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Opportune Safety and Efficacy Information for Therapies Intended for COVID-19: Balancing Evidence and Expectations in an Emergency Context

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Editorial

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Editorial

The SARS-CoV-2 outbreak has not only caused hundreds of thousands of deaths worldwide. It has also produced an accelerate and a notable increase in information about treatments that, in most cases, become rapidly outdated. The urgent need for effective therapies for COVID-19 prompted some regulatory bodies to allow the compassionate use of medicines authorized or in development for other indications with no sound-based evidence. The findings reported in some papers are widely discussed in mass media, despite their very preliminary nature and low methodological quality, and some politic leaders have announced some drugs as effective.

Efficacy Data

Papers also flow scientific publications. Someones are in vitro studies or observational studies in a small number of patients or so-called clinical trials not peer-reviewed; many others are reviews or opinion articles. Scientists and decision-makers can feel overwhelmed by this excess of information. At the same time, concerns and bewilderment arise because of the lack of meaningful clinical data about the safety and efficacy of therapies intended for controlling the SARS-CoV-2 infection or COVID-19. This delay is due to the dynamics of the clinical trials conducting. Despite the efforts timely undertaken by regulatory agencies to accelerate the process, most of the results of clinical trials assessing treatments for SARS-CoV-2 and COVID-19 are not available yet [1-3].

In the first half of the past century, the US and most countries in Europe have developed increasingly comprehensive regulations to control over manufacture, sale, supply, advertising and labelling of many medicinal products. However, it was not until the thalidomide disaster that states were prompted to build regulatory procedures to demonstrate the quality, safety and efficacy of medicinal products. Following this global and striking disaster, regulatory systems were created in these somewhat stable contexts to provide a reliable assessment of medicines. When the Committee of Safety of Drugs (CSD) was established in 1964 in the UK, the time for review and approval the documentation voluntarily submitted was 1-2 months. In the 1990s, under the EU, the review times were about 1-2 years and currently are about one year [4]. Regulatory times have been accelerated to allow a rapid assessment of agents intended to control the SARS-CoV-2 infection and the COVID19 [2,3]. However, this rapidly spreading pandemic is going much faster, and currently, there are no specific compounds approved for COVID-19 and SARS-CoV-2. The compassionate use of existing marketed products or investigational ones has been allowed with the hope of control the disease.

To May 25thth 2020, 1684 studies are registered in www.clinicaltrials.gov investigate COVID19, roughly a half observational and a half interventional [5]. To date, the results of published clinical trials have not resulted in a difference in meaningful clinical outcomes favouring a drug intervention (in a preliminary report remdesivir have shown a shorter time of recovering in treated patients) [6]. With the general limitations of non-randomized design and analysis, this gap can be helpfully saved by observational studies that provide data on effectiveness and safety. Additional efforts should be devoted to evaluating the proper adjustment and interpretation of data.

Chloroquine(CQ) and hydroxychloroquine (HCQ) are

used for malaria and autoimmune conditions, at doses of 25 g/base CQ and 400-600 mg of HCQ as an initial dose followed by 200-400 mg/day. CQ and HCQ have been repurposed as antiviral treatments for SARS-CoV-2, alone or in combination with azithromycin, following the results of an in vitro and one small observational studies (26 patients exposed to HCQ) published in March 2020 [7,8]. Two months later, four observational studies that have assessed the effectiveness of CQ and or HCQ did not find any differences in significant clinical outcomes such as death and the need of UCI or mechanical ventilation [9-11].

Safety Data

The need for safety data is even more compelling to protect patients from known or emerging harms when repurposed medicines are massively used. This is particularly important for agents that can be administered orally and prescribed to outpatients or that is worse, self-medicated. Type A adverse drug reactions, that is, those which related to pharmacological properties of the drug and in which the severity of adverse effects are dose-dependent , are especially crucial if drugs are used in doses higher than the ones approved for other indications. We should not consider safe or acceptably safe agents that are not used at doses for different conditions.

For repurposed medicines, doses proposed as antiviral should be contrasted to those for approved indications: any increased in doses can cause an increase in the expected number or intensity of adverse effects. The mentioned observational studies have also found an increased risk of QTc prolongation, which is higher in the therapeutic scheme combined with azithromycin [9,11]. A two-arms clinical trial suspended the CQ high-dosage arm because of an increase in the number of deaths [12]. Two researchers have investigated adverse effects of CQ and HCQ on QTc Interval and arrhythmias in Pharmacovigilance databases [13,14].

Concerns about neuropsychiatric effects of CQ and HCQ have also emerged from the Pharmacovigilance system. The National Pharmacovigilance centers receive and process the reports of adverse reactions occurred in clinical practice. On May 14, the Spanish regulatory agency published a summary of adverse reactions reported to all the products used as potential COVID-19 therapies (remdesivir, lopinavir/ritonavir, hydroxychloroquine, chloroquine, tocilizumab and interferon beta-1B among others, time frame from March 1 2020 to May 3 2020). Apart from 12 reports of cardiac rhythm alterations in patients taking HCQ, including QTc interval prolongation (total number of reports 13), the Spanish Pharmacovigilance System received six reports of psychiatric events in patients treated with HCQ (800 mg on day 1 and 400 mg the four following days). The reports included three deaths due to completed suicide and a suicide attempt [15].

To May 20, no other Pharmacovigilance national center systems have provided a publicly available summary of the reports received during the pandemic and involving drugs used to treat the infection or the disease. The Australian Therapeutics Good Administration website allows the consultations of adverse events sent to the Database of Adverse Event Notifications up to 90 days before the date of access to check these reports to ensure they are complete and accurate [16]. In present circumstances, this lapse could cover all the course of the pandemic. However, the Pharmacovigilance databases' information is open to researchers. A disproportionality analysis for the detection of neuropsychiatric adverse events signals associated with the use of CQ or HCQ reported to FDA Adverse Event Reporting System (FAERS) database from 2012 to 2019 found that CQ was associated with a statistically significant high reporting of amnesia, delirium, hallucinations, depression, and loss of consciousness [17]. As reports were pre-pandemic, patients were treated for malaria and autoimmune diseases, although the total dose was not included in the analysis.

People need hope and physicians need to be reassured. Excessive expectations and urgency can lead to using ineffective and perhaps harmful medicines. The nature of scientific evidence generation has shown to be much slower than the spreading of the COVID-19 pandemic. When evaluation timeframes have been accelerated to make decisions opportune, regulatory and clinical decisions should not resign the rigorous benefit/harm assessment required for any repurposed medicines and investigational products. In the meantime, well-designed and well-conducted observational research can provide evidence to guide clinical decision-making in this scenario of urgencies. Timely pharmacovigilance information helps to raise awareness and prevent harms.

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