TreatmentUpdate 237

Vol. 32, No. 3 · July 2020

Available online at
www.catie.ca/en/treatmentupdate

Contents

I ANTIVIRAL AGENTS FOR COVID-19

A. Problems interpreting some COVID-19 clinical trials 1

B. Remdesivir—background and safety 2

C. Preliminary results from a placebo-controlled study of remdesivir 3

D. Remdesivir moves forward 5

E. Recovery trial finds cheap steroid can reduce deaths from COVID-19 6

F. Kaletra—from HIV to SARS to COVID-19 6

G. Triple therapy with interferon-beta + Kaletra + ribavirin 8

H. EIDD-2801 enters clinical trials 9

I. Could Pepcid help people with COVID-19? 10

J. Does interferon-lambda have potential in COVID-19? 11

K. Recovery trial finds no clinical benefit for hydroxychloroquine in COVID-19 12

L. Chloroquine, hydroxychloroquine and clinical trial issues in COVID-19 12

M. Can hydroxychloroquine prevent COVID-19? 14

I ANTIVIRAL AGENTS FOR COVID-19

A. Problems interpreting some COVID-19 clinical trials

As the COVID-19 pandemic began sweeping around the world, many clinical trials were initiated to test drugs that were already approved for one condition (usually to treat viral infections or inflammatory diseases) for treating COVID-19.

Given the emergency nature of the pandemic, many of the initial trials were developed hastily and implemented quickly. This has led to trials that do not provide definitive answers to important biomedical questions, particularly those concerning the treatment of COVID-19.

A team of scientists at Johns Hopkins University has reviewed 201 COVID-19 clinical trials that were planned or implemented in the first three months of the pandemic. They found that many trials

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"lacked features to optimize their scientific value." Specifically, they noted the following:

> "Because one-third of trials exclude clinical endpoints, nearly one half are designed to enrol fewer than 100 patients and two-thirds are open label, many of these studies are likely to yield only preliminary evidence of a given treatment's safety and effectiveness against COVID-19."

The scientists further stated:

> "Our findings provide reason for both optimism and caution. Many registered COVID-19 trials have been designed expediently, and while case series and single-arm trials have value and may provide early signals, randomised study designs provide higher quality evidence and will maximise chances for finding effective and safe treatments during this wave of the pandemic. These trial designs, however, need adequate funding as well as scientific leadership, especially as frontline clinicians are tasked with saving lives. In addition, it is important that surrogate outcomes, biomarkers or clinical scales are strongly and directly linked to what matters most for providers and patients—improved chances of recovery from COVID-19."

Due to these and other issues, while there are many potential treatments for COVID-19 in clinical trials, it may take some time before definitive results about such therapies emerge. In this issue of *TreatmentUpdate* we review several leading potential treatments. A future issue will review other potential interventions for COVID-19, including ones that affect the immune system.

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B. Remdesivir—background and safety

Remdesivir (GS-5734) was originally developed for the potential treatment of Ebola virus infection. However, in clinical trials it was not as effective as other treatments. As remdesivir has antiviral activity against many RNA viruses, it has been repurposed against SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19).

Remdesivir is a nucleotide analogue and is classed as a "prodrug" by medicinal chemists. Prodrugs do not inherently have antiviral activity. They must enter a cell and be activated by enzymes within that cell. Once the activation process is complete, the activated form of remdesivir tends to remain inside a cell for at least a day.

The viral assembly line

When viruses such as SARS-CoV-2 infect a cell, they hijack the operation of the cell. In effect, viruses turn cells into mini-virus factories, forcing them to churn out copies of SARS-CoV-2. Copies of viruses are assembled in a series of steps analogous to the assembly line in factories. To an infected cell, remdesivir looks like a building block that it would use to make copies of SARS-CoV-2. However, once remdesivir enters and becomes part of the viral assembly line, it causes problems and the cell's ability to make copies of the virus is compromised.

Entering the body

Remdesivir must be given by intravenous infusion. If remdesivir is taken orally, it is broken down by the liver.

Potential drug interactions

In theory, remdesivir could interact with several enzymes in the liver that break down other medicines. These enzymes include the following:

- CYP2C8
- CYP2D6
- CYP3A4

However, after intravenous infusion, remdesivir rapidly enters cells. Its developer, Gilead Sciences, does not expect it to have significant drug interactions.

The U.S. Food and Drug Administration (FDA) cautions that doctors should not co-prescribe chloroquine or hydroxychloroquine to people who are taking remdesivir, as these other drugs could reduce the antiviral effect of remdesivir. The FDA does not know of actual cases of such an interaction but warns that they could occur.

Another potential drug interaction is between remdesivir and the drug metformin, which is used to help control blood sugar. This potential interaction also needs to be better understood.

Toxicity in animals

Laboratory experiments with cells and animals are a first step to try to explore the potential toxicity of a drug. The results of these experiments can serve as a guide as to what might happen in people with a drug. However, what occurs in animals does not always occur in people.

Remdesivir does not appear to have the potential to cause mutations in cells. However, lab experiments with liver cells suggest that remdesivir can cause temporary liver injury. Further information on the impact of remdesivir on the liver appears below.

Phase I studies

At least four phase I studies (these focus on safety) have been done with 138 healthy human volunteers. In these studies, different doses of remdesivir were administered, ranging from 3 to 225 mg in a single intravenous dose. Multiple doses of 150 mg given intravenously once daily for seven or 14 days were also administered. In some of these people, remdesivir caused a temporary increase in liver enzymes.

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C. Preliminary results from a placebo-controlled study of remdesivir

Researchers in North America, Europe and Asia conducted a randomized, placebo-controlled study of remdesivir in adults hospitalized with COVID-19. Analysis found that, overall, the time needed for participants to recover was shorter in people who received remdesivir (11 days) vs. placebo (15 days). These results were statistically significant. After 14 days of monitoring, 7% of people given remdesivir had died vs. 12% who were given placebo. However, this difference in survival was not statistically significant.

Study details

Researchers randomly assigned 531 people to receive remdesivir and 522 to receive placebo. Both interventions were given intravenously once daily. Remdesivir was given at a dose of 200 mg on day one, followed by subsequent doses of 100 mg daily for nine consecutive days.

The average profile of participants upon entering the study was as follows:

- age – 59 years
- 64% men, 36% women
- common underlying conditions: higher-than-normal blood pressure – 50%; obesity – 37%; type 2 diabetes – 30%
- proportion of participants with at least one underlying condition – 27%; proportion of participants with two or more underlying conditions – 52%

Results

Overall, participants who received remdesivir recovered faster—11 days vs. 15 days in people who received placebo. This was statistically significant. Although fewer people who received remdesivir died (7%) compared to people who received placebo (12%), this difference was not statistically significant. In the interim analysis released to date, data were collected for only the first 14 days of the study. Further monitoring is ongoing, and participants will be monitored for up to 28 days.

Adverse events

The term *adverse events* encompasses all unfortunate incidents that can occur during a clinical trial, including drug side effects, symptoms related to the underlying disease process and even issues unrelated to the study, such as accidents.

According to the study team, there was a range of problems that were "slightly more common among patients in the placebo group," including the following:

- acute respiratory failure
- severely low blood pressure
- viral pneumonia
- acute kidney injury

Serious and/or life-threatening adverse events occurred in 156 people distributed as follows:

- remdesivir – 29%
- placebo – 33%

According to the study team, the distribution of adverse events was generally similar between remdesivir and placebo groups, with the exception of the following:

Anemia or decreased hemoglobin
- remdesivir – 8%
- placebo – 9%

Acute kidney injury and other kidney-related issues
- remdesivir – 7.4%
- placebo – 7.3%

Fever
- remdesivir – 5%
- placebo – 3%

Higher-than-normal levels of blood sugar
- remdesivir – 4%
- placebo – 3%

Higher-than-normal levels of liver enzymes in the blood
- remdesivir – 4%
- placebo – 6%

Bear in mind

Reflecting on these results, the study team made the following statements:

- "Our findings highlight the need to identify COVID-19 cases and start antiviral treatment before the pulmonary disease progresses to require mechanical ventilation."
- "…given the high mortality despite use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient."

We will have more about remdesivir in the next article.

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D. Remdesivir moves forward

In the midst of a major health emergency—widespread COVID-19—researchers were able to conduct a well-designed study of remdesivir vs. placebo. Here are some issues arising from this and other studies of remdesivir.

Remdesivir was able to hasten recovery from serious symptoms of COVID-19 by about four days vs. placebo. That is, participants who received remdesivir took about 11 days to recover vs. 15 days in people on placebo. There was a trend to reduced deaths among people on remdesivir—7% vs. 12% on placebo. However, this was not statistically significant. These results have caused doctors unaffiliated with the study to write an editorial in *The New England Journal of Medicine* noting that "the clinical effect of remdesivir was relatively modest."

The benefit of treatment with remdesivir was seen mostly in people who entered the study with severe (but not critical) disease. In this subgroup, recovery occurred in 12 days among people who received remdesivir vs. 18 days among people who received placebo.

The doctors also underscored that people who entered the study with "mild-to-moderate disease" had a similar time to recovery (five days) as did people who received placebo.

The doctors stated that "remdesivir did not appear to improve outcomes in patients who required mechanical ventilation or extra corporeal membrane oxygenation [ECMO] but estimates of recovery require further follow-up in this group." In ECMO, blood is withdrawn from the body, carbon dioxide is removed and oxygen is added, and then the blood is returned to the body.

It is important to note that the trial allowed participants to receive a range of other therapies. It will be important to analyse the data to assess any potential impact on recovery that these other therapies may have had.

Another study has compared two different courses of remdesivir—five vs. 10 days. As there was no placebo in that study, no overall evaluation of remdesivir could be made. However, either course of treatment seemed equally effective.

Analyses of subgroups of people in the placebo-controlled remdesivir study are needed in order to find out if there were differences in the response to therapy based on age, gender or ethno-racial group.

An evolving understanding

Infection with SARS-CoV-2 can cause a range of serious symptoms in some people. The virus appears to cause complications that affect different organ-systems, including the lungs, heart and blood vessels, brain, nervous system, kidneys, liver and the immune system. In some people this virus causes severe inflammation. Therefore, it is possible that a combination of drugs—antivirals and powerful anti-inflammatory agents as well as anti-clotting drugs—may be needed.

A sudden epidemic

SARS-CoV-2 was isolated about six months ago and it has spawned a worldwide pandemic. It normally takes at least several years to develop drugs specifically designed to treat an emerging virus and sometimes longer for an effective vaccine.

As a result of the sudden and widespread dissemination of SARS-CoV-2, existing medicines are being repurposed. Results from clinical medicines will not be ideal, as such medicines were not made to attack the new virus. Despite this, the effects of remdesivir are an important step forward. Here are some issues to consider about the future of remdesivir:

- How early in the course of COVID-19 should remdesivir be initiated?
- What other drugs are best combined with remdesivir?

- Should antiviral and immune modulating drugs be initiated at the same time or should there be a sequence for the use of these drugs (one category before the other)?
- Is intravenous administration the best way to administer remdesivir? Gilead has begun clinical trials of an inhaled formulation of this drug.
- What will be the price of remdesivir?

Access

In Canada and some other countries, remdesivir is being made available through an expanded access program. Further information is available here: https://clinicaltrials.gov/ct2/show/NCT04323761

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E. Recovery trial finds cheap steroid can reduce deaths from COVID-19

In the UK, scientists have established the Recovery trial to test several treatments for SARS-CoV-2 infection. A preliminary analysis has found that some people hospitalized with COVID-19 were less likely to die when given the steroid dexamethasone.

In the Recovery trial, 2,104 people hospitalized with COVID-19 were randomly assigned to receive dexamethasone 6 mg once daily, taken either by tablet or injection for 10 days. They were compared to 4,321 people who received standard care for the same period. Participants were monitored for up to 28 days.

Results

Analysis found that dexamethasone had the following impact:

- deaths were reduced by 33% in people on ventilators
- deaths were reduced by 20% in other people who received supplemental oxygen (but who were not on ventilators)

These reductions in the proportions of deaths were statistically significant. They were not seen in people who received standard care.

Among people who were not on ventilators or who were not receiving supplemental oxygen, dexamethasone had no impact on survival.

Over the entire course of the study (28 days), deaths among dexamethasone users were reduced by 17% overall. People who required ventilation had the greatest benefit from dexamethasone.

Full results from the dexamethasone analysis will become available in the future.

Dexamethasone has been prescribed for decades to treat inflammatory conditions. It is available in generic formulations and is relatively inexpensive.

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F. Kaletra—from HIV to SARS to COVID-19

One of the medicines that has been undergoing extensive testing in people with COVID-19 is a fixed-dose formulation of two drugs: lopinavir + ritonavir. In Canada and other countries this formulation is sold under the brand name Kaletra and is available in generic formulations. In some other countries it is sold under the name Aluvia.

Lopinavir is the active antiviral drug in Kaletra. The relatively small dose of ritonavir is to delay the breakdown of lopinavir and to raise its levels in the body. This allows for once- or twice-daily

dosing of Kaletra. The small dose of ritonavir has no antiviral activity.

For the first decade of the 21st century, Kaletra was a leading part of combination HIV treatment. However, Kaletra has been supplanted by better tolerated and more potent treatments for HIV. It is no longer a recommended treatment for the initial treatment of HIV today in Canada and many high-income countries.

In 2003 a new virus called SARS-CoV-1 (severe acute respiratory syndrome-coronavirus-1) first appeared in East Asia. This virus caused severe and in some cases, lethal pneumonia in infected people. Some doctors, encouraged by anecdotal reports at the time, repurposed Kaletra to treat cases of this viral infection. Unfortunately, based on the poor quality of studies hastily done in the time of SARS, definitive conclusions about the effectiveness of Kaletra could not be drawn. The subsequent disappearance of SARS meant that interest in this syndrome and funding for research on it dried up.

SARS-CoV-2

In late 2019 a new virus called SARS-CoV-2 appeared in China. Since the new virus was related to SARS-CoV-1, it made sense in a medical emergency to test potential treatments for the new virus even though doctors were uncertain precisely how it caused severe disease in some people.

On January 18, 2020, doctors in Beijing began a randomized controlled trial called Lotus. In Lotus, participants were given either Kaletra + standard care vs. standard care alone, both interventions for 14 consecutive days in people hospitalized with COVID-19. About 85% of participants required high-flow oxygen or non-mechanical ventilation.

Overall, researchers found no benefit of Kaletra on time to clinical improvement. After 28 days of monitoring, 19% of people who had taken Kaletra + standard care died vs. 25% who had been on standard care alone. This difference was not statistically significant.

Although these results are disappointing, it would be premature to dismiss Kaletra from further clinical trials of people who are at risk for SARS-CoV-2 infection or who have COVID-19.

Why didn't Kaletra work in the Lotus study?

There are several potential reasons for the lack of significant clinical benefit of Kaletra in Lotus:

- People enrolled in Lotus were very ill. The overall death rate in this study was 22%. This figure is much greater than what was generally reported in other hospitalized patients with COVID-19 in China (15%) during the early days of the pandemic.
- People initiated Kaletra about 14 days after the onset of symptoms. This is relatively late in the course of COVID-19, perhaps too late for Kaletra to help them.
- Lotus did not enroll sufficient people to demonstrate a statistically significant impact of Kaletra on endpoints (outcomes) such as survival.
- The study was not placebo controlled. Due to the sudden emergence of COVID-19 and the need to rapidly conceive and implement a clinical trial, it was not possible to create placebo pills in time. Therefore, it is at least plausible that knowledge of which participants received Kaletra could have inadvertently biased the outcome and interpretation of some of the results.

Doctors who reviewed the data from Lotus commented in *The New England Journal of Medicine*, stating: "Lopinavir simply isn't particularly potent against SARS-CoV-2. The concentration necessary to inhibit viral replication is relatively high as compared with historical data about the absorption and concentration of lopinavir. We currently know little about drug concentrations in the tissues where SARS-CoV-2 is replicating."

The future of Kaletra in COVID-19

Despite the disappointing news from the Lotus study, it is still possible that Kaletra may be beneficial under the following circumstances, which require exploration in a clinical trial:

- It is used by people who have been exposed to SARS-CoV-2 before symptoms of COVID-19 have appeared.
- It is used early in the course of COVID-19.

- It is used as part of an experimental combination therapy against COVID-19. Combining Kaletra with other potential treatments may enhance lopinavir's antiviral activity. In some other viral infections, such as HIV and chronic hepatitis C virus, combination therapy is now the standard of care. Furthermore, preliminary data suggest that a combination of interferon-beta + Kaletra + ribavirin is more effective in facilitating recovery from COVID-19 than Kaletra alone. We have more information about this study next.

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G. Triple therapy with interferon-beta + Kaletra + ribavirin

Individual drugs that are approved to treat a well-known virus and which are then repurposed to treat a new and sometimes unrelated virus will likely have only modest antiviral effects, particularly against SARS-CoV-2. However, when repurposed drugs are combined in an experimental regimen, they are likely to be more effective than just one drug alone (monotherapy). This was the concept underpinning the rationale for combining three drugs in this study (we also provide some information about how those drugs might work against SARS-CoV-2):

- interferon-beta – Interferons can have a number of roles in viral infections: they can reduce the ability of infected cells to produce copies of the virus; they can cause virus-infected cells to self-destruct; and they can cause uninfected cells to invoke an antiviral defence mechanism that protects them from infection. Preliminary information suggests that in some people SARS-CoV-2 is able to suppress the ability of cells in the lungs to produce interferon in the early stages of infection. Experiments with mice with viral pneumonia suggest that one form of interferon, interferon-beta, can reduce the formation of scar tissue in the lungs. Other preliminary information from laboratory studies suggests that interferon-beta has antiviral activity against cells infected with SARS-CoV-2.
- Kaletra (containing lopinavir-ritonavir) – Lopinavir may have some antiviral activity against SARS-CoV-2.
- ribavirin – This is an old antiviral drug with activity against a broad range of viruses in lab experiments with infected cells. It causes mutations in the production of copies of the virus. Many of these copies are defective.

Doctors in Hong Kong enrolled 127 hospitalized participants with COVID-19 and randomly assigned them to receive, in a 2:1 ratio, either triple therapy with the previously mentioned drugs or Kaletra monotherapy. All drugs were given for 14 days. Study drugs were dosed as follows:

- interferon-beta – Participants received a total of three doses of 8 million units per dose given on alternate days. This was injected just under the skin (subcutaneous injection).
- Kaletra – The standard dose of two tablets (400 mg lopinavir with 100 mg ritonavir) every 12 hours.
- ribavirin – 400 mg every 12 hours (this is a moderate dose of ribavirin).

At the start of the study, participants were about 52 years old, 54% men and 46% women. About 40% of participants had underlying conditions, including diabetes, higher-than-normal blood pressure and elevated levels of cholesterol.

Participants had mild-to-moderate disease—generally fever and cough for about five days—caused by SARS-CoV-2 infection.

Results

Researchers found that there were significant differences in outcomes when comparing participants who received the two study regimens:

Reduction in the number of days producing virus
- triple therapy – seven days
- Kaletra alone – 12 days

Time to resolution of symptoms
- triple therapy – four days
- Kaletra alone – eight days

Length of time hospitalized
- triple therapy – nine days
- Kaletra alone – 15 days

These differences in the regimens were statistically significant.

About half of the participants reported side effects, including the following:

- diarrhea – 41%
- fever – 38%
- nausea – 34%
- elevated liver enzymes – 14%

There were no significant differences in the distribution or duration of these side effects by study regimen. The study team stated: "These side effects mostly resolved within three days after drug initiation."

No serious side effects occurred in people who received triple therapy. One person who received Kaletra monotherapy developed liver injury graded as serious by doctors and had to prematurely stop taking this regimen.

Bear in mind

The results from this prospective phase II randomized study are promising for triple combination therapy. The study design is an improvement over the many retrospective studies that bedevil many COVID-19 clinical trials.

According to the study team, a larger phase III study with interferon-beta as the "backbone" of a combination regimen vs. placebo "should be considered." Such a study should be able to yield a definitive answer about interferon-beta-based therapy for COVID-19.

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H. EIDD-2801 enters clinical trials

Scientists at the Emory Institute of Drug Development (EIDD) at Emory University in Atlanta have developed an antiviral drug they called EIDD-2801. This drug is well absorbed when taken orally and is active against many viruses. EIDD-2801 is an analogue of the nucleoside cytidine. This is a building block of RNA molecules. In lab experiments with cells, EIDD-2801 has antiviral activity against certain RNA viruses, including ones that cause influenza A and B, Ebola and coronaviruses such as the following:

- SARS-CoV-1 – this causes severe acute respiratory syndrome (SARS)
- MERS-CoV – this causes Middle East respiratory syndrome (MERS)
- SARS-CoV-2 – this causes COVID-19

EIDD-2801 appears to work by causing extensive changes, or mutations, in copies of the target virus. By inducing a high degree of mutations in copies of a virus, EIDD-2801 causes many copies of a virus to become non-infectious.

Experiments with mice suggest that EIDD-2801 can prevent disease caused by SARS-CoV-1 if taken as little as two hours prior to experimental exposure.

When EIDD-2801 was given to mice after infection with this virus, the drug reduced the amount of SARS-CoV-1 produced in the lungs. Autopsies of the mice found that the drug reduced the degree of lung injury caused by this virus. As with all antiviral drugs, benefit from EIDD-2801 was greatest if given shortly after infection.

A compressed timeline

Note that coronavirus disease in mice caused by SARS-CoV-1 is accelerated compared to what happens in humans. For instance, in the case of infection with SARS-CoV-1, peak virus levels in the lungs of mice occur on the first or second day after infection. In contrast, in people, virus levels may not peak until seven to 10 days after symptoms have appeared.

About mutations

EIDD-2801 works by causing mutations to appear in copies of coronaviruses made by infected cells. In general, cells infected by viruses tend to have a shortened lifespan. It is plausible that cells not infected by viruses could, in theory, incorporate EIDD-2801 into their regular development and develop mutations. Such mutations in theory have the ability to cause changes to the functioning of cells and perhaps cause abnormal development in such cells. However, according to publicly available documents, such mutations have not been found in lab experiments with EIDD-2801. Still, further experiments and studies in animals are needed to confirm the safety of EIDD-2801.

Another approved broad-spectrum antiviral drug is ribavirin. It works by causing extensive mutations in copies of viruses made by infected cells. However, ribavirin has the potential to cause mutations in uninfected cells. The prescribing information for ribavirin cautions against its use in pregnant women and advises that people planning to conceive children should wait until a certain period of time has passed after cessation of ribavirin.

Historically, ribavirin has been taken for months as part of combination therapy by people with chronic hepatitis C virus. In contrast, treatment with EIDD-2801, if it is eventually approved by regulatory authorities, is likely to be for a shorter period—probably one or two weeks. This reduced exposure should contribute to EIDD-2801's long-term safety.

Resistant virus

If all goes well, another broad-spectrum antiviral drug, remdesivir, is likely to be approved for use as a treatment for people with COVID-19. It is plausible that one day SARS-CoV-2 could mutate, as many viruses do, and develop reduced susceptibility to remdesivir. Based on research with coronaviruses that infect mice, EIDD-2801 is able to treat mouse coronaviruses that are resistant to remdesivir. These experiments need to be repeated with SARS-CoV-2.

Clinical development

Unpublished data suggest that EIDD-2801 is generally safe in a phase I clinical trial. The pharmaceutical company Merck, called MSD outside of Canada and the U.S., will be developing EIDD-2801.

The broad antiviral activity of EIDD-2801 suggests that it has potential for being tested in clinical trials against seasonal and pandemic influenza and coronaviruses.

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I. Could Pepcid help people with COVID-19?

As mentioned earlier in this issue of *TreatmentUpdate*, doctors are repurposing many medicines to find ones that have potential for preventing and treating COVID-19. One such medicine is the anti-ulcer/antacid drug famotidine. It is sold under the brand name Pepcid and is also available in generic formulations. Doctors became interested in this drug when they reviewed medical records of more than 6,000 people with COVID-19 in Wuhan, China. The doctors found that many people had been taking famotidine prior to developing COVID-19 (because of excess stomach acid) and during this infection. An analysis of these patients revealed that 14% of people taking famotidine died after developing COVID-19 vs. 27% of people not taking famotidine. However, such findings are merely suggestive, not definitive.

Spurred by the findings in Wuhan, doctors at the Columbia University Medical Center in New York reviewed the health records of 1,620 people

hospitalized with COVID-19. They also found a suggestion that famotidine may be beneficial.

Scientists are not certain how or why famotidine might be helpful in people with COVID-19. It does not appear to have antiviral activity against coronaviruses or any enzymes used by SARS-CoV-2. It is possible that famotidine has an effect(s) on the immune system. The suggested immunological mode of action of famotidine is extremely complex and beyond the scope of this article. However, it is plausible that famotidine ultimately is able to reduce inflammation in the lungs—a hallmark of severe COVID-19. Clinical trials with this drug in people with COVID-19 are underway and will hopefully shed light on how famotidine might work.

We now report details of 10 people who took famotidine after becoming infected with SARS-CoV-2 and who were monitored by their doctors. Although the findings from these 10 people are at best anecdotal and cannot be used to justify the use of famotidine outside of clinical trials, they are nonetheless interesting.

Case reports

Participants ranged in age from their 20s to their 70s. There were six men and four women. Four people had underlying conditions, mostly some form of cardiovascular disease. None were hospitalized. Participants initiated famotidine when they developed symptoms of COVID-19.

Most participants (70%) were diagnosed with SARS-CoV-2 infection via virus detected from nasal swabs. Two others were found to have antibodies to the virus and one was diagnosed solely on the basis of their symptoms.

The most commonly used dose of famotidine was 80 mg three times daily, taken orally. Half of the participants took famotidine for between five and 11 days and the other half for up to 21 days.

Results

None of the participants required hospitalization. They reported feeling some improvement in symptoms beginning 24 hours after taking their first dose of the drug. Subsequently, symptoms continued to decrease such that 14 days after initiating famotidine they had resolved.

Three participants reported adverse events as follows:

- one person – mild dizziness and occasional "racing heart beats"
- one person – mild dizziness, dry skin and sleeping problems
- one person – mild, unspecified "gastrointestinal symptoms" and temporary forgetfulness

The doctors who monitored these patients noted that with the exception of temporary forgetfulness, all the other adverse events were probably famotidine-related side effects. The doctors also stated that "all side effects resolved on discontinuation of famotidine."

Bear in mind

This report on 10 people is intriguing. However, definitive answers about famotidine's potential impact on the course of COVID-19 will hopefully emerge from ongoing randomized clinical trials.

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J. Does interferon-lambda have potential in COVID-19?

One part of the immune system, called the innate immune system, can usually detect and respond to invading germs, including viruses, in the early stages of an infection, long before antibodies can be made and T-cells mobilized.

Part of the innate immune system's defensive response to a virus is the release of interferon-lambda. Lab experiments with cells, animals and viruses suggest that the cells that line the respiratory tract, lungs and gastrointestinal tract,

as well as some cells of the immune system called neutrophils, are particularly sensitive to the effects of interferon-lambda. In theory, this interferon could do the following:

- activate the innate immune system and protect uninfected cells from becoming infected with SARS-CoV-2, thereby preventing people from developing COVID-19
- slow the production of SARS-CoV-2 in people recently infected with this virus, which could help their immune systems bring the infection under control and help them recover

Scientists need to test the effect of interferon-lambda in animals infected with SARS-CoV-2. Such testing is important to find out if interferon-lambda treatment works or contributes to COVID-19-associated organ injury.

Clinical trials done in people without SARS-CoV-2 infection have suggested that interferon-lambda is relatively well tolerated. A long-lasting formulation of interferon-lambda is available for clinical trials; it can be dosed once weekly. Such a formulation may mean that if this interferon is tested in people with COVID-19, only one or two doses may be necessary. An important issue with interferon-lambda is the timing of such a potential therapy relative to the stage of COVID-19.

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K. Recovery trial finds no clinical benefit for hydroxychloroquine in COVID-19

Scientists in the UK are running a large clinical trial called Recovery, which involves testing different therapies for the treatment of COVID-19.

In early June, scientists with Recovery released preliminary results from their study that assessed hydroxychloroquine (HCQ) as a potential treatment. According to these scientists, the distribution of randomized participants, all of whom were hospitalized due to COVID-19, was as follows:

- HCQ + usual care – 1,542 people
- usual care alone – 3,132 people

After 28 days the proportions of people who died were distributed as follows:

- HCQ + usual care – 26%
- usual care alone – 24%

This difference was not statistically significant. Furthermore, HCQ did not cause a reduction in the duration of a person's hospitalization.

Details about this trial will be released in the future.

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L. Chloroquine, hydroxychloroquine and clinical trial issues in COVID-19

Chloroquine (CQ) and its analogue, hydroxychloroquine (HCQ), have been used for many years to prevent and treat malaria. Both drugs can reduce the production of inflammatory chemical signals produced by the immune system, and thus reduce inflammation. As a result, CQ and HCQ in particular are used to treat rheumatoid arthritis, lupus and other conditions.

Lab experiments with cells have found that both drugs can inhibit the production of a broad range of viruses, including HIV. Note that lab experiments are greatly simplified systems, consisting of cells, culture medium and viruses. This simplicity can never reproduce the complex workings of an organ, a system or an entire person. Still, lab experiments are an important first step on the path to develop a drug for a condition. Subsequent steps include testing the drug in question in an animal model of the relevant disease and then a series of complex experiments in people called clinical trials. At each

of these steps, analysis can reveal problems, toxicity or a lack of effectiveness. This is a normal part of the drug development process and estimates are that about nine out of 10 drugs fail to transition from the lab to the pharmacy.

CQ and HCQ – looking great in the test tube

As mentioned earlier, CQ and HCQ can inhibit the activity of many different viruses, including HIV and coronaviruses in lab experiments with cells. However, when CQ and HCQ were tested in people with HIV, their antiviral effects were modest. This underscores a common issue in biomedical research: Results that look great in the test tube are not always reproducible in people. Thus, caution is needed when extrapolating from lab experiments to what might happen in people.

Clinical trials of CQ and HCQ in COVID-19

Earlier in this issue of *TreatmentUpdate* we mentioned that there were issues with many initial clinical trials of potential medicines for COVID-19. Some were small, not prospective, not randomized, did not have a placebo or other control, or had flaws. As a result, particularly with early clinical trials of CQ and HCQ (whether alone or in combination with azithromycin or other drugs), these issues were overlooked because of the emergency nature of the COVID-19 pandemic. This may have inadvertently caused some scientists to exaggerate the significance of the results of early studies with CQ or HCQ.

However, results from large well-designed clinical trials with CQ and HCQ are being released. These trials suggest that neither CQ nor HCQ are associated with significant clinical benefit. Furthermore, there are reports from some studies that these drugs are associated with serious heart problems.

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M. Can hydroxychloroquine prevent COVID-19?

In the early days of the first wave of the COVID-19 pandemic, doctors in Canada and the U.S cooperated and launched a randomized, double-blind, placebo-controlled trial of hydroxychloroquine to assess its potential to prevent the development of COVID-19. Participants were adults who may have been exposed to SARS-CoV-2 via contact with an infected person at home or at work.

Overall, 821 people were enrolled and began taking the study pills (drug or placebo) within four days of potential exposure to the virus. There was no statistically significant difference in the proportions of people who developed COVID-19: 12% of people on HCQ and 14% of people who received placebo. Side effects were more common in people who received HCQ (40%) than in people on placebo (17%).

Study details

The average profile of participants upon entering the study was as follows:

- age – 40 years
- 50% men, 50% women
- 67% were healthcare workers
- co-existing health condition – 73% had none of the underlying health conditions associated with increased susceptibility to COVID-19. However, smaller proportions had higher-than-normal blood pressure (12%), asthma (8%) or diabetes (4%). (Percentages do not total 100 due to rounding.)

Results

The proportions of people who developed COVID-19 did not differ by the drug/placebo they used.

Four infectious disease experts reviewed the symptoms of people who developed them to reach consensus as to whether or not these people had COVID-19. The trial was done in the early part of the COVID-19 epidemic and there was a shortage of tests for SARS-CoV-2. Therefore, most people were diagnosed based on their symptoms and not viral assays.

Adherence to the study regimens was self-assessed and was reported as follows:

- HCQ – 75% of participants took all of their pills over the course the study
- placebo – 83% of participants took all of their pills over the course of the study

The study team stated that the most common reason that participants stopped taking their pills was "side effects." Common side effects were "nausea, loose stools and abdominal discomfort."

Bear in mind

It is a major accomplishment to have conducted a randomized clinical trial of HCQ for the prevention of COVID-19 relatively early in the course of the pandemic.

Participants were rapidly recruited from across North America; this increases the generalizability of the study results. However, participants were relatively young and many did not have the underlying conditions usually seen in hospitalized people with COVID-19. This may reduce the applicability of the study's findings in people at high risk of hospitalization due to COVID-19.

The study was not reliant on viral tests to diagnose SARS-CoV-2 infection; as mentioned, there was a shortage of tests at the time the study was done. However, this means that doctors cannot be certain how many people ultimately became infected with the virus. Note that a large proportion of people who become infected with SARS-CoV-2 do not have symptoms of infection or develop symptoms of COVID-19.

Commenting on the study in *The New England Journal of Medicine*, infectious disease specialist Myron Cohen, MD, said it is possible that what the trial inadvertently assessed was "prevention of symptoms or progression of COVID-19 in people who became infected, rather than prevention of SARS-CoV-2 infection."

Due to these concerns, it is important that other randomized controlled trials of HCQ to prevent and treat SARS-CoV-2 infection continue so that definitive evidence can be found about the potential value of this drug.

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Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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ISSN 1181-7186 (print)
ISSN 1927-8918 (online)

Production of this document has been made possible through a financial contribution from the Public Health Agency of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada.

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