

LETTER

High doses of hydroxychloroquine do not affect viral clearance in patients with SARS-CoV-2 infection

1 | INTRODUCTION

The use of hydroxychloroquine (HCQ) has been considered a therapeutic option by international guidelines and expert opinions during the first phase of COVID-19 pandemics,¹⁻¹⁰ although scientific evidence remained too scarce to make a definitive recommendation.¹¹ While HCQ use has now been questioned by recent data,⁷ some previous works draw attention to contrasting results on enhanced viral clearance after HCQ treatment.^{1-6,10} In our hospital, we started using high dose of HCQ at the beginning of the epidemics, associated with tocilizumab and/or methylprednisolone in case of severe pneumonia. In this context, we analysed the data on the rate of nasal swab clearance of SARS-CoV-2, 7 days after HCQ initiation.

2 | MATERIALS AND METHODS

All consecutive patients diagnosed with confirmed SARS-CoV-2 and respiratory symptoms admitted to IRCCS Policlinico San Martino Hospital from 9 March 2020 to 29 March 2020 were enrolled in the present prospective observational study. All enrolled patients gave their consent for off-label HCQ use and for inclusion in the study. Diagnosis of SARS-CoV-2 was made on the basis of a positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay performed on nasal swabs at the time of hospitalization. HCQ was administered at the dose of 400 mg q 12 hours for 5-20 days, based on clinicians' judgement of clinical improvement. Laboratory and clinical data, including time of symptoms onset before HCQ administration, were collected. The primary endpoint was viral clearance at day 7(± 2 days), defined as the achievement of the first negative RT-PCR for SARS-CoV-2 at nasal swab. The secondary endpoints were viral clearance at day 10 and median time from symptom onset to viral clearance. We described categorical data as percentages and continuous data as median and range. Nonparametric comparative test for continuous data and chi-square test for categorical data were used to compare variables between groups. $P < .05$ was considered statistically

significant. The study was conducted in accordance with the International Conference on Harmonization guidelines, applicable regulations, and the principles of the Declaration of Helsinki. The study protocol has been approved by the Ligurian Ethical Committee on March 2020.

3 | RESULTS

Out of 140 patients included in the study at the time of writing (19 April 2020), 97 had an available nasal swab seven days after initiation of HCQ treatment. Twenty-four (25%) were female, and median age was 64.6 years (range 32.0-89.8). At first clinical presentation, they had median PaO₂/FiO₂ of 167 (range 57-423) at the time of hospitalization. All were treated with HCQ 400 mg twice daily, 95 received tocilizumab at 8 mg/kg (85 single dose, 12 two doses) and 71 also received methylprednisolone (1 mg/kg). Only 6 patients received azithromycin. After 7 (± 2) days of HCQ treatment, only 22 patients (23%) had a negative nasal swab, while the remaining 75 (77%) still carried SARS-CoV-2. The proportion of 7-day viral clearance was not statistically different in patients who received or not methylprednisolone (20% and 31%, respectively, $P = .25$). Among 56 patients who had an available nasal swab ten days after initiation of HCQ, 12 were negative (21%) and 44 still positive (79%). Of the six patients treated with azithromycin, two had negative nasal swab at day 7. Moreover, at 7-day evaluation, we found that the median time from symptom onset was longer in people who cleared the virus (15 days, range 10-31) than in people who did not (13 days, range 6-21), $P = .024$.

4 | DISCUSSION

These findings suggest that the time from symptoms onset, and not that from HCQ initiation, is an important driver of viral clearance. In our study, the exposure to high doses of HCQ did not bring benefits on viral clearance. Stopping the viral shedding could be considered as an important outcome in terms of global health, although not yet clearly related to

a clinical outcome in patients with COVID-19. Indeed, it is reasonable to think that patients who clear SARS-CoV-2 stop to be contagious for other people, and all international consensus is based on this assumption to allow the hospital discharge or discontinuation of quarantine.¹²

Then, finding a drug capable of guaranteeing 7-day viral clearance would be of pivotal importance for stopping the cycle of viral transmission in the general population. However, according to our data, HCQ did not allow to achieve this important outcome in a high proportion of patients, even if given at a higher dosage than previously reported.^{3,5} The study is limited by the fact that we do not have a control group, and thus, we cannot exclude that the viral shedding could be even longer without HCQ treatment. Additionally, because of the discomfort associated with collection of consecutive nasopharyngeal swabs, we did not perform a daily collection of specimens; as a consequence, we were not able to estimate the overall median duration of viral shedding. Also, we did not analyse viral load. Moreover, the study was conducted in patients treated with steroids or tocilizumab in association with HCQ and we cannot exclude that the immunosuppression given by these drugs might have slowed down the time to viral clearance. However, most patients hospitalized with severe forms of COVID-19 require immune modulatory treatment and thus data collected in this population likely reflect those of hospitalized patients in real-life context. With these limitations, in our study, a relevant proportion of patients with COVID-19 did not achieve rapid viral clearance after 7-day course of high dose of HCQ treatment.

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CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Lucia Taramasso and Antonio Di Biagio had the idea for and designed the study and had full access to all data. Malgorzata Mikulska, Antonio Vena, Marco Berruti and Chiara Russo take responsibility for the integrity of the data and the accuracy of the data analysis. Lucia Taramasso, Antonio Di Biagio, Malgorzata Mikulska, Daniele Roberto Giacobbe, Antonio Vena, Chiara Dentone, Andrea De Maria, Marco Berruti and Chiara Russo contributed to writing of the report. All authors contributed to data acquisition, data analysis or data interpretation, and reviewed and approved the final version.

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