Original Article นิพนธ์ต้นฉบับ

การศึกษาประสิทธิผลของยาเรมเดสิเวียร์ในการรักษาผู้ป่วยโควิด 19 ที่มีอาการปานกลางถึงรุนแรงและวิกฤต: การศึกษาย้อนหลัง

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วัตถุประสงค์: เพื่อศึกษาผลทางคลินิกในผู้ป่วยโรคโควิด 19 ระหว่างกลุ่มที่มีอาการปานกลางถึงรุนแรง และอาการวิกฤต หลังการรักษาด้วยยาเรมเดสิเวียร์ 7 วัน และศึกษาผลทางคลินิก และอัตราตายหลังการรักษาด้วยยาเรมเดสิเวียร์ 14 และ 30 วัน

ระเบียบวิธีวิจัย: การศึกษาแบบย้อนหลัง โดยเก็บข้อมูลตั้งแต่เดือนเมษายน 2564 - ตุลาคม 2564 ในผู้ป่วยผู้ใหญ่อายุมากกว่าหรือเท่ากับ 16 ปีที่ได้รับการวินิจฉัยเป็นโรคโควิด 19 ในโรงพยาบาลนครพิงค์และได้รับยาเรมเดสิเวียร์ จำแนกเป็นกลุ่มอาการปานกลางถึงรุนแรง และกลุ่มอาการวิกฤต ศึกษาข้อมูลทางคลินิก ระยะเวลารักษา ผลการรักษา หลังการรักษาด้วยยาเรมเดสิเวียร์ โดยประเมินที่ 7 วันและ 14 วันหลังการรักษา รวมถึงอัตราการตายที่ 30 วันหลังการรักษา วิเคราะห์และทดสอบความแตกต่างระหว่างกลุ่มด้วย Fisher's exact test, chi square test , t-test หรือ Mann-Whitney U test ตามเหมาะสม

ผลการศึกษา: ผู้ป่วยทั้งหมด 156 คน แบ่งเป็นกลุ่มอาการปานกลางถึงรุนแรง 84 คน อาการวิกฤต 72 คน ลักษณะพื้นฐานของทั้งสองกลุ่มไม่มีความแตกต่างกันยกเว้นลักษณะดังต่อไปนี้ ได้แก่ จำนวนผู้ป่วยที่มีอายุเกิน 60 ปี โรคประจำตัว เช่น ความดันโลหิตสูง โรคไตเรื้อรัง โรคธัยรอยด์ ภาพรังสีทรวงอก การได้รับการรักษาด้วยการฟอกเลือด ค่าการอักเสบในเลือด ค่า NEWS แรกรับ การได้รับยาปฏิชีวนะและยาป้องกันการเกิดลิ่มเลือดอุดตัน

ผลการศึกษา: กลุ่มผู้ป่วยอาการปานกลางถึงรุนแรงมีอาการดีขึ้นหลังได้รับการรักษา 7 วันได้กลับบ้านเป็นสัดส่วนมากกว่ากลุ่มผู้ป่วยอาการวิกฤตอย่างมีนัยสำคัญทางสถิติคือ 32.1% และ 0% ตามลำดับ (P=0.015)

ผลการศึกษารอง: กลุ่มผู้ป่วยอาการปานกลางถึงรุนแรงมีอาการดีขึ้นหลังได้รับการรักษา 14 วันได้กลับบ้านเป็นสัดส่วนมากกว่ากลุ่มผู้ป่วยอาการวิกฤตอย่างมีนัยสำคัญทางสถิติคือ 59.6% และ 11.1% ตามลำดับ (P = 0.006) ส่วนอัตราตายที่ 30 วันหลังการรักษาพบว่าในกลุ่มผู้ป่วยอาการปานกลางถึงรุนแรงยังคงน้อยกว่ากลุ่มผู้ป่วยอาการวิกฤตอย่างมีนัยสำคัญทางสถิติ (19% และ 32.6%), P = 0.041

สรุปผลการศึกษา: ในกลุ่มผู้ป่วยอาการปานกลางถึงรุนแรง การให้ยาเรมเดสิเวียร์มีแนวโน้มที่จะได้ประโยชน์ เนื่องจากอัตราการหายกลับบ้านสูงกว่า และอัตราตายน้อยกว่าในกลุ่มผู้ป่วยอาการวิกฤต ดังนั้นในผู้ป่วยอาการวิกฤตควรได้รับการรักษาด้วยยาอื่นที่มีประสิทธิภาพนอกเหนือจากยานี้

คำสำคัญ: Remdesivir, COVID-19, Thailand, retrospective cohort, effectiveness

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Clinical effectiveness of remdesivir in the treatment of moderate to severe and critical COVID-19 Infections: a retrospective study

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Objectives: To evaluate clinical outcome on day 7 after treatment with remdesivir including discharge status, clinical outcome on day 14 after treatment with remdesivir and 30 days mortality in COVID 19 adult.

Methods: A retrospective cohort study was conducted between April 2021 to October 2021 at Nakornping hospital, Chiang Mai, Thailand. All hospitalized patients aged ≥16 years diagnosed with COVID-19 who received remdesivir, categorized in moderate to severe group and critical group. Clinical data including laboratory, radiographic finding and clinical course outcome were collected. Comparison was made between two groups by using Fisher's exact test or chi square test when appropriate and t-test or Mann-Whitney U test to compare quantitative variables.

Results: A total of 156 COVID-19 patients were included in the analysis and classified into moderate to severe illness (n = 84) and critical illness (n = 72) groups. Baseline characteristics between groups were compared and found no significant difference except for age, underlying hypertension, chronic kidney disease and thyroid disease, chest radiography, hemoperfusion, C-reactive protein (CRP) and national early warning score (NEWS) at admission, treatments with antibiotics and venous thromboembolism (VTE) prophylaxis. For the primary endpoints, the proportion of patients discharge at day 7 was significantly higher in the moderate to severe group (32.1%) compared to the critical group (0%) (P = 0.015). For secondary endpoints, the proportion of patients discharge at day 14 was also significantly higher in the moderate to severe group (59.6%) compared to the critical group (11.1%) (P = 0.006). Thirty days mortality was significantly lower in the moderate to severe group (19.0%) compared to the critical group (32.6%) (P = 0.041).

Conclusion: Among COVID-19 patients with moderate to severe illness, remdesivir showed effects to improve clinical outcomes, but in COVID-19 patients with critical illness, remdesivir showed less benefit and clinical outcome improvement. More effective treatment options are suggested and should be considered especially in a critical group.

Keyword: Remdesivir, COVID-19, Thailand, retrospective cohort, effectiveness

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Introduction

Coronavirus disease 2019 (Covid-19) is an emerging pandemic caused by newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the end of 2019. SARS-CoV-2 is transmitted through the respiratory tract of the infected person by droplets and aerosols. This condition is characterized by a wide range of symptoms varying from minor flu-like symptoms up to severe acute respiratory distress syndrome and death.[1]

Remdesivir (GS-5734), an inhibitor of the viral RNA-dependent RNA polymerase with in vitro inhibitory activity against SARS-CoV-1 and the Middle East respiratory syndrome (MERS-CoV) was identified early as a promising therapeutic candidate for Covid-19 because of its ability to inhibit SARS-CoV-2 in vitro. In addition, in nonhuman primate studies, remdesivir initiated 12 hours after inoculation with MERS-CoV reduced lung virus levels and lung damage.[2-3]

A first randomized, placebo-controlled trial of remdesivir among patients with COVID-19 conducted in Wuhan, China, could not complete enrollment to meaningfully assess efficacy. However, in a larger randomized, double-blind clinical trial, patients with severe COVID-19 treated with a 10-day course of remdesivir had a significantly shorter time to recovery than those receiving placebo (11 days vs 15 days). (4) Subsequently, a randomized, open-label trial showed that patients with severe COVID-19 with relative hypoxia or requiring oxygen support but not requiring ventilatory support had outcomes with 5- and 10-day courses of remdesivir that were not significantly different.[4-6] These results prompted the US Food and Drug Administration to grant Emergency Use Authorization of remdesivir for patients with severe COVID-19 and the European Medicines Agency to grant conditional marketing authorization to remdesivir for treatment of COVID-19 in patients 12 years of age or older with pneumonia who require supplemental oxygen.[7-8]

WHO recommendation released on 20 November 2020 against the use of remdesivir in hospitalized patients, regardless of disease severity, as there was no supporting evidence that remdesivir improves survival and other outcomes in these patients.[9]

In Thailand, the prevalence of COVID-19 was 10% among patients with risk factors for COVID-19 acquisition at during the outbreak period. Most COVID-19 patients had mild disease, and approximately 18% had severe or critical disease.[10] Antiviral treatment is recommended for all symptomatic COVID-19 patients according to Thailand national

treatment guideline, favipiravir was selected according to disease severity and the presence of risk factors for disease progression.

Nakornping hospital is a tertiary care hospital in Chiang Mai, the second largest city in Thailand, which is a referral center for most of patients with moderate to severe and critical COVID-19 infections from many rural hospitals. These patients needed more intensive care and more potent antiviral agents. Thus, remdesivir was frequently used in this populations, either as step-up or first-line regimen but there are few published studies about outcome and safety of remdesivir in Thailand.

This study was conducted to evaluate the effectiveness i.e., clinical outcomes of remdesivir administered for 5 or 10 days in hospitalized patients with moderate to severe and critical COVID-19 in Nakornping hospital, Chiang Mai, Thailand.

Methods

Design and Study setting

A retrospective cohort study was conducted between April 2021 and October 2021 at Nakornping hospital, a 700-bed, tertiary-care hospital in Chiang Mai, Thailand.

Population

All hospitalized patients aged ≥16 years diagnosed with moderate to severe and critical COVID-19 are included. (Figure 1) Diagnosis of COVID-19 was made based on the detection of at least 2 of SARS-CoV-2 genes by reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal (NP) swab, throat swab, and/or any respiratory samples. Briefly, after collection of the NP or throat swab, the specimen was placed into viral transport media (VTM) and processed as fully automated by Cobas 6800 (Roche diagnostics, Basel, Switzerland).

Treatments

According to the Thailand national clinical practice guidelines for treatment of COVID-19, the regimen of antiviral medications was selected based on disease severity and the presence of risk factors for disease progression. Patients with one or more of the following were considered to be at risk for disease progression: age > 60 years, chronic pulmonary disease, chronic kidney disease, cardiovascular disease, cerebrovascular disease, hypertension, diabetes mellitus, obesity (body mass index [BMI] ≥30 kg/m^2), cirrhosis, immunocompromised status, lymphocyte count < 1000 cells/ mm^3, as well as the severity of illness (mild and presence of pneumonia).

Favipiravir is considered for treatment of patients with mild disease regardless of the risk factors for disease progression, and also recommended for patients with COVID-19 pneumonia and should be given for at least 5 days, but the duration can be extended to

as long as 10 days based on patient's clinical response. remdesivir is considered for treatment of patients with disease progression despite being treated with favipiravir, patients' presence with severe or critical COVID-19 on admission and should be given for at least 5 days, but the duration can be extended up to 10 days based on patient's clinical response as well. All patients with confirmed COVID-19 must be hospitalized for at least 14 days after symptom onset and must be isolated for another 14 days at home or at designated facilities.

Data collections

Data were collected from patient medical records including demographic data, clinical features, underlying illnesses, baseline laboratory parameters, chest X-ray, antiviral therapy, oxygen support, use of mechanical ventilation, hemoperfusion, length of stay, and outcomes of treatment.

Definitions

- The date of disease onset was defined as the day when the first symptom was observed.

- Pneumonia was defined as fever and/ or respiratory symptoms with appearance of new or progressive infiltrate on chest imaging.

- The disease severity of COVID-19 was classified according to WHO definitions as

1) moderate (defined as pneumonia);

2) severe (defined as pneumonia with presence of dyspnea, respiratory rate ≥ 30/min, oxygen saturation (SpO2) ≤ 94% in ambient air;

3) critical (defined as acute respiratory failure/acute respiratory distress syndrome (ARDS), septic shock, and/or multi-organ dysfunction).

Outcome Measures

Primary outcome measure: clinical outcome of patients with moderate to severe COVID-19 infection compared with critical COVID-19 infection on day 7 after treatment with remdesivir, which included discharge status.

Secondary outcome measure: clinical outcome of patients with moderate to severe COVID-19 infection compared with critical COVID-19 infection on day 14 after treatment with remdesivir, NEWS after treatment, duration of treatment with remdesivir, length of stay, multi-organ failure/ECMO, mortality at 30 days.

Statistical analysis

Data are presented as number and percentage for categorical data, and as mean ± standard deviation for normally distributed data or median and range for nonnormally distributed data. Fisher's exact test or chi square test was used to compare qualitative variables, and t-test or Mann-Whitney U test was used to compare

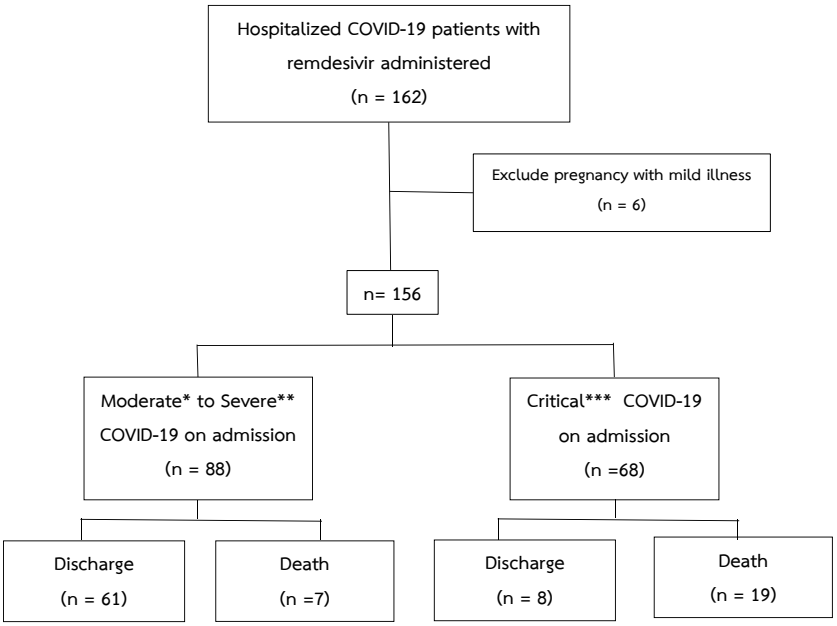
quantitative variables. All statistical analyses were performed using Stata statistical software version 15.0 (Stata Statistical Software: Release 15.0, Stata Corporation, College Station, TX, 2015). A two-sided test at a p-value of <0.05 was used to indicate statistical significance.

Ethics statement

This study was approved by the Institutional Review Boards of each participating hospital and the requirement for informed consent was waived because de-identified retrospective data collected by governmental authority were used for analysis.

Results

Figure 1. Flow diagram of all hospitalized patients with moderate to severe and critical COVID-19 with remdesivir administered



Baseline characteristics of COVID-19 patients

Of 162 hospitalized COVID-19 patients included, 6 patients were excluded due to pregnancy with mild disease, a total of 156 COVID-19 patients were included in the analysis and classified into moderate to severe (n = 84) and critical (n = 72) groups (Figure 1).

Baseline characteristics of cohort patients are presented in Table 1, and there were not significantly different between groups except age, underlying hypertension, chronic kidney disease and thyroid disease, chest radiography, hemoperfusion,

C-reactive protein (CRP) level, and National Early Warning Score (NEWS) at admission, treatments with antibiotics and VTE prophylaxis. The median age was 55.2 ± 12.1 years, 65% were male. The average BMI was 26.83 ± 3.8 kg/m^2. Hypertension and diabetes were the most common comorbidities. Median time of onset was 4.3 day and most common route of acquisitions of COVID-19 were close contact confirmed patients and visiting public area. Patients were admitted to the hospital on average 4.3 days (range 1 to 11 days) from symptom onset. Remdesivir was administered on average 6.3 days (range 2 to 10 days) from symptom onset for both groups.

Clinical outcomes compared between groups

Clinical outcomes of the cohort patients are presented in Table 2 and 3. Among the primary endpoints, the proportion of patients discharge at day 7 was significantly higher in the moderate to severe group (32.1%) compared to the critical group (0%) (p = 0.015). For secondary endpoints, the proportion of patients discharge at day 14 was also significantly higher in the moderate to severe group (59.6%) compared to the critical illness group (11.1%) (P = 0.006). Death in hospital on day 7 and day 14 after treatment was also significantly lower in the moderate to severe group (7.1% and 1.8%) compared to the critical group (16.7% and 9.7%, P = 0.009 and 0.029, respectively). About 6% and 7% of patients in moderate to severe group have clinical worsen and required invasive ventilation on day 7 and 14 after treatment, respectively. NEWS at day 7 and 14 after treatment was significantly lower in the moderate to severe group compared to the critical group (p = 0.026 and 0.007, respectively) and 30 days mortality was significantly lower in the moderate to severe illness group (19.0%) compared to the critical illness group (32.6%) (P = 0.041).

TABLE 1. Demographic characteristics, comorbidities, clinical and laboratory values of patients treated with remdesivir compared those with moderate, severe and those with critical illness.

Characteristics	All patients (n =156)	Moderate to severe (n =84)	Critical (n =72)	p-value*
Male gender	102(65.4)	58(69.0)	44(61.1)	0.696
Age, y	55.2±12.1	49.8±13.9	63.0±10.4	0.005
Age > 60 y	77(49.4)	31(36.9)	46(63.9)	0.006
BMI, kg/m2	26.8±3.8	21.3±3.9	27.9±3.5	0.839
BMI ≥ 30 kg/m2	47(30.1)	33(39.3)	14(19.4)	0.222
Days from symptom onset, d (median)				
To admission	4.3(1-11)	3.3(3-11)	6.2(1-9)	0.053
To remdesivir treatment	6.3(2-10)	6.1(4-10)	6.3(2-8)	0.299
Comorbidities				
Hypertension	70(44.9)	28(33.3)	42(58.3)	0.002
Uncontrolled Diabetes	55(35.3)	21(25)	24(33.3)	0.619
Chronic kidney disease	21(13.5)	6(7.1)	15(20.8)	0.005
Cerebrovascular disease	15(9.6)	9(10.7)	6(8.3)	0.668
Thyroid disease	9(5.8)	7(8.3)	2(2.8)	0.016
NEWS at admission	8.3 ± 2.6	6.8 ± 1.7	10.1 ± 4.5	0.007
Presenting symptoms				
Fever/history of fever	64(41.0)	39(46.4)	25(34.7)	0.060
Cough	127(81.4)	67(79.8)	60(83.3)	0.083
Dyspnea	146(93.6)	74(88.0)	72(100)	0.204
Ageusia/Anosmia	88(56.4)	56(66.7)	32(44.4)	0.353
Acquisitions				
Contact confirmed patients	71(45.5)	35(41.7)	36(50.0)	0.430
Visiting public area	74(47.4)	41(48.8)	33(45.8)	0.263
Travelling	8(5.1)	5(6.0)	3(4.2)	0.781
Unknown	3(1.9)	2(2.4)	1(1.4)	0.151
Chest radiography on admission				
Bilateral alveolar infiltration	111(71.1)	52(61.9)	59(81.9)	0.050
Bilateral interstitial infiltration	13(8.3)	5(6.0)	8(11.1)	0.048
Mixed infiltration	8(5.1)	4(4.8)	4(5.6)	0.826
ARDS	24(15.4)	11(13.1)	13(18.1)	0.636
Initial Ct values	25.2±5.5	25.7±3.8	24.4±4.9	0.357
Favipiravir prior use	143(91.7)	83(98.9)	60(83.3)	0.072
Hemoperfusion	43(27.6)	16(19.0)	27(37.5)	0.050*
Other treatments				
Corticosteroids	150(96.2)	78(92.9)	72(100)	0.281
Antibiotics	123(78.8)	53(63.1)	70(97.2)	0.032*
VTE prophylaxis	87(55.8)	21(25.0)	66(91.7)	0.009*
Other immunomodulators				
IL-6 inhibitors	9(5.8)	2(2.4)	7(9.7)	0.169

TABLE 1. Demographic characteristics, comorbidities, clinical and laboratory values of patients treated with remdesivir compared those with moderate, severe and those with critical illness. (Cont.)

Characteristics	All patients (n =156)	Moderate to severe (n =84)	Critical (n =72)	p-value*
Baseline laboratory values				
WBC, ×103/mm3	5.7±2.2	5.6±2.1	5.9±2.6	0.672
Lymphocyte, ×103/mm3	1.3±0.5	1.2±0.5	1.3±0.4	0.341
Hemoglobin, g/dL	12.8±3.5	12.1±2.1	13.7±2.1	0.161
Platelet count, ×103/mm3	176.3±51.2	177.9±58.8	169.7±50.4	0.227
AST, IU/L	44.1±24.6	42.4±22.4	44.9±23.6	0.390
ALT, IU/L	32.3±22.7	32.6±22.2	33.5±23.4	0.448
BUN, mg/dL	17.2±10.3	18.1±12.4	15.5±8.3	0.296
Creatinine, mg/dL	0.92±0.4	0.91±0.4	0.94±0.5	0.352
LDH, IU/L	426.8±183.2	424.1±205.1	447.7±149.8	0.081
CRP, mg/dL	88.2±64.4	74.2±24.2	97.4±56.8	0.040*
PT, INR	1.1±0.1	1.0±0.1	1.1±0.2	0.559

Data are expressed as the number (%) of patients or mean ± standard deviation.

p-value< 0.05 indicates statistical significance.

Abbreviations: BMI body mass index, Ct = cycle threshold, WBC = white blood cell, AST = aspartate transaminase, ALT = alanine transaminase, BUN = blood urea nitrogen, LDH = lactate dehydrogenase, CRP = C-reactive protein, PT = prothrombin time, INR = international normalized ratio, VTE = venous thromboembolism, IL-6 = interleukin-6, ARDS = acute respiratory distress syndrome, HFNC = high flow nasal cannula, NIV = non-invasive ventilation

TABLE 2. Clinical outcomes of patients treated with remdesivir compared those with moderate, severe and those with critical illness at day 7 after treatment.

Characteristics	All patients (n =156)	Moderate to severe (n =84)	Critical (n =72)	p-value*
Duration of remdesivir (days)	5.0±1.5	4.8±2.7	5.3±2.2	0.869
Minimum	2	3	2	
Maximum	10	10	10	
Length of stay (days)	13.5±9.9	10.2±3.2	18.3±13.7	0.022
Minimum	2	4	2	
Maximum	50	35	50	
Clinical status on day 7 after treatment				
Discharge	27(17.3)	27(32.1)	0(0)	0.015
O2 with nasal prong	28(17.9)	22(26.2)	6(8.3)	0.029
HFNC/NIV/Facial mask	38(24.4)	24(28.6)	14(19.4)	0.011
Invasive ventilation*	15(11.6)	4(7.0)	11(15.3)	0.018
Multi-organ failure/ECMO	1(0.6)	0(0)	1(1.4)	0.628
Death in hospital	18(11.5)	6(7.1)	12(16.7)	0.009
NEWS at day 7 after treatment	7.0±2.6	5.9±2.3	9.1±2.9	0.026
30 days mortality	38(24.4)	16(19.0)	22(30.6)	0.041

TABLE 3. Clinical outcomes of patients treated with remdesivir compared those with moderate, severe and those with critical illness at day 14 after treatment.

Characteristics	All patients (n =129)	Moderate to severe (n =57)	Critical (n =72)	p-value*
Clinical status on day 14 after treatment				
Discharge	42(32.6)	34(59.6)	8(11.1)	0.006
O2 with nasal prong	34(24.4)	7(12.3)	27(37.5)	0.003
HFNC/NIV/Facial mask	21(16.3)	9(15.8)	12(16.7)	0.194
Invasive ventilation*	15(11.6)	4(7.0)	11(15.3)	0.018
Multi-organ failure/ECMO	9(7.0)	2(3.5)	7(9.7)	0.035
Death in hospital	8(6.2)	1(1.8)	7(9.7)	0.029
NEWS at day 14 after treatment	2.85±3.47	1.85±1.89	4.17±4.53	0.007

Data are expressed as the number (%) of patients or mean ± standard deviation.

p-value< 0.05 indicates statistical significance.

Abbreviations: BMI body mass index, Ct = cycle threshold, WBC = white blood cell, AST = aspartate transaminase, ALT = alanine transaminase, BUN = blood urea nitrogen, LDH = lactate dehydrogenase, CRP = C-reactive protein, PT = prothrombin time, INR = international normalized ratio, VTE = venous thromboembolism, IL-6 = interleukin-6, ARDS = acute respiratory distress syndrome, HFNC = high flow nasal cannula, NIV = non-invasive ventilation

Discussion

This study showed significantly better clinical outcome among moderate to severe COVID-19 patients receiving remdesivir compared to its critical group counterpart regarding proportion of discharged patients, mechanical ventilation supports, NEWS score and mortality rate after 7 and 14 days of treatment. Overall mortality in moderate to severe group at 30 days was significantly lower compared to critical group (Absolute reduction of 11.6%).

Evidence of remdesivir efficacy in COVID-19 patients remains inconclusive. The first randomized controlled trial conducted in China did not show a benefit of remdesivir in the treatment of COVID-19.[4] The Solidarity trial, conducted by World Health Organization, also did not show any benefit of remdesivir.[9] Whereas numbers of study and meta-analysis suggest probability of efficacy in patient without mechanical ventilation supports. Early treatment with remdesivir shortened the length-of-stay in patients hospitalized with COVID-19.

In this study, among COVID-19 patients with moderate to severe illness, there is an obvious positive trend in clinical outcomes both on day 7 and 14 after treatment but none in critical group. These positive outcomes may be resulted from the response to the treatment. The differences in clinical characteristic features may have certain impacts on outcomes as the critical group had more advanced age, hypertension, chronic kidney disease, and clinical severity at presentation as the significantly higher

NEWS and CRP level at the presentation.

There are several strengths in this study. The clinical and laboratory data of patients during outbreak in Thailand was collected which might be beneficial regarding the decision of treatment in certain patients' group that could be benefited from remdesivir. Secondly, this tertiary medical center is well-equipped with medical armamentarium including interleukin-6 inhibitors, as well as more advanced interventions such as hemoperfusion and Extracorporeal Membrane Oxygenation (ECMO). Patients met the indications for these treatment was treated accordingly under the critical care specialist supervision. Finally, using of antiviral agents per the national guidance on COVID-19 management reflected true clinical outcomes of the recommended treatment and might be used as supplementary to make adjustment to the current guidance, especially after proving the efficacy of the first-line antiviral agent, favipiravir.

There are also several limitations of this study. Firstly, due to the nature of retrospective study, clinical and laboratory data which might affect the clinical outcomes may be missing. Secondly, the clinical characteristic of the patients in both groups were not matched, which might exert effects on clinical outcomes. However, this study compared the outcomes of remdesivir in moderate to severe and critical groups, these differences were expected. Thirdly, the reviewer was not blinded to the severity group, however the outcomes of the study were objectively measured, thus biased due to the unblinded nature could be minimized. This study did not have any comparator to remdesivir, the true efficacy of remdesivir cannot be estimated in both groups. As the using of antiviral agents was based on the national guidance, the efficacy of upfront remdesivir or comparative efficacy against favipiravir, the first-line antiviral in Thailand could not be investigated. Finally, this study was conducted at a single institution, so our results may not be generalizable to other hospitals.

From this study, the clinical outcomes of patients with COVID-19 receiving remdesivir was shown. Further clinical studies and trials with larger population and more robust statistical methodology regarding efficacy of remdesivir are required. Clinical questions such as which patients might be benefited from remdesivir, best timing of initiation, role of upfront remdesivir use in general population, and the efficacy against other variants are remained to be answered. Specifically in Thailand, randomized controlled trials comparing

efficacy of favipiravir and remdesivir could have major impact on the national guidance.

Conclusions

From our study, among COVID-19 patients, the use of remdesivir was associated with better clinical outcomes in moderate to severe illness patients. Thus, remdesivir could be used in the moderate to severe group. While the true efficacy and timing are remained to be investigated, more effective treatments should be pursued for the critically ill populations.

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