



Belfast, UK

chrisbaraniuk@gmail.com

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BRIEFING

Where are we with drug treatments for covid-19?

A year since the pandemic began, just a handful of lifesaving drugs have emerged as approved covid-19 treatments. **Chris Baraniuk** looks at the ongoing major trials

Chris Baraniuk

Where are the major trials for covid treatments?

Dozens of large trials and hundreds of smaller studies are investigating potential covid-19 treatments around the world. The largest is the Recovery trial, which began in March 2020 and has paved the way for the UK to become a leader in covid-19 treatment trials, running more of them than anywhere else in the world.

Nevertheless, experts warn of the continuing need for funding and support for ongoing robust treatment studies amid the more intense spotlight on vaccines, along with concern over the World Health Organization's flagship Solidarity trial having completed its initial assessment of four drugs but having yet to add or begin any others since it last reported in October 2020.¹

Selected covid-19 treatment trials under way

| Name of trial | Participants to date | Location(s) | Examples of drugs evaluated |
|---------------|----------------------|--|---|
| Recovery | 40 000 | UK; now expanding internationally | Dexamethasone, tocilizumab, azithromycin, convalescent plasma |
| Solidarity | 12 000 | 30+ countries across all six WHO regions | Remdesivir, hydroxychloroquine, lopinavir |
| Activ-3 | 10 000 | Mainly US | Remdesivir, Vir antibody treatments |
| Remap-Cap | 6700 | 19 countries including US, UK, Ireland, Spain, France, and Germany | Hydrocortisone, lopinavir-ritonavir, aspirin, vitamin C |
| Principle | 4600 | UK | Budesonide, colchicine |
| Anticov | 2000-3000 expected | 13 African countries | Amodiaquine, colchicine, ivermectin, nitazoxanide |
| Protect | 12 000 expected | UK | TBA (looking at prophylaxis in care homes) |

What treatment types are there?

Covid-19 is a viral disease. Therefore, researchers have sought drugs such as antivirals that target viruses, to debilitate SARS-CoV-2 or block its activity in the human body.

Medics have also sought interventions that can treat the illness caused by the virus and the hyperactive immune response that generally manifests in the most severe cases. It's this later stage of disease that can cause a series of complications such as organ failure or sepsis, potentially leading to death. To this end, trials have evaluated the efficacy of anti-inflammatory medicine to arrest the immune response and treatments to deal with other issues such as blood clotting.

Another approach involves using drugs such as antibody treatments, to prevent covid-19 infection from occurring in the first place.

In general, many treatments currently being investigated for use in covid-19 are not bespoke but are repurposed existing drugs that have previously been used to treat other conditions.

The fact that a couple of treatments emerged within a matter of months remains remarkable, says Paul Glasziou, professor of evidence based medicine at Bond University in Australia. "We've never, ever before in a pandemic or, I think, even in a major epidemic, been able to get a trial result that's been able to influence practice," he says.

What treatments work?

Mainly two types, both of which are immune modulators that treat patients already admitted to hospital. The use of these drugs for covid-19 remains off label and for emergencies.

Corticosteroids, mainly the cheap and readily available dexamethasone, have emerged as arguably the most significant intervention to date for treating severe symptoms of covid-19 by reducing inflammation. "People are having steroids as soon as they come through the doors of the emergency department, and the big difference is hopefully that we won't see them at all [in the intensive care unit]," says Matt Morgan, an intensive care doctor at the University Hospital of Wales and columnist for *The BMJ*. NHS England has estimated that a million lives

have been saved from covid-19 worldwide thanks to dexamethasone alone.²

In a study involving nearly 6500 patients enrolled in Recovery in the UK, dexamethasone was found to reduce deaths of ventilated patients by a third and deaths of patients receiving oxygen by a fifth.³ These findings have been backed by a further review of seven trials by the WHO Rapid Evidence Appraisal for Covid-19 Therapies (React) Working Group, which added that another corticosteroid, hydrocortisone, was as effective as dexamethasone and could be used as an alternative.⁴ The NHS recommends that the steroids be used only for patients with severe and critical disease.⁵

Monoclonal antibodies have achieved some success in helping the body's immune response to fight the virus. Tocilizumab is one such treatment traditionally used to treat rheumatoid arthritis, although it is expensive in comparison with drugs such as dexamethasone. In the UK the NHS recommends use of tocilizumab in conjunction with dexamethasone or a similar drug for inpatients.⁶ Preliminary data from Recovery showed that tocilizumab could save one additional life in every 25 patients who received the drug.⁷ Another monoclonal antibody, sarilumab, was found to improve outcomes including survival and reliance on organ support in the international Remap-Cap trial.⁸

The Principle trial has shown some promising signs regarding the inhaled drug budesonide, which is usually used to treat asthma and COPD. Interim data from a preprint study, which is yet to be peer reviewed, suggested that the use of budesonide at home for two weeks shortened average recovery times by a median of three days.⁹

What treatments do not work?

Hydroxychloroquine is the antimalarial drug once touted by the former US president Donald Trump as an effective treatment but, despite the hype, large trials have found no evidence for its efficacy against covid-19. Hydroxychloroquine “produce[s] little or no reduction in the mortality of hospitalized covid-19 patients when compared to standard of care,” concluded the WHO's Solidarity trial.

Remdesivir, the antiviral that was the first covid-19 treatment to be approved in the European Union and the US, was also the first to be administered in the UK outside a clinical trial. Disappointingly, this turned out to have little or no impact on survival among inpatients, concluded the Solidarity researchers in late 2020.¹⁰

Colchicine, an anti-inflammatory often used to treat gout, has also had disappointing results so far. The UK's Recovery trial reported in March 2021 that it had not found any convincing evidence to suggest that colchicine was effective, although other, smaller studies are ongoing.¹¹ Glasziou says, “Certainly, if I was a funder funding new trials, it's not something I would bother with—but I'm always prepared to be surprised.”

Physicians and patients around the world are currently discussing the potential value of many other drug and treatment options, but the evidence for most remains thin and often anecdotal, so many have not progressed to major national or international treatment trials.¹²

What gaps in treatment remain?

No drugs are recommended for prophylaxis against infection and hospital admission, as none have yet been shown to prevent covid-19 infection in large scale clinical trials. Duncan Richards, professor of clinical therapeutics at the University of Oxford, says that this is an important gap to tackle “as we think ahead to next winter when,

despite vaccination, we expect there will be significant numbers of patients.”

In general, researchers' options are limited in terms of existing drugs to test for efficacy against the disease, notes Saye Khoo, professor in the Department of Pharmacology at the University of Liverpool. “We have a moderate pipeline of drugs—we're not swimming in lots of new candidates and lots of new classes of drugs at the moment,” he says.

Antivirals, which could be given to inpatients who have not yet reached a critical stage of illness, could perhaps have a prophylactic function. This was one of the reasons for excitement over remdesivir, but sadly, says Richards, “We still don't have a decent antiviral.”

That could change if the UK government's recently announced Antivirals Taskforce finds success.¹³ This ambitious initiative will support the inclusion of antivirals in covid-19 clinical trials and aims to identify two or more effective treatments by the autumn.

Then there are the problems that patients with covid-19 can develop while in hospital. Morgan says that patients with severe illness often develop blood clots, which can be life threatening. “Preventing these clots from happening would be very valuable,” he says. Such patients often receive anticoagulants to avoid blood clots but, because the cause may be inflammation, doctors are often unsure how helpful these drugs would be.

Long covid

And then there is “long” covid. This can take many forms but may include fatigue, headaches, breathing issues, and memory loss or cognitive impairment. Some patients undergo physiotherapy or mental health therapy after leaving intensive care, but there are few pharmaceutical options, says Morgan.

For instance, some patients who recover from covid-19 are left with pulmonary fibrosis, a scarring of their lung tissue. Richards notes that the drug based treatments that do exist for this condition are not highly effective and have complicated safety profiles.

Ideally, he says, doctors would be able to accurately predict which patients have the greatest risk of developing fibrosis so that drugs designed to tackle this could be applied judiciously, before serious symptoms develop.

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