I COVID-19

A. The promise of molnupiravir

Molnupiravir is an experimental antiviral drug under development to assess its effects in people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes symptoms called coronavirus disease 2019 (COVID-19). In this issue of TreatmentUpdate, we present some background information on this drug as well as its current developmental status.

Molnupiravir was discovered by scientists affiliated with Emory University in Atlanta. The drug is also known under the code names MK-4482 and EIDD-2801.

How it works

Here is a simplified explanation of how molnupiravir works. Molnupiravir is an analogue of a natural molecule called cytidine—a nucleoside. This means that molnupiravir is classified as a nucleoside analogue. Cells use cytidine to make strings of RNA. To a cell, molnupiravir looks like cytidine. When a cell makes RNA molecules and molnupiravir is present in high concentrations, cells mistakenly incorporate molnupiravir into RNA. This results in a defective string of RNA. As RNA is essential for making new copies of coronaviruses such as SARS-CoV-2, defective RNA means that the copies of the virus that the infected cell makes are defective or incomplete and cannot be used to infect other cells. Thus, production of new coronaviruses greatly slows or stops.
Many laboratories studying SARS-CoV-2 use animals such as Syrian hamsters (also known as Middle Eastern hamsters) and ferrets, as they are susceptible to infection with this virus. In lab experiments with hamsters and ferrets, molnupiravir is highly effective at preventing infection with SARS-CoV-2. Furthermore, the drug is also effective at reducing the amount of virus produced by infected animals if it is given shortly after infection.

**In combination**

The drug favipiravir is approved in Japan for the treatment of severe flu infections. It is sold under the brand name Avigan. On its own, favipiravir has modest antiviral activity against SARS-CoV-2. However, lab experiments with a combination of favipiravir and molnupiravir suggest that the combination has significantly greater antiviral activity than either drug alone in hamsters infected with SARS-CoV-2.

**Safety**

Over the past 25 years, the development of some experimental nucleoside analogues has been halted because they have caused injury to an important component of cells—mitochondria. This component functions as a power plant, producing the energy that cells need. When mitochondria are injured, cells do not receive enough energy and can malfunction or die.

Molnupiravir has been tested in lab experiments with human liver cells. Results of experiments in which these cells were exposed to the drug for up to 14 consecutive days found that molnupiravir does not harm cellular power plants. Long-term experiments are underway to assess the safety of this drug both in cells and in rats and dogs. Short-term data from animals are very promising in that no safety concerns were found. In particular, molnupiravir does not appear to cause mutations in healthy cells.

**Clinical development**

The pharmaceutical company Merck has taken over clinical development of molnupiravir. Data from a phase I clinical trial has been released. In this study, 65 healthy volunteers without COVID-19 took different doses of molnupiravir for up to five and a half days.

In this study, molnupiravir was found to be well absorbed and generally safe. The drug did not cause any serious side effects or death. Overall, molnupiravir seemed better tolerated than placebo, with moderate side effects such as headache and diarrhea reported by a minority of participants. One person who received molnupiravir at a very high dose developed temporary rash. The drug had no significant effect on laboratory analysis of blood and urine samples from participants.

Molnupiravir’s absorption is not significantly reduced when it is taken with food.

Molnupiravir has entered phase II/III clinical trials. In these studies, the drug is given orally every 12 hours in different doses in capsules, as follows:

- 200 mg
- 400 mg
- 800 mg

**A phase II study**

At the recent Conference on Retroviruses and Opportunistic Infections (CROI), researcher Wendy Painter, MD, presented limited data from a placebo-controlled study of molnupiravir in people with COVID-19 who did not have any other conditions/infections.

All 75 participants were adults who had signs/symptoms of respiratory illness and tested positive for SARS-CoV-2 by PCR (polymerase chain reaction). Participants were randomly assigned to receive molnupiravir or placebo in a 2:1 ratio. Molnupiravir was taken in capsules at different doses twice daily for five days. Below are the pooled results of different doses of molnupiravir vs. placebo.

The proportions of participants who tested positive for SARS-CoV-2 on different days are as follows:

**Day three**
- molnupiravir – 20%
- placebo – 28%

**Day five**
- molnupiravir – 0%
- placebo – 24%
The results on day five with no detectable SARS-CoV-2 was seen with all doses of molnupiravir. The drug did not cause serious side effects. There were no details about non-serious side effects. These findings show that molnupiravir can quickly reduce the amount of SARS-CoV-2 relatively early in the course of COVID-19 in non-hospitalized people.

In development

Other clinical trials for molnupiravir have enrolled people who are ill with COVID-19, some of whom have been hospitalized. Studies are taking place in many countries, including the following:

- Canada (Toronto General Hospital)
- France
- Israel
- Philippines
- Russia
- Spain
- South Africa
- United Kingdom
- Ukraine

Merck is also investigating the potential for molnupiravir to interact with other medicines.

The clinical trials described above will be completed in a few months. If the studies confirm molnupiravir’s effectiveness and safety, it is highly likely that Merck will submit a dossier to regulatory authorities in the summer, first in the U.S. and subsequently the European Union and Canada, as it seeks approval for sale of the drug.

REFERENCES:


B. Plitidepsin – sea creature extract being tested for COVID-19

Scientists have been trying to repurpose drugs that have already been approved for one purpose for a new use—as treatment or prevention for SARS-CoV-2 infection.

For instance, the steroid dexamethasone, detailed later in this issue of TreatmentUpdate, has been found to improve the chances of survival of hospitalized people with COVID-19 who are receiving supplementary oxygen or invasive mechanical ventilation. Dexamethasone probably had this effect because it reduced the severe inflammation that is associated with serious symptoms of COVID-19. Dexamethasone may also have other effects on this new disease that are as yet little understood.

Dexamethasone is also used as part of a treatment against a cancer of B-cells called multiple myeloma. Due to this connection, some scientists in Spain and the U.S. think that another drug used for multiple myeloma—plitidepsin—could be repurposed as a potential treatment for COVID-19.

A biological mini-factory

Like many viruses, when SARS-CoV-2 infects a cell, it attempts to hijack the cell’s processes—its biological machinery—for its own purpose. That is, the virus (or nearly all viruses) attempts to turn an infected cell into a mini-virus factory, churning out copies of the infecting virus. SARS-CoV-2 does this by taking over the cellular machinery, particularly the parts of the cell that are used to make proteins. One cellular factor involved in the production of proteins has been labelled by scientists as eEF1A (eukaryotic translation elongation factor IA).
Several viruses interfere with or attempt to take over eEF1A, including the flu virus, HIV and now SARS-CoV-2.

**Plitidepsin in the lab**

A Spanish company, PharmaMar, has extracted a compound found in ocean-dwelling creatures called sea squirts and made it into a drug called plitidepsin, which is used to treat multiple myeloma. In lab experiments with cells infected with SARS-CoV-2, very small concentrations of plitidepsin can significantly reduce production of this virus. Plitidepsin is also active against a common variant of SARS-CoV-2 called B117.

In experiments with mice infected with SARS-CoV-2, plitidepsin reduced levels of this virus by almost 100-fold and significantly reduced inflammation in the lungs caused by the virus.

**Plitidepsin in people**

PharmaMar has conducted a phase I/II study of plitidepsin, in which three groups of participants were given one of the following doses of the drug intravenously over three consecutive days:

- 1.5 mg
- 2.0 mg
- 2.5 mg

According to PharmaMar, plitidepsin reduced the amount of SARS-CoV-2 in people by 50% on day seven and 70% on day 15. The company has stated that 81% of participants were able to leave the hospital on or before their fifteenth day of hospitalization.

PharmaMar has expanded its study by enrolling more participants. It is also in discussion with regulatory authorities about a phase III clinical trial.

The doses of plitidepsin used in this study are relatively low and the company stated that they are “well tolerated in patients with minimal side effects.”

This is an important consideration because drugs that affect cellular processes (rather than having direct antiviral effects) carry the possibility of injuring cells, and this manifests as side effects. However, like most drugs that are being tested for potential in COVID-19, plitidepsin would only be used for a short period, which would reduce its potential for side effects.

**For the future**

The combination of plitidepsin and dexamethasone has been used safely in clinical trials with people who have multiple myeloma. This raises the possibility that both drugs could also be tested in people with severe symptoms of COVID-19.

Plitidepsin has to be given intravenously, which is not ideal in a pandemic where hospitals, clinics and their staff are busy or overwhelmed. If plitidepsin is successful in further clinical trials, it is possible that PharmaMar can invest in the science underpinning the development of an oral formulation of plitidepsin or an analogue.

As plitidepsin acts on cellular processes rather than directly on the virus, it is likely that the drug will retain its antiviral activity against variants of SARS-CoV-2 as well as other coronaviruses. This latter property may make it useful should a future coronavirus pandemic arise.

**REFERENCES:**


**C. Exploring the family of interferons for clues about COVID-19 and its treatment**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes symptoms called coronavirus disease 2019 (COVID-19). In many people who become infected with this virus, perhaps as many as 40% have no symptoms of infection. However, a portion of people develop symptoms that can resemble a flu. In a smaller proportion of people,
the symptoms can become severe and include breathing problems and pneumonia.

Interactions between SARS-CoV-2 and the immune system underpin the body’s response to this virus. In this issue of TreatmentUpdate, we bring together emerging research that outlines some of the immunological events that occur during infection with coronaviruses. Learning about these events can be useful in understanding why some potential treatments, such as members of the interferon family, are being tested against the pandemic coronavirus. Delving into the immunology of SARS-CoV-2 may help explain some of the complications that arise in people with COVID-19.

Enter the virus

Cells lining the nose, throat and upper part of the lungs are usually the first places in the body where germs that are inhaled are encountered by the immune system. SARS-CoV-2 enters cells using a protein (or receptor) found on the surface of cells called ACE2.

Once inside a cell, the presence of the virus should trigger the cellular equivalent of multiple alarms. Cells have internal sensors that are supposed to detect invading germs. If these sensors detect SARS-CoV-2, they trigger a series of events that quickly leads to the production of molecules, particularly ones from a family used for sending signals. These molecules are called interferons.

Getting to know the interferons

There are three main types of interferons:

- Type 1 – interferon-alpha and subtypes such as interferon-alpha-1, 2, 3 and so on; interferon-beta and subtypes; and several less-studied interferons such as interferon-delta
- Type 2 – interferon-gamma
- Type 3 – interferon-lambda and subtypes such as interferon-lambda-1, 2, 3 and so on

To respond to interferon, cells need to have a protein on their surface called an interferon receptor. Some of these receptors are sensitive to one type of interferon, while other receptors are sensitive to other types of interferons.

How interferons work

A greatly simplified explanation of how interferons work in the initial stages of viral infection follows. Once interferon is produced, it triggers genes in a cell to make proteins that do the following:

- limit the ability of infected cells to produce copies of SARS-CoV-2
- let other cells near the infected cell know that a viral invasion is underway and that uninfected cells can take steps to protect themselves
- activate cells of the immune system so they can come to the help of the infected cell
- help sentinel cells of the immune system learn the identity of the invading germ
- enhance the functioning of T-cells, such as CD4+ and CD8+ cells, which can release antiviral substances that destroy virus-infected cells

Timing is everything

Scientists who study viruses and the immune system have said that “the timing of interferon production is crucial for its influence on the immune response to virus infection.” That is, interferon production needs to be triggered very early in the course of viral infection for the best results in limiting the spread of infection.

Viruses and SARS-CoV-2

As interferon is such an important part of the immune system’s defence against viruses, these germs have evolved ways of interfering with the activity of interferon.

Scientists who have carried out lab experiments with cells and SARS-CoV-2 have found that this virus can somehow weaken or delay the production of interferon.

Some studies have found that in people with moderate and severe COVID-19 sometimes there is hardly any detectable interferon present. In some experiments, very low or absent levels of interferons in the blood have coincided with high levels of SARS-CoV-2 in people.
Looking at SARS-CoV-1 for clues

In 2003 there was an outbreak of severe pneumonia (SARS) caused by the virus SARS-CoV-1. Analysis of this virus found that it carried instructions in its genetic material to make many proteins that interfered with interferon. These viral proteins had the effect of limiting interferon production and activity.

SARS-CoV-2 has about 82% similarity to SARS-CoV-1. It is very likely that SARS-CoV-2 also carries instructions in its genetic material to make similar proteins that weaken and limit interferon’s production and activity. Although preliminary results from lab experiments suggest this, these findings require confirmation.

Friendly fire and defective genes

In one large study of about 1,000 people with COVID-19 pneumonia, researchers found that about 10% had antibodies that attacked and disabled interferon. These anti-interferon antibodies were present in blood samples taken from some of the participants in the pre-COVID-19 era. This suggests the possibility that SARS-CoV-2 infection did not trigger the production of antibodies that attacked interferon. In this study, most people (94%) with these antibodies were men. The age of people with the antibodies in their blood ranged from 25 to 87 years. However, 50% of participants were between 65 and 87 years. Participants were from different continents and a range of ethno-racial groups. The form of interferon attacked by the antibodies was interferon-alpha.

Another study has found defects in the genes that produce interferon-alpha in some people with severe COVID-19. The researchers compared genes from 659 people critically ill with COVID-19 and genes from 534 people infected with SARS-CoV-2 who were either symptom free or who had mild symptoms. In about 4% of critically ill people, there was very little interferon alpha in their blood and these people had defective genes.

Taken together, the findings from these two studies can probably explain why about 14% of people who are infected with SARS-CoV-2 have severe symptoms.

Emerging research suggests the possibility that antibodies that attack interferon may affect more than 14% of people with severe COVID-19. However, such emerging research is controversial because it has not been embraced by many scientists and requires firm evidence to prove its findings.

Attacking antibodies

The presence of antibodies that attack interferons was first detected in the 1980s in some people with the autoimmune disease lupus who were treated with interferon-alpha and interferon-beta.

The findings from studies in people with severe COVID-19 are intriguing and surprising and should serve as a starting point for much more research focused around the following questions and issues:

- Why do some people with COVID-19 have antibodies that attack interferon-alpha; do they serve a useful purpose?
- How widespread is the issue of antibodies that attack interferon-alpha?
- Are antibodies that attack interferon-alpha common in older people?
- Are antibodies that attack interferon-alpha linked to other health problems such as increased susceptibility to other viral infections and cancer?
- In people with COVID-19 who have antibodies that attack mostly interferon-alpha, why do the antibodies not attack other interferons?
- The previously mentioned studies assessed interferon levels in the blood. It might be useful to assess interferon levels in the lungs.

New approaches

In theory, it is possible to develop countermeasures to help people with COVID-19 who have antibodies that attack interferon. For instance, some researchers have suggested filtering the blood of people with these antibodies, in the hope of removing them. However, such filtration does not address why the antibodies developed in the first place or which subset of B-cells made them. If the antibody-producing cells are not removed, presumably they will keep making antibodies that attack interferon.

It is noteworthy that the vast majority (98%) of antibodies in the previous studies attacked the interferon-alpha family and the remaining 2%
attacked interferon-beta. About one-third of people with these antibodies who developed pneumonia died. Therefore, it may be helpful to test other members of the interferon family, such as the following, in people with severe COVID-19:

- interferon-beta
- interferon-lambda

**Early vs. late use of interferon**

Experiments with cells and animals suggest that, in general, interferons play a key role very early in the viral infection process. In the early stages of infection, interferons appear to help elaborate a number of useful defensive activities. However, in later stages of infection, large amounts of interferon may not be useful and may even contribute to harm.

Lab experiments with animals suggest that when type I interferons are given late in the course of disease, these interferons can cause the immune system to release chemical signals that suppress the body’s ability to fight infections. This can happen in a number of different ways, including weakening the ability of CD8+ cells to attack virus-infected cells and even stimulating large numbers of uninfected cells to destroy themselves.

These findings collectively suggest that the timing of interferon treatment in COVID-19 needs to be carefully chosen.

**REFERENCES:**


**D. A phase II study of inhaled interferon beta**

Interferons are an important part of the immune system’s defence against viruses. Research suggests that SARS-CoV-2-infected cells can make proteins that suppress the production of interferons. Furthermore, this coronavirus appears to cause infected cells to produce proteins that weaken the activity of interferons. Perhaps these properties of SARS-CoV-2 against interferons may in part explain its ability to cause severe disease in some people. Some studies have found little detectable interferon in the blood of people with severe COVID-19. In some cases, low levels of interferon were associated with the production of antibodies that attacked interferons, particularly interferon-alpha. This raises the possibility that treatment with other members of the interferon family maybe useful.
A pilot study

Researchers in England conducted a randomized, double-blind, placebo-controlled pilot study of aerosolized interferon-beta vs. placebo. Both interventions were taken once daily for up to 14 consecutive days in hospitalized people with COVID-19.

Participants who received interferon-beta were twice as likely to have an improvement in their condition and to recover faster than those who took the placebo. Further studies are underway in people with COVID-19.

Study details

The Synairgen corporation provided purified interferon-beta-1a for the study. The drug was given at a dose of 6 million international units (IU) daily. Interferon-beta or placebo was dispersed into tiny droplets and inhaled via a nebulizer.

The average profile of the 98 participants at the start of the study was as follows:

- age – 57 years
- 59% men; 41% women
- 80% were white and 20% were people of colour
- 54% had comorbidities – high blood pressure, cancer, cardiovascular disease, diabetes, chronic lung disease
- 77% were receiving oxygen via mask or nasal prong
- participants had symptoms of COVID-19 for 10 days prior to initiating the study interventions

Participants were monitored for up to 28 days.

Results

Participants who received interferon-beta were more likely to recover and to do so faster than participants on placebo.

However, by the 28th day of the study, broadly similar proportions of participants were released from the hospital—81% who had received interferon-beta and 75% who received placebo.

Side effects

As interferon was delivered directly to the throat, airways and lungs rather than into the blood, it likely caused limited side effects. The most common side effect was headache, distributed as follows:

- interferon-beta – 15%
- placebo – 10%

More people who received interferon-beta complained about coughing.

Three people died, all of whom received placebo.

Bear in mind

The present study was a well-designed pilot study. Its findings are encouraging but not definitive. The study was not designed to assess the impact of interferon-beta on survival. Larger studies will be needed to provide definitive answers about the role of interferon-beta in people with COVID-19 and its impact on survival. Phase II and III trials of aerosolized interferon-beta are underway.

REFERENCES:


E. A Toronto study of interferon-lambda shows promise in COVID-19

In lab experiments with cells and in some people, infection with SARS-CoV-2 is associated with decreased production of proteins called interferons. These proteins help cells resist viral infections or, if cells are already infected, slow the production of copies of the invading virus. Interferons can also marshal help from the immune system.

One family of interferons is called interferon-lambda. There are subtypes of interferon-lambda, such as lambda-1, -2 and so on. Cells lining the lungs and intestines are sensitive to interferon-lambda. In lab experiments with cells and viruses, interferon-lambda has potent antiviral activity and is not generally associated with inflammation.

A long-lasting form of interferon-lambda-1 called peg-interferon-lambda-1 has been developed. It has been previously tested in more than 3,000 people with viral hepatitis. In these studies, it was as effective as interferon-alpha and better tolerated.

Lab experiments have found that interferon-lambda can reduce production of SARS-CoV-2 in mice. All of the findings with interferon-lambda suggest that it is worth studying in people with COVID-19.

A team of researchers in Toronto, led by Jordan Feld, MD, conducted a randomized, placebo-controlled, double-blind pilot study of peg-interferon-lambda-1 (hereinafter called interferon-lambda) in people in the early stages of COVID-19. The researchers found that interferon-lambda “accelerated viral decline in outpatients with COVID-19, increasing the proportion of patients with viral clearance by day 7.” They further stated that interferon-lambda has the potential to “prevent clinical deterioration and shorten duration of viral shedding.”

Study details

Researchers enrolled volunteers from many clinics in Toronto. All participants had SARS-CoV-2 infection confirmed with nasal swab analysis.

The average profile of participants at the start of the study was as follows:

- age – 46 years
- 42% men, 58% women
- 52% were white and 48% were people of colour
- 19% had no symptoms of COVID-19
- viral loads were more than 1 million copies/mL
- most people had mild-to-moderate symptoms of COVID-19

Twenty-nine participants received a single injection of interferon-lambda (180 micrograms) and 30 others received an injection of placebo with a weak salt solution.

Participants were taught how to perform nasal swabs to collect virus for the study.

Nurses monitored participants for up to two weeks.

Results

Clinical trial procedures such as randomization, use of placebos and double blinds are useful and help to reduce possible bias when interpreting the results. In theory, randomization helps to distribute people with different characteristics more evenly in a trial between the group getting the active drug and the group getting the placebo.

Despite randomization, at the start of this study the amount of virus was higher in people who were given interferon-lambda. Regardless of this difference, the amount of virus decreased
significantly in people who subsequently received interferon-lambda. The greatest decline was found in people who entered the study with viral levels of 1 million copies/mL or greater. The distribution of people with an undetectable viral load by day seven of the study was as follows:

- interferon-lambda – 79%
- placebo – 38%

Participants who received interferon-lambda cleared SARS-CoV-2 faster (seven days) vs. those who received placebo (10 days).

Side effects and complications
Researchers assessed symptoms of participants at the start and throughout the study, and they classified the symptoms as follows:

- gastrointestinal
- mood
- muscles and bones
- neurological
- respiratory
- skin
- systemic

The researchers stated: “Overall, most symptoms in both groups were mild to moderate and we found no difference in frequency or severity of any of the seven symptom categories between treatment groups.”

Seven participants who received interferon-lambda graded their symptoms as severe on multiple occasions; these generally involved the temporary loss of sense of smell and taste. These symptoms could have been due to infection with SARS-CoV-2.

Seven participants who received placebo graded their symptoms as severe on multiple occasions, specifically, fever, chills, shivering and fatigue.

Note that symptoms decreased over the course of the study.

Respiratory symptoms—including chest pain, cough, runny nose, shortness of breath and sore throat—decreased faster among people given interferon-lambda.

Lab tests
Levels of liver enzymes in the blood increased very modestly in most people taking interferon-lambda. Only two people who received interferon-lambda had severely elevated levels of liver enzymes—ALT in one person and AST in another. In comparison, three people on placebo had highly elevated levels of ALT and one other person had highly elevated levels of AST.

Inflammation and clotting
D-dimer is a small protein in the blood that increases with inflammation and excess blood clots. At the start of the study, D-dimer levels were elevated in both groups of participants. They declined significantly only in people who took interferon-lambda. This is a promising finding.

Hospital visits
Five participants sought care in a hospital emergency room within 14 days of entering the study, distributed as follows:

- interferon-lambda – one person
- placebo – four people

All five went to the ER because of worsening respiratory symptoms, but only one person from each group was hospitalized:

- interferon-lambda – shortness of breath due to a blood clot in the lung
- placebo – shortness of breath due to complications of COVID-19

No one died while in the study.

Bear in mind
A single subcutaneous injection of interferon-lambda resulted in faster time to clearance of SARS-CoV-2 compared to placebo. This effect of interferon-lambda was greatest in people with high levels of SARS-CoV-2.

Interferon-lambda was well tolerated, with similar side effects to placebo. About 20% of participants entered the study without symptoms of COVID-19. In this subgroup of people there were no side effects when they received interferon-lambda. These results may seem surprising to some because
interferons have a historical reputation for causing unpleasant side effects. This reputation arose because interferons, specifically interferon-alpha, had to be injected repeatedly over time in people with hepatitis C virus (HCV). In the COVID-19 study, however, only one injection was needed because the cells that are sensitive to interferon-lambda are distributed in a limited way in the body. This should reassure future study participants that, for treating COVID-19, interferon-lambda is well-tolerated.

Altogether, the tolerability and antiviral activity from a single injection of interferon-lambda make this drug a very promising candidate for future research in people with COVID-19. California-based Eiger Biopharmaceuticals is in discussion with the U.S. Food and Drug Administration about conducting a phase II/III trial of interferon-lambda in people with COVID-19.

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F. Dexamethasone and COVID-19

SARS-CoV-2 causes no or mild symptoms in most people it infects, but a substantial minority develop symptoms that are serious, including difficulty breathing, cough and, in some cases, pneumonia. As the lungs become inflamed and injured, they become less efficient at extracting oxygen from the air and exchanging it for the waste product carbon dioxide. Thus, some people who are hospitalized with COVID-19 can require supplemental oxygen and, in some cases, invasive mechanical ventilation.

A team of researchers in the UK conducted a large study with people hospitalized with COVID-19. They randomly assigned participants to receive one of the following:

- a low daily dose of the steroid dexamethasone (6 mg) for up to 10 days + supportive care
- supportive care alone

Overall, 23% of participants who received dexamethasone and 26% who did not receive it died during the study. However, among people who were on some degree of what the researchers called respiratory support, results were different. Among participants who were on such support, such as invasive mechanical ventilation, 29% who
had received dexamethasone died compared to 41% who did not receive the steroid who also died. This research has found that dexamethasone can save the lives of some people with COVID-19, but additional research is needed.

Study details
As the clinical trial was done during the first wave of COVID-19, limited information was collected from participants’ hospital charts.

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

- age – 66 years
- 64% men, 36% women
- 56% of participants had at least one underlying condition such as the following:
  - heart disease – 27%
  - diabetes – 24%
  - chronic lung disease – 21%

Respiratory assistance:
- 60% were receiving oxygen
- 16% needed invasive mechanical ventilation
- 24% were not receiving either of these interventions

Data were collected for an interim analysis, as researchers were interested in survival 28 days after participants entered the study.

A total of 6,425 participants were randomly assigned in a 2:1 ratio to receive one of the following interventions:

- dexamethasone + supportive care – 4,321 people
- supportive care alone – 2,104 people

Results
The overall effect of dexamethasone on survival may seem initially modest, with deaths distributed as follows:

- dexamethasone + supportive care – 23% died
- supportive care alone – 26% died

However, when researchers took into account the level of what they called “respiratory support” (invasive mechanical ventilation, oxygen) that people were on at the start of the study, there were larger differences in the deaths seen, as follows:

Invasive mechanical ventilation
- dexamethasone + supportive care – 29% died
- supportive care alone – 41% died

Among people who were on oxygen at the start of the study without invasive mechanical ventilation, the distribution of deaths was as follows:

- dexamethasone + supportive care – 23% died
- supportive care alone – 26% died

Readers should note the distribution of deaths among people who were not receiving respiratory support at the start of the study:

- dexamethasone + supportive care – 18% died
- supportive care alone – 14% died

Taking these and other findings into account, the researchers made the following statement:

“…there was no clear effect of dexamethasone among patients who were not receiving any respiratory support [at the start of the study].”

They also said that “patients who were receiving invasive mechanical ventilation [at the start of the study] were on average 10 years younger than those not receiving any respiratory support and had a history of symptoms before randomization for an average of seven days longer.”

Other findings
People who received dexamethasone spent one day less in the hospital than people who did not receive the drug.

Bear in mind
The British study uncovered a clear role for dexamethasone in some people with COVID-19 who were hospitalized. Specifically, the drug is useful in people who are receiving some degree of respiratory support—invasive mechanical ventilation or supplementary oxygen. However, dexamethasone was not beneficial among people who were not receiving respiratory support at the start of the study.
The researchers stated that the beneficial effect of steroids “on severe viral respiratory infections is dependent on a selection of the right dose, at the right time, in the right person.”

Several teams of researchers have suggested that SARS-CoV-2 seems to cause a high level of virus production early in the course of COVID-19. During this stage, steroids and other treatments that suppress inflammation could also hamper the immune system’s ability to contain the virus. They suggest that in later stages of COVID-19 the immune response may be excessive and cause harm, and that steroids and other drugs that dampen the immune system may be more useful at that point.

For the future

The present study, which examined survival 28 days after participants entered the study, is important. Although many participants have recovered and left the hospital, they are still being monitored and the research team will perform an analysis to assess the impact of dexamethasone on long-term survival.

Many potential volunteers were screened by research nurses for possible participation in the study—1,707 were excluded and it is not clear why. It is possible that for some people steroids may not have been safe due to certain pre-existing conditions, such as the following:

- uncontrolled diabetes
- a state of confusion, disorientation, memory loss and/or an inability to think clearly
- cancer
- immune suppression because of medicines for transplanted organs or autoimmune disorders such as arthritis

The present study did not assess the impact of steroids on SARS-CoV-2 replication. This would be an important point for future studies of steroids. Laboratory research suggests that dexamethasone can impair the ability of SARS-CoV-2 to enter cells. Does this drug have a significant antiviral effect in people with COVID-19?

REFERENCES:

G. Inhaled ciclesonide for SARS-CoV-2 in clinical trials

In some people, SARS-CoV-2 infection can cause inflammation of the lungs and pneumonia. A large randomized clinical trial has found that the steroid dexamethasone can reduce the risk of death in people hospitalized with COVID-19 who are also receiving respiratory support (supplementary oxygen, invasive mechanical ventilation).

Researchers are continuing to experiment with dexamethasone and other steroids in people with COVID-19. One steroid of interest is ciclesonide, which is sold in the following formulations:

- Omaris – a nasal spray used for relieving runny nose, sneezing and other symptoms that can accompany seasonal allergies
- Alvesco – an aerosol formulation that is inhaled through the mouth and used to treat symptoms of asthma (difficulty breathing, wheezing)

Lab experiments with cells suggest that ciclesonide has potent antiviral activity against SARS-CoV-2.

Experiments in people with asthma in the pre-COVID-19 era suggest that when inhaled most aerosolized ciclesonide stays in the lungs.

Reports suggest that ciclesonide has been used as part of the successful treatment of some cases of COVID-19-related pneumonia. The totality of the evidence (lab studies and case reports) indicates that ciclesonide could be a candidate for testing to help prevent or even treat COVID-19. Clinical trials of this drug in people with COVID-19 are underway at McGill University in Montreal and in South Korea and Sweden.
REFERENCES:


Disclaimer
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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What CATIE Does
CATIE is Canada’s source for up-to-date, unbiased information about HIV and hepatitis C. We connect people living with HIV or hepatitis C, at-risk communities, healthcare providers and community organizations with the knowledge, resources and expertise to reduce transmission and improve quality of life.
For more than 20 years, CATIE has been there to provide information that enables people to make informed choices about their health and enhances the ability of healthcare providers and other frontline organizations to respond to their clients’ needs.
CATIE provides such information through a comprehensive website (www.catie.ca), electronic and print resources, webinars and other online learning, a national reference library, regional conferences, subscriptions to e-newsletters and a confidential phone inquiry service.

CATIE Publications
TreatmentUpdate
CATIE’s flagship treatment digest on cutting-edge developments in HIV/AIDS and hepatitis C research and treatment. Subscribe to TreatmentUpdate and automatically receive an email notifying you the moment a new issue is available online.

CATIE News
CATIE’s bite-sized HIV and hepatitis C news bulletins.

HepCInfo Updates
CATIE’s bi-weekly electronic newsletter highlighting key hepatitis C prevention, treatment and epidemiology information.

A Practical Guide to HIV Drug Side Effects
The latest on what is known about various side effects related to treatment, from appetite loss to sexual difficulties, and tips for countering or preventing them.

The Positive Side magazine
Holistic health information and views written by and for people living with HIV.

Fact Sheets
Concise overviews of conditions, symptoms, medications, side effects, complementary therapies, vitamins, herbs and other treatment issues.

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