Step 3.7 Finding treatments for COVID-19

Dr Anna Seale describes in this mini-lecture the process for identifying treatments for COVID-19, the range of treatments being investigated, and gives specific examples of current trials of different medicines. As you watch it think about the challenges of setting up trials – even for existing medicines – in the context of an outbreak. What difficulties are encountered? And since this was recorded (1st May 2020), what more have we learnt from the results of randomised controlled trials? We've put some recent articles in the See Also section you could look at.

Video transcript:

ANNA SEALE: So how do we treat COVID-19? Many people with the infection will get better at home with rest, drinking plenty to avoid dehydration, and taking medicine to lower their temperature as needed. A small proportion will need care in hospital which is supportive, for example, through oxygen. And those most unwell may need ventilation.

One option is to develop a new treatment for COVID-19. For this, there is a set process to ensure medicines that are used are both safe and effective. Another option is to use a medicine or treatment that is already being used for other conditions. These would still need to be tested to see if they're effective for COVID-19 in clinical trials.

But they would likely be available much more quickly if studies demonstrated benefit, as we know a lot more about them in terms of their safety, dosing, and side effects. There are also different ways to give a medicine. In some cases, medicines can be used to prevent disease, for example, in those exposed in a household where there is a confirmed case of COVID-19 or to health care workers exposed. In many other instances, medicines are used to treat those who already have the disease to help them get better.

Treatments are also tested and used in different patient groups. For example, some medicines may be tested to see if they are of benefit in people who need hospital treatment or only in the group of people who need intensive care. So how are new medicines developed?

Well, first, medicine has to be identified or made and undergo preclinical testing. Then it can enter clinical trials. The first phase of clinical trials is the first time a treatment is tested in humans.

The medicine is usually given to a small group of healthy volunteers. In some cases, it may be given to a small group of those who have the condition it aims to treat. At this stage, the aim is to make sure there are no major safety issues and any early suggestion of its value in treatment. Many medicines do not progressed beyond this phase.

In the second phase, trials are done including people with the condition to determine the effectiveness in treatment or prevention and dose needed. Even fewer medicines progressed to phase-3 trials. These trials are much larger, often involving hundreds or thousands of people from several countries.

These studies aim to demonstrate the safety and effectiveness of the treatment in the patient group in which it will be used, confirm the dose and side effects, as well as identifying any groups of people who shouldn't use it. If results are successful, regulatory approval may then be sought to use the medicine. Often people talk about randomised controlled trials.

Most phase-3 studies are randomised controlled trials. They're a way of testing drugs in an unbiased, fair way. A simple randomised controlled trial would involve a group of people included in the study being given either the study medicine or not, at random. The control group is the group of people who have care without the medicine being tested. Randomisation means that the new medicine can't unconsciously be allocated, for example, to those who are slightly less unwell than those who are not allocated to it. Often these trials are also blinded. This can be in terms of the patient not knowing which group they're in and/or those treating them not knowing.

In the control group, those included are often given a placebo, a tablet that looks exactly like the study medicine but doesn't have those ingredients in it. Blinding and using placebos prevents those looking after the person and/or the person in the study unconsciously reporting improvement because they've been given a new medicine. And that can bias results, making it an unfair test.

When approved, further studies are still needed. And these are called phase-4 trials and involve the safety surveillance of the medicine. And sometimes it's used in different formulations.

Developing a drug from the start is therefore a long process. For COVID-19, whilst in the long term, new medicines may be developed and used, a lot of work is currently being done to see whether medicines used for other conditions could be effective for COVID-19. But these medicines still need to be tested in randomised controlled trials to see if they work for COVID-19.

There are many therapies being investigated for COVID-19. And these include pharmacological treatments, such as antivirals, which kill or stop the virus replicating; immunosuppressive treatments, which dampen down a person's immune response to infection. But these medicines have to be carefully monitored because reducing the immune response can also potentially cause harm.

Monoclonal antibodies, which are laboratory-based substitute antibodies that can restore, enhance, or mimic the immune system's response to a trigger. There are also

advanced therapy medicinal products being tested. And an example of this is the use of convalescent plasma, which contains antibodies produced by a person who's recovered.

There are also studies on traditional medicines, for example, in China, and investigations of the benefit of other supportive therapies. This is an illustration of the network of completed, ongoing, and planned COVID-19 interventional clinical trials published at the end of April 2020. Of the many pharmacological options, key examples are firstly, chloroquine/hydroxychloroquine, which are used in malaria and dermatological conditions. There was suggestion of benefit and people with pneumonia in China and France, but randomised controlled trials are still needed to see if there is effectiveness in COVID-19.

Secondly, ritonavir and lopinavir, which are licenced for use in people with HIV. There has been laboratory work suggesting benefit in some trials already conducted. Data are limited from these trials, and results are inconclusive so far.

Thirdly, remdesivir, which is not yet licenced for other conditions, but it has been tested to see if it could be a benefit in Ebola. In animal studies, there have been suggestions it could be a benefit to MER-CoV and SARS. Results of studies in COVID-19 are coming out, but are not yet conclusive. However, one study found some evidence that there could be a faster time to clinical improvement.

There are many clinical trials worldwide, testing many different treatment options. One example of a large clinical trial in the UK is RECOVERY. It is investigating whether different treatments can improve clinical outcomes in terms, for example, of survival, the need for ventilation, and the length of hospitals stay. It would include people who consent to the study in hospitals where the study's being done.

The study compares standard of care versus standard of care, plus lopinavir-ritonavir or low-dose dexamethasone or hydroxychloroquine or azithromycin. If those in the study become more unwell, there is an option for a second randomisation to test a monoclonal antibody, as well as standard supportive care. The "Solidarity" trial is another example launched by the World Health Organisation and partners.

It aims to identify treatments to slow disease progression and/or improve survival and COVID-19. It will compare the standard of care, plus one of four treatment options against standard of care in multiple countries to identify whether any of the drugs slow disease progression or improve survival. Other drugs may be added to the trial based on emerging evidence.

A concern with using medicines which are already available is that they may be used whilst of unproven benefit. WHO has cautioned against health workers recommending or administering unproven treatments to patients with COVID-19 or people self-medicating with them. There have also been shortages of medicines which are identified as potentially useful for COVID-19 prior to trials confirming this. This has reduced the availability of these medicines for those who have conditions for which there is established benefit. For those wanting more detail on treatments and trials, there's a landscape analysis available from WHO.

See Also

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext

Landscape analysis of therapeutics

https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1

Global Coronavirus COVID-19 Clinical Trial Tracker

https://www.covid-trials.org/

RECOVERY Trial

https://www.recoverytrial.net/

"Solidarity" clinical trial for COVID-19 treatments

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

https://www.nejm.org/doi/10.1056/NEJMoa2001282