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

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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 immuno-modulatory 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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