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Antivirals for Coexistence with COVID-19: Brief Review for General Physicians

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ABSTRACT

In order to end the coronavirus disease 2019 (COVID-19) pandemic that has lasted for nearly two years, it is most necessary to introduce antiviral drugs specific to COVID-19 along with the establishment of herd immunity by vaccination. Candidates currently being studied include nucleoside analogues that inhibit replication, protease inhibitors, and entry blockers. Not only the virus itself, but also the host protein that the virus uses in its pathogenesis is the target of treatment. Although the severe acute respiratory syndrome coronavirus 2 will not be completely eradicated, if the use of antiviral drugs is established, the COVID-19 pandemic will end through coexistence with the virus.

Keywords: Antiviral; COVID-19; SARS-CoV-2; With-Corona

'WITH-CORONA'

Now that almost two years have passed since the start of the coronavirus disease 2019 (COVID-19) pandemic,[1] the Korean government seems to be judging that the domestic pandemic has entered an adjustable range to some extent now. Starting in November 2021, the government is going to launch a policy - so-called 'With-Corona' - that it focuses all the capacity mainly on severe patients and relax regulatory policies such as social distancing. In fact, the term 'With-Corona' is a grammatically incorrect expression in English. However, the Korean government and media have already spread the word 'With-Corona' to the public to express the era of coexistence with the coronavirus, and the public has already accepted it as a routine term. Therefore, in this review, I will mainly use the term 'With-Corona' although it is close to a misnomer.

Many experts are concerned about this coexistence with COVID-19 policy. The first thing to consider is the fact that the current COVID-19 situation in Korea is not good. Since the summer of 2021, the number of confirmed cases, which had previously remained at around 1,000 per day, began to exceed 2,000 at the end of June. At the same time, the ratio of delta-variant also started to increase, and eventually, it accounted for nearly 100% of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) isolated from Korea as of October 2021.[2]

Another thing to consider is the vaccination completion rate. Since the COVID-19 vaccination campaign started in South Korea from the end of March 2021, as of October 25, the national vaccination rate has just exceeded 70%.[3] Considering the current vaccination rate, it is expected that the minimum requirement of over 70% to 80% will be reached by November.[4]

COVID-19 WILL NEVER EVER SAY GOODBYE TO US

It can be asserted that COVID-19 is unlikely to be completely eradicated.[5] Experts believe the pandemic could end as soon as protection system for high-risk groups is complete. However, even after completion of high-risk group protection, a complete recovery to the good old days will not be easy. COVID-19 will continue to occur and re-emergence will repeat every year. After all, we have to live with the virus by getting a regular vaccine every year. This is almost similar to coexistence with influenza. However, one more puzzle is needed.

THE FINAL PIECE OF THE PUZZLE FOR COEXISTENCE WITH COVID-19

We can live with influenza because there are vaccines such as flu-shot as well as specific antiviral agents such as oseltamivir. Therefore, 'With-Corona' is possible only when antivirals that specifically act on SARS-CoV-2 are added as a final puzzle.

However, the pandemic is still with us and there is not enough time to develop brand new antivirals right now. Therefore, most of the antivirals being reviewed so far can only be repurposed drugs.

In this review, I will briefly summarize the available antivirals that are currently under development or coming soon, and consider which antiviral should be selected as the most appropriate piece of the puzzle for the realization of 'With-Corona.'

THE IDEAL ANTIVIRAL AGENTS

Most of the antibiotics we use to attack bacteria exert a mechanism that directly destroys the bacteria themselves. So naturally, we tend to think that it would be ideal for antivirals to attack viruses directly as well. In fact, such an agent does exist. That is a disinfectant. However, the disinfectant is not a specific antiviral, and even harms human cells. Therefore, drugs that directly destroy and kill viruses cannot guarantee safety to humans. As such, the gap between the ideal antiviral and reality is very large. We have to target the other side of the virus. Thus, we examine the life cycle of the virus in detail and find the target there.[6,7]

ANTIVIRALS ON THE ASPECT OF VIRAL LIFE CYCLE

SARS-CoV-2 initiates invasion into the host cell with attachment and entry, and then produces viral proteins therein and proceeds with replication. After that, it advances through assembly and packaging, goes out of the cell, finds a new host cell, and moves on to the next life cycle. In this series of processes, we can select several targets (**Fig. 1**).

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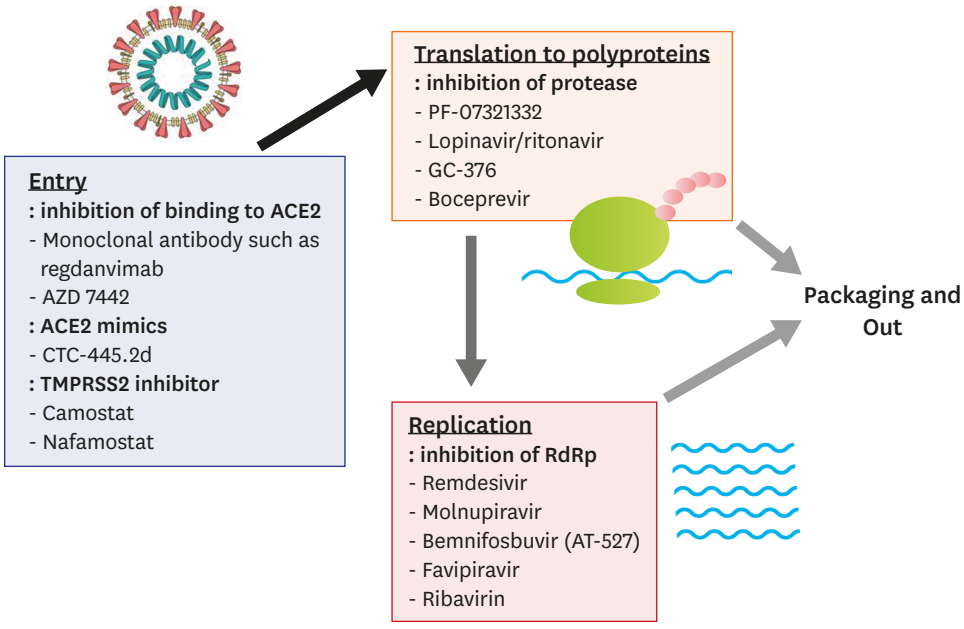

Fig. 1. Antivirals for the treatment of severe acute respiratory syndrome coronavirus 2 on the basis of viral life cycle.
ACE2 = angiotensin converting enzyme 2, TMPRSS2 = transmembrane protease serine subtype 2, RdRp = RNA-dependent RNA polymerase.
Part of the graphic of viral particle is from a site of the free vector image site, Image credit: Davian Ho for the Innovative Genomics Institute at https://innovativegenomics.org/free-covid-19-illustrations/.

Replication inhibitor

First of all, we must stop the virus from multiplying. RNA virus replication is driven by RNA-dependent RNA polymerase (RdRp).[8] Since the target of RdRp action is nucleotide or nucleoside, its analogues are used as antiviral agents to interfere with RdRp.[9]

The agents currently being tried for this purpose are remdesivir, molnupiravir, favipiravir, or ribavirin. However, before reviewing these drugs, there is a viral enzyme that must be noted: Do not forget the exoribonuclease.

Exoribonulcease corrects misreading by removing a mismatched nucleoside from the 3'-end of the RNA strand during RNA replication.[10]

RdRp inhibitors are nucleoside or nucleotide analogues that ultimately induce chain termination through mutation of viral RNA. However, when this exoribonuclease is activated, it is difficult for antivirals as RdRp inhibitors to perform properly. Corona virus is the most well equipped with this ribonuclease in particular among several RNA viruses.[11] For this reason, ribavirin is fundamentally poorly effective to coronavirus.[12]

Ultimately, overcoming this ribonuclease is the key to treatment success.

Remdesivir, which is currently being actively used in clinical battle field, is a 1'-cyano-substituted adenine C-nucleoside analogue.[13] Because remdesivir has a 3'-OH group in its structure, it does not cause immediate chain termination unlike other nucleoside analogues. Once chain elongation is in progress, the monitoring network of exonuclease is avoided for a while, and after all, chain termination occurs late only when three nucleosides are added more.[14]

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Molnupiravir (MK-4482, EIDD-2801) has a beta-D-N4-hydroxycytidine-5'-isopropyl ester structure and can be taken orally. This drug induces viral mutagenesis.[15]

As an analogue of cytosine, hydroxycytidine smoothly joins the RNA replication process and does not interfere with chain elongation. However, the trouble with viruses is that they are promiscuous, unlike pure cytosine. In principle, cytosine (C) should only bind to guanine (G), but hydroxycytidine also binds to adenine (A). More in detail, the hydroxylamine structure maintains a normal C:G relationship, but the oxime structure enables C:A bonding. The nucleotides that should not have been originally incorporated become members of the mRNA sequence. As a result, RNA mutation is induced, and the virus cannot survive any longer. Since molnupiravir is not a chain terminator, it safely survives viral exonuclease and is added to the viral RNA chain.[16,17]

AT-527 is an orally available hemi-sulfate salt of AT-511(bemnifosbuvir), originally for the treatment of hepatitis C virus (HCV).[18] This agent is also currently in the clinical trial process (ClinicalTrials.gov Identifier: NCT04889040).

Protease inhibitor (PI)

Coronaviruses have two types of viral protease: 3 chymotrypsin-like cysteine protease (3CLpro or Mpro, main protease) and Papain-like serine protease (PLpro). Among them, several PIs targeting Mpro are being investigated.[19]

PF-07321332 is an oral drug derived from PF-07304814, an injectable Mpro inhibitor, and is currently in clinical trial.[20]

Anti-retroviral PI such as lopinavir/ritonavir for the treatment of HIV-1 was once tried as a treatment regimen for COVID-19. While anti-retroviral PIs such as lopinavir/ritonavir are aspartic PIs, Mpro is a cysteine protease. In addition, HIV protease has a catalytic site for anti-retroviral PI, whereas coronavirus does not.[21] Therefore, it is probably difficult to expect any anti-coronavirus activity.

GC-376, originally used for feline infectious peritonitis due to coronavirus, and boceprevir, an HCV PI, are also being considered as treatments for COVID-19, but further validation is needed.[22]

Entry inhibitor

The most fundamental protection is to block the entry of the virus. In particular, several neutralizing antibodies that directly block the spike protein of coronavirus have been developed and used in actual clinical practice. In Korea, regdanvimab (CT-P59) has been developed and used in mild to moderate patients within limited indications. In animal experiments, it was suggested that regdanvimab could be effective for delta-variant, but verification is still needed in actual clinical practice. [23]

AZD 7442 is an antibody preparation that has recently received attention.[24] This is an antibody mixture obtained from convalescent patients' serum, which has been engineered to be maintained for close to a year. In particular, it significantly reduced the risk of antibody-dependent enhancement, which was feared as a long-term complication, by greatly reducing Fc-receptors. A phase III trial is currently underway for the AZD7442 (NCT04625725).[25]

ANTIVIRALS TARGETING HOST PROTEINS

In the development of antiviral, we also need to shift our paradigm of thinking. Antivirals do not necessarily attack only viruses, and even if we interfere with pathways in the host used by the virus, we can sufficiently suppress the virus. Therefore, drugs targeting the host protein used by SARS-CoV-2 are also being actively investigated. Viruses can resist virus-targeting antivirals by mutation, whereas host proteins do not betray us. These drugs also have the potential to become broad-spectrum antivirals. In this respect, host-targeting antiviral may be a more ideal treatment than virus-targeting antiviral. However, there is a concern about toxicity in that it acts on the host. As of 2021, as host-targeting antivirals, CTC-445.2d, an angiotensin converting enzyme 2 (ACE2) mimic, is investigated.[26] As another entry-inhibitor, camostat and nafamostat, which inhibit transmembrane protease serine subtype 2 (TMPRSS2), are being studied.[27,28] In particular, camostat is an oral drug that is currently in clinical trial.[29]

OTHER ORAL ANTIVIRALS

Several antiparasitic agents were being considered for the treatment of COVID-19, but chloroquine and hydroxychloroquine were found to be ineffective.[30] Ivermectin is also being considered for potential as a treatment for COVID-19.[31] Artesunate/pyronaridine will be tested in the next phase of WHO solidarity trial.[32]

CURRENT STATUS IN SOUTH KOREA

In the early days of the COVID-19 pandemic, remdesivir was expected as a specific treatment agent. The effect was also verified in Korea, and relatively encouraging results were obtained.[33] Regrettably, in the WHO solidarity trial, remdesivir has reported to be little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients. The disappointing results came out that there was no clinical benefit.[30]

Currently, the Korean government is announcing that it will purchase molnupiravir by the end of 2021.

In a recent study, it has been reported that molnupiravir had a superior viral clearance rate compared to placebo group and was generally well tolerated.[34] As good results are coming out in the phase 2/3 clinical trial of molnupiravir that has been carried out so far, it is expected to be the most promising game changer as of October 2021.[35]

The most worrying aspect of the mechanism of this drug is that it is a mutation inducer. Of course, it is a drug that causes mutations in viruses and has little effect on human polymerase. However, as inferred from the case that nucleoside analogues used in anti-retroviral treatment are harmful to human mitochondrial DNA polymerase,[36] molnupiravir may induce mutations in human DNA or RNA.[37] Perhaps the risk will increase if this antiviral intervenes at a time when nucleoside replication in human cells is active. A typical example is pregnancy. Therefore, administration of this drug to pregnant women or children should be carefully considered.

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WE ARE STILL IN THE AGE OF UNCERTAINTY

The treatment agent for 'With-Corona' should satisfy the following conditions. First, it must be a drug that can be taken by mouth. Second, non-hospitalized patients with mild to moderate symptoms should be targeted. Finally, it should not be expensive. Among the above three conditions, molnupiravir currently satisfies the first two. However, the problem is that it is still expensive.

But we are optimistic that the price will be eventually adjusted to a reasonable level if demand for the drug grows. And this is an issue that should be dealt with as a concept of welfare at the government level. Fortunately, the South Korean government says it will pay for the drug for patients for the time being.[38]

Of course, no one knows yet whether molnupiravir will succeed in ending the COVID-19 pandemic. Unfortunately, if molnupiravir fails, we should hope for other RdRp inhibitors such as AT-527 or PIs, and so on. If specific antiviral is added to achieving herd immunity through vaccination, can we get out of the yoke of the COVID-19 pandemic? I expect that is possible, although COVID-19 will not completely disappear from the planet and will continue to accompany us as a seasonal cold. We are still living in an age of uncertainty, but I think we are wisely overcoming hardships with the power of rational thinking and science.

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