

## Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19

The use of hydroxychloroquine (HCQ) in the prophylaxis and treatment of coronavirus disease 2019 (COVID-19) has received significant attention by politicians and media figures. This has occurred despite limited data supporting its efficacy in COVID-19 as well as considerable concern about its safety when used at high doses (>400 mg daily) and in combination with other QT interval prolonging drugs.<sup>1-4</sup>

An inaccurate narrative has emerged in recent weeks that patients with systemic lupus erythematosus (SLE) who are taking HCQ as a baseline therapy are less affected by or do not develop COVID-19.<sup>5-7</sup> This assumption has been challenged by Monti and Montecucco,<sup>8</sup> referencing data from the COVID-19 Global Rheumatology Alliance registry on patients with rheumatic disease that previously identified 19/110 (17%) patients with SLE.<sup>9</sup> A case series of 17 patients with lupus or antiphospholipid syndrome who developed COVID-19 on a median HCQ dose of 400 mg daily (median HCQ blood level of 648 ng/mL) has since become available.<sup>10</sup> As of 17 April 2020, we have now identified 80 patients with SLE and COVID-19 in the global physician-reported registry. Patients were predominantly female (72/80, 90%) and less than 65 years of age (69/80, 86%). Importantly, 64% (51/80) of patients with SLE were taking an antimalarial (HCQ or chloroquine) prior to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (30% as monotherapy). Notably, 21.1% (121/573) of all reported patients with rheumatic disease in the registry were treated with an antimalarial prior to onset of COVID-19, yet 49.6% (60/121) required hospitalisation. In patients with SLE, frequency of hospitalisation with COVID-19 did not differ between individuals using an antimalarial versus non-users (55% (16/29) vs 57% (29/51),  $p=ns$ ;  $\chi^2$  test). In patients with lupus, escalation to maximum level of care (non-invasive ventilation, invasive ventilation or extracorporeal membrane oxygenation (ECMO)) was required regardless of HCQ use (online supplementary table S1). Thus, patients with lupus—even if they are using an antimalarial such as HCQ as baseline therapy—can develop SARS-CoV-2 infection and severe COVID-19 at similar frequency as lupus patients not on antimalarials.

There are currently >40 ongoing clinical trials examining HCQ in the prophylaxis or treatment of SARS-CoV-2 infection that employ highly variable strategies with regards to dosing (total oral loading dose 400–1400 mg), duration and time of initiation.<sup>11</sup> However, dosing considerations of HCQ in COVID-19 may be critical to understand why patients with lupus may not be protected from SARS-CoV-2 infection.

Similar to in vitro studies indicating activity of antimalarial 4-aminoquinoline derivatives against SARS-CoV-1 and MERS-CoV,<sup>12,13</sup> a putative role for HCQ in the treatment of COVID-19 has been suggested by its antiviral effect in cell culture systems.<sup>14,15</sup> Given the assumptions made when moving from a cell-based model to a complex in vivo system, in vitro potency cannot be expected to translate into in vivo efficacy,<sup>16</sup> as observed for chloroquine in a mouse model of SARS-CoV-1 infection.<sup>17</sup> To date, no in vivo exposure response data are available for HCQ in COVID-19. Few data are available to extrapolate what drug concentrations must be achieved to observe in vivo efficacy and in which compartment (eg, whole blood vs

epithelial lining fluid vs lung parenchyma). Even for influenza and approved antiviral drugs (oseltamivir), the direct relationship between drug concentration and in vivo activity is uncertain.<sup>18,19</sup> Current in vitro data suggest that the concentration of HCQ at which 50% of the maximal activity against SARS-CoV-2 is obtained (EC50) is 0.72–4.51  $\mu\text{M}$  (ie, ~242–1515 ng/mL),<sup>14,15</sup> similar to the EC50 observed in SARS-CoV-1 and MERS-CoV.<sup>13</sup> Ninety per cent inhibition of SARS-CoV-2 (EC90) with HCQ was achieved at ~5–15  $\mu\text{M}$  (~1679–5038 ng/mL), while clearance required ~20  $\mu\text{M}$  (~6717 ng/mL).<sup>14,15</sup> Importantly, both EC50 and EC90 concentrations may be insufficient to improve clinical outcomes. Instead, the concentration of HCQ required to eliminate SARS-CoV-2 may be a more meaningful target.<sup>20</sup> Such concentrations of HCQ (ie, ~6700 ng/mL), however, are not safely achievable in whole blood, and little is known about the concomitant concentrations obtainable in lung parenchymal cells in humans (assuming this represents a critical site for antiviral activity in COVID-19). Without an understanding of effective HCQ concentrations in target tissues, effective therapeutic doses remain difficult to predict by simulation. For dosing strategies to be informed, an intricate understanding of HCQ transfer constants between the blood and the lung tissue is required.

HCQ used in the treatment of SLE is typically prescribed at doses of 5.0–6.5 mg/kg, with a maximum dose of 400 mg daily. The majority of patients with SLE on chronic HCQ treatment do not achieve whole blood concentrations of 5–15  $\mu\text{M}$  (~1679–5038 ng/mL),<sup>10,21</sup> corresponding to the EC90 for SARS-CoV-2.<sup>14,15</sup> While pulmonary drug concentrations in mice are known to reach much higher levels than in blood, these HCQ concentrations may be required to achieve meaningful antiviral activity in blood. The difficulty of achieving potentially meaningful blood concentrations at HCQ doses typically prescribed in SLE may have important implications for trial design in COVID-19 and needs to be considered when interpreting outcomes of these studies. Notably, results from an open-label, randomised, controlled trial using doses as high as HCQ 1200 mg for 3 days (followed by a maintenance dose of 800 mg daily for 2–3 weeks) did not suggest efficacy of HCQ in suppressing viral replication.<sup>22</sup> These efficacy data, and the irrefutable clinical data collected through the COVID-19 Global Rheumatology Alliance registry, establish that patients with lupus on baseline therapy with HCQ are not universally protected from COVID-19.

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