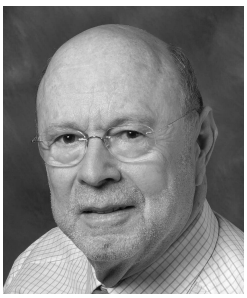
Editorial

Hydroxychloroquine — How Much Is Too Much?



Although initially approved for medical use in the United States by the Food and Drug Administration in the 1950s, antimalarial treatment of clinical disease actually dates back to the 1630s in Peru, stemming from the "fever tree," later identified as *Cinchona officialis* in 1742 by Carl Linnaeus in Europe[1]. Later, quinine was isolated from *Cinchona* bark[2], yielding the subsequent boom in the development of these agents for the antimalarial market. When the Dutch *Cinchona* plantations were overrun and captured during World War II, a synthetic version of quinine was created — quinacrine — and was used for malaria prevention, an activity funded and supported by the war effort in the United States[3,4]. The quinacrine story bears an uncanny similarity to the development of synthetic corticosteroids, which was also supported by the needs of the US government for the war effort during the exact same time period. It was in 1951, after the war was over, that Allied soldiers taking longterm quinacrine demonstrated improved signs and symptoms of systemic lupus erythematosus (SLE)[5]. Just a few years later (1955), hydroxychloroquine (HCQ) was synthesized, and a successful scale-up created this cornerstone drug for treating SLE. It is now on the World Health Organization list of essential medications needed in a basic health system[6].

In this issue of *The Journal*, Tselios, *et al*[6a], report from their cohort the diagnosis, disease course, and outcome of 8 patients with antimalarial-induced cardiomyopathy, an underrecognized complication that has been reported with longterm use and higher cumulative doses of chloroquine and HCQ[7]. To better understand the risks posed by this case series, we must first review the biological pharmacology and pharmacodynamics of HCQ.

HCQ is a 4-aminoquinolone with an elimination half-life of 40-50 days and a volume of distribution of 50 l/kg[8], which allows for sustained sequestration in the tissues and sometimes leads to irreversible organ damage. It differs from chloroquine by a single hydroxyl group, and is composed of both hydrophilic and hydrophobic regions. The hydrophilic region allows HCQ to be rapidly absorbed from the gut and metabolized by CYP450 in the liver to N-desethylhydroxychloroquine, a weak base that accumulates in acidic vesicles (endosomes, lysosomes), resulting in an increase in the pH of these cellular compartments. Although the exact therapeutic mechanism of action of this drug in patients with SLE is still a subject of debate, modern tools in the laboratory have narrowed the focus. Its presence *in vivo* inhibits the activation of intracellular Toll-like receptor signaling, antigen processing, and presentation through the MHC class II pathway, and subsequently modulates the production of proinflammatory and antiinflammatory cytokines[8,9,10]. However, the toxicity or off-target effects of this agent have never been adequately characterized, perhaps largely owing to the rather commonly accepted safety profile of the drug. Nevertheless, the hydrophobic region plays a role in partition of the molecule into membranes that interact with membrane phospholipids and neutralize phosphate charges, which displaces calcium and results in a process that may also cause muscle necrosis[10].

While generally well-tolerated systemically, the side effect profile of HCQ is typically mild and ranges from rash (rarely severe) to central nervous system symptoms (principally headaches) or diarrhea. Retinal toxicity is a known, albeit rare, complication of longterm use, and this effect has been extensively studied, allowing for formal recommendations from the American Academy of Ophthalmology on screening techniques and dosing[11,12].

In contrast, cardiomyopathy remains widely underreported and without clear recommendations for screening methods or intervals. Antimalarial-induced cardiomyopathy may manifest as hypertrophic or restrictive cardiomyopathy or conduction disturbances like bundle-branch block or atrioventricular block[13]. Because such changes may also be seen in cardiomyopathy due to SLE, differentiating antimalarial-induced cardiomyopathy from that due to SLE may prove difficult. One may begin with an electrocardiogram (ECG) for analysis of cardiac conduction, ischemic change, and left ventricular function, but these findings are

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not diagnostic because SLE and antimalarials may both be associated with various nonspecific ECG changes. Echocardiography may help to identify SLE-related structural and functional abnormalities, but again similar findings may be noted with antimalarials, leading us to use cardiac magnetic resonance imaging (cMRI). T2 changes noted on cMRI identify myocardial relaxation abnormalities in SLE even in the preclinical stage[14]. Tselios and colleagues confirmed septal hypertrophy from echocardiography on subsequent cMRI testing but also identified late gadolinium enhancement in 4 patients[6a]. However, the significance of the latter findings remains unclear because it pertains to myocardial fibrosis without differentiating the underlying cause. As has been noted, T1 mapping may help to overcome this weakness but more studies evaluating this are necessary.

While consensus on imaging modalities is lacking when faced with diagnosing SLE or antimalarial-induced cardiomyopathy, endomyocardial biopsy remains the gold standard, with recommendations to obtain at least 5 right ventricular samples[15]. The histological findings of antimalarial-induced cardiotoxicity are classically noted to be myofiber necrosis, and autophagic vacuoles are seen ultrastructurally as lamellar inclusion bodies ("myeloid bodies") and "curvilinear bodies" in the cytoplasm[10,16,17]. However, such vacuoles may also be seen in acid maltase deficiency, inclusion body myositis, and some muscular dystrophies, and while these conditions were not suspected in the 8 reported cases here, other diagnostic possibilities must also be taken into consideration. Additionally, while curvilinear bodies are very specific for antimalarial toxicity, lamellar inclusion bodies may also be seen in lysosomal storage diseases and amiodarone use[13]. Cardiomyopathy due to SLE generally yields a nonspecific biopsy with myocyte injury and perivascular and interstitial infiltrate of mononuclear cells with occasional progression to focal muscle fiber necrosis and atrophy[15]. The histological differences here may have clinical and biological significance regarding primary causation (inflammation vs degeneration).

Risks associated with antimalarial-induced cardiotoxicity include older age, female sex, greater duration of therapy, high daily dose, preexisting cardiac disease, and renal dysfunction[18,19]. This study clearly makes an important clinical contribution by reiterating these risks and discussing cardiomyopathy in patients receiving greater cumulative doses of HCQ and chloroquine in their cohort when compared to prior case reports (2419 g vs 1542 g and 2055 g vs 1005 g, respectively). However, more information is needed, and greater research required, to establish concrete recommendations for case ascertainment and diagnosis of antimalarial-induced cardiomyopathy. In an era when the majority of patients with SLE are receiving antimalarial therapy, establishing a means to distinguish cardiomyopathy due to SLE itself from antimalarial-induced cardiomyopathy is of utmost relevance and importance. If one is taking HCQ or chloroquine chronically, how long is too long? Who is truly at the highest risk? Is checking drug levels going to help? Prospective studies are necessary to answer these questions and ultimately establish a clinically useful risk assessment tool to prevent cardiotoxicity in patients receiving antimalarial therapy for rheumatic diseases.

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J Rheumatol 2019;46:340-2; doi:10.3899/jrheum.180639