LETTERS—CONCISE RESEARCH REPORTS

Chronotherapy in COVID-19 Disease

J Gen Intern Med 36(8):2466–7
DOI: 10.1007/s11606-021-06719-3

To the Editor,

We read with interest the paper by Elavarasi et al., entitled "Chloroquine and Hydroxychloroquine for the Treatment of COVID-19: a Systematic Review and Meta-analysis" recently published in the *Journal of General Internal Medicine* 2020 (1).

Further to this article, we would like to point out that all the referenced studies, which evaluated the efficacy of hydroxychloroquine in COVID-19, included hospitalized patients, some of which included severe cases requiring oxygen therapy. Noteworthy, the meta-analysis by Fiolet et al., which showed no efficacy of hydroxycloroquine, also included almost only hospitalized patients (2).

Basically, to the best of our current knowledge, it should be understood that COVID-19 infection evolves into two distinct phases:

- A first phase of viral replication, during which the patients do not experience dyspnea and during which hydroxychloroquine may be of particular interest
- A second inflammatory phase (the so-called cytokine storm), where the virus disappears while lung lesions appear, and during which cortisone treatment seems to be the most effective therapy

Although hydroxychloroquine could have an anti-cytokinic action during the second phase, its main interest is to decrease the replication of the virus before the clinical worsening of COVID-19 patients. Therefore, ideally the treatment should be administered as early as possible, i.e., in patients who are not yet hospitalized (3).

As a matter of fact, looking at the relationship from a treatment perspective, Ladapo et al.'s meta-analysis showed that early ambulatory hydroxychloroquine treatment was associated with a 24% reduction in COVID-19 infection, hospitalization, or death, P=0.025 (RR, 0.76 [95% CI, 0.59 to 0.97]) (4).

Concerning the toxicity of the treatment, it should be borne in mind that there are specific cardiac disorders related to COVID infection. It may be thus difficult to attribute a rhythm cardiac disorder to hydroxychloroquine with absolute certainty. In addition, hospitalized patients benefit from heart monitoring via electrocardiogram and kalemia monitoring. Last but not least, Lagier et al. study did not show any cardiac toxicity attributable to this treatment (600 mg daily hydroxychloroquine in combination with azithromycin) (3).

In conclusion, we believe that studies and meta-analyses, which evaluate the efficacy of hydroxychloroquine, should no longer include hospitalized patients, as in this situation this treatment is in the majority of cases no longer indicated.

Thus, the efficacy of therapy should be based upon the chronology of the COVID infection phases: hydroxychloroquine in the early replication viral phase, corticosteroid therapy in the immunological storm.

Received October 3, 2020
Accepted March 14, 2021
Published online March 26, 2021

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Declarations:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

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