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Treatment of COVID-19 Patients with Remdesivir: A Systematic Review and Meta-Analysis

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Introduction

The ongoing Coronavirus Disease 2019 (COVID-19) pandemic has challenged the global health community in unprecedented ways. To date, the novel coronavirus has infected over 25.6 million people and caused more than 853,000 deaths globally [1]. Although 80% of cases manifest as mild disease, approximately 6% of individuals develop life-threatening pneumonia requiring intensive care [2,3]. In the absence of efficacious antivirals, current disease management mainly involves supportive care, including oxygen support and treatment with antibiotics. Many off-label or compassionate-use therapies, such as anti-parasitic agents, anti-inflammatory medications, and convalescent plasma, have also been tried in hospitalized patients [4,5]. Among the many drugs repurposed for the treatment of COVID-19 patients, remdesivir was identified early as a promising candidate.

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Remdesivir is a viral RNA-dependent, RNA polymerase inhibitor with demonstrable activity against a broad range of virus families, including the coronaviruses [6]. *In vitro* studies have shown that remdesivir has activity against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, in human airway epithelial cells [7]. Its use in human subjects is also supported by a favorable clinical safety profile, as reported based on observations in about 500 healthy volunteers and patients treated for Ebola virus infection [8]. In May 2020, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization to allow the use of remdesivir for the treatment of hospitalized patients with severe COVID-19. Many clinical trials assessing the therapeutic efficacy of this experimental drug have been undertaken [3,9,10]. However, conflicting results have been published.

The present study aimed to (1) review the existing scientific literature on treatment outcomes associated with remdesivir in COVID-19 patients and (2) perform a meta-analysis on available data to ascertain any possible therapeutic advantage of remdesivir over placebo or standard of care. Through these two goals we hope to use the data procured to determine if Remdesivir has benefit in treating COVID-19, and using this data we hope to improve how clinicians treat COVID-19.

Materials and methods

Search criteria

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. To identify studies for inclusion in this review, detailed search strategies were developed for the following four databases: PubMed (US National Library of Medicine, National Institutes of Health), Scopus (Elsevier), Web of Science (Clarivate Analytics), and Cochrane Library (Wiley). Databases were searched from date of inception through August 6, 2020. The search strategies used a combination of subject headings (e.g., MeSH in PubMed) and keywords for the following two concepts: COVID-19 and remdesivir. The PubMed search strategy was modified for the other three databases, replacing MeSH terms with appropriate subject headings, when available, and maintaining similar keywords. To identify additional articles, the reference lists of relevant articles were hand-searched, as well as citing articles. References were exported into the review management software, Covidence, for study selection.

Selection criteria

Only studies reporting on outcomes of patients with suspected or laboratory-confirmed COVID-19 treated with remdesivir were included. Studies were considered for inclusion if they were: (1) double- or single-blinded randomized controlled trials, (2) double- or single-blinded randomized comparison trials, (3) non-randomized controlled trials, and (4) prospective or retrospective observational studies. Abstracts were first independently assessed by two reviewers (YN and EY) to identify all articles that met the inclusion criteria. Conflicts were resolved by a third reviewer (SAN). Non-English studies, non-human studies, review articles, pre-prints, case series (<20 patients), and case reports were excluded. Studies evaluating the prophylactic role of remdesivir were also excluded.

Data extraction was performed by two reviewers (YN and EY) independently. Data extracted from studies include: author, country of publication, study design, study characteristics, patient demographics, and treatment outcomes. Disagreements were resolved in a discussion with a third reviewer (SAN). In instances of incomplete data, two attempts were made to contact the primary author via email for clarification or sharing of primary data. Included articles were critically appraised to assess level of evidence using the Oxford Center for Evidence-Based Medicine criteria [12].

The risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions version 6.0 [13]. The ROBINS-I tool was used specifically to evaluate non-randomized studies. Two authors (YN and EY) performed a pilot assessment on three studies to check for consistency of assessment. Both then performed independent risk assessments on the remaining studies. All disagreements were resolved by the way of discussion with a third author (SAN). For randomized studies, risk of bias items included the following: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The risk of bias for each aspect is graded as low, unclear, or high. For non-randomized studies, risk of bias items included the following: bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results. The risk of bias for each aspect is graded as low, unclear, or high.

Statistical analysis

Meta-analysis of selected studies with an Odds Ratio (OR) comparing Remdesivir (treatment) group versus a placebo (control) group was performed with Cochrane Review Manager 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, 2020, Copenhagen, Denmark). In addition, a meta-analysis of proportions was performed using MedCalc Statistical Software version 19.4.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020). Primary outcomes (mortality, adverse events, and clinical improvement on Day 7, 14, and 28) were expressed as pooled proportion with 95% Confidence Interval (CI). MedCalc used a Freeman-Tukey transformation [14] to calculate the weighted summary proportion under the fixed and random effects model [15]. Cochrane Review Manager uses the Mantel-Haenszel method for calculating the weighted summary OR under the fixed effects model [16]. Next the heterogeneity statistic is incorporated to calculate the summary OR under the random effects model. For meta-analysis of OR, the null hypothesis stated that there was no difference between treatment and control with respect to the treatment of patients with COVID-19. The pooled OR with 95% CI is given for both the fixed effects model and the random effects model. If the value 1 is not within the 95% CI, then the OR is statistically significant at the 5% level ($P<0.05$).

Both the fixed and random effects were used for meta-analysis of odds ratio and meta-analysis of proportions. Under the fixed effects model, it was assumed that all studies come from a common population and that the effect size (OR) was not significantly different among the trials. Under the random effects model, the true effects in the studies are assumed to vary among studies, and the summary effect is the weighted average of the effects reported in the different studies [17]. This assumption was tested by the heterogeneity test, or I^2 statistic. If this test yielded a low P value ($P<0.05$), then the fixed effects model was invalid. In this case, the random effects model was more appropriate, in which both the random variation within

the studies and the variation among the different studies are incorporated. Finally, a comparison of weighted proportions was done to compare outcomes (mortality, adverse events, and clinical improvement on Day 7, 14, and 28 improvement) between Remdesivir group vs Placebo group. A *P*-value<0.05 was considered indicative of statistical significance for all statistical tests.

Results

The literature search yielded a total of 505 unique articles after de-duplication. Screening by title and abstract excluded 478 articles. A full-text review of remaining studies further eliminated 22 articles, leaving a total of 5 articles [3,9,10,18,19] for inclusion in the final analysis. A diagram outlining the summary of the search process is shown in (Figure 1). Assessment of risk of bias is shown in (Figure 2).

Of the five included studies, three involved international collaboration. The remaining two originated from Italy and China. With respect to study design, three were randomized controlled trials and two were observational studies. A total of 1,784 patients were identified through this review. There were 1,143 males and 641 females but four were ultimately excluded from primary analysis due to missing data in one study. Treatment consisted of remdesivir for 1,184 patients and placebo for 600 patients. The therapeutic regimen for remdesivir was similar across all studies, consisting of 200 milligrams (mg) on the first day followed by 100 mg daily for nine additional days. Descriptive features and reported results of included studies are summarized in (Tables 1 & 2).

Only studies that provided sufficient data on treatment outcomes were included in the meta-analysis. The present study pooled data from all five studies to examine three outcomes associated with the two treatment arms: (1) mortality, (2) adverse events, and (3) clinical improvement at 7, 14, and 28 days.

Summary of Findings

Mortality

Five studies reported data on mortality for 1,780 patients treated with remdesivir (n= 1,181) or placebo (n= 599). Meta-analysis of proportions revealed that 9.06% of patients who received remdesivir died compared to 10.68% of those treated with placebo. However, the difference in weighted proportions was not significant (p= 0.27) (Table 3). Meta-analysis of odds ratios (OR) showed that remdesivir conferred a mortality benefit over placebo (OR 0.65, 95% CI: 0.44 to 0.96) (Figure 3).

Adverse events

Five studies provided data on adverse events for 1,781 patients treated with remdesivir (n= 1,181) or placebo (n= 600). Meta-analysis of proportions demonstrated that 45.89% of patients in the experimental group experienced an adverse event compared to 31.83% in the placebo group. The difference in weighted proportions was significant (p<0.0001) (Table 4). Meta-analysis of ORs showed that subjects receiving remdesivir therapy were less likely to have an adverse event, but this was not statistically significant (OR 0.78, 95% CI: 0.61 to 1.01) (Figure 4).

Clinical improvement

Data from three studies was pooled to examine this therapeutic outcome for 668 patients treated with remdesivir (n= 590) or placebo (n= 78). Meta-analysis of proportions showed that a higher percentage of participants receiving remdesivir compared to placebo demonstrated clinical improvement on day 7 (23.24% *vs.* 2.56%), 14 (50.09% *vs.* 23.07%), and 28 (64.77% *vs.* 57.69%). The difference in weighted proportions was significant (p<0.0001) at all endpoints except on day 28 (p= 0.28) (Tables 5-7). Meta-analysis of ORs did not show any benefit in clinical improvement with remdesivir over placebo (Figures 5-7).

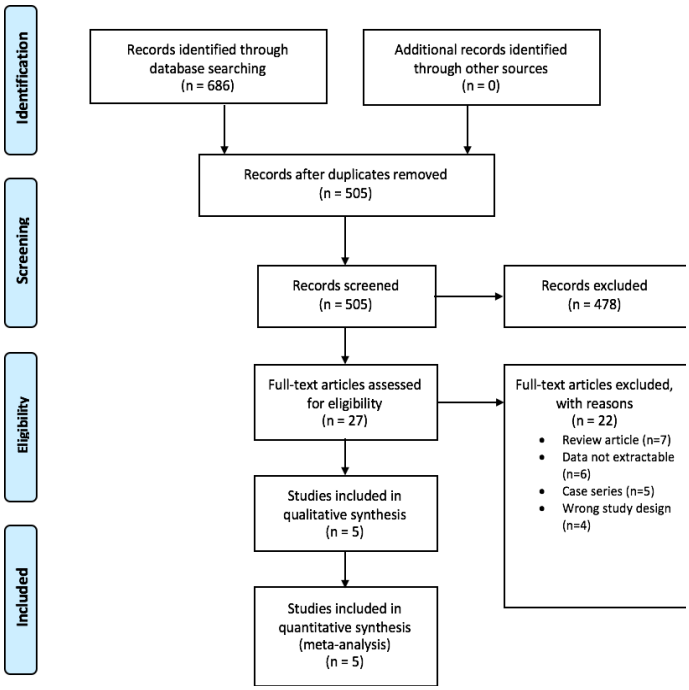

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

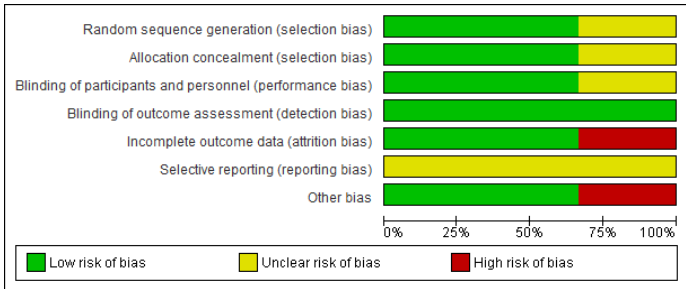

Figure 2a: Risk of bias graph for randomized studies: review authors' judgements about each risk of bias item presented as percentages across all included studies.

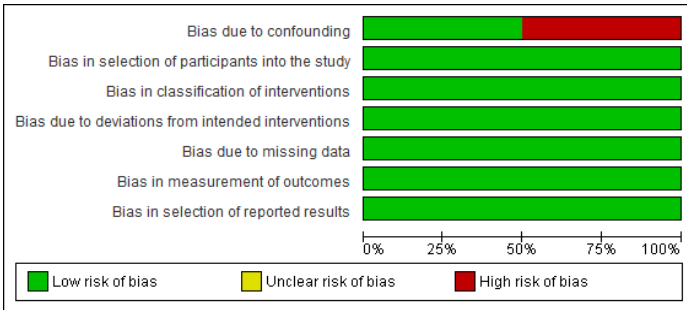

Figure 2b: Risk of bias graph for non-randomized studies: review authors' judgements about each risk of bias item presented as percentages across all included studies.

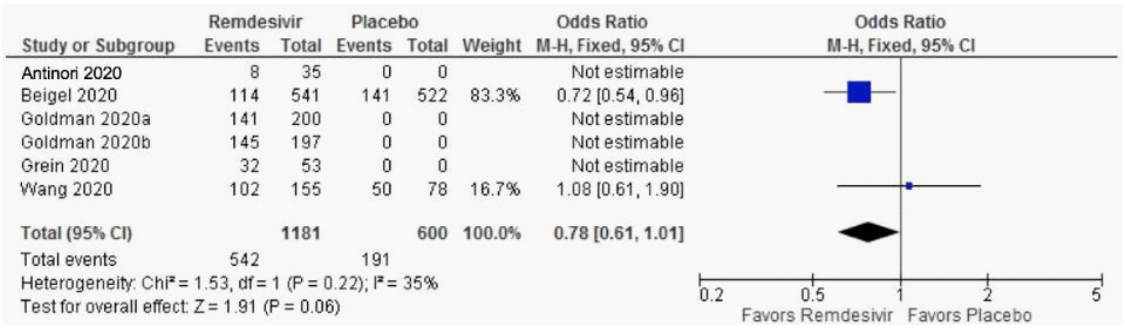

Figure 3: Forest plot of mortality events, CI: confidence interval; Goldman 2020a: Remdesivir (5 days); Goldman 2020b: Remdesivir (10 days).

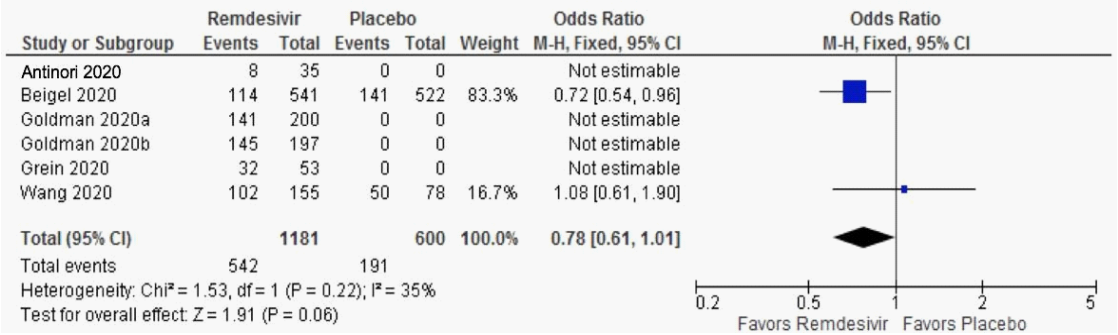

Figure 4: Forest plot of adverse events, CI: confidence interval; Goldman 2020a: Remdesivir (5 days); Goldman 2020b: Remdesivir (10 days).

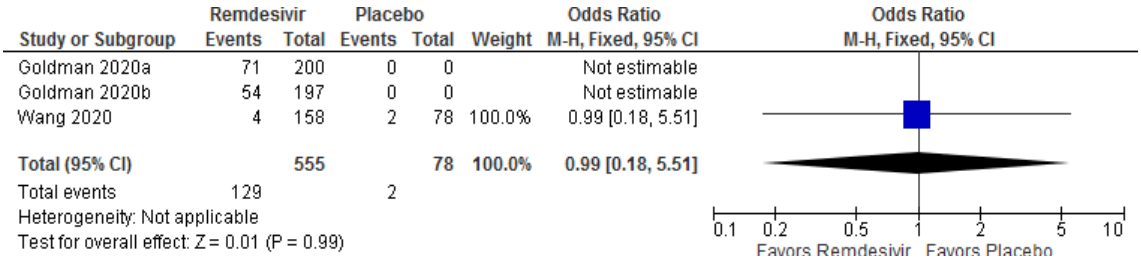

Figure 5: Forest plot of adverse events, CI: confidence interval; Goldman 2020a: Remdesivir (5 days); Goldman 2020b: Remdesivir (10 days).

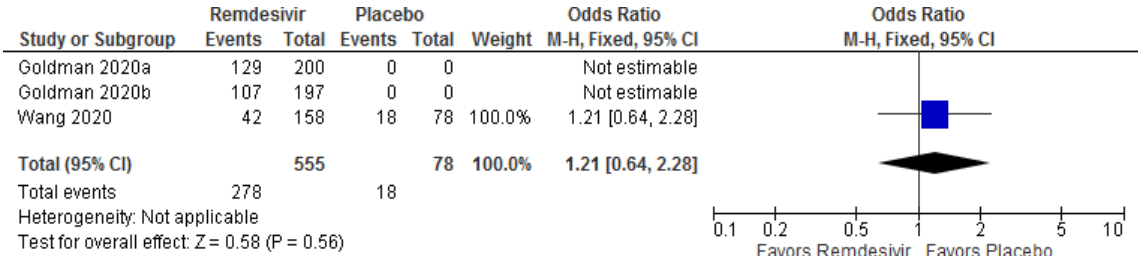

Figure 6: Forest plot of clinical improvement events on day 14, CI: confidence interval; Goldman 2020a: Remdesivir (5 days); Goldman 2020b: Remdesivir (10 days).

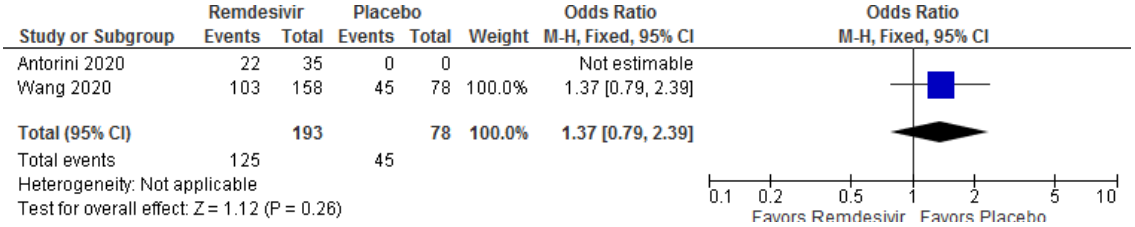

Figure 7: Forest plot of clinical improvement events on day 14, CI: confidence interval; Goldman 2020a: Remdesivir (5 days); Goldman 2020b: Remdesivir (10 days).

Table 1: Descriptive features of included studies.

Author	LOE	Country	Study Design	Comparison	Total Patients (n)	RDV group (n)	Placebo group (n)	Median Age [IQR], y	Male (n)
Antinori	3	Italy	Prospective observational	RDV alone	35	35	0	ICU: 60.5 [49.25- 63.75]; IDW: 64.0 [51.0-75.0]	26
Beigel	2	International	Double-blinded, placebo-controlled RCT	RDV vs. placebo	1063	541	522	58.9 ± 15*	684
Goldman	3	International	RCT	RDV x 5 d vs. RDV x 10 d	397	197	200	5-d RDV: 61 [50-69]; 10-d RDV: 62 [50-71]	253
Grein	3	International	Observational	RDV alone	53	53	0	64 [48-71]	40
Wang	2	China	Double-blinded, placebo- controlled RCT	RDV *vs.* placebo	236	158	78	65 [56-71]	140

D: Day; ICU: Intensive Care Unit; IDW: Infectious Disease Ward; IQR: Interquartile Range; LOE: Level Of Evidence; RCT: Randomized Controlled Trial; RDV: Remdesivir; Y: Year.

Table 2: Reported outcomes of included studies.

Author	Study endpoint(s)	Outcomes	Conclusion
Antinori	(1) Hospitalization status [1] on D10 and D28, (2) AE	(1) On D10, 22.2% and 35.3% of ICU and IDW patients, respectively, showed improvement in hospitalization status. On D28, 39.9% and 88.2% of ICU and IDW patients, respectively, demonstrated improvement. (2) AE leading to treatment discontinuation was observed in 33.3% (ICU) vs. 11.7% (IDW) of patients.	Data suggests RDV can benefit patients with SARS-CoV-2 pneumonia hospitalized outside the ICU, as proven by better clinical outcomes where AEs were less frequently observed.
Beigel	(1) Time to recovery [2], (2) mortality, (3) AE	(1) Median recovery time was significantly shorter in RDV group (11 d) vs. placebo (15 d). (2) Mortality by D14 was not significantly lower with RDV (7.1%) vs. placebo (11.9%). (3) Incidence of AE was not significantly different between RDV (21.1%) and placebo (27%) groups.	RDV was superior to placebo in shortening the time to recovery in adults hospitalized with COVID-19 and evidence of LRTI.
Goldman	(1) Clinical status on D14 [3], (2) mortality, (3) AE, (4) time to clinical improvement	(1) By D14, 64% in the 5-d group and 54% in the 10-d group achieved a clinical improvement of 2 points or more. (2) Mortality was numerically lower in the 5-d group (8%) than 10-day group (11%). (3) AEs were similarly reported between the two groups (70% vs. 74%). (4) Median time to recovery was not significantly different (10 d vs. 11 d).	In patients with severe COVID-19 not requiring mechanical ventilation, no significant difference in efficacy was observed between a 5-d course and a 10-d course of RDV.
Grein	(1) Clinical improvement [4], (2) mortality, (3) changes in oxygen- support requirements, (4) AE	(1) By 28 d follow-up, cumulative incidence of clinical improvement was 84%. (2) 13% died after completion of RDV treatment. (3) 68% showed an improvement in the category of oxygen support. (4) 32 AEs were reported, of which 12 were serious.	In this cohort of patients hospitalized for severe COVID-19 who were treated with compassionate- use RDV, clinical improvement was observed in 36 of 53 patients (68%).
Wang	(1) Time to clinical improvement up to D28 [5], (2) AE, (3) duration of oxygen therapy and hospital admission, (4) virological measures, (5) mortality at D28	(1) Time to clinical improvement was not significantly different between the 2 groups. (2) 102 (66%) and 50 (64%) patients in RDV and placebo groups, respectively, had an AE. (3) No significant differences in length of oxygen support and hospital admission were observed. (4) No significant difference in virological measures was observed. (5) Mortality was similar on D28.	Among adult patients admitted for severe COVID- 19, RDV was not associated with significant clinical benefits.

AE: Adverse Event; D: Day; D10/14/28: day 10/14/28; ICU: Intensive Care Unit; IDW: Infectious Disease Ward; LRTI: Lower Respiratory Tract Infection; RDV: Remdesivir

[1]Assessed by 7-category ordinal scale

[2]Assessed by 8-category ordinal scale

[3]Assessed on a 7-point ordinal scale

[4]Live hospital discharge, a decrease of at least 2 points from baseline on a modified 6-point ordinal scale, or both

[5]Time from randomization to point of decline of two levels on a 6-point ordinal scale of clinical status or hospital discharge, whichever came first.

Table 3: Mortality: meta-analysis and comparison of weighted proportions.

Intervention 1	Weighted proportion, %	n	Intervention 2	Weighted proportion, %	n	p-value
Remdesivir	9.06	1181	Placebo	10.68	599	0.27

Table 4: Adverse events: meta-analysis and comparison of weighted proportions

Intervention 1	Weighted proportion, %	n	Intervention 2	Weighted proportion, %	n	p-value
Remdesivir	45.89	1181	Placebo	31.83	600	<0.0001

Table 5: Clinical improvement on day 7: Meta-analysis and comparison of weighted proportions.

Intervention 1	Weighted proportion, %	n	Intervention 2	Weighted proportion, %	n	p-value
Remdesivir	23.24	555	Placebo	2.56	78	<0.0001

Table 6: Clinical improvement on day 14: Meta-analysis and comparison of weighted proportions.

Intervention 1	Weighted proportion, %	n	Intervention 2	Weighted proportion, %	n	p-value
Remdesivir	50.09	555	Placebo	23.07	78	<0.0001

Table 7: Clinical improvement on day 28: Meta-analysis and comparison of weighted proportions.

Intervention 1	Weighted proportion, %	n	Intervention 2	Weighted proportion, %	n	p-value
Remdesivir	64.77	193	Placebo	57.69	78	0.28

Discussion

The purpose of this review and meta-analysis was to examine the limited literature on the efficacy of remdesivir in the treatment of COVID-19, a viral illness characterized by progressively worsening severe pneumonia and Acute Respiratory Distress Syndrome (ARDS) that has resulted in a high mortality rate in hospitalized patients [2]. The present study found that treatment with remdesivir conferred a mortality benefit over placebo in COVID-19 patients. However, the results should be interpreted with caution due to the limitations imposed on each included study, as discussed below. Since well-designed studies are difficult to conduct during an ongoing pandemic, conclusive findings may remain elusive during the early phase of the outbreak.

We report on five global studies, two of which contributed most to our analysis; Beigel et al., [10] and Wang et al., [9]. Of the five articles these two were the only ones that compared the therapeutic efficacy of remdesivir to placebo and thus best demonstrated the mortality benefit of remdesivir. Neither one demonstrated that remdesivir had a mortality benefit [9,10]. Beigel et al., [10] found that on day 14, there was no significant lowering of mortality between remdesivir and placebo (7.1% *vs.* 11.9%). Wang et al., [9] found that the mortality rate between the two groups was also similar on day 28. Non-comparative trials contributed less to our analysis; Goldman et al. showed that the cohort treated with 5 days compared to 10 days of remdesivir had a lower mortality rate (8% *vs.* 10%) but the difference was not significant. The remaining two non-comparative studies [3,19] reported a similar mortality rate of 13-14% among patients treated with remdesivir.

The present meta-analysis demonstrated that a significantly higher proportion of patients treated with remdesivir experienced an adverse event compared to those receiving placebo (45.89% *vs.* 31.83%). Commonly reported adverse events associated with remdesivir treatment across the five studies include increased hepatic enzymes, anemia, renal impairment, and diarrhea/constipation. Serious adverse events, including ARDS, septic shock, multi-organ dysfunction, and cardiac arrest, reportedly ranged from 18-35 % [9,18]. Although the clinical profile of remdesivir has previously been studied [8], there is limited data concerning its safety and risks for drug interactions in COVID-19 patients, particularly those with underlying comorbidities and receiving other experimental therapies.

In terms of clinical improvement, our analysis showed that a significantly higher proportion of patients demonstrated benefit with remdesivir therapy compared to placebo on the seventh and fourteenth day but not on the twenty-eighth. The odds of improvement were not significantly different between the two groups at any measured interval. However, due to varying definitions of this outcome across all included studies, comparison of results was challenging. All studies used the ordinal scale to track clinical improvement. Two studies [9,19] used the six-point scale, two studies [3,18] used the seven-point scale and one [10] used an eight-point scale. Three studies [9,18,19] specified a two-point decline on the ordinal scale as an indicator of clinical improvement. Of note, the time to clinical improvement was assessed in the two placebo-controlled trials. While Wang et al., [9] demonstrated that time to clinical improvement was not significantly different between the two groups (21 *vs.* 23 days), the other [10] showed that median recovery time was

significantly shorter in the remdesivir group (11 *vs.* 15 days). When comparing the duration of remdesivir treatment, Goldman et al., [18] found that patients given 5 days compared to 10 days of therapy did not differ significantly in median time to recovery (10 days *vs.* 11 days).

We acknowledge that the articles included in our meta-analysis had some limitations. Two double-blinded, placebo-controlled trials contributed the most to our meta-analysis. Two of the remaining articles were non-comparative studies with a single treatment arm while the last compared two treatment arms consisting of remdesivir. Some limitations involved in these studies may have affected the outcomes of our data analysis. The study by Wang et al., was terminated early due to marked reductions in presenting cases due to successful public health efforts to curtail viral transmission. Therefore, it may have been underpowered to detect any therapeutic advantage using remdesivir versus placebo. Similarly, the trial conducted by Beigel et al., did not complete full enrollment due to the end of the COVID-19 outbreak, potentially contributing to the observed lack of benefit with remdesivir treatment. Furthermore, the study experienced early unblinding due to a shortened time to recovery observed in the remdesivir group compared to placebo. Future randomized, placebo-controlled trials with adequate sample sizes and statistical power should help clarify the efficacy and safety of remdesivir in COVID-19 patients.

Conclusion

During the early phase of the pandemic, remdesivir emerged as a promising therapeutic candidate and was repurposed for the treatment of COVID-19 patients. Although the present study demonstrated some clinical benefit with remdesivir use compared to placebo, no conclusive statements can be made due to several limitations. Future studies with improved methodological design are needed to verify the results presented herein.

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