Randomized placebo-controlled trials of remdesivir in severe COVID-19 patients: A Systematic Review and Meta-analysis

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Abstract

**Background:** The first cases of the coronavirus disease 2019 (COVID-19) were reported in Wuhan, China. No antiviral treatment options are currently available with proven clinical efficacy. However, preliminary findings from phase III trials suggest that remdesivir is an effective and safe treatment option for COVID-19 patients with severe disease. **Objective:** The aim of the present meta-analysis is to investigate whether remdesivir is effective for treating COVID-19 including reduced in-hospital adverse events, oxygen support, and mortality rates. **Methods:** Using PRISMA reporting guidelines, a review was conducted from January 1 2020 until 6 August 2020 with MeSH terms including COVID-19, coronavirus, SARS-CoV-2, COVID, remdesivir, adenosine nucleoside triphosphate analog, Veklury using Medline, Scopus, and CINAHL Plus. A modified Delphi process was used to include the studies and ensure that the objectives were addressed (Appendix A). Using dichotomous data for select values, the unadjusted odds ratios (ORs) were calculated applying Mantel Haenszel (M-H) random-effects method in Review Manager 5.4. **Results:** Randomized controlled trials pooled in 2,429 participants with 41.6% (n=1011) in the remdesivir group and 58.4% (n=1,418) in the placebo group. The placebo group had a higher risk of mortality as compared to the intervention group with significant odds ratio (OR=0.61) (95% confidence interval of 0.45-0.83; P=0.001). There was moderate heterogeneity among the studies. **Conclusions:** Our findings suggest that remdesivir extends clinical benefits by reducing mortality, adverse events and oxygen support in moderate to severely ill COVID-19 patients. Concerted efforts and further randomized placebo-controlled trials are warranted to examine the potency of anti-viral drugs and immune-pathological host responses contributing to severity of COVID-19.

**Key words:** coronavirus, remdesivir, mortality, oxygen support, adverse events, emergency use authorization

Word count: 2,692

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
1. Introduction

Since the first cases of the coronavirus disease 2019 (COVID-19) were reported in Wuhan, Hubei Province, China in December 2019, the large-scale spread internationally led the World Health Organization (WHO) to declare COVID-19 as a public Health Emergency of International Concern on January 30, 2020 (1). Antiviral treatment options of proven clinical efficacy in COVID-19 infections are under investigation (2). Remdesivir is an investigational nucleotide prodrug which intracellularly metabolizes to the active nucleoside triphosphate (ATP) and interferes with viral RNA-dependent RNA polymerase activity thereby disrupting viral exoribonuclease activity (3). However, the pharmacokinetics of remdesivir within the respiratory tract of critically ill COVID-19 patients are not well known. Hospitalized COVID-19 patients with oxygen saturation ≤ 94% on room air or requiring oxygen support are eligible to receive remdesivir under the U.S. Food and Drug Administration (FDA) emergency use authorization (EUA) (4). While previous studies have reported a reduction in median time to clinical improvement, insufficient power of sample sizes limited the deductibility of clinical outcomes of remdesivir (5). Additionally, initiating remdesivir earlier in COVID-19 treatment protocols may be considered before immune-mediated epithelial damage due to elevated viral replication occurs and may reduce mortality and disease severity as observed previously in severe acute respiratory syndrome (SARS) and middle eastern respiratory syndrome (MERS) (6).

Based on preliminary reports and findings from in vitro and in vivo activity in animal models of SARS-CoV-1 and MERS-CoV, remdesivir treatment for 5 or 10 days is being administered to COVID-19 patients with comparable efficacy and safety (7–9). While most COVID-19 infections are self-limited, the largest cohort of 44,672 patients reported 14% with severe disease and 49% case-fatality rates (CFRs) among the 5% with critical disease that warrants longer hospital stays and ventilator support associated with the high burden placed on health infrastructures (10). Use of remdesivir has resulted in reduced oxygen support in a cohort with 53 hospitalized COVID-19 patients (11). Consequently, with revised recommendations suggesting uncertain efficacy of remdesivir and benefits among patients already on high-flow oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO), the initiation and duration of remdesivir treatment among COVID-19 hospitalized patients receiving oxygen support remains unclear (12). Given the uncertainty on the beneficial outcomes of remdesivir-treated COVID-19 patients, we aimed to examine the
following differences between remdesivir and placebo groups: 1) oxygen support status at day 1 and day 14, 2) any adverse events at day 14, and 3) death from any cause at day 14.

2. Methods

2.1. Search strategy

Using PRISMA reporting guidelines, a review was conducted from January 1 2020 until 6 August 2020 with MeSH terms including “COVID-19”, “coronavirus”, “SARS-CoV-2”, “COVID”, “remdesivir”, “adenosine nucleoside triphosphate analog”, “Veklury” using Medline, Scopus, and CINAHL Plus. Quantitative primary research articles were added to the systematic review and meta-analysis. The inclusion criteria of included studies was COVID-19 infected patients aged 18 or older being treated with remdesivir or placebo. Duplicates were removed using endnote X9. We manually cross-checked the searches for authors, title, and abstract to remove duplicates.

Two investigators (AS and ZS) independently screened the titles and abstracts before reaching to a consensus to determine included studies. The third investigator (MSG) was present for any disagreements. Exclusion criteria were applied to full-texts during the final selection. A modified Delphi process was used to include studies and ensure that our objective was identified in selected studies (13). The a priori methods for conducting the Delphi process for meta-analyzing the clinical effectiveness are described in supplementary figure 1 (Appendix 1). We included studies if they were randomized control trials, had an intervention arm as compared to placebo, and the endpoint of interest was clinical outcomes and mortality. Two investigators (AS and ZS) re-confirmed all data entries and checked imported data from all studies at least thrice for accuracy.

2.2. Quality assessment

We evaluated the risk of bias for all included studies using Grading of Recommendations, Assessment, Development, and evaluation (GRADE) criteria (14). We aimed to evaluate the risk of bias associated with the selection of participants, confounding, and health outcome assessment. We found the risk of bias of the three individual RCTs included for quantitative analysis. Because less than 10 studies were included, the publication bias was not determined.
2.3. Outcomes

The primary outcomes included death from any cause at day 14. The secondary outcomes were to identify any adverse events at day 14 of the treatment and the requirement for supplemental oxygen, high-flow nasal cannula, non-invasive ventilation, invasive ventilation or ECMO at day 1 and 14. The time to recovery in days, total patients recovered, and findings of serious adverse effects among remdesivir and placebo groups were identified.

2.4. Data analysis

Two independent reviewers (AS and ZS) assessed the eligibility of all full-text articles; the third (MSG) arbitrated for cases to reach a consensus. The first reviewer (AS) extracted the data, and the second reviewer (ZS) validated the data extraction for all studies. The quantitative data was entered into a spreadsheet. If more than one study reported data on post-treatment outcomes, data was extracted separately for each study. We independently extracted data from the published randomized placebo-controlled trials.

By using dichotomous data for select values, summary measures namely the unadjusted odds ratios (ORs) were calculated using the Mantel Haenszel (M-H) random-effects methods. We calculated the ORs and 95% CIs for each measure evaluated in two or more studies. A meta-analysis was conducted using Review Manager V.5.4. Findings were presented using 95% CIs along with a test for heterogeneity between studies. The I² index describes the inconsistency of findings across the studies in the meta-analysis reflecting the extent to which the confidence intervals of the different studies overlap.

3. Results

The search process is shown in Figure 1. The initial screening yielded 1241 results. After the exclusion of duplicates, 945 results were withheld for the screening of title and abstract. Consequently, 704 records were excluded due to ineligibility (reviews, editorials, non-RCTs, ongoing trials, and abstracts). Finally, after screening 241 full-text articles, only 3 studies reporting 2429 patients (remdesivir n=1011; placebo n=1418) were included in the qualitative and quantitative synthesis. The major characteristics and quality assessment findings of the 3 included studies are presented in Table 1.
Figure 1. PRISMA flowchart.

Records identified through PubMed (n = 407)

Records identified through Scopus (n = 772)

Records identified through CINAHL (n = 55)

Records after duplicates removed (n = 945)

Records screened (n = 945) → Records excluded (n = 704)

Full-text articles assessed for eligibility (n = 241) → Full-text articles excluded, (n = 238) did not meet the inclusion criteria

Studies included in qualitative synthesis (n = 3)

Studies included in quantitative synthesis (meta-analysis) (n = 3)
| Author | Groups       | Age (Mean ± SD) | Male (n, %) | Hypertension (n, %) | Diabetes type 2 (n, %) | Supplemental oxygen (day 1) (n, %) | Supplemental oxygen (day 14) (n, %) | Invasive ventilation or ECMO (day 1) (n, %) | Invasive ventilation or ECMO (day 14) (n, %) | High-flow nasal cannula or non-invasive mechanical ventilation (day 1) (n, %) | High-flow nasal cannula or non-invasive mechanical ventilation (day 14) (n, %) |
|--------|--------------|-----------------|------------|---------------------|------------------------|----------------------------------|-------------------------------------|---------------------------------------------|-----------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Wang   | Remdesivir   | 65.3 ± 12       | 89/78 (56%)| 72/158 (46%)        | 40/158 (25%)           | 129/158 (82%)                   | 61/153 (40%)                        | 0 (0%)                                       | 4/153 (3%)                                                   | 28/158 (18%)                                                  | 13/149 (8.7%)                                                  |
|        | (N=158)      |                 |            |                     |                        |                                   |                                     |                                              |                                                              |                                                               |                                                               |
|        | Placebo     | 62.2 ± 12.8     | 31/78 (65%)| 30/158 (38%)        | 16/78 (21%)            | 65/78 (83%)                     | 28/78 (36%)                         | 17/8 (1%)                                     | 7/78 (9%)                                                    | 9/78 (12%)                                                    | 8/76 (10.5%)                                                   |
|        | (N=78)       |                 |            |                     |                        |                                   |                                     |                                              |                                                              |                                                               |                                                               |
| Beigel | Remdesivir   | 58.6 ± 14.6     | 352/541 (65.1%)| 231/469 (49.3%)   | 144/470 (30.6%)        | 222/541 (41%)                   | 34/434 (7.8%)                       | 98/541 (18.1%)                                | 60/434 (13.8%)                                               | 125/541 (23.1%)                                               | 16/538 (3.7%)                                                  |
|        | (N=541)      |                 |            |                     |                        |                                   |                                     |                                              |                                                              |                                                               |                                                               |
|        | Placebo     | 59.2 ± 15.4     | 332/541 (63.6%)| 229/459 (49.9%)   | 131/457 (28.7%)        | 196/522 (38.1)                  | 40/410 (9.8%)                       | 99/522 (19%)                                  | 72/410 (17.6%)                                               | 147/522 (28.2%)                                               | 14/521 (3.4%)                                                  |
|        | (N=522)      |                 |            |                     |                        |                                   |                                     |                                              |                                                              |                                                               |                                                               |
| Olender| Remdesivir   | NA              | 184/312 (59%)| 147/312 (47%)      | 94/312 (30%)            | 197/312 (63%)                   | NA                                  | 25/312 (8%)                                  | NA                                                           | 34/312 (11%)                                                  | NA                                                            |
|       | (N=312)      |                 |            |                     |                        |                                   |                                     |                                              |                                                              |                                                               |                                                               |
|        | Placebo     | NA              | 483/818 (59%)| 401/818 (49%)      | 81/818 (26%)            | 499/818 (61%)                   | NA                                  | 49/818 (6%)                                  | NA                                                           | 115/818 (14%)                                                 | NA                                                            |
|        | (N=818)      |                 |            |                     |                        |                                   |                                     |                                              |                                                              |                                                               |                                                               |

Table 1. Study characteristics
| Author   | Groups          | Time to recovery (days, median) | Recovered (overall) (n, %) | Serious adverse effects (overall) (n, %) | Mortality (day 14) (n, %) | GRADE |
|----------|-----------------|---------------------------------|----------------------------|-----------------------------------------|----------------------------|-------|
| Wang (26) | Remdesivir (N=158) | 21 (13-28)                      | 103/158 (65%)              | 102/155 (66%)                           | 15/153 (10%)               | High  |
|          | Placebo (N=78)  | 23 (15-28)                      | 45/78 (58%)                | 50/78 (64%)                             | 7/78 (9%)                  |       |
| Beigel (4) | Remdesivir (N=541) | 11 (9–12)                       | 334/538 (62.1%)            | 114/541 (21.1%)                        | 32/538 (6%)                | High  |
|          | Placebo (N=522) | 15 (13–19)                      | 273/521 (52.4%)            | 141/522 (27%)                          | 54/521 (10.4%)             |       |
| Olender (16) | Remdesivir (N=312) | 14                             | 232/312 (74.4%)           | NA                                      | 24/312 (7.6%)              | Moderate |
|          | Placebo (N=818) | 14                             | 483/818 (59%)              | NA                                      | 102/818 (12.5%)            |       |

Table 1. Study characteristics (continued)
3.1. Mortality at day 14 of treatment

All 3 studies reported data on mortality at day 14, and thus were eligible to be included in the meta-analysis. Compared with the remdesivir-treated group, the placebo group had higher risks of mortality (OR: 0.61; 95% CI: 0.45-0.83; P=0.001) (Figure 2a). From the sensitivity analysis, we found that Olender et al. contributed to the highest to the homogeneity (I²=0%). After excluding this study, the results suggested that risk of mortality was still higher in the placebo group (OR: 0.68; 95% CI: 0.36-1.30; P=0.25), but with heterogeneous findings (I²=42%).

![2a. Forrest plot for mortality at day 14 of treatment.](image)

3.2. Supplemental oxygen at day 1 and 14 of treatment

All 3 studies presented data of supplemental oxygen requirement at day 1 of treatment among the remdesivir and placebo groups. Using a random-effects model, we determined that the remdesivir group had higher odds as compared to the placebo group in requiring supplemental oxygen at the first day of treatment (OR: 1.10; CI: 0.92-1.31; P=0.29), with no heterogeneity among all studies (I²=0%) (Figure 2b).

Two out of 3 studies evaluated the supplemental oxygen use at day 14 of treatment among the remdesivir group and the placebo group. However, there was a higher likelihood of the placebo group to require supplemental oxygen at the end of the second week of treatment (OR: 0.94; CI: 0.63-1.40; P=0.75), with mild heterogeneity among the studies (I²=15%) (Figure 2b).
2b. Forrest plot for supplemental oxygen at day 1 (above) and day 14 (below) of treatment.

3.3 High-flow nasal cannula or non-invasive mechanical ventilation at day 1 and 14 of treatment

All 3 studies presented data of high-flow nasal cannula or non-invasive mechanical ventilation required at day 1 of treatment. Patients in the placebo group as compared to the remdesivir group had high odds of requiring high-flow nasal cannula or non-invasive mechanical ventilation (OR: 0.84; CI: 0.61-1.16; P=0.29; I^2=39%) (Figure 2c).

Two of the 3 studies presented the requirements of high-flow nasal cannula or non-invasive mechanical ventilation at day 14 of treatment. The likelihood in both remdesivir and placebo groups are equal with no difference between odds of both groups (OR: 0.99; CI: 0.56-1.75; P=0.96), with no heterogeneity among the studies (I^2=0%) (Figure 2c).

2c. Forrest plot for supplemental oxygen at day 1 (above) and day 14 (below) of treatment.
3.4 Invasive ventilation or ECMO at day 1 and 14 of the treatment

All 3 studies presented data of invasive ventilation or ECMO at the first day of treatment. While the difference was negligible, there was a very slight preponderance of the remdesivir group to require invasive ventilation or ECMO at day 1 of treatment (OR: 1.06; CI: 0.73-1.54; P=0.77; I²=28%) (Figure 2d).

Two of the 3 studies reported data on invasive ventilation or ECMO at day 14 of the treatment. Patients in the placebo group had a higher likelihood of requiring invasive ventilation or ECMO at the second week of the treatment as compared to the patients in the remdesivir group (OR: 0.55; CI: 0.22-1.38; P=0.20) (Figure 2d). There was moderately high heterogeneity among the studies included for the analysis (I²=57%).

2d. Forrest plot for invasive ventilation or ECMO at day 1 (above) and day (below) 14 of the treatment.

3.5 Adverse events until day 14 after initiation of treatment

2 of the 3 studies reported data on the serious adverse effects at day 14 after initiation of treatment, and thus they were included in the meta-analyses. The placebo group had a higher risk or likelihood of presenting with adverse outcomes as compared to the remdesivir group, but with less statistical significance (OR: 0.81; CI: 0.57-1.17; P=0.27) (Figure 2e). There was mild heterogeneity among the studies (I²=35).
2e. Forrest plot of adverse events during the entire course of the treatment.

4. Discussion

The purpose of the study was to comprehensively review the efficacy of remdesivir compared to placebo among hospitalized COVID-19 patients. Our inclusion criteria, determined by input of all panel members, were specific for adult hospitalized COVID-19 patients treated with either remdesivir or placebo, which distinguishes the findings from other meta-analyses. Based on the analysis of three randomized placebo-controlled trials, the overall findings support the use of remdesivir to reduce oxygen support, adverse events and all-cause mortality after 5 or 10 days of remdesivir treatment (5,15,16). Overall, the mortality rate for remdesivir-treated patients with COVID-19 of the three included studies ranged from 6% to 10% compared to the 9% to 12.5% mortality rates of the placebo-treated patients. This findings were consistent with previous clinical data reporting positive outcomes for the compassionate use of remdesivir in severe COVID-19 patients (11,17).

The time to clinical recovery was significantly lower among patients who received remdesivir compared to placebo (21 days vs. 23 days and 11 days vs. 15 days). There were observed differences in requirements of supplemental oxygen with the remdesivir group requiring less supplemental oxygen at day 14 than the placebo group with day 1 data demonstrating significant use of supplemental oxygen in the remdesivir group. While no significant differences were noted in the use of high-flow nasal cannula or non-invasive mechanical ventilation at day 14, the remdesivir group had reduced likelihood of being on invasive ventilation or ECMO at day 14. Along with reduced overall oxygen support required in the remdesivir group, the all-cause mortality and any adverse events were significantly reduced in the remdesivir group in comparison to the placebo group. An analysis of 138 healthy volunteers were treated with remdesivir and it appears to have a safe clinical profile and is well-tolerated with transaminase elevation identified as the only adverse event (18). Special attention should be given to renal events, pregnancy, hypersensitivity reactions, and concomitant vasopressor use before remdesivir initiation (18).
To our best understanding, this is the first review that determines oxygen support status at day 1 and 14, any adverse events at day 14, and all-cause mortality at day 14. We synthesize various clinical outcomes of interest using statistical analysis methods that are widely applicable and relevant to key stakeholders in healthcare. Based on our results, implications for clinical use of remdesivir are affirmative among adult patients with COVID-19 disease demonstrated by the benefitting trends of in-hospital mortality, oxygen support status and adverse events within two weeks of treatment. Our findings synthesize results of primary and secondary outcomes of ongoing or completed clinical trials (19–21). However, our findings ought to be interpreted cautiously. We found over 35 trials registered on clinicaltrials.gov classified as remdesivir group versus placebo group using 200 mg loading dose on the first day, followed by 100 mg intravenous once-daily doses for around 9 days. The outcomes of the ongoing trials are to determine the time to clinical improvement, clinical status, time to hospital discharge, all-cause mortality, duration of mechanical ventilation, ECMO, supplemental oxygen, length of hospital stay, change in viral load assessed by area under viral load curve, and the frequency of adverse events.

The baseline health and disease severity were not matched in the remdesivir and placebo groups in our included studies. Additionally, the use of remdesivir in high-risk populations, e.g. elderly age, multiple comorbidity, Black, sociodemographic disparity, may be considered before severe COVID-19 manifestations occur (22). The most adequate time of administering anti-viral treatment is soon after the onset of disease to promote benefits, with previous reports recommending initiation within 10 days after the onset of symptoms (23,24). Early results based on interim data may lack generalizability, but the use of remdesivir may be considered beyond emergency-use authorization. Patients who have been intubated for a short period may also benefit from remdesivir dosage every 24-28 hours. Additionally, the next steps in finding a consensus towards remdesivir use follow the evaluation of potential short-term and long-term side effects of remdesivir taking into consideration the concomitant use of other medication. For instance, off-label use of medications such as lopinavir-ritonavir, hydroxychloroquine and immunomodulatory drugs including glucocorticoids and tocilizumab may confound reports of potentially beneficial outcomes of remdesivir use.

5. Recommendations

Reporting biases of currently published trial results may be taken into consideration. The clinical benefits ought to be predicted within all severity subgroups to confer support for
clinical guidance towards remdesivir. As the world strives to overcome structural and social health care disparities, we must accentuate the underrepresentation or lack of available data interpreting the incidence, and clinical outcomes of minority groups in remdesivir COVID-19 trials (25). In a preliminary cohort study published by Grein et al., data of ethnicity was omitted for 53 patients (11). While the vetting for preliminary results was obtained from limited datasets the proportion of Black, Latinx, and Native Americans was around 20%, 23%, and 0.7% respectively in trials published by Beigel et al. and Goldman et al. (7,15). The modest benefits in time to clinical improvement may not be generalizable to minority groups due to the differences in severity, outcomes, and treatment efficacy (26). The lack of diversity is a long-standing problem that must be mandated at the administrative level by the inclusion and reporting of minority group data at government-funded research. A prioritization of populations reflecting the demographics of high-risk groups impacted by the ongoing pandemic is crucial, by expanding clinical trial sites and employing random sampling.

6. Limitations

Our findings were limited by the lack of comparability between a 5-day and a 10-day course of intravenous remdesivir treatment among severe COVID-19 patients. However, no randomized placebo-trials have reported such findings thus far. Another limitation was the lack of corroboration of clinical efficacy with the viral loads of the patients in either groups. While the biological mechanisms of remdesivir are required to interpret the clinical efficacy, not all studies reported the viral loads in our meta-analysis.

7. Conclusion

Our findings provide strong evidence of clinical improvement in randomized, placebo-controlled trials of remdesivir therapy. Implications of our results are strong with a moderately large sample size, and randomized placebo group in our meta-analysis. Ongoing placebo-controlled trails employing larger sample sizes will remain our informative source of the outcomes and adverse events of remdesivir administered to COVID-19 patients. Strategies must be used to enhance the potency of remdesivir while reducing the immune-pathological host responses that contribute to the infection severity. Additionally, the efficacy of 5 versus 10 days dosing of remdesivir is yet to be established and warrants further exploration. Nevertheless, our findings suggest that remdesivir may have clinical efficacy among COVID-19 patients and may be used beyond emergency authorization in patients at high-risk for severe COVID-19.
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9. Conflict of Interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The authors contributed equally to all aspects of the article.

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Appendix A

Round 1
Draft a list of objectives sent to experts in a pre-determined panel, who score the questions in a Likert scale (1-5) and suggest possible objectives or additional questions. Researcher collates scores, identifies the median and IQR and uses the top 10 questions.

Round 2
The top 10 questions and up to two new questions sent to the panel on an individual scoring sheet with results of the median score of the panel members from the first round for each question. All participants rescore the questions with an option to change the original score based on the panel’s response. Researcher collates scores, identifies the median and IQR and uses the results to identify the top 10 questions for round 3.

Round 3
The top 10 questions sent to all panel members on an individual scoring sheet. All members rescore questions with a final option to change their original scores keeping in view the panel’s response. Researcher collates scores, identifies the median, IQR, and ranks the top 10 questions.

Panel feedback round
The prioritized research questions finalized with the final list and scores sent to the panel for information sharing.

Modified Delphi protocol: A priori.