Can hydroxychloroquine protect patients with rheumatic diseases from COVID-19? Response to: 'Does hydroxychloroquine prevent the transmission of COVID-19?' by Heldwein and Calado and 'SLE, hydroxychloroquine and no SLE patients with COVID-19: a comment' by Joob and Wiwanitkit

We thank Dr Heldwein and Calado[1] and Dr Joob and Wiwanitkit[2] for their interest and comments on our paper.[3] The authors raised the hypothesis that chronic use of hydroxychloroquine (HCQ) for the currently approved indications, such as systemic lupus erythematosus (SLE), could have an impact on the rate of COVID-19 and possibly on the clinical course of the infection.

An in vitro antiviral effect of HCQ has been demonstrated on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Evidence suggests that HCQ can interfere with the virus-receptor binding and proliferation, potentially suggesting a prophylactic and therapeutic role of the drug, together with the advantages of its immunomodulatory activity.[4 5] Given the urgent need to identify an efficacious treatment to reduce mortality during the COVID-19 pandemic, HCQ has been included in a number of national protocols and guidelines to treat the infection, based on the results of preliminary clinical data. Nevertheless, the evidence supporting the use of HCQ in vivo is still based on limited evidence. Two open-label, randomised trials with small sample sizes, short follow-up and methodological limitations have led to conflicting results on the efficacy of HCQ in obtaining negative nasopharyngeal swab within 6–7 days from the initiation of treatment.[6 7] Moreover, uncertainty still exists on the optimal dosing regimen that would rapidly ensure the adequate therapeutic target concentrations in a drug that is known to have a very long half-life, large distribution into blood and tissues, and slow achievement of the steady-state concentrations, usually within weeks and with wide individual variability.[8]

Speculating on a preventive role of HCQ when the drug has been administered chronically is a currently unresolved issue of particular interest for rheumatologists. From our small published case series, three of eight symptomatic patients were taking HCQ, which did not seem to prevent the infection in these cases.[3] It is still unknown whether the concomitant use of other immunosuppressive drugs might impair the supposed protective role of HCQ. Dr Joob and Wiwanitkit[2] noted how, to date, there have been no reports of patients with SLE affected by COVID-19 in the literature and wondered whether this could be linked to the extensive use of HCQ in this population. However, this may only have been true for the time the authors wrote their correspondence and it might be only a matter of time to learn about SLE patients with COVID-19. Moreover, a recently published paper adds complexity to this scenario and warns on epigenetic dysregulation mechanisms that could lead to an increased risk and severity of SARS-CoV-2 infection in patients with SLE, regardless of the concomitant immunosuppressive medications. Patients with lupus would be characterised by hypomethylation and overexpression of ACE2, which encodes the receptor for SARS-CoV-2 spike glycoprotein, facilitating viral entry and enhancing viraemia. Moreover, oxidative stress induced by viral infections would exacerbate the DNA methylation defect, possibly perpetuating the mechanism. Similar modifications on interferon-regulated genes would then exacerbate the immune reaction to SARS-CoV-2 in these patients. The oxidative stress and DNA demethylation of ACE2 would be particularly activated during SLE flares, making the maintenance of disease remission even more critical in the course of COVID-19 pandemic.[9] In our paper we had highlighted the need to ensure sustained remission in patients with rheumatic diseases, avoiding unnecessary withdrawal of treatments which would lead to increased disease activity, which is a well-known risk factor for infections. With this regard, several authors have been reporting on the shortage of HCQ supplies and the connected risk of relapses that patients with SLE and other rheumatic diseases are facing.[10]

These findings and the available evidence highlight how, even during these difficult and urgent times of the pandemic, rigorous, properly powered, well-conducted, randomised controlled trials on HCQ will be the only way to find reliable responses to the uncertainty regarding the optimal treatment of SARS-CoV-2 and the role of antirheumatic drugs in this infection. Large registry data are needed to clarify the incidence of COVID-19 in patients with SLE and other rheumatic diseases, the presence of potentially protective factors and treatments, and the outcome of these patients.

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