Coronavirus Disease 2019 (COVID-19) Spread and Pharmacovigilance Implications: Expert Opinion

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Abstract
The Coronavirus Disease 2019 (COVID-19) is rapidly spreading throughout the world after emerging in China in December 2019. Currently, there are no approved treatments for COVID-19 based on large clinical trial data, and hence, management involves infection prevention and control measures and supportive care. With anecdotal reports and in vitro studies suggesting that certain medicines already in use for treatment of other conditions could be viable treatment options, there has been an increased demand for these therapies which could have adverse consequences on patients and healthcare systems. Toxicity from these medicines resulting from a mad rush for them at community pharmacies and pressure on physicians to prescribe for individuals who do not have the infection are worth noting. Furthermore, the indiscriminate use of these medicines could result in viral resistance as well as acute shortage such that patients who routinely take them for other conditions may not get them.

Keywords COVID-19 · Coronaviruses · Pharmacovigilance · Chloroquine · Hydroxychloroquine

Background
The Coronavirus Disease 2019 (COVID-19) which started in China was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020, following its spread to several other countries across the globe [1]. The outbreak in China began in December 2019 after some health institutions reported clusters of patients reporting with pneumonia of unknown cause that were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei province [2, 3]. Coronaviruses, a large family of viruses, have caused two pandemics in the past two decades—Severe Acute Respiratory Disease (SARS) in 2002 [4] and Middle East Respiratory Syndrome (MERS) in 2012 [5]. The SARS coronavirus (SARS-CoV-1) is similar to the novel coronavirus (SARS-CoV-2) and scientists believe that SARS-CoV-1 which is mainly found in bats could cause a future disease outbreak.

Aside from pneumonia, it has been observed that other clinical symptoms of COVID-19 include fever, dry cough, and breathing difficulties (dyspnoea). Disease onset of COVID-19 may result in progressive respiratory failure owing to alveolar damage (as observed by transverse chest computerized-tomography images) and even death [6].

According to the WHO, COVID-19 had spread to 180 countries and territories, killing more than 50,000 people and infecting about 1 million people with 202,000 recoveries as of April 2, 2020 [7]. The spread of the disease has forced many countries to activate their public health surveillance systems with the intention of tracing contacts of identified cases for quarantine and isolating and treating active cases to reduce the spread of the disease. As COVID-19 continues to rapidly spread, efforts are being made to discover vaccines and other interventions to prevent and treat the infections as well as to flatten the infection curve to the barest minimum.
as soon as possible. In the meantime, some medicines in use for other conditions are being relied upon for the treatment of active cases based on anecdotal reports. This paper presents the Pharmacovigilance implications of the introduction of these medicines.

**Intervention**

The development of vaccines and their remarkable success in preventing several infectious diseases such as Ebola virus disease and the swine flu (H1N1) infection has given mankind hope that infectious diseases could be controlled or even eliminated. Vaccines typically prevent the occurrence of infectious diseases in the uninected population thus creating the opportunity to flatten the infection curve. Vaccines work by eliciting an immune response in the individual in order to fight the active infection should it occur in future [8].

In most pandemics, the media, public, research institutions, pharmaceutical companies, and other stakeholders focus largely on the design of vaccines rather than therapies to treat patients with the active disease. This leaves healthcare professionals in a predicament as to deciding the best therapeutic agents to use in order to achieve optimal treatment outcomes. As a result of the self-limiting nature of most viral infections, physicians manage the symptoms and complications of infection while the patients are advised to rest and maintain good nutrition and hydration to enhance immune function [9, 10]. However, with COVID-19, there are emerging therapies which are purported to be associated with very good treatment outcomes. The Food and Drugs Administration (FDA) of the USA for instance has sanctioned the compassionate use of chloroquine [11], a 4-aminquinoline medicine which has been used for many years to treat rheumatoid arthritis, systemic lupus erythematosus, and porphyria cutanea tarda even though its use in the treatment of malaria in sub-Saharan Africa was banned in the early 2000s due to the incidence of adverse reactions and resistance [12]. This compassionate approval of chloroquine as well as a statement made by President Trump on the possible benefits of chloroquine in the treatment of COVID-19 has led many into believing that chloroquine is a magical COVID-19 drug.

Aside from the approval of the compassionate use of chloroquine by the FDA, the National Institutes of Health (NIH) of the USA has recently published a new study that found hydroxychloroquine which is also a 4-aminquinoline and a derivative of chloroquine as more effective and potent than chloroquine against COVID-19 in vitro [13]. Moreover, a recently conducted randomized controlled study by Gautret et al. in France showed that 100% of patients who received a combination of hydroxychloroquine and azithromycin tested negative and were virologically cured within 6 days of treatment [14]. Consequently, large pharmaceutical companies are considering re-positioning themselves to manufacture chloroquine and hydroxychloroquine in larger volumes and seeking to establish contacts with markets where profitability could be maximized with the resulting increase in the demand for chloroquine and hydroxychloroquine. Bayer and Teva Pharmaceutical Industries for instance have donated chloroquine products to the USA while Mylan plans to restart production of chloroquine tablets [11]. Currently, many countries have drafted their COVID-19 treatment protocols using these medicines and there have been varying treatment outcomes which corroborate what another French study on the efficacy of hydroxychloroquine and azithromycin has found out—there is no evidence of rapid antiviral clearance or clinical benefit [15].

**Possible Negative Effects of Initial COVID-19 Medicines**

A recently conducted systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19 observed that there is rationale, preclinical evidence of effectiveness and evidence of safety from long-time clinical use for other indications to justify clinical research on chloroquine in patients with COVID-19. However, the authors advised that the clinical use of chloroquine should either adhere to the Monitored Emergency use of Unregistered Interventions (MEURI) framework or be ethically approved as a trial as required by the WHO [16]. While the compassionate use of chloroquine and other medicines pending the approval of potent medicines from clinical trial data might be good news for medical professionals and COVID-19 patients, there are likely consequences these unlicensed indications could have on people who do not have the disease as well as the healthcare system. These include toxicity of medicines, shortage of medicines, and viral resistance to medicines in case they finally get approved by drug regulatory agencies. These are pharmacovigilance issues that must be addressed to ensure the safety of the general population and COVID-19 patients during this crisis period.

**Chloroquine/Hydroxychloroquine Toxicity**

Chloroquine and hydroxychloroquine are associated with cardiotoxicity (prolonged QT syndrome) with prolonged use particularly in patients with hepatic and renal dysfunction. These drugs could also cause immunosuppression, aplastic anemia, agranulocytosis, retinal damage, and peripheral neuropathy with hydroxychloroquine associated with a lower incidence of side effects [17, 18]. There has been a surge in the demand for chloroquine and hydroxychloroquine in...
many parts of the world. In China, there have been complaints about people ordering chloroquine from online drug stores and self-medicating at fatal doses. Moreover, in Nigeria, West Africa, two cases of chloroquine poisoning have already been reported which have raised concerns among healthcare professionals [19]. Furthermore, in the Arizona state of the USA, a man died after ingesting a high dose of chloroquine in an attempt to protect himself from COVID-19 while the wife who also ingested the same drug was admitted at the hospital under critical care [20].

Shortage of Medicines for Patients Who Genuinely Need Them

The rush for these medicines because of the COVID-19 scare could deny those whose conditions require their prescriptions. Patients with rheumatoid arthritis and systemic lupus erythematosus rely on chloroquine and hydroxychloroquine as part of their treatment regimen [21]. Chloroquine and hydroxychloroquine are particularly indispensable in managing the constitutional, musculoskeletal, skin, and mild pleuritic symptoms of systemic lupus erythematosus, an autoimmune disease that is very challenging to manage. The shortage of these medicines could therefore cause poor treatment outcomes. With the current lock-downs being enforced in many countries across the globe to reduce the movement of people toward mitigating the spread of the virus, the situation could be worsened by panic buying to keep these medicines for use at home as first aid pharmaceutical products to prevent COVID-19. Moreover, the disruption in supply chain due to the restricted movement of humans and goods could aggravate the situation as the stocks of these medicines get depleted. A recent scoping review conducted by Phuong et al. [22] has revealed that medication shortages resulted in negative patient clinical, economic, and humanistic outcomes. Consequently, efforts must be made to curb this impending crisis.

Resistance to the Medicines

The indiscriminate use of chloroquine and hydroxychloroquine could lead to resistance of SARS-CoV-2 to these medicines in an event where the ongoing clinical trials establish that these medicines must be approved for the full-scale treatment of the disease. Resistance of the Plasmodium parasite to chloroquine which used to be a potent medicine for the treatment of uncomplicated malaria in the twentieth century resulted from the indiscriminate over the counter use. A repetition of same could pose a challenge to COVID-19 treatment and even complicate cases if the efficacies of these medicines are lost through their misuse. Given the fact that drug development is a long, laborious and expensive process, already existing therapies like chloroquine and hydroxychloroquine must be preserved.

The Way Forward

The way forward in assuaging the situation is to intensify public campaign against the routine or over the counter use of chloroquine and hydroxychloroquine for the prevention of COVID-19. All community pharmacists must adhere strictly to this recommendation and seize the opportunity to educate patients on methods of preventing the spread of the disease such as regular hand washing with soap under tap water, the use of alcohol-based sanitizers with alcohol concentration not less than 60% v/v, eating balanced diet, resting well, and reducing stress [23] rather than self-medicating with chloroquine and hydroxychloroquine in the bid to prevent the disease.

Doctors must also ensure that only patients diagnosed with COVID-19 are given prescriptions for these medicines. This will require that laboratory tools are made available in all health institution to facilitate diagnosis as continual empirical treatment could lead to resistance of virus to the medicines.

Lastly, regulation of these medicines must be strengthened and enforced. In sub-Saharan Africa for instance, drug regulation has been very challenging over the years. Unapproved border trade of pharmaceuticals and drug counterfeiting resulting from high demand must be vigorously checked through the collaborative efforts of drug regulatory and security agencies. This could save patients from taking sub-standard medicines and consuming medicines they do not really need.

Conclusion

In conclusion, as COVID-19 continues to spread and efforts are being made to flatten the infection curve, the general population must be monitored and educated on indiscriminate medication use in an attempt to prevent the virus from infecting human hosts. They must be made aware that current medicines are served on prescription basis at hospitals and COVID-19 isolation and treatment centers and are not for COVID-19 prevention. Rather, they must be educated on approved methods of preventing the spread of the virus recommended by the WHO. In spite of the global panic to quickly resolve the COVID-19 pandemic, scientists must be vigilant and ensure rational medicine use while repurposing old remedies.
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