SD-OCT, their extra expense, and the fact that some or all of these modalities may not be readily accessible for many ophthalmologists has resulted in broad heterogeneity in the application of the 2011 guidelines; indeed, a large-scale cost-effectiveness study has found that screening as per the guidelines is severely underutilized [24]. Even so, it is not clear that perfect adherence to the 2011 guidelines would be the most cost-effective way to screen for HCQ retinopathy.

The ambiguity of the cost-effectiveness of screening for HCQ retinopathy is complicated by the fact that the true prevalence of HCQ is difficult to assess. Reports have been widely variable, and much of this variability is most likely due to sensitivity of the screening technique. The prevalence assumption employed by the 2011 guidelines (1% or less) was based on retrospective studies that relied heavily on subjective testing such as scotomas or visual fields [25], utilized a less-sensitive test such as full-field ERG [26], relied heavily on surveys from practicing ophthalmologists [27], or used a sensitive technique such as mfERG but incompletely applied it to the study population [28]. Therefore, it is unsurprising that the 2014 study by Melles and Marmor, which employed the more sensitive SD-OCT as an

inclusion criterion, reported a significantly higher prevalence of 7.5% [3].

Unfortunately, these differences in diagnostic techniques renders direct comparison between newer studies and those that formed the basis for the 2011 guidelines nearly prohibitively difficult. The data on which the 2011 guidelines are based is substantially different than the data we have today, and the "true prevalence" and "true incidence" of HCQ retinopathy remain elusive. Without a consistently defined incidence or prevalence, it is difficult to determine the "number needed to screen" for the regimen suggested by the 2011 recommendations. Without a number needed to screen, cost-effectiveness analysis is nearly impossible.

Perhaps more importantly, rather than redefining the disease with better technology, we must determine the clinical utility of these screening measures. That is, at what stage should we stop HCQ? We now have highly sensitive technology at our disposal, and with it, we will be able to diagnose a higher number of early-stage cases, and more cases overall. With this ability we must face the inevitable and uncomfortable trade-off between continuing to maximize the therapeutic benefits of HCQ and stopping the progression of subclinical HCQ retinopathy. The borders of this trade-off are not clear - cessation may not always stop progression [10,18], patients value sight and symptom control differently, and advanced testing is costly- and these borders will become even more blurred as greater numbers of subclinical HCQ retinopathy are diagnosed.

Fortunately, the Academy is due to publish a new set of screening guidelines for HCQ retinopathy this year. The issues of body weight dosing, genetic risk factors, and highly-sensitive and cutting-edge diagnostic modalities represent just the tip of the iceberg but demonstrate the rapidly evolving nature of HCQ retinopathy screening. Using the results from many new studies (including the non-exhaustive list reviewed here), we have great faith that the new guidelines will represent an approach to HCQ retinopathy screening that is clinically efficacious, cost-effective, and cutting-edge.

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