Response to 'Is there a future for hydroxychloroquine/chloroquine in prevention of SARS-CoV-2 infection (COVID-19)?' by Moiseev *et al*

We thank Sergei Moiseev and colleagues for their comment in response to our letter 'To consider or not antimalarials as a prophylactic intervention in the SARS-CoV-2 (Covid-19) pandemic'.[1 2]

Antimalarial drugs hydroxychloroquine (HCQ) and chloroquine have been largely used for treating patients with systemic lupus erythematosus and other autoimmune rheumatic diseases (ARDs) for decades, and they are safe and well tolerated in such patients.[3] Conversely, there is still little evidence on their effectiveness in patients with Covid-19. As Moiseev and colleagues have pointed out, more data have been published after the submission of our letter; therefore, we welcome the opportunity to give an update. The results of five studies are now available: three open-label and two randomised controlled trials[4–8] (table 1). All studies have small sample sizes and enrolled non-critically ill patients. Gautret *et al* extended their previous results confirming the fast reduction of viral load in 80 hospitalised Covid-19 patients treated with HCQ, achieved in 93% of them after 8 days and in 100% after 12 days.[5] Moreover, 81% of treated patients were discharged after an average of 4.6 days and all patients improved, except for one still in intensive care unit and another 86-year-old patient who was not admitted in intensive care and died in infectious disease ward.[5] A randomised Chinese trial (not yet peer reviewed), on 62 patients with Covid-19, confirmed the effectiveness of HCQ added to standard of care, compared with standard of care alone, in improving both signs and symptoms of pneumonia (significantly faster resolution of cough and fever) and CT findings (improved in 80.6% of patients receiving HCQ compared with 54.6% of those receiving standard therapy); moreover, none of the patients in the active arm were admitted in the intensive care unit.[7]

Of course, the open-label nature of some studies and the small sample size, together with the heterogeneity of data, do not allow to conclude whether HCQ could effectively change the disease course, especially in more severe patients. International, randomised, ongoing studies will provide more robust evidence on the antiviral effect of different drugs, including HCQ.

Moiseev and colleagues may be right when referring to the attempt to provide antimalarials for off-label use to people at risk of infection. Perhaps, we should also consider that almost half of SARS-CoV-2-infected subjects are asymptomatic.[9] However, in such a global health emergency, with more than 2.600.000 people with confirmed infection and almost 185.000 deaths (as of 23 April 2020), we do not feel to give any judgement on the opportunity of planning studies on the prophylactic effect of HCQ in subjects at highest risk of infection.

As rheumatologists, we are facing every day the consequences of the enthusiasm around HCQ: the optimistic perception of its effectiveness among lay public people has contributed to the shortage of the drug and to the serious risk of widespread self-medication. As the European League Against Rheumatism President Iain McInness has recently underlined, the consequence of this diffuse use of HCQ is already evident, and there is an urgent need to increase its production to protect people with ARDs who depend on it for their well-being.[10]

In Italy the drug supply has been problematic; luckily, the pharma companies ensured the availability of HCQ both for patients with Covid-19 and chronic illnesses. The issue of fair allocation of resources is a matter of debate and the necessity of not overlooking the needs of non-Covid-19 patients is becoming evident.

In conclusion, we appreciate the great effort of the scientific community in the search for prevention and cure for Covid-19 through well-designed studies; on the other hand, we firmly believe that the pandemic-generated focus on antimalarials should not penalise patients with rheumatological diseases, in whom such drugs have widely demonstrated their benefits.

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Table 1 Clinical trials on hydroxychloroquine in patients with Covid-19

Study	Enrolled patients, n	Controls (Y/N, n)	HCQ regimen	Primary endpoint	Main results
Gautret *et al*[8]	36	Y (16)	HCQ 200 mg three times daily for 10 days±azithromycin (500 mg on day 1, 250 mg on days 2–5)	Viral load	HCQ induces viral clearance in a significantly higher percentage of patients after 6 days of treatment (70% HCQ alone, 100% HCQ+azithromycin vs 12.5% controls).
Gautret *et al*[6]	80	N	HCQ 200 mg three times daily for 10 days+azithromycin (500 mg on day 1, 250 mg on days 2–5)	Viral load, oxygen requirement or ICU admittance, hospital stay length	83% negative at day 7, and 93% at day 8. 12/80 (15%) required oxygen and 3/80 (3.75%) ICU. Mean length of stay of 4.6 days.
Chen *et al*[5]	30	Y (15)	HCQ 200 mg two times per day for 7 days	Viral load	No difference in viral load at day 7.
Chen *et al*[7]	62	Y (31)	HCQ 200 mg two times per day for 5 days	Time to clinical recovery	Median time to body temperature and cough recovery were significantly shorter in HCQ arm. Significantly greater percentage of HCQ-treated patients with CT improvement of pneumonia.
Molina *et al*[4]	11	N	HCQ 200 mg three times daily for 10 days+azithromycin (500 mg on day 1, 250 mg on days 2–5)	Viral load	8/10 patients still positive at day 5. (1/11 discontinued for QT prolongation).

HCQ, hydroxychloroquine; ICU, intensive care unit.

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