

## Response to: 'Hydroxychloroquine ineffective for COVID-19 prophylaxis in lupus and rheumatoid arthritis' by Singer *et al*

We thank Singer *et al* for their correspondence<sup>1</sup> about our article related to hydroxychloroquine (HCQ) use, COVID-19 and rheumatology.<sup>2</sup> The authors present an interesting analysis using electronic health records from 36 US healthcare organisations, including patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). They found no association of HCQ use versus non-use with COVID-19, influenza/pneumonia/other lower respiratory infections and any outpatient visit, suggesting that baseline use of antimalarials such as HCQ does not prevent COVID-19.







These results suggesting no prophylactic benefit for antimalarials complement findings from the physician-based registry of the COVID-19 Global Rheumatology Alliance (GRA). Among 80 patients with SLE and COVID-19 in the GRA registry, the rates of hospitalisation and requirement of supplemental oxygen were similar in those who were using antimalarials prior to the onset of COVID-19 and those who were not.<sup>3</sup> In the entire registry, which included 600 patients with systemic rheumatic disease (RMD) at that time, antimalarials were not associated with lower odds of hospitalisation after adjustment for age, sex, smoking, underlying RMD, comorbidities, use of glucocorticoids, non-steroidal anti-inflammatory drugs, or conventional, biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) in monotherapy or in combination (excluding antimalarials).<sup>4</sup> Their results are also consistent with a recent trial showing that HCQ did not reduce COVID-19 risk compared with placebo when given prophylactically.<sup>5</sup> This lack of efficacy of HCQ prophylaxis for COVID-19 in humans—despite encouraging results from *in vitro* studies—could be related to differences in dosing as well as viral replication mechanisms *in vitro* versus *in vivo*.<sup>6</sup> Moreover, we previously outlined a pharmacokinetic rationale why HCQ, at doses prescribed for the treatment of RMD, is unlikely to result in meaningful blood levels to inhibit viral replication.<sup>3</sup>

Patients with systemic RMD had similar rates of COVID-19 compared with the general population according to several reports.<sup>7–9</sup> In contrast, patients with RMD had a higher prevalence of PCR-confirmed COVID-19 compared with the reference population (0.76% vs 0.58%, OR=1.32, 95% CI 1.15 to 1.52) in a Spanish study.<sup>10</sup> However, that study only identified patients presenting to emergency departments, and patients with a milder disease were not included.<sup>10</sup>

Additionally, RMDs have been associated with a slightly increased risk of mortality due to COVID-19 in a large analysis of primary care records of more than 17 million adults.<sup>11</sup> That study found that a composite variable of RA/SLE/psoriasis was associated with an increased risk of death (HR=1.19, 95% CI 1.11 to 1.27) compared with absence of these diseases.<sup>11</sup>

These studies suggest that patients with RMDs may have a moderately increased risk of mortality due to COVID-19 and that antimalarials neither prevent severe acute respiratory syndrome coronavirus 2 infection nor reduce its severity. Whether the modest increase in COVID-19 mortality is due to the underlying RMD, associated with specific immunosuppressant use, or related to unmeasured risk factors (eg, accelerated cardiovascular disease or pulmonary damage from disease manifestations) currently remains uncertain. Further studies identifying disease-specific and DMARD-specific risks are needed to

define the best approach for the prevention and management of COVID-19 in patients with systemic RMDs. In this regard, the real-world data provided by Singer and colleagues help provide a clearer picture of the long-lasting HCQ debate.

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