Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL COMMENT

''The new normal''? Lessons from the treatment of emerging infectious diseases with old drugs

«O novo normal»? Lições a retirar do tratamento de doenças infeciosas emergentes com fármacos conhecidos

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The World Health Organization declared coronavirus disease 2019 (COVID-19) a global pandemic on 11 March 2020.[1] Worldwide, even in high-income countries, health systems have faced an almost apocalyptical scenario, with a shortage of personal protective equipment, a lack of critical care resources, and a lack of healthcare workers. The burden of COVID-19, a new infectious disease with significant morbidity and mortality that spread around the planet in a few weeks, was and still is tremendous. At the beginning of 2020, the social and economic impact of the disease, as well as the media and political pressure, drove unprecedented research programs and clinical trials to identify effective medications for the prevention and treatment of COVID-19 patients. At that time, a true search for the *Holy Grail* in health care was triggered.

Hydroxychloroquine is an approved medicine for the treatment and prophylaxis of malaria, and more recently, for the treatment of rheumatoid arthritis and systemic lupus erythematosus. Due to its immunomodulatory and antiviral activity, hydroxychloroquine was tested in vitro for SARS-CoV-2, and its efficacy was confirmed.[2] Anecdotal reports of the use of hydroxychloroquine and chloroquine on COVID-19 patients have come to light, and a small non-randomized open-label trial established that hydroxychloroquine decrease the viral load and carriage duration in COVID-19 patients.[3] Suddenly, hydroxychloroquine and chloroquine were labeled as potential ''game-changers'' in the media, and the United States Food and Drugs Agency (FDA) issued an emergency use authorization for hydroxychloroquine in the treatment of COVID-19, in March 2020. Soon after, an in-depth evaluation of the data suggested that hydroxychloroquine did not have any clinical benefits in COVID-19 patients. The New England Journal of Medicine and The Lancet retracted papers that had been published on the subject, and the FDA revoked the authorization for use in June 2020 due to safety concerns and lack of efficacy.[4] Nowadays, most scientific societies and international guidelines advise not to use hydroxychloroquine to treat COVID-19 and pre- or post-exposure prophylaxis for SARS-CoV-2, except in the setting of a clinical trial. Suddenly, hydroxychloroquine has vanished from the official choices to treat SARS-CoV-2 infection.

Besides the lack of evidence of the benefit of hydroxychloroquine on COVID-19 patients, there were concerns regarding its safety due to the risk of QT interval prolongation and malignant ventricular arrhythmias.[5] Although this side-effect was already known, for conventional indications, the benefit outweighs the risks. In COVID-19 patients, several factors could contribute to the additional impact on risk; such as the severity of the illness that potentially affects the myocardium, concomitant medication with azithromycin, or other drugs that could prolong the QT interval. This risk is even higher in children because although pediatric patients usually have fewer comorbidities, they

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may have unidentified rhythm abnormalities, such as long QT syndrome.

In March and April 2020, the clinical behavior of the infection by SARS-CoV-2 was largely unknown. There were several doubts related to its significance in pediatric patients, particularly in children with chronic diseases. The approach and management of these patients were particularly difficult; physicians had to undertake quick-thinking decision processes based on little published scientific evidence, local expertise, and personal wisdom.

Hormigo et al.[6] reported their two-month experience with hydroxychloroquine in 14 pediatric patients infected with SARS-CoV-2, applying a protocol adapted from the Mayo Clinic to monitor cardiac toxicity.[7] The observational retrospective study included all pediatric patients admitted to a tertiary pediatric hospital with a COVID-19 diagnosis treated with hydroxychloroquine between March and April 2020. Patients with criteria for hydroxychloroquine underwent meticulous evaluation, including serum electrolytes and baseline electrocardiogram reviewed by a pediatric cardiologist. According to the measured corrected QT interval (QTc), patients were classified in one of three groups (normal QTc, increased QTc lower than 500 msec, and QTc higher than 500 msec). For patients with prolonged QTc, the risk-benefit of treatment was considered. After hydroxychloroquine initiation, sequential electrocardiograms were performed at different time points to ascertain QTc. Two patients briefly suspended hydroxychloroquine at 48 hours of treatment due to QTc prolongation (>500 ms). All patients completed the whole treatment. No other side effects or deaths occurred. The authors conclude that hydroxychloroquine appears to be safe in COVID-19 pediatric patients, although cardiotoxicity monitoring during therapy is mandatory.

This study is a clear example of the exhaustive and cautious evaluation required to use hydroxychloroquine in COVID-19 patients. Pediatric patients were admitted to a highly differentiated hospital, a reference in the management of emerging infectious diseases. A monitorization protocol was defined with pediatric cardiology and implemented. In 14 patients, two had to discontinue therapy due to QTc prolongation, even if only temporarily, demonstrating the high risk of its widespread use as a treatment or even as pre- and post-exposure prophylaxis. Safety requires knowledge and resources.

Nonetheless, the paper from Hormigo et al. has some limitations and weaknesses. It is a short-duration study of an off-label application of hydroxychloroquine. Moreover, it included a small number of patients with atypical severity characteristics, probably related to the fact that it was performed at a national reference center for treating emerging infectious diseases, as stated by the authors. The selection of patients to treat with hydroxychloroquine is dubious. Children were classified according to their severity, but even the four cases considered mild were treated with hydroxychloroquine. The eight cases classified as severe required oxygen, but no patients were admitted to intensive care, indicating that despite being serious situations, they were not critical. Most patients had comorbidities; for instance, several were on antibiotics due to bacterial pneumonia. We now know that co-infection with other agents in COVID-19 patients is a late finding, usually in intensive care patients. Truthfully, immunosuppressive therapies and extracorporeal membrane oxygenation are increasingly recommended in critical COVID-19 patients to avoid bacterial infection associated with prolonged invasive ventilation. In the light of current knowledge, data from the Hormigo et al. paper are more suggestive of children with complex chronic diseases, with pneumonia/infection from other bacterial agents, who also had isolation of SARS-CoV-2. Nevertheless, at an atypical time, physicians on the front line of the pandemic had to decide how to treat complex patients infected with a new virus, based on scarce information after FDA authorization of the use of hydroxychloroquine in adult COVID-19 patients.

Management of emerging infectious diseases and catastrophe medicine is challenging. Health professionals sometimes need to be audacious and trust their background knowledge, but still exceptionally cautious. Regarding the COVID-19 pandemic, doubt and controversy around the disease remain on the agenda; issues related to treatment, vaccination, and the long-term impact of the disease are largely unknown and a source of debate. We, physicians, should always invoke the Hippocratic principle of ''Primum non nocere'', meaning first, do no harm or, in a more pragmatic interpretation, may the benefits outweigh the risks. Protect the patient, and always ensure that any treatment is carried out in a controlled and safe environment.

Conflicts of interest

The author has no conflicts of interest to declare.

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