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Blood being taken in August from a participant of a Covid-19 vaccination study at the Research Centres of America in Hollywood, Florida. While the results of the World Health Organisation's Solidarity trial are disappointing for clinicians treating Covid-19 patients, there are still a number of trials under way with repurposed drugs to prevent the disease, and new drugs in development to try to treat those infected. PHOTO: AGENCE FRANCE-PRESSE

ScienceTalk

You can't always teach an old drug new tricks

Results of WHO trial may be disappointing but it serves as a model for future studies

Paul Tambyah and Mikael Hartman

The Covid-19 pandemic is unprecedented in terms of its impact on the world.

While other pandemics have been more deadly, such as the plague, cholera and the 1918 Spanish flu, they occurred before the modern era of antimicrobials.

Since the start of the Covid-19 pandemic, doctors and scientists have been looking hard for drugs which can be used to treat and prevent Sars-CoV-2 infection.

Public health interventions such as quarantine and contact tracing were and still are widely used to prevent infection.

However, once infection occurs, there is only supportive care. This often means time in an intensive care unit (ICU) with the use of oxygen and other standard medical treatments, but no specific targeted options against either the virus or the host immune response.

With the development of penicillin and other antibiotics for bacterial infections, many previously deadly infectious diseases such as pneumonia and meningitis are no longer as deadly, and neither are malaria and tuberculosis.

Highly active antiviral agents were also developed for the human immunodeficiency virus and hepatitis C.

When developing new virus-specific drugs from scratch, it can take years (probably about 10 to 15 years on average) to move from discovery to patients, so the only option initially in treating Covid-19 patients was to consider existing licensed medicines.

This process is known as repurposing of drugs. It is not a new process and, in fact, one of the most effective cardiac drugs used to treat heart attacks is aspirin, which was initially developed as a fever and pain medicine from the bark of the willow tree.

When any treatment is used for a disease, especially for a brand new disease such as Covid-19, it is important to know whether the treatment works. This is particularly important for drugs which may have side effects that are potentially harmful to patients.

The reality, however, is that when a patient is in front of us, we do not have time to wait for the results of studies published in medical journals. So we use whatever drugs available that may have some benefit.

After a while, we accumulate enough data from the patients we have treated to analyse the outcomes in observational studies and report whether the drugs have any benefit at all.

There have been multiple observational studies published since the early days of the Covid-19 pandemic and many have made the headlines, not without controversy and some confusion to the public.

The reason is that these observational studies tend to be biased and unreliable. Treatment outcomes and confounding issues may not be standardised.

Sometimes patients who are only moderately ill are more likely to receive certain drugs while patients who are looked after by certain physicians may receive no treatment at all, based on the preferences or beliefs of the individual patients.

CLINICAL TRIALS

The solution to this is the randomised clinical trial (RCT), which has been conducted in clinical medicine, including infectious diseases, for many years.

In the 1960s and 1970s, the definitive treatment for tuberculosis was established through the United Kingdom Medical Research Council trials conducted in many centres, including Singapore.

Randomisation ensures that patients in all treatment groups are roughly comparable, with the only difference being the treatment assigned to the group.

This reduces the bias found in observational studies and allows us to determine if the effect is due to the drug being studied itself.

RCTs also have standardised end points – such as length of hospitalisation, need for oxygen, or death – which ensure that the results from the different treatment arms can be accurately compared.

Multiple small randomised clinical trials have been published of the various treatments for Sars-CoV-2, initially from China and then, later, from all over the world. These studies have been funded by either the drug companies which developed the drugs or the national health authorities from the United States, Britain and China.

Due to differences in study design – such as when the drugs were started – as well as drug dosing regimens and end points, the results were often contradictory, and the confusion from the observational studies was only slightly reduced.

Enter the World Health Organisation's (WHO) Solidarity trial.

In a remarkably short time, the Solidarity therapeutics trial randomised 11,266 adults admitted to 405 hospitals in 30 countries, from Albania to South Africa.

The trial design was remarkably simple.

Once the patients gave informed consent to participate in the trial, they were randomised online to one of up to five treatments, depending on local availability of the drugs and standard of care.

The drugs used were remdesivir, hydroxychloroquine, lopinavir-ritonavir and interferon, which was initially used in combination with lopinavir-ritonavir.

There were no forms to fill up but the doctors in charge of the patients had to return to the online system to report the outcomes and provide details such as how long the patients were hospitalised and whether they had any serious adverse effects or died.

An "adaptive trial design" was used for the study, which allowed investigators to drop any of the arms if it did not work in interim analyses.

WHY DIFFERENT TRIALS PRODUCE DIFFERENT RESULTS

The trial started on March 22 with some enthusiasm.

But by June 18, hydroxychloroquine was discontinued for futility, lopinavir-ritonavir was stopped on July 4 and interferon, on Oct 16.

An interim analysis of the patients enrolled up to Oct 4 was published recently as a pre-print, which means it has yet to be peer reviewed.

The results indicate that remdesivir, hydroxychloroquine, lopinavir-ritonavir and interferon regimens appeared to have no effect compared with standard of care on the 28-day mortality of Covid-19 among hospitalised patients.

The results differ from the optimistic reports from studies conducted by Gilead and the US National Institutes of Health on remdesivir – a drug initially developed to treat Ebola. There are several possible reasons for the disparity.

First, the primary end point of the Solidarity trial is death. For many of the other trials, end points have included duration of hospitalisation or time to clinical improvement.

It is possible that remdesivir may speed up recovery in those who are going to recover but still has no impact on overall survival. The same has been true of RCTs of other antivirals such as oseltamivir for influenza.

RCTs of treatment with hydroxychloroquine and lopinavir-ritonavir have not shown significant benefits as well.

While it is disappointing to note the results of the Solidarity trial, it is not all gloom as the Recovery trial in the UK reported meaningful benefit in mortality using dexamethasone in ICU patients but not in those not requiring oxygen therapy.

This study did report an unusual and alarmingly high ICU mortality, which may hamper its generalisability to other parts of the world.

The other drugs in the Recovery trial, hydroxychloroquine (which has been published in pre-print) and lopinavir-ritonavir (not published but reported), also have no significant benefits – similar to the WHO Solidarity trial.

This is important as the ability to reproduce results is one of the key tenets in science.

COMMERCIALISATION OF SCIENCE

Many people are confused about the data from scientific research on Sars-CoV-2, which often appears on television before it has gone through rigorous scientific peer review. That is partly due to the commercialisation of science and medicine in the modern era.

American theoretical physicist Richard Feynman described the scientific method very well when he said that first, we make a guess or come up with a hypothesis. Then we design the experiment and see if our guess or hypothesis is right.

Professor Feynman said: "If it disagrees with experiment, it's wrong." That simple statement is the key to science.

So when large RCTs, which are the best-designed experiments in clinical medicine, are published, we can change the way we treat our patients.

Sometimes it is painful and we have to give up our beliefs based on good observational studies, especially when multiple large, well-designed trials show the same thing.

Historical examples of this problem are many. For example, Vitamin A and E had, in large cohort studies, been shown to reduce the risk of lung cancer.

However, when a large RCT was finally done, not only did they not work, but instead, the vitamins increased the risk of death in the participants.

Similar findings were observed in studies of high-dose chemotherapy with stem cell transplants for advanced breast cancer, where four RCTs showed no benefit compared with standard chemotherapy despite observational studies appearing to show some improvements in survival for these women.

Once again, while the results of the Solidarity trial are disappointing for clinicians who treat patients with Covid-19, there are still a number of trials under way with repurposed drugs to prevent the disease, and also new drugs in development to try to treat those infected.

The Solidarity trial is really unique in that it enrolled so many patients from middle-income countries who are often not included in large research trials.

Also, its simple study design with minimal paperwork, online reporting and an objective, meaningful end point – death – is a model for future studies of other infectious and even non-communicable diseases in future.

Ultimately, the people benefit when we have objective data from science to guide our treatment and prophylaxis of the diseases which affect our well-being.

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