# HCQ and the Heart

By Zahi Touma, MD, PhD, FACP, FACR

Despite much in the media these days about antimalarials (AM) for the treatment of COVID-19, hydroxychloroquine (HCQ) and chloroquine have been used for a long time for the treatment of different rheumatic diseases, and HCQ remains the cornerstone of systemic lupus erythematosus (SLE) therapy. HCQ is preferred because of the lower incidence of adverse retinal effects. The evidence supporting HCQ use in SLE is very compelling and based on a large body of evidence. HCQ controls SLE disease activity and allows glucocorticoid discontinuation, improves survival rates, reduces some traditional cardiovascular risk factors, has antithrombotic effect, reduces damage and risk of flares, and is safe during pregnancy.[1] In rheumatoid arthritis (RA), HCQ is one of the commonly prescribed traditional non-biologic disease-modifying antirheumatic drugs, and triple therapy for RA includes HCQ.[2,3]

AM can cause serious toxicity and are stored long term in different organs including skin, eyes, skeletal muscle, and cardiac tissue. Retinal toxicity is the most discussed adverse effect, but other adverse events can also occur – skin hyperpigmentation, neuromyopathy and cardiotoxicity.

We have recently studied whether cumulative AM use is associated with ECG abnormalities in 453 patients (SLE duration at ECG 19.7 ± 10.4 years).[1] Conduction abnormalities (bundle-branch block, incomplete or complete AV block, QTc-prolongation and consequent torsades de pointes) were slightly more prevalent than ECG features suggestive of structural abnormalities (concentric hypertrophy with biatrial enlargement and biventricular hypertrophy), 16% vs. 13% respectively; 26% of patients had both abnormalities. In this cohort, 56% had cumulative AM dose above the median of 1207 grams at time of their ECG, with 44% at or below the median. While a cumulative AM dose above the median predicted structural ECG abnormalities in univariate analysis, in multivariate analysis the increased risk (OR 1.82; 95% CI: 0.95–3.47) was not statistically significant. More importantly, AM cumulative dose was protective for conduction abnormalities (OR 0.42; 95% CI: 0.22– 0.77, p=0.006). In the nested case-control analysis, the protective effect of AM against conduction abnormalities was also demonstrated (OR 0.36), and an AM dose higher than median was not significantly associated with structural abnormalities.

Other studies found similar prevalence for conduction abnormalities (17%) in SLE after a 10-year follow up.[4] Others confirmed that the prevalence of conduction abnormalities in SLE is similar to the general population.[5] We have also demonstrated a low prevalence of prolonged QTc (3 patients; 0.7%)[1] while others reported a higher prevalence (6.5%) and found an association with anti-Ro/SSA antibodies.[6]

Cardiac AM adverse effects are potentially reversible if detected early and withdrawal of AM is essential. While ECG may be normal or nonspecific, it might allow for early detection and promote further assessment. More specific tests for heart muscle damage (troponin I) might also facilitate screening for cardiotoxicity in patients with elevated creatine kinase.[7] Though cardiac MRI and PET scan can be utilized in the assessment for AM cardiotoxicity, endomyocardial biopsy remains the gold standard test.

Recognition of potential adverse effects and potential risk factors (excessive daily dose by weight, duration of use, cumulative dose, existing renal disease, increasing age, liver disease and other genetic factors) for AM toxicity along with appropriate screening is crucial. Lastly, we recognize that more specific tests for AM cardiotoxicity are needed for appropriate risk stratification.

The COVID-19 pandemic resulted in the unconventional use of HCQ as a therapeutic option in combination with azithromycin. Concerns raised by the media and Health Canada about the potential serious side effects associated with HCQ are based on the fear that some patients may obtain HCQ to prevent or treat COVID-19. Side effects with the unsupervised use of HCQ can occur, but rheumatologists are familiar with this drug and the potential side effects. Rheumatologists have used HCQ for decades without major side effects – we weigh the risks and benefits and, more importantly, we follow patients closely and monitor for HCQ toxicities. This is crucial for the successful management of patients with rheumatic diseases on HCQ.

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