No evidence so far on the protective effect of hydroxychloroquine to prevent COVID-19: comment by Joob and Wiwanitkit

We read with interest the comment by Joob and Wiwanitkit[1] on the letter published by Monti *et al* in the *Annals of the Rheumatic Diseases* (ARD).[2] In it, the authors state that there are no reported cases of patients with systemic lupus erythematosus (SLE) with COVID-19 and suggest that this may be due to a protective effect of hydroxychloroquine, a mainstay treatment taken by most patients with SLE. A similar suggestion had already been made earlier this month in the ARD by colleagues from Italy,[3] the first hardly-hit western country, and was reinforced by yet another recently published letter.[4]

As is now widely known, this old antimalarial drug, which has been part of the daily therapeutic armamentarium of rheumatologists for decades, has reached the global spotlight after demonstration of antiviral efficacy in vitro[5] and some suggestions of clinical efficacy in studies with methodological limitations and fast peer-review processes.[6] The scientific discussion on the potential validity of these findings—which were to be confirmed—was seized by some politicians who quickly transformed it into a matter of belief and conviction. Moreover, an additional problem was created in several countries, where a general run to antimalarials led to nationwide drug shortage and prevented patients with rheumatic diseases from accessing these critical drugs to control their disease.

The yearning for an effective treatment for COVID-19 should not deter the scientific community from critically evaluating available evidence. Rather, it should make it raise the bar even higher to avoid that possible spurious findings are used in the wrong way.

In this regard, we would like to dispute both the statement and the suggestion by Joob and Wiwanitkit in their comment.[1] Indeed, the authors comment on the letter by Monti *et al*, who studied a cohort of 320 patients with rheumatoid arthritis (RA) or spondyloarthritis, but did not have a single patient with SLE.[2] Still, out of the eight patients who developed a clinical picture compatible with COVID-19, three were already on hydroxychloroquine, making it confusing to suggest a protective effect of this drug. Recently, the COVID-19 Global Rheumatology Alliance launched a worldwide register for patients with rheumatic diseases with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[7] In the initial report that was just published, 19 out of 110 patients had SLE, although no treatment/outcome details were provided specifically for these patients.[8]

Additionally, we report two cases of patients with SLE under long-term treatment with hydroxychloroquine, who developed COVID-19 (table 1). Both were young patients, with controlled disease activity prior to the infection. Both had confirmed close contacts with subjects later diagnosed with COVID-19, developed mild disease and fully recovered. While these two cases do not provide any definite answer to the question of whether antimalarials can prevent COVID-19 or severe disease, they show that, indeed, patients with SLE can develop disease, even if on stable hydroxychloroquine therapy. The mild disease course should not be attributed to the concomitant antimalarial. Rather, it is likely related to other factors known to be associated with better outcomes, such as female sex and younger age.

Table 1 Clinical features of two patients with SLE who developed COVID-19

	Patient 1	Patient 2
Age	30	38
Sex	Female	Female
Disease duration	6.8 years	2.1 years
SLE clinical manifestations	Oral ulcers, photosensitivity, inflammatory arthralgia	Malar rash, photosensitivity, alopecia, fatigue, inflammatory arthralgia, Raynaud's phenomenon
SLE-related laboratorial features	ANA (1/320), anti-Sm, anti-dsDNA, LAC	ANA (1/320), anti-Sm, anti-RNP, anti-Ro, anti-dsDNA, leucopenia, neutropenia, hypergammaglobulinaemia
Comorbidities	Chronic urticaria	Plaque morphea (childhood onset), hypothyroidism
Smoking status	Non-smoker (ever)	Non-smoker (ever)
csDMARDs, dose (duration)	HCQ, 400 mg/day (7 years)	HCQ, 400 mg/day (2.8 years) MTX, 15 mg/week (3.5 years)
Glucocorticoids, dose (duration)	No	PDN, 5 mg/day (2.1 years)
NSAIDs	No	No
ACEi/ARB	No	No
SLEDAI (prior to COVID-19)	0	0
Epidemiological link	Close contact with confirmed case (colleague)	Short close contact (30 min) with two subjects arriving from Madrid (Spain)
Time from contact to symptom onset	6 days	6 days
COVID-19 symptoms	Headache, myalgia, rhinorrhoea, mild unproductive cough	Anosmia, dysgeusia
Time from symptom onset to first positive RT-PCR test	8 days	5 days
Hospitalisation	No	No
Antiviral treatment	No	No
Symptom duration	16 days	7 days
Time from symptom onset to two negative RT-PCR tests	26 days	28 days
csDMARD discontinued	No	MTX, stopped until recovery
SLE symptoms/flare post-COVID-19	Inflammatory arthralgia, oral ulcers	No
Complete recovery	Yes	Yes

ACEi, angiotensin-converting enzyme inhibitor; ANA, antinuclear antibody; ARB, angiotensin-II receptor blocker; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HCQ, hydroxychloroquine; LAC, lupus anticoagulant; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PDN, prednisolone; RNP, ribonucleoprotein; RT-PCR, reverse transcription polymerase chain reaction; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index.

In these agitated, confusing times, caution is warranted in interpreting the vast amount of information emerging on COVID-19. Until robust evidence is available, we should stick to what we know by now: antimalarials are crucial drugs for patients with SLE, RA and other rheumatic diseases, who also seem to be susceptible to infection by SARS-CoV-2. Whether they are effective drugs for the prevention or treatment of COVID-19 is yet an open avenue. One we should not rush into without decisive, firm steps.

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