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Systematic Review

Role of Remdesivir therapy in COVID-19 patients: a systematic review and meta-analysis

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ABSTRACT

The rapid global spread of corona virus disease has created an adversity for the scientific community in managing the disease with appropriate therapeutic measures. The use of remdesivir was initiated as an experimental drug and the later studies analyzing its efficacy showed mixed results. In this meta-analysis, we systematically review the efficacy and safety of remdesivir for the treatment and prevention of COVID-19. A systematic search of databases such as Pubmed, Lancet, Medline, Google Scholar, Cochrane, Embase was carried out through which 1451 articles were identified. 8 articles among it were finally taken for the meta-analysis after several stages of exclusion, to improve the quality and accuracy of the results, out of which the results of 4 studies were in favour of the efficacy of remdesivir, while other 4 studies were against the efficacy of remdesivir. The total sample size is 12,028. The result of our statistical analysis was that OR=0.965 (95% CI; 0.6633 to 1.47) for the effect of remdesivir on mortality reduction in COVID-19 patients. Remdesivir therapy for COVID-19 did not show reduced time to clinical recovery or improved mortality rate. Other outcomes of study like requirement of oxygen support, easier weaning off of mechanical ventilation were also not significantly improved with administration of remdesivir in critically ill COVID-19 patients.

Keywords: Antivirals, Pharmacotherapy, Remdesivir, SARS CoV 2

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) was first identified as an emerging infectious disease in China in December 2019. Since then, it has spread rapidly across the globe, and was declared by the World Health Organization (WHO) as a global health emergency on 30 January 2020.[1]

The causative organism was found to be a β-coronavirus, a ribonucleic acid (RNA) virus which belongs to the same subclass as the severe acute respiratory syndrome (SARS) virus. Hence, it has been designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] The clinical profile of COVID-19 ranges from asymptomatic or mild respiratory symptoms to severe life-threatening pneumonia and death.[3,4] With high mortality rate in vulnerable populations and no definitive insight for treatment, health authorities focus on the repurposing of existing drugs to develop timely and cost-effective therapeutic treatment measures targeting the diseased.

There are studies showing the in vitro activity of remdesivir, an inhibitor of the viral RNA-dependent RNA polymerase, against the Middle East respiratory syndrome (MERS-CoV) and SARS-CoV-1.[5] In addition to this, there are studies showing administration of remdesivir in non-human primates 12 hours after inoculation with MERS-CoV, reduced the lung viral levels and lung damage. Hence, remdesivir was attempted as a candidate drug for the treatment of COVID-19.[6,7]

The aim of the study was to analyse the safety and efficacy of remdesivir in the management of COVID-19.

METHODS

This systematic review was performed in concordance with the preferred reporting items of the systematic review and meta-analysis (PRISMA) checklist.

All steps were conducted based on the Cochrane handbook of systematic review and meta-analysis.

Search strategy

We searched the databases like PubMed, Lancet, Google scholar, Elsevier, Medline, WHO, Cochrane. The following search terms were used: 'remdesivir' 'pharmacotherapy' 'drug trials' 'antivirals' 'randomized control trials'. The search also included reference chaining, citation tracking and website searching.

Inclusion criteria

For the systematic review and meta-analysis, the following were set as the inclusion criteria: studies on COVID-19 conducted between March 2020 and July 2021; studies with enrolled sample >100; studies on pharmacotherapy for COVID-19 specially focussing remdesivir; studies with strong methodologies; and studies with well explained safety profile of remdesivir.

Exclusion criteria

The following were set as exclusion criteria: studies on COVID released before 2020; studies showing the in-vitro effects of remdesivir; articles where full texts was not available and abstract-only papers; articles with only protocol of randomised control trials of remdesivir usage; and articles in languages other than English.

Data extraction

From the eligible studies, the data was extracted independently. Multiple other systematic reviews of various authors were perused to assess the reliability of the data. The odds ratios (ORs) or the proportions of patients were estimated for primary outcome variables with 95% confidence intervals (CIs) using a generic inverse variance method (random-effects model). 'Selection bias' was eliminated by taking results after adjustments and propensity score matching.

Statistical analysis

The results of the individual studies in terms of odds ratio with 95% confidence intervals were compiled. The results were analysed using the statistical package for the social sciences (SPSS) software version 20.0.

RESULTS

Study selection

A sum of 1451 articles were identified via comprehensive search of database, citation tracking, website searching and reference chaining. Following elimination of duplicate studies (230), screening of title and abstract (284) and exclusion of studies that did not fit the eligibility criteria (284), 17 articles were eligible.

After quality assessment, 8 studies were taken for the meta-analysis, of which 5 were randomized control trials, 1 WHO solidarity trial and 1 cohort study (Figure 1).

Study characteristics

The following details in all studies were considered: publication date, study design, sample size, country where the study was conducted, number of patients in each intervention group - treated with remdesivir, combination of drugs if given, mortality rate, length of hospital stay, number of patients who required invasive mechanical ventilation, viral clearance time, comorbidities and number of individuals in the control group who received standard care of treatment/placebo.

Synthesis of results

In our meta-analysis, the following parameters were evaluated: time to improvement; requirement of O_2 support; need for mechanical ventilation; mortality rate; and time to recovery.

Data of 12028 patients collected from 8 studies conducted in different parts of the world are shown in Table 1.

Of the 8 studies analysed, the results of 4 studies were in favour of the efficacy of remdesivir, while other 4 studies showed that there was no significance in using remdesivir. The result of our statistical analysis was that the odds ratio for mortality reduction of remdesivir in COVID-19 patients is 0.965 (95% CI; 0.6633 to 1.47) (Figure 2).

Risk of bias assessment

We assessed the risk of bias ('low risk', 'unclear', or 'high risk') for the studies included in the meta-analysis using the Cochrane risk of bias assessment tool version 2 for randomised control trials (Figure 3) and The New Castle Ottawa scale for non-randomised controlled trials (Figure 4).

Disagreements aroused during this process were resolved through discussion. The grading of recommendations assessment, development and evaluation (GRADE) approach was used to assess the quality of the evidence obtained from various studies.

Table 1: Summary of studies analysed in the meta-analysis.

S. no	Study ID	Country	Study design	Sample size	Experimental group	Comparative group	Results	Description
1	Beigel et al[8]	US, Denmark, UK, Germany	Double-blind placebo controlled RCT	1062	Patients treated with remdesivir (541)	Patients on placebo (521)	OR=0.73 for mortality of patients receiving remdesivir than the placebo group.	In hospitalized patients, remdesivir was seen to be superior to placebo in shortening the time to recovery.
2	Pan et al[9]	WHO	International randomized solidarity trial	11330	Patients who received remdesivir (2750)	Patients who did receive remdesivir (4088)	Rate ratio=0.95 for death in patients receiving remdesivir than in those of control group (p=0.50).	Remdesivir did not have significant benefit among hospitalized COVID-19 patients, in terms of overall mortality, requiring ventilation support and duration of hospital stay.
3	Kalil et al[10]	US, Singapore, South Korea, Mexico	Double-blind placebo controlled RCT	1033	Patients treated with remdesivir + baricitinib (515)	Patients treated with remdesivir alone (518)	Rate ratio=1.51 for recovery in patients with combination therapy than those taking remdesivir alone.	Remdesivir + baricitinib was superior to remdesivir alone in lowering recovery time and accelerating clinical status improvement among COVID-19 patients with O_2 support.
4	Olender et al[11]	US, Italy, Spain, Germany, Hong Kong, Singapore	Open-label retrospective cohort study	1130	Patients treated with remdesivir (312)	Patients treated with standard care (818)	aOR=0.38 for mortality in patients treated with remdesivir compared to those who were not (p=0.001).	In severe COVID-19 patients, treatment with remdesivir showed significant reduction in mortality rate.
5	Spinner et al[12]	US, Europe	Placebo controlled open-labelled RCT	596	Patients who received remdesivir (396)	Patients who received standard care (200)	OR=1.65 for better clinical status distribution in patients receiving remdesivir than those with standard care.	Patients randomized to remdesivir had no significant difference in clinical status when compared with standard care.
6	Gupta et al[13]	India	Single-center retrospective, observational study	735	Patients who received remdesivir/tocilizumab/(521)	Patients who received neither drug (214)	Mortality rates were 35.9% and 65.45% in patients receiving drugs and in those receiving neither drug	The mortality benefit offered by remdesivir and tocilizumab was statistically significant.
7	Goldman et al[14]	US, Italy, Spain, Germany, Hong Kong, Singa-pore, Taiwan	RCT	397	Patients who administered remdesivir for 5 days (200)	Patients who administered remdesivir for 10 days (197)	At day 14, the clinical status of 10 days remdesivir group was similar to the 5 days group (p=0.14)	In COVID-19 patients not requiring ventilatory support, there was no significant difference between 5- and 10-days groups of remdesivir administration.
8	Wang et al[15]	China	Double blind, placebo controlled multicentre RCT	237	Patients who received remdesivir (158)	Patients on placebo (79)	HR=1.23 for clinical improvement in patients who received remdesivir when compared to those of the placebo group	In hospitalised COVID-19 patients, use of remdesivir did not show significant clinical benefits.

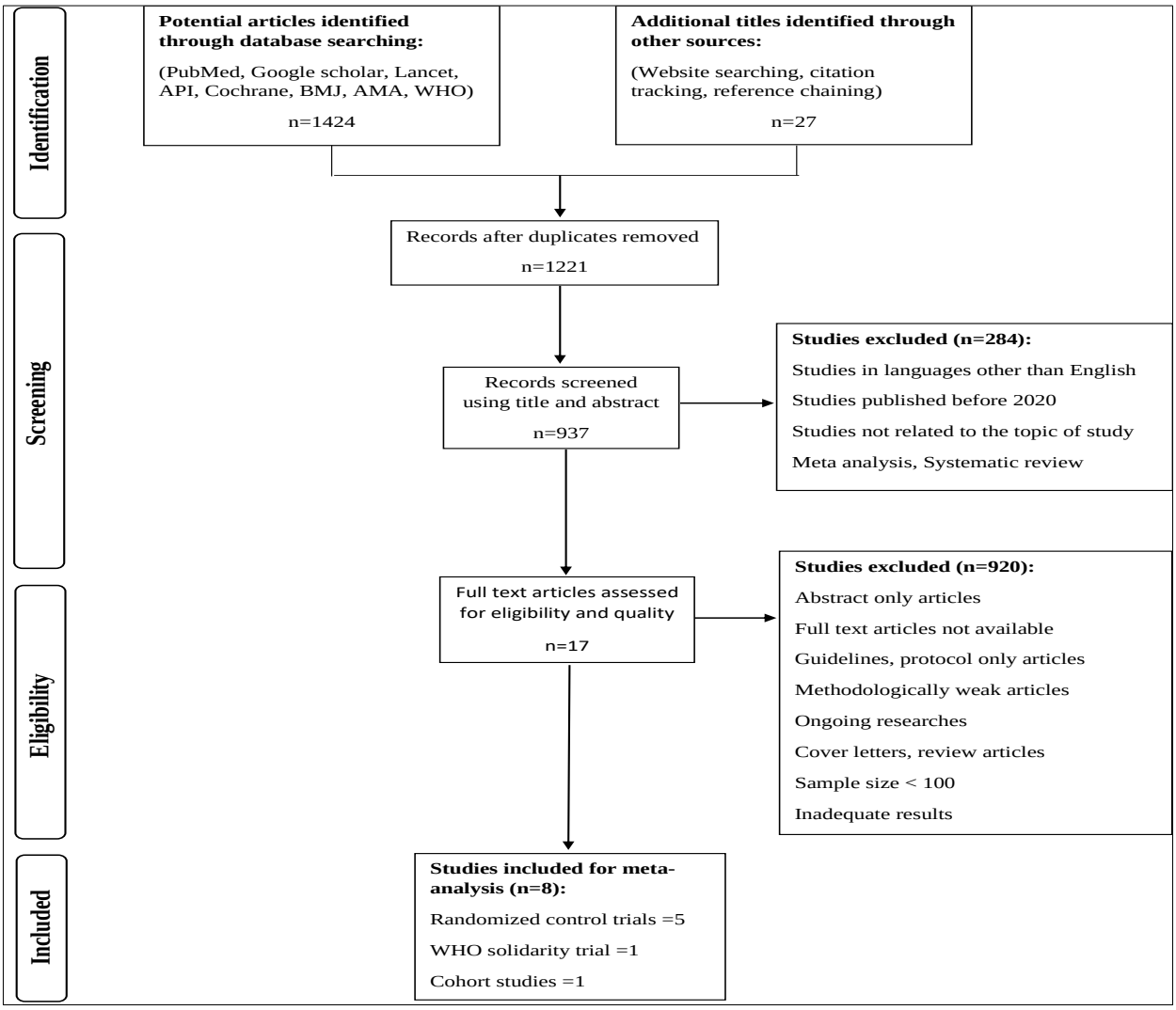

Figure 1: Prisma flowchart showing study selection.

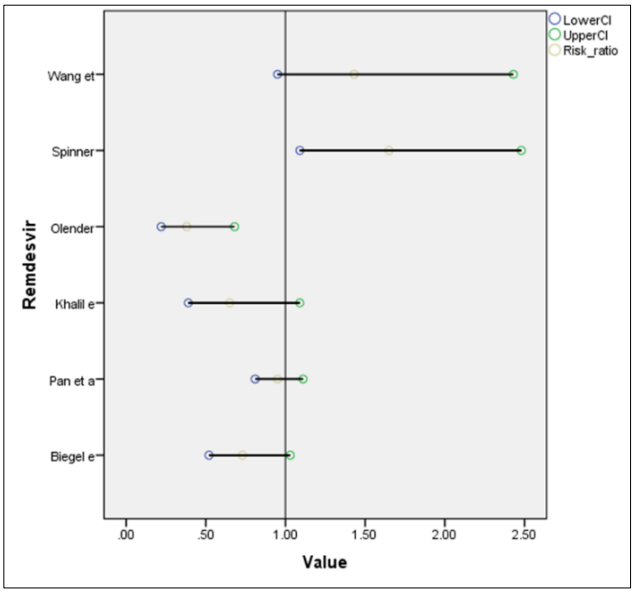

Figure 2: Risk ratio of mortality reduction of remdesivir as per the analysed studies.

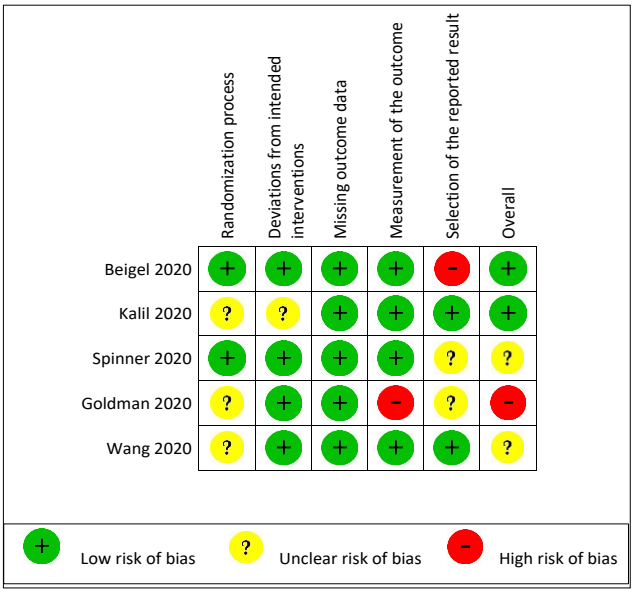

Figure 3: The Cochrane risk of bias assessment for randomized control trial studies analyzed.

Study ID	Selection			Comparability*	Outcome		Total (7★)
	Representativeness of exposed cohort (★)	Selection of non-exposed cohort (★)	Ascertainment of exposure (★)	(★★)	Assessment of outcome (★)	Adequacy of follow up (★)	
Olender 2020	★	★	★	★★	★	-	★★★★★★ (6)
Gupta 2021	★	-	★	★-	★	-	★★★★ (4)

Figure 4: The New Castle Ottawa scale for non-randomized controlled trial studies analyzed.

DISCUSSION

Remdesivir, also known as GS-5734, is an adenosine analogue that was first identified as an experimental drug to treat Ebola virus during its outbreak in 2013-2016 in West Africa.[16] It is a prodrug that requires metabolism by the host cell to its active form, GS-441524. It has an extended-spectrum of antiviral activity against RNA viruses. The active form acts on the viral RNA-dependent RNA polymerase (RdRp) enzyme causing a delay in chain termination, thereby arresting RNA synthesis and viral replication.[5,16] There are studies showing inhibition of viral replication in both MERS-CoV and SARS-CoV on in-vitro administration of remdesivir.[5]

The first case report of use of remdesivir in the treatment of COVID-19 was from the United States. It was a 35-year-old man with history of hypertriglyceridemia, who was otherwise healthy, admitted for isolation and monitoring.[17] During the first 6 days of his admission, he was stable. But then his illness progressed with persistent fevers and he required oxygen supplementation. Remdesivir was administered as a trial drug on day 11 of illness. There was significant clinical improvement over the next 24 hours. Following this case report, few small cohort and prospective studies conducted suggest that on judicial use of remdesivir, there was reduction in oxygen requirement, ability to wean off ventilatory support was easier and improved clinical outcomes on the whole.[9,18,19]

There is also a proposition that intravenous infusion of remdesivir alone has low tissue distribution and poor lung penetration and is unlikely to achieve adequate concentration in lung tissues. Thus, a combination of pulmonary and intravenous administration of remdesivir is considered for more effective results.[20]

Time to improvement

In a study conducted by Beigel et al involving 1062 patients from US, Denmark, UK and Germany, use of remdesivir in hospitalised patients showed significant reduction in their time to improvement.[8] The rate ratio for recovery was 1.23 (95% CI; 1.08 to 1.41). The study conducted by Kalil et al with 1033 patients from US, Singapore, South Korea and Mexico also showed improvement in clinical status at day 15 with the use of remdesivir.[10] The odds ratio for improvement was 1.3 (95% CI; 1.0 to 1.6). In the study conducted by Spinner et al involving 596 patients from US and Europe, patients randomized to the 5-day remdesivir group had significantly better clinical status than those randomized to standard care (odds ratio=1.65; 95% CI, 1.09-2.48; p=0.02).[12] These studies were also supported by the results of the study conducted by Wang et al in China involving 237 patients.[15]

Requirement of O_2 support

According to the study conducted by Kalil et al involving 1033 patients from US, Singapore, South Korea and Mexico, the median time to recovery among patients receiving non-invasive ventilation or high-flow oxygen was 10 days in the remdesivir receiving group and 18 days in the control group.[10] The rate ratio for recovery was 1.51 (95% CI; 1.10 to 2.08).

Need for mechanical ventilation

In the study conducted by Beigel et al involving 1062 patients from US, Denmark, UK and Germany, for those receiving mechanical ventilation or ECMO at enrolment, the rate ratio for recovery was 0.98 (95% CI, 0.70 to 1.36).[8] The study conducted by Kalil et al involving 1033 patients from US, Singapore, South Korea and Mexico also showed similar results.[10] The rate ratio for recovery was 1.08 (95% CI, 0.59 to 1.97) for those receiving mechanical ventilation or ECMO at enrolment. The odds of progression to death or invasive ventilation were 31% lower in the remdesivir taking group when compared to the control group (HR=0.69; 95% CI, 0.50 to 0.95). In addition, the patients in the remdesivir group had 11 days fewer receiving new mechanical ventilation than those in the control group.

Mortality rate

In the study conducted by Beigel et al involving 1062 patients, the mortality by day 15 were 6.7% in the remdesivir group and 11.9% in the placebo group (HR=0.55; 95% CI, 0.36 to 0.83).[8] The study conducted by Kalil et al involving 1033 patients also showed similar results.[10] After randomization, mortality at day 28 were 5.1% (95% CI, 3.5 to 7.6) in the remdesivir group and 7.8% (95% CI, 5.7 to 10.6) in the control group (hazard

ratio for death=0.65; 95% CI, 0.39 to 1.09). Mortality at 14 days after randomization were 1.6% in the remdesivir group and 3% in the control group (hazard ratio=0.54; 95% CI, 0.23 to 1.28). The results of the study conducted by Olender et al involving 1130 patients from US, Italy, Spain, Germany, Hong Kong and Singapore were also consistent with the above studies.[11] Adjusted odds ratio for mortality at day 14 was 0.38 (95% CI: 0.22-0.68, p=0.001).

Time to recovery

According to Beigel's study, patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (10 days versus 15 days, respectively).[8] The rate ratio for recovery was 1.29 (95% CI, 1.12 to 1.49; p<0.001). Patients who were administered remdesivir during the first 10 days of the illness had a rate ratio for recovery of 1.37 (95% CI, 1.14 to 1.64), whereas patients who were administered remdesivir after 10 days of the onset of symptoms had a rate ratio for recovery of 1.20 (95% CI, 0.94 to 1.52). According to Kalil's study, patients who received combination treatment with baricitinib plus remdesivir recovered 1 day faster than patients who received remdesivir and placebo.[10] The rate ratio for recovery was 1.16 (95% CI, 1.01 to 1.32; p=0.03). According to Olender's study, adjusted odds ratio for recovery at day 14 was 2.03 (95% CI: 1.34-3.08, p<0.001).[11]

Adverse effects

Brought into use as an experimental drug, the safety data on remdesivir is limited. Initial studies of phase 1 clinical trial of remdesivir within the dose range of 3 mg and 225 mg exhibited a linear pharmacokinetics. It was well tolerated with no evidence of hepatic or renal toxicity. However, evidences show that multiple doses of remdesivir resulted in elevated hepatocellular enzyme levels that were reversible on the stoppage of drug.[21]

Limitations

Our study had three limitations. One, not all studies were randomised controlled trials, which increases the risk of bias. Two, not all studies administered remdesivir at the optimal time of viral replication. So, negative results regarding the efficacy are not very reliable. Three, only 8 studies were taken for the review as not many studies were qualitatively eligible to take up. Many randomized controlled trials with massive sample size, with a comparator group, reliable data collection and good quality results are essential to arrive at more reliable outcomes.

CONCLUSION

The articles studied show that remdesivir is associated with reduced time to recovery, decreased requirement of oxygen support, easier weaning off of mechanical ventilation and reduction in mortality rate. Although the results seem to favour the efficacy of remdesivir, it was not statistically significant. The benefit of remdesivir was evident when given earlier in the illness, though the benefit persisted in most analyses of duration of symptoms.

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