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I RESEARCH ON TREATMENTS FOR COVID-19

A. Antiviral treatments for COVID-19 – implementation issues

The virus called SARS-CoV-2 causes disease called COVID-19. In this issue of *TreatmentUpdate*, we provide summaries of research on both authorized and experimental treatments for mild-to-moderate COVID-19.

Treatment for SARS-CoV-2 infection is relatively new and it will take time for doctors, nurses and health systems to develop expertise in deploying treatment.

Antiviral drugs are not a substitute for vaccines

Note that COVID-19 treatments are not a substitute for COVID-19 vaccinations. These vaccines, particularly ones made by Moderna and Pfizer-BioNTech, are generally safe, highly effective at preventing severe illness and hospitalization, and provide longer protection than antiviral drugs. Vaccines are also much cheaper.

Cleaning and protection

People with early-stage COVID-19 tend to have high levels of SARS-CoV-2. As a result, hospitals and clinics that treat people in the early stages of COVID-19 need to take precautions to protect their staff and other patients from the risk of infection. This requires disinfecting surfaces, wearing protective equipment and, when necessary, filtering

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the air or getting fresh air into a treatment room. Furthermore, sufficient time between patient visits is needed so that rooms where patients have been treated can be cleaned. All of these precautions can add to necessary delays in treating patients.

There is another important factor to consider: The past 18 months of the pandemic have left healthcare personnel exhausted and some clinics may be short-staffed. This can result in additional delays in the administration of treatment and may impact the number of people with COVID-19 that can be treated in one day. Thus, there are many issues that can affect the ability of hospitals and clinics to deploy antibody therapies such as sotrovimab and Regen-CoV (both antibodies are detailed later in this issue of *TreatmentUpdate*).

Antiviral treatments for SARS-CoV-2

This issue of *TreatmentUpdate* covers two types of treatment for COVID-19: antibody infusions and oral antiviral drugs. At the time this issue was drafted, the only treatment that was currently available in Canada was antibodies that attack SARS-CoV-2. These are available in liquid formulation and are meant to be given as intravenous infusions. If the antibodies were swallowed, the digestive system would degrade them.

There are also oral formulations of antiviral drugs. Currently some oral treatments are in clinical trials while others are under review by regulatory authorities. These treatments – whether antibody infusions or antiviral drugs in pill form – are most effective when taken very early in the course of COVID-19.

Treatments for COVID-19 are expensive and scarce relative to the number of people who test positive for SARS-CoV-2. Most intravenous antivirals cost about US$2,100 for one dose (only one dose is needed). The experimental oral treatment, molnupiravir, is projected to cost about US$700 per course of treatment.

However, Canada's federal government has negotiated with pharmaceutical companies, signed contracts and engaged in bulk purchasing (thousands of doses) of antibody treatments for COVID-19. These must be administered intravenously. They have been distributed to Canada's provinces and territories and can be used at no cost to patients.

A path to treatment

People who may have been exposed to COVID-19 need swift, low-barrier access to SARS-CoV-2 testing. If they test positive, patients need to be assessed by an experienced healthcare professional to find out if they are at high risk for developing severe COVID-19. If they are at such risk, patients require a clear and simple path forward so that they can access treatment. People who could be prioritized for treatment might include some members of vulnerable populations (outlined below) whose ability to contain SARS-CoV-2 are weakened despite having received COVID-19 vaccines.

A closer look at some potentially vulnerable populations

The large clinical trials that took place last year with many COVID-19 vaccines did not include sufficient numbers of people with compromised immune systems to draw firm conclusions about vaccine effectiveness in these populations. As a result, teams of researchers around the world have had to do vaccine studies in such people.

Populations that could have some degree of immune compromise include the following:

- people with cancer
- people with chronic inflammatory conditions that require treatment, including arthritis, Crohn's and colitis, multiple sclerosis and psoriasis
- people with HIV
- elderly people in long-term care homes
- people with transplanted organs

Important to note

Not every person from a vulnerable population will have a poor response to COVID-19 vaccination and therefore be at high risk for developing COVID-19 should they become infected with SARS-CoV-2. For instance, emerging data from Canada, Israel and the UK suggest that two doses of COVID-19 vaccines work just as well in many HIV-positive people who are on successful HIV treatment (their viral load is suppressed) as they do in the average HIV-negative person. And many people who have the other conditions previously listed may have an adequate response to at least two COVID-19 vaccinations.

Doctors are trying to understand which members of vulnerable populations who become infected with SARS-CoV-2 will require treatment for this virus.

Implementation

Ideally, implementation of pilot projects to assess how antibody therapies can be administered across Canada would be helpful. This would allow more doctors to better understand which patients and groups might benefit from treatments for COVID-19. It could also help uncover barriers that can prevent people from accessing treatment for early COVID-19.

In high-income countries, despite the widespread availability of potent and generally safe COVID-19 vaccines, the pandemic continues, though at a much-reduced pace compared to the time before vaccines. Many people take precautions to minimize their potential exposure to SARS-CoV-2. Despite such measures and vaccinations, a minority of people may still become infected with SARS-CoV-2, and a very small proportion of these people —such as some who have the issues previously mentioned — may go on to develop serious complications of COVID-19.

Physicians can assess the potential risk of worsening COVID-19 in people who are diagnosed with early SARS-CoV-2 infection. They can then help guide members of vulnerable populations to receive treatment for early COVID-19. Such treatment has several potential benefits, as follows:

- it reduces the spread of SARS-CoV-2 to other people
- it reduces the risk of severe illness requiring hospitalization
- it reduces the risk of death

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B. About sotrovimab

Sotrovimab (formerly called VIR-7831) is an antibody that can attack SARS-CoV-2 (the virus that causes COVID-19) and cells in the body that become infected with this virus.

Sotrovimab has been developed by Vir Biotechnology in cooperation with the pharmaceutical company GlaxoSmithKline (GSK). The design for sotrovimab was based on an antibody found in the blood of a survivor of SARS-CoV-1. This virus caused a severe outbreak of pneumonia almost 20 years ago. As SARS-CoV-1 is related to SARS-CoV-2, which is the cause of the current pandemic, sotrovimab can work against both viruses.

Sotrovimab can bind or attach itself to SARS-CoV-2 and a broad range of coronaviruses (and cells that they infect in the body). By binding to SARS-CoV-2, sotrovimab can prevent this virus from infecting cells and turning them into mini-virus factories. Also, sotrovimab can bind to cells of the body that are infected by SARS-CoV-2. By binding to these cells, sotrovimab attracts cells of the immune system, which then destroy the infected cells.

Lab experiments with sotrovimab have found that this antibody is effective against major variants of SARS-CoV-2, including the following:

- alpha (B.1.1.7)
- beta (B.1.351)
- gamma (P.1)
- delta (B.1.617.2)
- kappa (B.1.617.1)
- lambda (C.37)

In Canada

The Canadian government has purchased 10,000 doses of sotrovimab. These have been distributed to Canada's provinces and territories for use. Patients are not charged for receiving sotrovimab. The drug is administered by intravenous infusion over one hour.

According to GSK Canada, sotrovimab is authorized for the following use: "The treatment of mild-to-moderate COVID-19 confirmed by direct SARS-CoV-2 viral testing, in adults and adolescents (12 years of age and older, weighing at least 40 kg) who are at high risk of progressing to hospitalization and/or death."

Furthermore, GSK states that sotrovimab has **not** been authorized for use in the following people:

- those who are hospitalized due to COVID-19
- those who require oxygen therapy due to COVID-19
- those on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity who require an increase in baseline oxygen flow rate due to COVID-19

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C. Sotrovimab in early COVID-19

Sotrovimab is a powerful antibody that attacks SARS-CoV-2 (the virus that causes COVID-19) and is meant to be used in the early stages of COVID-19 infection. Sotrovimab is available in Canada, the U.S. and some other countries.

Sotrovimab has been tested in a large randomized clinical trial called Comet-Ice. This study analyzed data from 291 people who were given sotrovimab and 292 people who were given placebo. All participants had early-stage COVID-19 and were not hospitalized at the time they entered the study.

Researchers found that sotrovimab significantly reduced (by 85%) the chance of participants requiring hospitalization for more than 24 hours or dying. No participant given sotrovimab required admittance to an intensive care unit or died. Sotrovimab was generally well tolerated with rates of adverse events similar to those seen in people who took placebo.

Researchers overseeing Comet-Ice halted further recruitment to the study because the drug was highly effective.

Study details

Researchers recruited participants from the following countries:

- Brazil
- Canada
- Spain
- United States

All participants had been diagnosed with SARS-CoV-2 infection several days prior to entering the study. All had mild-to-moderate symptoms of COVID-19.

The researchers stated that participants were considered at "high risk" for worsening symptoms of COVID-19 because of underlying conditions and/or their age (55 years and older). Researchers recruited participants between late August 2020 and early March 2021.

Participants were randomly assigned to receive one of the following intravenous interventions over the course of one hour:

- sotrovimab 500 mg
- placebo

The average profile of participants at the time they entered the study is as follows:

- age – 53 years (the proportion who were aged 65 and older was 22%; the proportion older than 70 years was 11%)
- 54% women, 46% men

- major ethno-racial groups: White – 87%; Hispanic – 63%; Black – 7%; Asian – 6% (numbers do not total 100 due to overlap of categories)
- major underlying conditions/and older age: age 55 and older – 47%; obesity – 63%; diabetes requiring medication – 23%; moderate-to-severe asthma – 16%
- common symptoms of COVID-19 – cough, muscle ache or soreness, headache, fatigue

Results

Participants who received sotrovimab were 85% less likely to require hospitalization that lasted more than 24 hours compared to participants on placebo. The distribution of participants was as follows:

- sotrovimab – 1% (3 people) required hospitalization
- placebo – 7% (21 people) required hospitalization

Short periods of hospitalization (less than 24 hours) are consistent with people going to the emergency room because of possible unstable underlying conditions. Many well-designed studies of treatments for COVID-19 focus on prolonged periods of hospitalization because those can be associated with worsening symptoms of COVID-19.

The hospitalizations that occurred in Comet-Ice were generally associated with worsening symptoms of COVID-19. The one exception was a person who had a history of intestinal obstruction prior to the study. This person required hospitalization 22 days after an infusion of sotrovimab because they developed another bout of intestinal obstruction.

In the intensive care unit

Five participants required admission to an intensive care unit, all of whom received placebo. Two of these five people were given invasive mechanical ventilation. A third person required invasive mechanical ventilation but declined this intervention and died 29 days after entering the study.

Safety

During a clinical trial, participants can develop adverse events. These require investigation to determine whether they are caused by the underlying disease process, the study drug(s) or something unrelated to the study.

The proportions of participants with adverse events were distributed as follows:

- sotrovimab – 17%
- placebo – 19%

COVID-19 is a relatively new and scary disease, so participants and their doctors were likely hypervigilant about reporting any symptoms that occurred during the study. Most adverse events that occurred in Comet-Ice were due to COVID-19. Furthermore, the distribution of adverse events that were serious was greater in people who received placebo:

- sotrovimab – 2%
- placebo – 6%

This result is not surprising, as more people who were on placebo would have become sicker over time and therefore reported more adverse effects.

One adverse effect—diarrhea—was more common in people who received sotrovimab:

- sotrovimab – 1% (6 people) reported diarrhea
- placebo – less than 1% (3 people) reported diarrhea

The diarrhea was mostly graded as mild.

Very rare side effects

The Canadian product monograph for sotrovimab states that one hospitalized person who received the drug developed anaphylaxis. Doctors injected the person with epinephrine and the person recovered. Note that sotrovimab is not meant to be used in hospitalized people with COVID-19.

Sotrovimab is derived from an antibody found in a survivor of SARS-CoV-1; this virus caused an outbreak of pneumonia almost 20 years ago. This antibody was only minimally modified into its present form (sotrovimab). It attacks a viral target. Due to these features, researchers do not expect sotrovimab to cause rare side effects.

About infusions in general

Antibody-based therapies are routinely used to treat many conditions, including arthritis, some forms of cancer, Crohn's and colitis, and psoriasis. Doctors and nurses have found that reactions to infusions of these antibodies are relatively common but are generally mild to moderate in people with cancer and inflammatory conditions. General symptoms that can be associated with infusions of antibodies include the following:

- headache
- fatigue
- redness
- nausea
- fever
- pain

These symptoms usually resolve within hours to a day after infusion.

In very rare cases, more serious symptoms, such as anaphylaxis, can occur.

Sotrovimab and infusion-related reactions

The proportion of participants in Comet-Ice who developed infusion-related reactions were 1% among those who received sotrovimab and 1% in those who received placebo. These reactions appeared during or after infusion, were generally graded as mild and resolved within 24 hours. They included the following:

- fever
- chills
- dizziness
- rash
- itchy skin

One of the people who received sotrovimab had an infusion-related reaction of moderate intensity—shortness of breath.

Bear in mind

The data from Comet-Ice strongly suggest that sotrovimab can protect many people with mild-to-moderate COVID-19 from deteriorating. Sotrovimab was generally well tolerated.

For the future

Preliminary results from another clinical trial called Comet-Tail have been issued by GSK and ViiV through a press release. These preliminary results suggest that sotrovimab administered via intramuscular injection is not less effective than when given intravenously. The companies are planning or initiating discussions with regulatory authorities about authorizing intramuscular administration of sotrovimab in Canada, the European Union and the U.S.

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D. About Regen-CoV

Regen-CoV is the name given to a combination of the following two antibodies:

- casirivimab
- imdevimab

The antibodies in Regen-CoV can bind or attach themselves to SARS-CoV-2. By binding to SARS-CoV-2, the antibodies in Regen-CoV can prevent this virus from infecting cells and turning them into mini-virus factories. Also, the antibodies in Regen-CoV can bind to cells of the body that are infected by SARS-CoV-2. By binding to these cells, the antibodies attract cells of the immune system, which then destroy the infected cells.

In lab experiments with cells and SARS-CoV-2, the antibodies in Regen-CoV, when used in

combination, are effective against a range of variants of the virus, including the following:

- alpha (B.1.1.7)
- beta (B.1.351)
- delta (B.1.617.2)
- gamma (P.1)

These antibodies attack SARS-CoV-2 in lab experiments and in clinical trials with people. The antibodies were developed by Regeneron Pharmaceuticals in cooperation with Hoffmann-La Roche. The latter pharmaceutical company is the distributor of Regen-CoV in Canada and other countries. According to Roche, the combination of antibodies in Regen-CoV are authorized for use in Canada for "the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19), confirmed by direct SARS-CoV-2 viral testing, in adults and adolescents (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to hospitalization and/or death."

Roche states that the antibodies in Regen-CoV are **not** meant to be used in the following people:

- those who are hospitalized due to COVID-19
- those who require oxygen therapy due to COVID-19
- those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity who require an increase in baseline oxygen flow rate due to COVID-19

The antibodies in Regen-CoV are meant to be administered together via intravenous infusion over the course of one hour. It is possible that in the future Health Canada may approve an additional way of administering Regen-CoV—such as injecting the antibodies just under the skin (subcutaneous injection).

The Canadian government has negotiated the price of Regen-CoV and bulk purchased many doses. These have been distributed to provinces and territories and are available at no cost to the patient.

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E. Regen-CoV in early COVID-19

Regen-CoV is the name given to a combination of the following two antibodies:

- casirivimab
- imdevimab

These antibodies attack SARS-CoV-2 (the virus that causes COVID-19) and are used as a treatment in some people in the early stages of COVID-19. Regen-CoV is given via intravenous infusion over the course of one hour.

Regen-CoV has been tested in multiple clinical trials. In a phase III trial, participants with mild-to-moderate COVID-19 were randomly assigned to receive a single infusion of different doses of Regen-CoV (1,200 mg or 2,400 mg) or placebo. As the 2,400-mg dose is now the authorized dose in Canada, we will focus on results from participants who received either that dose or placebo.

Researchers found that Regen-CoV reduced the risk of hospitalization or death by 70% compared to placebo. Participants who received Regen-CoV spent less time in hospital (10 days vs. 14 days) compared to participants on placebo. Regen-CoV also reduced the amount of virus in people given the drug. Side effects were not common.

Study details

Participants were enrolled between late September 2020 and mid-January 2021. Their average profile upon study entry was as follows:

- age – 50 years (14% were 65 years or older)
- 52% women, 48% men
- major ethno-racial groups: White – 85%; Hispanic – 35%; Black- 5%; Asian – 4% (numbers do not total 100 due to overlap of categories)

- BMI (body mass index) – 31 kg/m^2
- common underlying conditions – obesity (58%), cardiovascular disease (36%)

Results

Hospitalization and/or death are commonly assessed outcomes in large studies of treatments for COVID-19. The following proportions of participants were hospitalized and/or died during the study:

- Regen-CoV – 1.3% (18 of 1,355 participants)
- placebo – 4.6% (62 of 1,341 participants)

Statistical analysis found that Regen-CoV reduced the risk of hospitalization or death by 71%.

Deaths were distributed as follows:

- Regen-CoV – 1 person
- placebo – 3 people

Regen-Cov's ability to reduce the risk of hospitalization or death became apparent between one and three days after participants received the antibodies.

Safety

During a clinical trial, participants can develop adverse events. These require investigation to determine whether they are caused by the underlying disease process, the study drug(s) or something unrelated to the study.

Participants who received placebo were more likely to have adverse events (4%) than people who received Regen-CoV (1.3%). Most of these adverse events were related to COVID-19.

About antibody infusions in general

Antibody-based therapies are routinely used to treat many conditions, including arthritis, some forms of cancer, Crohn's and colitis, and psoriasis. Doctors and nurses have found that reactions to infusions of these antibodies are relatively common but are generally mild to moderate in people with cancer and inflammatory conditions. General symptoms that can be associated with infusions of antibodies include the following:

- headache
- fatigue
- redness
- nausea
- fever
- pain

These symptoms usually resolve within hours to a day after infusion.

In very rare cases, more serious symptoms, such as anaphylaxis, can occur.

Infusion-related reactions and Regen-CoV

Infusion-related adverse events were generally mild and resolved within a day. In a small number of people, infusion-related adverse events were graded as moderate or of greater severity:

- Regen-CoV – 2 people
- placebo – 0 people

These proportions of people represent less than 1% of participants who received Regen-CoV or placebo.

Regen-CoV has been tested in several thousand people in clinical trials. There have been rare cases of hypersensitivity and anaphylactic reactions to the drug.

Bear in mind

The antibodies in Regen-CoV are potent when used in people with early SARS-CoV-2 infection who have mild-to-moderate symptoms. Regen-CoV was generally well tolerated in this study.

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2. Austin D. Why do placebos work? Scientists identify key brain pathway. *Science*. 27 October 2021

F. Molnupiravir – the first antiviral pill for early COVID-19

Molnupiravir (also known as Lagevrio, MK-4482, formerly EIDD-2801) is a drug under development by the pharmaceutical companies Merck and Ridgeback Biotherapeutics. Molnupiravir works by mimicking a molecule needed by a coronavirus enzyme (called RNA polymerase). When molnupiravir is incorporated into a copy of SARS-CoV-2 it causes the resulting virus to be defective. As a result, cells infected with SARS-CoV-2 (the virus that causes COVID-19) produce copies of this virus that are not functional.

Antiviral therapies that are currently authorized for use against SARS-CoV-2 must be given via intravenous infusion. This is cumbersome and time consuming. It also requires the help of healthcare personnel. Molnupiravir's advantage is that it can be taken in pill form.

The Move-Out study

Merck conducted a randomized, double-blind, placebo-controlled study of molnupiravir in 1,433 adults with mild-to-moderate COVID-19. This study was called Move-Out. None of the participants were hospitalized when they entered the study. Molnupiravir was taken at a dose of 800 mg every 12 hours for five consecutive days. The study took place in many countries, including Canada. Merck has released preliminary information in a press release about the study.

Results

Molnupiravir reduced the risk of hospitalization or death by about 30% over the course of one month after people started taking it. The proportions of participants who were hospitalized or died in the study were as follows:

- molnupiravir – 6.8% (48 of 709 people)
- placebo – 9.7% (68 of 699)

One of the participants who received molnupiravir died, while nine deaths occurred among people who received placebo.

Safety

As in earlier clinical trials, molnupiravir was generally well tolerated. Adverse events that were related to the study drug or placebo were distributed as follows:

- molnupiravir – 12%
- placebo – 11%

Molnupiravir was effective in participants with a range of variants of SARS-CoV-2, including the following:

- gamma (P.1)
- delta (B.1.617.2)
- mu (B.1.621, B.1.621.1)

As molnupiravir works against an essential viral enzyme, there is no reason why it should not work against the major variants of SARS-CoV-2.

An independent data monitoring committee performed an interim analysis while the study was ongoing and determined that molnupiravir was clearly more effective than placebo. The committee then recommended that further recruitment be halted because of these positive results.

Regulatory agencies

Merck is in discussion with regulatory agencies in many countries and regions. It has submitted a dossier on the drug, seeking authorization for molnupiravir for the treatment of mild-to-moderate COVID-19 in at least Canada, the European Union, and the U.S..

Why the excitement?

There has been a lot of media coverage about the results of the Move-Out study. Although clinical trials of antibody therapy (such as sotrovimab and Regen-CoV) have found that they are highly effective, molnupiravir appears to be somewhat less effective (to be fair, no clinical trial has directly compared molnupiravir against antibody therapy). Yet, there is excitement in medical circles about the looming authorization of molnupiravir because its advantage over currently authorized treatments is that it comes in pill form. This means that, in theory, it should be easier for people to access and take compared to antibody therapies that require an intravenous infusion and the assistance

of healthcare personnel. Like other antivirals, molnupiravir works best against SARS-CoV-2 when used early in the course of disease caused by this virus.

Severity of illness is important

Merck has licensed some companies in India to make generic copies of molnupiravir so it can be sold to people in low- and middle-income countries. The Indian pharmaceutical companies Aurobindo Pharma and MSN Laboratories conducted a clinical trial of generic molnupiravir in people with COVID-19 who had moderate symptoms of disease. It did not work.

Merck notes these companies defined "moderate" differently than Merck did. Merck used a definition of "moderate" COVID-19 defined by the U.S. Food and Drug Administration (FDA). Patients in the generic study were sicker than those in Merck's Move-Out study; they had lower levels of oxygen in their blood, suggestive of severe lung injury. If such a trial had been conducted in the U.S., the patients would likely have been classed as "severely" ill with COVID-19.

Molnupiravir is not meant for people who are severely ill with COVID-19. Indeed, Merck previously halted a clinical trial of molnupiravir in the U.S. in people with COVID-19 who required hospitalization. In the latter stages of COVID-19, inflammation causes serious complications. Drugs with potent anti-inflammatory activity are likely better candidates for consideration in clinical trials of people in late-stage COVID-19.

Mutation spotlight

Molnupiravir works by mimicking a natural molecule used by an enzyme needed by SARS-CoV-2-infected cells. As molnupiravir fools the viral enzyme RNA polymerase into using it rather than a normal molecule there are concerns that it could, in theory, interfere with human RNA molecules used by healthy cells, perhaps leading to an increased risk for mutations in cells. However, healthy cells have multiple mechanisms to screen for and correct potential mutations in their genetic material. Also, according to scientists associated with the development of molnupiravir, tests conducted so far have not found any increased risk for mutations in either healthy human cells or in animals exposed to very high doses of the drug for prolonged periods. However, Merck needs to make public the data that it has accumulated on molnupiravir's potential effect on healthy cells in people. Merck also needs to provide guidance to physicians about the safety of molnupiravir during pregnancy.

Understanding treatment failure

As mentioned earlier, in the Move-Out study the proportions of participants who required hospitalization or died were distributed as follows:

- molnupiravir – 6.8% (48 of 709 people)
- placebo – 9.7% (68 of 699 people)

Merck needs to do an analysis of what happened to those 6.8% of people who deteriorated despite having received molnupiravir. There may be at least two reasons for treatment failure:

- the severity of their underlying conditions
- the development of SARS-CoV-2 that is resistant to molnupiravir

Uncovering the reasons for deterioration in people who received molnupiravir could help inform the deployment of this drug in the future.

Bear in mind

Molnupiravir is a very promising drug. However, it is just one drug (monotherapy). In the case of other viral infections such as HIV and hepatitis C, combination therapy is routinely used. Therefore, it is possible that molnupiravir may be more effective when combined with other oral drugs that show promise against SARS-CoV-2 infection, such as Paxlovid (mentioned later in this issue of *TreatmentUpdate*). However, laboratory experiments with cells and then, if these are encouraging, experiments with animals will first be necessary. Once such experiments reveal the preliminary safety of potential combinations, regulatory agencies can then consider applications for studies of combination therapy for SARS-CoV-2 in people. Laboratory experiments could also explore the effect of molnupiravir in combination with the antidepressant fluvoxamine (Luvox). Reports about fluvoxamine appear later in this issue of *TreatmentUpdate*.

Given the favourable publicity about molnupiravir's effectiveness and ease of use, it is likely that demand for this drug will be high in many countries. Merck has committed to making millions of doses of the drug in the short-term. However, given the high demand, it is possible that shortages of molnupiravir may occur over the next several months. It is therefore likely that access to molnupiravir will be rationed during this time.

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G. Molnupiravir as post-exposure prophylaxis against COVID-19

The virus SARS-CoV-2, which causes COVID-19, is highly transmissible, especially the variant called Delta. This variant is common in Canada, the U.S., Europe and other parts of the world.

People who have been in close contact with someone who has recently been diagnosed with SARS-CoV-2 infection, such as people living in the same household, are at high risk for also becoming infected with SARS-CoV-2.

Preventing infection and illness after exposure

Taking medicine to prevent an infection (and subsequent illness) after exposure to a virus is called post-exposure prophylaxis (PEP).

The pharmaceutical company Merck is conducting a randomized, placebo-controlled trial of molnupiravir (Lagevrio, MK-4482) called Move-Ahead. This study will recruit adults who are living in the same household as someone diagnosed with SARS-CoV-2 infection. Participants are expected to have at least one sign or symptom of COVID-19 but not for more than five days. Molnupiravir will be given at a dose of 800 mg every 12 hours for five consecutive days. Placebo pills will be taken at the same schedule.

The Move-Ahead Study plans to recruit about 1,300 people and will take place in many countries and regions, including Latin America, France, Japan, South Africa, Spain, Turkey and the U.S.

Hopefully, results from this study will become available later in 2021 or in early 2022.

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Merck. Merck and Ridgeback Biotherapeutics announce initiation of pivotal phase 3 Move-Ahead Study evaluating molnupiravir for post-exposure prophylaxis of COVID-19 infection. *Press release*. 1 September 2021.

H. Fluvoxamine – background and a preliminary study

For at least the past 20 years, some scientists have been exploring the intersection of inflammation, depressive illness and the effect of antidepressants. Some research suggests that excess inflammation may contribute to many chronic conditions, including depression.

Antidepressants work by helping brain cells build up the chemical signals— neurotransmitters— that they use to communicate. However, emerging research suggests that antidepressants can also have modest anti-inflammatory activity. This may, at least in part, account for their beneficial effects.

Fluvoxamine belongs to a class of antidepressants called SSRIs (selective serotonin reuptake inhibitors). In addition to its anti-inflammatory activity, it may also reduce the risk of excessive blood clots.

In COVID-19

Infection with SARS-CoV-2, the virus that causes COVID-19, can cause mild or even no symptoms in some people. However, in other infected people, proteins produced by cells infected with SARS-CoV-2 can impair the functioning of the immune system. This can incite excessive levels of inflammation. If this inflammation is not contained, the immune system can degrade. Also, because cells of the immune system patrol different parts of the body, they can release inflammatory chemical messengers that trigger inflammation in tissues. Altogether, the inflammation caused by SARS-CoV-2 infection can lead to serious tissue injury in susceptible people.

Therefore, researchers are testing drugs that have anti-inflammatory activity in people who have symptoms of COVID-19. One of these drugs is fluvoxamine. Lab experiments with fluvoxamine and SARS-CoV-2 suggest that this drug has potential antiviral and anti-inflammatory effects. Fluvoxamine may also interfere with the ability of SARS-CoV-2-infected cells to produce new copies of this virus.

These lab experiments are interesting. However, they cannot reproduce the complexity of the human body with its multiple organ systems that interact with each other. Many compounds that appear promising in lab experiments with cells or animals subsequently fail to show benefit in studies with people. This failure is normal in the course of drug development. It also underscores the need for well-designed clinical trials so that the potential benefits of experimental drugs can be explored.

Research is planned or underway with fluvoxamine in people with early-stage COVID-19 in the U.S. and at McGill University in Montreal.

A preliminary study

A small randomized, placebo-controlled study of fluvoxamine was conducted in adults in the U.S. who were not hospitalized. Participants were recruited from Eastern Missouri and southern Illinois.

Upon entering the study, participants had recently been infected with SARS-CoV-2 and did not require hospitalization. Common symptoms of COVID-19 in participants included fatigue and loss of sense of smell. Participants were randomly assigned to receive one of the following interventions for 15 consecutive days:

- fluvoxamine 100 mg three times daily – 80 people
- placebo three times daily – 72 people

The study was made up of 72% women and 28% men and the average age of participants was 46 years old.

Results

None of the participants who took fluvoxamine deteriorated. In contrast, 8% of participants given placebo deteriorated. For the purposes of this study, researchers defined deterioration as any of the following:

- shortness of breath
- shortness of breath that required hospitalization
- pneumonia that required hospitalization

Four out of six participants who deteriorated required hospitalization, but none of them died.

Bear in mind

This study was similar to a well-designed phase II study. It was small and there were not many people who deteriorated. Therefore, its findings should be viewed as promising but preliminary. The results of this study could be used to design a bigger trial to better understand the effects of fluvoxamine in early stage COVID-19. Our next report covers a large, well-designed study of fluvoxamine in COVID-19.

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I. Fluvoxamine – generic antidepressant looks very promising in treating early COVID

Researchers in Australia, Brazil, Canada and the U.S. designed and conducted a randomized, placebo-controlled study of fluvoxamine, 100 mg twice daily, in people with early-stage COVID-19. The trial was called Together. Participants had at least one underlying condition that heightened their risk for deteriorating. In Together, researchers randomly assigned 3,238 participants to receive one of the following interventions:

- fluvoxamine – 739 people
- placebo – 733 people
- other experimental drugs – 1,766 people

Although Together is testing different interventions, the latest analysis from this study focused on the comparison between people who received fluvoxamine or placebo. The researchers found that participants who received fluvoxamine were significantly less likely to deteriorate than people who received placebo; that is, they were less likely to require a prolonged stay in the emergency room of a hospital or be admitted to a hospital. The Together study was well designed, and its findings may have implications for the medical management of people with early-stage COVID-19.

Study details

The study began in mid-January 2021. Participants were recruited at 11 clinics in Brazil.

Participants were adults who had recent onset of symptoms consistent with acute COVID-19. They underwent screening and tested positive for SARS-CoV-2. All participants had at least one underlying condition or issue that has been associated with an increased risk for developing complications associated with COVID-19. According to the researchers, these underlying conditions/issues included the following:

- type 2 diabetes
- pulmonary hypertension that required treatment
- heart disease
- lung disease
- obesity
- smoking
- age greater than 50 years

Additionally, some participants had medical interventions that weakened their immune systems, such as the following:

- use of immunosuppressive drugs because of organ transplantation
- severe kidney disease or the need for dialysis
- use of corticosteroids
- undergoing treatment for cancer

All participants were not vaccinated against COVID-19.

About key clinical trial results

Many clinical trials are designed to assess the effects of drugs on an infection or disease process. When designing a clinical trials, statisticians and scientists meet beforehand to choose the key results or "endpoints" that the trials will seek to measure.

For instance, some clinical trials assess the length of time people survive after they were given an intervention – drug A or drug B. In such a case, the endpoint was length of survival. Other trials might assess how many people survived after given different interventions. In this case, the endpoint would be the proportions of people surviving.

In Together

The main endpoint of the Together study was the proportion of participants who required one of the following:

- a prolonged stay (more than six hours) in a hospital emergency room
- hospitalization because of worsening symptoms of COVID-19 and/or its complications within 28 days of entering the study

According to the researchers, "all participants received [the] usual standard of care for COVID-19" at local public health facilities (unless they were hospitalized). Such care included the provision of drugs to reduce fever, and, if doctors suspected that bacterial pneumonia had developed, antibiotics could be prescribed.

The average profile of participants at the time they entered the study is as follows:

- age – 50 years
- 58% women, 42% men
- major ethno-racial groups: mixed – 95%; White – 1%; Black – 1%
- most common underlying conditions – obesity, type 2 diabetes and high blood pressure

Results

In August 2021, the study's independent data safety monitoring committee recommended that researchers stop recruiting and randomizing people to receive fluvoxamine. Other sub-studies within Together continue to assess other potential treatments. This decision to stop assigning people to receive fluvoxamine arose because, statistically, the effect of this drug had been found superior to placebo. That is, people who received fluvoxamine were at reduced risk for an extended emergency room visit or hospitalization due to COVID-19. The proportions of participants who underwent an extended emergency room visit or who were hospitalized due to COVID-19 were distributed as follows:

- fluvoxamine – 11%
- placebo – 16%

The benefit from fluvoxamine was similar regardless of the following:

- age
- gender
- number of days since the onset of COVID-19 symptoms
- underlying conditions that increase a person's risk for severe COVID-19
- other health conditions
- whether a person smoked

The proportions of people who died were as follows:

- fluvoxamine – 2%
- placebo – 3%

Fluvoxamine had no impact on any of the following:

- clearance of SARS-CoV-2 after one week
- number of days hospitalized
- risk of death
- number of days on mechanical ventilation
- time to recovery from COVID-19

Vaccination

When the study began, COVID-19 vaccines were not available in Brazil. As the study progressed, the distribution of vaccines occurred. According to the researchers, "only 6% of participants reported at least one dose of COVID-19 vaccine at the end of the trial." The researchers stated that this likely had "minimal effect" on the study's findings.

Adverse events and adherence

Statistical analysis found no difference in the severity of adverse events reported by participants who took fluvoxamine vs. placebo. However, more participants on fluvoxamine (11%) than placebo (8%) prematurely stopped taking these interventions because of issues of tolerability.

The researchers also found that participants who had what they termed "optimal" adherence to fluvoxamine were significantly less likely to suffer deterioration due to COVID-19.

Other studies

The results from Together are in line with an earlier randomized but smaller study in the U.S. that used a higher dose of fluvoxamine—100 mg three times daily for 15 consecutive days. Participants in that study were generally at lower risk for deterioration than those in the Brazilian study.

A larger study in France reviewed hospital records of 7,230 adults with COVID-19. Researchers noted that this group there were 345 people who initiated treatment with antidepressants within 48 hours of hospitalization. The researchers found that the risk of serious complications or death due to COVID-19 was significantly reduced among these 345 people. Among these 345 people a majority were taking antidepressants similar to fluvoxamine.

Advantages and disadvantages of fluvoxamine

Fluvoxamine has at least the following advantages:

- a long record of generally safe use in the pre-COVID-19 era
- can be taken in pill form
- relatively inexpensive
- widely available

However, fluvoxamine, like many antidepressants, has the potential to interact with some other medicines. Many people at high risk for COVID-19 have underlying conditions that require treatment. If fluvoxamine were to be prescribed to people who are taking other medicines, consultation with a pharmacist would be necessary to reduce the risk of potential drug interactions.

For the future

The results from the Together study are exciting. In the relatively short history of the COVID-19 pandemic, it has been unusual for an existing medicine that has a different use to be successfully repurposed in a clinical trial against SARS-CoV-2. Perhaps additional clinical trials could be done with a combination of fluvoxamine and emerging oral antiviral drugs for the treatment of early COVID-19, such as molnupiravir or Paxlovid.

An important question for the future is: Was the effect of fluvoxamine in the Together study due to this particular drug or would a similar effect be seen with other antidepressants chemically related to fluvoxamine? Large, randomized clinical trials would be needed to answer this question.

Bear in mind

The Together researchers state that there have been more than 2,800 registered randomized clinical trials for assessing potential interventions against COVID-19. However, according these researchers, results from less than 300 have been reported. Other researchers have catalogued that many COVID-19 clinical trials have not been well designed, which makes a clear interpretation of their results difficult. In a situation where there are limited resources and time is of the essence, implementing poorly designed clinical trials is not good practice.

The Together trial should serve as an inspiration for other scientists, showing that it is possible to conduct a well-designed clinical trial that leads to robust conclusions even in the midst of a global health crisis.

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J. Why many drugs fail their development pathway

Readers should be aware that many drugs fail to achieve the therapeutic hopes of the researchers developing them. This is normal, as drug development is an enterprise with a high risk of failure. A first step in the development process might be a computer simulation of how a potential drug might interact with a virus-infected cell. If the simulation suggests promise, then the next step might be lab experiments with cells, viruses and the drug in question.

Even if a simulation was promising, a drug might prove to have unwanted effects in lab experiments or there may be unexpected findings. For example, a computer simulation might first suggest that a drug could be an effective antiviral against SARS-CoV-2. However, lab tests could reveal that the concentrations of the drug required to suppress this virus are far higher than what can safely be achieved in people.

Even if a drug advances past initial test tube studies, it then has to be tested in animals. Again, unexpected effects could occur, such as unforeseen toxicity.

Having passed all these stages, the drug may then be a candidate for preliminary safety assessments in people (a phase I clinical trial). Here again, drugs can fail because laboratory and animal experiments may not replicate the identical symptoms or effects a germ can have on people.

Even if a drug passes phase I in people, it is possible that it will fail in subsequent phases because of other reasons. The organs and systems in the human body are interconnected and interact in ways that are not always captured by laboratory and animal experiments.

Many scientists are aware of these issues and have been trying to find ways of increasing the likelihood of success for candidate drugs that enter the development pathway. Several analyses have found that rates of success for candidate drugs are generally higher today than they were decades ago. Despite that good news, many candidate drugs will encounter challenges in their development process.

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K. Other oral antivirals under development for COVID-19

Earlier in this issue of *TreatmentUpdate*, we presented some information on molnupiravir. This drug is likely to become the first potent oral antiviral drug for the treatment of mild-to-moderate COVID-19. It is also possible that molnupiravir could become the first oral drug to be used as a

form of post-exposure prophylaxis (PEP). If that happens, people who have been in close contact with someone diagnosed with COVID-19, such as people who live in the same household, may be prescribed molnupiravir in the future to prevent the onset or worsening of COVID-19. A clinical trial to explore this issue is underway.

Other oral antivirals for SARS-CoV-2

Here are summaries of other oral antiviral drugs in development for the potential treatment of SARS-CoV-2:

Paxlovid (**PF-07321332**)
This antiviral is being developed by Pfizer. Paxlovid is a protease inhibitor that works against an enzyme of SARS-CoV-2 called main protease. Pfizer has several clinical trials of Paxlovid + a low dose of an older drug called ritonavir. The purpose of ritonavir is to slow the breakdown of Paxlovid and/or to boost levels of Paxlovid in the body. Studies underway with the Pfizer protease inhibitor will assess its ability to prevent worsening disease in people (with or without underlying conditions) who have early COVID-19. Preliminary analysis of the clinical trial suggests that the combination of Paxlovid + ritonavir is highly effective in people with mild to moderate COVID-19. Pfizer is also testing the combination of Paxlovid + ritonavir in people who live in the same household as someone diagnosed with COVID-19.

In the early to mid-1990s, ritonavir was tested as a treatment for HIV. Ritonavir works by interfering with an enzyme (called protease) used by HIV. Although ritonavir was lifesaving when used as part of combination treatment in people with HIV, it caused severe side effects at high doses, particularly diarrhea and nausea. In the late 1990s, infectious disease doctors repurposed ritonavir as a booster for some HIV drugs. In such cases, it was used at lower doses and was better tolerated by some people.

However, ritonavir also has many potential drug interactions—it can raise levels of other drugs, causing side effects or intensifying pre-existing side effects. Ritonavir can also lower levels of other drugs, increasing the risk of treatment failure for other drugs. Therefore, if ritonavir is used in people who are taking other medicines, particularly for underlying conditions, consultation with a pharmacist is important.

EDP-235
This antiviral is being developed by Enanta Pharmaceuticals. EDP-235 works by interfering with the main protease of SARS-CoV-2. This drug achieves high concentrations in the lungs in animal experiments and is effective against main protease from different variants of SARS-CoV-2. A phase I clinical trial is expected to start in early 2022.

S-217622
This antiviral is being developed by Shionogi Pharma. Compound S-217622 is an inhibitor of the SARS-CoV-2 main protease and is effective in experiments with animals. S-217622 is in a phase II/III clinical trial in participants with SARS-CoV-2 infection who have no or mild symptoms. The drug will be given once daily for five consecutive days.

Ensovibep (**MP0420**)
This antiviral is being developed by a company called Molecular Partners in cooperation with the pharmaceutical company Novartis. Ensovibep belongs to a class of compounds called DARPins (designed ankyrin repeat proteins). DARPins are small molecules that can mimic some of the function of antibodies. As DARPins are much smaller, they can reach more tissues. Molecular Partners has developed a DARPin that can simultaneously attach to three different parts of SARS-CoV-2. This property is useful, as the virus can change its structure from time to time, making it difficult for antibodies to attack SARS-CoV-2. By simultaneously binding to three different parts of the virus, researchers hope that ensovibep will be effective against a broad range of variants of SARS-CoV-2 and more effective at stopping the virus from infecting cells. The drug is in several clinical trials, including one phase II/III study.

PBI-0451
This antiviral is being developed by Pardes Biosciences. Compound PBI-0451 is a protease inhibitor that works against SARS-CoV-2 main protease. A randomized, double-blind, placebo-controlled phase I study is underway.

AT-527 (**also known as RO7496998**)
This antiviral is being developed by Atea Pharmaceuticals in cooperation with Hoffmann-La Roche. The drug has potent antiviral activity in lab experiments with cells and SARS-CoV-2. It works by interacting with an enzyme used by SARS-CoV-2-infected cells called RNA polymerase. In a phase II study called Moonsong, Atea reported

disappointing results with AT-527 vs. placebo in participants with COVID-19. Most participants in Moonsong had mild symptoms and underlying conditions were not common. The drug might be more effective in patients who are sicker. Atea and Roche are trying to understand the results of Moonsong and how they may be used to influence the design of a phase III clinical trial called Morningsky.

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