Response to: 'Correspondence on 'Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus under long-term treatment with hydroxychloroquine" by Nikpour *et al*

We thank Nikpour *et al* for their interest in our study reporting on the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease 2019 (COVID-19 in a case series of 17 patients with systemic lupus erythematosus (SLE) under long-term treatment with hydroxychloroquine (HCQ).[1 2] As mentioned in our study, we did not intend to analyse the incidence rate and the severity of COVID-19 in SLE because we are aware that our cohort most likely over-represents the most symptomatic and severe cases, resulting from a selection bias. Our conclusion was rather that patients with SLE treated with HCQ are not universally protected from COVID-19, a finding recently confirmed in another observational study in which data collected through the COVID-19 Global Rheumatology Alliance registry were analysed.[3]

We agree with Nikpour *et al* that it is next to impossible to identify the denominator of patients with SLE treated with HCQ who are at risk of infection with SARS-CoV-2, apart from the difficulty to assign relevant control subjects, and that, for these reasons alone, one should be careful in the interpretation of the data as to the preventive effects of HCQ against SARS-CoV-2 infection.

Moreover, we also agree with Nikpour *et al* that the increased prevalence of comorbidities in the SLE population could lower the putative protective effect of HCQ against COVID-19 and that a protective effect of HCQ against viral infection cannot be ruled out based on the results from our observations alone.

However, there is no evidence as yet that HCQ has any preventive or curative efficacy on SARS-Cov-2 except in in vitro experimental settings and in a few clinical studies marked by numerous methodological flaws.[4 5] Conversely, several recent observational studies[6–8] and a multicentre, randomised controlled trial[9] have shown that administering HCQ to patients hospitalised for COVID-19 was associated with neither a lowered nor an increased risk of death,[7 8] death or intubation,[6] survival without transfer to an intensive care unit,[8] alleviation of symptoms or negative conversion.[9] Together, these studies do not support the notion of a therapeutic effect of HCQ in both mild to moderate and severe forms of COVID-19. HCQ is also under investigation in several clinical trials for prophylaxis of SARS-CoV-2 infection,[10] but their results have not yet been reported. Nevertheless, an irrefutable demonstration of the usefulness of HCQ for the treatment of COVID-19 will be very difficult to obtain, because its therapeutic effectiveness (or ineffectiveness) is very likely to depend on the administered dose, as well as its combined use with azithromycin. Indeed dosages of HCQ above 400 mg/day (ie, a dose rarely exceeded in the treatment of SLE), together with the administration of azithromycin, have been reported to be more effective than HCQ alone.[4] Physicians should also keep in mind that even if the cardiac safety at doses of HCQ at 200–400 mg/day is not compromised, the administration of larger doses of HCQ, or its combination with azithromycin, is much more problematic because of an enhanced risk of a significant QT interval prolongation.[11 12] Thus, rather than promoting an uncertain preventive role of HCQ in the protection against COVID-19 and given the lack of agents with clinically proven antiviral efficacy, we believe, like Favalli *et al*, that physical distancing and the adoption of strict rules for the prevention of contagion are the key elements of COVID-19 prophylaxis in patients with SLE, especially for those suffering from comorbidities and/or treated with immunosuppressants.[13]

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