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Editorial

Hydroxychloroquine: An Old Drug With New Tricks

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Hydroxychloroquine (HCQ) is widely used in the treatment of systemic lupus erythematosus (SLE). The drug's origins lie in the preparation of the cinchona bark, which was used for centuries to treat febrile maladies. HCQ is still classified as an antimalarial, though it is rarely used for that purpose[1]. In the present era, with many new therapeutics showing promise for improving outcomes in SLE, HCQ nevertheless has retained its central role in treatment, and is recommended for all patients with SLE whenever there are no contraindications to its use. In clinical practice, HCQ is also often used in patients who have some features of SLE but who do not satisfy classification criteria for SLE. The SLE spectrum is now recognized to extend into early stages of disease that are characterized by the presence of autoantibodies and cytokines along with symptoms such as joint pain or skin rashes[2,3]. Some of these patients are designated as having incomplete lupus erythematosus (ILE), with antinuclear antibody (ANA) positivity and other clinical or laboratory findings suggestive of SLE that are not present in sufficient number to satisfy classification criteria. The patients with ILE include a subset at increased risk for transition to classifiable SLE[4,5]. Factors contributing to risk of progression include female sex, younger age, and germline genetic variation[5,6]. One retrospective study has shown that starting treatment with HCQ in ILE patients delays the onset of SLE[7], a finding that has generated interest in the idea that this medication may modify early disease stages and have long-term effects to reduce the severity of subsequent disease.

The mechanisms by which HCQ exerts its therapeutic effects on the spectrum of SLE disease are only partially understood, despite the many years of clinical experience with this drug. Known actions of HCQ include altered lysosomal processing, inhibition of endosomal toll-like receptors, and disruption of GMP-AMP synthase signaling[8]. These pathways have the potential to modulate diverse components of the immune response including autophagy, lymphocyte activation, and cytokine production. Plasmacytoid dendritic cells from SLE patients treated with HCQ show lower levels of induced production of interferon (IFN)-α and tumor necrosis factor-α[9]. Levels of autoantibodies are also reduced following treatment with HCQ[7,10]. Since soluble mediators and autoantibodies are present in the preclinical stages of SLE, it might be postulated that such immune effects could alter the trajectory of clinical disease manifestations over time. An interesting clue to this prospect is a recent report that the cooccurrence of more than one autoimmune disease in a patient, or polyautoimmunity, is less common in patients treated with HCQ, suggesting a protective effect of this drug[11].

In the current edition of *The Journal of Rheumatology*, Lambers and colleagues show that HCQ treatment of patients with ILE or new-onset SLE is associated with decreased expression of IFN-inducible genes and reduced levels of B cell activating factor (BAFF)[12]. This is a small, open-label study, with a relatively short treatment duration of 16 weeks, but it has the strength of a longitudinal design. Decreases in the type I IFN score and BAFF levels observed with HCQ treatment were statistically significant. A downward trend was also observed for the IFN-related chemokine IP-10 ($P = 0.078$) in some patients. Of interest were observations in 2 patients who did not respond with IFN or BAFF reductions. One, in whom IFN score was increased, later developed SLE. Another, with increasing BAFF and IP-10 levels, subsequently developed Sjögren syndrome. While the numbers are very small, these might be clues to potentially useful biomarkers to identify individuals who are at risk of progressive disease.

The results of this study are similar to cross-sectional data that we have previously reported, in which ILE patients treated

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See HCQ reduces IFN score, *page 847*

with HCQ had lower expression levels of type I IFN-inducible genes[13]. We also found that the expression of IFN genes was generally higher in patients with SLE than ILE, and that while SLE patients treated with HCQ did not have significantly lower levels overall, the lowest levels were seen exclusively in HCQ-treated patients. The ILE patients treated with HCQ also had significantly lower levels of interleukin-9 ($P = 0.00046$) and trended lower for levels of IP-10 ($P = 0.0744$) than those who were not taking HCQ.

These new insights into mechanisms and clinical efficacy of HCQ lead to the question of whether its disease-modifying potential deserves greater respect (Figure 1). We likely underestimate the influence of HCQ since its onset of action is slow and some of its effects, such as on survival, may not be fully recognized. It took long-term studies such as those in the LUMINA cohort to document the beneficial effects of HCQ on renal disease in SLE, for example[14]. While this is certainly not the key treatment for lupus nephritis, it is an essential cofactor for a successful outcome and longer survival[14,15]. The association of HCQ treatment with decreased risks of major infections and thrombotic events perhaps also points to better outcomes[16,17].

Another likely reason for the newly recognized effect of HCQ is the focus on early or preclinical stages of SLE, rather than in patients with established disease. In their longitudinal

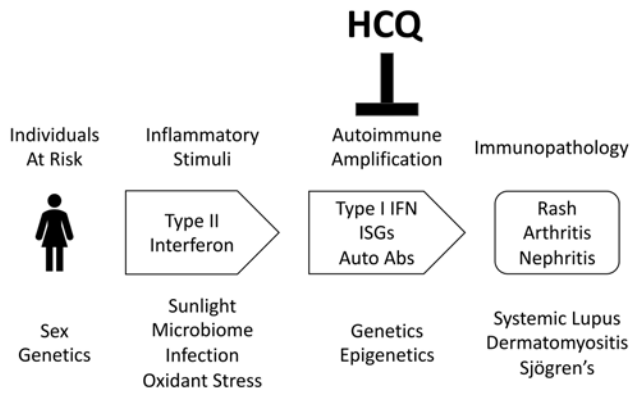

Figure 1. Proposed role of HCQ in the prevention of SLE. A hypothetical schema for the development of SLE in people at risk is shown. Certain innate features including, but not limited to, female sex and germline genetic variation put individuals at higher risk than the general population[6]. The earliest biomarker for immune stimulation in people who develop SLE may be IFN-γ[3]. The possible causes of upregulation of type II IFN include photodamage to skin, particular gut microbiota, viral infections, and exposure to environmental oxidants. This is followed by the generation of autoantibodies, the upregulation of type I IFN, and the activation of ISG. While this may be a benign life-long state for some individuals, others go on to a self-sustaining state of immune pathology due to genomic and epigenetic variation favoring T and B cell activation and effector cytokine generation. This phase, where type I IFN is driving the immune response, is the likely place for HCQ's action. While SLE is the focus of progression in this schema, it may not be the only autoimmune condition that is the outcome, because the IFN signature has been seen in other diseases such as dermatomyositis and Sjögren syndrome. Ab: antibody; HCQ: hydroxychloroquine; IFN: interferon; ISG: IFN-stimulated genes; SLE: systemic lupus erythematosus.

study of US military personnel, Monroe, *et al*[3] show that type I IFN begins to rise around 2 years prior to the time when patients are classified with SLE. These patients had ILE by definition and already had elevated autoantibody, BAFF, and IP-10 levels. It is in this phase during the year or two prior to symptomatic SLE onset when HCQ has the greatest potential for long-term disease modulation. With use of HCQ early in the disease process, the onset of full SLE may be delayed, the disease that does develop may be milder, and in addition, there is the tantalizing prospect that disease might be prevented altogether, at least in some patients. A related unanswered question is whether early use of HCQ will change the trajectory of SLE, rendering it possibly less heterogeneous and making it more targetable by emerging biotherapeutics.

The potential for HCQ to modify the course of ILE is currently being investigated in a multicenter trial, the SMILE study, in which patients with ANA positivity and 1 or 2 additional Systemic Lupus International Collaborating Clinics (SLICC) criteria are randomized to receive either HCQ or placebo for 24 months[18]. The primary outcome of this study is accumulation of SLICC criteria, testing the hypothesis that HCQ slows or prevents movement towards SLE. The biobank that is being generated as part of this trial will facilitate investigations into immunologic mechanisms and potential biomarkers of progression risk, such as BAFF, IP-10, or other IFN-regulated mediators.

Current estimates are that about half of SLE patients present with mild disease and less than half of these patients are receiving HCQ[19]. This leaves significant room for improvement in treatment and outcome for these patients, especially if HCQ is started early in the disease course. However, development of reliable prognostic biomarkers to identify those patients who present with the greatest risk of disease progression is needed to facilitate the institution of appropriate therapy. Although HCQ is an old drug with a long-standing record of safety, it is not without risks, and prescribing this medication broadly for the many ANA-positive patients referred to our clinics will not be a valid approach.

The coronavirus disease 2019 (COVID-19) pandemic focused a spotlight on HCQ that has now faded, but this drug remains essential for optimal care of patients with SLE and other autoimmune conditions. Further insights into underlying mechanisms and development of biomarkers to target its use will be needed to improve outcomes in SLE. Notably, HCQ affects several distinct pathways, and identification of which of these is most important for beneficial rather than toxic effects of this drug has potential to further improve the development of novel and effective treatments for SLE[8].

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