Rethinking the Hydroxychloroquine Dosing and Retinopathy Screening Guidelines

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• PURPOSE: To describe the rationale for revising the hydroxychloroquine (HCQ) dosing and screening guidelines and to identify the barriers to more effective guidelines in the future.
• DESIGN: Literature review.
• METHODS: A PubMed query of studies on HCQ dosing and HCQ retinopathy (HCQR) screening was conducted with a selective review of the English language literature.
• RESULTS: Three iterations of the American Academy of Ophthalmology HCQ dosing and HCQR screening guidelines have been published without including prescribing physicians on the writing committees. This may contribute to prescribing physicians' low adherence to the guidelines. As ancillary tests have improved, asymptomatic HCQR is being detected earlier, leading to a higher reported prevalence of HCQR and a drop in the ceiling for safe dosing. These trends put stricter constraints on prescribers and their patients, who may have had well-controlled autoimmune disease on HCQ doses that were previously considered to be below the high-risk threshold for HCQR. Indeed, stopping HCQ at the earliest sign of HCQR should be reconsidered; for cases of early HCQR, dose reduction and more intensive monitoring for retinopathy may strike a more appropriate balance between HCQ risk and benefits. A prospective study using the Diabetic Retinopathy Clinical Research Retina Network with standardized collection of data, HCQ blood levels, centralized grading of ancillary tests, and community and academic ophthalmologists would provide a stronger evidence base for future HCQ guidelines.
• CONCLUSIONS: The HCQ dosing and screening guidelines should be updated and a prospective study of HCQ dosing and HCQR should be initiated with the joint efforts of ophthalmologists and prescribing physicians. (Am J Ophthalmol 2020;219:101–106. © 2020 Elsevier Inc. All rights reserved.)

IT IS TIME TO REVISE THE HYDROXYCHLOROQUINE (HCQ) dosing and retinopathy screening guidelines. New guidelines should include overdue input from medical specialists who prescribe HCQ and reflect a more nuanced approach to HCQ dosing that acknowledges both the limitations of the current evidence base and the balance between managing autoimmune disease and minimizing the risk of HCQ retinopathy (HCQR). Daily dosing is the most important risk factor for HCQR and is the only modifiable one.[1]

The revised guidelines should also make it clear, for the first time in 3 versions (2002, 2011, and 2016), that detecting HCQR at the earliest possible stage is an important subsidiary goal, not the primary goal. Both prescribing physicians and screening ophthalmologists aim to control systemic disease without endangering vision. Pending clarification by further study of the point at which retinopathy progresses despite drug cessation, we suggest reconsidering the recommendation that HCQ be stopped at the earliest sign of toxicity, as is commonly done now[2]; our ability to detect HCQR at a subclinical stage has markedly improved, leading to a much higher prevalence of milder HCQR.[3] Instead, early HCQR should lead to more frequent testing and possible reduced daily dosing with recognition that cessation eventually might be necessary to avoid more advanced HCQR that may progress despite cessation of the drug.[1,4]

HCQ is effective in many autoimmune diseases, particularly in patients with systemic lupus erythematosus (SLE).[5] HCQ is recommended to all patients with SLE unless contraindicated because of the multiple beneficial effects on survival, disease activity, and the risks of organ damage and thromboembolic episodes.[5] Using pre-2016 dosing guidelines from the American Academy of Ophthalmology (AAO),[6] these benefits have been obtained with minimal side effects, the most significant of which is HCQR.[7] There are alternatives to HCQ, but they are more expensive and have more side effects, and the loss of HCQ because of concerns of HCQR handicaps patients with autoimmune disease and their physicians.

Based primarily on 1 retrospective study with selection bias, but a much larger sample size than other retrospective

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studies (Table 1),[8] the AAO revised the HCQ dosing guidelines in 2016 to recommend a ceiling of 5 mg/kg of real body weight (RBW).[10] This was a major change from the recommendation of the 2011 guideline, which discounted the importance of daily dosing; the 2011 guideline was in turn a major change from the original 2002 guideline, which recommended a conversion factor of 6.5 mg/kg ideal body weight (IBW) for the ceiling daily dose (Table 2).[10–12] The choice of 5.0 mg/kg RBW was based on the sample-specific facts that RBW was 25%-30% higher than IBW and a relationship of consumed to prescribed HCQ dose unlikely to generalize to other settings.[8,13]

The 2016 AAO dosing guidelines have 5 shortcomings. First, they failed to acknowledge that the relationship of RBW to IBW is a moving target, with RBW increasingly diverging from IBW as the obesity epidemic intensifies.[9,14] Second, other suggested methods of dosing were not considered in their analyses. For example, Browning and associates[1,15,16] have suggested 6.5 mg/kg of the lesser of RBW and IBW. Petri and associates[6] have used 6.5 mg/kg RBW with a ceiling of 400 mg. Scherbel[17] has recommended 6.0 mg/kg RBW. Third, the assertion of risk invariance across body mass index using the 5 mg/kg RBW, but not using the 6.5 mg/kg IBW methodology, could not be replicated in an independent data set, and there is evidence that a high body mass index makes IBW dosing safer.[9,18] Fourth, the guidelines neither included prescribing medical specialists as authors nor acknowledged the potential impact of a recommended 5.0 mg/kg RBW daily dosing ceiling on patients with well-controlled autoimmune disease on doses above this threshold.[19,20] Lastly, the guidelines were developed without using a systematic methodology, such as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses method.[21] Modern guideline development attends to a rigorous checklist of steps and reports the flow of information that leads to conclusions less compromised by poor evidence quality, conflicts of interest, and a lack of transparency.[22] The evidence base suggests not that a liberalization of dosing beyond that of the 2011 guideline is in order, but rather that the choice of the 5 mg/kg RBW threshold for unsafe dosing was made without consideration of the alternatives.

Including prescribing physicians provides an invaluable perspective.[19] Rheumatologists comprise a large portion of the physicians who prescribe HCQ. Rather than emphasizing a ceiling for avoiding HCQR, rheumatologists emphasize daily dosing that produces clinically meaningful systemic effects. A recent clinical trial using 6.5 mg/kg IBW dosing confirmed therapeutic effects[23] with pharmacokinetics.[24] There has been no study looking at the pharmacokinetics and clinical outcomes using 5.0 mg/kg RBW dosing.[25] Rheumatologists need to know whether the clinical efficacy of 5.0 mg/kg RBW dosing is similar to the proven 6.5 mg/kg IBW standard or not before they can confidently adopt this guideline.[13]

From an ophthalmologist's perspective, advances in diagnostic testing, including multifocal electroretinography (mfERG), fundus autofluorescence, microperimetry, fluorescence lifetime imaging ophthalmoscopy, 10-2 format standard automatic perimetry (10-2 VF), and spectral-domain optical coherence tomography (OCT) led to earlier detection of HCQR and upward revisions in estimated prevalence of HCQR based on new definitions.[4,15,26] In most cases, objective signs were found in asymptomatic patients and their medications were stopped to avoid progression to symptomatic HCQR.[3] To balance this beneficial effect, a proportion of asymptomatic patients were advised to stop HCQ, which had heretofore provided improved quality of life and better prognoses for various end-organ effects. The availability of more sensitive ancillary testing has made recommendations from ophthalmologists to stop HCQ more common and introduced new management challenges for prescribing physicians and patients. In the early 2000s, most of the errors we saw in HCQR diagnosis were failures to diagnose.[27] In 2020, it is far more common to see patients taken off HCQ because of aggressive approaches to early HCQR in 10-2 VFs and spectral-domain OCT scans.

It is a fair question, therefore, whether the emphasis on early detection of HCQR has been pushed too far. Ophthalmologists set the guidelines based on a concern for HCQR, but the prescribing physicians and their patients are the ones who must live with the ramifications of the guidelines. Premature discontinuation of HCQ can harm patient survival (Jorge A, et al. Arthritis Rheumatol 2018; 70[suppl 10]:abstract 2896). By failing to adequately capture the prescribers' perspective, the AAO 2016 guidelines risk being ignored as suggested by the persistently high proportion of patients taking excessive daily doses of HCQ—whether based on RBW or IBW.[1,28,29] This practice pattern places prescribing physicians in jeopardy as they appear to be neglecting patient safety, when in many cases they and their patients are making calculated decisions balancing the risks of HCQR with damage to other organ systems.

A more collaborative approach, dependent upon close communication between the prescribing physician, monitoring ophthalmologist, and patient, would be to tolerate sensitive ancillary testing indicators of HCQR while raising the possibility of dose reduction and instituting more frequent retinal monitoring before drug cessation.[2,4,30] For example, subtle decreased reflectivity of the parafoveal ellipsoid zone line and interdigitation line on spectral-domain OCT scans may not need to trigger cessation of drug.[30,31] In this vein, a decision to stop HCQ would be made based on accumulated ancillary testing evidence but before visual symptoms or progression to parafoveal ellipsoid zone loss occurs on spectral-domain OCT. Evidence from a small sample suggests that cessation of drug before funduscopic evidence of retinopathy occurs and symptoms develop is associated with a low rate of

TABLE 1. Comparison of 3 Studies Investigating Hydroxychloroquine Dosing and Retinopathy

Characteristic	Melles and Marmor,[8] 2014		Browning and Lee,[9] 2016		Petri et al,[6] 2020	
Study design	Retrospective chart review		Retrospective chart review		Prospective cohort study	
Source of patients	Managed care network		Private practice		Medical university clinic	
Testing methods	10-2 VF and spectral-domain OCT		10-2 VF, spectral-domain OCT, mfERG, and FAF		Spectral-domain OCT, mfERG, MP, and FAF	
	Retinopathy	No retinopathy	Retinopathy	No retinopathy	Retinopathy	No retinopathy
N	177	2184	41	524	23	514
Female (%)	92	82	100	98	83	92
Kidney disease (%)	37.3	22.7	4.9	2.9	ND	
Tamoxifen use (%)	6.8	1.2	0	0.6	ND	
Age at the start of therapy (years) ± SD	52.2 ± 13.3	52.2 ± 13.8	51.3 ± 13.7	51.2 ± 15.6	<45: $n = 1$ 45-59: $n = 8$ ≥60: $n = 14$[a]	<45: $n = 215$ 45-59: $n = 175$ ≥60: $n = 124$[a]
Weight (kg) ± SD	67.2 ± 16.7	76.9 ± 19.5	68.1 ± 20.0	76.1 ± 19.0	ND	
BMI (kg/m^2) ± SD	25.8 ± 5.8	28.3 ± 6.5	26.5 ± 7.2	28.9 ± 6.7	<20: $n = 1$ 20-25: $n = 4$ 25-30: $n = 8$ 30-35: $n = 4$ ≥35: $n = 6$	<20: $n = 50$ 20-25: $n = 171$ 25-30: $n = 159$ 30-35: $n = 76$ ≥35: $n = 58$
Daily dose (mg/kg) RBW/d ± SD	5.4 ± 1.4	4.0 ± 1.2	5.7 ± 1.6	4.4 ± 1.5	≤8.5[b]	
Duration of therapy (years) ± SD	15.1 ± 5.5	12.0 ± 5.0	13.8 ± 8.9	7.8 ± 6.9	≤5: 4.3% 6-10: 8.7% 11-15: 13.0% 16-20: 47.8% ≥21: 26.1%	≤5: 22.6% 6-10: 23.7% 11-15: 19.5% 16-20: 18.8% ≥21: 15.3%
Cumulative dose (g) ± SD	1856 ± 668	1275 ± 585	1976 ± 1199	921 ± 883	ND	

BMI = body mass index; FAF = fundus autofluorescence; mfERG = multifocal electroretinogram; MP = microperimetry; ND = not done; OCT = optical coherence tomography; RBW = real body weight; SD = standard deviation; VF = visual field.

[a]Not explicitly stated that these ages were at start of therapy.

[b]Maximum of 400 mg/d. Dose reduced for renal impairment, elderly, and high blood hydroxychloroquine level.

TABLE 2. American Academy of Ophthalmology Guidelines on Hydroxychloroquine Dosing, 2002-2016

2002: "The great majority of reports of hydroxychloroquine toxicity have occurred in individuals taking >6.5 mg/kg/d, which suggests that daily dosage is of paramount importance…. Obesity is a risk factor because antimalarials are not retained in fatty tissues. Ingested amounts of the drug accumulate only in lean weight, and the "safe" dose for a high percentage of fat is <6.5 mg/kg…."[10]
2011: "…recent surveys of patients taking hydroxychloroquine found that the risk of toxicity depended on the cumulative exposure and was independent of daily dose or dose/kg…. We suggest that daily doses be limited to 400 mg hydroxychloroquine and that lower doses (in the range of 6.5 mg/kg hydroxychloroquine…calculated on the basis of ideal body weight) be used for individuals who are of short stature…. Obese individuals should be dosed on the basis of height, which allows estimation of an asthenic or 'ideal' body weight."[11]
2016: "…we recommend that all patients using hydroxychloroquine keep daily dosage <5 mg/kg real weight…. Ideal weight formulas result in overdose in thin individuals…. The most cited risk factor for the development of hydroxychloroquine toxicity is excessive daily dose by weight."[8]

progression of ancillary testing abnormalities.[2,4] More study is needed to determine if the observation is true. If it is, then in practice, if successive testing were to show progressive signs of retinopathy, a more serious decision to stop drug could be made by all involved.

For these reasons, we suggest that revised guidelines are needed now. However, as the indications for HCQ use are expanding, it is also worthwhile to identify limitations in the evidence base that hamper formulation of more helpful HCQ dosing guidelines in the future. The evidence base could be improved by addressing the following topics:

1. Can dosing based on blood levels solve the dosing controversy?[32] One recent study reported that higher HCQ levels predicted later HCQR (Table 2).[6] Current dosing methods based on RBW or IBW can lead to supratherapeutic blood levels caused by wide—and possibly genetically determined—variation across patients.[33] Dosing based on blood levels could provide more direct guidance to prescribers than current dosing based on RBW or IBW. Further study is merited to make blood testing more widely available and to explore its link to HCQR.
2. What is the relative distribution of HCQ between adipose tissue and lean tissue? For years the laboratory data based on animal studies was accepted as showing a relative sequestration of hydroxychloroquine away from fat.[34–36] However, the authors of the 2016 AAO guidelines changed their interpretation of these studies without apparent cause and this decision helped guide the recommendation to use HCQ dosing based on RBW rather than IBW.[18]
3. What is the threshold among the key diagnostic indicators of HCQR at which progression of retinopathy—despite cessation of HCQ—becomes expected? Are there patients who progress upon cessation of drug with only mfERG evidence of toxicity or upon decreased reflectivity of the parafoveal ellipsoid zone line on OCT?[3] Do clinicians need to follow outer nuclear layer thickness—a demanding requirement dependent on retinal segmentation—based on evidence that thinning is an early sign of HCQR?[37,38] If so, it will be important to encourage OCT manufacturers to provide more targeted data displays with comparisons using previous studies and to address the lack of comparability of laminar norms across various OCT models.
4. What are the relative sensitivities and specificities of the tests for HCQR? Although small studies suggest that the decreasing order of sensitivity is mfERG > 10-2 VF > spectral-domain OCT and the decreasing order of specificity is spectral-domain OCT > 10-2 VF > mfERG,[39,40] where do fundus autofluorescence imaging, retromode imaging, en face near-infrared reflectance imaging, fluorescence lifetime imaging ophthalmoscopy, and microperimetry fit into the overall scheme?[26,41–44]
5. What is the best way to quantitate renal disease with respect to HCQ dosing? How should dosing be modified in the presence of renal insufficiency given that elimination half-life of HCQ tends to increase with decreasing glomerular filtration rate (Yokogawa N, et al. Arthritis Rheumatol 2019; 71[suppl 10]:abstract 2541)?
6. What is the true relationship of the HCQ cumulative dose to HCR risk? One retrospective study reported 20% but another reported 8%.[6,8]

Except for 1 rheumatologic report,[6] all studies on HCQR using modern ancillary testing have been retrospective. HCQR is not rare, as was once claimed,[45,46] and the number of patients taking HCQ is increasing.[47] We have the organizational infrastructure for a prospective ophthalmologic study to address the previous questions, and others, in a methodologically sound, prospective fashion. The Diabetic Retinopathy Clinical Research Network (DRCR.net) is now performing studies on retinal diseases other than diabetic retinopathy.[48] The DRCR provides a platform for assessing many aspects of HCQR, settling outstanding controversies, and putting physician prescribers of HCQ and ophthalmologists on firmer ground in advising their patients on dosing, monitoring, and thresholds for dose reduction and drug cessation. This need not be a prospective,

randomized clinical trial of dosing taking decades to complete; rather, we envision a prospective study in which ancillary testing would be obtained and interpreted in a standard manner, blood levels of HCQ gathered, and a large enough sample size accumulated to have the statistical power to answer prespecified questions such as those suggested above. Such a trial might take 2-3 years, but not 10-20, and it would be feasible through the DRCR network.

While we wait for better quality evidence, however, it is imperative that the various specialties involved in HCQ prescribing and monitoring have a place on the committee tasked with next revision of the AAO HCQ dosing guidelines. By acknowledging the complementary roles of prescribers and ophthalmologists, this approach will lead to wider acceptance of the guidelines and better care for our patients.

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