Case Series

Remdesivir for COVID-19 in Indonesia: A Case Series

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Abstract

To date, COVID-19 still gives rise to a high mortality rate in Indonesia. The definitive therapy has yet to be found. However, some medications are said to be potential in subduing the infection, e.g. remdesivir. United States, Japan, and some countries in Europe had use remdesivir against severe COVID-19 infection. In Indonesia, no study has shown to discuss remdesivir therapy for severe COVID-19. This case series shows the first five remdesivir usages in severe COVID-19 patients in RSDC Wisma Atlet Kemayoran, Jakarta. In this retrospective case series, we include the first five severe COVID-19 patients that got remdesivir plus standard therapy in Rumah Sakit Darurat COVID-19 Wisma Atlet Kemayoran, Jakarta in October 2020. Five patients who got remdesivir in this case series experienced clinical and laboratory improvement. The ventilation and oxygenation status, as well as PF ratio and the neutrophils-lymphocytes ratio (NLR), got better. The possible side effect of remdesivir usage, renal function impairment, was not seen in these patients. At last, the five patients were discharged home with negative swab results, three until seven days after remdesivir therapy finished. Remdesivir therapy for COVID-19 in this case series is associated with a good outcome. Compassionate use of remdesivir should be considered in severe COVID-19. However, a bigger sample of randomized control trial needs to be done to show the effectiveness of remdesivir against COVID-19.

Keywords: GS-5734, SARS-COV-2, coronavirus

INTRODUCTION

COVID-19 infection is one of the major problems in the world. An increase in mortality and morbidity rate caused by this infection is still being reported to have a high number in some countries and associated with high severity from COVID-19 itself. Indonesia has a high Case Fatality Rate (CFR) compared with other Asia countries. In April 2020, CFR in Indonesia reaches 8.13%, followed by other countries such as the Philippines (6.66%), Myanmar (3.36%), and Thailand (1.84%).[1] It showed that the COVID-19 problem in Indonesia has not been resolved and still receives a 'bad report card' set against others.

Up until this day, definitive therapy has not been found. One of the antivirals that should be considered is remdesivir,

which is an adenosine analog class that was originally used in several viral infections such as a Respiratory syncytial virus (RSV), Nipah virus, ebola virus, and Marburg virus.[2] Remdesivir was used in coronavirus infections such as SARS-CoV-1 and middle east respiratory syndrome (MERS-CoV) and is effective and proved by in-vitro tests.[3,4] Remdesivir confirmed has half-life in 12 hours after the infection of MERS-CoV and inhibit lung damaged. Remdesivir acts on the RNA-dependent RNA polymerase (RdRp) structure in the virus, furthermore inhibits the replication of the SARS-CoV- 2 virus in the airway epithelial cells.[5]

Several countries are already using remdesivir as a therapy for COVID-19. Remdesivir usage in the USA has been authorized by the US Food & Drug Administration.[6] Comparable things were done by Japan in patients with severe COVID-19 conditions based on the preliminary phase 3.[7] Based on data reported by research on 500 subjects divided into healthy groups infected with the acute ebola-virus, remdesivir has a safe clinical profile.[8] Indonesia has not yet had a preliminary report regarding the use of remdesivir as an antiviral, especially in the case of COVID-19. In this case series, a further description of COVID-19 patients who received remdesivir therapy was described.

METHOD

This case series is a retrospective study by collecting all patients who received remdesivir therapy within 5 and 7 days at the Emergency Hospital for COVID-19 Wisma Atlet Kemayoran Jakarta in October. The patient is admitted to the High Care Unit (HCU) with Acute Respiratory Distress Syndrome (ARDS) confirmed by Berlin Definition criteria, with or without comorbid or weighting factors. Patients receiving remdesivir were monitored daily from the start to the end of their HCU treatment and thereafter continued monitoring in the ward until the patient was discharged. Administration of remdesivir was followed by administration of standard therapy that had been determined in the hospital as well as additional therapy that was given based on the clinical situation in each patient

RESULT

All the 5 cases hospitalized status from the start of admission to the emergency room, receiving remdesivir therapy until the patient is discharged can be seen in Figure 1. Table 1 shows case's background, assessment, and therapy received during treatment. Table 2 and Figure 2 illustrate the ventilation and oxygenation status, as well as clinical parameters of cases before and after receiving remdesivir therapy.

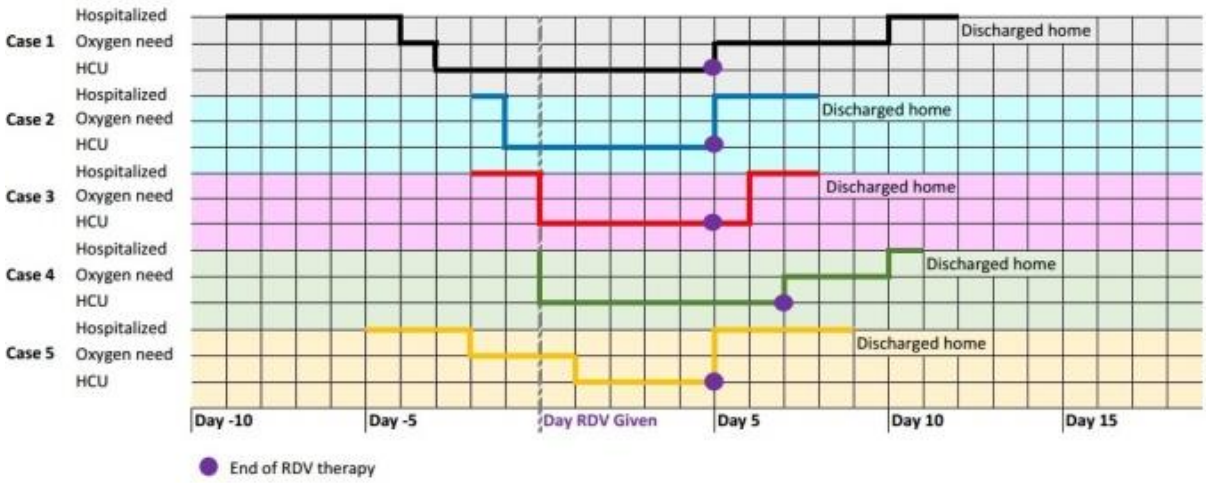

Figure 1. Timeline of confirmed COVID-19 patients who got remdesivir therapy

Table 1. Patient background, assessment and medications

	Case 1	Case 2	Case 3	Case 4	Case 5
Patient's background					
Age (Years old)	64	46	33	43	61
Gender	Male	Male	Male	Male	Male
Symptoms on admission	Headache	Cough, fever, fatigue	Nausea, vomiting, stomachache, loss ofappetite, fever	Nausea, vomiting, lossof appetite, dysgeusia	Cough, fever
BMI (kg/m^2)	27.8	25.6	27.5	27.1	22.7
Comorbidity	Absent	Absent	Absent	Absent	Diabetes Mellitus
Assessment					
Assessment on admission	Confirmed Covid-19 with mild symptom	Confirmed Covid-19 with moderate symptom	Confirmed Covid-19 with mild symptom	Confirmed Covid-19 with moderate symptom	Confirmed Covid-19 with mild symptom
Assessment on HCU	Confirmed Covid-19 with severe symptom	Confirmed Covid-19 with severe symptom	Confirmed Covid-19 with severe symptom	Confirmed Covid-19 with severe symptom	Confirmed Covid-19 with severe symptom
Adverse Events	Severe ARDS Respiratory alkalosis Pneumonia Bilateral Elevated Liver Enzyme Electrolit Imbalance	Mild ARDS Ischemic Heart DiseaseElevated Liver Enzyme Dyslipidemia Deltoid hematoma	Mild ARDS Elevated Liver Enzyme Deltoid Hematome Deltoid, Heparin-Induced Thrombocytopenia	Moderate ARDS Respiratory alkalosis Pneumonia Bilateral Elevated Liver Enzyme	Moderate ARDS Respiratory alkalosis Hypertension Left pleural effusionAKI Elevated Liver Enzyme
Medications					
Antiviral	Oseltamivir, Remdesivir	Remdesivir	Remdesivir	Remdesivir	Oseltamivir, Remdesivir
Antibiotic	Azithromycin, Levofloxacin, Cefoperazone Meropenem	Ceftriaxone, Cefixime	Moxifloxacin, Ceftriaxone	Cefotaxime, Moxifloxacin, Meropenem, Cefepime	Azithromycin, Ceftriaxone, Moxifloxacin, Cefepime
Corticosteroids	Dexamethasone	Methylprednisolone	Methylprednisolone	Methylprednisolone, Dexamethasone	Dexamethasone
Anticoagulant	Heparin	Fondaparinux	Heparin	Heparin	Heparin

Figure 2. Patients' laboratory parameter before and after Remdesivir therapy

Table 2. Patient ventilation and oxygenation status before, during and after Remdesivir therapy

Before Remdesivir Therapy				Day of Remdesivir Therapy							Day After Remdesivir Therapy		
Case number		**Day of HCU admission**	**Day of Remdesivir therapy**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**1**	**2**	**Clinical outcome**
Ventilation and Oxygenation													
1	Time vs Remdesivir	5 d after adm	5 d after										D 5 post Remdesivir remains. In hospital onward with NC 2 lpm
	O_2 delivery method	NRM		HFNC	HFNC	HFNC	NRM	NRM			NRM	NRM	
	FiO_2 (%)	100		60	50	50	100	100			80	60	
	PF *ratio* (mmHg)	181.75		165	60	166	198	161			175	233	Discharged home D7 post Remdesivir
	SpO_2 (%)	96		98	98	98	97	96			96	97	
2	Time vs Remdesivir	2 d after adm	1 d after										Discharged home D 3 post Remdesivir
	O_2 delivery method	NC		NC	NC	RA	RA	RA			RA	RA	
	FiO_2 (%)	37		33	33	21	21	21			21	21	
	PF *ratio* (mmHg)	218		290		466		466			471		
	SpO_2 (%)	98		98	98	98	98	99			98	98	
3	Time vs Remdesivir	2 d after adm	Same day										Discharged home D 3 post Remdesivir
	O_2 delivery method	NC		NC	NC	RA	RA	RA			RA	RA	
	FiO_2 (%)	37		34	33	21	21	21			21	21	
	PF *ratio* (mmHg)	262		291		471		466			466		
	SpO_2 (%)	98		98	99	99	99	99			99	99	
4	Time vs Remdesivir	Same day	Same day										Discharged home D 4 post Remdesivir
	O_2 delivery method	NRM		HFNC	HFNC	HFNC	NRM	CPAP	NRM	NC	NC	NC	
	FiO_2 (%)	100		70	55	55	100	65	100	40	37	29	
	PF *ratio* (mmHg)	309		164	342.7	180	176.9	169	323	245	275	341	
	SpO_2 (%)	99		99	98	98	97	98	98	98	95	96	
5	Time vs Remdesivir	5 d after adm	5 d after										Discharged home D 4 post Remdesivir
	O_2 delivery method	NC		NC	NC	RA	RA	RA			RA	RA	
	FiO_2 (%)	29		29	29	21	21	21			21	21	
	PF *ratio* (mmHg)	476		277		457		452			461		
	SpO_2 (%)	98		98	98	97	98	99			99	99	

Case 1

A 64-year-old male patient came to the hospital complaining of a headache. The patient was treated in the ward with standard COVID-19 therapy in the form of Oseltamivir, Azithromycin, Vitamin B Complex, Zinc. On the 6th day of treatment, the patient was transferred to HCU due to desaturation by SpO_2 of 89% with room air, the presence of moderate ARDS and bronchopneumonia. During the HCU treatment, the patient experienced desaturation with SpO_2 of 85% with non-rebreathing mask (NRM) 15 lpm and a respiration rate of 36 times per minute in the presence of severe ARDS so that oxygen therapy was changed into high flow nasal canule (HFNC) Flow 40 FiO_2 90% and was replaced with CPAP PEEP 5 mbar FiO_2 70% after the condition was improved.

Patients received antibiotic therapy in the form of Azithromycin, Levofloxacin, Cefoperazone and Meropenem. Remdesivir 2x100 mg was given on day 6 of treatment in HCU and continued 1x100 mg for 5 days. The patient received heparin therapy while in HCU. The patient was admitted in HCU for 15 days, then transferred to the ward with a saturation of 98% using 2 lpm nasal canule. On the 22nd day of treatment, the PCR results were negative and the patient was discharged.

Case 2

A 46-year-old male patient came to the hospital with a cough, sore throat and a history of fever since 4 days before admitted to the hospital. The patient was transferred to the HCU on the 2nd day due to a decrease in SpO_2 of 92-93% with room air and the presence of mild ARDS. During HCU treatment, the patient was given 4 lpm nasal canule oxygen therapy with a saturation of 98-99%. The patient was given 2x100 mg remdesivir on the first day of treatment in HCU, followed by 1×100 mg for 5 days. The patient was allergic to moxifloxacin and meropenem, so he was given antibiotic therapy in the form of ceftriaxone.

The patient received fondaparinux therapy for 4 days then discontinued it due to hematoma in the right arm. This condition occurred 1 day after the pain and heavy breathing. The patient was treated in HCU for total of 5 days, on the 6th day of treatment the patient did not complain of coughing and sore throat, the hematoma in the right arm become better so that the patient was transferred to a ward with SpO_2 of 99% with room air. On the 10th day of treatment, PCR results were negative and the patient was discharged.

Case 3

A 33-year-old male patient came to the hospital complaining of vomiting more than four times, headache, weakness and a history of fever 2 days before he was hospitalized. The patient had taken Oseltamivir 2x75 mg and Azithromicyn 1x500 mg for 5 days before coming to the emergency room. Patients are treated in the ward and receive standard COVID-19 therapy. On day 2 of the treatment patient was transferred to HCU due to worsening of the patient's condition accompanied with desaturation of SpO_2 by 95% with room air

and mild ARDS. During HCU treatment, the patient was given 4 lpm nasal canule with SpO2 of 98-99%. The patient was given 2x100 mg remdesivir on the first day of treatment in HCU, followed by 1×100 mg for 5 days. The combination of antibiotics given in HCU is Moxifloxacin and Ceftriaxone. Patients received heparin therapy while being treated in HCU, on the third day of treatment the heparin was changed to 10,000 IU drip depleted in 2 hours. At 2 hours of administration of heparin drip, the patient complained of a hematoma on the left arm.

Complete blood count and coagulant factors were carried out and the results of thrombocytopenia ($87x10^3$/uL) and an increase in D-Dimer (814 ng/mL) were performed without other bleeding complaints such as nosebleeds, bleeding gums, and melena, then the patient was diagnosed with Hematoma due to Heparin-Induced Thrombocytopenia (HIT). Heparin was stopped, and the patient was given heparin sodium gel and warm compresses to the area of the hematoma. The patient was admitted to the HCU for a total of 5 days, on the 6th day of treatment at the HCU the patient had no complaints of nausea, vomiting, and headaches, the hematoma in the left arm had improved so that the patient was transferred to the ward with SpO_2 of 99% room air. On the 10th day of treatment, PCR results were negative and the patient was discharged.

Case 4

A 43-year-old male patient came to the hospital with complaints of dysgeusia and dry cough 5 days before admitted to the hospital. At the time of examination in the ER, the patient's respiration rate was 28 times per minute with SpO_2 of 89% room air, moderate ARDS and Bilateral Pneumonia. The patient was immediately transferred to HCU. During HCU treatment, oxygen therapy was replaced from NRM 15 lpm into HFNC Flow 30 FiO_2 70%. On the 5th day of treatment, the patient still complaining of shortness of breath accompanied by a productive cough. HFNC was changed into NRM 15 lpm with SpO_2 of 97%. On the 6th day of treatment, the symptoms were getting worse, so that the oxygen therapy was changed to CPAP 6 mbar FiO_2 65%. On the 7th day of treatment, the CPAP oxygen therapy was changed to NRM 15 lpm with SpO_2 of 98%. On the 8th day of treatment oxygen therapy was changed to a 5 lpm nasal canule with SpO_2 of 95%. On the 10th day of treatment, the complaints of shortness of breath and cough were reduced with SpO_2 of 95% with 2 lpm nasal canule.

Remdesivir was given 2x100 mg on the first day of treatment in HCU, followed by 1x100 mg for 5 days and continued for 7 days in consequence of patient deterioration condition. The combination of antibiotics given is cefotaxime, moxifloxacin, meropenem and cefepime. The patient received heparin therapy during his HCU stay. The patient was admitted to the HCU for a total of 10 days. On the 10th day of treatment, the patient did not complain of coughing and shortness of breath, so the patient was transferred to the ward with SpO_2 of 95% using a 3 lpm nasal

canule. On the 14th day of treatment, PCR results were negative and the patient was discharged.

Case 5

A 61-year-old male patient came to the hospital with complaints of fever for 9 days accompanied by cough and runny nose. The patient had a history of Diabetes Mellitus and Hypertension. Patients are treated in the ward with standard therapy. On day 6 of treatment, the patient experienced desaturation by SpO_2 of 95% room air accompanied by Mild ARDS with left pleural effusions so that the patient was transferred to HCU. During the HCU treatment, the patient was given oxygen therapy in the form of 2 lpm Nasal Canul with SpO_2 of 98-99%.

The patient was given 2x100 mg remdesivir on the first day of treatment in HCU, followed by 1×100 mg for 5 days. The combination of antibiotics given at HCU is azithromycin, ceftriaxone, moxifloxacin. The patient received heparin therapy during his HCU stay. The patient was admitted to the HCU for 5 days. On the 6th day of treatment at the HCU, the patient did not complain of coughing, so the patient was transferred to a regular treatment room with 99% saturation of room air. On the 14th day of treatment, PCR results were negative and the patient was discharged.

DISCUSSION

This case series describes the first five severe COVID-19 patients who got remdesivir therapy in RSDC Wisma Atlet Kemayoran, Jakarta. It is a retrospective, uncontrolled, and open-label study. However, this study needs to be published to show the potency of remdesivir against COVID-19, particularly in Indonesia.

United States Food Drug Administration released the Emergency Use Authorization (EUA) for emergency use of remdesivir in Mei 2020. Remdesivir therapy is allowed for adults and children with severe COVID-19 confirmed by PCR swab, and severe symptoms are showed by oxygen saturation below 94% on room air, require oxygen therapy, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) in high intensive care unit (HCU) setting.[1]

Remdesivir is pharmacologically effective against several viral infections. Remdesivir acts as a monophosphate nucleotide analog inside cells. It alters the monophosphate structure to nucleoside triphosphate, later it will be the adenosine triphosphate (ATP) analog. This structure will compete against ATP substrate to inhibit the RNA-dependent RNA polymerase of the virus, and consequently, the virus replication process will be slow down.[2]

Remdesivir was found to be effective against MERS-CoV and SARS-CoV-1 according to in vitro studies.[3–5] A better outcome was obtained by combining remdesivir with interferon beta group medication and lopinavir-ritonavir.[3]

Some studies have shown the efficacy of remdesivir against COVID-19 and related viral infection. A case report

from Washington, USA demonstrated progressive clinical and radiological improvement of the patient with pneumonia after 7 days of remdesivir therapy. Besides remdesivir, vancomycin and cefepime were also given.[4] In-vitro trial using vero cells showed that remdesivir was effective in inhibiting SARS-CoV-2 infection.[5] Another study showed that the active agents of remdesivir could reduce the viral load in the bronchoalveolar lavage sample and lung infiltrate in the rhesus macaque model.[6] A study by Pizzorno *et. al.* demonstrated SARS-CoV-2 replication is inhibited by remdesivir on the respiratory cell of bronchus and nasal.[7] A double-blind randomized control trial study found that COVID-19 patients who got remdesivir were recovered faster compared to the placebo group (P<0.001).[8] Our case series showed that clinical and laboratory improvement was achieved by five patients after remdesivir therapy combined with antibiotics, anticoagulants, corticosteroids, antioxidants, and vitamins.

A randomized control trial study by the National Institute of Allergy and Infectious Diseases (NIAID) on 1063 COVID-19 patients from February until April 2020 compared time to clinical improvement of remdesivir group and placebo group. Clinical improvement was achieved within 11 days in remdesivir group, while the placebo group 15 days.[8]

Another open-label, randomized, and phase 3 study by Gilead Science compared clinical improvement of severe COVID-19 patients who got 5 and 10 days of remdesivir therapy. Fourteen days after the first remdesivir therapy, clinical improvement was evaluated and insignificant outcomes were obtained (Odds Ratio=0.75; 95% CI=0.51-1.12). Some 60% of the patients in 5 days remdesivir group were discharged home on day 14, while 10 days group was 52.3%. Early remdesivir therapy within 10 days after symptoms appeared resulting in clinical improvement of 62% of the patient on day 14 of hospitalization.[2]

The five patients in our case series got remdesivir therapy within 10 days after admitted to the hospital. Good clinical outcomes were seen in these patients as well as the short length of hospital stay. The longest stay was 21 days, while the shortest was 10 days. The patient with the shortest length of stay got remdesivir on his second day of hospitalization, while the longest got remdesivir on his ninth day of hospitalization.

One of the inflammatory markers that is known as a prognostic factor for pneumonia is the neutrophil-lymphocyte ratio (NLR).[9] Neutrophils are one of the leukocyte components that appears when inflammatory factors, such as IL-6, IL-8, TNF, and IGF are released, consequently induce reactive oxygen species (ROS) formation and DNA damages. Meanwhile, CD4+ T lymphocyte will decrease and CD8+ suppressor T lymphocyte will increase in systemic inflammation caused by a viral infection, as a result, neutrophil-lymphocyte ratio (NLR) will rise. The

higher NLR, the more severe inflammation will be and it is linked to high mortality and worse prognosis in COVID-19 patients.[10] NLR predicts greater severity in the range of 3.3 to 5.9, while between 7.9 to 11.8 mortality rate will be higher.[11] Four out of five cases in these case series demonstrated lowering of NLR after remdesivir therapy ends, it is associated with better outcomes.

Acute respiratory distress syndrome (ARDS) contributes to a high mortality rate in COVID-19 cases.[12] Severity of ARDS is determined by the partial pressure of oxygen (PaO_2) per fraction of inspired oxygen (FiO_2) also known as PF ratio. Mild ARDS is defined by PF ratio of 300 to 200, 200 to 100 is moderate and less than 100 is severe.13 The five patients in these case series got the first dose of remdesivir after they were admitted to high intensive care unit (HCU) because of ARDS. After five until seven days of remdesivir therapy, three patients recovered from ARDS, one patient had milder severity, and one patient still had moderate ARDS but a higher PF ratio. We associate remdesivir therapy with milder ARDS severity. However, more studies need to be done to prove this.

Remdesivir therapy has some known side effects. A phase one clinical trial demonstrated phlebitis, constipation, headache, ecchymosis, nausea, vomiting and extremities pain after remdesivir was given to healthy subjects. In laboratory examination, the elevation of liver enzymes (SGOT and SGPT), prothrombin, and blood glucose level was founded in less than five percent of subjects.[13] Another study reported diarrhea, skin rash, hypotension, and nephrotoxicity following remdesivir administration.[13] In these case series four patients already had high SGOT and SGPT levels before remdesivir therapy and the level was various after therapy. High initial liver enzyme levels was associated with liver damage caused by SARS-CoV-2 bound with ACE-2 receptor in hepatocyte and hepatic ischemia induced by a cytokine storm.[14]

Renal function tests, such as ureum and creatinine levels should be monitored during remdesivir therapy. Although only a few of remdesivir active forms are excreted in the kidney, they still can be found in urine. To date, there is no specific guideline on remdesivir therapy in mild and moderate renal impairment, but it is not recommended to give remdesivir to the patient with eGFR less than 30 ml/minutes. No study has reported renal impairment in healthy subjects induced by remdesivir therapy, but cautious usage must be done.[13] These case series showed no significant renal impairment in five patients before and after remdesivir was given.

The recommended dosage for remdesivir in COVID-19 was given for 10 days, with an initial bolus dose of 200 mg IV dissolved in 0.9% NaCl or 5% dextrose given for 60 minutes during the first day, for the second day to the tenth day was administered in a dose of 100 mg IV which was diluted and administered for 60

minutes.[15] Patients in this case series received 200 mg of remdesivir on the first day and continued with 100 mg for the following day until the fifth day. For patients with a clinical condition which has not been improved within five days, then remdesivir administration will be continued for up to seven days. Clinical improvement was achieved in four patients after receiving remdesivir therapy for five days, whereas one patient experienced clinical improvement after receiving therapy for seven days. Three to seven days after the last remdesivir administration, these five patients were eventually discharged from the hospital with negative PCR swabs.

In this case series, a good outcome was described, when the patient tested negative on PCR swab after patient with severe symptoms received remdesivir therapy. The administration was following the recommendations of the clinical practice guideline study by Rochwerg et al. published in the British Medical Journal that giving remdesivir intravenously at a dose of 100 mg for 5–10 days is recommended for COVID-19 patients with severe symptoms. We agree with the recommendation while waiting for the results of the large multicenter randomized control trial.[16]

CONCLUSION

The administration of remdesivir in cases of COVID-19 can result in a good outcome, especially its role in reducing the severity and length of treatment. Interaction between remdesivir and other drugs such as heparin, antibiotics, corticosteroid and other therapies need to be considered. Post therapy follow-up needs to be studied further, concerning the assessment of the effectiveness of the therapy. Research on remdesivir is also needed with a larger sample size to prove that it can be used or proven effective in COVID-19.

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