Guidance of antiviral drug treatment for COVID-19 1st edition
(26 Feb. 2020)

The Japanese Association for Infectious Diseases

1. Purpose

At present, there is limited knowledge about the treatment of COVID-19 with antiviral drugs. In the past, existing antiviral drugs have been used for patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Based on these facts, it is the purpose of this guideline to provide tentative guidance on antivirals for COVID-19 in Japan. The knowledge of COVID-19 is accumulating as the day progresses, and this guideline is scheduled to be revised when new and important findings regarding COVID-19 treatment emerge. In addition, since the causative virus of COVID-19 is SARS-CoV-2, strictly speaking, the term SARS-CoV-2 should be used in this guideline, but for clarity, it was unified to COVID-19.

2. Procedures for use

Currently, there are no drugs indicated for COVID-19 in Japan. The treatment that can be performed is the off-label use of drugs that have already been approved in Japan. In use, necessary procedures shall be taken in accordance with the guidelines for off-label use of each medical institute.

3. Subjects and timing of initiation of antiviral drugs

At present, the timing of antiviral drug initiation in a patient's clinical course requires that the patient develop hypoxemia and require oxygenation. And then, think as the following should be considered[1)].

1. In most cases, pneumonia is cured in the natural course of patients younger than 50 years old, so the course may be monitored without administration of antiviral drugs.
2. Patients aged 50 years or older are more likely to have severe respiratory failure and have high mortality, so consider administering antiviral drugs when hypoxemia requires oxygenation.
3. Patients with diabetes mellitus, cardiovascular disease, chronic lung disease, or chronic obstructive pulmonary disease due to smoking, immunosuppressive status, etc. shall also conform to the above 2.
4. Regardless of age, consider administration of antiviral drugs in patients whose respiratory failure tends to be worse with oxygen and symptomatic treatment alone.

4. Selection of antiviral drugs

This guideline presents the following drugs as therapeutic drugs from the viewpoint of availability and adverse events in Japan at this time. With the accumulation of findings such as clinical efficacy

and adverse events, it is highly likely that new information will be obtained on options and dosages of antiviral drugs for the treatment of COVID-19.

<Favipiravir>

Mechanism:

Favipiravir was approved by the Ministry of Health, Labor and Welfare in March 2014, limiting its indications and effects to "new or re-emerging influenza virus infections (limited to those in which other anti-influenza virus drugs are ineffective or insufficiently effective)".

Favipiravir is converted into T-705-ribosyl triphosphate (T-705RTP) in vivo, hence inhibiting viral RNA polymerase selectively. Therefore, it may be effective against RNA viruses as well as influenza virus.

In vitro and animal models:

The EC_{50} for COVID-19 in vitro is 61.88 μM, indicating an inhibitory effect. The EC_{50} is similar to that for Ebola virus.

Overseas clinical reports:

Currently, clinical trials (ChiCTR2000029600, ChiCTR2000029548) on the efficacy of Favipiravir against COVID-19 are ongoing according to the Chinese clinical trial registration site (results not yet disclosed).

Dosage in Japan:

There has been no use record of this drug in COVID-19 as of February 21, 2020.

Administration method (dosage and administration):

1. 3,600 mg (1,800 mg BID) (Day 1) + 1,600 mg (800 mg BID) (Day 2 or later) for up to 14 days

Precautions for administration:

1. Regarding the efficacy of favipiravir, it is unknown as to the appropriate severity and timing for administration.
2. The following drugs should be used with caution in combination with favipiravir due to potential drug interactions: 1) pyrazinamide, 2) repaglinide, 3) theophylline, 4) famciclovir, 5) sulindac.
3. Oral administration may be extremely difficult depending on the patient's condition. In this case, prepare the drug suspension by adding water heated to 55 ° C (simple suspension method). Insert a nasogastric tube into the subject, confirm that the nasogastric tube is in the stomach by chest X-ray, and slowly inject the suspension using a piston. Thereafter, the nasogastric tube is washed with 5

mL of water.

4. In animal studies, this product should not be administered to pregnant women or women who may be pregnant, as early embryos have been found to be lethal and teratogenic.

5. When administering to women who may become pregnant, perform a pregnancy test and confirm that the result is negative before starting treatment

The risk should be fully explained to patients, and guidance should be given with the partner during the administration period and for 7 days after the administration to ensure that extremely effective contraceptive methods are implemented.

If pregnancy is suspected during the administration of this drug, discontinue administration immediately and instruct patients to contact a physician.

6. Since this drug is transferred into semen, the risk should be sufficiently explained when administering to male patients, and it is extremely important to have sexual intercourse during the administration period and up to 7 days after the end of administration. Instruct that birth control methods should be thoroughly enforced (males must wear condoms).

Do not allow sexual intercourse with pregnant women during this period.

7. Prior to the start of treatment, the efficacy and risks (including the risk of exposure to the fetus) must be fully documented in patients and their families, etc., and administration should be started after obtaining written consent.

8. Careful consideration should be given to the necessity of this product for the administration of this product.

5. Other antiviral drugs against COVID-19 [2,3)]

Potential antiviral drugs that can be used to treat COVID-19 include remdecivir, interferon, and chloroquine. Future knowledge is awaited.

References

1) Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID19) in China]. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 2020;41(2):145-51.

2) Chong YP, Song JY, Seo YB, Choi JP, Shin HS, Rapid Response T. Antiviral Treatment Guidelines for Middle East Respiratory Syndrome. Infect Chemother. 2015;47(3):212-22.

3) England PH. Treatment of MERS-CoV: Information for Clinicians Clinical decisionmaking support for treatment of MERS-CoV patients 2015. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/459835/merscov_for_clinicians_sept2015.pdf.