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Clinical trial and therapeutical progress of COVID-19 treated with remdesivir: A review

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that first reported in Wuhan City, China. Most confirmed cases of COVID-19 develop mild, moderate, severe to critical symptoms. One of the therapies given and of concern is remdesivir. Remdesivir is an antiviral with a broad spectrum that has activity against various types of viruses including Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV. The aim of this review was to evaluate the clinical trial and the therapeutical progress of remdesivir in the treatment of COVID-19 patients. Databases used for this review were Google Scholar, JAMA, PubMed and Science Direct library. The inclusion criteria were covering any literature using remdesivir in clinical studies and COVID-19 therapy published from December 2019 to October 2020. Overall no pattern of laboratory abnormalities and clinically significant changes in vital signs or ECG shifts was observed in patients receiving remdesivir. The decision to use remdesivir in COVID-19 treatment should consider its potential benefits and risks.

ABSTRAK

Coronavirus disease 2019 (COVID-19) merupakan penyakit menular yang disebabkan oleh *severe acute respiratory syndrome coronavirus*-2 (SARS-CoV-2) dan pertama kali dilaporkan di Kota Wuhan, Cina. Sebagian besar kasus terkonfirmasi COVID-19 berkembang dengan gejala ringan, sedang, berat hingga kritis. Salah satu terapi yang diberikan dan menjadi perhatian adalah remdesivir. Remdesivir merupakan antivirus spektrum luas yang memiliki aktivitas terhadap berbagai jenis virus termasuk *Middle East respiratory syndrome coronavirus* (MERS-CoV) dan SARS-CoV. Tujuan dari tinjauan pustaka ini untuk mengkaji uji klinis dan perbaikan terapi oleh remdesivir pada pengobatan pasien COVID-19. Tinjauan pustaka dilakukan dengan mengakses beberapa database, yakni pada Google Scholar, JAMA, PubMed dan Science Direct. Kriteria inklusi meliputi seluruh artikel yang menggunakan remdesivir pada uji klinis dan terapi COVID-19 antara Desember 2019 hingga Oktober 2020. Secara keseluruhan tidak ada pola kelainan laboratorium dan perubahan klinis yang signifikan pada tanda vital atau pergeseran EKG yang diamati pada pasien yang menerima remdesivir. Keputusan dalam penggunaan remdesivir harus mempertimbangkan potensi manfaat dan risikonya.

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INTRODUCTION

The first suspect coronavirus disease 2019 (COVID-19) was initially reported at 31 December 2019 in Wuhan, China by local Department of Health, Chinesse Center for Disease Control and Prevention (CCDCP) and World Helath Organization (WHO) with 27 cases.[1] Contagious spread of this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was followed by signicant number of hospitalizaed patients e.g. with pneumonia and multiorgan diseases. Not all the COVID-19 or novel SARS-CoV-2 infected patients exhibit promiment symptoms.[2]

The most common clinical manifestations of COVID-19 are including fever, cough, dispnea, chest pain, and or pneumonia. 'Ground-glass opacification' is among the most common tomographic imaging of COVID-19 suspect patient.[3,4] Considering the bad impact to the health as well as its contagious properties, this Emerging Infectious Disease (EID) is becoming global health problem.[5,6] The easiness of mobility, the transmission process from human to human, and the limited knowledge related to this virus has causing a quick spread of COVID-19 infection to many countries, including to Indonesia.[5,7]

To date, the SARS-CoV-2 infection spreads are believed by droplets of the suspects through direct contact. Those droplets are inhaled into the lung thus entering the breath system. It is estimated that a suspect could spread this infection to 2-3 people, which shows its contagiousness prevalence more than Middle East respiratory syndrome coronavirus (MERS-CoV). As a consequence, minimizing the physical contact people both healthy people and suspect have to be performed in order to reduce the infection rate of COVID-19.[8,9] Moreover, there are evidences that some healthy people may act as carrier.

Remdesivir is an antiviral given to treat Ebola virus in 2015 (FIGURE 1). Recently, remdesivir gained permission to be used for COVID-19 patients. Clinical trial has been conducted, eventhough remdesivir is not solely design with the purpose to treat COVID-19, however, COVID-19 patients treated with remdesivir exhibit significant recovery progress.[10] The mechanism of action of remdesivir against COVID-19 has been proposed by several articles. Hence, in this study we review the clinical trials, the effectiveness and the progress therapy of COVID-19 engangges remdesivir.

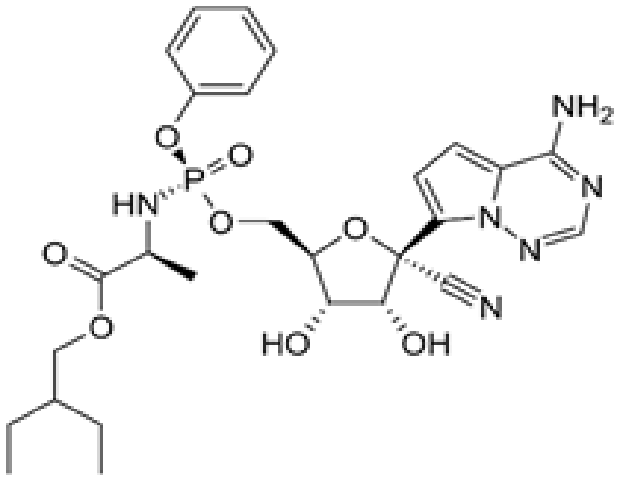

FIGURE 1. Chemical structure of remdesivir

METHOD

Google scholar, JAMA, PubMed and science direct databases were employed in order to collect the data. The keywords used were including COVID-19, SARS-CoV-2, remdesivir, mechanism action, effectiveness. Two inclusion parameters i.e. a). Remdesivir was given in the clinical trial and/or therapeutical treatment of COVID-19, b). It was published between December 2019 - October 2020.

RESULT AND DISCUSSION

Coronavirus disease 2019

Coronavirus disease 2019 is an infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The SARS-CoV-2 is a type of newly coronavirus that has never been identified to be occurred in the human being. Several people suffering from COVID-19 symptoms initially were found in Wuhan City, Hubei Province of China on December 2019. On the January 30, 2020, WHO stated this incident as Public Health Emergency of Internal Concern (PHEIC) and got further status as global pandemic in Maret 11, 2020. The incubation period of COVID-19 is mostly between 5-6 days, while several cases shown its incubation period up to 14 days.[11]

The majority patients of COVID-19 were mild (40%), moderate (40%), and severe (15%). The severe level might be requiring oxygenation supplement. However, the critical level (5%) usually followed by health complication such as breathless, acute respiratory distress syndrome (ARDS), sepsis, shock sepsis, tromboembolia, and/or multiorgans destruction (e.g. acute kidney failure and cardiac disease. Age related problem (i.e. elderly), smoker and any other noninfectious diseases such as hypertention, diabetes, cardiac disease, chronic lungs and cancer have been reported as the risk factor for those COVID-19 patient with death and fatality.[12]

Coronavirus is a virus with big single strand RNA, veiled, found in humans and other mammals (e.g. dogs, cats, chickens, cattle, pigs, and birds). The first generation of Corona virus type which causing severe illness was known as severe acute respiratory syndrome (SARS). It is believed that SARS come from Foshan in China. This SARS-CoV was also cause pandemic in 2002-2003. The second type of coronavirus was found in Arabian Peninsula in 2012, which known as Middle East respiratory syndrome (MERS). While the latest corona virus, SARS-CoV-2, is belong to the third generation of coronavirus and cause deathly and serious health problem condition for many people all over the world. This virus has diameter of 60 - 140 nm and spike ca. 9 - 12 nm, makes it look like the corona of a sun.[2]

Patients of COVID-19 are mostly showing elevation level of leukocytes, abnormal breathing or even severe pneumonia, as well as evelation of plasma cytokines pro-inflamation. High level of blood cytokines and chemokines of the COVID-19 patients such as IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA are a lot of reported. Several serious cases that was found in intensive care unit shown high cytokines pro-inflamation level including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNF.[5]

COVID-19 has many clinic manifestation, with the most common symptoms were fever, dry cought, short of breath, chest pain, exhaustness and myalgia. Less common symptoms but sometimes appear were including headache, dizziness, stomachache, diare, neausea, and gag. However, it was very less common for COVID-19 patients to show several SARS-CoV and MERS-CoV symptoms such as upper respiratory tract symptoms e.g. rinore, sneeze, or sore throat. Meanwhile, severe complications due to COVID-19 are including hypoxemia, acute respiratory

distress syndrome (ARDS), aritmia, syok, acute cardiac injury, and acute kidney failure.[13] A study involving 99 patients with 2019-nCoV pneumonia found 17% of the COVID-19 patients are experiencing ARDS which 11% of them die due to multiple organs dysfunction.[14] The average duration required from the first symptom to ARDS was 8 days.[15] The death rate of hospitalized patients due to COVID-19 is around 15% - 20%.[2]

Mechanism and efectivity of remdesivir

Remdesivir is a prodrug of nucleoside monophosphoramidat with intracellular metabolic converted to become active metabolite of nucleoside triphosphat (NTP). Similar to several others direct acting antiviral, the active metabolic of remdesivir (remdesivir triphosphate [remdesivir-TP] or GS-443902) is designed to target the RNA genom for virus replication. Nucleoside analogue is a synthetic compound that works by competing the natural endogenous nucleoside for RNA virus replication. Remdesivir acts like virus physiologic, its binding as analogue molecular destruct further molecular processes. Drug target and accurate process to inhibite the virus replication has extensively studied in Ebola virus. For SARS-CoV and MERS-CoV, remdesivir-TP inhibits polimerase nsp12, which take a role as complex synthesis of the RNA multisubunits from the protein non structural virus (nsp) produced as product of the poly-protein virus myosis.

Since the nsp12 exists in all variant of corona virus, probably, remdesivir has no different mechanism of action (MOA) when it is used to treat the CoV.[16,17] Like the Ebola virus, remdesivir-TP works efficiently to inhibit SARS-CoV replication and MERS-CoV by cutting the chain during RNA replication.[18] Recent biochemical analysis has revealed that remdesivir-TP intiates the stoping synthesis of RNA in 3 positions within SARS-CoV-2. This mechanism almost identic in RdRps from the SARS-CoV and the MERS-CoV.[19]

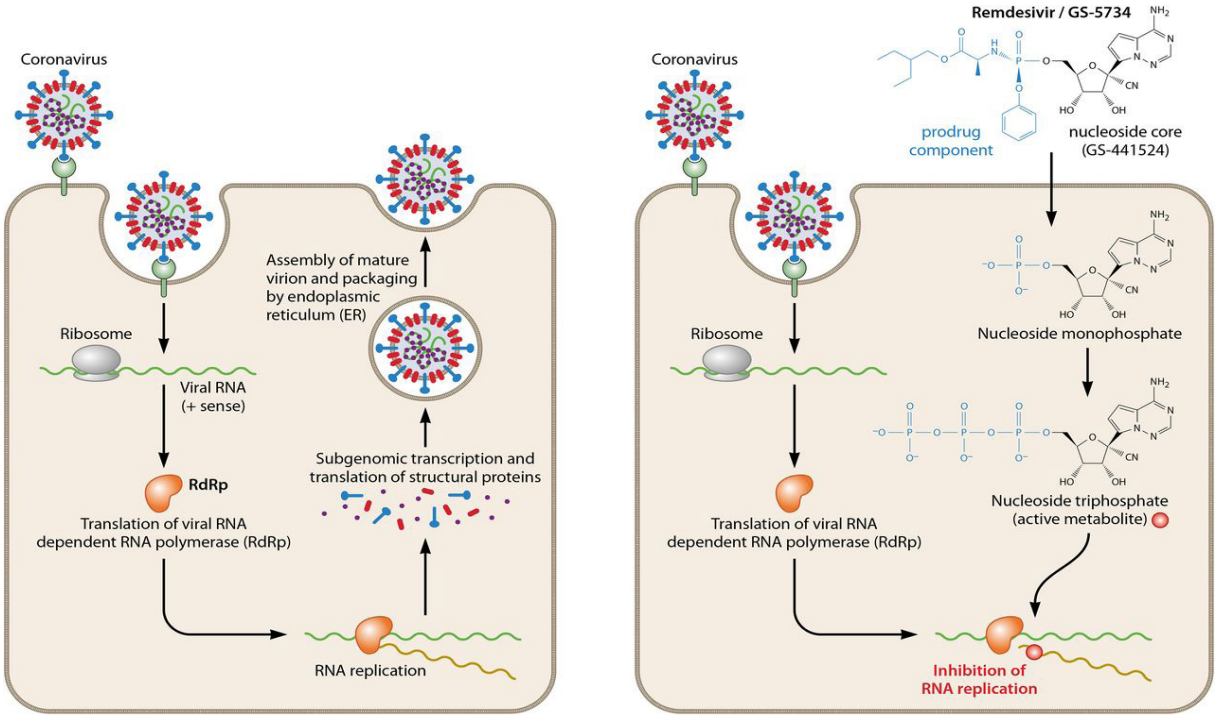

FIGURE 2. The mechanisme of remdesivir in the inhibition coronavirus replication.[20]

Potensial role of remdesivir in COVID-19 treatment

As antiviral

Remdesivir has antiviral activities to many variants of virus including MERS-CoV and SARS-CoV-1.[21,22] Remdesivir is an antiviral that was initially developed for Ebola virus treatment, which was then given to the coronavirus patients i.e. MERS-CoV dan SARS-CoV.[23] Remdesivir belongs to the nucleotide prodrug from the adenosine analogue with intravena administration. This antivirus works by bind to the RNA-dependent RNA virus polimerase, to inhibit the virus replication through termination of the premature RNA transcription. RNA-dependent RNA polimerase virus so called as NSP 12 (non-structural protein 12).[16] RNA-dependent RNA polimerase catalyses the RNA synthesis that plays role in the transcription dan replication proseses. NSP7 and NSP8 supposed to be responsible as the co-factors in these steps.[24] Therefore, RNA-dependent RNA polimerase is the main target of the analogue inhibitor of nucleocide.[15,16,25] Remdesivir has been proven quite effective in order to reduce the severity of COVID-19.[15,25] Besides, either itrakonazol (antifungal) and novobiosin (antibiotic) were also effective to inhibit the RdRp.[26]

Clinical trials of remdesivir in COVID-19 patiens

A study found that remdesivir was prominently elevates the recovery rate of COVID-19. Safety and tolerability of the use of remdesivir were evaluated, during and after the treatments, for its adverse event, as well as the clinical laboratorium tests i.e. the hematologic profile, the chemical profile, and the urinalisis evaluation.[27] According to that study, adverse events with severity level 1 and 2 were reported. These adverse events found in 17 out of 78 subjects (21.8%). WHO stated the adverse event of remdesivir in placebo group of control was also found in 2 out of 18 patients (11.1 %). Constipation is the most commone adverse event (3 out 78 patients (3.8%)) that was reported by the used of remdesivir. Another study found, lyophilized, being reported to have adverse effects such as: skin infection (1 subject; dosage: 3 mg), ecchymosis (1 subject; dosage: 10 mg), presinkop (1 subject; dosage: 75 mg).

Based on the laboratory examination, 44.9% (35/78 patients) taking remdesivir for their therapy got abnormality level 1, whereas 15.4% (12/78 patients) being reported to have abnormality level 2. Indicators used to measure these abnormalities were including on the elevation on their total cholesterol and the raisen of their LDL (low density lypoprotein). However, no clinical abnormalities were found nor significant vital signs of EKG observed.

A study by Goldman *et al.*[28] involved 397 patients which is fairly divided to get remdesivir for 5 days (200 patients) and 10 days (197 patients), by intravena 200 mg day-1 and 100 mg/day on the following days of intervention. The evaluation was conducted at the day-14. As the result, clinical condition of level 2 or more in the scale of ordinal occurred at 64% patients in the group of 5 days of treatment, while 54% in the group of 10 days of treatment. After the adjustment of basic clinical status, patients in the group of 10 days have distribution clinical status withing 14 days which is similar to the patients in the groups of 5 days (p= 0.14). Adverse effect which is commonly occurse was nauseous (9 %), breath disfunction (8%) and constipation (7%).

Beigel *et al.*[29] engaged 1062 patients to be involved in a clinical trial, with 541 subjects taking remdesivir and 521 subjects for placebo. The initial dose was 200 mg in the day-1 and 100 mg on the following days, up to 9-10 days. The recovery period was measured as the main outcome. Patients those get remdesivir had recovery period around 9 days. However, patients with placebo had recovery time of 15 days. The patients with placebo got recovery ratio

as 1.29; 95% CI, 1.12 – 1.149; p< 0.001, with log-rank score evaluation. Kaplan – Meier examination predict the death presentation of the patients as 6.7% and 11.9% for remdesivir and placebo respectively.

Overall, remdesivir administration by intravena, single dose, as the treatment therapy; or lyophilized for 2 hours at the dosage of 3 mg - 225 mg; and administration of remdesivir IV 150 mg once daily for 7 - 14 days in general can be accepted by the patients. The adverse effect that was reported during research for single dose got severity level 1 or 2.[30] In the double doses, all the adverse effect has low severity level index while there was no serious injury. The elevation level of ALT and AST was observed, with prolongation time of mild protrombin without clinical evidence of other hepatitis. Therefore, single dose intravenous of remdesivir, i.e. GS-704277 and GS-441524 more than 2 hours may elevate proportionaly with range of dosage (3 mg - 225 mg).

Two higher dosages level that was evaluated in the range of 75 mg - 150 mg, exhibite more than 2 hours to gain similar effectivity formulation.[31] Taking into consider into the pandemic situation, this study has given sufficient scientific evidence. The active trifosfat metabolite of GS-443902 may be reached after 2 hours, or, with the infuse time of 30 - 120 minutes (150 mg/day, aprrox. 7 - 14 days). Overall, data shown from the regiment dosages for COVID-19 therapy: single dose remdesivir (200 mg IV) in addition with a loading dose in day-1 followed by 100 mg/day for 5 - 10 days duration of therapy is sufficient.[31]

Spinner *et al.*[32] revealed that among the COVID-19 patients with moderate symptom, it was found that 10 days' administration of remdesivir results unsignificant clinical status compared to the standard care (11 days), statistically. Patients got therapy with remdesivir for 5 days have signficiantly different clinical status than the standardard care, however, that difference has no robust clinical evidence. In additionally, systematic review and meta-analysis of 6 studies (5 randomized controlled trial and 1 cohort) which made comparison between those groups whose got remdesivir (10 days) and plasebo/ control group show that therapy with remdesivir did not significantly reduce toward the mortality in days-14 of treatment. Nevertheless, remdesivir shows significant clinical recovery effect to the COVID-19 patients in comparison to the plasebo/control group, as well as reduces the serious side effect of COVID-19 infection.[33]

CONCLUSION

The COVID-19 pandemic has strongly encouraged accelerations on research either by academician, by pharmaceutical companies, or even by research community in order to develop and evaluate the therapeutical and potential appropriate drugs for COVID-19. Among those therapeutical candidates, remdesivir has shown potential candidate against SAR-CoV-2 both in the *in vitro* and *in vivo* studies. Recent study has successfully giving evidence that remdesivir has strong potential effect in order to produce some clinical improvement in COVID-19 patients. Based on these findings, Indonesian Ministry of Health has issued Emergency Use Authorization (EUA) to use remdesivir for treating hospitalized COVID-19 patients. Remdesivir has decreases the morbidity, mortality, dan anxiety in the global health care system that were caused by COVID-19. The more on-going clinical trials studies will result the more reliability and accurate evidence to those drugs with EUA status for COVID-19 treatment. Remdesivir has significant effect in the clinical recovery than the placebo, at day-14.

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