

# Coronavirus Disease 2019 (COVID-19) Treatment & Management

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## TREATMENT

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### Investigational Drugs and Biologics

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No drugs or biologics have been proven to be effective for the prevention or treatment of COVID-19. Numerous antiviral agents, immunotherapies, and vaccines are being investigated and developed as potential therapies.

#### Antiviral Agents

##### Remdesivir

The broad-spectrum antiviral agent remdesivir (GS-5734; Gilead Sciences, Inc) is a nucleotide analog prodrug. It has been shown to inhibit replication of other human coronaviruses associated with high morbidity in tissue cultures, including severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. Efficacy in animal models has been demonstrated for SARS-CoV and MERS-CoV. In addition, remdesivir is in clinical trials for Ebola virus infections. [38]

Several phase 3 clinical trials are underway for testing remdesivir for use in COVID-19 in the United States, South Korea, and China.

An in vitro study showed that the antiviral activity of remdesivir plus interferon beta (IFN $\beta$ ) was superior to that of lopinavir/ritonavir (LPV/RTV; Kaletra, Aluvia; AbbVie Corporation). Prophylactic and therapeutic remdesivir improved pulmonary function and reduced lung viral loads and severe lung pathology in mice, whereas LPV/RTV-IFN $\beta$  slightly reduced viral loads without affecting other disease parameters. Therapeutic LPV/RTV-IFN $\beta$  improved pulmonary function but did not reduce virus replication or severe lung pathology. [39]

##### Lopinavir/ritonavir

Unconfirmed media reports from China reported lopinavir/ritonavir to be effective for COVID-19 treatment. A press release by AbbVie indicated that Chinese clinical information was not accessible to the company, so accuracy has not been confirmed. AbbVie is working with global health authorities to

determine efficacy and safety of lopinavir/ritonavir for the treatment of COVID-19. [40] A combination of lopinavir/ritonavir plus IFN $\beta$  treatment improved clinical parameters in marmosets and mice infected with MERS-CoV. [38]

### **Rintatolimod**

The toll-like receptor 3 (TLR-3) agonist rintatolimod (Poly I:Poly C12U; Ampligen; AIM ImmunoTech) is being tested as a potential treatment for COVID-19 by the National Institute of Infectious Diseases (NIID) in Japan and the University of Tokyo. [41] It is a broad-spectrum antiviral agent. [42]

### **Other investigational antivirals**

Other investigational antivirals being tested for efficacy against COVID-19 include azvudine (nucleoside reverse transcriptase inhibitor), danoprevir (NS3/4A HCV protease inhibitor), and favipiravir (viral RNA polymerase inhibitor).

### **Immunomodulators and Other Investigational Therapies**

Ifenprodil (NP-120; Algernon Pharmaceuticals) is a N-methyl-d-aspartate (NDMA) receptor glutamate receptor antagonist. NMDA is linked to inflammation and lung injury. An injectable and long-acting oral product are under production to begin clinical trials for COVID-19 and acute lung injury. [43]

CEL-SCI corporation announced that it is developing a preferentially directed immunotherapy using ligand antigen epitope presentation system (LEAPS) peptide technology to reduce COVID-19 viral load and consequent lung damage. [44]

Brilacidin (Innovation Pharmaceuticals) is a defensin-mimetic. It mimics the immune system and disrupts the pathogen membrane, leading to cell death. It is undergoing clinical stage testing at a US regional biocontainment laboratory. [45]

Remestemcel-L (Mesoblast Ltd) is an allogeneic mesenchymal stem cell (MSC) product candidate being investigated as a treatment for ARDS associated with COVID-19. [46]

A vascular leakage therapy (Q BioMed and Mannin Research) is being developed. It targets the angiotensin-Tie2 signaling pathway to reduce endothelial dysfunction. [47]

Eli Lilly and AbCellera are co-developing an antibody treatment from more than 500 unique antibodies isolated from one of the first US patients who recovered from COVID-19. [48]

Vir Biotechnology is collaborating with the NIH to develop human monoclonal antibodies against coronaviruses, including COVID-19. [49]

Anti-SARS-CoV-2 polyclonal hyperimmune globulin (TAK-888; Takeda) is being developed to treat COVID-19 in high-risk patients. [50]

### **Interleukin-6 inhibitors**

Interleukin-6 (IL-6) inhibitors may ameliorate severe damage to lung tissue caused by cytokine release in patients with serious COVID-19 infections. An anti-interleukin-6 receptor monoclonal antibody (TZLS-501; Tiziana Life Sciences and Novimmune) is currently being developed. [51]

Studies to evaluate existing IL-6 inhibitors (eg, tocilizumab [Actemra; Roche], sarilumab [Kevzara; Sanofi and Regeneron]) are reportedly being initiated. [52]

## Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine are widely used antimalarial drugs that elicit immunomodulatory effects and are therefore also used to treat autoimmune conditions (eg, systemic lupus erythematosus, rheumatoid arthritis). Published reports stemming from the COVID-19 Chinese outbreak have evaluated the potential usefulness of these drugs in controlling cytokine release syndrome in critically ill patients. [27, 53]

The pharmacological activity of chloroquine and hydroxychloroquine was tested using SARS-CoV-2–infected Vero cells. Physiologically based pharmacokinetic models (PBPK) were conducted for each drug. Hydroxychloroquine was found to be more potent than chloroquine in vitro. Based on PBPK models, the authors recommend a loading dose of hydroxychloroquine 400 mg PO BID, followed by 200 mg BID for 4 days. [27]

## Vaccines

INO-4800 (Inovio Pharmaceuticals): Phase 1 human clinical trials are expected to begin in April 2020. In addition, Inovio has received a grant from the Bill and Melinda Gates Foundation to accelerate testing and scale up a smart device (Collectra 3PSP) for large-scale intradermal vaccine delivery. [54]

mRNA-1273 (Moderna Inc): Vials have been shipped to the National Institute of Allergy and Infectious Diseases to be used in a phase 1 study in the United States. [55]

CureVac has an mRNA vaccine in development that is not yet ready for human testing. [56]

COVID-19 S-Trimer (GlaxoSmithKline [GSK] and Clover Biopharmaceuticals): Preclinical development is underway using GSK's adjuvants (compounds that enhance vaccine efficacy) and Clover's proprietary proteins, which stimulate an immune response. [57]

SARS-CoV-2 vaccine (Johnson & Johnson [J&J]): J&J is partnering with the Biomedical advanced Research and Development Authority (BARDA) to utilize Janssen's AdVac and PER.C6 technologies, which provide rapid upscale production of an optimal vaccine candidate. [58]

Sanofi is also collaborating with BARDA to develop a vaccine using their recombinant DNA platform. [59]

Novavax is developing a vaccine utilizing their saponin-based Matrix-M adjuvant, which stimulates the entry of antigen-presenting cell into the injection site and enhances antigen presentation in local lymph nodes to boost the immune response. [60]

Codagenix, a clinical-stage biotechnology company, is collaborating with the Serum Institute of India to co-develop a live-attenuated vaccine. [61]

Applied DNA Sciences and Takis Biotech have designed four COVID-19 vaccine candidates utilizing PCR-based DNA manufacturing systems for preclinical testing in animals. [62]

Design and synthesis of an intranasal COVID-19 vaccine (Altimune, Inc) has been completed and is advancing toward animal testing. [63]

