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Everything you need to know about the COVID-19 therapy trials

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There are thousands of clinical trials investigating treatments and preventative measures for COVID-19.

Latest:

- Investigational antiviral antibody treatment, REGN-COV2, has been added to the 'Randomised Evaluation of COVID-19 Therapy' (RECOVERY) trial (14 September 2020);
- New therapy added: [Nitric oxide](#);
- New therapy added: [Leronlimab](#).



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People hospitalised with COVID-19 often require oxygen therapy

Researchers around the world are working at record speed to find the best ways to treat and prevent COVID-19, from investigating the possibility of repurposing existing drugs to searching for novel therapies against the virus.

[Current approaches to COVID-19 therapies generally fall into two categories](#): antivirals — which prevent the virus from multiplying — and immune modulators — which help the immune system to fight the virus or stop it from overreacting dangerously. Some potential therapies act in a different way or via multiple mechanisms.

There are thousands of clinical trials of COVID-19 therapies taking place across the world. On 15 June 2020, the European Medicines Agency said it was in discussion with the developers of 132 potential COVID-19 treatments^[1].

This article collates the main treatments being studied, the evidence supporting their use and the trials they are being evaluated in. It will be updated on a regular basis.

Only evidence from randomised controlled trials comprising more than 100 participants is included, with the exception of select observational studies that have had a significant influence on ongoing research.

Contents

Antivirals:

- [Remdesivir](#)
- [Chloroquine/hydroxychloroquine](#)
- [Lopinavir/ritonavir combination](#)
- [Favipiravir](#)
- [Umifenovir](#)
- [Ribavirin](#)
- [EIDD-2801](#)
- [Niclosamide](#)

Immune modulators:

- [Dexamethasone](#)
- [Hydrocortisone](#)
- [Convalescent plasma](#)
- [Azithromycin](#)
- [Interferons](#)
- [Tocilizumab](#)
- [Sarilumab](#)
- [Canakinumab](#)
- [Anakinra](#)
- [Baricitinib](#)
- [Ruxolitinib](#)
- [Acalabrutinib](#)

- Brensocatib
- Ravulizumab
- Gemtuzumab ozogamicin
- Namilumab
- Infliximab
- Otilimab
- Medi3506
- Antiviral antibody cocktail
- Leronlimab

Other or multiple mechanisms:

- Colchicine
- Angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers
- Statins
- Aspirin
- Clopidogrel
- Anticoagulants
- Bemcentinib
- Omeprazole
- Famotidine
- Zilucoplan
- Ascorbic acid/vitamin C
- Aviptadil
- Opaganib
- Tradipitant
- AZD1656
- Nitric oxide

Antivirals



Source: Shutterstock.com

Remdesivir is a broad-spectrum antiviral which was originally developed to treat hepatitis C. It was the first COVID-19 treatment to be made available for use in the UK outside a clinical trial.

Remdesivir

- Broad-spectrum antiviral originally developed to treat hepatitis C and was then tested against Ebola;
- *In vitro* activity against SAR-CoV-2;
- Some evidence of efficacy against COVID-19 in humans;
- Available on a 'compassionate use' basis in many countries;
- [First COVID-19 treatment to be made available for use in the UK outside a clinical trial](#);
- In the EU, remdesivir is now [licensed for the treatment of COVID-19](#) in adults and adolescents with pneumonia requiring supplemental oxygen.

Evidence

- In moderate COVID-19, a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, but the difference was of uncertain clinical importance ([Spinner *et al*](#), 21 August 2020)
- [No significant efficacy difference between five and ten day courses of remdesivir in patients with severe COVID-19](#) ([Goldman *et al*](#), 27 May 2020);
- "No statistically significant differences" for mortality and serious adverse events in COVID-19 patients treated with remdesivir ([National Institute for health and Care Excellence \[NICE\]](#));
- First randomised trial of remdesivir suggests antiviral drug is not associated with significant clinical benefits, but numerical reduction in time to clinical improvement suggests more

research needed ([Wang et al](#), 29 April 2020);

- Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalised with COVID-19 ([Beigel et al](#), 22 May 2020).

Ongoing trials

- [Adaptive COVID-19 treatment trial \(ACTT\)](#);
- [Adaptive COVID-19 treatment trial 2 \(ACTT-II\)](#);
- [Trial of Treatments for COVID-19 in Hospitalized Adults \(DISCOVERY\)](#);
- [Study to Evaluate the Safety and Antiviral Activity of Remdesivir \(GS-5734\) in Participants With Severe Coronavirus Disease \(COVID-19\)](#);
- [Study to Evaluate the Safety and Antiviral Activity of Remdesivir \(GS-5734\) in Participants With Moderate Coronavirus Disease \(COVID-19\) Compared to Standard of Care Treatment](#);
- [SOLIDARITY clinical trial for COVID-19 treatments](#);
- [Phase III trial to investigate combination of tocilizumab and remdesivir in severe COVID-19 pneumonia \(REMDACTA\)](#).

Chloroquine/hydroxychloroquine

- Antimalarials with *in vitro* activity against various viruses, including SAR-CoV-2 — the virus that causes COVID-19;
- Anecdotal evidence in humans;
- Recommended for use in COVID-19 in several countries, including Italy, France;
- The US Food and Drug Administration has cautioned against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems;
- Approved for the treatment of rheumatoid arthritis and lupus.

Evidence

- Among patients hospitalized with mild-to-moderate COVID-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care ([Cavalcanti et al](#), 23 July 2020)
- Hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19 ([Skipper et al](#), 16 July 2020)
- [UK Medicines and Healthcare products Regulatory Agency \(MHRA\) suspends recruitment to COVID-19 hydroxychloroquine trials](#) (5 June 2020)
- [Preliminary results from ‘Randomised Evaluation of COVID-19 Therapy’ \(RECOVERY\) trial](#) (5 June 2020): no significant difference in mortality rate at 28 days (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% confidence interval 0.98–1.26]; $P=0.10$);
- Hydroxychloroquine did not prevent illness compatible with COVID-19 or confirmed infection when used as postexposure prophylaxis within four days after exposure ([Boulware et al](#), 3 June 2020);
- No evidence of benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias ([Mehra et al](#), 22 May 2020). Study retracted by *The Lancet* on 5 June 2020 following [concerns about the data](#);

- Not enough data available to support the routine use of hydroxychloroquine and chloroquine as therapies for COVID-19 ([Chowdhury *et al*, 29 May 2020](#));
- Administration of hydroxychloroquine did not result in a significantly higher probability of negative conversion than standard of care alone ([Tang *et al*, 14 May 2020](#)).

Ongoing trials

- RECOVERY trial (recruitment to hydroxychloroquine arm closed as of 5 June 2020);
- Chemoprophylaxis for COVID-19 infectious disease (the PROLIFIC trial);
- An adaptive phase 2/3, randomised, open-label study assessing efficacy and safety of hydroxychloroquine for hospitalised patients with moderate to severe COVID-19;
- ‘Randomised, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia’ [REMAP-CAP] (paused by MHRA as of June 2020);
- ‘Platform Randomised trial of Interventions against COVID-19 In Older People’ [PRINCIPLE] (paused by MHRA as of June 2020);
- ‘Chloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting’; a randomised, placebo-controlled prophylaxis study (COPCOV) (given green light by MHRA to continue recruiting patients on 26 June 2020);
- ‘(Hydroxy)chloroquine Repurposing to Healthworkers for Novel Coronavirus Mitigation: An international, multi-site, Bayesian platform adaptive, randomised, double-blind, placebo-controlled trial assessing the effectiveness of varied doses of oral chloroquine’ (CROWN CORONATION);
- Prophylaxis for patients at risk of COVID-19 infection (PROTECT);
- SOLIDARITY (recruitment to hydroxychloroquine arm closed as of 17 June 2020);
- DISCOVERY;
- Hydroxychloroquine or Diltiazem-Niclosamide for the Treatment of COVID-19 (HYDILIC);
- Health Care Worker Prophylaxis Against COVID-19 (HERO).

Lopinavir/ritonavir combination

- HIV type 1 aspartate protease inhibitors, indicated for treatment of HIV infection in combination with other antiretroviral drugs;
- Lopinavir has *in vitro* inhibitory activity against SARS-CoV, the virus that causes severe acute respiratory syndrome (SARS);
- Ritonavir is combined with lopinavir to increase its half-life;
- Recommended for use in COVID-19 in several countries, including Italy and France.

Evidence

- Following a review of emerging data from the RECOVERY trial, researchers concluded that there was no beneficial effect of lopinavir/ritonavir on 28-day mortality in patients hospitalised with COVID-19 compared to usual care alone ([Horby *et al*, 29 June 2020](#));
- Evidence that early treatment with triple antiviral therapy of interferon (IFN) beta-1b, lopinavir/ritonavir, and ribavirin — alongside standard care — is safe and shortens duration of viral shedding compared with lopinavir-ritonavir alone (average 7 days vs. 12 days), in patients with mild-to-moderate COVID-19 ([Hung *et al*, 8 May 2020](#));
- Some evidence that lopinavir/ritonavir initiation within 12 days after symptom onset is associated with shorter time to clinical improvement. No significant differences in reduction of

viral RNA load, duration of viral RNA detectability, duration of oxygen therapy, duration of hospitalisation, or time from randomization to death. Lopinavir/ritonavir stopped early in 13 patients because of adverse effects ([Cao *et al*, 7 May 2020](#)).

Ongoing trials

- REMAP-CAP;
- RECOVERY (recruitment to lopinavir/ritonavir arm closed as of 29 June 2020);
- SOLIDARITY (recruitment to lopinavir/ritonavir arm closed as of 4 July 2020);
- DISCOVERY;
- [Lopinavir/ Ritonavir, Ribavirin and IFN-beta Combination for nCoV Treatment](#).

Favipiravir

- Broad-spectrum antiviral with *in vitro* activity against various viruses, including coronaviruses;
- Licensed in Japan and China for treatment of influenza;
- Not currently included in any of the UK trials for COVID-19.

Ongoing trials

- [Phase III Clinical Study to Evaluate the Performance and Safety of Favipiravir in COVID-19](#);
- [Oral Favipiravir Compared to Placebo in Subjects with Mild COVID-19](#);
- [A Randomized Controlled Trial for Favipiravir Tablets Combine with Chloroquine Phosphate in the Treatment of Novel Coronavirus Pneumonia \(COVID-19\)](#);
- [Favipiravir Combined with Tocilizumab in the Treatment of novel coronavirus pneumonia \(COVID-19\) — a multicentre, randomised, controlled trial](#);
- [The Efficacy and Safety of Favipiravir for novel coronavirus–infected pneumonia — a multicentre, randomised, open, positive, parallel-controlled clinical study](#).

Umifenovir

- Antiviral treatment used for influenza infection in Russia and China;
- Proposed as a standard care option for COVID-19 based on its mechanism of action and its effects in treating influenza-associated pneumonia;
- *In vitro* inhibitory activity against SARS-CoV, the virus that causes severe acute respiratory syndrome (SARS)

Ongoing trials:

- [Clinical Study of Arbidol Hydrochloride Tablets in the Treatment of Pneumonia Caused by Novel Coronavirus](#)

Ribavirin

- Broad-spectrum antiviral used to treat hepatitis C, respiratory syncytial virus (RSV) and bronchiolitis;
- *In vitro* activity against SARS-CoV, the virus that causes severe acute respiratory syndrome (SARS);

- Some evidence of efficacy as an adjunct therapy in SARS;
- Evidence from mouse models in SARS-CoV suggested it could increase infectivity.

Evidence

- Evidence that early treatment with triple antiviral therapy of IFN beta-1b, lopinavir-ritonavir, and ribavirin — alongside standard care — is safe and shortens duration of viral shedding compared with lopinavir-ritonavir alone (average 7 days vs. 12 days), in patients with mild to moderate COVID-19 ([Hung *et al*](#), 8 May 2020).

EIDD-2801

- Investigational oral nucleoside analogue with broad-spectrum antiviral activity against RNA viruses, including influenza and coronaviruses like SARS and Middle East respiratory syndrome (MERS).

Ongoing trials

- [‘COVID-19 First in Human Study to Evaluate Safety, Tolerability and Pharmacokinetics of EIDD-2801 in Healthy Volunteers’](#)

Niclosamide

- Anti-helminthic drug with potential antiviral activity against SARS-CoV-2;
- Unlicensed in the UK.

Ongoing trials

- HYDILIC;
- [Niclosamide for mild-to-moderate COVID-19](#) (Not yet recruiting).

Immune modulators



Source: Shutterstock.com

Dexamethasone was the first drug to be shown to improve survival in patients hospitalised with COVID-19

Dexamethasone

- Steroid that reduces inflammation by mimicking anti-inflammatory hormones produced by the body;
- Indicated for the suppression of inflammatory and allergic disorders;
- Only suitable for people who are already in hospital and receiving oxygen or mechanical ventilation;
- [It is the first drug to be shown to improve survival in COVID-19](#);
- Approved for NHS use by UK government.

Evidence

- Intravenous dexamethasone plus standard care, compared with standard of care alone, resulted in a statistically significant increase in the number of days alive and free of mechanical ventilation over 28 days. ([Tomazini *et al*](#), 2 September 2020);
- Preliminary results from the RECOVERY trial suggest that dexamethasone reduced deaths by 35% in ventilated patients and by 20% in other patients receiving oxygen only. There was no benefit among those patients who did not require respiratory support ([Horby *et al*](#), 17 July 2020).

Ongoing trials

- RECOVERY;
- REMAP-CAP.

Hydrocortisone

- Steroid that reduces inflammation by mimicking anti-inflammatory hormones produced by the body;
- Used for a variety of conditions including adrenocortical insufficiency, rheumatoid arthritis, dermatitis, asthma and chronic obstructive pulmonary disorder;
- Commonly used to manage septic shock in patients with COVID-19;
- Evidence regarding corticosteroid use for severe COVID-19 is limited.

Evidence

- Patients with severe COVID-19 who are treated intravenously with the steroid, hydrocortisone, are up to 93% more likely to have a better outcome compared to patients who are not given the drug, principal findings from the REMAP-CAP trial suggest ([Angus *et al*](#), 2 September 2020);
- Low-dose hydrocortisone did not significantly reduce treatment failure in patients with COVID-19–related acute respiratory failure; however, the study was stopped early and was therefore likely underpowered ([Dequin *et al*](#), 2 September 2020).

Ongoing trials

- [Hydrocortisone for COVID-19 and Severe Hypoxia \(COVID STEROID\)](#).

Convalescent plasma

- Antibody-rich plasma of someone who has recovered from COVID-19;
- There is some evidence suggesting possible benefits of convalescent plasma in patients with COVID-19, but available data to date are largely from case reports or series; confirmation from additional randomised controlled studies is required ([Malani *et al*](#), 12 June 2020);
- Has been approved for use in critically ill patients in the United States and UK.

Evidence

- No significant difference in time to clinical improvement within 28 days, mortality or time to hospital discharge in patients treated with convalescent plasma. Trial was terminated early and may have been underpowered to detect a clinically important difference ([Li *et al*](#), 3 June 2020).

Ongoing trials

- RECOVERY;
- [‘Convalescent Plasma for Hospitalised Adults With COVID-19 Respiratory Illness’ \(CONCOR-1\)](#);
- REMAP-CAP.

Azithromycin

- Macrolide antibiotic;
- Some *in vitro* activity against some viruses, such as influenza A and zika;

- May reduce cytokine levels, which can promote inflammation.

Evidence:

- In patients with severe COVID-19, adding azithromycin to standard of care treatment (which included hydroxychloroquine) did not improve clinical outcomes ([Furtado *et al*](#), 4 September 2020);
- Among patients hospitalized with mild-to-moderate COVID-19, the use of hydroxychloroquine, alone or with azithromycin, did not improve clinical status at 15 days as compared with standard care ([Cavalcanti *et al*](#), 23 July 2020)

Ongoing trials

- RECOVERY;
- PRINCIPLE.

Interferons

- Modulate immune response to some viral infections;
- Only limited clinical trial data are currently available on the efficacy of IFNs for treatment of COVID-19;
- Clinical trials are currently evaluating IFN beta-1a or IFN beta-1b, generally added to antivirals.

Ongoing trials

- REMAP-CAP;
- [Comparing efficacy and safety of inhaled SNG001 to placebo](#);
- SOLIDARITY;
- DISCOVERY;
- RECOVERY.

Tocilizumab

- Monoclonal antibody that inhibits interleukin-6 (IL-6), which is vital in the immune response to SAR-CoV-2;
- Indicated for treatment of rheumatoid arthritis;
- May combat cytokine release syndrome in severely ill COVID-19 patients;
- There are no well-controlled published studies on the efficacy and safety of tocilizumab for the treatment of COVID-19; however, numerous clinical trials are planned or under way globally.

Ongoing trials

- [‘A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia’ \(COVACTA\)](#);
- REMAP-CAP;
- RECOVERY;
- [A randomised, double-blind, placebo-controlled multicentre study to evaluate the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia](#);

- ‘Tocilizumab in COVID-19 Pneumonia’ (TOCIVID-19);
- Phase III clinical trial, part of a global effort, to assess whether tocilizumab might have therapeutic value for COVID-19 patients who have developed or at high risk of developing serious lung damage from SARS-CoV-2 infections.

Sarilumab

- Monoclonal antibody that inhibits IL-6, which is vital in the immune response to SAR-CoV-2;
- Indicated for treatment of rheumatoid arthritis;
- May combat cytokine release syndrome and pulmonary symptoms in severely ill COVID-19 patients.

Evidence

- Sarilumab (Kevzara) demonstrates mixed efficacy results in ongoing COVID-19 trial of hospitalised patients with severe or critical respiratory illness secondary to COVID-19 (27 April 2020).
- Sarilumab fails to meet its primary and key secondary endpoints in US COVID-19 patients requiring mechanical ventilation. Minor positive trends were demonstrated in the primary pre-specified analysis group, but the results did not achieve statistical significance (2 July 2020).

Ongoing trials

- REMAP-CAP;
- Evaluation of the efficacy and safety of sarilumab in hospitalised patients with COVID-19.

Canakinumab

- Inhibits interleukin-1 (IL-1), which is vital in the immune response to SAR-CoV-2;
- Indicated to treat certain periodic fever syndromes and gouty arthritis;
- Potential to treat cytokine release syndrome in severely ill COVID-19 patients.

Ongoing trials

- Study of Efficacy and Safety of Canakinumab Treatment for CRS in Participants With COVID-19-induced Pneumonia (CAN-COVID)

Anakinra

- Inhibits IL-1, which is vital in the immune response to SAR-CoV-2;
- Indicated for treatment of rheumatoid arthritis, Still’s disease and cryopyrin-associated periodic syndromes;
- Might help to neutralise the cause of acute respiratory distress syndrome (ARDS) among patients with COVID-19;
- Anakinra has been used (off label) for cytokine storm syndromes triggered by other viruses and is reported to be relatively well tolerated, with a favourable safety profile.

Ongoing trials

- REMAP-CAP.

Baricitinib

- Janus-associated tyrosine kinase (JAK) 1 and JAK 2 inhibitor;
- Modulates the immune response by regulating overactive signalling through the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway;
- Indicated for treatment of rheumatoid arthritis;
- May potentially combat cytokine release syndrome (CRS) in severely ill patients;
- Currently no known published controlled clinical trial evidence supporting efficacy or safety in patients with COVID-19.

Ongoing trials

- [Multi-arm Therapeutic study in Pre-ICU Patients Admitted with COVID-19-Repurposed Drugs \(TACTIC-R\)](#);
- ACTT-II;
- [Phase III, randomized, double-blind, placebo-controlled study \(COLCORONA\)](#);
- [A Study of Baricitinib \(LY3009104\) in Participants With COVID-19 \(COV-BARRIER\)](#).

Ruxolitinib

- Selective inhibitor of JAK 1 and JAK 2;
- Modulates the immune response by regulating overactive signalling through the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway;
- Indicated for specialist treatments;
- May combat CRS in severely ill patients;
- Currently no known published clinical trial evidence supporting efficacy or safety in patients with COVID-19.

Ongoing trials

- [‘Phase III Randomised, Double-Blind, Placebo-Controlled Multicentre Study to Assess the Efficacy and Safety of Ruxolitinib in Patients with COVID-19-Associated Cytokine Storm’ \(RUXCOVID\)](#);
- [‘Assessment of Efficacy and Safety of Ruxolitinib in Participants with COVID-19-Associated ARDS who Require Mechanical Ventilation’ \(RUXCOVID-DEVENT\)](#).

Acalabrutinib

- Bruton’s tyrosine kinase inhibitor;
- In clinical development for people with chronic lymphocytic leukaemia, approved for this use in the United States.
- Early clinical data have shown it can lead to a decrease in inflammation and reduction in the severity of COVID-19-induced respiratory distress.

Ongoing trials

- ‘A Multicentre, Seamless, Phase II Adaptive Randomisation Platform Study to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID 19 in Hospitalised Patients’ (ACCORD);
- ‘Acalabrutinib Study with Best Supportive Care versus Best Supportive Care in Subjects Hospitalised with COVID-19’ (CALAVI).

Brensocatib

- Reversible inhibitor of the dipeptidyl peptidase-1 enzyme, which is known to be associated with pathogen destruction and inflammatory mediation;
- Not licensed in the UK;
- Could be beneficial for ARDS in severely ill COVID-19 patients.

Ongoing trials

- ‘Superiority Trial of Protease Inhibition in COVID-19’ (STOP-COVID19).

Ravulizumab

- Recombinant monoclonal antibody;
- Used routinely in blood diseases where complement activation destroys red blood cells;
- Potential to treat CRS in severely ill COVID-19 patients.

Ongoing trials

- TACTIC-R;
- ‘Efficacy and Safety Study of IV Ravulizumab in Patients With COVID-19 Severe Pneumonia’.

Gemtuzumab ozogamicin

- Monoclonal antibody that binds to CD33-expressing tumour cells to induce cell cycle arrest and apoptotic cell death;
- Indicated for CD33-positive acute myeloid leukaemia.

Ongoing trials

- ‘A Randomised Phase II Proof of Principle Multi-Arm Multi-Stage Trial Designed to Guide the Selection of Interventions for Phase III trials in Hospitalised Patients with COVID-19 Infection’ (CATALYST).

Namilumab

- Human immunoglobulin G1 monoclonal antibody currently in late-stage trials for the treatment of rheumatoid arthritis and ankylosing spondylitis;
- Currently being investigated to see if it can help manage inflammation associated with COVID-19.

Ongoing trials

- CATALYST.

Infliximab

- Chimeric monoclonal antibody indicated to treat inflammatory conditions, including rheumatoid arthritis and irritable bowel syndrome;
- Currently being investigated to see if it can help manage inflammation associated with COVID-19.

Ongoing trials

- CATALYST.

Otilimab

- Monoclonal antibody already in trials for the treatment of arthritis;
- May be able to help to block the effects of one of the types of cytokine (known as GM-CSF).

Ongoing trials

- [‘A Randomised, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Otilimab IV in Patients with Severe Pulmonary COVID-19-Related Disease’ \(OSCAR\).](#)

Medi3506

- Interleukin-33 monoclonal antibody developed for skin disorders.

Ongoing trials

- ACCORD.

Antiviral antibody cocktail

- Several companies are developing novel monoclonal antibodies to bind to and neutralise the SARS-CoV-2 virus;
- This ‘antiviral antibody cocktail’ contains two antibodies and trials will investigate whether the therapy can improve the outcomes for COVID-19 patients;
- It will also be tested as a preventive therapy in those who are healthy but at high risk of getting sick because they work in a healthcare setting or have been exposed to an infected person;
- REGN-COV2 comprises two monoclonal antibodies, REGN10933 and REGN10987, and was designed specifically by Regeneron scientists to block infectivity of SARS-CoV-2.

Ongoing trials

- RECOVERY (REGN-COV2);
- [‘Safety, Tolerability and Efficacy of Anti-Spike \(S\) SARS-CoV-2 Monoclonal Antibodies for Hospitalised Adult Patients with COVID-19’;](#)
- [Safety, Tolerability, and Efficacy of Anti-Spike \(S\) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult Patients With COVID-19;](#)

- Phase III trial will evaluate the use of the antibody cocktail, REGN-COV2, to prevent infection among uninfected people who have had close exposure to a COVID-19 patient;
- REGN-COV2 has also moved into the Phase 2/3 portion of two adaptive Phase 1/2/3 trials testing the cocktail's ability to treat hospitalised and non-hospitalised (or “ambulatory”) patients with COVID-19.

Leronlimab

- An investigational humanised monoclonal antibody targeted against the CCR5 receptor, which appears to play a central role in modulating immune cell trafficking to sites of inflammation;
- Being looked at as a potential therapy in the treatment of triple negative breast cancer and HIV infection as well as COVID-19.

Ongoing trials

- Study to Evaluate the Efficacy and Safety of Leronlimab for Patients With Severe or Critical Coronavirus Disease 2019 (COVID-19).

Other or multiple mechanisms



Source: Shutterstock.com

Colchicine is used for treating inflammation and pain in conditions such as gout and could help ameliorate COVID-19 complications

Colchicine

- Medicine for treating inflammation and pain in conditions such as gout;
- Could help ameliorate COVID-19 complications, but there is minimal anecdotal experience and clinical trial data reported to date in COVID-19.

Evidence

- Participants who received colchicine had statistically significant improved time to clinical deterioration compared with a control group that did not receive colchicine. However, the authors said that the findings should be considered only hypothesis-generating, given the low enrolment and event rates ([Deftereos et al](#), 24 June 2020).

Ongoing trials

- COLCORONA;
- [The Greek Study in the Effects of Colchicine in COVID-19 Complications Prevention \(GRECCO-19\)](#);
- [‘Colchicine Counteracting Inflammation in COVID-19 Pneumonia’ \(COLCOVID-19\)](#);
- [‘The ECLA PHRI COLCOVID Trial: Effects of Colchicine on Moderate/High-risk Hospitalized COVID-19 Patients’ \(COLCOVID\)](#).

Angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers

- Indicated for the treatment of hypertension and heart failure;
- There have been suggestions that the drugs can increase both the risk of infection and the severity of SARS-CoV2, but data are lacking;
- May also have a protective effect against lung damage.

Evidence

- Severity of COVID-19 is not associated with the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers;
- The BRACE CORONA trial, which tested temporarily stopping an ACE inhibitor/ARB for 30 days versus continuing ACE inhibitors/ARBs in patients who were taking these medications chronically and were hospitalised with a confirmed diagnosis of COVID-19, found no clinical difference, suggesting the medication should generally be continued for those with an indication ([Lopes et al](#), presented at the European Society of Cardiology Congress 2020 on 1 September 2020)

Ongoing trials

- [‘Losartan for Patients With COVID-19 Requiring Hospitalization’](#);
- [‘Recombinant Human Angiotensin-Converting Enzyme 2 \(rhACE2\) as a Treatment for Patients with COVID-19’ \(APN01-COVID-19\)](#).

Statins

- Indicated for the treatment of cardiovascular disease;
- Decrease inflammation, reduce blood clots, and prevent damage to endothelial tissue;
- Some evidence they can act as antivirals;
- Could potentially combat CRS in severely ill patients, but concrete data are lacking.

Ongoing trials

- [‘Preventing Cardiac Complication of COVID-19 Disease With Early Acute Coronary Syndrome Therapy: A Randomised Controlled Trial’ \(C-19-ACS\)](#).

Aspirin

- Triple effect of inhibiting virus replication, anticoagulation and anti-inflammatory.

Ongoing trials

- C-19-ACS;
- [‘Protective Effect of Aspirin on COVID-19 Patients’ \(PEAC\)](#).

Clopidogrel

- Anti-platelet drug that could help prevent blood-clots associated with COVID-19.

Ongoing trials

- C-19-ACS.

Anticoagulants

- Potential role of anticoagulation in specific COVID-19 patients for improved mortality.

Ongoing trials

- REMAP-CAP;
- [‘Weight-Adjusted versus Fixed Low Doses of Low-Molecular-Weight Heparin for Venous Thromboembolism Prevention in COVID-19’ \(COVI-DOSE\)](#);
- [‘Antithrombotic Therapy to Ameliorate Complications of COVID-19’ \(ATTACC\)](#);
- [‘Preventing COVID-19 Complications with Low- and High-Dose Anticoagulation’ \(COVID-HEP\)](#);
- [‘Effect of Anticoagulation Therapy on Clinical Outcomes in COVID-19’ \(COVID-PREVENT\)](#);
- C-19-ACS.

Bemcentinib

- Selectively inhibits AXL kinase, which blocks viral entry and enhances the antiviral type I IFN response;
- Investigational treatment for COVID-19;
- Reported to exhibit potent anti-viral activity in pre-clinical models against several enveloped viruses, including Ebola and Zika virus.

Ongoing trials

- [A Multicentre, Seamless, Phase 2 Adaptive Randomisation Platform Study to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID 19 in Hospitalised Patients \(ACCORD-2-001\)](#).

Omeprazole

- Proton-pump inhibitor indicated for the treatment of gastroesophageal reflux disease (GORD);
- Being investigated as an additive treatment for COVID-19.

Ongoing trials

- C-19-ACS.

Famotidine

- Histamine-2 receptor antagonist used in the treatment of GORD;
- Some evidence to suggest it is associated with improved patient-reported outcomes in non-hospitalised patients with COVID-19.

Ongoing trials

- [‘Multi-Site Adaptive Trials for COVID-19’](#).

Zilucoplan

- Synthetic macrocyclic peptide inhibitor already in trial for potential treatment of the skeletomuscular disorder myasthenia gravis;
- Could reduce damage to lung tissue caused by the virus.

Ongoing trials

- ACCORD.

Ascorbic acid/vitamin C

- Use of vitamin C could be effective in terms of mortality and secondary outcomes in patients with COVID-19 pneumonia due to its anti-inflammatory and antioxidant properties.

Ongoing trials

- [‘Lessening Organ Dysfunction with Vitamin C \(LOVIT\)’](#);
- [‘Use of Ascorbic Acid in Patients with COVID 19’](#);
- [Coronavirus 2019 \(COVID-19\)- Using Ascorbic Acid and Zinc Supplementation \(COVIDAtoZ\)](#)

Aviptadil

- Synthetic form of human vasoactive intestinal peptide;
- Indicated for treatment of erectile dysfunction;
- Reduces inflammation in the lungs and protects the alveolar type II cells that are believed to be an entry route for the SARS-CoV-2 to invade the lungs.

Ongoing trials

- [‘Inhaled Aviptadil for the Treatment of Non-Acute Lung Injury in COVID-19’ \(AVINALI\)](#);
- [‘Intravenous Aviptadil for Critical COVID-19 With Respiratory Failure’ \(COVID-AIV\)](#).

Opaganib

- Selectively inhibits sphingosine kinase-2 (SK2), a lipid-signalling molecule that promotes cancer growth
- Currently under investigation for oncology, inflammatory and gastrointestinal indications
- Pre-clinical studies have shown opaganib to have anti-inflammatory and anti-viral activity
- *In vivo* studies have shown opaganib to decrease fatality rates from influenza

Ongoing trials:

- [Opaganib, a Sphingosine Kinase-2 \(SK2\) Inhibitor in COVID-19 Pneumonia](#)

Tradipitant

- A neurokinin-1 receptor antagonist that works by blocking substance P, a neuropeptide secreted by neuronal cells and inflammatory cells that has multiple effects in different tissues;
- Currently in clinical development for gastroparesis, motion sickness and atopic dermatitis.

Evidence

- [Interim analysis of the ODYSSEY study demonstrated that hospitalised patients with COVID-19 pneumonia improved sooner when treated with tradipitant as compared to placebo \(18 August 2020\)](#).

Ongoing trials

- [ODYSSEY: A Study to Investigate the Efficacy of Tradipitant in Treating Severe or Critical COVID-19 Infection](#)

AZD1656

- A glucokinase activator that has been shown to reduce blood glucose for up to four months in humans;
- Has also been shown to activate the migration of T regulatory cells to sites of inflammation in preclinical experiments;
- May prevent the development of cardiorespiratory complications observed in hospitalised patients with COVID-19;
- AZD1656 has already undergone phase II trials for use in type 2 diabetes and is currently under clinical investigation for renal transplant rejection.

Ongoing trials

- [AZD1656 in Diabetic Patients Hospitalised With Suspected or Confirmed COVID-19 \(ARCADIA\)](#)

Nitric oxide

- Nitric oxide (NO) inhalation has been used as a pulmonary vasodilator and has been found to have antiviral activity against other coronavirus strains;
- Preliminary data support a microbicidal effect of high concentration inhaled NO;
- NO is being investigated to see if it can prevent the deterioration to a severe form of COVID-19 when administered at an early stage of the disease.

Ongoing trials

- [Nitric Oxide Inhalation Therapy for COVID-19 Infections in the ED \(NO COV-ED\)](#);
- [Inhaled Nitric Oxide Gas Therapy in Mechanically Ventilated Patients with Severe Acute Respiratory Syndrome in COVID-19](#);
- [Nitric Oxide Releasing Solution to Treat and Prevent Exacerbation of Mild COVID-19 Infection](#).

This article will be updated regularly as more information emerges. If there are any trials or treatments we have missed, [let us know](#).

References:

[1] European Medicines Agency. 2020. Available at: <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19> (accessed June 2020)

Other sources of information:

- American Society of Health-System Pharmacists: <https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx?la=en&hash=B414CC64FD64E1AE8CA47AD753BA744EDF4FFB8C>
- National Institute of Health Research: <https://www.nihr.ac.uk>
- ClinicalTrials.gov: <https://clinicaltrials.gov>
- EU Clinical Trials Register: <https://www.clinicaltrialsregister.eu>

Citation: The Pharmaceutical Journal, PJ June 2020 online, online | DOI: 10.1211/PJ.2020.20208126

Readers' comments (4)

- [Kat Beq](#) 12 JUL 2020 14:21
Okay
- [Stephen Fay](#) 4 SEP 2020 15:46
There are two significant potential therapies being tested that were missing from your list.....Nitric Oxide and Leronlimab. Any particular reason?
- [Julia Robinson](#) 4 SEP 2020 15:50

Hi Stephen, it's possible that the trials for these two drugs did not fit the criteria (randomised controlled trial with minimum 100 patients) at the time of writing. However, if you know of trials involving these two drugs that do fit this criteria please do send me the details via email - julia.robinson@rpharms.com - and I would be happy to consider adding them in my next update. Thanks very much

- **Laurence Goldberg** 16 SEP 2020 8:32

Observational studies with indomethacin have been reported from USA and India and a clinical trial has commenced in Iran.

