REVIEW

Updated recommendations on the use of hydroxychloroquine in dermatologic practice

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Hydroxychloroquine has unique immunomodulatory properties and an attractive adverse effect profile. Over the past 10 years, research has led to significant updates in clinical recommendations concerning the optimal use of hydroxychloroquine and monitoring of patients taking it. We discuss updated recommendations concerning hydroxychloroquine daily dosing, retinopathy screening, serologic monitoring, use in smokers, use in pregnant women, and adverse effect risk and monitoring. This review can hopefully serve as an aid to dermatologists and help ensure they continue using hydroxychloroquine safely and effectively. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2017.01.012.)

Key words: adverse effects; hydroxychloroquine; lupus erythematosus; monitoring; recommendations; retinopathy screening; whole blood levels.

Since hydroxychloroquine's (HCQ) introduction in 1955, its uses in medicine and dermatology have persistently expanded (Table I). Using HCQ to treat inflammatory and rheumatic skin diseases may allow for the reduction in the use of glucocorticoids and other immunosuppressive medications with more concerning adverse effects (AEs).[1-19] HCQ has been found to have antithrombotic, antifibrotic, antidyslipidemic, and antihyperglycemic properties,[1-5,17,20-22] and substantial changes have been made in its clinical recommendations during the past decade. This article provides a focused update concerning HCQ recommendations arising in dermatologic practice (Table II).

METHODS

A PubMed search for hydroxychloroquine from January 2005 to June 2016 was conducted, revealing 1929 articles. These articles were evaluated by reviewing titles and abstracts. Those containing information of high clinical importance to dermatologists were examined completely and are referenced if information was extracted for this review.

Abbreviations used:

ABW:	actual body weight
AE:	adverse effect
CLE:	cutaneous lupus erythematosus
G6PD:	glucose-6-phosphate dehydrogenase
HCQ:	hydroxychloroquine
IBW:	ideal body weight
LE:	lupus erythematosus
SLE:	systemic lupus erythematosus
RPE:	retinal pigment epithelium
WB-HCQ:	whole blood hydroxychloroquine levels

RESULTS

Dosing

It has classically been that recommended daily doses not exceed 6.5 mg/kg ideal body weight (IBW) or 400 mg daily, whichever is lower. Using IBW and not actual body weight (ABW) for daily dosing was rationalized because HCQ does not accumulate well in fat. ABW dosing was thought to potentially increase the amount accumulated in tissues and increase AE risk, namely retinopathy.

New HCQ-dosing recommendations were proposed after a study examining the risk for HCQ-induced

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retinopathy found optimal doses would be ≤5.0 mg/kg ABW.[23] The new recommendations are thought to be similar to the previous IBW-dosing regimen given most patients are overweight and not perfectly adherent, but they are particularly important for thin patients. Although ≤5.0 mg/kg ABW daily dosing in thin patients is recommended, appropriate dosing in obese patients is unclear. In contrast with IBW dosing, ABW dosing might result in relative overdosing of obese patients (Table II).[24] Pending further research, it seems reasonable to calculate 5.0 mg/kg ABW and 6.5 mg/kg IBW doses in obese patients and prescribe the lowest of the 2, with a 400 mg/day maximum.

Because HCQ has a long elimination half-life, alternate-day dosing can be used to optimize daily dose. For example, 400 mg alternating with 200 mg daily can be used to reach effective daily dosing of 300 mg/day. In addition, because stable blood concentrations are not reached for 3-6 months, loading during the initial 1-2 months with daily doses ≤1200 mg can be used to accelerate response, with the caveat that this might increase gastrointestinal intolerance.[2,24-26]

CAPSULE SUMMARY

- Hydroxychloroquine is a medication with unique immunomodulatory properties and broad applicability in dermatologic practice.
- Updates to clinical recommendations concerning hydroxychloroquine use and patient monitoring are reported.
- Implementing these updated recommendations will help ensure dermatologists continue using hydroxychloroquine safely and effectively.

Monitoring response

High-performance liquid chromatography is routinely available for quantifying mean whole blood HCQ (WB-HCQ) levels. Measuring WB-HCQ levels is becoming increasingly valued because of its correlation with systemic (SLE) and cutaneous (CLE) lupus erythematosus severity; patients achieving significant LE disease activity decreases and remission have significantly higher WB-HCQ levels than those with persistently high disease activity.[27-29] Measuring WB-HCQ levels also allows identification of noncompliant patients, which is not trivial.[30] Noncompliance lacks correlation with education and income. Noncompliant patients were found unexpectedly because many of them routinely attended clinic appointments, received routine ophthalmology examinations, and were not forthcoming about noncompliance.[30] Furthermore, reeducating patients about HCQ benefits and safety resulted in increased WB-HCQ levels and thus improved compliance, supporting that monitoring is cost-effective.[30-32]

An important question is how best to treat compliant patients with both inadequate WB-HCQ levels and inadequate responses. This was addressed in a study involving refractory CLE patients with low WB-HCQ levels (<750 ng/ml) despite most taking 400 mg daily.[33] By increasing HCQ daily doses (to a median of 9.8 mg/kg ABW) all patients achieved adequately increased WB-HCQ levels (median 1187 ng/ml) and statistically significant improvements in CLE disease activity. Doses were decreased back to 400 mg daily for these patients; however, some subsequently experienced disease relapse and required transient HCQ increases again. Only one patient developed preclinical retinopathy, but median cumulative HCQ dose in this cohort was lower than expected for retinopathy (523 g). Determining whether this strategy is safe long-term will require additional research, especially because patients taking 800-1000 mg HCQ daily developing rapid-onset retinopathy have been reported.[34,35]

Overall, studies suggest clinicians should not consider that HCQ treatment failed without measuring WB-HCQ levels. A limitation of this approach is a lack of a current standard effective WB-HCQ level, although median WB-HCQ levels in cohorts demonstrating significant improvement and remission have typically been >750 ng/ml and levels >500 ng/ml can be considered adherent.[27-29,33] Also, although it seems appropriate to extrapolate findings in LE cohorts for now, research assessing utility of measuring WB-HCQ levels in patients with other diseases is needed.

Efficacy in smokers

The idea that smoking interferes with HCQ efficacy was first reported in 1993 and is well-known throughout the dermatology community.[36] Research studies, however, have shown mixed results. Several found no significant difference in HCQ response between smokers and nonsmokers, no increased prevalence of smokers in treatment failure populations versus improved and remission populations, and no smoking effect on WB-HCQ levels.[9,29,37] A study examining smoking influence on antimalarial therapy in CLE patients found