Remdesivir: A potential game-changer or just a myth? A Systematic Review and Meta-analysis

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Abstract

Aim COVID-19 outbreak spread all over the world and created a public health catastrophe. Here, we have aimed to conduct a systematic review and meta-analysis on remdesivir use for COVID-19. Methods We searched Pubmed, Pubmed Central, Scopus, Embase, clinicaltrials.gov, and preprint sites and identified ten studies for qualitative and four studies for quantitative analysis using PRISMA guidelines. The quantitative synthesis was performed using fixed and random effect models in RevMan 5.4. Heterogeneity was assessed using the I-squared (I2) test. Results Comparing remdesivir group with placebo or standard of care (SOC) group, remdesivir reduces 14 days mortality (OR 0.61, CI 0.41- 0.91), need of mechanical ventilation (OR 0.73, CI 0.54-0.97), and overall severe adverse effects (OR 0.69, 95% CI 0.54 to 0.88). There is better clinical improvement on day 28 (OR 1.59, CI 1.06- 2.39); day 14 clinical recovery (OR 1.48, CI 1.19-1.84); day 14 discharge rate (OR 1.41, CI 1.15-1.73) among remdesivir groups. Earlier clinical improvement (MD -2.51, CI -4.16 to -0.85); and clinical recovery (MD -4.69, CI -5.11 to -4.28) seen among remdesivir group. While no difference on 28 days mortality rate; discharge rate; overall adverse effect. Longer course (10 days) of remdesivir showed higher discharge rate at day 14 (OR 2.11, CI 1.50-2.97), but there are significantly higher rates of serious adverse effects, and drug discontinuation than the shorter course. Conclusion Remdesivir showed a better 14 days mortality profile, clinical recovery, and discharge rate. Overall clinical improvement and clinical recovery were earlier among remdesivir group.

Title page

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Research Question

Research Question: Does remdesivir safely improve the clinical outcome in patients suffering from COVID-19?

ABSTRACT

Aim

COVID-19 outbreak spread all over the world and created a public health catastrophe. Here, we have aimed to conduct a systematic review and meta-analysis on remdesivir use for COVID-19.

Methods

We searched Pubmed, Pubmed Central, Scopus, Embase, clinicaltrials.gov, and preprint sites and identified ten studies for qualitative and four studies for quantitative analysis using PRISMA guidelines. The quantitative synthesis was performed using fixed and random effect models in RevMan 5.4. Heterogeneity was assessed using the I-squared (I^2) test.

Results

Comparing remdesivir group with placebo or standard of care (SOC) group, remdesivir reduces 14 days mortality (OR 0.61, CI 0.41- 0.91), need of mechanical ventilation (OR 0.73, CI 0.54-0.97), and overall severe adverse effects (OR 0.69, 95% CI 0.54 to 0.88). There is better clinical improvement on day 28 (OR 1.59, CI 1.06- 2.39); day 14 clinical recovery (OR 1.48, CI 1.19-1.84); day 14 discharge rate (OR 1.41, CI 1.15-1.73) among remdesivir groups. Earlier clinical improvement (MD -2.51, CI -4.16 to -0.85); and clinical recovery (MD -4.69, CI -5.11 to -4.28) seen among remdesivir group. While no difference on 28 days mortality rate; discharge rate; overall adverse effect.

Longer course (10 days) of remdesivir showed higher discharge rate at day 14 (OR 2.11, CI 1.50-2.97), but there are significantly higher rates of serious adverse effects, and drug discontinuation than the shorter course.

Conclusion

Remdesivir showed a better 14 days mortality profile, clinical recovery, and discharge rate. Overall clinical improvement and clinical recovery were earlier among remdesivir group.

Key-words: Remdesivir, COVID 19, therapeutic efficacy, severe acute respiratory syndrome coronavirus 2

1. Introduction

COVID-19 outbreak which was first seen in Hubei province of China in late December of 2019 has become a widespread pandemic. The infection is caused by a new strain of coronavirus which was later named as Severe Acute Respiratory Syndrome – Coronavirus 2 (SARS-CoV 2). The virus has spread all over the globe and created a public health catastrophe meanwhile dragging several countries into economic crisis. The symptoms of infection range from mild viral illness symptoms including sore throat, headache, cough, fever to severe symptoms of pneumonia and ARDS. As of August 28 2020, 24 million cases have been confirmed and more than 800,000 deaths have been recorded due to COVID-19 [1]. However, a lack of standardized treatment makes the situation even more frightful. While several trials are being conducted everywhere there are no specific answers yet. Remdesivir is being used as one of the repurposed drugs in combating the illness all around the world.

Remdesivir, a nucleotide analogue pro-drug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2 [2]. This agent was originally evaluated in 2014 to thwart the Ebola outbreak. Subsequent evaluation by numerous virology laboratories demonstrated the ability of remdesivir to inhibit coronavirus replication, including SARS-CoV-2 [3]. As a nucleoside analog, remdesivir acts as an RNA dependent RNA polymerase (RdRp) inhibitor, targeting the viral genome replication process. The RdRp is the protein complex coronaviruses use to replicate their RNA-based genomes. After the host metabolizes remdesivir into active NTP, the metabolite competes with adenosine triphosphate (ATP: the natural nucleotide normally used in this process) for incorporation into the nascent RNA strand. In addition, the drug is believed to outpace the proofreading property of the virus, thus maintaining the antiviral activity [4], [5]. The WHO has considered this drug as one of the promising therapeutics against fighting COVID-19. Multiple clinical trials are underway on the use of remdesivir for treatment of COVID-19 in the USA and all around the world [6].

We aimed to search for clinical evidence to support the use of remdesivir regarding its safety and side effects to actually find out whether the drug is a real game changer or just another drug being used in vain.

2. Objective

To assess therapeutic efficacy in terms of clinical improvement and recovery, treatment outcome, need for mechanical ventilation and respiratory support, along with side effects following treatment with remdesivir in COVID-19.

3. METHODS

PRISMA guideline was used for our systematic review [7].

3.1 Criteria for considering studies for this review

3.1.1 Types of studies

We included the studies focusing on mortality rate, clinical improvement and recovery, discharge rate, adverse effects, mechanical ventilation, and respiratory support, mean difference of clinical improvement as well recovery among patients taking remdesivir compared to the patients receiving standard of care alone. Also we included studies comparing longer regimen and shorter regimen of remdesivir comparing above outcomes.

3.1.2 Types of participants

We included patients diagnosed with COVID-19 who received remdesivir in addition to the standard of care (SOC) or only receiving standard of care or placebo with comparison made with remdesivir group.

3.1.3 Types of interventions

Our treatment arm consists of patients taking remdesivir along with the SOC while the control arm consists of patients receiving SOC or placebo.

3.1.4 Types of outcome measures

For our quantitative analysis, mortality, clinical improvement and recovery, discharge rate, mechanical ventilation, and respiratory support, adverse effects, mean difference of clinical improvement as well recovery and treatment outcome at day 14 and day 28 among the treatment and control group that occurred during treatment were outcomes of interest.

3.1.5 Outcomes

We compared mortality, clinical improvement and recovery, discharge rate, mechanical ventilation, and respiratory support, adverse effects, mean difference of clinical improvement as well recovery and treatment outcome at day 14, and day 28 between treatment and control arms. Also, we compared the longer regimen and shorter regimen of remdesivir for above outcomes.

3.2 Search methods for identification of studies

Pubmed, PubMed Central, Embase, Scopus, and preprint servers like medRxiv and bioRxiv were accessed by our reviewers (PB and DBS) who independently searched and evaluated the quality of the studies till August 25, 2020. We filtered the studies using COVIDENCE and extracted data for quantitative and qualitative synthesis. Any potential conflict was solved taking the final opinion of another reviewer (SK). Another reviewer (ER) assessed the risk of bias and cross-checked all the selected studies.

3.2.1 Electronic searches

We have documented the detailed search strategy in Supplementary file no. 1.

3.3 Data collection and analysis

We extracted the data for quantitative synthesis through COVIDENCE and did the analysis using RevMan 5.4. Assessment of heterogeneity was done using the I-squared (I^2) test. We used a random/fixed effect for pooling of selected studies.

3.3.1 Selection of studies

We have included RCTs, prospective, and retrospective observational studies in which the patients received remdesivir for the treatment of COVID-19 in the qualitative analysis. For the quantitative analysis, we included only RCTs with a treatment arm and a control arm. We excluded studies in which remdesivir was used for treatment among the pediatric age group, pregnant women, patients with AIDS, end-stage liver disease, and cancer in the entire study population. We excluded meta-analysis, reviews, protocols, in-silico studies, AI-based simulation studies, and the studies in which the outcome was not properly defined among the patients treated with remdesivir.

3.3.2 Data extraction and management

We evaluated the quality of studies thoroughly and also took into account only the outcomes that were of our interest.

3.3.3 Assessment of risk of bias in included studies

We used the Cochrane ROB 2.0 tool for analysis of our RCTs shown in figure 1 [8]. We used the NHLBI (National Heart, Lung, and Blood Institute) quality assessment tools to assess the risk of bias in our prospective and retrospective observational studies (Table 1) [9]. We used RevMan 5.4 for creating a summary of biases for RCTs using the Cochrane ROB 2.0 tool.

Figure 1 : Risk of bias assessment of trials

Table 1: NHLBI assessment of bias for observational studies

3.3.4 Assessment of heterogeneity

TheI-squared (I^2) test was used for the assessment of heterogeneity. We interpreted the I-squared (I^2) test done based on the Cochrane Handbook for Systematic Reviews of Interventions as follows[15]: -

i) 0% to 40%: might not be important

ii) 30% to 60%: may represent moderate heterogeneity

iii) 50% to 90%: may represent substantial heterogeneity

iv) 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P-value from the chi-squared test, or a confidence interval for I^2)."

3.3.5 Assessment of reporting biases

Reporting bias was checked by prefixed reporting of the outcome.

3.3.6 Data synthesis

Statistical analysis was performed using RevMan 5.4 software. Risk Ratio (RR)/ Odds Ratio (OR) was used for outcome estimation whenever appropriate with 95% Confidence Interval (CI). The fixed/random-effects model was used according to heterogeneities. We analyzed the mean differences among the two groups for the duration of clinical improvement and recovery using the median, sample size, and interquartile range whenever the means and standard deviations were not provided in the study [16].

3.3.7 Subgroup analysis and investigation of heterogeneity

We used the random effect model, in cases of heterogeneity.

3.3.8 Sensitivity analysis

We did not run sensitivity analysis being there were only three RCTs comparing remdesivir with SOC and two only comparing shorter and longer regimen of remdesivir. Also there is low-moderate heterogeneity in most fields of our analysis so sensitivity analysis was not used.

4. RESULTS

A. Qualitative synthesis

We identified a total of 5573 studies after electronic database searching. We removed 600 duplicates. Screening of the title and abstracts of 4973 studies was done. We excluded 4942 studies and checked 31 articles for full-text eligibility. We excluded 21 studies with definite reasons mentioned in the PRISMA flow diagram in figure 2. At last, 10 studies were selected for qualitative analysis. A discussion of these studies is done in table 2.

Figure 2: PRISMA flow chart

Table 2: Qualitative analysis

B. Quantitative synthesis

Overall 4 RCTs are included in the quantitative synthesis.

4.1. Treatment outcome

We have compared outcomes of randomized studies with different duration of remdesivirversus placebo or standard of care (SOC). Mortality rate, clinical improvement ([?]2-point improvement in the ordinal score), clinical recovery (an improvement from a baseline score of 2 to 5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7 in the ordinal score),and discharge rate were our primary outcome variables. Development of adverse effects (severe, overall and grade [?]3 adverse event), invasive and non-invasive mechanical ventilation requirement, and mean duration of clinical recovery and improvement were our secondary outcome variables between remdesivir versus placebo or standard of care (SOC) and shorter (5 days) versus longer (10 days) use ofremdesivir. Among the included studies meta-analysis, we found there is low-high heterogeneity, may

be due to different study design, biological variability among studies, and risk of bias among studies that could not be omitted fully.

4.1.1 Remdesivir versus placebo or standard of care: Mortality rate

The meta-analysis of odds ratios (OR) for remdesivir compared with placebo or SOC using fixed effect model among three randomized studies showed that remdesivir reduces 14 days mortality (OR 0.61, 95% CI 0.41 to 0.91; participants = 1688; studies = 3; I^2 = 0%). Meanwhile, there is no significant difference between two groups for 28 days mortality (OR 1.02, 95% CI 0.50 to 2.06; participants = 629; studies = 2; I^2 = 0%) (Fig. 3).

Figure 3. Forest plot for mortality comparing remdesivir versus placebo or standard of care

4.1.2 Remdesivir versus placebo or standard of care: Clinical improvement and recovery

Meta-analysis for clinical improvement ([?]2-point improvement in ordinal score) showed slight improvement with statistical significance only in day 28. (Day 14; OR 1.45, 95% CI 1.00 to 2.08; participants = 629; studies = 2; I^2 = 0%; Day 28; OR 1.59, 95% CI 1.06 to 2.39; participants = 629; studies = 2; I^2 = 0%) (Fig. 4). Similarly, there is clinically significant clinical recovery in day 14 among remdesivir groups compared to placebo or SOC (OR 1.48, 95% CI 1.19 to 1.84; participants = 1452; studies = 2; I^2 = 0%) (Fig. 5).

Figure 4. Forest plot for clinical improvement comparing remdesivir versus placebo or standard of care

Figure 5. Forest plot for clinical recovery comparing remdesivir versus placebo or standard of care

4.1.3 Remdesivir versus placebo or standard of care: Discharge rate

Result on discharge rate showed increased discharge rate among remdesivir group both in 14 days and 28 days but it is statistically significant for 14 days only (day 14; OR 1.41, 95% CI 1.15 to 1.73; participants = 1688; studies = 3; I^2 = 0%; day 28; OR 1.35, 95% CI 0.91 to 2.02; participants = 629; studies = 2; I^2 = 53%) (Fig. 6).

Figure 6. Forest plot for discharge rate comparing remdesivir versus placebo or standard of care

4.2 Remdesivir versus placebo or standard of care: Adverse effects

The meta-analysis of three randomized controlled trials showed that the odds of having severe adverse effects is less among remdesivir group (OR 0.69, 95% CI 0.54 to 0.88; participants = 1688; studies = 3; I^2 = 0%) though odds for the development of overall adverse effect (OR 1.10, 95% CI 0.70 to 1.72; participants = 1688; studies = 3; I^2 = 74%) and grade [?]3 adverse event (OR 0.85, 95% CI 0.52 to 1.38; participants = 629; studies = 2; I^2 = 32%) among two groups is statistically insignificant (Fig. 7).It is also important to note that the discontinuation of the drug(due to adverse effects in patients) is not significant among the groups. (OR 1.26, 95% CI 0.50 to 3.19) (Supplementary file 3. Fig. 1).

Figure 7. Forest plot for adverse events comparing remdesivir versus placebo or standard of care

4.3 Remdesivir versus placebo or standard of care: Mechanical ventilation and respiratory support

Meta-analysis of baseline mechanical ventilation and respiratory support among included studies showed no statistical differences between two arms (OR 0.87, 95% CI 0.71 to 1.06; participants = 2991; studies = 5; I^2 = 16%). Also there is no difference for both NIMV and high-flow oxygen (OR 1.01, 95% CI 0.76 to 1.34; participants = 1692; studies = 3; I^2 = 0%) and IMV or ECMO (OR 0.76, 95% CI 0.57 to 1.00; participants = 1299; studies = 2; I^2 = 0%) (Supplementary file 3. Fig. 2).

But, at 14 days, the need for mechanical ventilation and respiratory support is significantly lower among remdesivir groups (OR 0.73, 95% CI 0.54 to 0.97; participants = 3377; studies = 6; I^2 = 27%). On subgroup analysis the result support for IMV or ECMO requirement (OR 0.69, 95% CI 0.49 to 0.97; participants =

1689; studies = 3; I^2 = 49%). While for NIMV and high-flow oxygen it is of no statistical significance (OR 0.84, 95% CI 0.49 to 1.45; participants = 1688; studies = 3; I^2 = 16%) (Fig. 8).

Figure 8. Forest plot for day 14 ventilation and respiratory support comparing remdesivir versus placebo or standard of care

4.4 Remdesivir versus placebo or standard of care: Mean differences of duration of clinical improvement and recovery

Meta-analysis on clinical improvement ([?]2-point improvement in ordinal score) showed clinical improvement among remdesivir group (MD -2.51, 95% CI -4.16 to -0.85; participants = 629; studies = 2; I^2 = 10%) approximately 2.5 days earlier. While clinical recovery (an improvement from a baseline score of 2-5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7 in the ordinal score) was seen about 4.5 days earlier among remdesivir group (MD -4.69, 95% CI -5.11 to -4.28; participants = 1452; studies = 2; I^2 = 97%) (Fig. 9).

Figure 9. Forest plot of mean differences of duration of clinical improvement and recovery among remdesivir group versus placebo or SOC

4.5 Treatment outcome at day 14: Remdesivir shorter (5 days) vs longer (10 days) course of treatment

Meta-analysis comparing the longer 10 days course of remdesivir with shorter five days course showed higher discharge rate at day 14 (OR 2.11, 95% CI 1.50 to 2.97; participants = 781; studies = 2; I^2 = 96%). But there is significantly higher rates of serious adverse effects (OR 1.77, 95% CI 1.19 to 2.65; participants = 781; studies = 2; I^2 = 20%), grade [?]3 adverse event (OR 1.53, 95% CI 1.09 to 2.16; participants = 781; studies = 2; I^2 = 0%), and drug discontinuation due to medication intolerance (OR 2.74, 95% CI 1.06 to 7.07, participants = 781, studies = 2, I^2 = 0%) among longer (10 days) course than shorter (5 days) treatment group. Also IMV or ECMO requirement is higher among longer (10 days) course group (OR 2.34, 95% CI 1.26 to 4.35, participants = 781, studies = 2, I^2 = 0%) than shorter (5 days) remdesivir group.

There is no statistical significance among two groups for overall 14 days mortality rate (OR 1.41, 95% CI 0.73 to 2.72, participants = 781, studies = 2, I^2 = 0%), clinical improvement at 14 days (OR 0.79, 95% CI 0.58 to 1.07, participants = 781, studies = 2, I^2 = 48%), clinical recovery (OR 0.75, 95% CI 0.55 to 1.02, participants = 781, studies = 2, I^2 = 31%), overall adverse effects (OR 1.26, 95% CI 0.93 to 1.69, participants = 781, studies = 2, I^2 = 0%), and NIMV or high flow oxygen requirement (OR 0.78, 95% CI 0.34 to 1.77, participants = 781, studies = 2, I^2 = 58%) (Fig 10).

Figure 10. Forest plot of treatment outcome at day 14: Remdesivir shorter (5 days) vs longer (10 days) course of treatment

C. Clinical trials

A total of 48 trials for the assessment of Remdesivir on COVID-19 has been registered until now in ClinicalTrials.gov (ClinicalTrials.gov) (Supplementary file 4.) [6]. In most cases,these trials are being conducted with the primary outcome of time to recovery, mortality, clinical improvement, and need for mechanical ventilation. Including the United States (23 trials), France (4 trials),a total of 15 countries (among the locations provided) are managing such trials around the globe. One of them in France has an enrollment of 6 hundred thousand participants as the largest type. Total of 38 trials are clinical trials while the rest of the trials are of observational types or expanded access. Twenty-six of such trials are recruiting participants. A total of 10 trials are not yet recruiting participants, whereas 1 trial is active but not recruiting participants. A trial run in the US is in a status of enrolling by invitation. Among the rest, 2 are available and 1 each is withdrawn, suspended and terminated.

5. Discussion

Although multiple studies are conducted around the world there is no specific treatment that proves to be

efficacious with minimal adverse effects. To obtain precise evidence to date, this meta-analysis is conducted with available four RCTs to gauge the effectiveness of remdesivir in comparison to placebo or standard of care.

Our meta-analysis of odds ratio showed reduced 14-day mortality (OR 0.61, 95% CI 0.41 to 0.91) in patients taking remdesivir for ten days, whereas no significant difference in 28 days mortality between remdesivir groups and SOC or placebo (OR 1.02, 95% CI 0.50 to 2.06). In contrast, Piscayo et al. showed no reduction of all-cause mortality in 14 days (RR 0.71, 95% CI 0.39 to 1.28) [21]. This may be due to inclusion of data from Spinner CD et al. in the present meta-analysis, which was not there in Piscayo et al[21]. Meta-analysis of clinical recovery on day 14 and 28 were clinically and statistically significant in favor of patients taking remdesivir in comparison to placebo or standard of care (day 14: OR 1.48, 95% CI 1.19 to 1.84; day 28: OR 2.09, 95% CI 1.09 to 4.03). The findings are concurrent with Piscoya et al.[21]. Findings on discharge rate on day 14 and 28 were higher among the remdesivir group, but it is statistically insignificant on day 28. Analysis of clinical improvement showed approximately 2.5 days earlier improvement among the Remdesivir group than SOC. Zhu et al also showed similar findings with the discharge rate that was reflective of the patient's recovery and clinical outcome [22]. A higher discharge rate was seen with 10 days use of remdesivir in comparison to 5 days. However, the difference in clinical improvement was not significant with 5 days and 10 days' use of drugs.

Severe adverse effects occurrence was less with remdesivir use in comparison with placebo or SOC, but its use for 10 days showed increased severe adverse effects, grade [?]3 adverse effect, and drug discontinuation in comparison with 5 days use. The overall adverse effect was less with placebo but it was statistically insignificant. Alexander et al.study also showed less severe adverse effect with remdesivir use with fixed-effect modeling but this result appeared statistically insignificant with random-effect modeling in their study [23].

Based on our meta-analysis, the need for mechanical ventilation and respiratory support at day 14 was significantly less with remdesivir, which was also supported with subgroup analysis among IMV and ECMO receiving patients, whereas among NIMV and high-flow oxygen receiving patients it was of no significance. Also, the 10 days course of the drug showed the increased requirement of ECMO and IMV in contrast to the 5 days drug course. Piscoya et al. study showed no significant decrease in the requirement of invasive ventilation with remdesivir (RR 0.57, 95% CI 0.23 to 1.42) [21].

In present meta-analysis, remdesivir showed a statistically significant reduction in 14-day mortality, speedy clinical improvement/ recovery leading to discharge, less requirement of the ventilator with a lesser degree of severe adverse events compared with placebo or SOC. Alike remdesivir many other drugs were repurposed as candidate treatment options for COVID-19. A study was done by Shrestha et al. on favipiravir- another potential candidate drug that showed significant results on clinical improvement at day 14 (RR 1.41, 95% CI 1.10 to 1.80) [24]. Many other potential treatment options like corticosteroids, convalescent plasma therapy,and hydroxyl-choloroquine showed mixed results in individual studies.

The available RCTs and meta-analysis still show a contrasting outcome with remdesivir. Although we have included four RCTs, they have several limitations, and also, the presence of heterogeneity among studies.Also, non-uniform treatment options lead to some difficulties comparing them. Few evident biases and issues were due to lack of complete follow-up, early reporting, and additional use of several therapeutic agents as supportive care. These all lead to some discrepancy in the study results and uncertainty on findings regarding the result of remdesivir use. Safety and efficacy of remdesivir in COVID-19 patients is still dubious. Henceforth, we believe that these findings should be supported by undergoing large scale double-blinded RCTs to increase the confidence of remdesivir use in COVID-19.

6. Conclusion

Remdesivir has been shown to enhance recovery with reduced oxygen support and better clinical outcome and decrease mortality among patients with COVID 19. However, the current studies are mostly open-label studies with a small sample size. Despite early promise, further ongoing large scale trials results should be

awaited to make a full decision.

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Figure legends

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Figure 2: PRISMA flow chart

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7. References:-

1. Worldometer. Coronavirus Cases. *Worldometer* . 2020:1-22.

2. Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *New England Journal of Medicine* . 2020;382(24):2327-2336. doi:10.1056/NEJMoa2007016

3. Eastman RT, Roth JS, Brimacombe KR, et al. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. *ACS Central Science* . 2020;6(5):672-683. doi:10.1021/acscentsci.0c00489

4. Amirian ES, Levy JK. Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses. *One Health* . 2020;9:100128. doi:10.1016/j.onehlt.2020.100128

5. Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Götte M. The antiviral compound remdesivir potently inhibits RNAdependent RNA polymerase from Middle East respiratory syndrome coronavirus. *Journal of Biological Chemistry* . 2020;295(15):4773-4779. doi:10.1074/jbc.AC120.013056

6. Search of: Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation Studies | Coronavirus - List Results - ClinicalTrials.gov.*https://clinicaltrials.gov/ct2/results?cond=Coronavirus&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&Search=Apply*. Accessed August 29, 2020.

7. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ (Clinical research ed)* . 2009;339. doi:10.1136/bmj.b2700

8. RoB 2.0: A revised tool to assess risk of bias in randomized trials [webinar] | Cochrane Training.*https://training.cochrane.org/resource/rob-20-webinar*. Accessed August 28, 2020.

9. Study Quality Assessment Tools | NHLBI, NIH.*https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools*. Accessed August 28, 2020.

10. Anderson MR, Bach PB, Baldwin MR. Hospital length of stay for severe COVID-19 patients: implications for Remdesivir's value. *medRxiv* . August 2020:2020.08.10.20171637. doi:10.1101/2020.08.10.20171637

11. Antinori S, Cossu MV, Ridolfo AL, et al. 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;158:104899. doi:10.1016/j.phrs.2020.104899

12. Augustin M, Hallek M, Nitschmann S. Remdesivir for patients with severe COVID-19. *Internist* . 2020;61(6):644-645. doi:10.1007/s00108-020-00800-5

13. Olender SA, Perez KK, Go AS, et al. Remdesivir for Severe COVID-19 versus a Cohort Receiving Standard of Care. *Clinical Infectious Diseases* . July 2020. doi:10.1093/cid/ciaa1041

14. Pasquini Z, Montalti R, Temperoni C, et al. OUP accepted manuscript.*Journal of Antimicrobial Chemotherapy* . 2020. doi:10.1093/jac/dkaa321

15. Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training.*https://training.cochrane.org/handbook*. Accessed August 28, 2020.

16. Mean Variance Estimation.*https://web.archive.org/web/20181224162602/http:/www.comp.hkbu.edu.hk/˜xwan/median2m* Accessed August 29, 2020.

17. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Preliminary Report. *New England Journal of Medicine* . May 2020. doi:10.1056/nejmoa2007764

18. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *New England Journal of Medicine* . May 2020. doi:10.1056/nejmoa2015301

19. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivirvs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA* . August 2020. doi:10.1001/jama.2020.16349

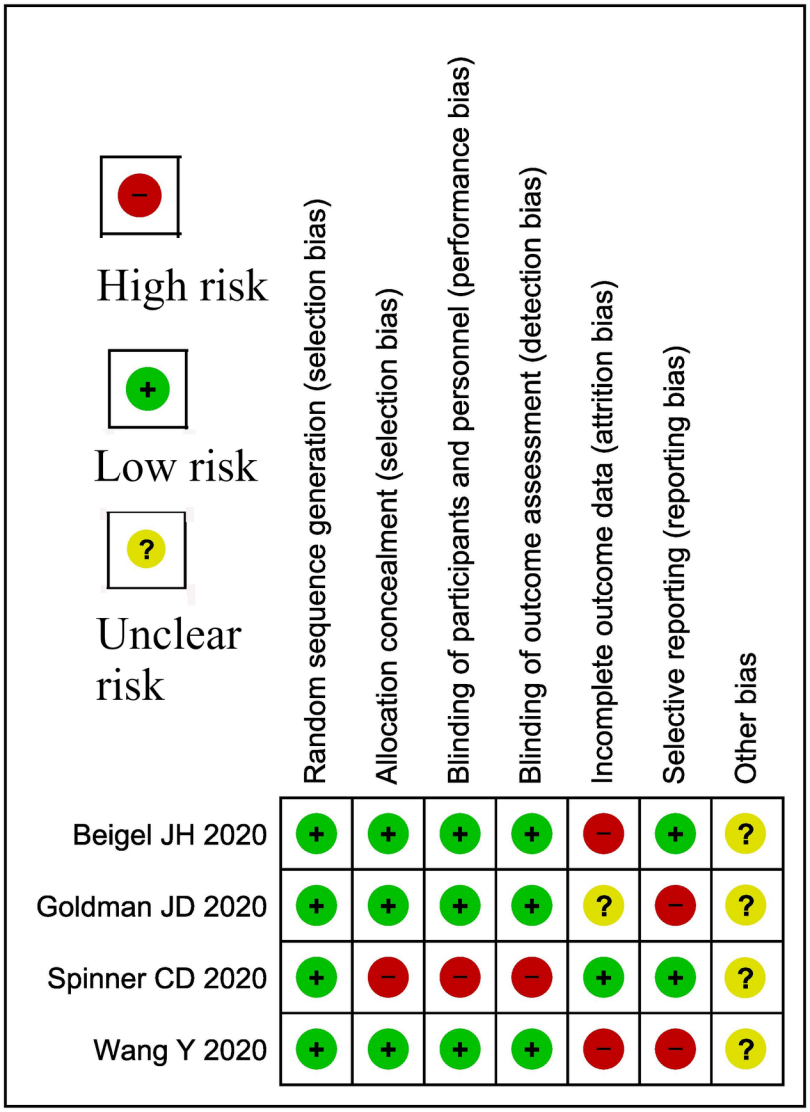
20. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet* . 2020;395(10236):1569-1578. doi:10.1016/S0140-6736(20)31022-9

21. Piscoya A, Ng-Sueng LF, Parra del Riego A, et al. Efficacy and harms of remdesivir for the treatment of COVID-19: a systematic review and meta-analysis. *medRxiv* . May 2020:2020.05.26.20109595. doi:10.1101/2020.05.26.20109595

22. Zhu Y, Teng Z, Yang L, et al. Efficacy and Safety of Remdesivir for COVID-19 Treatment: An Analysis of Randomized, Double-Blind, Placebo-Controlled Trials. *medRxiv* . June 2020:2020.06.22.20136531. doi:10.1101/2020.06.22.20136531

23. Alexander PE, Piticaru J, Lewis K, et al. Remdesivir use in patients with coronavirus COVID-19 disease: a systematic review and meta-analysis. *medRxiv* . May 2020:2020.05.23.20110932. doi:10.1101/2020.05.23.20110932

24. Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravirversus other antiviral or standard of care for COVID-19 treatment: A rapid systematic review and meta-analysis. July 2020. doi:10.21203/rs.3.rs-40775/v1



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`Figure 2. PRISMA diagram.docx` available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Figure 3. Forest plot for mortality (1).docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Figure 4. Forest plot for clinical improvement.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Figure 5. Forest plot for clinical recovery.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Figure 6. Forest plot for discharge rate.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Figure 7. Forest plot for adverse events.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Figure 8. Forest plot for day 14 ventilation and respiratory support.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Figure 9. Forest plot of mean differences of duration of clinical improvement and recovery.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Figure 10. Forest plot of treatment outcome at day 14.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Table 1. NHLBI table.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis

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Table 2. Qualititative table.docx available at https://authorea.com/users/329337/articles/479814-remdesivir-a-potential-game-changer-or-just-a-myth-a-systematic-review-and-meta-analysis