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INSIGHT

Treatment of COVID-19: Hydroxychloroquine and Chloroquine

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To date, the U.S. Food and Drug Administration (FDA) has not approved any therapeutics—drugs or biologics—for the treatment of COVID-19. However, FDA has authorized the emergency use of three drugs, including two drugs that have been approved by FDA for other uses: hydroxychloroquine sulfate ("hydroxychloroquine") and chloroquine phosphate ("chloroquine"). The agency authorized the emergency use of both drugs on March 28, 2020, determining that based on the totality of scientific evidence, "it is reasonable to believe that [chloroquine] and [hydroxychloroquine] may be effective in treating COVID-19," and that when used in accord with the conditions of the emergency use authorization (EUA), the known and potential benefits outweigh the known and potential risks of these drugs. Some stakeholders—including several former FDA officials—have expressed concern regarding FDA's EUA, stating that current data regarding the safety and effectiveness of these drugs for treatment of COVID-19 are largely anecdotal and that expanding access may jeopardize research into the drug. On April 24, 2020, FDA issued a drug safety communication warning against the use of these drugs for treatment of COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Further, the National Institutes of Health (NIH) treatment guidelines on use of antivirals for COVID-19 state that "[t]here are insufficient clinical data to recommend either for or against using chloroquine or hydroxychloroquine for the treatment of COVID-19" and recommend against using high-dose chloroquine for the treatment of COVID-19.

FDA Regulation of Drugs

FDA, under the Federal, Food, Drug, and Cosmetic Act, regulates the safety and effectiveness of drugs. Generally, before a new drug may be marketed in the United States, the manufacturer must submit to FDA for approval a new drug application containing evidence of the drug's safety and effectiveness, as derived from clinical studies. Under certain circumstances, such as a public health emergency, FDA may authorize the use of investigational, unapproved therapies.

On March 28, 2020, FDA authorized the emergency use of hydroxychloroquine—approved as an anti-inflammatory and antimalarial—and chloroquine—approved as an antimalarial. Neither drug is FDA-approved for treatment of COVID-19 (see **Table 1**), and the drugs' mechanisms of action are not entirely known.

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Table 1. FDA-Approved Hydroxychloroquine and Chloroquine

	Hydroxychloroquine sulfate	Chloroquine phosphate
Approved uses	Rheumatoid Arthritis, Lupus, treatment and prevention of malaria	Extraintestinal parasites, treatment and prevention of malaria
Initial U.S. approval date	1955	1949
Brand-name, manufacturer	Plaquenil (Concordia)	Aralen (Sanofi), discontinued
Generic manufacturers	14	3

Source: FDA Orange Book, accessed April 20, 2020.

Access and Shortages

Patients can generally access hydroxychloroquine and chloroquine in one of two ways. First, FDA-approved versions of these drugs may be dispensed by pharmacies pursuant to an off-label prescription from a licensed health care provider. Second, both of these drugs are available to patients through the Strategic National Stockpile (SNS)—including versions of chloroquine not approved by FDA—as authorized in FDA's EUA letter. The EUA specifically allows for chloroquine and hydroxychloroquine donated to the SNS by drug manufacturers and distributed to states to be used, pursuant to a prescription from a licensed health care provider, to treat adults and teenagers hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible.

The EUA imposes certain conditions on health care systems and providers receiving the drugs from the SNS (e.g., requiring reporting of all serious adverse events and clinical outcomes), although it is not clear how these data are being tracked and analyzed. Under normal circumstances, health care providers are encouraged, but not required, to report adverse drug events to FDA. As such, in cases where these drugs are not provided from the SNS—for example, when these drugs are prescribed off-label by a licensed health care provider—adverse event and outcomes data may not be submitted to FDA.

Increased demand for these drugs, primarily due to an increase in their off-label prescribing, has resulted in shortages, particularly for patients who rely on them for their approved indications. As a result, several states have limited dispensing of these drugs for treatment of COVID-19. For example, in New York, Governor Cuomo issued an executive order restricting dispensing of these drugs, except when prescribed for an FDA-approved indication or as part of a state-approved clinical trial. Other states have limited the quantity dispensed when prescribed for treatment of COVID-19. FDA's EUA authorizes the use of chloroquine and hydroxychloroquine from the SNS for treatment of COVID-19 only, not for other indications (e.g., Lupus).

While states generally regulate drug dispensing and prescribing, FDA is the federal agency tasked with preventing and mitigating drug shortages. FDA is required to maintain a public list of drugs that are in shortage. Hydroxychloroquine and chloroquine both appear on this list, with the shortages attributed to increased demand. In response, FDA has prioritized review of generic versions of chloroquine and hydroxychloroquine and enabled compounding (i.e., the process by which a physician or pharmacist makes a drug for an individual patient) of hydroxychloroquine.

State of Research

FDA's EUA is based on "limited in-vitro and anecdotal clinical data in case series" derived largely from international studies. For example, one study conducted in China evaluated the antiviral efficiency of five drugs in a laboratory-based setting and found that chloroquine was effective in controlling COVID-19 infection in vitro (i.e., outside of a living organism). A clinical study conducted in France found that

hydroxychloroquine was effective in reducing viral load in COVID-19 patients, particularly in combination with azithromycin—an antibiotic that treats various bacterial infections. However, numerous limitations have been identified regarding this small, nonrandomized study, such as how the data were collected and analyzed. Further, results were mixed regarding the effectiveness of hydroxychloroquine for treatment of COVID-19 based on other small, clinical studies conducted in China and France. Recent observational studies published in the New England Journal of Medicine and Journal of the American Medical Association found that treatment with hydroxychloroquine was not associated with lower mortality among patients hospitalized with COVID-19 in the New York area.

There are also concerns about the safety of these drugs for treatment of COVID-19, including appropriate dosing and the potential for adverse cardiac events among certain patients. For example, one observational study of hospitalized patients with COVID-19 in U.S. Department of Veterans Affairs medical centers reported (pre-peer review) an increased risk of death among patients treated with hydroxychloroquine alone and found no evidence that use of hydroxychloroquine, alone or with azithromycin, reduced the risk of mechanical ventilation in these patients. Further, the World Health Organization (WHO) has suspended the hydroxychloroquine arm of its international clinical trial in light of observational findings recently published in The Lancet that use of chloroquine or hydroxychloroquine was associated with an increased risk of in-hospital death among those with COVID-19.

A broader question has been raised about a cohesive research strategy moving forward. As of May 26, 2020, there were 200 ongoing clinical trials examining hydroxychloroquine or chloroquine for treatment of COVID-19, according to a database maintained by the National Library of Medicine (NLM) at the NIH. With certain exceptions, such as one recently announced trial funded by NIH, these trials are largely funded by the U.S. private sector or taking place internationally. However, many of the studies in the NLM database are in early stages—either recruiting or not yet recruiting patients—and there is some concern that off-label prescribing of these drugs may discourage patients from participating in such trials where there is a chance of receiving a placebo rather than the drug.

Overall, questions remain about the safety and effectiveness of hydroxychloroquine and chloroquine as treatment for COVID-19. Randomized controlled trials appear to still be needed to make more definitive conclusions about the safety and effectiveness of these drugs and the numerous other therapies under investigation for COVID-19.

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