Evidence Development and Access to Investigational Therapies During the COVID-19 Pandemic

Since the beginning of the COVID-19 pandemic, Hayes has received questions around balancing the need for evidence with providing patients rapid access to experimental therapies. This Hayes COVID-19 Information report provides an overview of the regulatory mechanisms that are in place to provide emergency access to drugs and biologics during the COVID-19 pandemic, highlights the candidate drugs and biologics for which evidence from clinical studies will be available in the upcoming weeks, as well as professional guidelines and position statements. Hayes will update this document as new information becomes available.

At a Glance

The COVID-19 Pandemic	Coronavirus disease 2019 (COVID-19) is an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel pathogen identified in 2019 after clusters of idiopathic atypical pneumonia prompted extensive epidemiologic investigation. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic (WHO, 2020). As of May 11, 2020, there are more than 4 million confirmed cases of COVID-19 in 215 countries/territories, and more than 278,000 deaths have been attributed to the disease (WHO, 2020). There is an urgent need to identify safe and effective drugs for treatment of COVID-19.
Access to Drugs and Biologics for COVID-19	The Food and Drug Administration (FDA) created an emergency program, the Coronavirus Treatment Acceleration Program, to accelerate the development and access to medical products for COVID-19. Patients have access to investigational products by participating in a clinical study. If there are no ongoing clinical trials for this condition, the patient is not eligible to participate in any of the ongoing studies, or if participation is otherwise not feasible, then the patient may still have access to investigational medical products through the FDA Expanded Access Program.
Drugs and Biologics with EUAs	A rapidly increasing number of drugs and biologics are in clinical trials. Most of these are repurposed for COVID-19 rather than specifically developed for COVID-19. Remdesivir, chloroquine phosphate and hydroxychloroquine sulfate have received Emergency Use Authorization (EUA) for the treatment of COVID-19.
Expected Earliest Results	More than 500 clinical studies investing anti-COVID-19 therapies are currently in progress. Among these, the largest body of evidence (> 5 investigational studies) will be available for chloroquine and hydroxychloroquine, ritonavir-lopinavir, convalescent plasma, tocilizumab, remdesivir, oseltamivir, and favipiravir. Earliest results are expected mid-May 2020.
Guidelines and Position Statements	On the basis of preliminary clinical trial data, the NIH recommends the investigational antiviral agent remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease, defined as SpO2 ≤ 94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. See Position Statements and Guidelines for recommendations against certain drugs and biologics.
Related Hayes Emerging Technology Reports	Chloroquine and Hydroxychloroquine for COVID-19 Convalescent Plasma for Treatment of COVID-19 Lopinavir/Rinoavir for COVID-19 Remdesivir for COVID-19 Spectra Optia Apheresis System for COVID-19

The COVID-19 Pandemic

Coronavirus disease 2019 (COVID-19) is an infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel pathogen identified in 2019 after clusters of idiopathic atypical pneumonia prompted extensive epidemiologic investigation. These early cases, reported in Wuhan, China, were linked to a wet animal wholesale market in the region. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic (WHO, 2020). As of May 11, 2020, there are more than 4 million confirmed cases of COVID-19 in 215 countries/territories, and more than 278,000 deaths have been attributed to the disease (WHO, 2020).

The signs and symptoms of COVID-19 vary, but most patients will experience:

- fever (83% to 99%)
- cough (59% to 82%)
- fatigue (44% to 70%)
- anorexia (40% to 84%)
- shortness of breath (31% to 40%)
- sputum production (28% to 33%)
- myalgias (11% to 35%)

COVID-19 symptoms may appear 2 to 14 days after exposure (CDC, 2020). Older adults and persons with medical comorbidities may have delayed presentation of fever and respiratory symptoms. Some individuals infected with the virus are asymptomatic and can act as carriers. Most cases of COVID-19 do not require hospitalization; approximately 5% of patients need to be admitted to the intensive care unit (ICU), most often due to severe and rapidly evolving hypoxemia (CDC, 2020; MacLaren et al., 2020; Wu and McGoogen, 2020).

Patients with COVID-19 who are critically ill are defined by the WHO as those with acute respiratory distress syndrome (ARDS) or sepsis with acute organ dysfunction (WHO, 2020). ARDS is characterized by fluid accumulation inside lung alveoli and the breakdown of surfactant. Loss of surfactant prevents the lungs from filling properly with air and moving enough oxygen into the bloodstream throughout the body.

Access to Treatments During the COVID-19 Pandemic

Coronavirus Treatment Acceleration Program (CTAP)

CTAP is an emergency program created by the Food and Drug Administration (FDA) to accelerate access to COVID-19 therapies. This program provides operational support to provide ultrarapid:

- interactive feedback on clinical development plans
- review of clinical trial protocols
- review of expanded access requests for individual patients (*see* FDA Expanded Access Program).

FDA Emergency Use Authorization

Drugs and biologics for the treatment of COVID-19 require FDA emergency use authorization (EUA) or similar FDA-recognized authorization from the overseeing State. The FDA conducts a limited review of data submitted by manufacturers and grants an EUA if no problems are identified. The purpose is to speed the access to experimental drugs and biologics to meet emergency needs. Only the most important aspects of the usual, more rigorous approval requirements are retained for EUA. The FDA provides a video overview of the EUA process.

As of May 7, 2020, remdesivir, chloroquine phosphate and hydroxychloroquine sulfate have received EUA status. More details are available in the EUA database.

EUA is a temporary authorization process that is valid only during the COVID-19 public health emergency. Once the emergency declaration is lifted, drugs and biologics will need to meet standard review requirements for FDA clearance or approval.

Clinical Trials

Patients have access to investigational products by participating in a clinical study. If there are no ongoing clinical trials for this condition, the patient is not eligible to participate in any of the ongoing studies, or if participation is otherwise not feasible, then the patient may still have access to investigational medical products through the FDA Expanded Access Program (*See* FDA Expanded Access Program).

FDA Expanded Access Program

The FDA Expanded Access Program, also referred to as compassionate use, is a *"potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available".*

As part of the Coronavirus Treatment Acceleration Program, the FDA reviews expanded access applications generally **within 3 hours**.

Evidence Development – the Clinical Trials Roadmap

As discussed above, patients with COVID-19 may have access to investigational drugs and biologics through clinical trials. A large number of studies are currently in progress. The majority have been repurposed for the treatment of COVID-19, although some new drugs and biologics are also under investigation. Among these, the largest body of evidence (> 5 investigational studies) will be available for chloroquine and hydroxychloroquine, convalescent plasma, ritonavir-lopinavir, tocilizumab, favipiravir, remdesivir, oseltamivir, and baricitinib (See Table 1; hyperlinks lead to Hayes Emerging Technology Report or the National Library of Medicine entry on the respective drug or biologic for COVID-19). The FDA has accelerated the development of clinical trials through the Coronavirus Treatment Acceleration Program (CTAP) providing ultrarapid review of clinical trial protocols. *See* Coronavirus Treatment Acceleration Program (CTAP). The number of studies in progress only reflect the body of evidence that will be available for the respective drug/biologic; it does not reflect the likelihood of effectiveness.

Find more detailed clinical trial information in the Hayes Clinical Trials Document: Ongoing Clinical Studies on Drugs and Biologics for COVID-19.

Table 1: Most Studied Experimental COVID-19 Drugs/Biologics in Clinical Trials*

Drug/Biologic	Number of Studies		Possible Mechanism of Action
	Interventional	Expanded Access	
Chloroquine-Hydroxychloroquine	83	0	Anti-maleria drugs Hydroxychloroquine is used to treat rheumatoid arthritis and lupus erythematosus Appear to block viral endocytosis
Convalescent plasma	45	6	Neutralizing antibodies
Ritonavir-Lopinavir	32	0	Viral protease inhibitor Orignially developed for HIV
Tocilizumab	29	0	Used to treat rheumatoid arthritis and polyarticular and systemic juvenile idiopathic arthritis Proposed as adjunct treatment Interleukin-6 inhibitor
Favipiravir	13	0	Pyrazinecarboxamide derivative with activity against RNA viruses Purine nucleotide Viral RNA-dependent RNA polymerase inhibitor
Remdesivir	10	2	Nucleoside analog prodrug Viral RNA polymerase inhibitor
Oseltamivir	10	0	For influenza treatment, the proposed mechanism of action is the inhibition of the viral neuraminidase, possibly impacting virus particle aggregation and release.
Baricitinib	6	0	Proposed as adjunct therapy Approved for treatment for rheumatoid arthritis Janus kinase (JAK) inhibitor

*Hayes does not endorse any of the drugs and biologics investigated in clinical trials. This table presents drugs and biologics that are the most studied and for which Hayes expects results will be available soon.

Position Statements and Guidelines

The National Institutes of Health (NIH) COVID-19 Treatment Guidelines note that at present, no drug has been proven to be safe and effective for treating COVID-19. Furthermore, except when used within a clinical trial, the NIH **recommends against**:

- *"The combination of hydroxychloroquine plus azithromycin (AIII) because of the potential for toxicities.*
- *Lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII) because of unfavorable pharmacodynamics and negative clinical trial data."*
- *The use of other immunomodulators, such as:*
    - *Interferons (AIII), because of lack of efficacy in treatment of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) and toxicity.*
    - *Janus kinase inhibitors (e.g., baricitinib) (AIII), because of their broad immunosuppressive effect."*

The NIH **recommends**:

- On the basis of preliminary clinical trial data, the NIH recommends the investigational antiviral agent remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease, defined as SpO2 ≤ 94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation.
- The Panel **does not recommend** remdesivir for the treatment of mild or moderate COVID-19 outside the setting of a clinical trial.

The U.S. Society of Critical Care Medicine and the European Society of Intensive Care Medicine guidelines on the management of critically ill adults with COVID-19 advise that there is insufficient evidence to issue a recommendation on the use of most antiviral agents in critically ill adults with COVID-19. In critically ill patients with COVID-19, the guideline **recommends against**:

- Routine use of convalescent plasma
- Routine use of lopinavir/ritonavir

Furthermore, the guideline states that there is **insufficient evidence** for making a recommendation on the use of the following in critically ill patients with COVID-19:

- Recombinant interferons (rIFNs), alone or in combination with antivirals

- Chloroquine and hydroxychloroquine
- Tocilizumab

The World Health Organization (WHO) guidance on clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected notes that there is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19. WHO recommends that investigational anti-COVID-19 therapies should only be administered in the context of an approved randomized controlled trial, or, if this is not possible to provide access under the Monitored Emergency Use of Unregistered Interventions Framework.

Bibliography

All references are provided as hyperlinks to websites and open access articles. Links were last accessed on May 11, 2020.