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Dear Hanik Badriyah Hidayati,

You are co-author in an article submitted to **Anaesthesia, Pain & Intensive Care** and entitled **Antiviral Therapy for Corona Disease 2019** (Manuscript Number: APIC-2021-04-047).

Corresponding author: Hanik Badriyah Hidayati (hanikhidayati@fk.unair.ac.id)

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4 messages

hanik badriyah hidayati <hanikhidayati@fk.unair.ac.id> Thu, Jun 3, 2021 at 5:38 PM
To: "Dr. Tariq Hayat Khan" <apicjournal@gmail.com>, Apicare Journal <apicarejournal@gmail.com>, APICARE <apicare@yahoo.com>

Dear dr. Tariq

Hopefully this email finds you well.
Hereby I attached "Antiviral Therapy for Corona Disease 2019" with red color for edited-sentences.

Stay safe, use your mask, always social distancing.
My best prayer for you, your friends and family.

Best regards,
Hanik Badriyah Hidayati.

---------- Forwarded message ---------
From: **Evi Octavia** <octaviaevi007@gmail.com>
Date: Thu, Jun 3, 2021, 15:53
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We are sorry for late reply and send the manuscript.

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Hanik B. Hidayati.

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Mini Review

Antiviral Therapy for Corona Disease 2019

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Abstract:

The whole world is experiencing a global pandemic caused by Coronavirus disease 2019. As the pandemic progresses, there are many research on antiviral therapy, namely hydroxychloroquin, chloroquine, remdesivir, lopinavir-ritonavir, favipiravir, oseltamivir, and umifenovir, has been increasing. Specific antiviral drugs proven to be effective against SARS-CoV-2 have not been found and approved for the medication of COVID-19. Currently, case detection, infection control, monitoring, prevention, and supportive care are the means focused on the treatment COVID-19. Studies are currently underway to analyze the safety and efficacy of antiviral drugs, while trials of the SAR-CoV-2 vaccine are rapidly expanding. This editorial briefly introduces the antiviral therapy for COVID-19.
Keyword: Antiviral therapy, drugs, virus, COVID-19
Citation: Octavia Evi,

1. Introduction

The whole world is experiencing a global pandemic caused by Coronavirus disease 2019[(1)]. Based on data according to the World Health Organization, as of May 28, 2021, 168.599.045 cases have been confirmed positive for COVID-19 globally, of which 3.507.477 died[(1,2)]. COVID-19 infection rates continues to increase sharply[(3)] When compared to the severe acute and Middle East respiratory syndrome, mortality rates are well understood, while the diagnosis of COVID-19 is still shifting and it may be take years for the the actual number of cases is known[(4)]. As the pandemic progresses, there are many research on antiviral therapy, namely hydroxychloroquin, chloroquine, remdesivir, lopinavir-ritonavir, favipiravir, oseltamivir, and umifenovir, has been increasing[(5)]. Hydroxychloroquine and Chloroquine, are antimalarial drug, but both drugs have mechanisms may inclusive of inhibiting viral enzymes or processes DNA and RNA polymerase of viral or inhibition viral entry.[(6)]

2. Antiviral therapy

Due to the clinical manifestations of COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication, antiviral therapy that can treat COVID-19 is being investigated. Mechanism of action antiviral drugs inhibits the entry of the virus (by transmembrane serine

protease 2 [TMPRSS2]) and the angiotensin-converting enzyme 2 [ACE2] receptor, fusion inhibitors inhibit the fusion process and endocytosis, or action of the RNA-dependent RNA polymerase and the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro)[3,6,7] Antivirals may have the biggest impact, because viral replication was probably very active initial in the progression of COVID-19 before the disease moves to the high inflammation syndrome state that can symptom the next step of disease, inclusive of hypercritical disease. Therefore, the role of antiviral drugs needs to be understood in curing minor, moderate, mayor, and critical disease the one may to optimize medication for COVID-19 patients (Figure 1)[3,6].

In clinical trials, anti-viral therapy were investigated to find the efficiency of SARS-CoV-2 virus treatment. It is reported that single therapy or combinations therapy for COVID-19 patients differ in countries of the world. These method of therapy usually depends on the number of deaths and the amount of ventilation the patients uses. In Addition, there is no specific medication for COVID-19. Currently, various countries from around the world were investigate their antiviral therapy using for COVID-19[8]. (Table 1).Specific antiviral drugs proven to be effective against SARS-CoV-2 have not been found and approved for the medication of COVID-19. Therefore, rapid assessment of the antiviral drugs currently available for used with COVID-19 patients is critical in this time of crisis as well as for finding newer drugs[9]

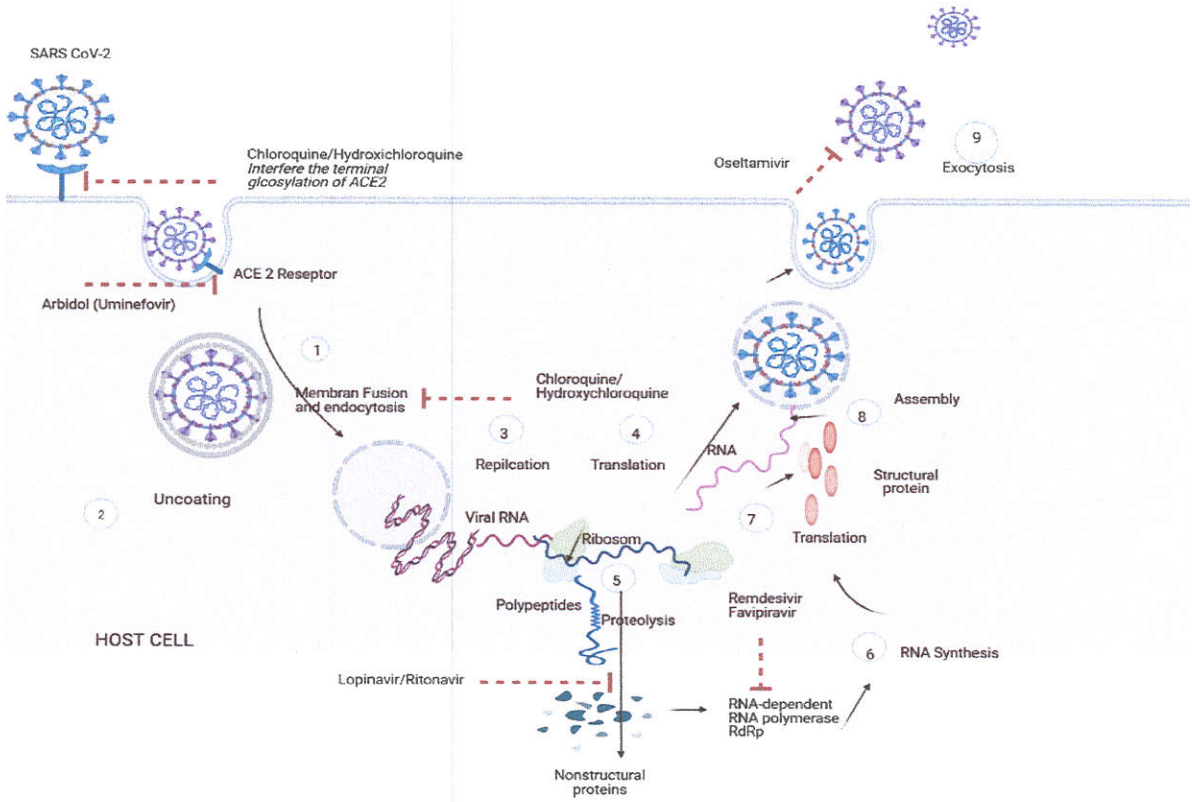

Figure 1. Severe Acute Respiratory Syndrome Coronavirus 2 life cycle and posible inhibition targets of antiviral drugs therapeutic. Membrane fusion and endocytosis (Chloroquine/Hydroxychloroquine), Proteolisis (Lopinovir/Ritonavir), RNA-dependent-RNA polimerase (Remdesivir/Favipiravir), Spike protein/ACE2 binding (Arbidol), virus release /Exocytosis (Oseltamivir)[2,9]

2.1 Antimalarial

Hydroxychloroquine and Chloroquine

Hydroxychloroquine and Chloroquine, are antimalarial drug. Hydroxychloroquine is an chloroquine analogue. Chloroquine was expanded in 1934, while Hidroxychloroqune was expanded in 1946[6]. Hydroxychloroquine used to medicate systemic lupus erythematosus (SLE), rheumatoid arthritis, and also malaria. In normally, hydroxychloroquine has less and lower toxicities (including smaller tendency to interval QTc prolongation) and minor drug-drug interactions than chloroquine[6].(Table 1) Mechanisms may inclusive of inhibiting viral enzymes or processes such as DNA and RNA polymerase of viral, protein glycosylation of viral, assembly of viral, new virus particles transport, and viral let-off. Other mechanisms may also associate inhibition of the ACE2 cellular receptor, acidification of the cell membrane at the surface so that viral fusion does not occur, and cytokine release immunomodulation[10]. Neither drugs are approved by FDA for the medication of COVID-19 patients. On June 15, 2020, the FDA withdrew the emergency use authorization for hydroxychloroquine throwing out that it is unlikely to be effective in medicating COVID-19. In Addition, given the processing serious cardiac adverse events and other serious side effects (mathemoglobinemia)of hydroxychloroquine do not justify continued[10,11].

2.2 HIV Protease inhibitor

Lopinavir/Ritonavir

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication of relies on the splitting of a helicase and polyproteins becomes an RNA-dependent RNA polymerase. In the splitting, protease which is responsible namely: 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro)[6] Ritonavir acts to increase plasma level of lopinovir by inhibiting the CYP3A-mediated metabolism of lopinavir[11]. The combined these drugs can increase the bioavailability of Lopinavir significantly and effect of antiviral is improved in vivo[12]. Lopinavir and ritonavir have mechanism of action may bind to primary enzyme, it called Mpro, supressing the repilication of the coronavirus so that it does not occur. This can suppress activity of the corona virus[13]. Lopinovir and ritonavir have been researched in patients with COVID-19. The clinical trials discussed that lopinavir/ritonavir have not established efficacy for the treatment of COVID-19[6,13]. The common adverse events for lopinavir/ritonavir such as diarrhea, nausea, and vomiting, severe adverse event include interval QTc prolongation, Hepatotoxicity[3,6](Table 1)

2.3 Nucleotide reverse transcriptase inhibitor

Remdesivir and Favipiravir

Remdesivir is nucleotide prodrug of an adenosine analog, the administration intravenously. Favipiraviris an a pyrazinecarboxamide derivative prodrug of an nucleoside analogue that can be triphosphory-lated in cells and act as virus RNA-dependent RNA polymerase (RdRp) substrate[12]

Remdesivir and favipiravir inhibits viral replication through premature termination of RNA transcription[6,12]. Food and Drug Administration (FDA) is approved remdesivir for the medication of COVID-19 in hospitalized, for pediatric about at least 40 kg and 12 years or older and adults[11]. Remdesivir should be administered in a

hospital or a health care setting that can provide a same level of care to an inpatient hospital[6]. Remdesivir is administered as a loading dose 200 mg on day 1, followed by once daily 100 mg IV dose for a total of 10 days, similar to the doses used in the clinical trials to medicate Ebola for adult[3,11] (Table 1). Remdesivir can leads gastrointestinal symptoms such as nausea, raised levels of transaminase, an elevated in time of prothrombin, and hypersensitivity, including infusion-related and anaphylactic reactions[6,14]

Favipiravir was developed in Japan, 2014. Initial clinical trial outcome indicate that favipiravir much greater improvement in chest imaging in COVID-19 patients compared to lopinavir. Faster viral clearance and fewer adverse events were also viewed in patients taking favipiravir compared to those taking lopinavir-ritonavir[3]. The most serious Adverse events of Favipiravir is teratogenicity, common adverse events were gastrointestinal symptoms , liver enzyme abnormalities, raised uric acid serum, and psychiatric[12].

Several clinical trials analyzing remdesivir and favipiravir for the medication of COVID-19 are currently or in development[6]

2.4. Neuraminidase inhibitor (Virus release inhibitor)

Oseltamivir

Oseltamivir, inhibitor of a neuraminidase used to treat of influenza A and B, is also being researched for the medication of COVID-19. It has been reported potential inhibiting for SARS-CoV-2. Case reports suggest a better prognosis in COVID-19 patients taking with oseltamivir. However, oseltamivir efficacy for the medication of COVID-19 needs long term clinical trial in RCTs[5]

2.5. Fusion Inhibitor

Uminefovir

umifenovir, also called as arbidol, is another antiviral agent acts by inhibiting spike protein /ACE2 binding and fusion of viral envelopes providing antiviral effects. Initial studies showed that arbidol medication likely to raise the discharge rate and reduce the mortality rate for patients with COVID-19. Currently, arbidol refinement still has no clear evidence, and needs further study[5].

Table 1. Review of antiviral therapy to treat COVID-19[3,8,11,13]

Drug	Mechanism of action	Trial or Clinical Experiance Dosage	Approved indication(s)	Adverse drug reaction	Drug interaction	country that use drugs
Remdesivir	inhibitor of RNA-dependent RNA polymerase	administration; 200 mg day 1 loading dose one times daily followed by 100 mg one times daily for a total of 10 days (IV)	None	Common: Gastrointestinal:nausea (3-7%) Serious: cardiac arrest, Transaminase level raised, hepatotoxicity, anaphylaxis, hypersensitivity reaction (less than 2%), infusion reaction	• CYP3A4 inducers decrease effectiveness • Major Interaction; Chloroquine , Hydroxychloroquine	Italy, spain, germany
Lopinavir-ritonavir (kaletra)	inhibitor of 3CL protease	400mg/100 mg twice daily for maximum to 14 days (oral)	HIV	Gastrointestinal disturbances (nausea 10.3% vomiting 6.8% adult ,pediatric 12%, diarrhea adult 19.5%, pediatric 12%), raised transaminase,raised bleeding, insulin resistance , hyperlipidemia, hyperglycemia, , prolong of QT interval, possible renal dysfunction risk, steven-Johnson syndrom, central nervous depression, respiratory depression	• inhibitor of CYP3A4 and substrate - substrate of CYP2D6 • Contraindicated Interaction: Amiodaron, fluconazole, simvastatin, phenytoin, rifampin, ketoconazole	Italy, pain, South Korea, USA, China
Favipiravir	inhibitor of RNA-dependent RNA polymerase	1600-1800 mg daily on day1, then 600 mg two times daily for 7-14 days (oral)	Ebola virus, Influenza A and B, Norovirus	Gastrointestinal disturbances (nausea, vomiting diarrhea), hyperuricemia, elevated transaminases, decreased neutrophil count	• Mainly mediated by aldehyde oxidase, not substrat CYPs	Turkey
Chloroquine (Aralen)	inhibitor of Viral entry	500 mg orally one or two times daily for 5–10 days (oral)	Autoimmune disease: rheumatoid arthritis (RA), Systemic lupus erythematosus (SLE). malaria	Gastrointestinal disturbances (e,g, vomiting diarrhea, nausea), headache, delirium, QT prolongation, Torsades de Pointes, arrhythmia, agranulocytosis, extrapyramidal disease, seizures, retina disorder rare renal toxicity, anorexia, bitter taste	• CYP3A4/5, 2D6, and 2C8 substrat • increased risk of prolonging QT interval with other QT prolongation agents (antibiotikquinolon, macrolide) • raised digoxin levels	Italy, spain, South Korea, USA, Brazil, China
Hidroxychloroquine(Plaquenil)	inhibitor of Viral entry	Day 1 400 mg two times daily, followed by 200 mg two times daily for 5–10 days Alternative: 200 mg Three times daily for 10 days or 400 mg one daily for 5 days (oral)		Gastrointestinal disturbances (nausea), QT prolongation, hypoglycemia, neuropsychiatric effects, agranulocytosis, extrapyramidal disease, disorder muscle, hearing loss, angiodema	• raised risk of hypoglycemia with blood glucose-lowering agents • major interaction: Azitromycin • Metabolized by CYP3A4; monitor closely CYP3A4 strong inducers/inhibitors • Antacids	Italy, Spain, Turkey, Russia, South Korea, Brazil
Oseltamivir	Neuraminidase inhibitor	75 mg every 12 hours (oral)	Influenza A and B	Gastrointestinal disturbances (nausea 8-10%, vomiting 2-8% adult 8-16% pediatric), headache, cardiac dyrhythmia, hepatitis, seizure, , anaphylaxis	Major interaction: warfarin	Italy,USA, China,
Umifenovir	Spike protein/ACE2 membrane fusion inhibitor	200 mg 3 times daily for duration of 7-10 days/longer (oral)	Influenza A and B	Gastrointestinal disturbances (nausea,vomitting), allergic reaction, elevated transaminases	Metabolized by CYP3A4; monitor strong inducers/inhibitors of CYP3A4	Russia

2.6 Up to date clinical practice guideline on therapeutics and COVID-19

Based on World Health Organization the Living guideline update, As December 17, 2020 contains on recommendations the use of antiviral therapy in COVID-19 patients, the recomendations are as follows:

- Strong recommendations against the use of hydroxychloroquine and lopinavir / ritonavir in COVID-19 patients, regardless of disease severity.

  These recommendations are appropriate for patients with any disease severity and symptoms.

  Dosage and administration of hydroxychloroquine and lopinavir / ritonavir (Table 1)

- Conditional recommendation against remdesivir (published 20 November 2020) in hospitalized patients with COVID-19

  The guidelines suggest offering remdesivir in addition to the usual for the treatment of hospitalized patients with COVID-19 care regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients. Evidence shows no significant effect on mortality, mechanical ventilation, time to clinical improvement, and other important outcomes for patients.[15,16]

  In this case, there were conditional recommendations not to use remdesivir, surrounding the risks and risks of the intervention being uncertain. this means there is insufficient evidence to support their use.[17]

  Remdesivir dosage and administration

  • Dosage: For adults and pediatric patients aged ≥12 years and weighing ≥40 kg: 200 mg on Day 1, followed by a maintenance dose of 100 mg once daily from Day 2 given only by intravenous infusion over 30 to 120 minutes.

  • Duration of treatment: For patients who do not require invasive mechanical ventilation and / or extracorporeal membrane oxygenation (ECMO): 5 days; Can be extended up to an additional 5 days (10 days total) if improvement is not observed. For patients requiring invasive mechanical ventilation and / or ECMO: 10 days[14].

3. Conclusion

COVID-19 infection rates continues to increase sharply, as well as antivirals that work as a treatment for COVID-19. Currrently, case detection, infection control, monitoring, prevention, and supportive care are the means focused on the treatment COVID-19[3,18]. At the present, no spesific antiviral therapy that have been confirmed as effective in curing COVID-19 .Studie are currently underway to analyze the safety and efficacy of antiviral drugs, While trials of the SAR-CoV-2 vaccine are rapidly expanding[3].

4. Conflict of Interest

The author states that has no conflict of interest.

5. Acknowledgement

The author is thankful to Hanik Badriyah Hidayati for Checking plagiarism and Celine Anindytha for helping hypelinking the reference.

6. Reference

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14. INDICATIONS AND USAGE VEKLURY is indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization . VEKLURY should only be administer. 2020; Available from: https://www.vekluryhcp.com/
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Antiviral Therapy