Original Research Article

Effectiveness of Inj. Remdesivir in treatment of Covid 19 infection at a tertiary care hospital

Nirmal Kumar Rawandale[1], Jinendra Jain[2], Pallavi Sapale[3], Sushant Chavan[4*], Amol D Kinge[5]

[1]Associate Professor, Department of Medicine, Shri bhausaheb Hire Gov. Medical College Dhule, Maharashtra, India

[2]Assistant Professor, Department of Medicine, Shri bhausaheb Hire Gov. Medical College Dhule, Maharashtra, India

[3]Professor, Dean, Shri bhausaheb Hire Gov. Medical College Dhule, Maharashtra, India

[4]Assistant Professor, Department of Commmunity Medicine, Shri bhausaheb Hire Gov. Medical College Dhule, Maharashtra, India

[5]Assistant Professor, Department of Commmunity Medicine, Shri bhausaheb Hire Gov. Medical College Dhule, Maharashtra, India

Received: 20-06-2021 / Revised: 26-07-2021 / Accepted: 28-08-2021

Abstract

Introduction: Remdesivir demonstrated clinical benefit in a placebo-controlled trial in patients with severe coronavirus disease 2019 (COVID-19), but its effect in patients with moderate disease is unknown. We tried to determine the efficacy of 5 or 10 days of remdesivir treatment compared with standard care on clinical status on day 11 after initiation of treatment**. Methodology:** A retrospective case control study from existing data where we enrolled hospitalized patients with confirmed SARS-CoV-2 infection. . We made two groups of patients. Those who received intravenous remdesivir for either 5 days or 10 days were enrolled as cases. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. Those who did not received remdesivir as treatment were enrolled as controls. Controls were matched with cases in terms of age, sex and clinical staging at the time of admission. Outcome measures like recovery, death, average time of hospitalization was analysed using proportion and odds ratio at 95% confidence interval using SPSS version 22. **Results:** 2336 patients were recruited in the study. Recovery rate was found to be positively associated with Remdesivir use (292 (84.63% Odds = 1.75 p value 0.0004). average duration of hospital stay was reduced to 10 days as compared to 15 days in patients who did not received remdesivir. Pateints with comorbidities showed increased recovery (228 (81.13%) odds = 1.86 p value = 0.0001). Deaths among Covid 19 infected patients was negatively assoiated with the use of remdesivir.{53 (15.36%) odds = 0.0580 p value 0.0001}**. Conclusion:** This study finds treatment of Covid 19 with Remdesivir as an effective method for treatment as the drug has shown to expedite recovery, decreases hospital stay, and decreases death rate among severe Covid 19 infections.

Key words- Covid 19, Remdesivir, Antiviral, Severe infection, Comorbidities

Introduction

A novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in December 2019 as the cause of a respiratory illness designated coronavirus disease 2019, or Covid-19.[1] Several therapeutic agents have been evaluated for the treatment of Covid-19.[2]

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),[3] was identified early as a promising therapeutic candidate for Covid-19 because of its ability to inhibit SARS-CoV-2 in vitro.[4] In addition, in nonhuman primate studies, remdesivir initiated 12 hours after inoculation with MERS-CoV[5] reduced lung virus levels and lung damage.

*Correspondence
Dr. Sushant S. Chavan
Department of Community Medicine,
S.B.H.G.M.C.,Dhule, Maharashtra, India
E-mail: drsushantchavan@gmail.com

MOHFW, AIIMS and ICMR have jointly issued treatment guidelines for management of Covid-19 patients.[6]

For this reason, Joint Monitoring Group under Chairmanship of DGHS took into consideration findings of the following studies to issue this advisory:

A. The 'Adaptive Covid – 19 Treatment Trial' found that Remdesivir is useful

In cases of Covid – 19 with SpO2 < 94% on room air (moderate to severe cases)

If it is administered within 7 to 10 days of illness. Remdesivir led to a shorter

median time from randomization to recovery (10 days, vs. 15 days with placebo) and may have reduced the time to hospital discharge (12 days vs. 17 days) but did not show a mortality benefit.[7]

B. The 'Solidarity Trial' conducted by WHO in 30 countries from March 2020 at 405 hospitals; 11330 adults underwent randomization; 2750 were assigned to receive Remdesivir. The interim results of the 'WHO Solidarity trial' published

on December 2020 showed that Remdesivir had little or no effect on hospitalized patients with COVID-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.[8]

In view of the above, MOHFW guideline stated that:

1. Remdesivir is to be used only in select moderate/ severe hospitalised Covid – 19 patients on supplemental oxygen as it is a reserve drug approved under Emergency Use Authorization only based on limited scientific evidence Globally.

2. It is not indicated in mild Covid – 19 patients who are in home care/ Covid Care Centres.

3. Physicians/ Doctors are advised to exercise extreme caution in using this Reserve/ experimental/ emergency use authorisation drug Remdesivir to stop Its misuse as this is only an experimental drug with potential to harm, has Relatively high cost and has limited availability.

Remdesivir is a nucleotide prodrug whose active metabolite inhibits viral RNA-dependent RNA polymerases, structurally conserved enzymes that play a key role in the replication of a broad range of viruses, including Coronaviridae.7-9 A first randomized, placebo-controlled trial of remdesivir among patients with COVID-19 conducted in Wuhan, China, could not complete enrolment to meaningfully assess efficacy.[9] 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).[10] Subsequently, a randomized, open-label trial showed that patients with severe COVID-19 with relative hypoxia or requiring oxygen support but not requiring ventilator support had outcomes with 5- and 10-day courses of remdesivir that were not significantly different.[11] 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.[12] Concurrent with these studies, this study was conducted to evaluate the efficacy of remdesivir administered for 5 or 10 days vs standard care in hospitalized patients with moderate to severe COVID-19.

Methodology

We conducted a retrospective case control study from existing data where we enrolled hospitalized patients with confirmed SARS-CoV-2 infection, oxygen saturation of 94% or less while they were breathing ambient air, and radiologic evidence of pneumonia. We made two groups of patients. Those who received intravenous remdesivir for either 5 days or 10 days were enrolled as cases. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. Those who did not received remdesivir as treatment were enrolled as controls. Controls were matched with cases in terms of age, sex and clinical staging at the time of admission. The ratio of cases to control was taken as 1:3. Patients were randomly assigned in a 1:3 ratio. Outcome measures like recovery, death, average time of hospitalization was analysed using proportion and odds ratio at 95% confidence interval using SPSS version 22. Ethical clearance was taken from institutional ethics committee.

Results

Since starting of pandemic we have experiences 2336 severe cases of Covid 19 in our hospital. Out of which 335 cases received Inj Remdesivir as one of the treatment option according to guidelines. The other 1991 cases received similar treatment except Inj Remdesivir. (Fig 1)

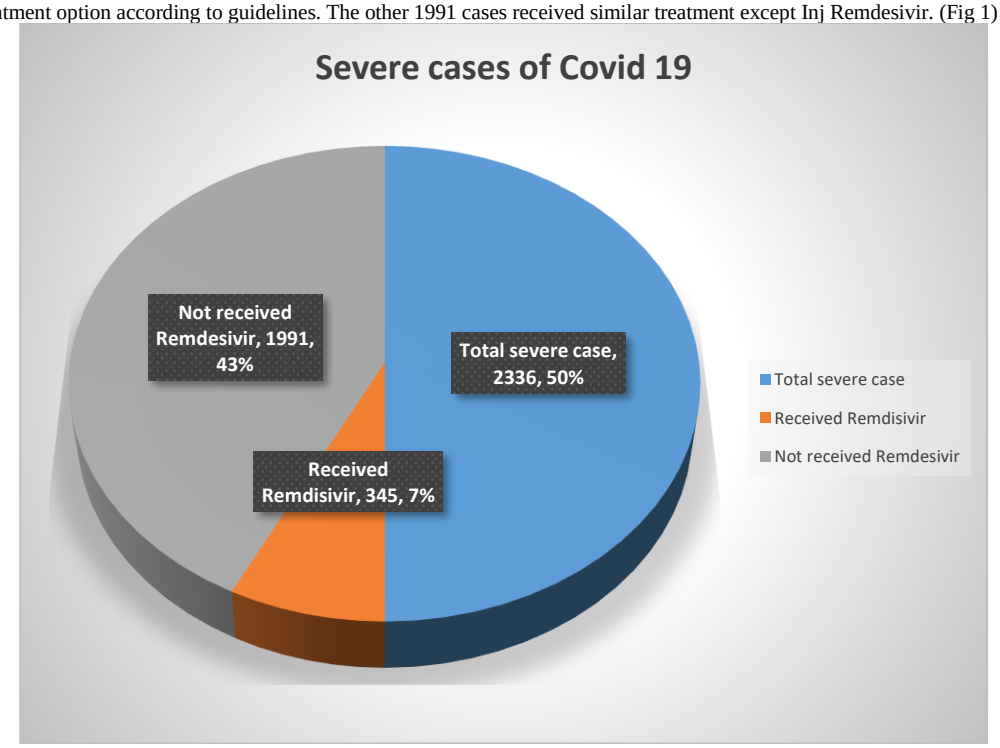

Fig 1:Distribution of Severe Covid 19 Cases

Out of recipients of Remdesivir 212 (61.44%) were male while 133 (38.55%) were females.(Figure 2)

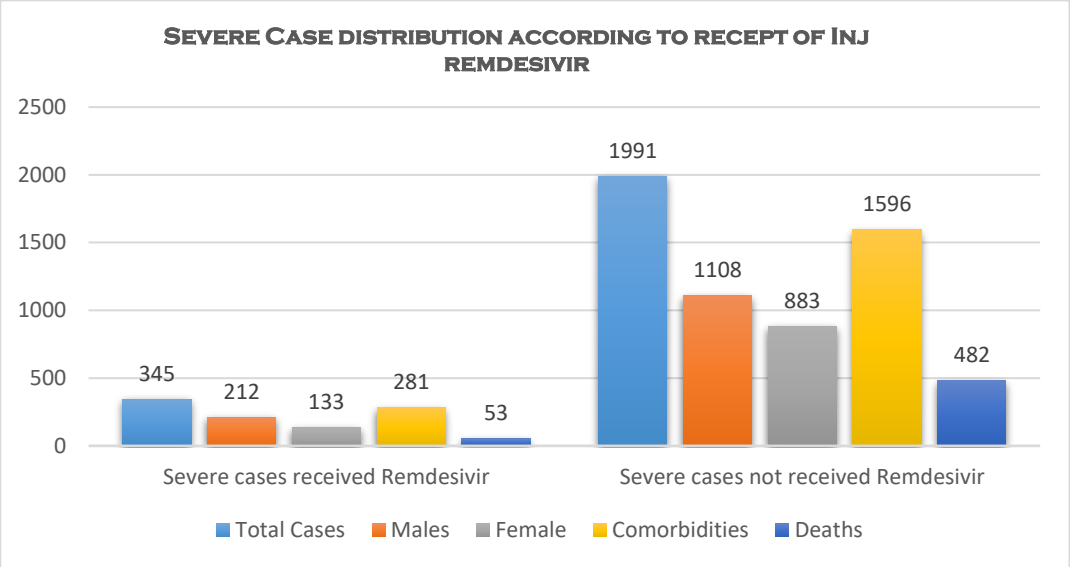

Fig 2:Distribution of cases according to Remdesivir use

175 (50.72%) males recovered after treatment while 37 succumbed to infection. 117 (33.91%) females recovered from infection while 16 expired. Positive association was seen between treatment with Inj. Remdesivir and recovery (odd ratio=2.1207, p value-0.0001). No association was found between recoveries among females who had received Remdesivir. (Odds ratio=1.3662, p value=0.2687) (Table 1)

Table 1: Covid 19 cases treated with and without Remdesivir

Variables Total Severe cases N=	Patients received Remdesivir	Patients not received Remdeisivir	Odds ratio	P value
Severe cases of Covid 19	345	1991	N.S	N.S.
Recovered Males	175 (50.72%)	765 (38.42%)	2.1207	0.0001
Recovered Females	117 (33.91%)	744 (37.36%)	1.3662	0.2687
Avg. duration of hospitalization in days	10	16	N.S	N.S
Patients with Comorbidities	281(52.46%)	1596 (80.16%)	1.8613	0.0001
Deaths	53 (15.36%)	482(24.20%)	0.0580	0.0001

Average duration of hospital stay among recipient of remdesivir was 10 days against 16 days in those patients who didn't received remdesivir.

There were 281(52.46%) comorbid patients with severe Covid Infection who received Inj Remdesivir out of which 228 (81.13%) recovered while 1596 (80.16%) severe patients with comorbidities who didn't received Remdesivir out of which 1114 (69.79) recovered.(figure 2) Positive association was found between recovery among Covid 19 patients with comorbidities with inclusion of Inj Remdesivir in treatment (odds ratio= 1.8613P value=0.0001)

53 (15.36%) deaths were observed in patients who received Remdesivir against 482(24.20%) deaths among those who didn't receive it. A significant negative association was seen in bad outcome of Covid 19 infected cases and use of Inj remdesivir. (Odds ratio= 0.0580 p value=0.0001)

Discussion

In a tertiary care hospital situated at district place we experienced 6229 Covid 19 positive cases out of which 3423 cases were severe. The Drug Controller General of India (DCGI) approved Mylan's Remdesivir Lyophilised Powder for Injection 100 mg/vial for restricted emergency use as a COVID-19 treatment in India in month of July 2020. The approval is part of the DCGI's accelerated approval process to address urgent, unmet needs amid the pandemic. There were major speculations about efficacy of this drug in the treatment of Covid 19 infections and anxiety about the adverse effect of this drug. Ministry Of health and family Welfare published detailed guideline for the use of this drug.[6]We proposed a study to determine effectiveness of Remdesivir in the treatment of Covid 19 infection by retrospectively analysing data of patients treated with Remdesivir and comparing the outcome with those who hadn't received it.

2336 cases were included in the study, out of which 345 received Remdesivir. 292 (84.63%) cases who received Remdesivir were recovered while 1506 (75.79%) were recovered who didn't received Remdesivir. We found a significant positive association between recovery among severe Covid cases and treatment with Remdesivir. Chih-Cheng Lai et al conducted a systematic review and network meta-analysis of randomized controlled trials (RCTs) to provide updated information regarding the clinical efficacy of remdesivir in treating coronavirus disease 2019 (COVID-19). It yield similar results and stated that Remdesivir can help improve the clinical outcome of hospitalized patients with COVID-19 and a 5 day regimen, instead of a 10 day regimen, may be sufficient for treatment. Moreover, remdesivir appears as tolerable as other comparators or placebo.[13]

Recovery among males who received Remdesivir (175 (50.72%)) was found to be positively associated with the use of drug. While recovery among females who received remdesivir was found to be insignificant. Zeno Pasquini in a randomized control trial on ICU patients provided contrary results. There was no significant difference in demographic characteristics, comorbidities and laboratory values between patients treated and not treated with remdesivir. Median follow-up was 52 (46–57) days. In this study the mortality rate of patients with COVID-19 under mechanical ventilation is confirmed to be high. The use of remdesivir was associated with a significant beneficial effect on survival.[14]

Average duration of hospitalization was seen to 10 days in patients who received remdesivir while it was 15 days in case of non-recipient of drug. Michael E et al provides contrary results in his retrospective cohort study of 2344 US veterans hospitalized with COVID-19, remdesivir therapy was not associated with improved 30-day survival but was associated with a significant increase in median time to hospital discharge. The study examination of days from matching to

hospital discharge showed a shift in discharges from days 1 to 4 among controls to day 5 or 6 among remdesivir recipients, in association with large numbers of patients completing 5-day remdesivir courses. These findings suggested that clinicians may have not discharged some patients who were receiving remdesivir until they completed a 5-day course. If this was the case, routine use of remdesivir for COVID-19 may have been associated with increased use of scarce hospital beds during the pandemic without being associated with improvements in patient survival.[15] The ACTT-1 trial produced similar results like our study. The primary outcome of this placebo-controlled randomized clinical trial was time to recovery, defined as how many days it took for the patient to either be discharged from the hospital or stay in the hospital but not require oxygen or ongoing medical care (i.e., for infection control purposes only). The ACTT-1 trial3 showed that patients receiving remdesivir recovered after a median of 10 days, compared with 15 days for the placebo group. There was also a numerical but not a statistically significant difference in mortality between groups.[16]John H Beigel et al in his double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection concluded that that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.[17]

Evidence from the global outbreak of SARS-CoV-2 has clearly demonstrated that individuals with pre-existing comorbidities are at a much greater risk of dying from COVID-19. This is of great concern for individuals living with these conditions, and a major challenge for global healthcare systems and biomedical research. Not all comorbidities confer the same risk, however, many affect the function of the immune system, which in turn directly impacts the response to COVID-19. Furthermore, the myriad of drugs prescribed for these comorbidities can also influence the progression of COVID-19 and limit additional treatment options available for COVID-19. In our study we found positive association between recovery among comorbid Covid 19 positive patients {281 (52.46)} and treatment with Remdesivir. Similar results were obtained from National Institute of Allergy and Infectious Diseases Adaptive COVID-19 Treatment Trial involving 1,063 patients, demonstrated that remdesivir accelerated recovered by 31% compared to placebo.[18] Furthermore, recent results from the Phase 3 SIMPLE trial investigating the use of remdesivir in patients with moderate COVID-19 showed that patients receiving remdesivir treatment were 65% more likely to have improved clinically by day 11 than standard of care patients.[19] Due to the success of these two trials, the use of remdesivir has been approved by the FDA, EMA, UK, and Japan as a treatment for COVID-19. Despite proven efficacy, adverse events in response to remdesivir have been reported in 60% of patients of which 12% were severe[20]. These included septic shock, multiple organ dysfunction syndrome, acute kidney injury and hypotension. Therefore, the use of remdesivir in comorbid patients with increased susceptible to these adverse events requires further evaluation.A significant negative association was seen death among patient and treatment with Remdesivir. A decrease in death rate was seen among Covid 19 patient who were treated with Remdesivir. Chen-Yang Hsu et al conducted a simulated two arm control study where he found similar results. Remdesivir treatment resulted in a 33% significantly higher odds of discharge, a 29% significantly lower risk of death, and a 39% significantly lower risk for the combined endpoint of severe status and death. The median time to discharge for the remdesivir treated group was around half of the median time-to-discharge compared with the control arm.[21]

Conclusion

This study finds treatment of Covid 19 with Remdesivir as an effective method for treatment as the drug has shown to expedite recovery, decreases hospital stay, and decreases death rate among severe Covid 19 infections.

Limitation

Data of only one tertiary care hospital was taken into account. There is a need of multicentre prospective cohort study to confirm the results.

References

1. Helmy YA, Fawzy M, Elaswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 Pandemic: A Comprehensive Review of Taxonomy, Genetics, Epidemiology, Diagnosis, Treatment, and Control. Journal of Clinical Medicine 2020;9(4):1225.
2. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19 | NEJM [Internet]. [cited 2021 Aug 2]; Available from: https://www.nejm. org/doi/full /10.1056/ NEJMoa2001282
3. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11(1):222.
4. Wang M,Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30(3):269–71.
5. Wit E de, Rasmussen AL, Falzarano D, Bushmaker T, Feldmann F, Brining DL, et al. Middle East respiratory syndrome coronavirus (MERS-CoV) causes transient lower respiratory tract infection in rhesus macaques. PNAS 2013 ;110(41):16598–603.
6. UpdatedDetailedClinicalManagementProtocolforCOVID19adultsdated24052021.pdf [Internet]. [cited 2021 Aug 2];Available from: https://www.mohfw.gov.in/pdf/UpdatedDetailedClinicalManagementProtocolforCOVID19adultsdated24052021.pdf
7. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. New England Journal of Medicine 2020;383(19):1813–36.
8. WHO Solidarity Trial Consortium. Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results. N Engl J Med 2021;384(6):497–511.
9. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet 2020; 395 (10236):1569–78.
10. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383(19):1813–26.
11. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. New England Journal of Medicine 2020; 383(19):1827–37.
12. Commissioner O of the. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment [Internet]. FDA2020 [cited 2021 Aug 9];Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment
13. Lai C-C, Chen C-H, Wang C-Y, Chen K-H, Wang Y-H, Hsueh P-R. Clinical efficacy and safety of remdesivir in patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials. Journal of Antimicrobial Chemotherapy [Internet] [cited 2021 Aug 9];Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8083728/
14. Pasquini Z, Montalti R, Temperoni C, Canovari B, Mancini M, Tempesta M, et al. Effectiveness of remdesivir in patients with COVID-19 under mechanical ventilation in an Italian ICU. Journal of Antimicrobial Chemotherapy 2020;75(11):3359–65.
15. Ohl ME, Miller, Lund BC, Kobayashi T, Richardson Miell K, Beck BF, et al. Association of Remdesivir Treatment With Survival and Length of Hospital Stay Among US Veterans

Hospitalized With COVID-19. JAMA Network Open 2021;4(7):e2114741–e2114741.
16. Remdesivir for the Treatment of Covid-19 — Final Report | NEJM [Internet]. [cited 2021 Aug 9];Available from: https://www.nejm.org/doi/10.1056/NEJMoa2007764
17. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383(19):1813–26.
18. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236): 1569–78.
19. Adaptive COVID-19 Treatment Trial (ACTT) - Full Text View - ClinicalTrials.gov [Internet]. [cited 2021 Aug 9];Available from: https://clinicaltrials.gov/ct2/show/NCT04280705
20. Gilead Announces Results From Phase 3 Trial of Remdesivir in Patients With Moderate COVID-19 [Internet]. [cited 2021 Aug 9];Available from:https://www.gilead.com/news-and-press/press-room/ press-releases/ 2020/6/gilead-announces-results-from-phase-3-trial-of-remdesivir-in-patients-with-moderate-covid-19
21. Hsu C-Y, Lai C-C, Yen AM-F, Chen SL-S, Chen H-H. Efficacy of remdesivir in COVID-19 patients with a simulated two-arm controlled study. medRxiv 2020;2020.05.02.20088559.

Conflict of Interest: Nil Source of support: Nil