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Antiviral Therapy in Corona Virus Disease-19 (Covid-19)

Laisa Azka[1], Irvan Medison[1], Dessy Mizarti[1]

[1]Department of Pulmonology and Respiration Medicine, Universitas Andalas, Padang, Indonesia.

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***Corresponding author:**
Laisa Azka

E-mail address:
pulmonologirespirologi@gmail.com

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a disease caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV), which was first identified in Wuhan City, Hubei Province, PRC. The total number of COVID-19 cases worldwide has reached 102 million cases with 54 million cases recovered and 2.3 million cases dead. Handling for this pandemic is still being carried out. In Indonesia, the antiviral drugs used are those that meet the Emergency Use Authorization (EUA) requirements, and are included in the COVID-19 management guidelines issued by the Ministry of Health. Antiviral options used are Oseltamivir, Favifirapir, Remdesivir. Until now, the use of antivirus is still being researched regarding the effectiveness and security of the antivirus used. Oseltamivir is used as an antiviral for COVID-19 with a mild clinical course, Favifirapir is used for mild to moderate clinical cases of COVID-19. For the use of remdesivir in COVID-19 patients with severe and critis clinical conditions.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a disease caused by a new coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, previously known as 2019-nCoV), which was first identified in Wuhan City, Hubei Province, PRC. Data from WHO until the second week of February 2021, the total number of COVID-19 cases worldwide has reached 107 million cases with 54 million cases recovered and 2.7 million cases died. Until now, the data continues to increase, this indicates that this pandemic will not end[1]

Handling of this pandemic is still being carried out, starting from non-pharmacological management, pharmacology, to vaccines to prevent the pandemic from continuing. Because COVID-19 is caused due to a viral infection, curative therapy for COVID-19 is to use antivirals. However, all antivirals used in COVID-19 therapy in almost all countries are still trial and error. Some of them refer to the antiviral therapy used during the SARS and MERS epidemics a few years ago, as well as in Indonesia, at the beginning of the pandemic there was no definite guide in dealing with COVID-19, and only relied on existing preparations. With the COVID-19 outbreak in China starting to subside, Indonesia is trying to refer to China regarding the drugs used, including chloroquine, oseltamivir, and avigan.[2,3]

In Indonesia, the antiviral drugs used are those that meet the Emergency Use Authorization (EUA) requirements and are approved by the Food and Drug Supervisory Agency (BPOM) and are included in the COVID-19 management guidelines issued by the

Ministry of Health. Based on the first edition of the COVID-19 management guidelines, July 2020, there is no antiviral option that is used to treat COVID-19. But BPOM has applied Chloroquine or hydroxylchloroquine as drugs with EUA status for this COVID-19 pandemic. This choice is based on the availability of drugs in Indonesia. In addition to chloroquine and hydroxychloroquine, azithromycin, oseltamivir and favipiravir began to be used in the early phases of the COVID-19 pandemic. Based on the August 2, 2020 edition of the COVID-19 management guidelines, antiviral therapy used is azithromycin, chloroquine or hydroxychloroquine, oseltamivir, lopinavir + ritonavir, fapivirapir, or remdesivir. The combination used is based on the degree of disease.[4] But in the third edition of the COVID-19 management guideline, December 2020, the use of chloroquine or hydroxychloroquine and lopinavir + ritonavir was discontinued by the BPOM for EUA status. on COVID-19.

Epidemiology of COVID-19

Coronavirus disease 2019 (COVID-19) was first reported to the World Health Organization (WHO) on 31 December 2019. On 30 January 2020, WHO declared the COVID-19 outbreak a global health emergency.[1]

Data from WHO until the second week of February 2021, the total number of COVID-19 cases worldwide has reached 107 million cases with 54 million cases recovered and 2.7 million cases died. Until now the data continues to increase, this indicates that the pandemic is not over.[2] The first COVID-19 was reported in Indonesia on March 2, 2020, in the number of two cases. As of the second week of February 2021, the total number of confirmed COVID-19 cases in Indonesia has reached 1.1 million cases with 900 thousand recovered cases and 28 thousand dead cases. The average increase in cases per day reached 10 thousand cases.[2]

Morphology and pathogenesis of COVID-19

The SARS-CoV-2 virus has a spherical morphology that looks like a solar corona with a diameter varying from about 60-140 nm and a spike of about 9-12 nm. The SARS-CoV-2 virus contains nucleocapsid protein (N), spiceglycoprotein (S), membrane glycoprotein (M), envelope glycoprotein (E) as structural components.[4.5]

This virus infects cells in the airways that line the alveoli. SARS CoV-2 will bind to receptors and create entry into cells. The virus enters the host cell by recognizing the ACE2 receptor via a spiceglycoprotein that induces membrane fusion, resulting in the release of the viral genome in the cytoplasm. Ribonucleic Acid (RNA) virus undergoes translation into polyproteins which are then cleaved by the coronavirus protease (CLpro) enzyme to form nonstructural proteins such as RNA dependent RNApolymerase (RdRp) for RNA virus replication. Positive sense RNA viruses then undergo translation into structural proteins (N, S, M and E) where S, M and E are processed in the endoplasmic reticulum (ER), while N protein is processed in the cytoplasm where it collects with RNA viral replicas. All components are then combined in the ER-golgi intercompartment (ERGIC), where virions are released inside the vesicle and secreted outside the cell by exocytosis.[5]

When the virus enters cells, its antigen will be presented to Antigen Presenting Cells (APC) cells which are the center of the body's antiviral immunity. The antigenic peptide presented a major histocompatibility complex (MHC) and was subsequently recognized by Cytotoxic T lymphocytes (CTL). The presentation of the SARS-CoV antigen depends on the MHC I molecule, but MHC II also contributes to the presentation. The antigen presentation further stimulates humoral and cellular immunity of the body which is mediated by B and T cell viruses. The antibody response to the SARS-CoV virus has a distinctive pattern of production of Immunoglobulin M (IgM) and Immunoglobulin G (IgG). SARS-specific IgM antibodies disappear at week 12, whereas IgG antibodies can last a long time.[5.6]

Case definition and degree of disease

The COVID-19 cases are divided into 3 categories, namely suspected cases, probable cases, confirmed cases, close contact.[8.9]

Suspect case

A suspect case is someone who has one of the following criteria: [8,9]

1. A person who meets one of the clinical criteria and one of the epidemiological criteria. The clinical criteria referred to are acute fever / history of fever and cough; or there are 3 or more acute symptoms / signs such as fever / history of fever, cough, fatigue (fatigue), headache, myalgia, sore throat, coryza / runny nose / stuffy nose, shortness of breath, anorexia / nausea / vomiting, diarrhea, decreased consciousness and epidemiological criteria, namely within 14 days before symptoms appear, having a history of living or working in a high-risk place or traveling in a country / territory of Indonesia that reports local transmissions or working in health care facilities, both performing medical and non-medical services, and officers carry out investigative, case monitoring and contact activities.
2. Someone with a serious ARI
3. A person without symptoms (asymptomatic) who does not meet epidemiological criteria with a positive SARS-CoV-2 rapid antigen

Probable case

A probable case is someone who has one of the following criteria: [8,9]

1. A person who meets clinical criteria, and has had a history of close contact with a probable or confirmed case or associated with the COVID-19 cluster.
2. Suspected cases with radiological images suggestive of COVID-19.
3. A person with acute symptoms of anosmia (loss of smell) or ageusia (loss of taste) with no other identifiable cause
4. Adult who died with respiratory distress and had a history of close contact with probable or confirmed cases, or related to the COVID-19 cluster

Confirmation case

A confirmed case is a person who has tested positive for the COVID-19 virus with the following criteria: [8.9]

1. A person with a positive RT-PCR result
2. A person with a positive SARS-CoV-2 rapid antigen result and meets the criteria for defining probable or suspected cases (criteria 2 or 3)
3. An asymptomatic person with a positive SARS-CoV-2 rapid antigen and has a history of close contact with confirmed or probable cases.

Confirmed cases are divided into 2:

a. Confirmation case with symptoms (symptomatic)
b. Confirmation cases without symptoms (asymptomatic)

Close contact

People who have a history of contact with probable cases or confirmed cases of COVID-19. The contact history referred to, if: face to face / adjacent to a probable case or a confirmed case within 1 meter and within 15 minutes or more; Direct physical contact with probable or confirmatory cases (such as shaking hands, holding hands, etc.); People who provide immediate care for probable or confirmatory cases without wearing standard-compliant PPE. [8.9]

Degree of disease

Based on the severity of the case, COVID-19 can be divided into asymptomatic, mild, moderate, severe and critical.

a. No Symptoms

The patient was confirmed but had no symptoms.

b. Light

Symptomatic patients without evidence of viral pneumonia or without hypoxia. Symptoms that appear include fever, cough, fatigue, anorexia, shortness of breath, myalgia and other non-specific symptoms.

c. Moderate

Patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia. Signs of severe pneumonia: including SpO2> 93% with room air or Children: patients with clinical signs of moderate

pneumonia (cough or difficulty breathing + rapid breathing and / or chest wall traction) and no signs of severe pneumonia.

d. Severe / Severe Pneumonia

Patients with clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) and respiratory rate> 30 bpm, severe respiratory distress, or <93% SpO2 in room air.

e. Critical

Patients with Acute Respiratory Distress Syndrome (ARDS), sepsis, and septic shock

Antivirus management

Antivirus compliant with COVID-19 protocol

Research on effective treatments and vaccines against this virus is still ongoing. Several drug options are available although the scientific evidence is disputed. In Indonesia, the antiviral drugs used are those that meet the Emergency Use Authorization (EUA) requirements.[10]

1. Azithromycin

Azithromycin is a macrolide antibiotic that can prevent respiratory infections. In vitro studies have shown that azithromycin can prevent the replication of the H1N1 influenza virus and the zika virus and has immunomodulatory and anti-inflammatory effects.[28] Azithromycin is a weak base that can accumulate intracellularly in endosome and lysosome vesicles, thereby increasing pH and inhibiting endocytosis and viral replication. Azithromycin does not affect viral adherence to the cell surface but inhibits internalization into the host cell during the initial phase of infection, targeting viruses that have just germinated from the host cell and deactivating their endocytic activity.[28] Because of this azithromycin can reduce viral load. Apart from that azithromycin provides immunomodulatory effects, Azithromycin is considered to have antiviral properties that may work in synergy with other antiviral drugs. In a non-randomized open label study in France, hydroxychloroquine and azithromycin showed the highest virological cure rates after 6 days of treatment. The results of these studies demonstrated a reduction in the duration of viral spread, less hospitalization and reduced mortality from azithromycin-hydroxychloroquine combination compared with those who were not treated.[28] But the combination of hydroxychloroquine and azithromycin led to a significant lengthening of the QT interval compared to patients on hydroxychloroquine alone. Multiple clinical trials are underway to evaluate azithromycin administration alone for COVID-19. Based on the guidelines for the management of COVID-19, the recommended dosage of azithromycin is:

- Mild degree: azithromycin 1 x 500 mg daily for 5 days
- Moderate degree: azithromycin 500 mg / 24 hours per iv or orally (for 5-7 days)
- Severe or critical degree: azithromycin 500 mg / 24 hours per iv or orally (for 5-7 days) [8.9]

Azithromycin has the side effect of prolonging the QT interval. Therefore EKG examinations prior to drug administration and serial ECG during drug administration should be performed. [28]

2. Oseltamivir

Oseltamivir is available in the form of oseltamivir phosphate which is metabolized by the gastrointestinal and hepatic esterase enzymes to form the active form oseltamivir carboxylate. The safety of this drug is quite good, and is only available in oral dosage form. Oseltamivir is approved for the treatment and prevention of influenza types A and B.[11] Oseltamivir has EUA status in Indonesia as an antiviral for COVID19. The reason for its use for the COVID-19 pandemic is because there are no other drugs available for mild COVID-19 infections. Effectively used for mixed infections with covid and influenza.[12]

Mechanism of action of oseltamivir phosphate is a selective and potent inhibitor of influenza A and B virus neuroimidase enzymes, thereby inhibiting influenza virus infection and replication in vitro.

Viral neuroimidase enzymes play an important role in the release of newly formed viral particles from infected cells and the spread of viral transmission. The dosage used is adults and children ≥ 13 years, 75 mg 2 times a day for 5 days. The dosage for children 1-12 years is adjusted according to body weight. Oseltamivir

has not been shown to be safe for pregnant and lactating women (category C). Contraindication to oseltamivir is hypersensitivity to oseltamivir phosphate and other additives. The most commonly reported side effects are nausea, vomiting, abdominal pain, epistaxis, hearing impairment and conjunctivitis. The elimination of this drug is mainly through the kidneys.[13]

The effectiveness of using this drug for COVID-19 is still inconclusive. Several clinical trials are still being conducted. Unlike the influenza virus, the corona virus does not require neuraminidase to escape from the host cell. After replicating in the host cell, the corona virus needs the help of viral E protein and the exocytosis process to escape. In January 2020, there were case reports in China of patients infected with the SARS-Cov2 (COVID-19) and influenza A viruses. In that case oseltamivir was given to treat coinfection with the influenza type A virus, not specific for COVID-19.[13,14] The most commonly reported side effects are nausea, vomiting, abdominal pain, epistaxis, hearing loss, and conjunctivitis.[13]

3. Favipiravir / Avigan

Favipiravir was first developed by Toyama Chemicals Japan (trademark: Avigan), and in 2014. Subsequent studies have shown the effectiveness of favipiravir against the Ebola virus.[15] This drug has EUA status in Indonesia for covid-19. Favipiravir is a prodrug that undergoes intracellular ribosylation and phosphorylation. to the active form favipiravir-RTP. Favipiravir-RTP binds to and inhibits viral RNA-dependent RNA polymerase (RdRp), resulting in inhibition of transcription and replication of the viral genome. The RdRp catalytic domain is similar among RNA viruses, giving favipiravir a broad spectrum of antiviral RNA. Because humans do not have RdRp, Favipiravir is relatively safe to use. However, the use of favipiravir should be avoided in pregnant women because it has teratogenic and embryotoxic risks.[16]

Favipiravir is widely distributed in the body, including to the trachea and lungs. Favipiravir is metabolized in the liver into the main metabolite (M1) by the enzyme aldehyde oxidase (AO), while the active metabolite (favipiravir-RTP) is formed intracellularly. Linear Cmax values at doses of 30 mg to 1600 mg. The half-life is +/- 6 hours, and is prolonged at high doses (≥800 mg). The favipiravir metabolite is excreted via the kidneys.[16,17] In phase 3 clinical trials for influenza treatment, the side effects of favipiravir were increased uric acid levels, gastrointestinal disorders, diarrhea, and increased AST & ALT. Favipiravir is also not recommended for children, pregnant and lactating women and those with impaired kidney function. Data on the clinical use of favipiravir in high-risk patients are limited. The doses given were 2 x 1600 mg / day for the first day and 2 x 600 mg / day for the second day to the fifth day. Especially for those who have impaired hepatic function, the dose given is 2 x 600 mg from day one to day five. This drug preparation is a 200 mg tablet.[17,18]

Research on favipiravir that includes A total of 320 COVID-19 patients in China are claimed to prove the efficacy and safety of favipiravir, but a full report on the results of the study has yet to be published. One of these studies, an open label non-randomized controlled study, was conducted in Shenzhen China in 80 COVID-19 patients (35 favipiravir and 45 lopinavir / ritonavir). In addition to receiving favipiravir, subjects in both groups received interferon alpha 1b 5 million units of inhaled aerosol twice a day. Favipiravir is given orally for 14 days with the first day dose of 1600 mg twice a day, followed by 600 mg twice a day (days 2 to 14). As a result, viral clearance time was shorter in the favipiravir group (median 4 days) than in the lopinavir / ritonavir group 11 days). There were no serious side effects in the favipiravir group, and fewer adverse events in the favipiravir group, including diarrhea, impaired liver function and nutritional deficiencies. Patients with severe respiratory disease requiring ICU care were excluded, so the efficacy and safety of favipiravir in this group need further investigation. Based on the results of the above study and other unpublished studies, favipiravir is licensed for distribution in China for indication of COVID-19 treatment. Other research into favipiravir is still ongoing in China and Thailand[18]

4. Remdesivir

Remdesivir is a broad spectrum antiviral that exhibits in vitro activity against SARS-Cov-2, SARS-Cov, and MERS-Cov. The study of remdesivir used in rhesus monkeys infected with SARS-Cov-2 demonstrated efficacy, but did not reduce viral load in the nose, mouth and rectum. A study conducted by Beigel et al in 2020 stated that remdesivir was effective in reducing mortality in severe cases of Covid.[19] On May 1, 2020, the US Food and Drug Administration (USFDA) issued an authority for the emergency use of Remdesivir for handling Covid 19. Based on this, remdesivir received EUA from BPOM Indonesia. From several in-vitro tests and in vivo, remdesivir exhibits strong antiviral activity. Indications are for adult, adolescent, and child confirmed positive for severe COVID-19 who are treated with oxygen saturation <94%, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[20,21]

The mechanism of action of remdesivir is an adenine nucleotide analogue with broad-spectrum antiviral activity against various RNA viruses, such as SARS, MERS and Ebola. Remdesivir undergoes efficient metabolic conversion in cells and tissues to an active nucleoside triphosphate metabolite which inhibits viral RNA-dependent RNA polymerase (RdRp) which will lead to termination of viral RNA replication, but does not inhibit the patient's RdRp. This drug is an enzyme inhibitor for several drug-metabolizing enzymes in the liver.[22,23]

Remdesivir is given by intravenous infusion. This medicine is not recommended for people with COVID-19 with chronic kidney disease (CKD), it is not recommended to give it together with other antivirals because antagonism, synergy or no effect may occur. Dosage for use in adults, day 1, 200 mg IV once a day (infused for> 30 minutes) as a loading dose. Days 2 to 10 are given 100 mg IV once a day (infused for> 30 minutes). Use in children weighing <40 kg, day 1, 5 mg / kg IV once a day (infused for> 30 minutes) as a loading dose. Day 2 to 10 2.5 mg / kg IV once daily (infused for> 30 minutes) .24 Modification of remdesivir dose in patients with renal impairment:[25]

- Pharmacokinetics has not been evaluated in patients with renal impairment
- Use in patients with renal impairment is based on consideration of potential risks and benefits
- eGFR ≥30 mL / min: no need for dose adjustment
- eGFR <30 mL / minute: not recommended unless potential benefits outweigh potential risks

Modification of the dose of remdesivir in patients with liver disorders:

- Not yet evaluated; it is not known if dosage adjustments are required
- Use only if the potential benefits outweigh the risks

A study comparing remdesivir (158 patients) vs placebo (79 patients) in severe COVID-19 patients showed that the duration of recovery was not significantly different in the two groups (21 days vs 23 days) .23 Mortality was also not significantly different in the two groups (14% vs 13%). Adverse events were reported in 102 (66%) / 155 remdesivir recipients vs 50 (64%) / 78 placebo recipients. Most common side effects of remdesivir: constipation, hypoalbuminaemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin.[23,25]

Based on a clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) comparing remdesivir vs placebo with a total of 1063 COVID-19 patients, it was found that remdesivir could shorten the recovery of COVID-19 from ± 15 days to 11 days (p <0.001) .22 Mortality in the remdesivir vs placebo arm: 8% vs 11.6% (p = 0.059). Gilead-sponsored clinical trials say the most common side effects (> 10%) are nausea and acute respiratory failure. Elevated liver enzyme (ALT) levels of 3 or more occurred in 7.3% (n = 28/385) of patients. Three percent (n = 12/397) of patients discontinued remdesivir treatment because of elevated liver enzymes. Data from the Gilead-sponsored compassionate use program consisting of 53 adult COVID-19 inpatients from various locations in the US, Italy, Japan, etc. who were given remdesivir with a follow-up of 18 days after the first dose of remdesivir showed that 36 patients

(68%) showed clinical improvement based on oxygen demand status, 8 patients (15%) worsened, and 7 patients died (13%), including 6 patients who received invasive ventilation. Adverse effects (elevated liver enzymes, diarrhea, rash, renal impairment, hypotension) were reported in 32 patients (60%); 12 patients (23%) had serious side effects (multiple organ dysfunction syndrome, septic shock, acute kidney injury, hypotension); 4 patients (8%) discontinued the drug because of side effects.[26]

5. Other antivirus

There are several other antivirus options used by several countries in the world to stop this pandemic. But it is not used in Indonesia because it is not available. On the basis of drug availability, the BPOM has determined that the antivirals with EUA status that are currently used in Indonesia are azithromycin, oseltamivir, favipirafir, and remdesivir. The following are other antiviral options: Chloroquine, hydrochloroquine, Lopinavir + Ritonavir (EUA status for COVID-19 has been withdrawn by the BPOM). Molnupiravir, sofosbuvir (both antivirals are not available in Indonesia), and several anti-parasitic drugs such as ivermectine, camostate, artesunate, niclosamid, and nitazoxadine, are thought to have antiviral effects, namely reducing viral load. In Japan, antiparasitic agents have begun to be used for COVID-19, although research on their effectiveness in humans is still being researched. In Indonesia, currently the use of this drug as an antiviral for COVID-19 has not been approved by the BPOM. [27,28]

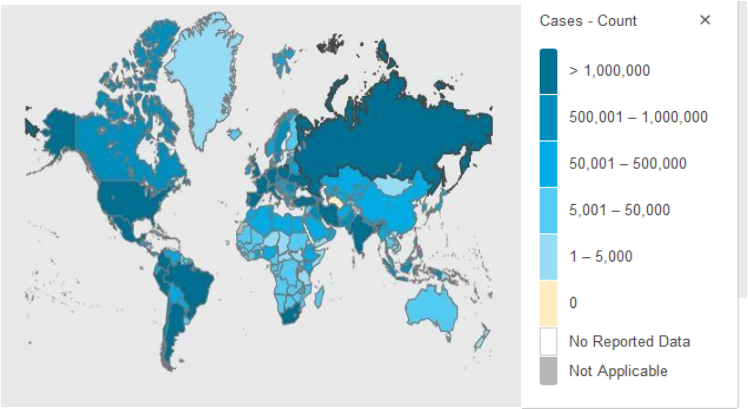

Figure 1.Map of the spread of COVID-19[2]

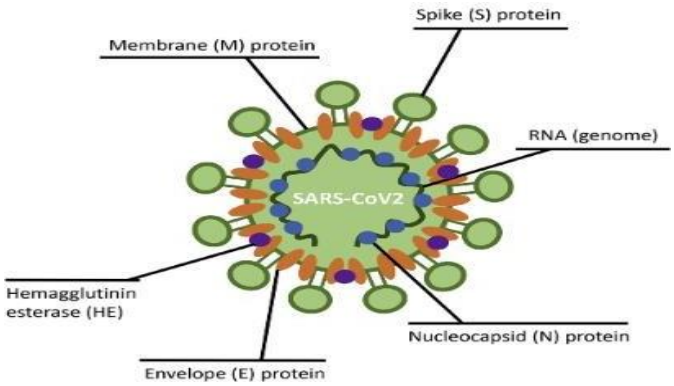

Figure 2. Morphology of SARS-COV-2[3]

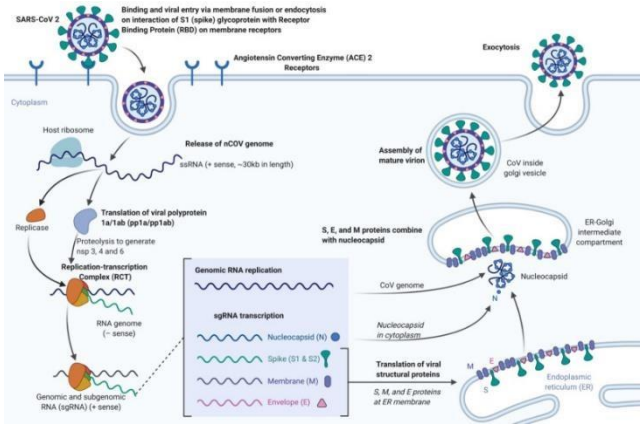

Figure 3. The mechanism of Coronavirus infecting cells[5]

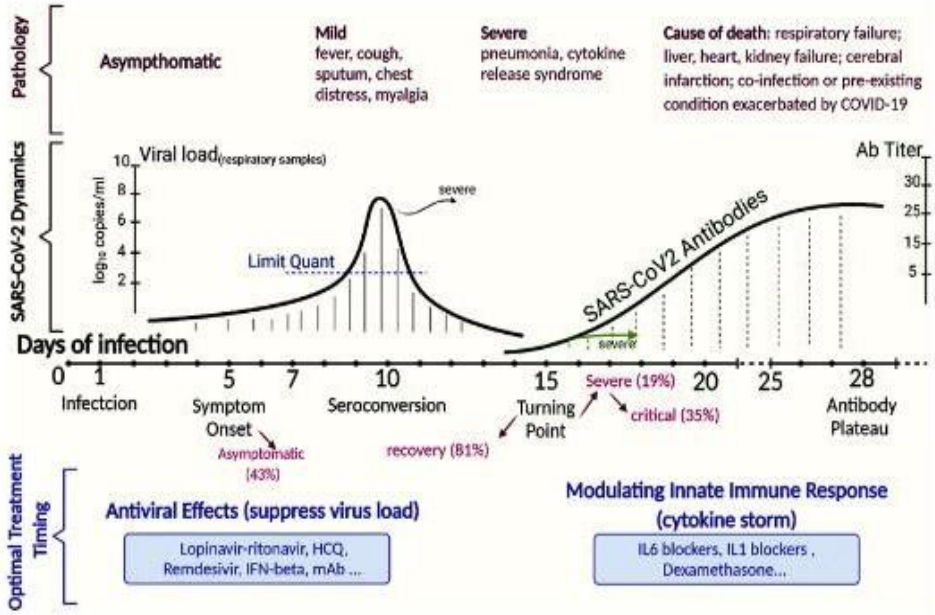

Figure 4. Time course of SARS-CoV-2 infection with viral load, pathology, host response, and antiviral effects[27]

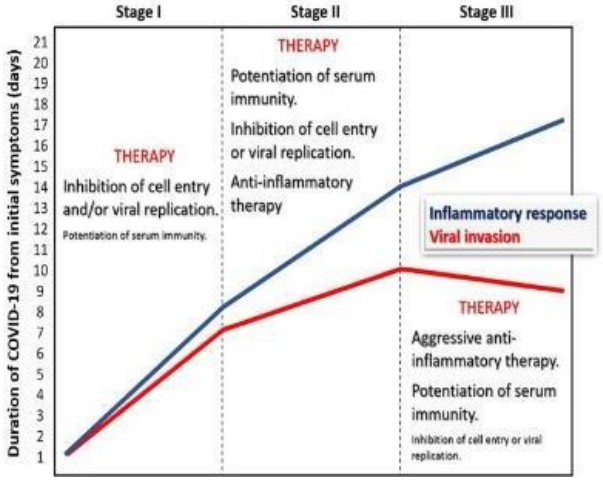

Figure 5. Phase-specific potential therapy[27]

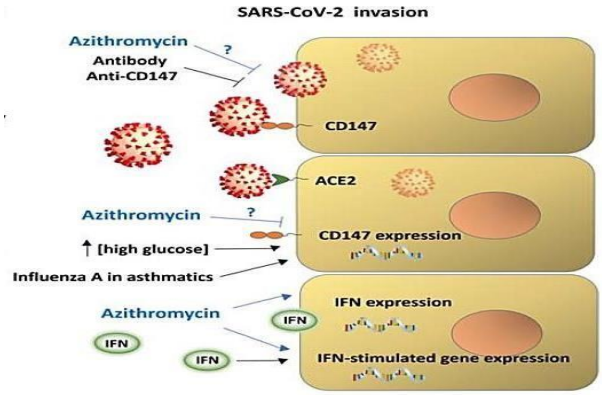

Figure 6. The potential mechanism of azithromycin in COVID-19 therapy[28]

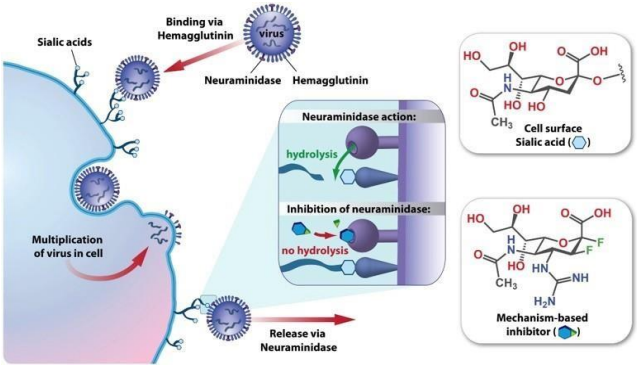

Figure 7. Mechanism of action of Oseltamivir[13]

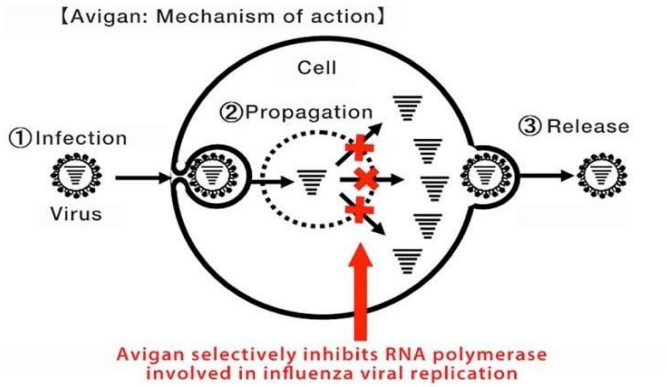

Figure 8. Mechanism of action of Favipiravir[17]

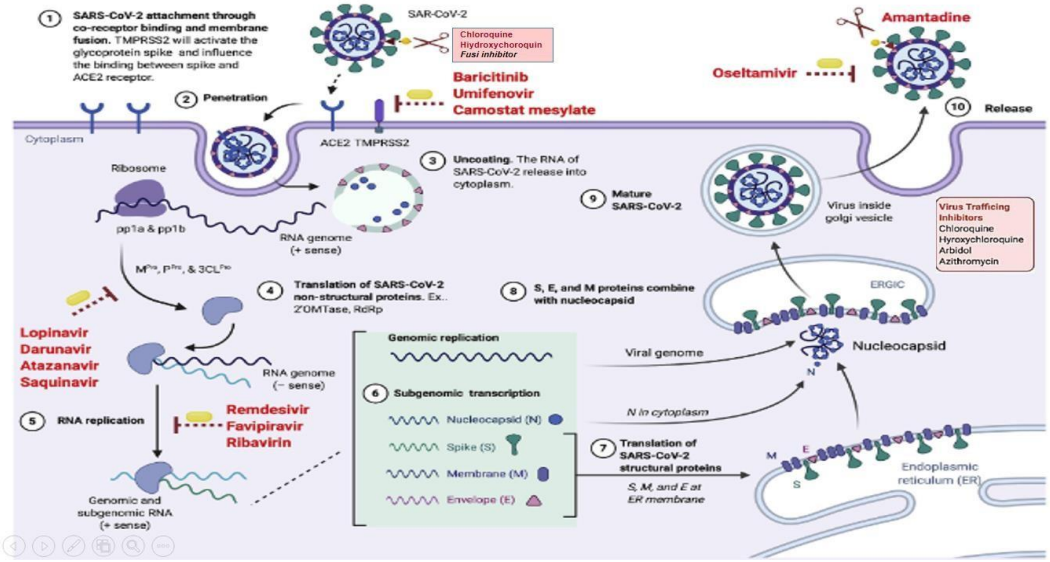

Figure 8. Mechanism of action of Remdesivir and several other drugs[21]

2. Conclusion

Antiviral therapy as a therapy for the management of COVID-19 is still being studied. Based on current management guidelines for COVID-19 in Indonesia, antivirals used as therapy for COVID-19 include: azithromycin, oseltamivir, favipiravir, remdesivir. Choice of antivirals and use of antivirals based on the degree of disease and the phase of disease course. There are several other antiviral options that are used as antiviral for COVID-19, but they have not been used in Indonesia due to availability issues and research on the effectiveness of these drugs is still ongoing.

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