

Research Article

Current Status of Drug development against the Novel Coronavirus, SARS-CoV-2 -Evaluation of therapeutic agents based on scientific evidence-

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Abstract

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for coronavirus disease 2019 (COVID-19), continues to spread worldwide with 6,057,853 people infected and 371,166 deaths in 216 countries as on June 2, 2020.¹⁾ Although the number of infected people in Japan is currently decreasing, the development of therapeutic agents able to confront a potential new comeback of the disease is highly expected. The news has provided several promising reports such as “I took medication and got dramatically better.” However, a prudent attitude is required and the efficacy of drugs needs to be judged based on sufficiently solid scientific evidence. In this review, I summarize the mechanisms of action and clinical trial results of representative candidate drugs and explain how to evaluate them based on the scientific evidence.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, Evidence based medicine, Drug repositioning

Introduction

In December 2019, unexplained cases of pneumonia began in Wuhan City, Hubei Province, China. Shortly after, a new species of coronavirus was detected in patients with pneumonia in January 2020 and was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This new type of coronavirus infection^{*1}, known as COVID-19, was initially confined to mainland China, but later spread to neighboring countries, including Japan, and subsequently swiftly to the entire world. As on June 2, 2020, 6,057,853 people have been infected and 371,166 people have died in 216 countries.¹⁾ Because of this rapid spread of infection, travel restrictions, curfews, and lockdowns (urban blockades) have been enforced around the world. A state of emergency was declared in Japan in early April, and various activities were self-restrained and restricted in some areas for a month and half (lifted on May 26). Thanks to these efforts, some countries including Japan have seen a decline in the number of cases. However, second and third waves of infection may potentially arise, and therefore the development of therapeutic drugs able to cope with them are sorely needed. Because developing new therapeutic drugs from scratch is expensive and time consuming, effective drugs

against COVID-19 are being researched among existing commercialized drugs used for the treatment of other diseases. This method, called drug repositioning, involves the use of therapeutic agents that have already been tested for safety and pharmacokinetics in humans with a well-established method for the manufacturing, thereby significantly shortening the period and cost of production. Several candidate drugs against COVID-19 identified by drug repositioning have been reported, and those that have attracted early attention are shown in **Table 1**. Several studies of these drug candidates appear promising. For example, condition of 60% and 90% of severely and mildly ill patients improved after treatment with avigan[®].²⁾ The following claim has also been made: “I was surprised by the dramatic recovery with ciclesonide”.³⁾ However, the efficacy of drugs must be judged based on sufficient solid scientific evidence, requiring a prudent attitude. This review provides a brief description of the coronavirus, summarizes the mechanisms of action and clinical trial results of the candidate drugs listed in **Table 1**, and describes the methods by which drugs can be evaluated based on scientific evidence.

Table 1. Candidate drugs for the treatment of COVID-19 (antiviral drugs).

General name	Remdesivir	Favipiravir (Avigan®)	Lopinavir / Ritonavir	Ciclesonide	Nafamostat
Target disease	Ebola hemorrhagic fever	anti-influenza	anti-HIV drug	Bronchial asthma	Pancreatitis
Form	Intravenous drug	Tablet	Tablet	Inhalant	Injection agent
Mechanism of action	RdRp inhibition	RdRp inhibition	Protease inhibition viral origin	NSP15 inhibition	Protease inhibition host origin
Domestic approval (Against the novel coronavirus)	Approved	Unapproved (diseases approved)	Unapproved (diseases approved)	Unapproved (diseases approved)	Unapproved (diseases approved)
RCT results	1. Recovery in 11 days in the remdesivir group, compared to 15 days in the placebo group (multinational study) 2. No significant difference in improvement in clinical symptoms between the two groups (China)	No significant difference in clinical improvement between the favipiravir and albidol (Chinese influenza drug) groups (China: pre-reviewed article data)	1. No significant difference in improvement in clinical symptoms between the placebo and Kaletra groups (China) 2. Suggested to be effective in combination with other drugs (China)	RCT planning and implementation in progress	RCT planning and implementation in progress

Abbreviations: RCT, randomized controlled trial; RdRp, RNA-dependent RNA polymerase

Coronavirus

Although viruses such as influenza virus and coronaviruses and bacteria such as pathogenic *Escherichia coli* can cause disease in humans and animals, the two are vastly different. Bacteria are similar to human cells, harboring factories that copy genes and synthesize proteins and energy. Thus, they can propagate themselves using their own factories provided they have enough resources. Viruses, in contrast, do not have any such factories and have a simple structure in which genes are wrapped in a protein capsule. Therefore, viruses cannot multiply on their own, but instead, infect cells and take over the host cellular machinery for their own multiplication. A virus is approximately 1/100 the size of an animal cell and 1/10 the size of a bacterium. Seven types of coronaviruses known to infect humans have been identified, four of which are responsible for 10–15% of common colds. The other three cause Middle East

respiratory syndrome (MERS) or SARS. Both MERS and SARS can result in severe pneumonia, and the latter includes COVID-19.⁴⁻⁶⁾ Coronaviruses can infect not only humans but also several other animals, including domestic animals, wildlife, and pets. However, coronaviruses are usually species-specific; for example, feline coronaviruses only infect cats, while human coronaviruses only infect humans. Although zoonosis is rarely seen in coronaviruses, three severe pneumoviruses, including SARS-CoV-2, are thought to have crossed the animal species barrier to infect humans. It appears that not only humans but also cats are susceptible to the infection.⁵⁴⁾ Genetic analysis of SARS-CoV-2 revealed its similarity to the bat coronavirus, suggesting the transmission from bats to humans or from bats to wildlife (e.g., pangolin) and then to humans.⁷⁻⁸⁾ However, the specific animal source of the infection remains to be identified.

Structure of coronaviruses and the targets of candidate drugs

Coronaviruses belong to a class of RNA viruses and have a single-stranded RNA genome. Coronaviral genome are encased in a protein capsule, which is further enveloped by a lipid membrane (**Figure. 1**).⁴⁾ A viral protein called a spike (S) is impaled on the lipid membrane. Understanding the mechanism of action of

candidate drugs requires an understanding of the growth machinery of coronaviruses—the most complex among RNA viruses. Therefore, to understand the mechanism of action of the candidate drugs in **Table 1**, I will elaborate the following three points.

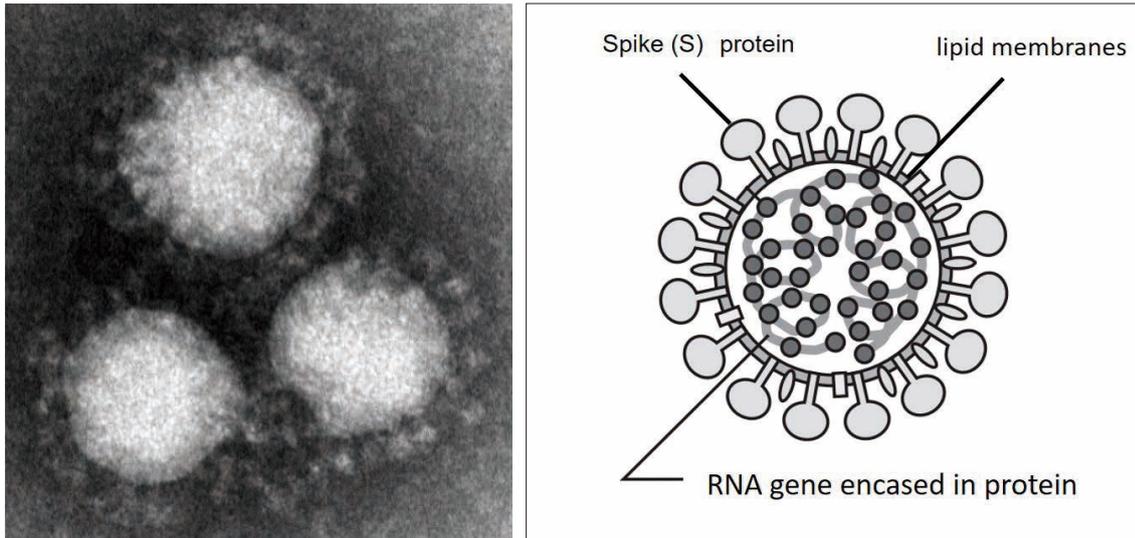


Figure 1. Coronavirus

Image of a coronavirus observed under an electron microscope. The name “corona,” which means “crown” in Latin, was given to the virus because of the appearance of protrusions on the surface of the virus, which look like a crown. The protrusions observed under an electron microscope are viral proteins that have been impaled on lipid membranes and are called spike. Images provided by National Institute of Infectious Diseases.

1. RNA dependent RNA polymerase: RdRp

Except for viruses^{*2}, all living organisms store genetic information in the form of DNA, and the information is transmitted in the order of DNA (nucleic acid), RNA (nucleic acid), and protein. Therefore, almost all organisms only have enzymes that replicate DNA from DNA or transcribe RNA from DNA. In contrast, RNA viruses, including

coronaviruses, are the only ones that conserve genetic information in the form of RNA. Thus, they require an enzyme that copies RNA from RNA, namely, RNA-dependent RNA polymerase (RdRp). Since RdRp is a special enzyme present only by RNA viruses, it is an ideal target for anti-viral drugs.

2. Virus-derived protease

When a coronavirus infects its host cell, it first produces a large polyprotein, which is then cleaved by viral proteases to form smaller functional proteins. To use a common example, when assembling a plastic model, scissors are needed to separate the parts; the protease has the role of

these scissors. Just as a plastic model cannot be made without scissors, the virus cannot grow as a large protein. Hence, it must be cut into smaller proteins. For this reason, viral proteases are also targets of antiviral drugs.

3. Host-derived protease

The coronavirus S protein mediates viral entry into the cell through a process of membrane fusion, whereby the membranes of the virus and the host cell are fused. For this process to occur, the S protein must be cleaved and activated

by a host protease. Thus, drugs that suppress host proteases, which are different in structure and location of action from the viral proteases mentioned above, may also have antiviral activity.

What is the scientific evidence-based evaluation of a therapeutic drug?

The antiviral effect of a candidate drug may be assessed *in vitro*, *in vivo* (animal experiment), or in a clinical study on human subjects. The quality of the scientific evidence clearly differs between different types of clinical studies, and the higher up the pyramid in **Figure 2** the study is, the higher is the level of evidence it provides. Clinical studies can be divided into two main types: observational studies, where the course of symptoms and side effects after administration of the candidate drug are observed without intended intervention; and interventional studies, where researchers actively intervene for the purpose of studying the effects of a therapeutic drug.⁹⁾ Interventional studies are further

divided into randomized (RCTs) and non-randomized (non-RCTs) control trials, depending on whether subjects were randomized (randomization). RCTs provide the highest level of evidence, while non-RCTs provide a lower level of evidence. In addition, there exist secondary studies (e.g., systematic reviews) that collect and comprehensively analyze the results of these RCTs. The current view by many experts that “the efficacy of a candidate drug must be adequately supported by scientific evidence from clinical studies” is tantamount to saying that “the efficacy must be evaluated based on the results from RCTs”.¹⁰⁾

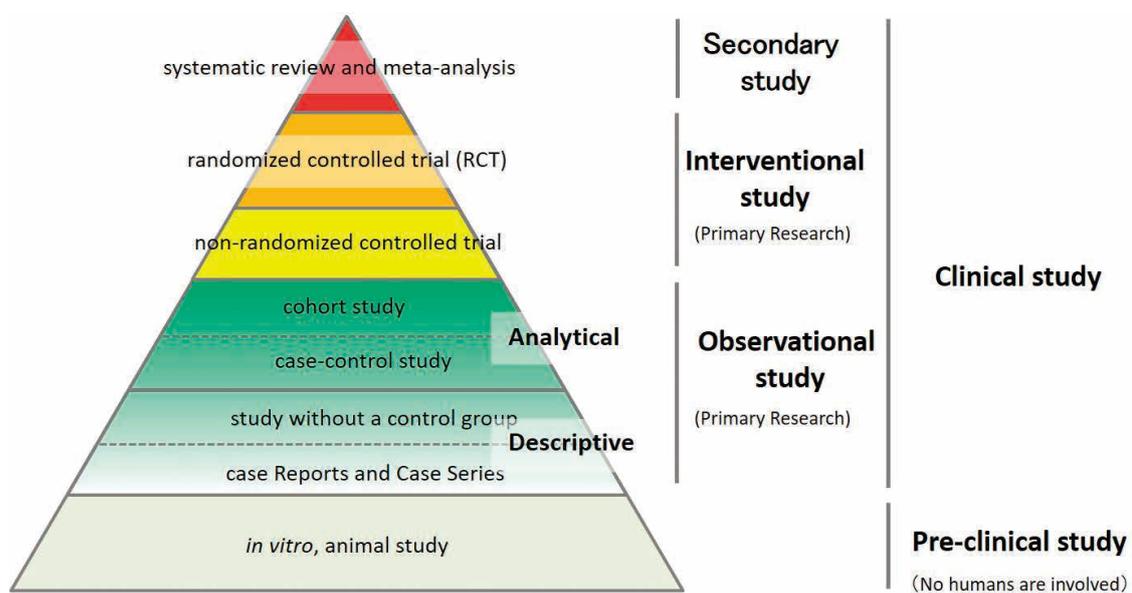


Figure 2. Classification pyramid of the level of evidence of different clinical studies

The strength of the scientific evidence gets stronger further up in the pyramid. Clinical studies are divided into two main categories: observational studies, where the researcher simply observes the treatment and course of events as they occur; and interventional studies, where a researcher adds an intervention to a subject for research purposes. Interventional studies are categorized into randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs), depending on whether the subjects are randomly assigned. Observational studies are classified into descriptive studies, which do not provide comparisons, and analytical observational studies, which provide comparisons and controls. As of June 2, 2020, the observational studies of domestic drug candidates fall into the category of descriptive observational studies without control group.

Randomized controlled trials: RCTs

These provide the highest level of evidence among interventional studies. Infected patients meeting certain conditions are randomly assigned to multiple groups (randomization); one group is given a candidate drug and the other is given a sham drug (placebo-controlled) or an existing treatment to evaluate treatment and side effects. To avoid potential bias in the data resulting from

information that may influence the patients or doctors, patients (single-blind) or both patients and doctors (double-blind) are often unaware of which group received the real medicine (blinding). In contrast, unblinded studies, known as “open-label,” studies, contribute to a lower level of evidence.

Observational studies

Although there are various levels of observational studies, they involve administration of a candidate drug for therapeutic purposes and the follow-up of subsequent symptoms and side effects. Following this, the collected data are analyzed. Observational studies are further divided into analytical, which provide comparisons with control groups, and descriptive, which do not provide comparisons with control groups (**Figure. 2**). In such studies, however, the use of an infected unmedicated group as a comparison (control) is challenging because the candidate drugs are administered for therapeutic purposes. Furthermore, since approximately 80% of the cases resolve on their own without treatment, it is not possible to clearly judge the effect of a medication, even if the symptoms improved after its administration. At present, most clinical studies reported in Japan are observational studies lacking a control group. The level of evidence of such studies, as shown in **Figure 2**, is rather low. For this reason, caution must be exerted in their interpretation.

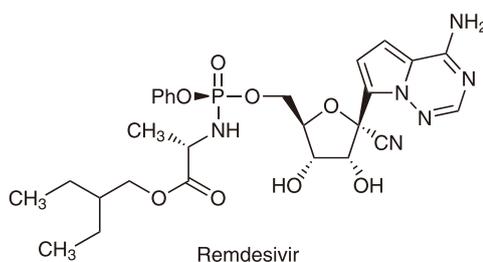
In addition, clinical trials are conducted after non-clinical studies in animals in stages ranging from Phase I to Phase III, and RCTs are often conducted in Phase III. Normally, a drug is approved if its therapeutic efficacy has been confirmed in clinical trials. However, in the case of COVID-19, drugs are being approved before the results from clinical trials are collected, as long as their efficacy and safety have been confirmed in observational studies.¹¹⁾ The Japan Medical Association has issued a statement saying that “candidate drugs with insufficient scientific evidence should not be approved as therapeutic drugs, even in an emergency situation.”¹⁰⁾ In addition, the results from RCTs are usually published in medical journals after rigorous peer review; however, there have been a few cases where the pre-peer review content was reported in the press, leading to misunderstandings.^{12,13)} Moreover, some journals have temporarily retracted those papers after peer review,¹⁴⁾ which results in significant challenges in the identification of accurate information.

Mechanism of action of candidate drugs and results from clinical studies

Candidate drugs can be classified into: antiviral drugs that directly suppress viral growth and drugs that improve acute respiratory distress syndrome and the cytokine

storms caused by severe illness. All the candidate drugs in **Table 1** belong to the antiviral category.

1. Remdesivir (Veklury® : Gilead Sciences, USA)



Remdesivir^{*3} was developed for the treatment of Ebola virus disease. RCTs in patients with Ebola showed that remdesivir was less effective than monoclonal antibody therapy, and it has now been discontinued.¹⁵⁾

Mechanism of action: RdRp inhibition

Remdesivir is a nucleotide analog. A nucleotide is a substance made up of sugar bases (abbreviated as A, C, G, T, U) and phosphate groups, which are connected to form DNA and RNA. The same A (adenine) has a slightly different structure in RNA and DNA, and when taken into the body, the structure of remdesivir resembles that of the A (adenine) used in RNA.¹⁶⁾ Humans have the enzyme DNA-dependent RNA polymerase (DdRp), which transcribes RNA from DNA and can distinguish between remdesivir and A (adenine). Therefore, DdRp

does not inadvertently take up remdesivir. In contrast, RdRp, present only in RNA viruses, cannot distinguish between the two. Therefore, it is thought that remdesivir exhibits antiviral activity by inhibiting viral RNA synthesis because of the accidental uptake of remdesivir.¹⁶⁾ Indeed, remdesivir shows antiviral activity against a wide range of RNA viruses, including coronaviruses.^{17,18)} However, although nucleotide analogs targeting RdRp have been widely developed, there are some cases where the analogs have been effective against other RNA viruses but not against coronaviruses.¹⁹⁻²¹⁾ This may be because some RNA viruses, including coronaviruses, have other viral proteins (ExoNs) that have a proofreading activity and remove nucleotide analogs.²²⁾ Therefore, the development of nucleotide analogs exhibiting anti-coronaviral activity has proven difficult,

because a fine balance between RdRp take-up and ExoN removal the analogs is not easily met. However, remdesivir is a drug that has this balance admirably.

Results from clinical studies

Two double-blind, placebo-controlled RCTs of remdesivir have been reported. The first was a global trial, in which Japan participated, involving 1,053 moderately and critically ill patients. Clinical outcomes were compared between the remdesivir and placebo groups. Time to recovery was 11 days in the remdesivir group and 15 days in the placebo group; mortality by day 14 was 7.1% in the remdesivir group and 11.9% in the placebo group. These results suggested the efficacy of remdesivir. Importantly, a significant difference was found in moderate cases, but not in severe cases requiring a ventilator. Notably, a significantly higher effect was found in the white population compared with the black population, and almost no effect was observed in Asians.²³⁾ The second trial was carried out on 237 moderately ill patients at a hospital in Hubei

Province, China. Although the number of cases was not enough to warrant a large trial, no clinical improvement was identified in the remdesivir group compared to the placebo group.²⁴⁾ In addition, a Gilliard-led RCT of 397 critically ill patients, open-label and without placebo group, compared remdesivir in a 5-day vs. 10-day group and found no difference in clinical symptoms between the two.²⁵⁾

Based on the above results, the United States Food and Drug Administration approved the drug on May 1. In response, Japan simplified the process, which usually takes more than a year from application to approval and gave special approval on May 7. This makes remdesivir the first new type of coronavirus treatment in Japan. However, remdesivir is intended for severely ill patients, and the supply of remdesivir to Japan is limited for the time being, it cannot be used for patients with minor illnesses. Further, it is important to note that the current data do not provide evidence of treatment efficacy in Asians.

2. Favipiravir (Avigan® tablet: Fujifilm Toyama Chemical, Japan)



Avigan® was developed as a flu treatment. According to the manufacturer's literature, a non-inferiority study comparing tamiflu® and avigan® without placebo group (which focused only on whether the developed drug was inferior to the existing drug) found no inferiority over tamiflu®.²⁶⁾ Incidentally, tamiflu® was found to be effective in reducing flu symptom by half a day (0.7 days) in healthy adults according to a 2014 systematic review.^{27,53)} In animal studies using avigan®, the risk of fetal deformities has been recognized. Thus, it is a special approved drug manufactured at the request of the government only when a new strain of influenza is prevalent and other drugs are ineffective.

Mechanism of action: RdRp inhibition

Avigan® is a nucleotide analogue similar to remdesivir. When ingested, its structure resembles that of A (adenine) and G (guanine), which are used in RNA, and is thought to exhibit antiviral activity by inhibiting the synthesis of RNA when it is mistakenly taken up by RdRp.²⁸⁾ Similar to remdesivir, it also shows antiviral activity against a wide range of RNA viruses.²⁹⁾ Although avigan® is not remarkably effective against the novel coronavirus *in vitro*, tests against the Ebola virus have shown good results in *in vivo* animal studies.

Thus, avigan® is expected to show good *in vivo* clinical results.¹⁸⁾

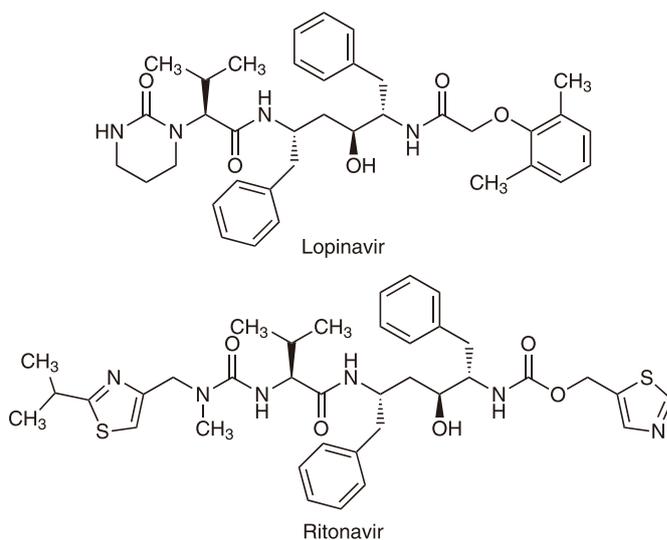
Clinical trial results

Results from a high level of evidence from an RCT (e.g., peer-reviewed article) for avigan® are yet to be reported. A study from China comparing 35 patients treated with avigan® to 45 patients treated with the anti-HIV drug kaletra® (see below) showed shorter viral resolution time and faster improvement in chest CT imaging.¹⁴⁾ However, this was an open-label, non-randomized RCT (additionally, both groups received concurrent interferon- α therapy). Another study from China, a pre-reviewed paper, compared 116 subjects who were administered avigan® with 120 subjects who were administered albidol (an influenza drug from China) in an open-label, uncontrolled RCT, and found no difference in clinical improvement between the two.¹³⁾ In Japan, an interim observational study showed that the symptoms of approximately 90% of patients with mild illness and 60% of patients with severe illness improved. However, since this was an uncontrolled observational study, it is impossible to clearly determine the treatment effect of avigan®.³⁰⁾

Avigan[®] is a highly anticipated drug candidate, with several studies from China and Japan, leaving the general public wonder why it has not been approved yet when it is supposed to be able to cure the disease. On the other hand, based on the interim report of a planned RCT in Japan,³¹⁾ the news have reported that “avigan[®] does not

show efficacy.”³²⁾ However, currently, there is insufficient scientific evidence, and it is premature to evaluate avigan[®] against novel coronaviruses. Clinical trials are still being conducted in various countries, and the results of these trials need to be carefully assessed.

3. Lopinavir/Ritonavir combination (Kaletra[®] tablets: AbbVie Inc., USA)



Kaletra[®] is one of the leading drugs in the primary and alternative treatment of HIV. It has been approved and commercialized domestically and internationally.

Mechanism of action: Viral protease inhibitor

When either coronavirus or HIV infects a cell, a large polyprotein is formed, which is then cleaved by a viral protease to produce smaller functional proteins. Lopinavir exhibits anti-HIV activity by inhibiting the action of the HIV protease. Ritonavir increases blood levels of the main ingredient, lopinavir, by inhibiting enzymes in the body involved in the metabolism and breakdown of the drug. In addition to case reports and observational studies showing that kaletra[®] improves symptoms of SARS and MERS,^{33,34)} computer simulations showed that lopinavir docked with the SARS-CoV-2 protease.³⁵⁾ However, the mechanism of HIV and coronavirus proteases is controversial because their structures are clearly different,³³⁾ high concentrations of lopinavir and ritonavir do not inhibit the growth of SARS-CoV in *in vitro* experiments,³⁶⁾ and no direct evidence of the inhibition of protease activity has been provided.

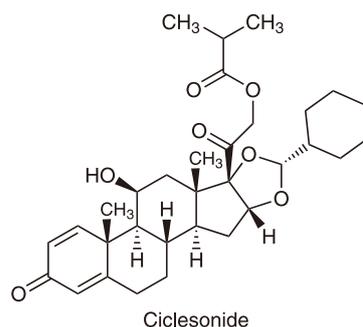
Clinical trial results

An open-label, controlled RCT of kaletra[®] was performed in 199 critically ill patients in China. When 99

patients in the kaletra[®] group were compared with 100 patients in the standard treatment group (no administration of kaletra[®]), there was no difference in time to clinical improvement.³⁷⁾ Thus, no effect of kaletra[®] on the novel coronavirus was observed. In contrast, an RCT (open-label, no placebo control) conducted in Hong Kong on 127 mild to moderate patients compared the kaletra[®] plus ribavirin (antiviral) group, the kaletra[®] plus interferon beta group, and the kaletra[®]-only group. The virus became undetectable in nasopharyngeal swabs after 7 days in the kaletra[®]-only group and after 5 days in the kaletra[®] plus other drugs groups, suggesting that the combination therapy with kaletra[®] and other drugs is effective for symptomatic relief and early virus elimination.³⁸⁾

Kaletra[®] has long been a promising candidate for the treatment of severe coronavirus diseases based on case reports and observational studies, and its RCT for MERS is planned.³⁹⁾ The drug was also used in China and Japan at the beginning of the COVID-19 epidemic.⁴⁰⁾ There is no doubt about the importance of case reports and observational studies, but the RCTs suggest that kaletra[®] alone is ineffective, indicating that clinical studies with high scientific evidence are essential.

4. Ciclesonide (Alvesco® inhaler: Teijin Pharma, Japan)



Ciclesonide is approved and commercialized in several countries for the treatment of asthma. In Japan, the antiviral effect of ciclesonide on novel coronaviruses was revealed in a study led by the National Institute of Infectious Diseases, in collaboration with Gunma University and the Nippon Veterinary and Life Science University (author).

Mechanism of action

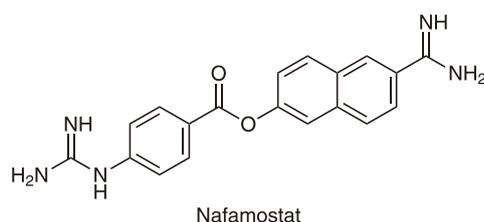
Ciclesonide is a steroidal anti-inflammatory drug, and a systematic review of SARS suggests that steroidal anti-inflammatory drugs have no benefit in the treatment of SARS and may rather delay viral exclusion in small RCTs.⁴¹⁾ Thus, the use of steroidal anti-inflammatory drugs in the treatment of severe coronaviruses has not been recommended. However, an examination of the anticoronaviral activity of ~90 steroidal compounds found strong antiviral activity in a small number of compounds, including ciclesonide.⁴²⁾ Analysis of the same in MERS suggests that ciclesonide acts on the NSP15 protein of the coronavirus.⁴²⁾ Although the mechanism of action is still unknown, it is known that host cells undergo apoptosis, which is a reaction that suppresses viral growth by

destroying infected cells before the virus multiplies, and that NSP15 suppresses this reaction.⁴³⁾ In other words, NSP15 suppresses apoptosis and increases the number of cells in which the virus can multiply, thus, ciclesonide may show antiviral activity by suppressing this process. Alternatively, since NSP15 is thought to be a member of the viral replication factory,⁴⁴⁾ the binding of ciclesonide to NSP15 may disrupt the overall balance of the viral replication factory. This, however, requires further analysis.

Clinical trial results

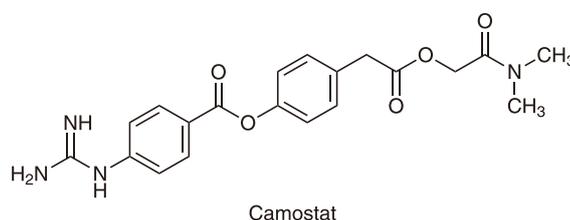
The antiviral effect of ciclesonide has been confirmed only *in vitro*.⁴²⁾ According to an interim report of an observational study of avigan®, ciclesonide was also concurrently administered in 865 of 2,081 of the 2,158 patients who received avigan® for whom dosing information was available (approximately 40%).³⁰⁾ A full observational study of ciclesonide is expected in June 2020, and an RCT is being planned.⁴⁵⁾ In addition, ciclesonide is an inhalational drug, so it acts only topically, has fewer side effects than medicated steroidal anti-inflammatory drugs, and is safer.

Nafamostat (Futhan® injection: Nichi-Iko Pharmaceutical, Japan)



Nafamostat has been developed and commercialized in Japan for the treatment of acute pancreatitis. The antiviral efficacy of nafamostat against SARS-CoV-2

has been presented by a group at the University of Tokyo.⁴⁶⁾ Camostat (Foipan®: Ono Pharmaceutical, Japan) is also a similar drug.



Mechanism of action: Host protease inhibitor

The S protein of coronaviruses becomes infectious when cleaved and activated by the host protease. Nafamostat acts by inhibiting the host protease. Coronaviruses, such as SARS and MERS, exploit two entry pathways depending on the localization of the host protease.^{48,49)} In the absence of an extracellular protease, the virus is taken up by the endocytosis. Following this, the S protein is activated by a protease (cathepsin)⁴⁷⁾ in the endosome, after which the virus enters the cell. By contrast, the presence of extracellular proteases (such as TMPRSS2) activates the S protein on the cell surface, allowing the virus to be invasive.⁵²⁾ For this reason, both cathepsin (E64d) and TMRPSS2 (nafamostat or camostat) inhibitors show strong antiviral activity when used together in *in vitro* evaluations, although camostat alone was found to be effective to a certain extent.^{18,50)}

Conclusion

We are currently taking a stand against SARS-CoV-2 with bare hands and need adequate weapons as soon as possible. Under these circumstances, research institutes, pharmaceutical companies, and government agencies worldwide are collaborating to develop therapeutic drugs and vaccines at an astonishing speed. It is a remarkable effort on the part of medical professionals who are obtaining data on candidate drugs for the treatment of COVID-19 amid confusion and fears of a medical collapse. Furthermore, to alleviate the anxiety of the public, which is under a great deal of self-restraint and restriction, the role of the press in releasing information on various candidate drugs and their effects and the government's attempt to approve promising candidate drugs earlier than usual are understandable. It is the hope of the scientific community that the therapeutic effects of the candidate drugs are proven as soon as possible and that lives are saved. However, given the lack of strong scientific data, the recommendation by the Japan Medical Association's recommendation¹⁰⁾ that "candidate drugs with insufficient scientific basis should not be approved as therapeutic drugs, even in an emergency situation." is a correct approach.

Current novel coronaviral drug candidates (some of which are therapeutic drugs) are just diversions of existing drugs (drug repositioning) whose efficacy is thought to be limited and are unlikely to become specialized agents like antibiotics against bacteria. Therefore, even if a drug

Nafamostat was reported to be more effective than camostat, and in an evaluation using calu-3 cells derived from airway epithelial cells, which are similar to the target cells of SARS-CoV-2, nafamostat alone inhibited infection at low concentrations.⁴⁶⁾ Thus, nafamostat is expected to be effective.

Clinical trial results

The antiviral efficacy of naphamostat has been confirmed only *in vitro*.⁴⁶⁾ In addition to observational studies, RCTs are currently being planned,⁵¹⁾ and the results will be closely monitored. Studies have shown that SARS-CoV-2 causes blood clot formation in the lungs, increasing the severity of the infection. Nafamostat is also effective in dissolving blood clots, thus, it may prevent not only the spread of the virus but also blood clot formation.

is scientifically proven to be "effective" on RCTs and other studies, it is crucial to judiciously evaluate the level of effectiveness. For example, tamiflu[®], thought to be a special agent against influenza, has been shown to shorten symptoms by about half a day in healthy adults.²⁷⁾ A press release from the British Medical journal that published the study said, "Approval and use of drugs should no longer be based on biased or incomplete information. The risk to the health and economy of our people is extremely high."⁵³⁾

All this information indicates that the press is going into overdrive, and we need a calm response to the various therapeutic agents behind which the public's overwhelming expectations are placed. Remdesivir, currently the only drug approved for COVID-19 treatment, is a potent weapon until the next good treatment is developed; however, it has not been shown to be effective in Asians to date, nor in treating severely ill patients on artificial respiration. In such an emergency, it is necessary to carefully consider the effectiveness, timing, and type of symptoms for the administration of the drug. The strongest weapon against SARS-CoV-2 appears to be a vaccine, unfortunately, it usually takes 1-1.5 years at the earliest to manufacture a practical vaccine.⁵⁵⁾ Fortunately, the search for candidate drugs and their clinical trials is still ongoing worldwide. Hopefully, we will find better treatments in the future.

*1 Infectious diseases caused by novel coronaviruses is called coronavirus diseases 2019 (COVID-19) and the causative virus is called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

*2 In textbook terms, a virus is not an organism because "anything that cannot grow on its own is not an organism."

*3 Candidate drugs have both generic names and brand names, but we have used names that are often seen in the press.

Avigan® is the product of Fujifilm Toyama Chemical Co., Tamiflu® is the product of F. Hoffmann-La Roche AG, Kaletra® is the product of AbbVie Inc., and Alvesco®

and Futhan® are owned by Covis Pharma B.V. and Torii Pharmaceutical Co, respectively. Foipan® is a registered trademark of Ono Pharmaceutical Co.

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