IFPMA

Media Backgrounder - IFPMA COVID-19 Media Briefing
Therapeutics: innovation, trials and access

Developing and distributing safe and effective therapies for treating or eventually curing COVID-19 has led to a wide array of potential medicines being tested. With 23 million coronavirus cases and 800,000 deaths, and with the ever-present threat of recurrent spikes, let alone continuing economic damage, political leaders and the global health community are eager to find treatments quickly, but timescales may be lengthening.

Today, a matter of seven months since the coronavirus SARS-CoV-2 was shared with the world's scientists, over 300 COVID-19 treatments are being researched or in clinical trials around the world – some repurposed drugs proven to work against other deadly diseases, others as novel as the virus itself. Finding effective treatments are vital if public health authorities and clinicians are to alleviate often excruciating symptoms such as inflamed lungs or reduce the spread of the virus within the body. Effective therapies are essential for containing the effects of the virus – and will remain so even if an effective vaccine becomes available. Not least because we do not and cannot know how long any immunity will last.

While there currently is no approved treatment to *cure* COVID-19, the unprecedented levels of research over the past few months by the biopharmaceutical industry has brought to light what may work to treat patients with COVID-19. Ultimately, there will not be one single effective therapy – or magic bullet – for everyone, instead we will need lots of options as different treatments may help different groups of patients, at different stages of their illness.

Different COVID-19 treatments being explored

There are three main avenues to treatment: antivirals, antibodies including convalescent plasma, as well as anti-inflammatories.

Antivirals - These drugs work by preventing a virus from developing and multiplying itself inside the body**.** Effectively, they stop the coronavirus from hijacking cells by inhibiting its replication. Each virus is different and requires antiviral drugs tailored to each individual virus. The research conducted by scientists is to find one or several antivirals that can combat COIVID-19. One way to fast track the process is to see if any existing antivirals can be repurposed, rather than starting from scratch, which would take longer.

Antibodies - The body, of course, generates its own defences when attacked by and recovering from infections caused by a virus. These defences, called antibodies, are a natural product that can be extracted from the blood of people who have recovered from COVID-19 (convalescent plasma) and administered to others to boost their immune responses. Antibodies can also be manufactured in a lab, designed to mimic the natural antibodies found in the body. These manufactured defences are called monoclonal antibodies. Either way, antibodies attach themselves to the intrusive virus and target it for destruction. They are particularly useful in warding off 'cytokine storm', an extremely aggressive inflammatory response by the body to invasion by the virus, often causing serious damage to body organs and ultimately may lead to death in some cases.

Anti-inflammatories - Anti-inflammatory drugs work, like a relatively simple painkiller many of may take for muscle ache, by effectively calming down the body. Anti-inflammatory drugs are being tested, as they may

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be able to stop or slow the immune system processes that trigger excessive inflammation of the lungs and can thus help manage the immune system's overreaction to the virus, so-called cytokine storms.

The COVID-19 treatments being tested differ both in terms of how they work in the body, and for which patient group they are most beneficial for. Antivirals look to treat the conditions caused by the virus directly while antibody therapies are also treating the conditions caused by the coronavirus more indirectly by boosting the patient's own immune system. Antivirals are destined for people infected by the virus. While anti-inflammatory drugs, like the steroid dexamethasone, may be beneficial for patients in a critical stage of the disease's development. Monoclonal antibody therapy and convalescent plasma could be useful in patients with very weak immune systems.

Status of COVID-19 treatment in the pipeline towards approval

Currently, many COVID-19 treatments are being used on a compassionate use basis by hospitals with the patients' consent. But to be able to use treatments that could be of help in treating patients with COVID-19 systematically, the treatments must be tested with clinical trials that record their effectiveness and safety on patients compared to other patients who don't receive the treatment. The results of the clinical trials are submitted to national regulatory authorities for scrutiny and if deemed safe and effective, they will get regulatory approval for stipulated conditions in that country. With treatments undergoing hundreds of clinical trials around the globe on thousands of patients, some are promising, others have been ruled out because trials have not found the treatment to be safe or effective. In some cases, a treatment alone can be ruled out as not helping treat COVID-19, but when used in combination or cocktail with other treatments may be found to be successful in treating patients in the end.

Some antivirals:

- Gilead's **remdesivir** (Veklury) is treating patients with COVID-19 in multiple countries worldwide. The FDA issued an Emergency Use Authorization (EUA) in May and the EMA issued a conditional approval in July.
- MSD and Ridgeback Bio have entered into a collaboration to develop **MK-4482** (previously known as EIDD-2801), an orally available antiviral candidate. In preclinical studies, MK-4482 has demonstrated antiviral activity against SARS-CoV-2, the virus that causes COVID-19, as well as the coronaviruses responsible for MERS and SARS. MK-4482 is currently being evaluated in Phase 2 clinical trials, with two pivotal trials anticipated to start in September 2020 evaluating treatment of both hospitalized and non-hospitalized patients.
- **Favipiravir**, an anti-flu drug originally discovered by Fuji in Japan, is currently undergoing clinical trials in a number of countries.
- Other antivirals, such as **lopinavir** and **ritonavir**, a drug combination used to treat HIV, have been tested to treat patients with COVID-19 but have shown little significant benefits for patients.

Monoclonal antibodies (Mabs) have excellent specificity, high safety and quality control and can be efficiently delivered to patients in the right amounts. Key companies such as Eli Lilly and Company, AstraZeneca, Roche/Genentech, Amgen, GSK and AbCellera are now sharing manufacturing information in a move designed to speed up production.

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- AstraZeneca, for instance, is working with Vanderbilt University, US, to trial two Mabs;
- Eli Lilly and Company is currently undertaking clinical trials for two experimental Mabs;
- AbbVie is working with Harbour BioM, Utrecht University and Erasmus Medical Center on a novel monoclonal antibody therapeutic;
- GSK has been working with Vir Biotechnology in the same field.

Antibodies made from convalescent plasma have shown to be safe and efficacious for the treatment of COVID-19, however more randomized clinical trials are needed, and supply depends on the altruism of blood donors, and blood donations cannot meet the demands of a pandemic. Takeda and CSL have entered an alliance with eight other plasma companies to develop a potential plasma-derived therapy for treating COVID-19.

Anti-inflammatory drugs - **Dexamethasone** has proven helpful for COVID-19 patients with severe or critical disease (meaning patients who are being on a ventilator or are receiving supplemental oxygen). **Dexamethasone** is a steroid that has been used for decades, and therefore is off-patent and is widely available. The World Health Organization (WHO) emphasizes that there is no evidence that the drug works for patients with mild disease or as a preventative measure, and warns it could instead be harmful.

Immunomodulators (Cytokine Inhibitors) are meant to halt cytokine storms, this is when the body produces an excess of signalling molecules called cytokines to fight off infections. Cytokines can trigger a severe overreaction of the body's immune system, causing a so-called cytokine storm. An example of immunomodulators is Roche's arthritis drug **tocilizumab** (Actmera) which has so far shown mixed results in clinical trials. There are hopes that wen used in combination therapy together **remdesivier**, **tocilizumab** could prove more effective.

The importance of clinical trials to prove safety and effectiveness before obtaining regulatory approval

Before drugs can win regulatory approval and be licensed for use, they must undergo clinical trials. Clinical trials are essential to prove that treatments are safe and effective, and ultimately inform patient care and public health about the best possible treatment options.

Clinical trials take place in three or four successive phases and involves 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'. IFPMA members are conducting clinical trials that involve over 46 000 participants for COVID-19 therapeutics.

One continuing problem to conduct clinical trials for COVID-19 treatments, is finding enough volunteers to take part in clinical trials who fit the strict criteria required to comprehensively test the treatment. In some cases, trials have struggled to get going during the pandemic, partly because people fear they will just be administered a placebo, while others have been well-subscribed.

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