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ROLE OF REMDISIVIR IN MODERATE AND SEVERE COVID PNEUMONIA PATIENTS IN PAKISTANI POPULATION

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ABSTRACT

Background: Remdesivir is a broad spectrum nucleotide analogue that inhibits RNA-dependent RNA polymerase activity among a diverse group of RNA viruses. Non-clinical and clinical data suggest that remdesivir may be useful for the treatment of COVID-19. **Objectives:** To evaluate outcome of remdesivir administration among patients with moderate and severe COVID pneumonia. **METHODS: Study Design:** Cross sectional Prospective study. **Study Setting:** Pakistan atomic energy commission hospital, Chashma. **Study Duration:** 06 months. **Data collection and analysis:** 207 subjects aged 12 years and above of either gender who had SARS-CoV-2 infection confirmed by polymerase-chain-reaction assay or through radiographic evidence and either had oxygen saturation of >94% or less while they were breathing ambient air or were receiving supplemental oxygen with moderate and severe COVID pneumonia admitted in hospital for routine care were included in the study through a non probability / consecutive sampling. The primary endpoint was final outcome of the treatment and time to clinical recovery. Data was entered and analysed in SPSS ver: 21.0. Frequencies and percentages were calculated for qualitative variables and mean and standard deviation for quantitative variables. Outcome was cross tabulated for independent variables and t –test was used for numerical variables and chi-square test was used for nominal variables with $p < .05$ as statistical significant. **Results:** 207 subjects included in the study among them 62.8% were male and 37.2% were females. Mean age of patients was 50.9 $\pm$ 13.796 years and mean duration of illness was 6.376 days with 1 – 12 days range. 96.6% of patient improved and 3.4% had deterioration in their condition. Outcome was cross tabulated with disease severity. 95.5% who had improved outcome was having moderate disease as compared to 93.1% who had severe disease as was statistically significant. ($p < .038$). **Conclusion:** The timely administration of remdesivir to moderate and severe COVID pneumonia patients can significantly reduce their mortality and morbidity and thus improve the outcome of the disease.

KEYWORDS: COVID-19, Pneumonia, Remdesivir.

INTRODUCTION

COVID-19 is an acute viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 primarily affects the respiratory system; however, it can affect other major organ systems as well.[1] It causes significant morbidity and mortality. Its rapid spread has challenged health systems. By May 5, 2021, more than 155 million individuals were infected, and over 3.2 million individuals had died from COVID-19 globally.[2,4] At the end of 2020, the US Centres for Disease Control and Prevention (CDC) reported a COVID-19-associated hospitalization rate of 326.7 per 100,000 population.[3,4] Data from China, Italy, the US, and other nations shows that mortality and morbidity are linked to age and gender, Old aged people and males being at high risk of adverse outcomes.[5,6] Moreover, early evidence in the US showed unequal mortality and hospitalization patterns in dense urban areas in different races and ethnicities.[7,8] Existing studies, however, are limited with respect to scope, data, and temporality.

Early evidence mainly comes from single, urban centre based studies or regional data during the first wave[9,10] of the COVID-19 pandemic. However, subsequent waves have not been studied. For example, it is unclear whether the same sets of populations were affected in fall versus the spring 2020. Early studies done in U.S in April 2020 suggested unequal infection rates among different racial groups.[11,12] By and large, no studies have been conducted in Pakistani population as regard COVID-19 effects on our population and their treatment. This descriptive analysis will be helping us in knowing our population's behaviour in COVID-19 and their response to the existing available treatment in our country.

There is currently no approved treatment for the patients with COVID-19. Global efforts to evaluate new antivirals and therapeutic strategies to treat COVID-19 have intensified. To quickly propose a first line of defence and fight against the virus in hospitalized patients, the World Health Organization (WHO) relies on already existing drugs, "repositioned", which are immediately available in large quantities and present a good security profile. Remdesivir (GS-5734)[12] is a broad-spectrum nucleotide analogue that inhibits RNA-dependent RNA polymerase activity among a diverse group of RNA viruses.[13,14] Non-clinical and clinical data suggest that remdesivir may be useful for the treatment of COVID-19.

Multiple trials have suggested its usefulness in COVID pneumonia. Considering its potential as a curative agent in COVID 19 pneumonia we conducted a retrospective observational study in our hospital on the patients who were admitted for routine treatment of COVID 19 pneumonia.

The main aim of this study is to indicate the usefulness of remdesivir in Pakistani population, especially in moderate to severe disease cases.

Mild cases usually don't require any treatment if they don't deteriorate and in moderate and severe cases the goal of treatment is to prevent worsening in clinical condition to the point that they require invasive ventilation or organ support.

In our clinical experience we saw that patients of our population respond very positively to the timely use of remdesivir and with its help we had been able to minimize the number of patients requiring referral to tertiary care hospital.

METHODS

A cross sectional prospective study was conducted on the patients admitted from December 2020 to May 2021 in the PAEC hospital Chashma after taking approval by ethical committee of PAEC hospital. Sample size of 207 subjects was calculated to estimate a proportion with 95% confidence level and acceptable difference of 0.052% with assumed proportion of patient responding to remdesivir of 82.3% and discharged from study of Antinori et al.[1] Patients age 12 years and above of either gender who had SARS-CoV-2 infection confirmed by polymerase-chain-reaction assay or through radiographic evidence having oxygen saturation of >94% or less while room ambient air or receiving supplemental oxygen with moderate and severe COVID pneumonia admitted in PAEC hospital chashma for routine care were included in the study through a non probability / consecutive sampling. Exclusion criteria included patients with mild disease and patients with critical illness who were receiving mechanical ventilation at screening and patients with signs of multi organ failure. Patients with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 5 times the upper limit of the normal range or estimated creatinine clearance of less than 50 ml per minute (by the Cockcroft–Gault formula). Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against Covid-19 were also excluded.

The criteria of severity was derived from NIH treatment guidelines.[14] Moderate illness is defined as evidence of lower respiratory disease during clinical assessment or imaging, with SpO_2 ≥94% on room air at sea level. Patients with COVID-19 are considered to have severe illness if they have SpO_2 <94% on room air at sea level, a respiratory rate >30 breaths/min, PaO_2/FiO_2 <300 mm Hg, or lung infiltrates >50%. Variables recorded were age, gender, duration of illness before coming to hospital (in days), SpO2, Pulse rate, respiratory rate, temperature at admission and at discharge, Remdesivir given for how many days and final outcome. Remdesivir was given to all of patients and we observed that their mortality and morbidity rate had significantly decreased. The primary endpoint was final outcome of the treatment and time to clinical recovery. The secondary endpoints were proportion of participants relieved from clinical symptoms defined at the time (in days) from initiation of the treatment, all-cause mortality, length of hospital stay, frequency of respiratory progression and treatment-emergent adverse events. Data was entered and analysed in SPSS ver: 21.0. Frequency and percentages were calculated for qualitative variables and mean and standard deviation for quantitative variables. Outcome was cross tabulated for independent variables and t –test was used for numerical variables and chi-square test was used for nominal variables with $p < .05$ as statistically significant.

RESULTS

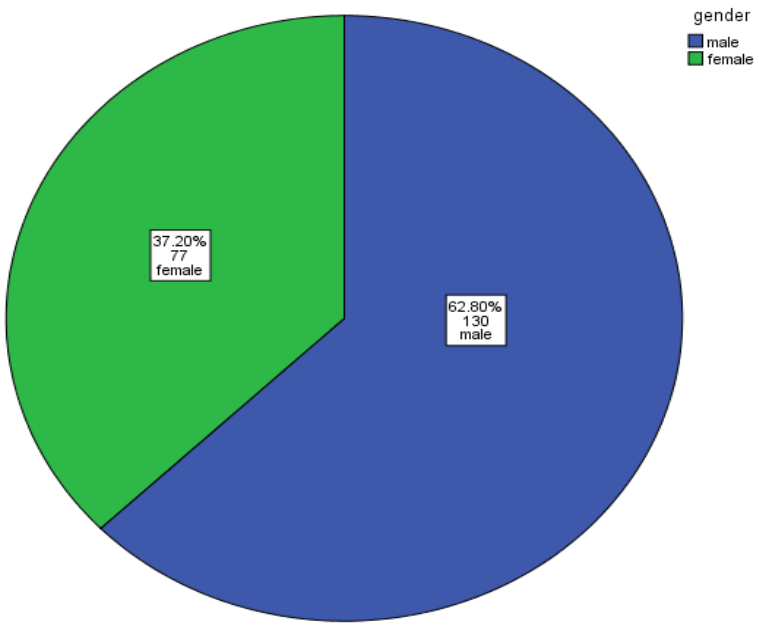
207 subjects were included in the study. Among them 62.8% were male and 37.2% were females. (Graph no: 1) Mean age of patients was 50.9 $\pm$ 13.796 years with minimum age of 15 years and maximum age of 86 years. Mean duration of illness was 6.376 days with 1 – 12 days range. Mean SpO2 at admission was 93.99 $\pm$ 2.88 and mean SpO2 at discharge was 97.99 $\pm$ 1.88.Mean pulse rate at admission was 97.65$\pm$ 14.9 and mean pulse rate at

discharge was 72.71± 12.7. Mean respiratory rate at admission was 30.4 ± 4.8 and mean respiratory rate at discharge was 15.7 ± 4.03. Mean temperature at admission was 98.86 ± 1.2 and mean temperature at discharge was 98.01 ± 0.22. Mean duration of stay in hospital was 6.1 ± 1.8 days. (Table no: 1).

96.6% of patient improved and 3.4% had deterioration in their condition. Outcome was cross tabulated with baseline clinical characteristics. Mean duration of stay in improved patients was 6.21 ± 1.78 and mean duration of stay in deteriorated patients was 4.5714 ± 3.10 as they were timely referred to tertiary care setting for further management (P<.065). Remdesivir days in improved patient was 5.17 ± 1.31 and in deteriorated patient was5.85 ± 4.059. (pvalue0.000).

This difference was basically determined by the fact that the patients who deteriorated required a longer course of remdesivir mostly of 8 to 10 days duration. SpO2 at admission in improved patients was 94.0220 ± 2.87 and in deteriorated patients was 92.3 ± 3.03 (p value 0.97). SpO2 at discharge was 97.52 ± 1.21 in improved patients and 90.57 ± 4.27 in deteriorated patients group (p value 0.000). Pulse rate at admission was 97.47 ± 15.03 in improved patients and 102.73 ± 13.13 in deteriorated patients (p value 0.760). Pulse rate at discharge in improved patients was 71.54 ±10.28 and in deteriorated patients was 106.28 ± 27.33 (p value 0.000). Respiratory rate at admission in improved patients was 30.48 ± 4.77 and in deteriorated patients it was 28.42 ± 7.13 (p value 1.71). Respiratory rate at discharge in improved patients was 15.09 ± 1.06 and in deteriorated patients was 33.42 ± 11.89 (p value 0.016). Temperature at admission in improved patients was 98.82 ± 1.186 and in deteriorated patients was 100.14 ± 2.19 (p value 0.16). Temperature at discharge in improved patients was 98 ± 0.00 and in deteriorated patients was 98.57 ± 1.133 (p value 0.000)(Table no:2).

Outcome was cross tabulated with disease severity. 95.5% who had improved had moderate disease as compared to 93.1% who had severe disease as was statistically significant (p < .038).



Graph no: 1 Gender of respondents.

Table no: 1 Central tendency of demographic and clinical parameters of respondents.

	Mean	Std. Deviation	Minimum	Maximum
Age (years)	50.9227	13.79686	15.00	86.00
duration of illness (days)	6.3768	2.57566	1.00	12.00
SPO2 Admission	93.9952	2.88703	75.00	99.00
SPO2 discharge	97.2850	1.88271	85.00	100.00
pulse admission	97.6522	14.97846	68.00	147.00
pulse discharge	72.7150	12.79263	50.00	140.00
Respiratory rate admission	30.4155	4.86032	16.00	42.00
Respiratory rate discharge	15.7101	4.03059	14.00	45.00
temperature admission	98.8647	1.24805	98.00	104.00
temperature discharge	98.0193	.21947	98.00	101.00
Stay	6.1546	1.85265	1.00	13.00

Table no: 2 Outcome and demographic and clinical parameters of respondents.

Group Statistics					
	Outcome	**N**	**Mean**	**Std. Deviation**	**P value**
Stay	Improved	200	6.2100	1.78094	.065
	Deteriorated	7	4.5714	3.10146	
remdesivir days	Improved	200	5.1700	1.31901	.000
	Deteriorated	7	5.8571	4.05909	
SpO2(admission)	Improved	200	94.0550	2.87110	.970
	Deteriorated	7	92.2857	3.03942	
SpO2 (discharge)	Improved	200	97.5200	1.21531	.000
	Deteriorated	7	90.5714	4.27618	
pulse admission	Improved	200	97.4750	15.03695	.760
	Deteriorated	7	102.7143	13.13664	
pulse discharge	Improved	200	71.5400	10.28823	.000
	Deteriorated	7	106.2857	27.33566	
Respiratory rate admission	Improved	200	30.4850	4.77217	.171
	Deteriorated	7	28.4286	7.13809	
Respiratory rate discharge	Improved	200	15.0900	1.06186	.000
	Deteriorated	7	33.4286	11.88637	
Temperature at admission	Improved	200	98.8200	1.18657	.016
	Deteriorated	7	100.1429	2.19306	
Temperature at discharge	Improved	200	98.0000	.00000	.000
	Deteriorated	7	98.5714	1.13389	

Group Statistics					
	Outcome	**N**	**Mean**	**Std. Deviation**	**P value**
duration of illness	improved	200	6.3350	2.52680	0.213
	deteriorated	7	7.5714	3.77964	

Table No 3: disease severity * outcome Cross tabulation.

Disease Severity	**Outcome**		**Total**	
	Improved	**Deteriorated**		
Moderate	133	2	135	X^2=4.289 P =.038
	98.5%	1.5%	100.0%	
Severe	67	5	72	
	93.1%	6.9%	100.0%	
Total	200	7	207	
	96.6%	3.4%	100.0%	

Table No 4: Clinical parameters before and after Remdesivir

		Mean	**N**	**Std. Deviation**	**Std. Error Mean**	**P value**
Pair 1	SPO2 Admission	93.9952	207	2.88703	.20066	.00
	SPO2 discharge	97.2850	207	1.88271	.13086	
Pair 2	pulse admission	97.6522	207	14.97846	1.04107	.00
	pulse discharge	72.7150	207	12.79263	.88915	
Pair 3	Respiratory rate admission	30.4155	207	4.86032	.33782	.00
	Respiratory rate discharge	15.7101	207	4.03059	.28015	
Pair 4	temperature admission	98.8647	207	1.24805	.08675	.00
	temperature discharge	98.0193	207	.21947	.01525	

DISCUSSION

The pandemic of coronavirus disease 2019 (COVID-19) has been waxing and waning since its start, and it is suspected that finally it may become a seasonal disease. Therefore, it is critical to develop therapies for COVID-19.Although several approved drugs and investigational agents have shown antiviral activity against SARS-CoV-2 in vitro. At present there are no antiviral therapies of proven effectiveness in treating severely ill patients with COVID-19.A systematic review and meta-analysis of the literature evaluating the efficacy of hydroxychloroquine and its related formulations in COVID-19 patients showed no benefit of hydroxychloroquine in patients affected by mild to moderate COVID-19 disease.[15] Recently, Cao and colleagues[16] reported the results of an open-label RCT comparing the efficacy of

lopinavir/ritonavir vs standard care in 199 patients with COVID-19. The primary outcome of time to clinical improvement defined by a 2-point improvement on a 7-category ordinal scale or hospital discharge was similar in both groups (16 days [IQR, 13-17] vs 16 days [IQR, 15-17]; hazard ratio [HR], 1.31 [95% CI, 0.95-1.85]; $P = .09$).

In a prospective, randomized, multicenter study, favipiravir (n = 120) was compared with Arbidol (n = 120) for the treatment of moderate and severe COVID-19 infections. Differences in clinical recovery at day 7 were observed in patients with moderate infections (71.4% favipiravir and 55.9% Arbidol, $P = .019$). No significant differences were observed in the severe or severe and moderate (combined) arms.[17] These data support further investigation with RCTs of the efficacy of favipiravir for the treatment of COVID-19.

Corticosteroids are another treatment option. The rationale for the use of corticosteroids is to decrease the host inflammatory responses in the lungs, which may lead to acute lung injury and acute respiratory distress syndrome (ARDS). However, this benefit may be outweighed by adverse effects, including delayed viral clearance and increased risk of secondary infection. A 2019 meta-analysis of 10 observational studies with 6548 patients with influenza pneumonia found that corticosteroids were associated with an increased risk of mortality (risk ratio [RR], 1.75 [95% CI, 1.3-2.4]; $P < .001$) and a 2-fold higher risk of secondary infections (RR, 1.98 [95% CI, 1.0-3.8]; $P = .04$).[18] While the efficacy of corticosteroids in ARDS and septic shock more generally remains debated, Russell and colleagues argued that those most likely to benefit from corticosteroids are those with bacterial rather than viral infections.[19] A recent retrospective study of 201 patients with COVID-19 in China found that, for those who developed ARDS, treatment with methylprednisolone was associated with a decreased risk of death (23/50 [46%] with steroids vs 21/34 [62%] without; HR, 0.38 [95% CI, 0.20-0.72]).[20]

As part of a 2015 systematic review, Mair-Jenkins and colleagues[21] conducted a post hoc meta-analysis of 8 observational studies including 714 patients with either SARS or severe influenza. Administration of convalescent plasma and hyperimmune immunoglobulin was associated with reduction in mortality (odds ratio, 0.25 [95% CI, 0.14-0.45]; $I^2 = 0\%$) with relatively few harms, although study quality was generally low and at risk of bias.[21]

Remdesivir is one of the most promising drugs to treat COVID-19 based on the following facts: remdesivir has a broad-spectrum antiviral mechanism of action; it demonstrated *in vitro* activity against SARS-CoV-2 and *in vivo* efficacy in animal models against the similar coronavirus MERS-CoV.[22]

Remdesivir was the first drug approved by the FDA for treating the SARS-CoV-2 virus. It is indicated for treatment of COVID-19 disease in hospitalized adults and children aged 12 years and older who weigh at least 40 kg. The broad-spectrum antiviral is a nucleotide analog prodrug.

Full approval was preceded by the US FDA issuing an EUA (emergency use authorization) on May 1, 2020 to allow prescribing remdesivir for severe COVID-19 (confirmed or suspected) in hospitalized adults and children.

Remdesivir, a nucleotide analog, has shown efficacy against SARS-CoV-2 in vitro. The remdesivir EUA was expanded to include moderate disease August 28, 2020. This expands the previous authorization to treat all hospitalized patients with COVID-19 regardless of oxygen status.

The initial EUA of remdesivir based on preliminary data analysis of the Adaptive COVID-19 Treatment Trial (ACTT) was announced April 29, 2020. The final analysis included 1,062 hospitalized patients with advanced COVID-19 and lung involvement, showing that patients treated with 10-days of remdesivir recovered faster than similar patients who received placebo.[23]

The open-label phase 3 SIMPLE trial (n = 397) in hospitalized patients with severe COVID-19 disease not requiring mechanical ventilation showed similar improvement in clinical status with the 5-day remdesivir regimen compared with the 10-day regimen on day 14 (OR: 0.75 [95% CI 0.51-1.12]).[24]

Similarly, the phase 3 SIMPLE II trial in patients with moderate COVID-19 disease (n = 596) showed that 5 days of remdesivir treatment had a statistically significant higher odds of a better clinical status distribution on Day 11 compared with those receiving standard care (odds ratio, 1.65; p = 0.02).[25]

In the randomized controlled Adaptive COVID-19 Treatment Trial-1 (ACTT-1), remdesivir was superior in reducing median recovery time to 10 days as compared with 15 days in the placebo arm. In another randomized controlled trial, for patients not requiring mechanical ventilation, there was no statistically significant difference between 5 days and 10 days of remdesivir use.[13] However, no studies on the role of remdesivir have been conducted on Pakistani population. This is the first study on the usefulness of this drug in our population.

The US Food and Drug Administration (FDA) has approved remdesivir for the treatment for hospitalized COVID-19 patients aged 12 years and older and weighing at least 40 kg (88 lbs). Remdesivir is given by intravenous infusion.The dose regimen of remdesivir is

an IV loading dose of 200 mg on day 1 followed by daily IV maintenance doses of 100 mg for 5–10 days.[13] Adverse effects include nausea, vomiting, and transaminitis.

In a study by Antinori et al 35 patients enrolled from February 23 to March 20, 2020, included 18 in intensive care unit (ICU), and 17 in infectious diseases ward (IDW). The 10-day course of remdesivir was completed by 22 patients (63 %) and discontinued by 13, of whom eight (22.8 %) discontinued because of adverse events. The median follow-up was 39 days (IQR 25–44). At day 28, 14 (82.3 %) patients from IDW were discharged, two were still hospitalized and one died (5.9 %), whereas in ICU 6 (33.3 %) were discharged, 8 (44.4 %) patients died, three (16.7 %) were still mechanically ventilated and one (5.6 %) was improved but still hospitalized. Hypertransaminasemia and acute kidney injury were the most frequent severe adverse events observed (42.8 % and 22.8 % of the cases, respectively).[26]

In our study only one patient developed acute threefold rise in LFTs for which remdesivir had to be stopped at day 3 of administration. All of other patients tolerated Remdesivir quite well.

An IDSA panel suggests remdesivir for hospitalized patients with severe COVID-19 pneumonia. For patients not on mechanical ventilation or ECMO, IDSA guidelines suggest remdesivir use for only 5 days. For patients without the need of oxygen and an oxygen saturation of greater 94% on room air, the IDSA panel suggests against the use of Remdesivir.[27]

CONCLUSION

Our data shows that the early use of remdesivir in moderate to severe COVID disease improves clinical outcome and shortens hospital stay in Pakistani population. It is generally well tolerated in our population. However more studies are requested to strength this evidence.

REFERENCES

1. Aleem A, Akbar Samad AB, Slenker AK. Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19) [Updated 2022 Jan 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2022 Jan.
2. Center for Systems Science and Engineering. COVID-19 Dashboard Baltimore: Johns Hopkins University; 2020 [cited 2020 Jul 19]. Available from : https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd4029942346
3. Dixon BE, Grannis SJ, Lembcke L, Roberts A, Embi PJ. The COVID-19 health equity twindemic: Statewide epidemiologic trends of SARS-CoV-2 outcomes among racial minorities and in rural America.
4. Dixon BE, Grannis SJ, Lembcke LR, Valvi N, Roberts AR, Embi PJ. The synchronicity of COVID-19 disparities: Statewide epidemiologic trends in SARS-CoV-2 morbidity, hospitalization, and mortality among racial minorities and in rural America. PloS one., 2021 Jul.
5. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases With Coronavirus Disease 2019 in Wuhan, China. Clinical Infectious Diseases, 2020.
6. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. Jama., 2020.
7. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA, 2020.
8. Gold JAW, Wong KK, Szablewski CM, Patel PR, Rossow J, da Silva J, et al. Characteristics and Clinical Outcomes of Adult Patients Hospitalized with COVID-19—Georgia, March 2020. MMWR Morb Mortal Wkly Rep., 2020.
9. Doidge JC, Gould DW, Ferrando-Vivas P, Mouncey PR, Thomas K, Shankar-Hari M, et al. Trends in Intensive Care for Patients with COVID-19 in England, Wales and Northern Ireland. Am J Respir Crit Care Med., 2020.
10. van Halem K, Bruyndonckx R, van der Hilst J, Cox J, Driesen P, Opsomer M, Van Steenkiste E, Stessel B, Dubois J, Messiaen P. Risk factors for mortality in hospitalized patients with COVID-19 at the start of the pandemic in Belgium: a retrospective cohort study. BMC infectious diseases, 2020 Dec.
11. DiMaggio C, Klein M, Berry C, Frangos S. Black/African American Communities are at highest risk of COVID-19: spatial modeling of New York City ZIP Code-level testing results. Ann Epidemiol, 2020.
12. Millett GA, Jones AT, Benkeser D, Baral S, Mercer L, Beyrer C, et al. Assessing differential impacts of COVID-19 on black communities. Ann Epidemiol, 2020.
13. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D. Remdesivir for the treatment of Covid-19. New England Journal of Medicine, 2020 Nov.
14. Remdesivir.NIH COVID-19 Treatment Guidelines. (2021, Dec 16). *NIH*.
15. Pathak SK, Salunke AA, Thivari P, Pandey A, Nandy K, Ratna HV, Pandey S, Chawla J, Mujawar J, Dhanwate A, Menon V. No benefit of hydroxychloroquine in COVID-19: results of systematic review and meta-analysis of randomized controlled trials". Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2020 Nov.
16. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X. A trial of lopinavir–ritonavir in adults hospitalized with severe

Covid-19. New England Journal of Medicine, 2020 Mar.
17. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M, Luo Y. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv, 2020 Jan.
18. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*, 2019.
19. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*, 2020.
20. Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, Zhang Y, Song J. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA internal medicine, 2020 Jul.
21. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, Makki S, Rooney KD, Convalescent Plasma Study Group, Nguyen-Van-Tam JS, Beck CR. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. The Journal of infectious diseases, 2015 Jan.
22. Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, Hall MD. Remdesivir: a review of its discovery and development leading to emergency use authorization for treatment of COVID-19. ACS central science, 2020 May.
23. Beigel JH. What is the role of remdesivir in patients with COVID-19?. Current opinion in critical care, 2021 Oct.
24. Jason D. Goldman, David C.B. Lye, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med., November 5, 2020; 383: 1827-1837.
25. Cennimo DJ, Bergman SJ, Olsen KM**.** What is the role of the antiviral drug remdesivir in the treatment of coronavirus disease 2019 (COVID-19)? Medscape Coronavirus Disease 2019 (COVID-19) Treatment & Management. Updated., Dec 09, 2021.
26. Antinori S, Cossu MV, Ridolfo AL, Rech R, Bonazzetti C, Pagani G, Gubertini G, Coen M, Magni C, Castelli A, Borghi B. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post-treatment hospitalisation status. Pharmacological research, 2020 Aug.
27. Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Muller WJ, O'Horo JC, Shoham S. Infectious Diseases Society of America Guidelines on the treatment and management of patients with coronavirus disease 2019 (COVID-19). Clinical Infectious Diseases, 2020 Apr.
28. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. Jama., 2020 May.
29. Frost MT, Jimenez-Solem E, Ankarfeldt MZ, Nyeland ME, Andreasen AH, Petersen TS. The Adaptive COVID-19 Treatment Trial-1 (ACTT-1) in a real-world population: a comparative observational study. Critical Care. 2020 Dec.