Dear Editor,

I have read with interest the paper entitled Deaths induced by compassionate use of hydroxychloroquine during the first COVID-19 wave: an estimate i published in your journal and available online on January 2, 2024, and would like to provide some comments.

All the virus that produced a probable lethal disease in humans have two phases: The infectious, which with SARS-CoV-2 in the first wave lasted about one week, and the inflammatory that in COVID-19 started at the beginning of the second week. ii All the medicines that prevent the reproduction of the virus must be used during the infectious moment, so nirmatrelvir iii and molnupiravir iv are indicated to be used during the first five days of symptoms. With hydroxychloroquine (HCQ), there are no deceased patients if treatment began in the first three days, and the number of days of taking it was the only condition associated with mortality. v

#Our reply

References provided by the author do not support his assertions. Many cases of serious adverse effects and deaths have been reported in clinical trials (1) and pharmacovigilance in daily clinical practice during the first wave of COVID-19 (2,3).

The association between chloroquine (CQ) and viruses is longstanding. In 1966, it was discovered that after a 6-hour treatment with CQ, infected mouse peritoneal macrophages produce markedly less mouse hepatitis virus than untreated cells, maybe for action over lysosomes vi. In 1978, CQ, an acidotropic dibasic agent, demonstrated that it increases the pH of lysosomes vii and alters cellular metabolismviii , suppressing viral replication. Together with its anti-inflammatory action, this drug seems to be ideal to treat SARS-CoV patients ix. In 2003, it was found that the S1 domain of the SARS-CoV protein binds to angiotensin-converting enzyme 2 (ACE2) for cell entry x. One year after, it was proved that CQ is an effective inhibitor of replication of the coronavirus SARS-CoV, with a high selectivity index of 30 xi . In 2005, cells previously treated with CQ were refractory to SARS-CoV infection, and when cells were already infected, CQ prevented viral replication xii.

Without SARS epidemic, which began in 2002 and finished in 2003, these encouraging results laid a solid scientific foundation for considering in 2006 the use of CQ for the treatment of a new SARS epidemic or other lethal coronavirus disease.xiii When COVID-19 pandemic started HCQ+AZT was used with excellent results in an open-label none randomized clinical trial for people who have this scientific information xiv.

During the COVID-19 pandemic, various studies confirmed that CQ also effectively blocked SARS-CoV-2 infection at low concentration, with mild cytotoxicity and a high selectivity index (mean effective concentration (EC50%) = 1.13 μM; CC50 > 100 μM, SI > 88.50) xv. It was identified that HCQ/CQ prevents the spike protein S binds to sialic acids and ECA-2 receptor gangliosides because they join to the same structures xvi, and besides HCQ/CQ blocks the transport of SARS-CoV-2 from early to late endosomes xvii.

When 1,520 compounds in clinical use were tested, there were fifteen products effective against SARS-CoV-2, showing HCQ one of the highest antiviral activities with a CE50% of

4.17 µM and the highest SI xviii. CQ/HCQ have lung concentrations 10 times higher than the EC50 xix. Furthermore, by binding to Sigma 1 and Sigma 2 receptors, HCQ effectively reduces the infection of SARS-CoV-2 xx.

All the studies with HCQ that started its use beginning during the first week of symptoms in COVID-19 patients, demonstrated protection for hospitalization and/or mortality xxi xxii . In Iran from 7,295 (25.37%) patients who received HCQ hospitalizations or deaths occurred in 523 (7.17%) and 27 (0.37%) respectively, and in 21,464 (74.63%) non-recipients 2,382 (11.10%) and 287 (1.34%) respectively, being the hospitalization reduced by 38% (p = < 0.001) and death by 73% (p = < 0.001) in HCQ recipients. xxiii In Marseille, between 30,423 COVID-19 patients 191/23,172 (0.82%) treated with HCQ-AZ died, compared to 344/7,030 (4.89%) who did not receive this treatment with HCQ-AZ, being after adjustment HCQ-AZ associated with a significantly lower mortality (aOR = 0.55). xxiv

#Our reply

The observational studies cited do not produce data enabling a demonstration of an effect. The author appears to overestimate the interest of these studies in demonstrating proof.

These last two observational retrospective studies included more patients than the two largest randomized controlled trials (RCT). Recovery (1,561 treated/3,155 controls) and Solidarity (954 treated/909 controls) only included hospitalized patients being in Recovery 60% requiring oxygen and 17% ventilation/ECMO, and in Solidarity 64% were on oxygen/ventilation. In both studies. 2400 mg was used the first day and 600 mg of HCQ the subsequent days, 4 and two times the recommended doses. xxv xxvi

#Our reply

The doses used in the trials are based on PK/PD modeling, allowing for the achievement of therapeutic concentrations (1,4). In France, the pharmacovigilance network has reported 8 deaths and serious adverse events during one month in COVID-19 patients despite national guidance (2). Consequently, it cannot be concluded that lower doses are free of lethal and non-lethal serious adverse effects, which is the argument put forth by the author of this letter.

Manaus study was designed to reduce at least 50% fatality when using high doses of CQ (600 mg twice daily for 10 days) than low doses (450 mg twice daily on day 1 and once daily for 4 days) in patients with severe COVID-19. Having a predefined sample size of 440 patients, they stopped the study when they reached 81, for the unexpected high-dose patients' day 13 lethality of 39.0% (16 of 41), more than double the 15.0% (6 of 40; p=0.03) in the low-dose group. Besides the 18.9% (7 of 37) of the high-dose group had a QTc greater than 500 milliseconds compared to 11.1% (4 of 36) in the dose group low (4 of 36 [11.1%]). xxvii

#Our reply

This trial reported the treatment effect of chloroquine for critically ill patients with COVID-19, coadministered with azithromycin and oseltamivir. This scope does not extend to patients with nonsevere COVID-19.

Pradelle et al in their study evaluated the probable impact of a medicine, HCQ, i which was not indicated for the inflammatory phase of COVID-19. Their findings illustrate the hazard of the drug, but at that moment. This will be comparable to an evaluation of the use of an anti-

inflammatory therapy applied too early during the infectious phase of COVID-19, which would produce a mortality increase because this treatment would provoke more viral replication. xxviii

#Our reply

These comments did not provide any additional useful data.

In conclusion, HCQ at appropriate doses and used within the first days of symptoms, during the infectious phase, prevents disease progression in patients with COVID-19.

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#Our reply

The opinion in conclusion of Dr Accinelli contradicts all trials testing hydroxychloroquine in COVID-19 (5,6).

RERERENCE

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