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ScienceTalk

# Covid-19 treatments and their role in war against pandemic


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For The Straits Times


The world is currently focused on the development of Covid-19 vaccines, with the expectation that these will protect the healthy population and allow for a return to normality.

However, it is important to bear in mind that not everyone will respond equally well to a vaccine.

In addition, vaccines are not designed to treat a patient who has already been infected.

This is where therapeutics come in, to treat infected patients and restore them to health.

Researchers and clinicians have been working hard to find the right mix of therapeutics to treat patients suffering from the disease.

As Covid-19 is a novel viral infection, one of the quickest routes to treatment is to repurpose existing drugs that have been used to treat similar diseases.

These drugs have already been approved by regulatory bodies for other indications and, therefore, securing approval to use them against Covid-19 can be achieved faster than developing entirely new drugs.

Take the antiviral drug remdesivir, for example. First created to treat Ebola, it has been used as part of clinical trials for Covid-19 patients in Singapore, and has been granted conditional approval by the Health Sciences Authority to be administered to severely ill Covid-19 patients.

However, repurposed drugs have limitations in terms of specificity and efficacy.

Several drugs initially touted as effective against Covid-19 were eventually found to have minimal efficacy, or even to have adverse effects.

One approach to get high-quality evidence about the safety and efficacy of the drugs in an accelerated timeframe has been multi-centre randomised controlled trials involving large numbers of patients.

These include Britain's Recovery trial, the World Health Organisation Solidarity trial, and the United States National Institutes of Health's (NIH) Adaptive Covid-19 Treatment Trial and Accelerating Covid-19 Therapeutic Interventions and Vaccines (Activ) trial, which have recruited thousands of patients over two to four months.

Indeed, these trials have shown that remdesivir and dexamethasone are effective therapeutics, while lopinavir-ritonavir and hydroxychloroquine are not.

Clearly, other therapeutic approaches besides repurposed drugs are required.

## HARNESSING ANTIBODIES TO HELP THE BODY FIGHT COVID-19

A more effective, but lengthier and more difficult approach to Covid-19 therapeutics is to develop an entirely new antiviral drug. Such a drug would be specific to the Sars-CoV-2 virus that causes the infection, or capable of addressing the body's immune response to infection.

There are two broad categories of antiviral treatments: small molecules and large molecules, referring to the molecular size of the treatment particles.

Small molecule drugs are commonly used today, and are typically chemically based and taken orally. Large molecule drugs are a relatively newer approach based on biological proteins, and typically administered via injections.

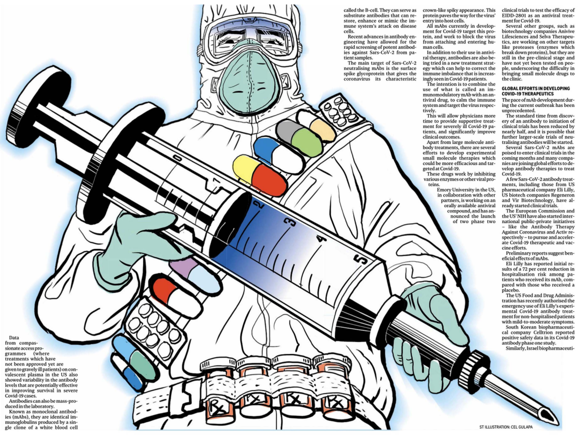
A potential treatment that offers much hope in the current pandemic is large molecule antibody-based therapy.

Antibodies are the body's soldiers, formed to fight off invaders from bacteria to viruses. They are generated by our immune systems and have the potential to be used for both treatment and prevention, and can be mass-produced in the laboratory relatively rapidly.

One way to manufacture antibody treatments is to harness them from the blood of recovered Covid-19 patients, which is also called convalescent plasma.

While convalescent plasma can be used to treat Covid-19 patients, we have yet to see high-quality published evidence to draw definitive conclusions on its relative efficacy and safety.

Moreover, the extraction and purification of convalescent plasma to produce neutralising antibodies is challenging, and large amounts of plasma are required to produce a uniform product in sufficient quantities, limiting the number of people who can be treated with this approach.



ST ILLUSTRATION: CEL GULAPA

Data from compassionate access programmes (where treatments which have not been approved yet are given to gravely ill patients) on convalescent plasma in the US also showed variability in the antibody levels that are potentially effective in improving survival in severe Covid-19 cases.

Antibodies can also be mass-produced in the laboratory.

Known as monoclonal antibodies (mAbs), they are identical immunoglobulins produced by a single clone of a white blood cell called the B-cell. They can serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on disease cells.

Recent advances in antibody engineering have allowed for the rapid screening of potent antibodies against Sars-CoV-2 from patient samples.

The main target of Sars-CoV-2 neutralising mAbs is the surface spike glycoprotein that gives the coronavirus its characteristic crown-like spiky appearance. This protein paves the way for the virus' entry into host cells.

All mAbs currently in development for Covid-19 target this protein, and work to block the virus from attaching and entering human cells.

In addition to their use in antiviral therapy, antibodies are also being tried in a new treatment strategy which can help to correct the immune imbalance that is increasingly seen in Covid-19 patients.

The intention is to combine the use of what is called an immunomodulatory mAb with an antiviral drug, to calm the immune system and target the virus respectively.

This will allow physicians more time to provide supportive treatment for severely ill Covid-19 patients, and significantly improve clinical outcomes.

Apart from large molecule antibody treatments, there are several efforts to develop experimental small molecule therapies which could be more efficacious and targeted at Covid-19.

These drugs work by inhibiting various enzymes or other viral proteins.

Emory University in the US, in collaboration with other partners, is working on an orally available antiviral compound, and has announced the launch of two phase two clinical trials to test the efficacy of EIDD-2801 as an antiviral treatment for Covid-19.

Several other groups, such as biotechnology companies Anivive Lifesciences and Selva Therapeutics, are working on other targets like proteases (enzymes which break down proteins), but they are still in the pre-clinical stage and have not yet been tested on people, underscoring the difficulty in bringing small molecule drugs to the clinic.

## GLOBAL EFFORTS IN DEVELOPING COVID-19 THERAPEUTICS

The pace of mAb development during the current outbreak has been unprecedented.

The standard time from discovery of an antibody to initiation of clinical trials has been reduced by nearly half, and it is possible that further larger-scale trials of neutralising antibodies will be started.

Several Sars-CoV-2 mAbs are poised to enter clinical trials in the coming months and many companies are joining global efforts to develop antibody therapies to treat Covid-19.

A few Sars-CoV-2 antibody treatments, including those from US pharmaceutical company Eli Lilly, US biotech companies Regeneron and Vir Biotechnology, have already started clinical trials.

The European Commission and the US' NIH have also started international public-private initiatives – like the Antibody Therapy Against Coronavirus and Activ respectively – to pursue and accelerate Covid-19 therapeutic and vaccine efforts.

Preliminary reports suggest beneficial effects of mAbs.

Eli Lilly has reported initial results of a 72 per cent reduction in hospitalisation risk among patients who received its mAb, compared with those who received a placebo.

The US Food and Drug Administration has recently authorised the emergency use of Eli Lilly's experimental Covid-19 antibody treatment for non-hospitalised patients with mild-to-moderate symptoms.

South Korean biopharmaceutical company Celltrion reported positive safety data in its Covid-19 antibody phase one study.

Similarly, Israel biopharmaceutical company Kamada announced that initial interim results for a clinical trial involving its plasma-derived antibody treatment showed improvement of symptoms in Covid-19 patients.

However, these remain early-stage studies, and further large clinical studies will be needed to evaluate the utility of mAbs in clinical development.

Meanwhile, it is critically important to monitor the emergence of antibody escape mutants – mutations which could elude antibody treatment and lead to reduced efficacy of the mAbs.

Researchers from the Global Initiative on Sharing all Influenza Data (Gisaid), a platform which promotes the international sharing of all influenza virus sequences, have done pioneering work in this regard.

The CoVsurver mutations app in Gisaid's database allows researchers, clinician scientists and surveillance labs to rapidly screen their sequences for potentially interesting mutations to identify candidates for phenotypic (observable) changes or special epidemiological relevance.

## SINGAPORE'S COVID-19 TREATMENT EFFORTS

Several research groups in Singapore are involved in the accelerated development of mAbs and therapeutics against Sars-CoV-2.

DSO National Laboratories, Singapore's defence research and development organisation, recently announced the discovery of five antibodies against Covid-19 after screening antibodies from recovered patients. It plans to initiate clinical trials in the coming months.

Singapore-based biotech company Tychan has also recently commenced clinical trials for a potential mAb treatment of Covid-19 which was developed in an accelerated timeframe.

Singapore's Agency for Science, Technology and Research (A*Star) is collaborating with Chugai Pharmabody Research, a research centre of Japan's Chugai Group in Singapore, on joint research on a therapeutic antibody to fight Covid-19.

The project focuses on a potential therapeutic antibody discovered by a research team at A*Star's Singapore Immunology Network, which worked in close collaboration with DSO at their high-containment Biosafety Level 3 facilities.

Lead candidates were isolated from a high-diversity synthetic human antibody library and they showed high potency in neutralising the live Sars-Cov-2 virus.

A national platform for drug development, the Experimental Drug Development Centre (EDDC) is supporting several local programmes to address the immediate situation at hand with a mid-to-long term view in mind.

Apart from active in-house drug discovery, its programmes include sharing technical know-how on drug development with local players, participating in the national discourse on Covid-19 in several forums, supporting the development of diagnostic assays (particularly the Fortitude Kit for detecting Sars-CoV-2) as well as the clinical translation of novel mAbs against Sars-CoV-2 from bench to bedside.

EDDC's discovery programme on small molecules that focuses on developing a broad-spectrum antiviral drug is a strategy to counter future novel infectious disease outbreaks under an accelerated timeframe. The centre is also supporting local biotech companies – Aslan Pharmaceuticals, Aum Biosciences, and Rhea Pharmaceutical Sciences – to test their compounds as possible treatments for Covid-19.

In addition, EDDC is working with DSO in the pre-clinical and clinical development of a potential Covid-19 therapeutic called AOD01, which is a Sars-CoV-2 neutralising mAb.

The safety and pharmacokinetics of AOD01 will be evaluated in healthy subjects during clinical studies in Singapore, followed by looking at the drug's antiviral activity in Covid-19 patients.

## SPEED AND SAFETY ARE CRITICAL

Drug discovery and development is a process that takes time.

Despite best efforts, it will be some time before we can establish whether some of the new treatments work for patients.

It is paramount that the drugs themselves do not cause harm.

In spite of all these hurdles, why are so many scientists working tirelessly to develop therapeutics on very accelerated timelines?

It is because we recognise the imperative role that these treatments can play to save lives, alleviate suffering and ease the burden on healthcare systems.

Infectious disease epidemics have plagued mankind for the longest time, and are not likely to go away any time soon.

New pathogens continue to be discovered, and existing ones may evolve as well.

With each battle however, we learn and adapt, and we develop new tools and technologies to enable safe and effective treatments and vaccines.

As the world tries to overcome the Covid-19 pandemic, and as scientists talk about the menacing "Disease X" yet to come, we can draw hope from the scale of cooperation that we are witnessing in Singapore and around the globe to develop therapeutics – for this pandemic and beyond.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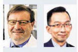

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