

## Benefit v. risk when using chloroquine in patients with severe COVID-19 disease

**To the Editor:** Chloroquine (CQ) is widely advocated as treatment for coronavirus disease 2019 (COVID-19), including the president of the USA publicly supporting the use of hydroxychloroquine (HCQ) as a 'game-changer' on the social media platform Twitter. CQ and HCQ are structurally similar, with HCQ having an *N*-hydroxyl-ethyl side-chain in place of the *N*-diethyl group.<sup>[1]</sup> Currently only CQ is being marketed in South Africa. We encourage the development of curative directed therapy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using appropriate designed trials and regulatory oversight, and caution against the indiscriminate use of CQ or HCQ. Careful patient selection is essential, including assessing prognosis, anticipated benefit and potential harms prior to initiating CQ/HCQ therapy.

The benefit of CQ/HCQ is not yet clearly defined. CQ/HCQ demonstrated *in vitro* antiviral activity against SARS-CoV-2.<sup>[2,3]</sup> Although the antiviral mechanisms of CQ/HCQ are still being investigated, a number of mechanisms have been proposed. CQ/HCQ inhibits autophagy by impairing membrane fusion of SARS-CoV-2 with intracellular endosomes or lysosomes, perhaps by increasing the pH of these organelles;<sup>[4]</sup> interferes with glycosylation intracellular receptors (angiotensin-converting enzyme 2);<sup>[5,6]</sup> or inhibits T-cell-mediated proinflammatory cytokines implicated in acute respiratory distress syndrome.<sup>[7]</sup> *In vivo* evidence is currently limited but increasing with multiple ongoing studies. A small French open-label non-randomised controlled trial of 26 patients diagnosed with COVID-19 receiving HCQ is widely cited.<sup>[8]</sup> Of the 26 patients, only 20 were included in the analysis; 6 were receiving concomitant azithromycin for bacterial infections. Sixteen control patients were included. Viral clearance on nasopharyngeal swabs was greater at day 6 in HCQ and greatest in the 6 HCQ plus azithromycin-treated patients. Although promising, the study suffered from many limitations, as outlined by Dahly *et al.*<sup>[9]</sup>

Others have argued that our understanding of the SARS-CoV-2 pathophysiology is incomplete and that the immune effects of CQ/HCQ are unknown.<sup>[10]</sup> CQ had a paradoxical effect, where the decrease in cytokines delayed the adaptive immune response with worsened disease in a primate study with Chikungunya virus.<sup>[11]</sup> Although CQ and HCQ have been used safely for decades to treat outpatients with rheumatic diseases and malaria, critically ill patients with severe SARS-CoV-2 disease and immune dysregulation may be at higher risk of CQ/HCQ toxicity. The toxic dose of CQ and HCQ is close to the therapeutic range.<sup>[12,13]</sup> CQ/HCQ cardiotoxicity includes dysrhythmias, depressed cardiac contractility and conduction associated with hypokalaemia due to potassium shifting. Renal and hepatic impairment may increase CQ/HCQ concentrations, as CQ and HCQ are renally eliminated and hepatically metabolised.<sup>[14]</sup> Underlying cardiac disease or cardiac risk factors, concomitant QT-prolonging medicines and enzyme inhibitors may therefore increase the risk of CQ/HCQ toxicity. Investigational therapy, treatment or prophylaxis, with unknown benefit v. harm, is best studied as part of a clinical trial with appropriate ethical and regulatory oversight. Lastly, CQ stock is limited worldwide, and CQ is an essential medicine to treat systemic lupus erythematosus (SLE). Stock prioritisation away from these patients may lead to acute disease flare-ups, which could add additional pressure to the health system and unnecessarily expose SLE patients to the hospital environment.

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