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LETTER TO THE EDITOR

A novel approach to managing COVID-19 patients: results of lopinavir plus doxycycline cohort—authors' reply

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We want to thank the author for allowing us to further discuss our study. Following the requests of the reviewers, we have changed our full manuscript to a more compact form while focusing on the pandemic management algorithm and doxycycline-supplemented treatment regimens [1]. Therefore, we have omitted some details in the final revision.

The author commented that our claims, "Home isolation of mild cases is an effective means to manage the burden of disease, while lopinavir plus doxycycline is an alternative to current treatment regimens for COVID-19," are misleading. Home isolation, sometimes along with lockdowns, has been applied as an outbreak-mitigating measure worldwide. In our country, the filiation teams of The Ministry of Health strictly follow home-isolated patients, and the rationale of this combination was discussed in the original paper. Briefly, past experience during SARS and MERS outbreaks showed clinical benefit with lopinavir treatment [2]. Because of high structural similarity between SARS-CoV-1 protease and SARS-CoV-2 protease, lopinavir is suggested as a potential treatment option. On the other hand, doxycycline has successfully used in the treatment of dengue hemorrhagic fever due to its immunomodulatory effects [3].

The author commented on using hydroxychloroquine (HCQ) in the home setting and stated that per the firm evidence produced by Solidarity and Recovery trials and precautions of the FDA, HCQ should not be used in the treatment or prevention of COVID-19. First, our study period was from March 22 to April 22, 2020, and the preprint of the Recovery trial HCQ study appeared almost 2 months later on June 15, 2020 [4]. Second, the authors of the Recovery report itemized explicitly that "the findings […] do not address its use as prophylaxis or in patients with less severe SARS-CoV-2 infection managed in the community." The Recovery paper, in other words, did not provide any evidence against the use of HCQ in home setting.

Another important point is that the side effects of HCQ depend on its cumulative dosage plus the COVID-19 disease severity [5]. Briefly, the dosing scheme we applied was almost half that used in the Recovery trial, and we administered HCQ in mild cases. We understand the perception created by the word "RECOVERY." However, we would like to clarify for the author that the Recovery trial is a large randomized study but is neither placebo-controlled nor blinded. Therefore, because of its design, the evidence produced by the Recovery trial might not conquer the summit of the "evidence pyramid" [6]. Carefully designed future studies are needed to eliminate existing concerns about the Recovery trial and show the reproducibility of the evidence [7, 8].

The author commented on instituting HCQ to home-isolated patients without a definitive diagnosis. Thus far, the PCR test is the only available method to establish a definitive diagnosis of COVID-19. However, the definitive diagnosis of COVID-19 remains challenging; the PCR test has variable sensitivity [9]. In other words, a negative test result would not exclude COVID-19. Moreover, during the peak of the pandemics, PCR test results were not available before at least 3 days. Therefore, in most cases, antiviral treatment should be initiated before a definitive diagnosis is available. The rationale behind the early initiation of treatment is that an antiviral benefit could be obtained before the cytotoxic destruction of infected cells is initiated.

We believe that the author has not encountered patients with COVID-19 and does not work in the field that involves managing the outbreak. During the peak of the pandemic, it was key to keep the hospital from collapsing due to the overcrowded applications of patients in fear. We successfully

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managed the pandemic-associated fear and spared hospital resources for patients who needed in-hospital supportive care via the presented algorithm. Therefore, we still believe that our approach merits interest.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval Not applicable.

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