

BMJ Open Efficacy of remdesivir in patients with COVID-19: a protocol for systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background Despite global containment measures to fight the coronavirus disease 2019 (COVID-19), the pandemic continued to rise, rapidly spread across the world, and resulting in 2.6 million confirmed cases and 185 061 deaths worldwide as of 23 April 2020. Yet, there are no approved vaccines or drugs to make the disease less deadly, while efforts are underway. Remdesivir, a nucleotide-analogue antiviral drug developed for Ebola, is determined to prevent and stop infections with COVID-19, while results are yet controversial. Here, we aim to conduct a systematic review and meta-analysis of randomised controlled trials (RCTs) to evaluate the efficacy of remdesivir in patients with COVID-19.

Method and analysis We will search MEDLINE-PubMed, Embase, Cochrane Library, ClinicalTrials.gov and Google scholar databases for articles published as of 30 June 2020 and we will complete the study on 30 August 2020. We will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines for the design and reporting of the results. We will include RCTs that assessed the efficacy of remdesivir versus placebo or standard of care. The primary endpoint will be time to clinical recovery. The secondary endpoints will be proportion of participants relieved from clinical symptoms defined at the time (in hours) from initiation of the study treatment, all-cause mortality, discharged date, frequency of respiratory progression and treatment-emergent adverse events. RevMan V.5.3 software will be used for statistical analysis. Random effects model will be carried out to calculate mean differences for continuous outcome data and risk ratio for dichotomous outcome data between remdesivir and placebo or standard of care.

Ethics and dissemination There are no ethical considerations associated with this study as we will use publicly available data from previously published studies. We plan to publish results in open-access peer-reviewed journals and present at international and national conferences.

PROSPERO registration number CRD42020177953.

INTRODUCTION

Coronavirus diseases 2019 (COVID-19) is caused by a novel β -coronavirus which is named as SARS-CoV-2. SARS-CoV-2 shares 79% RNA sequence identity with severe

Strengths and limitations of this study

- This will be the first systematic review and meta-analysis to evaluate the efficacy of remdesivir for COVID-19, which is a newly originated deadly disease.
- Its compliance with the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols 2015 (PRISMA-P 2015) will ensure the quality of reporting.
- The use of a combination of multiple electronic databases will include all eligible articles and provide accurate conclusions.
- The use of rigorous subgroup and sensitivity analysis will identify possible reasons that may cause significant heterogeneity between studies.
- Its singular focus on one antiviral treatment may preclude decision-making and calls for network meta-analyses once trial results are made available.

acute respiratory syndrome coronavirus (SARS-CoV) and 50% genomic sequence identity with Middle East respiratory syndrome coronavirus (MERS-CoV) which caused a major outbreak since 2002 and 2012 in China and Saudi Arabia, respectively.¹⁻⁴ Despite global containment measures to fight the disease, the pandemic continued to rise, rapidly spread across the world, and resulting in 2.6 million confirmed cases and 185 061 deaths worldwide as of 23 April 2020.^{5 6} The outbreak of COVID-19 infection has a significant threat to international health, the economy, psychological stress and mental health worldwide.⁷⁻¹⁰ Yet, there are no approved vaccines or drugs to make the disease less deadly; implying that searching therapeutic options are critical issues to overcome the outbreak.^{11 12}

Studies are strongly underway to discover rapidly drug candidates for COVID-19, and studies are looking into repurposing drugs that have been used for the treatment of other diseases. As of 29 March 2020, there were 209

clinical trials registered in ClinicalTrials.gov for COVID-19 therapeutic studies and this number is estimated to go over 500.¹³ Currently, several drugs including remdesivir, hydroxychloroquine, chloroquine, ritonavir+lopinavir, Arbidol and interferon are under randomised controlled trials (RCTs) for efficacy and/or safety evaluations in patients with COVID-19 in different countries.^{14–19} Remdesivir (GS-5734) is among these investigational drugs and some studies reported promising results.^{19 20} Remdesivir is a nucleotide analogue intravenous prodrug developed by Gilead Sciences, an American biopharmaceutical company, for treatment of Ebola virus during the 2014 Ebola outbreak in Western Africa. Remdesivir shows broad-spectrum antiviral activity against many RNA viruses including SARS-CoV-2 through blocking RNA polymerase thereby terminating RNA transcription. A recent study led by the US National Institutes of Health (NIH) that involved two groups of six rhesus macaque experiment monkeys, with one group treated with remdesivir, revealed a significantly lowered COVID-19 disease progression due to remdesivir.²¹ According to a recent report of the US Centers for Disease Control and Prevention (CDC), in vitro and cell culture studies demonstrated broad-spectrum activity of remdesivir against coronavirus.²² Nucleoside analogues such as remdesivir can have multiple mechanisms of action, including lethal mutagenesis, obligate or non-obligate chain termination, and perturbation of natural nucleotide triphosphate pools via inhibition of nucleotide biosynthesis.^{23 24} In vitro, remdesivir inhibits all human and animal coronaviruses including SARS-CoV-2, and has shown antiviral and clinical effects in animal models of SARS-CoV-1 and MERS-CoV infections.^{25–29} Remdesivir was among the first treatments used in China as the outbreak emerges and it has been reported as potential treatment options for COVID-19 in the USA, China and Italy.^{14 16 30} Following the topline data from the randomised, double-blinded, placebo-controlled trial conducted by National Institute of Allergy and Infectious Diseases (NIAID),³¹ the

US Food and Drug Administration (FDA) has issued an emergency use authorisation (EUA) of the antiviral drug remdesivir for the treatment of patients with COVID-19.³² Although clinical trials^{31 33} have showed remdesivir as a treatment option for COVID-19, results are controversial. Thus, the proposed systematic review and meta-analysis of RCTs aims to synthesise existing evidence on the efficacy and safety of remdesivir in patients with COVID-19.

METHODS

We will conduct a systematic review and meta-analysis that will comply with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 guidelines for the design and reporting of the results³⁴ (see checklist in online supplementary additional file 1). The protocol has been registered at PROSPERO database, ID: CRD42020177953.³⁵

Data sources and searches

We will search MEDLINE/PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>), Embase (<http://www.embase.com/>), The Cochrane Library (<http://www.cochranelibrary.com/>), ClinicalTrials.gov (<https://www.clinicaltrials.gov/>) and google scholar (<https://scholar.google.com/>) databases for primary articles published as of 30 June 2020 and we will complete the study by 30 August 2020. We will perform hand search from the reference lists of a key articles to identify eligible RCTs and supplement the searching. We will include all potential RCTs that evaluated the efficacy of remdesivir versus placebo or standard of care in patients with COVID-19 with no limitations on the geographical location of studies but published in English language. We will do a rigorous search strategy using the key words including 2019 novel coronavirus, 2019-nCoV, coronavirus disease 2019, COVID-19, SARS-cov-2, severe acute respiratory syndrome-coronavirus-2, remdesivir, GS-5734, nucleotide-analogue, antiviral agents, randomized controlled trials,

Table 1 Search strategy for the MEDLINE-PubMed database

"Antiviral agents"		"Coronavirus disease 2019"	
OR		OR	
"Nucleotide-analogue"		"COVID-19"	"Randomized controlled trials"
OR	AND	OR	AND
"Remdesivir"		"Severe acute respiratory syndrome-coronavirus-2"	"RCTs"
		OR	
		"SARS-Cov-2"	
OR		OR	OR
		"2019 novel coronavirus"	
"GS-5734"		OR	"Clinical trials"
		"2019-nCoV"	

clinical trials and RCTs. Table 1 summarises the search strategy that we will applied in PubMed database, while details of this strategy that we will also adapt for other databases searches are described in online supplementary additional file 2 (table 1).

Eligibility criteria

We will formulate our participant's eligibility criteria using PICOS (participants, interventions, comparison, outcomes, and study designs) description model.³⁶

- Participants.
 - Patients with confirmed COVID-19.
 - Men and/or women of any age.
 - At any clinical stage of the disease, thus mild, moderate or severe/critical case.
 - With or without other comorbid conditions.
- Intervention.
 - Remdesivir of any dose.
- Comparator.
 - Remdesivir placebo or standard of care.
- Outcomes/endpoints.
 - Primary endpoints.
 - Time to clinical recovery.
 - Secondary endpoints.

- Proportion of participants relieved from clinical symptoms defined at the time (in hours) from initiation of the study treatment.
- All-cause mortality.
- Discharged date.
- Frequency of respiratory progression.
- Oxygen saturation.
- Treatment-emergent adverse events.

Study design.

- Only RCTs evaluating the efficacy of remdesivir versus placebo or standard of care in patients with COVID-19.

Study selection

All the retrieved papers will be transferred to Endnote 7 and duplicates will be removed. Two investigators will independently assess the title and abstract of all the retrieved papers based on the eligibility criteria. The two investigators will independently evaluate the full texts. Disagreements between the two investigators will be settled through discussion, and if persisted, the third investigator will be involved as arbitrator. Figure 1 summarises the design that we will use to report the study result in line with the PRISMA-P 2015 guidelines (figure 1).

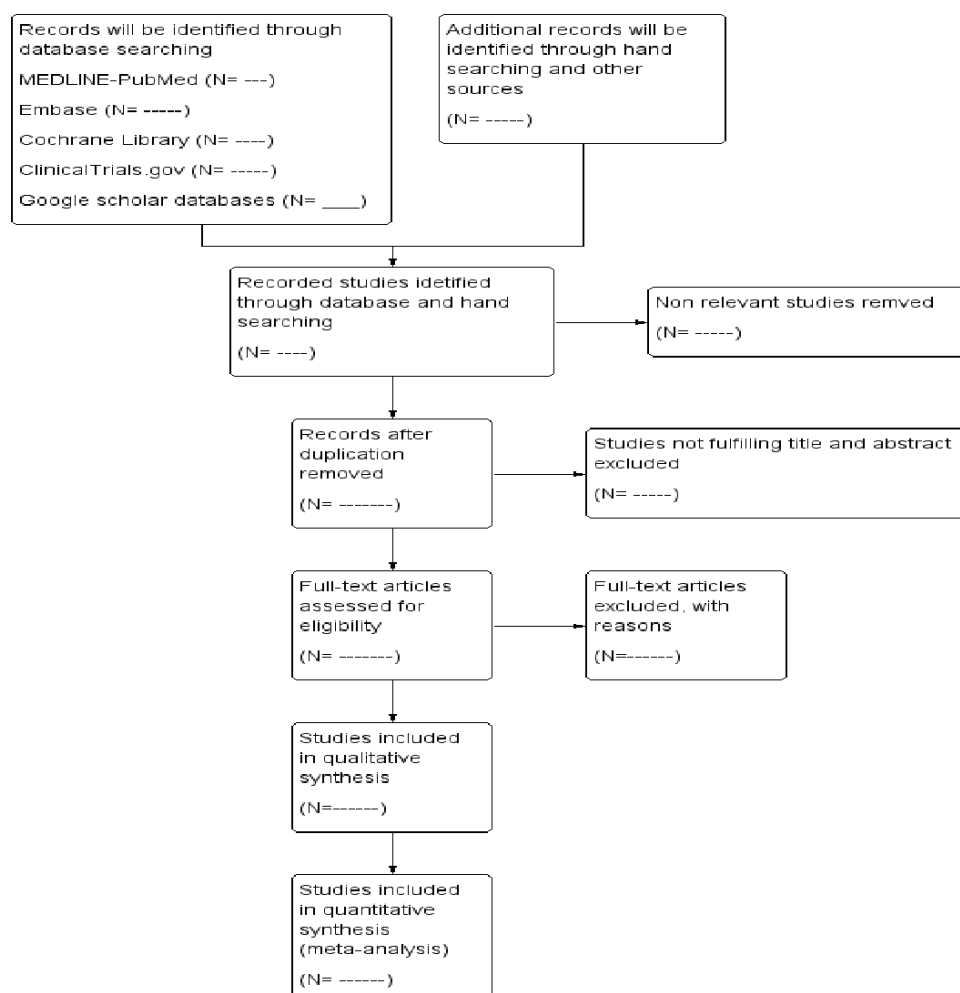


Figure 1 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols flow diagram of the study.

Data extraction

Two authors will independently extract data according to the predesigned data extraction tool. The following data will be extracted from each included RCTs.

- ▶ First author.
- ▶ Year of publication.
- ▶ Study country.
- ▶ Funding information.
- ▶ Patient characteristics (mean age of the participant, sex, comorbid conditions, number of comorbidities, symptom severity).
- ▶ Interventions (remdesivir, dose of remdesivir and route of administration).
- ▶ Comparators (remdesivir placebo, standard of care).
- ▶ Number of participants randomised in each group.
- ▶ Treatment follow-up period.
- ▶ Outcomes (primary, secondary and other outcomes).

Assessment of risk of bias

The Cochrane risk of bias tool³⁷ will be used to assess the risk of bias for each included study. The risk of bias of each trial will be judged by two independent investigators as 'Low', 'Some concerns' or 'High' based on the critical domains, including bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Disagreements will be resolved by discussion among the two investigators. If the disagreements persist, the third investigator will chip in as an arbitrator.

Statistical analysis

All statistical analyses will be carried out using the computer software packages RevMan V.5.3.³⁸ Mean differences (MDs) with 95% CIs will be used to measure the effects of treatment for continuous outcome data. We will convert other forms of data into MDs using standard conversion formula. For outcome variables reported in different scales, we will use standard mean differences with 95% CIs. The treatment effect of binary outcome data will be summarised using risk ratios (RRs) with 95% CIs. Other binary outcome data will be converted into RRs. Mantel-Haenszel method³⁹ will be used to pool effect estimates of dichotomous outcomes and inverse variance for continuous outcomes. Cochrane Q test⁴⁰ will be used to assess heterogeneity between studies, and I² testing⁴¹ will be done to quantify heterogeneity between studies, with values >50% representing moderate-to-high heterogeneity. A random effects model will be used to pool the data.⁴² Subgroup analysis will be carried out between studies with different duration of follow-up, age of participants, severity of the disease, comorbidities, settings and quality of studies for risk of bias. Following the subgroup analysis, we will look at the data for heterogeneity, and if acceptable, we will perform a meta-analysis. If the data are heterogeneous, we will do a narrative description of findings. To see the robustness of pooled data, sensitivity analysis will be conducted between low and

high risk of bias, and with or without biased studies. We will use the GRADEprofiler software from Cochrane Systematic Reviews to assess the quality of evidence per outcome and ultimately to create a summary of findings table and evidence profile. All statistical analysis with a p value<0.05 will be considered statistically significant.

Addressing missing data

When individual participant's data are initially unavailable, we will review the original source, and/or published trial reports, and we will contact the authors to obtain clarification for these data.

Reporting bias

We will conduct funnel plot and Egger test to check any possible reporting bias if a sufficient number of included studies (at least 10 trials) are available in this study.⁴³

Patient and public involvement

Patients and public will not be involved in this systematic review and meta-analysis. However, once our findings are disseminated, it will be shared through social networks.

Ethics and dissemination

There are no ethical considerations associated with this study as we will use publicly available data from previously published studies. We plan to publish results in open-access peer-reviewed journals and present at international and national conferences.

Amendments

The protocol for this study will be amended as necessary.

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Contributors DGe conceived the study, developed the study criteria, searched the literature, wrote the protocol and drafting the manuscript. DGe conducted the preliminary search and TM copyedited and revised the manuscript. All authors have read and approved the manuscript.

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Competing interests All review authors declare that they have no competing interests. The funder has no role in the design, syntheses and report of the study.

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