Evaluation of Clinical Outcomes After Remdesivir Therapy in Patients with Moderately Severe Covid-19 Disease. Prospective Study

Anam Liaqat (anamliaqat29@gmail.com)
Riphah International University
Iqra Ali Zafar
Riphah International University
Muhammad Asad
Armed Forces Hospital
Jan-Willem Alffenaar
The University of Sydney

Research Article

Keywords: Covid-19, Remdesivir, C-reactive protein, Oxygen demand, PCR negativity, Length of hospitalization, Pakistan

Posted Date: March 29th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1350373/v1

Abstract

Background

Despite the fact that a number of therapeutic agents have been tested for the treatment of coronavirus disease 2019 (Covid-19), no antiviral agents have yet been proven to be effective.

Objectives

This study aims to evaluate the favorable clinical outcomes after remdesivir treatment in hospitalized patients with moderately severe COVID-19 disease in Pakistan.

Methods

A prospective study in hospitalized patients with moderately severe Covid-19 disease was conducted between January 2021- October 2021. The patients were divided into remdesivir-treated and control groups. The Remdesivir-treated group received 200mg IV, followed by 100mg once daily for four days. In addition to standard care, all patients received corticosteroid therapy. The clinical status of remdesivir patients was assessed after the 5th day of treatment, including proportion negative polymerase chain reaction test for COVID-19, length of hospitalization, improvement in oxygen demand, and effects on C-reactive protein (CRP) levels. Multivariate analysis and paired sample T-test were performed to evaluate a favorable response to remdesivir treatment and results were compared with a control group.

Result

In total, 328 patients were enrolled in the study, with 162 of them receiving IV remdesivir on the day of admission. The C-reactive protein level in the remdesivir treated group [median 22.0 (14.0–36.7)] was significantly lower ($p < 0.001$) than in the remdesivir naive group [median 79.1 (57.4–139.0)]. The number of days spent in the hospital was significantly different between the remdesivir-treated and remdesivir-naive groups [6.2 0.5] ($p < 0.001$). In the remdesivir-treated group, 36.7% of patients were discharged with a negative PCR, compared to 21.6% in the control group ($p < 0.001$). In comparison to the control group, the remdesivir treated group showed a significant improvement in the ratio of arterial oxygen partial pressure to fractional inspired oxygen ($p < 0.001$).

Conclusion

The remdesivir treatment was found to be superior to improve clinical outcomes among moderately severe Covid-19 disease patients.

Summary Points

- In Pakistan, the number of Covid-19 cases, hospitalizations, and deaths continues to rise.
- High mobility, poor vaccination levels, and the likelihood of the introduction of a new escape variety, the situation remainsdelicate.
- Covid-19 illness presents a significant problem in terms of selecting an appropriate treatmentstrategy.
- The first observational study in Pakistan to assess the efficacy of remdesivir therapy in moderately severe Covid-19 diseasepatients.

Introduction

As of February 2, 2021, over 103 million global cases and 2.2 million deaths have been reported due to the pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. While the world waits for effective vaccines, several pharmacologic agents have been investigated for the treatment of coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2. Remdesivir, a nucleotide analog prodrug with in vitro activity against a wide range of RNA viruses, [2–4] has gained a lot of interest. [5–6]. Clinical trials evaluating the efficacy of remdesivir provided mixed results [7–11] and did not include a sufficient number of individuals from blacks or Asian populations most affected by COVID-19 [12], and also did not look at remdesivir in combination with other medications. Remdesivir has been approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19 disease in hospitalized adults and children 12 years and older who weigh at least 40 kg as of October 22, 2020 [13], based primarily on the results of the Adaptive COVID-19 Treatment Trial (ACTT-1) [14]. However, The SOLIDARITY trial was conducted by the World health organization (WHO) did not reveal a meaningful benefit of remdesivir use in COVID-19 disease [15].

We conducted a first prospective observational study in Pakistan to evaluate the clinical response after remdesivir treatment in patients admitted to our hospital with moderately severe Covid-19 disease.

Methods

A prospective observational study was conducted from January 2021-October 2021 in the Isolation and Infectious Treatment Centre, which is one of the largest tertiary care centers in Pakistan designated for the treatment of Covid-19 patients. The institutional ethical research committee reviewed and approved the study (ethics approval number A/28/EC/20/2020. Written informed consent was obtained from each patient or their legal representative. The research was carried out in accordance with the declaration of Helsinki [16].

Patients were eligible for inclusion if they met the following inclusion criteria: age > 18 years, have a positive SARS COV-2 RT-PCR assay in the respiratory tract sample, have an acute onset of mild to severe

acute respiratory distress syndrome (ARDS) identified as RR > 20, SpO2 < 94% on room air and pulmonary infiltrates < 50% on X-ray or CT scan, and patients with respiratory compromise sufficiently severe to include Non-Invasive Ventilation NIV (continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BIPAP)), high flow nasal cannula (HFNC), at the time of admission according to WHO interim Guidelines [17]. Patients were excluded from the study with alanine aminotransferase (ALT) > 5 times the upper limit, creatinine clearance < 50ml/min, scheduled corticosteroid therapy during the previous week, known corticosteroid contraindications, pregnancy or breastfeeding, patients needing mechanical ventilation, and ICU admission at the time of enrollment, or doses of remdesivir and dexamethasone discontinued during the study based on clinical conditions.

Treatment included intravenous Remdesivir 200 mg loading dose followed by 100 mg for the next 4 days along with standard care therapy. All patients received corticosteroid therapy at the time of admission. Patients were hospitalized for at least 5 days (duration of treatment). PCR of every patient was performed before discharge and after the 5th dose of remdesivir and patients were assessed for clinical improvement before discharge. Patients were discharged on stable clinical conditions with swab-negative results after two repeated PCRs within 24 hours. All participants were managed according to the general standard of care practices according to WHO guidelines. Oxygen flow rates were given by oxygen delivery devices (e.g., a nasal cannula for rates up to 5 L/min; face mask for flow rates 6–10 L/min; and face mask with reservoir bag for flow rates 10–15 L/min) to attain a target of > 90% SpO2 in moderately severe patients with respiratory distress. Non-invasive positive pressure ventilation in the form of CPAP and BIPAP is the cornerstone of respiratory support reserved for severe COVID-19 disease adults with emergency indications of occluded breathing, and serious respiratory distress [18–19]. Within 1 hour of initial assessment, empiric antimicrobials were started in severe COVID-19 patients based on clinical judgment, and blood cultures were obtained. Antimicrobial therapy was started per NICE recommendations [20]. To prevent venous thromboembolism in COVID-19 patients, pharmacological prophylaxis with low molecular weight heparin was given according to the guidelines (local or international) [21].

The following demographics were collected at the time of admission; blood pressure (BP), heart rate (HR), comorbidities, and body temperature were recorded. Serum electrolytes, D-dimers, Ferritin, glomerular filtration rate (GFR), serum creatinine, ALT, alkaline phosphatase (ALP), globulin, total protein, bilirubin T, albumin, leukocytes, neutrophils, hemoglobin, lymphocyte, platelets values were recorded at the baseline. Arterial blood gases (ABGS), CRP levels, and data on patients' oxygen-support requirements were recorded at the time of admission and after completion of remdesivir and corticosteroid therapy in remdesivir treated and control group patients respectively.

The response to treatment was specified as 1; swab PCR before discharge 2; length of hospitalization, 3; requiring high-flow oxygen therapy, non-invasive mechanical ventilation, or requiring invasive mechanical ventilation and 5; change in CRP levels from baseline.

A favorable response was defined as: discharged within 7 days of treatment on room air with more than 50% patients with swab negative PCR; reduction in CRP levels after 5th dose of remdesivir treatment in remdesivir treated group and standard care treatment in the control group; reduction in liters of oxygen demand and shift from BIPAP, CPAP, HFNC to low-flow oxygen delivery after remdesivir and corticosteroid therapy completion among remdesivir treated and control group patients respectively.

Statistical Analysis:

Categorical variables are presented as percentages, while numerical variables as means with standard deviations for normally distributed variables and medians with interquartile ranges for non-normally distributed variables. Kolmogorov-Smirnov test was used to check numerical variables for normalcy. Student t-test was used to test between-group differences among categorical variables such as gender, PCR negativity, and change in oxygen status. For independent variables which were not normally distributed Mann Whitney U test was employed, while the Wilcoxon Signed Rank Test was used for pre and post-treatment differences comparison to test between-group differences in numerical variables that were not normally distributed. The adjusted odds ratios were calculated using a multivariate stepwise regression model which included factors with a significant association to the outcome. Statistical significance was defined as a p-value of less than 0.001. SPSS v25.0 (IBM, Armonk, NY, USA) was used to analyze the data.

Results

Total 328 patients were included in the study of which 162 patients were treated with remdesivir and 162 were included in the remdesivir naive group. The baseline values for clinical characteristics, electrolytes, liver function tests, blood cells count, and inflammatory cells in both groups are given in Table 1. Comorbidities data showed that Hypertension and diabetes as well as asthma, arthritis, and cancer were common in these groups (Table 1).

Table 1
Baseline Demographic and Clinical Characteristics of the Patients treated with remdesivir/dexamethasone (n = 328)

Demographics		*Reference*	*Remdesivir treated group*	*Control group*	*p-value*
Age	*Years (mean ± SD)*		60.67 ± 13.56	61.57 ± 12.27	0.743
Gender	*Female (n)*		64(39.02%)	75(45.7%)	0.849
	Male		100 (61.72%)	89 (54.26%)	0.824
Clinical features	*Heart rate*	60–100 beats/min	96.11 ± 12.3	99.39 ± 13.37	0.892
Blood pressure	*SYSTOLIC*	< 120 mmHg	129.04 ± 13.45	132.36 ± 13.29	0.234
	DIASTOLIC	< 80mmHg	81.72 ± 12.7	84.39 ± 10.73	0.293
	Respiratory rate	12–16 *(breath/minute)*	23.38 ± 4.20	23.6 ± 3.57	0.789
	Body temperature		99.23 ± 1.29	99.05 ± 1.114	0.500
Co-morbidities	*Hypertension*		24 (14.6%)	26 (39.4%)	0.002
	Diabetes		24 (36.3%)	6 (3.7%)	< 0.01
	Asthma		4 (2.5%)	8(12.1%)	0.036
	Arthritis		2 (1.23%)	6 (9.1%)	0.039
	Cancer		2 (1.23%)	6 (9.1%)	0.039
Baseline electrolyte	*Serum NA*	*(135-145mmol/l)*	128.6 ± 8.4	128.0 ± 7.1	0.360
	Serum K	*(3.5–4.5 mmol/l)*	4.35 ± 0.76	4.38 ± 0.68	0.849
	Serum Cl	*(100mmol/l)*	104.00 ± 6.11	101.83 ± 5.37	0.065
Baseline liver function	*ALT*	*0–50 (U/l)*	38.3 ± 17.7	44.2 ± 12.4	0.087
	ALP	*(40–80 U/l)*	62.7 ± 20.1	70.8 ± 13.5	0.036

Abbreviations; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; A/G, Albumin/Globulin ratio; GFR, Glomerular filtration rate;

Demographics		*Reference*	*Remdesivir treated group*	*Control group*	*p-value*
	Albumin	*(3.4-4.8g/dl)*	3.09 ± 0.47	3.01 ± 0.39	0.405
	Total protein	*(6-7.8) g/dl*	6.93 ± 0.73	6.79 ± 0.65	0.320
	Bilirubin total	*(0.2-1.2mg/dl)*	0.61 ± 0.5	0.88 ± 0.45	0.019
	A/G Ratio	*(1.5–2.4)*	1.11 ± 0.93	1.03 ± 0.33	0.723
Baseline Renal function	*Creatinine*	*(0.7–1.1 mg/dl)*	0.89 ± 0.53	0.78 ± 0.17	0.233
	GFR	*(> 60)*	96.46 ± 15.41	96.18 ± 15.45	0.894
Baseline inflammatory	*Lactic acid*	(*280 U/L)*	400.2 ± 119.4	450.2 ± 120.2	0.048
	Ferritin levels	*(20–350 ng/ml)*	488 (369–582)	982 (888–1072)	0.001
	D-Dimers levels	*(< 250ng/ml)*	316 (247–408)	796 (508–909)	0.001
	Procalcitonin	*(< 0.1ng/mL)*	0.195 ± 0.063	0.194 ± 0.081	0.913
Blood routine examination	*Leukocytes, × 10^9*	*(3.5–9.5)*	10.081 ± 5.14	10.43 ± 4.18	*0.728*
	Monocytes× 109	*(0.2 to 0.6)*	2.54 ± 1.95	2.484 ± 1.67	*0.873*
	Granulocytes× 10^9	*(1.5–8.5)*	79.77 ± 16.5	84.46 ± 6.56	*0.117*
	Hemoglobin, g/L,	*(130–175)*	12.33 ± 1.92	12.53 ± 1.713	*0.607*
	Lymphocyte, × 109	*(1.1–3.2)*	14.72 ± 8.6	13.02 ± 5.68	*0.301*
	Platelets ×	*(150 to 400*	228.54 ± 75.5	218.18 ± 77.74	*0.512*
	Neutrophil	*(1–3).*	7.80 ± 5.08	7.59 ± 3.12	0.823

Abbreviations; ALT, Alanine aminotransferase; ALP, Alkaline phosphatase; A/G, Albumin/Globulin ratio; GFR, Glomerular filtration rate;

Table 2 shows the oxygen support requirement among remdesivir treated and control groups at the time of admission and after treatment. Overall, remdesivir treated patients showed an improvement in the oxygen support compared to control group patients (OR: 16.0 [5.87–43.9] p < 0.001). Both groups had similar P/F ratios at baseline however, the remdesivir treated group had a higher P/F ratio after treatment

(395 [214.0–464.5]) than the control group (114 [97.8–186.0] p < 0.001). Approximately, 26.23% of remdesivir treated patients were discharged at room air compared to 9.5% of patients in the control group with a mean hospitalization duration of 6.2 ± 0.5 VS 13.1 ± 3.6 respectively (p < 0.001). After 5 days of treatment with remdesivir, 14.5% were shifted to low flow oxygen requirement before discharge compared to 7.9%. CRP levels in patients dropped significantly compared to the control group after completion of remdesivir therapy (p < 0.001).

Table 2
Treatment response showing hospitalization duration, PCR negativity, and PF ratio

	BEFORE TX ***Total patients*** ***N = 324***	***Remdesivir treated group*** ***N = 162***	***Control group*** ***N = 162***	***P-value***
Room air	*0*	85 (26.23%)	*31 (9.5%)*	<0.001
Low flow	124 (38.27%)	47 (14.5%)	24 (7.4%)	< 0.001
High flow	86 (26.54%)	22 (6.7%)	62 (19.1%)	<0.001
Noninvasive ventilation	114(35.1%)	*7(2.1%)*	38 (11.7%)	< 0.001
Mechanical ventilation	*0*	*7 (2.1%)*	16 (9.8%)	< 0.001
P/F ratio	55.8 (44.8–70.2)	395 (214.1–464.5)	114.2 (97.8–186.0)	< 0.001
Crp levels	124 (68.9–152.9)	22.0 (14.0–36.7)	79.1 (57.4–139.0)	< 0.001
Negative RT-PCR at discharge	324 (100%) positive	119 (36.7%) negative	70(21.6%) negative	< 0.001
Hospitalization duration (days)		6.2 ± 0.5	13.1± 3.6	< 0.001

Abbreviations; CRP, C-reactive Protein; P/F ratio, the ratio of arterial oxygen partial pressure to fractional inspired oxygen; PCR, Polymerase chain reaction

A multivariate regression model was created using factors showing significant association with a patient's response status. Baseline CRP levels, serum ferritin (Adjusted OR 1.048 [1.004–1.093] p = 0.031), D dimers (OR 1.024 [1.002–1.046] p = 0.031), and LDH (OR 1.048 [1.001–1.098] p = 0.033) remained significantly associated with patient's response to treatment.

Discussion

The world is focusing to ensure the implementation of therapies that can reduce COVID-19 related mortality and morbidity. Remdesivir has been the subject of debate since the ACTT-1 study, funded by the National Institutes of Health, found a faster time to clinical improvement, but the larger Solidarity study, funded by the World Health Organization, found no mortality advantage. Even though the findings of Solidarity suggest that remdesivir has not a significant mortality benefit for COVID-19 patients, it could still play an important role in shortening the duration and disease severity, both of which are important outcomes when hospitals are overburdened with COVID-19 patients.

Receiving remdesivir resulted in a significantly shorter time to clinical improvement and a higher percentage of patients discharged and responding to the antiviral therapy in this prospective study. The direction of these associations was similar to that of an open-label randomized controlled trial in which 5 days of remdesivir was associated with a higher odds of a better clinical status distribution than those receiving standard care [22].

Remdesivir active metabolite inhibits the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease, resulting in a reduction in viral RNA production. It causes RNA-dependent RNA polymerases to stop in some viruses, such as the respiratory syncytial virus, but its main effect is to induce irreversible chain termination [23]. In comparison to control group patients, a considerably higher percentage of responders from the remdesivir treated group reported negative RT-PCRs before discharge, which indicates the reduction in SARSCoV2 viral load as a surrogate marker of therapy efficacy. The innate immune system's spontaneous response to viral entry results in a massive production of pro-inflammatory cytokines and chemokines, which is often referred to as a "cytokine storm," and this spontaneous response directly leads to the onset of acute respiratory distress syndrome (ARDS) and major organ failure, mostly kidney and liver failure [24]. Significant reduction in CRP levels and inflammatory cytokines levels were seen in remdesivir treated group patients indicating the immunomodulatory and anti-inflammatory role of remdesivir as well as corticosteroids therapy [25–26]. Also, these findings are consistent with the study by Kate Stoeckle et al which shows CRP levels decreased significantly after remdesivir administration in patients who remained non-intubated over the study period [27]. The decrease in CRP levels after corticosteroids administration has also been well documented in the literature. Dexamethasone has been demonstrated to downregulate IL-6 and decrease CRP production. This could, therefore, simply be a result of a general improvement in clinical health. Cui Z et al. observed that a 50% drop in CRP levels was predictive of response and subsequent mortality in individuals treated with dexamethasone in a trial. [28–29] CRP levels remain higher after treatment in control group patients who did not significantly respond to treatment with corticosteroids alone with standard care of therapy. This emphasizes the importance of serial and early CRP levels in predicting treatment response and potentially justifying more aggressive therapy and treatment escalation.

9.8% of patients among the control group progressed to the need for mechanical ventilation as compared to remdesivir treated group patients (2.1%) indicating the remdesivir decreases the need for mechanical ventilation among moderately severe patients. This low percentage of mortality in our hospital was consistent with the findings of Thomas B et al, who found low mortality among COVID-19 patients

associated with remdesivir dexamethasone combination therapy in their study [30]. The disappointing results in the control group could be explained by COVID-19's immunopathology. The main reason for mortality and progression to mechanical ventilation was due to hyperinflammatory response and high levels of CRP, Ferritin, D dimer at baseline as well as multiple comorbidities and old age among these patients. These findings help clinicians look for alternative therapeutic approaches for such a group of patients who needs mechanical ventilation and more aggressive treatment strategies [31–32].

However, there are limitations to our research. The sample size was modest because of a trough in the Covid-19 wave over Pakistan near the end of our study period, and also whether remdesivir has a benefit in patients with severe COVID-19 who require high-flow oxygen or mechanical ventilation were not evaluated. Despite these limitations, our study is a good representation of the admitted population of covid-19 patients in Pakistan.

Conclusions

Antiviral therapy with Remdesivir was reported to be effective in the treatment of Covid-19 in this study. Our cumulative results show that the 5-day course of Remdesivir was beneficial in hospitalized patients with moderately severe Covid-19 disease. A higher proportion of patients responded to remdesivir treatment and showed a shorter recovery time, more reduction in CRP levels after the therapy. Our results also indicate that Remdesivir therapy may have avoided the progression of more serious respiratory disease, as well as a lower proportion of patients in the study needing higher levels of respiratory support and need for mechanical ventilation.

Declarations

Ethical approval and consent to participate

Ethical approval has been taken by the institutional ethical committee and appropriate consent has been taken from participants and their blood relations

Consent for publication

All authorsgive the consent for publication of the manuscript in this journal

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

None

Funding

Not required

Author contributions

Anam Liaqat wrote the text of the manuscript, Iqra Aziz and Muhammad Asad perform data collection, Jan William Alfeenar performed the analysis; all authors reviewed the manuscript

Acknowledgments

Not applicable

References

1. Johns Hopkins University. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Accessed February 2, 2021. https://coronavirus.jhu.edu/map.html
2. TchesnokovEP,Feng JY, Porter DP, Götte M.2019. Mechanism of inhibition of Ebola virus RNA-dependent RNA polymerase by remdesivir. *Viruses*. 11(4):326.
3. Jorgensen SCJ,Kebriaei R, Dresser LD. 2020. Remdesivir: a review of pharmacology, pre-clinical data, and emerging clinical experience for COVID 19. *Pharmacotherapy*. 40(7):659-671.
4. Mulangu S, Dodd LE, Davey RT Jr, et al; PALM Writing Group; PALM Consortium Study Team. 2019. A randomized, controlled trial of Ebola virus disease therapeutics. *N Engl J Med*. 381(24):2293-2303.
5. Wang M, Cao R, Zhang L, et al. 2020. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 30(3):269-271.
6. Williamson BN,Feldmann F, Schwarz B, et al. 2020. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*. 585(7824):273-276.
7. Davis MR,McCreary EK, Pogue JM. 2020. That escalated quickly: remdesivir's place in therapy for COVID-19. *Infect Dis Ther*. 9(3):525-536.
8. Wang Y,Zhang D, Du G, et al.2020. Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial. *Lancet*. 395(10236):1569-1578.
9. Goldman JD,Lye DCB, Hui DS, et al. 2020. GS-US-540-5773 Investigators. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med*. 383(19):1827-1837.
10. Spinner CD,Gottlieb RL, Criner GJ, et al. 2020. GS-US-540-5774 Investigators. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. *JAMA*. 324(11):1048-1057.
11. Pan H, Peto R, Henao-Restrepo AM. 2021. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for Covid-19—interim WHO Solidarity trial results. *N Engl J Med*. 384(6):497-511.
12. Chastain DB, Osae SP, Henao-Martínez AF, Franco-Paredes C, Chastain JS, Young HN. Racial disproportionality in Covid clinical trials. 2020. *N Engl J Med*. 383(9):e59.

13. FDA Approves First Treatment for COVID-19. FDA.gov. 2020 Oct 22. Available at https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19
14. BeigelJH,Tomashek KM, Dodd LE, et al. 2020. ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med*. 383(19):1813-1826.
15. WHO Solidarity Trial Consortium Repurposed antiviral drugs for Covid-19 – interim WHO SOLIDARITY trial results N Engl J Med. 2021;384: 497-511.
16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013; 20:2191-4. DOI: 10.1001/jama.2013.281053. PMID: 24141714.
17. Clinical Spectrum of SARS-CoV-2 Infection. https://www.covid19treatmentguidelines.nih.gov/management/therapeutic-management/
18. WHO-ICRC Basic Emergency Care: an approach to the acutely ill and injured. Geneva: World Health Organization; 2018 (https://www.who.int/publications-detail/basic-emergency-care-approach-to-the-acutely-ill-and-injured, accessed 14 May 2020).
19. Clinical care for severe acute respiratory infections toolkit: COVID-19 adaptation. Geneva: World Health Organization; 2020 (https://www.who.int/publications-detail/clinical-care-of-severe-acute-respiratory-infections-tool-kit, accessed 14 May 2020).
20. COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital. NICE guideline Published: 1 May 2020 nice.org.uk/guidance/ng173
21. Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline [NG89] 21 March 2018, last updated 13 August 2019. London: National Institute for Health and Care Excellence; 2019 (https://www.nice.org.uk/guidance/ng89, accessed 15 May 2020).
22. Spinner CD, Gottlieb RL, Criner GJ, et al.2020. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients with Moderate COVID-19: A Randomized Clinical Trial. 324(11):1048–1057.
23. Eastman, R. T., Roth, J. S., Brimacombe, K. R., Simeonov, A., Shen, M., Patnaik, S., & Hall, M. D. 2020. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS central science*, *6*(5), 672–683.
24. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-coV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 55:105924.
25. Sikandar YB, Kheya IS, Noor R. Remdesivir and Dexamethasone: The Two Eligible Candidate Drugs Against Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) Infection. Biomed Res J [serial online] 2020 [cited 2021 Dec 30]; 7:29-33.
26. Theoharides TC, Conti P. Dexamethasone for COVID-19? 2020. Not so fast. J BiolRegulHomeost Agents 34:1241-3.

27. Stoeckle K, Witting B, Kapadia S, An A, Marks K. 2021. Elevated inflammatory markers are associated with poor outcomes in COVID-19 patients treated with remdesivir. J Med Virol. 94(1):384-387.
28. Cui Z, Merritt Z, Assa A, et al. 2021. Early and Significant Reduction in C - reactive protein Levels after Corticosteroid Therapy Is Associated with Reduced Mortality in Patients with COVID-19. Hosp. Med. 16:142–8.
29. RECOVERY Collaborative Group, Horby P, Lim WS, et al. 2021. Dexamethasone in Hospitalized Patients with Covid-19. The New England journal of medicine. 384:693–704.
30. Thomas Benfield, Jacob Bodilsen, Christian Brieghel, et al. 2021. Improved Survival Among Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) Treated With Remdesivir and Dexamethasone. A Nationwide Population-Based Cohort Study, *Clinical Infectious Diseases*. 73(11), 2031–2036.
31. Kelleni, M.T. Tocilizumab, Remdesivir, Favipiravir, and Dexamethasone Repurposed for COVID-19: a Comprehensive Clinical and Pharmacovigilant Reassessment. *SN Compr. Clin. Med.* **3,** 919–923. https://doi.org/10.1007/s42399-021-00824-4
32. Alam W, Bizri AR. Efficacy of tocilizumab in COVID-19: 2021. A review of the current evidence. Sci Prog.104:(3)