PERSPECTIVE

Off-Label Therapies for COVID-19—Are We All In This Together?

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Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) continues to spread rapidly outside of mainland China. As of April 6, 2020, there are over 300,000 cases and 10,000 deaths in the United States. Effective therapies for the novel coronavirus are urgently needed and over 200 clinical trials are now underway across the globe. Recognizing the need for robust randomized control trials, the World Health Organization (WHO) recently organized a multinational randomized trial—the SOLIDARITY trial—to study the effect of drugs that have been identified as promising based on *in vitro* data and the early clinical experience with coronavirus disease 2019 (COVID-19): remdesivir, lopinavir, and ritonavir; lopinavir and ritonavir + interferon; and chloroquine or hydroxychloroquine (Plaquenil).[1]

Among these, hydroxychloroquine, US Food and Drug Administration (FDA)-approved in the 1950s for treatment of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and malaria, has become the poster child for promising COVID-19 therapies in the United States. Interest in hydroxychloroquine as a therapeutic agent for COVID-19 arose because it is a closely related compound, but more tolerable than chloroquine, and has a known safety profile due its long history in patients with SLE and RA. However, data supporting its use in COVID-19 is limited, including *in vitro* studies, extrapolation from clinical studies with chloroquine, and two small clinical trials, one of which was not randomized and did not study clinical outcomes.[2] More clinical trial data are needed to determine whether hydroxychloroquine has a role in treatment or post-exposure prophylaxis in COVID-19.

Meanwhile, interest in hydroxychloroquine has dominated headlines in recent weeks and demand for hydroxychloroquine in the United States has skyrocketed. Hospitals across the country are administering hydroxychloroquine to patients with COVID-19 and have stockpiled the drug in anticipation of the inevitable surge of patients requiring hospitalization. According to Premier Healthcare Improvement, hospital purchase orders for hydroxychloroquine have doubled, from an average of 8,800 units per month to 16,110 units between March 1 to March 17, 2020.[3]

The early adoption of hydroxychloroquine is reminiscent of combination treatment with high-dose vitamin C, corticosteroids, and thiamine, for sepsis. The "HAT" cocktail became popularized by the press and administered routinely by clinicians as part of sepsis bundles. Recent studies have not found a survival benefit with use of this cocktail for sepsis.[4] However, the circumstances surrounding hydroxychloroquine usage now is unprecedented considering we are in the midst of a pandemic caused by a virulent pathogen for which no proven therapy exists.

Although off-label use of hydroxychloroquine for the treatment of COVID-19 is understandable—particularly within a clinical trial—the spike in demand is now impacting Americans who have an FDA-approved indication for the drug. According to the American Society of Health-Systems Pharmacists, four of the seven generic manufacturers currently selling hydroxychloroquine in the United States are now in shortage, and patients are having difficulty obtaining sufficient supply. Hydroxychloroquine is the cornerstone of medical management of SLE and has been proven to prevent flares and improve survival. Interruptions in therapy can be detrimental to patients' health and should be avoided at all costs.

The Emergency Use Authorization (EUA) approved by the FDA on March 28, 2020, for use of oral hydroxychloroquine, and chloroquine may exacerbate the current hydroxychloroquine shortage affecting patients with SLE and RA. The new ruling is intended to expedite availability of these drugs to hospitalized patients with

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COVID-19 not part of a clinical trial. Drugs will be stored in the strategic national stockpile for distribution to health facilities. The FDA's rationale was that both drugs may be effective, the potential benefits outweighed the risks, and no alternative treatments are available.[5]

Other FDA-approved therapies being used off-label for COVID-19 will also be susceptible to supply disruptions, especially if there is favorable clinical trial data and demand increases (**Table 1**). During the H1N1 pandemic in 2009, increased demand for oseltamivir (Tamiflu) oral suspension in the United States resulted in supply disruptions in some areas, prompting the strategic national stockpile to release the drug in order to increase availability.[6] Similarly, increased demand for a drug being repurposed for treatment of COVID-19 could limit access to a potentially beneficial therapy for COVID-19—if clinical trial data supports its use—but also impact vulnerable Americans currently taking the drug. Examples include rheumatologic and HIV drugs that treat chronic conditions, such as tocilizumab, colchicine, and darunavir and cobicistat (Prezcobix). In addition, consider inhaled nitric oxide (iNO), FDA-approved for the treatment of infants with acute hypoxemia with persistent pulmonary hypertension and used off-label in adults with recalcitrant acute respiratory distress syndrome. The iNO is an important therapy for critically ill patients for which limited therapeutic options exist. Anticipating the surge of patients with COVID-19 in the United States who may require iNO, the manufacturer of the outpatient delivery system for the drug recently received emergency expanded access from the FDA for its use in patients outside of the hospital diagnosed with COVID-19.[7]

Table 1 FDA-Approved Drugs Used Off-Label for the Treatment of COVID-19

Drugs	Primary indication in the United States	Number of clinical trials for COVID-19[10 a]
Hydroxychloroquine sulfate	Systemic lupus erythematosus; rheumatoid arthritis	26
Lopinavir; ritonavir	HIV	18
Chloroquine phosphate	Treatment and prevention of malaria	14
Nitric oxide inhaled gas	Neonatal respiratory failure	7
Tocilizumab	Multiple rheumatologic conditions[b]	6
Methylprednisolone	Multiple conditions	5
Sarilumab	Adults with moderate to severe RA	5
Oseltamivir	Treatment of influenza	5
Ascorbic acid	Vitamin C deficiency	4
Ritonavir	HIV infection	4
Colchicine	Treatment and prevention of gout	4
Ribavirin	Hepatitis C	3
Darunavir; cobicistat	HIV	3
Bevacizumab	Multiple cancers	2
Baricitinib	Treatment of moderate to severe RA	2
Anakinra	RA	2
Interferon beta 1a	Multiple sclerosis	2
Sildenafil	Erectile dysfunction; pulmonary artery hypertension	1
Fingolimod	Relapsing multiple sclerosis	1
Siltuximab	Multicentric Cascleman's disease	1
N-acetylcysteine	Acetaminophen overdose	1
Interferon beta 1b	Multiple sclerosis	1
Peg-interferon alpha 2b	Hepatitis C	1
Emapalumab	Hemophagocytic lymphohistiocytosis	1

COVID-19, coronavirus disease 2019; RA, rheumatoid arthritis.
[a]Data collected from clinicaltrials.gov on March 31, 2020. [b]Treatment of RA; giant cell arteritis, polyarticular/systemic juvenile idiopathic arthritis; cytokine release syndrome.

A multifaceted approach is needed to ensure that off-label therapies for COVID-19 remain available to patients who require these drugs for their FDA-approved indication, and for which strong clinical data exists. First, rational prescribing must be practiced. The decision to administer a drug off-label for COVID-19 should be determined on a case-by-case basis, weighing the risks and benefits of treatment with each patient using shared decision making. Because no drug has been proven to be effective in the treatment of COVID-19, routine off-label prescribing outside of a clinical trial setting should be avoided until there are data to support a drug's use. In the case of hydroxychloroquine and chloroquine, the FDA's recent EUA ruling will likely have an impact on patients' expectations and could lower clinicians' threshold to administer these therapies. Multidisciplinary COVID-19 stewardship teams with infectious disease involvement can be leveraged to assist clinicians, providing recommendations in real-time to clinicians when a drug is being considered. In addition, as COVID-19 diagnostic testing capacity improves in the United States and more patients are diagnosed and managed outside of the hospital, off-label prescribing practices in the clinic setting will also need to be monitored. Pharmacies across the country have reported an increase in off-label prescriptions of hydroxychloroquine and chloroquine, including reports of hoarding and doctors prescribing these drugs for themselves and family members. Such practices should be discouraged.

Second, thoughtful drug purchasing by hospitals and health systems is needed. In the same way that healthcare systems are using models to forecast bed and ventilator needs for hospital surge planning, these models could also be used to inform the bulk purchasing of drug products. For example, if clinical trial data supports the use of a drug in certain critically ill patients, models that forecast new intensive

care unit admissions due to COVID-19 could also be leveraged to estimate drug supply needs. Decisions to purchase a drug in bulk for off-label use in COVID-19 should consider not only the data for its use in COVID-19, but also the drug's use as an FDA-approved therapy. For example, bulk purchasing of darunavir and cobicistat (Prezcobix) should be reconsidered because there are little data to support its use in COVID-19, and it is an important therapy for patients living with HIV.

Third, the FDA should work with manufacturers of drugs being used off-label for COVID-19 to identify those products at increased risk of sustaining a shortage, such as drugs with a limited number of suppliers.[8] In such cases, solutions could be identified to ramp up production capacity. In addition, the FDA should eliminate barriers to generic entry for off-patent drugs being studied in COVID-19 clinical trials. The presence of additional drug manufacturers could mitigate the risk of a significant supply disruption in the face of increased demand. The FDA currently expedites the review of abbreviated new drug applications for those products with no more than one manufacturer listed in the FDA's Orange Book.[9] The FDA could expand its criteria for expediting the review of generic applications to include any FDA-approved off-patent drug being studied in a COVID-19 clinical trial, regardless of the number of manufacturers marketing the drug. This could incentivize more companies to enter the market for a drug like iNO, which currently has three listed manufacturers, and is not eligible for expedited review in the policy's current form.

As COVID-19 cases continue to increase exponentially in the United States, our healthcare system is being tested in new ways. Conserving critical resources, like personal protective equipment and ventilators, will be no small task. In concert with these efforts, we must also be judicious in our allocation of prescription drugs. Our patients depend on it.

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