

SHORT COMMUNICATION

Effectiveness of remdesivir for the treatment of hospitalized COVID-19 persons: A network meta-analysis

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Abstract

Several randomized clinical trials (RCTs) that investigated the effectiveness of remdesivir for the treatment of coronavirus disease-2019 (COVID-19) have generated inconsistent evidence. The present study aimed to synthesize available RCT evidence using network meta-analyses (NMAs). Both blinded and open-label RCTs in PubMed database from inception to 7 June 2020 that contained “remdesivir”, “Covid-19”, and “trial” in the abstracts conducted on hospitalized COVID-19 persons were identified and screened. The studies must have at least one remdesivir arm and evaluated one of the pre-specified outcomes. The outcomes were clinical improvement between days 10 to 15 after randomization and clinical recovery during the follow-up period. The identified literature was supplemented with relatively recent studies that were known to the researchers if not already included. Frequentist NMAs with random effects were conducted. Both 10-day and 5-day remdesivir regimens were associated with higher odds of clinical improvement (odds ratio [OR] of 10-day regimen: 1.35, 95% confidence interval [CI], 1.09-1.67); OR of 5-day regimen: 1.81, 95% CI, 1.32-2.45, and higher probabilities of clinical recovery (relative risk [RR] of 10-day regimen: 1.24, 95% CI, 1.07-1.43; RR of 5-day regimen: 1.47, 95% CI, 1.16-1.87 compared with placebo. Remdesivir may have clinical benefits among hospitalized COVID-19 persons.

KEYWORDS

COVID-19, improvement, network meta-analysis, recovery, remdesivir

1 | INTRODUCTION

The ongoing coronavirus disease-2019 (COVID-19) pandemic represents a major public health threat and health care burden globally.¹ Without approved pharmacological therapies,² several randomized clinical trials (RCTs) investigated the potential effectiveness of remdesivir for the treatment of COVID-19, which was already granted emergency use authorization for the disease by the United States Food and Drug Administration.² However, not all of these RCTs generated consistent evidence.³⁻⁵ As such, the present study aimed to synthesize available RCT evidence using network meta-analyses (NMAs).

2 | METHODS

Two researchers (Dan C and SJ) searched the PubMed database from inception to 7 June 2020 for the literature that contained “remdesivir”, “Covid-19”, and “trial” in the abstracts. Both blinded and open-label RCTs among hospitalized COVID-19 persons were included. To be eligible for inclusion, studies must have included at least one remdesivir group. We also required that the studies reported data on any of the predetermined outcomes. The primary outcome was clinical improvement between days 10 to 15 after randomization. The secondary outcome was clinical recovery. For the secondary outcome, the longest follow-up was used when studies

reported different study durations. The identified literature was supplemented with relatively recent studies that were known to the researchers if not already included. The risk of bias of studies was assessed by two researchers (YJ and Daqin C) independently using the Cochrane Collaboration risk of bias tool over the five domains of selection, performance, detection, attrition, and reporting.⁶

Data were independently extracted by two investigators (YJ and Daqin C) using prespecified forms. The types of information extracted from the studies included participant characteristics, sample sizes, inclusion criteria, interventions, follow-up periods, and outcomes data. The relative effect was evaluated using odds ratio (OR) for clinical improvement and relative risk (RR) for clinical recovery to accommodate differential reporting routines of the endpoints. When not presented in the original reports, ORs and RRs were calculated using data of sample sizes and event frequencies. When data were inadequate to calculate RRs, rate ratios were used instead.

Frequentist NMAs with random effects were conducted.⁷ I^2 was used to quantify cross-study heterogeneity and NMAs using full design-by-treatment interaction specifications were used to test network inconsistency.^{8,9} Sensitivity analyses were conducted by restricting the primary outcome to a minimum 2-score improvement in ordinal scales and excluding studies that did not contain patients with severe conditions.

All analyses were performed using Stata 15 (Stata Corp, College Station, Texas) and R 3.6.1. The study protocol was registered and available at International Prospective Register of Systematic Reviews (CRD42020190560).

3 | RESULTS

The initial search identified 13 publications. After screening for randomized clinical trials, two studies remained eligible.^{3,4} The list was manually supplemented with two relatively recent studies that were not indexed in PubMed by the time of searching.^{5,10,11} The four studies covered three comparators, namely, remdesivir 10-day treatment, remdesivir 5-day treatment, and placebo. The baseline characteristics of the included studies are listed in Table 1.

The four studies provided data from 2049 individuals on the primary outcome. A network graph is presented in Figure S1. The follow-up period ranged from 11 days to 15 days. Two of the studies exclusively recruited severe patients (defined in the footnote of Table 1), one study dominantly included severe patients (88.7%), and one study only enrolled moderate patients. The results of the base-case NMA are illustrated in Figure 1. According to the results, both 10-day (OR: 1.35, 95% confidence interval [CI], 1.09-1.67) and 5-day (OR: 1.81, 95% CI, 1.32-2.45) remdesivir therapies were associated with higher odds of clinical improvement. Also, the 5-day remdesivir treatment was associated with higher odds of clinical improvement when compared with the 10-day regimen (OR: 1.33, 95% CI, 1.01-1.76).

Results of sensitivity analyses are displayed in Figure S2. The ACCT-1 trial defined 1-point improvement in the ordinal scale as

TABLE 1 Characteristics of the studies that were included for analyses

Acronym/ identifier (reference)	Patient severity ^a	#Groups	Interventions	Samples sizes of groups (for clinical improvement)	Clinical outcome evaluation scale	Follow-up period for clinical improvement (d)	Clinical improvement definition	Follow-up period for clinical recovery (d)	Clinical recovery definition
Hubei study ³	Severe patients only	2	Remdesivir 10-d/ placebo	158/78	6-Category ordinal (1 = best)	14	2-Point improvement	28	Categories 1-2 ^b
ACCT-1 ⁴	88.7% severe patient	2	Remdesivir 10-d/ placebo	428/404 ^c	8-Category ordinal (1 = best)	15	1-Point improvement	29 ^d	Categories 1-3
SIMPLE- severe ⁵	Severe patients only	2	Remdesivir 10-d/ remdesivir 5-d	197/200	7-Category ordinal (7 = best)	14	2-Point improvement	14	Categories 6-7
SIMPLE-II ¹⁰	Moderate patients only	3	Remdesivir 10-d/ remdesivir 5-d/ placebo	193/191/200	7-Category ordinal (7 = best)	11	2-Point improvement	NA	NA

Abbreviation: NA, not available.

^aSevere patients were defined as those requiring mechanical ventilation, requiring supplemental oxygen, having an oxygen saturation by pulse oximetry (SpO₂) ≤ 94% on room air, having a respiratory rate ≥ 24 breaths/min, or having a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less. Moderate patients were those with evidence of pneumonia but without reduced oxygen levels.

^bThree individuals in the placebo arm of the Hubei study were in category 2 at randomization and, therefore, were not included in the analyses of the relative risk (RR).

^cThe numbers were calculated using data in Figure S1 of the original report in the reference.

^dThe study reported the rate ratio instead of the RR or numbers of events, failing the estimation of RR. Therefore, the rate ratio was used as an approximation of the RR.

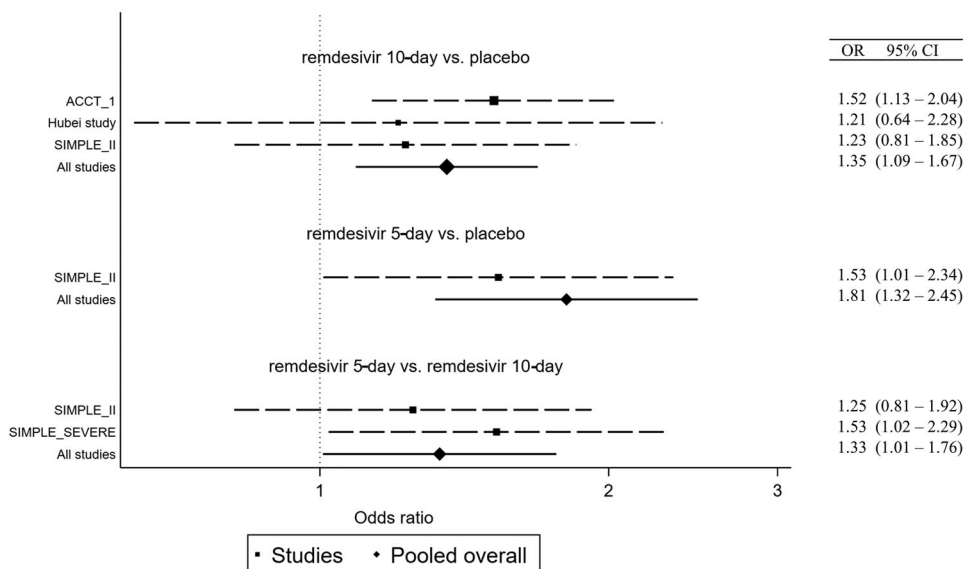


FIGURE 1 Base-case results of the clinical improvement NMA. CI, confidence interval; NMA, network meta-analysis; OR, odds ratio

clinical improvement and was dropped in the first sensitivity analysis. Compared with placebo, the 10-day regimen was insignificantly associated with higher odds of clinical improvement (OR: 1.20, 95% CI, 0.88–1.62) whereas the 5-day regimen continued to demonstrate significant effect (OR: 1.65, 95% CI, 1.17–2.35) in the first sensitivity analysis. In the second sensitivity analysis, The SIMPLE-II trial was not included because it only recruited individuals with moderate conditions. As in the base case, both 10-day (OR: 1.44, 95% CI, 1.12–1.86) and 5-day (OR: 2.21, 95% CI, 1.37–3.56) remdesivir regimens had significant benefits on clinical improvement compared with placebo in this specification.

Data on the same three treatments from three studies were included to analyze clinical recovery. For the ACCT-1 trial, the rate ratio was used to approximate the RR because the latter was not available. The results (Figure S3) showed that both 10-day (RR: 1.24, 95% CI, 1.07–1.43) and 5-day (RR: 1.47, 95% CI, 1.16–1.87) remdesivir regimens were associated with greater probabilities of clinical recovery.

Results related to I^2 , inconsistency tests, and risk of bias are provided in Table S1. We did not spot substantial heterogeneity or significant inconsistency in any analyses. The I^2 was 0.0% and 19.2% in the analyses of the two outcomes, respectively. The test of inconsistency in the analysis of the primary outcome was statistically insignificant ($P = .528$), whereas inconsistency was not applicable to the analysis of the secondary outcome because direct and indirect comparison data were not available for any pairs of contrast.

4 | DISCUSSION

In the present analysis, the effectiveness of remdesivir regimens in relation to placebo were evaluated using NMAs of RCTs. Our

findings showed that both 10-day and 5-day remdesivir treatments had positive effects on clinical improvement and clinical recovery. In addition, the 5-day treatment might be superior to the 10-day treatment with regard to clinical improvement. These results have important clinical implications. To the extent that it is accessible, remdesivir should be considered for clinical use among hospitalized patients with COVID-19. In particular, the 5-day regimen may be recommended among severe hospitalized individuals since it may have noninferior efficacy at the expense of fewer time and costs.

The individual studies provided mixed results of remdesivir effectiveness. In particular, at least one trial showed an absence of statistically significant clinical benefit of remdesivir.³ In the meantime, other trials suggested no difference between 10-day and 5-day remdesivir treatments.^{5,10} Such differential results might have been driven by heterogeneity in study design and sample sizes. The present study provided relatively comprehensive evidence to document the benefits of remdesivir among hospitalized Covid-19 persons as well as differential effects between 10-day and 5-day regimens. These results indicate that it may be advisable to prescribe the 5-day remdesivir regimen for the treatment of COVID-19.

The result of the sensitivity analysis when the study that only included moderate patients was excluded suggested that the point estimates of effects on clinical improvement associated with remdesivir regimens were higher than those in the base case. A potential cause was that the effect of remdesivir may be stronger among severe patients than in moderate patients.

Several limitations must be noted when interpreting the results. First, there was discrepancy in the definition of endpoints and reporting of effects. Specifically, the studies engaged scales using different numbers of points to gauge the scales and considered either 1-point or 2-point alleviation as clinical improvement. Such

differential scales would impact the estimated effect sizes. Second, the baseline severity of the participants varied across trials, which might compound the heterogeneity across trials. Although sensitivity analyses were conducted to mitigate the impacts of the first and the second limitations on the results, remaining consequences due to such complexity may exist. Finally, it has been suspected that remdesivir might demonstrate better efficacy if administered within 10 days of symptom onset compared with beyond that.³ However, data from the studies were not sufficient to conduct subgroup NMAs by timeliness of treatment for the outcomes that were specified in the present study. Future studies should try to fill such gaps.

5 | CONCLUSIONS

Remdesivir may have positive effects on clinical improvement and clinical recovery among hospitalized COVID-19 persons, and may be considered as a clinical option if accessible.

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CONFLICTS OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Conceptualization, design, data extraction, analysis, interpretation, and writing: YJ; data collection, data extraction, and analysis: Daqin C; literature identification and data collection: Dan C; interpretation, writing, and editing: YY; literature identification, data collection, and interpretation: SJ.

DATA AVAILABILITY STATEMENT

The data analyzed during the current study that support the findings of this study have been submitted for editorial and peer review and are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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