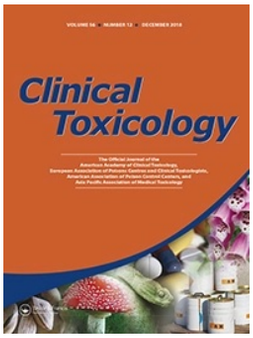

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LETTER TO THE EDITOR

Chloroquine and hydroxychloroquine to treat COVID-19: between hope and caution

To the editor,

Since December 2019, a pandemic outbreak of emerging coronavirus disease (COVID-19) due to SARS-CoV-2 is spreading, resulting in exponentially increasing numbers of infected individuals, clinical illness, and fatalities worldwide. Based on data from mainland China where the pandemic started, the COVID-19 spectrum was reported to include mild (~81%), severe (~14%) and critical presentations (~5%) with *a* ~2% fatality rate [1]. Beyond standard care, antiviral and immunomodulatory drugs were proposed to treat the most severe patients, aiming at controlling viral replication and regulating the immune response. However, to date, no therapy has proven effective. A randomized trial showed no benefit of a lopinavir/ritonavir combination to alter detectable viral RNA kinetics and improve patient clinical status, discharge from hospital, or 28-day mortality [2]. Interestingly, encouraged by experimental data assessing the anti-SARS-CoV properties of hydroxychloroquine *in vitro* [3] and exploratory clinical observations suggesting superiority of chloroquine *versus* control to inhibit COVID-19 pneumonia exacerbation [4], a French non-randomized open-label trial was conducted showing significant decrease in viral load and carriage duration in COVID-19 patients receiving hydroxychloroquine (600 mg/day during ten days) with enhanced effects in combination with azithromycin [5].

The study findings were considered remarkable and promising by some scientists but questioned by others, due to major study limitations, including small sample size ($N = 36$), no intention-to-treat analysis, no analysis of clinical benefit and only short-term follow-up. Misinterpretations of the study results claiming that antimalarial drugs are effective to treat COVID-19 patients spread spectacularly through internet, social media, television news, and the popular press. Consequently, people frightened by COVID-19 started seeking these drugs, at the risk of misuse and overdose. Physicians began prescribing these off-label drugs indiscriminately in a desperate attempt to fight COVID-19, despite the absence of good evidence to support their clinical benefit. Political personalities and even health authorities urged drug-makers to boost drug availability, as they were already in short supply.

The decades-old chloroquine/hydroxychloroquine pharmaceuticals are remarkable drugs with anti-inflammatory and antiviral properties [3]. They are cheap to produce and would be immediately available to treat COVID-19 patients, and safe, if found to be effective and prescribed and monitored properly. However, due to a relatively tight therapeutic index, cardiac toxicity may occur following QT prolongation and sodium-channel inhibition, resulting in ventricular arrhythmias, conduction blockade and cardiovascular collapse. Increased toxicity risk due to drug-drug interaction, underlying cardiac morbidities and acute kidney injury, as frequently observed in COVID-19 patients, represent a challenging clinical scenario. Self-medicating is also dangerous as supported by the recently reported fatality in a 60-year old man who ingested chloroquine phosphate, an additive commonly used at aquariums to clean fish tanks, when trying to prevent or treat the virus [6]. In addition, these drugs may carry other societal risks. Clinical toxicologists still remember the 1982 suicide outbreak in France following "Suicide: a how-to guide" publication that encouraged chloroquine ingestion to complete suicide [7]. Additionally, they acknowledge the dangers of uncontrolled delivery of these antimalarial drugs. Interestingly, in January 2020 without suspecting its renewed interest as COVID-19 treatment, the French government classified hydroxychloroquine in the list of "poisonous substances" [8]. Following the recent worldwide buzz, the French national drug agency sent messages of caution to warn practitioners about the abusive and non-regulated prescriptions of chloroquine/hydroxychloroquine.

Therefore, while awaiting urgent, adequately powered, randomized trials to assess chloroquine/hydroxychloroquine-attributed benefits to treat COVID-19, these drugs should be prescribed cautiously, with initial cardiac evaluation in outpatients and daily ECG and twice-weekly residual blood concentration monitoring in hospitalized patients. If antimalarial drug effectiveness further disappoints, the onset of well-established drug-induced toxicity will not be forgiven. Physicians should always keep in mind the Hippocratic maxim of "*Primum non nocere*".

Disclosure statement

The author declare no conflict of interest.

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