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REVIEW ARTICLE

The efficacy of remdesivir in coronavirus disease 2019 (COVID-19): a systematic review

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ABSTRACT

Background and Objectives: Researchers all around the world are working hard to find an effective treatment for the new coronavirus 2019. We performed a comprehensive systematic review to investigate the latest clinical evidence on the efficacy and safety of treatment with Remdesivir in hospitalized patients with COVID-19.
Materials and Methods: We performed a systematic search in Pubmed, Embase, Web of Science, Google scholar and MedRxiv for relevant observational and interventional studies. The outcomes measures were mortality rates, improvement rates, time to clinical improvement, all adverse event rates and severe adverse event rates.
Results: Three randomized controlled trials and 2 cohort studies were included in our study. In the 2 cohort studies, patients received Remdesivir for 10 days. 2 RCTs evaluated 10-day efficacy of treatment with Remdesivir versus placebo group and the other RCT compared its 5-day regimen versus 10-day regimen. Visual inspection of the forest plots revealed that the efficacy of Remdesivir was not much different in reducing 28-day mortality versus 14-day mortality rates. Besides, 10-day treatment regimen overpowered 5-day treatment and placebo in decreasing time to clinical improvement. All adverse event rates did not have a significant difference; however, severe adverse event rate was lower in the 5-day Remdesivir group compared to the 10-day and placebo groups.
Conclusion: 5-day course of Remdesivir therapy in COVID-19 patients is probably efficacious and safe, and patients without invasive mechanical ventilation benefit the most. Treatment can be extended to 10 days if satisfactory improvement is not seen by day 5. Most benefits from Remdesivir therapy take place in the first 14 days of the start of the treatment.

Keywords: Coronavirus disease 2019 (COVID-19); SARS-CoV-2; Remdesivir; Efficacy

INTRODUCTION

Since the beginning of the coronavirus disease of 2019 (COVID-19) in Wuhan, it has infected more than 32 million people and caused more than 990,000 deaths worldwide (1). The rapid spread of the virus has devastated the global health and economy (2). Therefore, researchers are working hard to find an

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effective treatment for the new coronavirus 2019.

Currently, there is no established treatment and supportive care is the only management in these patients (3). Many drugs tend to show up in many *In-Vitro* drug screens. However, their clinical effects are still under investigation. The medical community is actively trialing repurposed and novel medications to find an effective treatment (4). Drugs such as Remdesivir have been the subjects of recent studies in this situation.

Remdesivir (also known as GS-5734) is a monophosphoramidate prodrug of an adenosine analogue, firstly developed against the Ebola virus in 2017 (5). Recent studies showed that Remdesivir has promising results against the RNA coronaviruses (SARS-CoV and MERS-CoV) (6). A study reported its clinical benefits in rhesus macaques infected with SARS-CoV-2 (7). In addition, *in vitro* studies revealed its efficacy against SARS-CoV-2 in human cell lines (8). However, *in vivo* efficacy of Remdesivir has not been proven yet. Some studies investigated clinical efficacy of Remdesivir in human patients; however, some of the studies did not have enough power to show conclusive results (9).

On May 1, 2020, FDA issues emergency use authorization for the administration of Remdesivir in COVID-19 patients (10). However, its efficacy is still controversial among the specialists and doctors. Therefore, it is essential to collect and evaluate all available clinical studies to provide unified evidence on its efficacy.

Here, we performed a comprehensive systematic review to investigate the latest clinical evidence on the efficacy and safety of the treatment with Remdesivir in hospitalized patients with COVID-19.

MATERIALS AND METHODS

Protocol. In this study, we adhered to the recommendations provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement 2015 (11).

Literature search. We performed a systematic search in the MEDLINE(PubMed), EMBASE and Web of Science databases with the MeSH and non-MeSH terms and the keywords of 'coronavirus' OR 'COVID-19' OR 'SARS-COV-2' OR '2019-ncov' AND 'GS-5734' OR 'Remdesivir' on May 29, 2020. Google scholar and MedRxiv were also searched with these keywords manually to retrieve the gray literature. The publication year was limited to 2020. Details about search strategy and the keywords are presented in the Additional file. Except for the time, no other restriction was considered for our search. We also looked into the references of the included papers for more relevant studies.

Screening was done independently by M.A and A.R. Firstly, duplicated retrieved search results were identified and excluded. We screened the titles and the abstracts of the papers to exclude the irrelevant studies. Accordingly, search results were categorized into three categories of included, excluded and unclear. Then, the full texts of the retrieved studies were reviewed for final inclusion. Any disagreement was discussed in our project team.

Inclusion criteria. Original articles were included about comparing treatment efficacy and safety of COVID-19 patients with Remdesivir and placebo. Also, studies that evaluated the treatment outcomes of COVID-19 patients with Remdesivir in groups with different duration of treatment or with dissimilar disease severity were included.

Exclusion criteria. The exclusion criteria were review articles, duplicate studies, meeting abstracts, letters and editorials, case reports and case series, and studies with no original information about Remdesivir therapy. *In vitro* and animal studies were also excluded.

Data extraction. Data on the author's name, study design, number of patients, inclusion criteria, duration of illness before Remdesivir therapy, arms or subgroups of the patients, improvement and/or mortality rates, viral load changes and adverse events were extracted.

The two authors, A.R and R.R, performed literature search, screening and inclusion of the studies, and data extraction independently and disagreements were discussed with another author, M.A and resolved.

Risk of bias assessment. We used Cochrane Risk of Bias Tool (12) and Newcastle-Ottawa Scale (13) for assessing the risk of bias in randomized controlled studies and observational studies, respectively. The two authors, A.R and R.R, independently assessed

the risk of bias with the mentioned tools and M.A rechecked it.

Statistical analysis. Results of the final studies were reported separately in a narrative way. The measured outcomes were mortality rates, time to clinical improvement, any adverse events, severe adverse events and improvement rates. We used Review Manager version 5.3 to draw the forest plots of these outcomes. I^2 was considered as the indicator of heterogeneity. Random effect model was used when I^2 exceeded 50%. Mantel–Haenszel odds ratio (OR) and mean difference (MD) were used for reporting the effects of dichotomous and continuous outcomes, respectively. High heterogeneity was seen in the forest plots; therefore, meta-analysis was not possible. However, forest plots comparing the measured outcomes in different subgroups were drawn. The day of measuring the outcomes (28-day vs. 14-day), types of the studies (RCT vs. Cohort), and design of the control group (placebo-control vs. 5-day treatment regimen) were used for categorizing the studies into different subgroups. Median and interquartile range (IQR) were converted to mean and SD according to the formulas suggested by Hozo et al. (14).

RESULTS

Out of 329 identified records through database searching and references lists, 21 full text articles were selected. After matching with our eligibility criteria, 5 studies were chosen for final inclusion (Fig. 1). Remdesivir was administered in these five studies with a single 200 mg intravenous dose on the first day followed by once-daily 100mg intravenous dose from the second day up to 10 days (15-19). Three multicenter randomized clinical trials were included in our study. Adaptive COVID-19 Treatment Trial (ACTT) and a trial in ten hospitals in China were both placebo-controlled, and the patients in the test arms received Remdesivir. Also, those who were assigned to the control arms received intravenous placebo with the same frequency and duration of Remdesivir infusions (17, 19). However, participants in both arms of the third trial received Remdesivir but in different durations (18). Also, 2 cohort studies, both of which assessed the compassionate use of Remdesivir between the 2 groups of patients, were included: In Grein et al.'s study, the patients were categorized based on the need for invasive oxygen support, while Antinori et al. divided the patients into ICU and ward groups (15, 16) (Tables 1 and 2). The inclusion criteria of the final studies are presented in Table 1.

Randomized controlled trials. In the preliminary report of ACTT, the results of the analysis on 1059 participants with lower respiratory tract involvement with COVID-19 were published (17). In this double-blinded study, 77% of the patients required oxygen administration on enrollment. The mean time of the illness onset and random entry of the participants was 9 days (IQR 6 to 12); no significant imbalance was found between the baseline characteristics of 538 participants in the test arm and 521 patients in the control arm. Primary outcome in this trial was time to recovery, defined as the time duration from the enrollment to the first day the patient was discharged or when hospitalization was extended only for infection-control reasons. The time to recovery was 11 days in the test arm (95% CI, 9 to 12) and 15 days in the control arm (95% CI, 13 to 19). The rate ratio of recovery till 14^{th} day was 1.32 (95% CI, 1.22 to 1.55), with no significant interaction with baseline clinical status. Mortality was higher in the test arm; however, the difference was not statistically significant with or without adjustment of the severity of baseline illness. 21% of the participants in the test arm and 27% in the control arm experienced serious adverse events. Several points should be taken into account when interpreting these results.

First, the patients were allowed to use other medications along with Remdesivir or placebo according to each hospital policy. Thus, the observed effects might result from the combined effects of different medications and Remdesivir; therefore, this makes the results less generalizable. Second, careful evaluation of the study tables revealed that only 180 out of 541 (33.3%) patients in the Remdesivir group and 185 out of 522 (35.4%) patients in the placebo group received the full 10 doses of complete treatment at the time of data analysis. Accordingly, the results might be different from the responses given if the participants had received the complete course of therapy. Lastly, this trial is still continuing and only the preliminary results were published. Therefore, the analyses of safety and efficacy of Remdesivir in this study has not been completed yet and this causes a high risk of bias (Fig. 2).

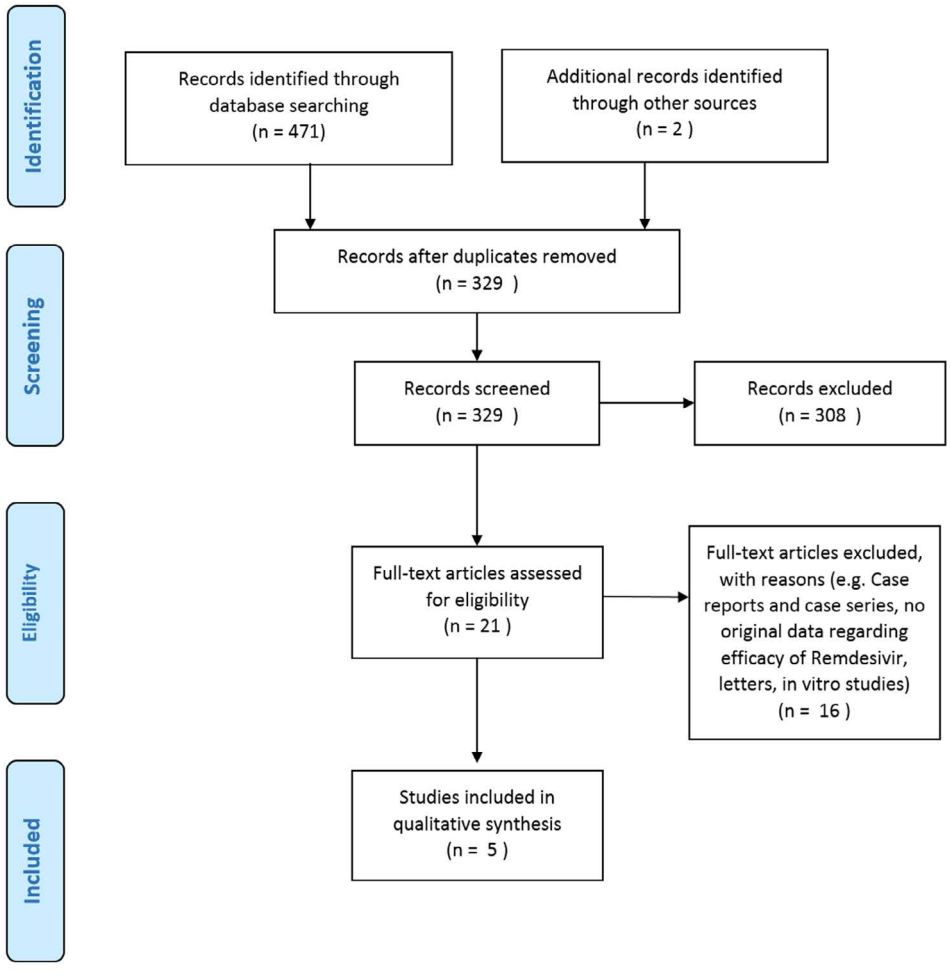

Fig. 1. PRISMA flow chart

In a study on 237 patients with COVID-19 pneumonia and concomitant impaired oxygenation, the effect of Remdesivir on clinical improvement was shown to be statistically non-significant (19). The mean time to clinical improvement was 21 days (IQR 13 to 28) in the test arm compared to 23 days (IQR 15 to 28) in the control arm, and the rate of clinical improvement by day 28 was 65% in the test arm and 58% in the control arm. Also, the administration of Remdesivir did not reveal a significant increase in negative conversion rate of viral load reduction in nasopharyngeal and sputum samples, as compared to placebo. Researchers in this study calculated a sample size of 453 for 80% event rate within the study duration (28 days) and 10% drop out rate. However, only 237 patients were enrolled. There is a high risk of bias due to the imbalance in the baseline characteristics resulting from inadequate sample size (Fig. 2); participants in the test arm had more comorbidities, more tachypnea, and longer duration of illness. Also, they showed more adverse events (66% vs. 64%) and patients in the control arm had more serious adverse events (26% vs. 18%).

An open-label RCT demonstrated that a 5-day course of Remdesivir, with a dose of 200 mg on first day and 100 mg on the next 4 days, might be sufficient (18). In this trial, out of 397 COVID-19 hospitalized patients who did not require invasive ventilation at enrollment, 200 patients received 5-day course of Remdesivir and 197 of them received Remdesivir for 10 days. Randomization was done, but lack of stratification led to worse baseline clinical status of 10-day arm patients. The rate of clinical improvement, defined as improvement of more than one point on a 7-point ordinal scale by day 14, was 65% in 5-day arm patients and 54% in 10-day arm patients. Nevertheless, the rates of clinical improvement, clinical recovery, discharge or mortality by day 14 were not

Table 1. The study design and participants

Authors	Type of study	Selected details of study design and participants	Group 1 sample size	Group 2 sample size	Median duration of illness before RDV therapy
Jonathan Grein, et al.	Cohort study	Group 1: patients needed Invasive oxygen support Group 2: patients needed non-invasive oxygen support	34	19	12 days (IQR 9-15)
Spinello Antinori, et al.	Cohort study	31 patients had previously received LPV/r and HCQ Group 1: 18 ICU patients Group 2: 17 ward patients	18	17	7 days (IQR 5-10)* 4 days (IQR 3-5)**
Yeming Wang, et al.	Double-blind, placebo-controlled RCT	Use of other medicines was permitted. Group 1: test arm Group 2: control arm	158	79	10 day (IQR 9-12)
Beigel et al.	Double-blinded, placebo-controlled RCT	Other specific treatment for COVID 19 were prohibited after enrollment, unless a written guideline implemented by hospital. Group 1: test arm Group 2: control l arm	538	521	9 days (IQR 6-12)
Jason D. Goldman, et al.	Open-label, RCT	Group 1: 5-day arm Group 2: 10 day arm	200	197	8 days (IQR 5-11)† 9 days (IQR 6-12)††

Abbreviations: LPV/r - Lopinavir/Ritonavir, HCQ - Hydroxychloroquine, IQR - interquartile range, RDV – Remdesivir
*median duration of illness before hospitalization
**median duration from hospitalization to Remdesivir therapy
† median duration of illness before RDV therapy in 5-day arm
†† median duration of illness before RDV therapy in 10-day arm arm

significantly different between the two arms after adjustment of baseline clinical status. However, among the patients who received invasive mechanical ventilation on day 5, those assigned to 10-day (n=41) regimen had lower mortality as compared to 5-day (n=25) regimen (17% vs. 40%). The analysis of drug safety revealed that both arms were statistically similar in occurrence of adverse events; however, serious adverse events were more prevalent in 10-day arm patients after adjustment of the baseline clinical status. Interpretation of the efficacy of Remdesivir based on the results of this study is limited by the lack of placebo group.

Cohort studies. In a cohort study, Grein et al. analyzed the data of 53 patients (15). The mean duration of the illness before Remdesivir therapy and mean follow up time were 12 (IQR 9-15) and 18 days (IQR 13-23), respectively. 34 out of 53 patients needed invasive oxygen support and the other 19 patients needed non-invasive oxygen support. 59% of the patients in the invasive oxygen support group showed improvement in the category of oxygen support, as compared to 89% of patients in the other group at the end of the follow-up. Mortality rate was higher in the invasive group (18% vs. 5%). Participants in the invasive group experienced more adverse events (65% vs. 53%). For entering the study, the patients' physicians had to apply for receiving Remdesivir. This limits the generalizability of the results. Besides, lack of control group and insufficiency of the follow up time are also other sources of bias in this study (Table 3).

In another cohort study on 35 patients, the mean duration of the illness before hospitalization and mean duration of admission before Remdesivir therapy were 7 (IQR 5-10) and 4 (IQR 3-5) days, respectively (16). 31 patients had been treated with Lopinavir/Ritonavir and Hydroxychloroquine previously, but after enrollment, Lopinavir/Ritonavir treatment was stopped. 9 out of 18 ICU patients and 13 out

Table 2. The measured outcomes in the included studies

Author	Clinical improvement rate†		Rate ratio to recovery	Time to improvement†		Mortality*		Adverse events rate N (%)		Severe adverse events rate	
Jonathan Grein, et al.	Total Group 1 Group 2	n=36 (68%) n=19 (59%) n=17 (89%)	-	-		Total Group 1 Group 2	n=7 (13%) n=6 (18%) n=1 (5%)	Total Group1 Group2	n=32 (60%) n=22 (65%) n=10 (53%)	Total Group1 Group2	n=12 (23%) n=9 (26%) n=3 (16%)
Spinello Antinori, et al.	Total Group 1 Group 2	n=22 n=7 n=15	-	-		Total Group 1 Group 2	n=9 n=8 n=1	-**			
Yeming Wang, et al.	Test arm Control arm	n=103 (65%) n=45 (58%)	-	Test arm Control arm	21 days (IQR, 13 to 28) † 23 days (IQR, 15 to 28)	test arm control arm	n=22 (15%) n=10 (13%)	test arm control arm	n=102 (66%) n=50 (64%)	test arm control arm	n=28 (18%) n=20 (26%)
Beigel et al.	-		1.32 (95% CI, 1.12 to 1.55)	Test arm Control arm	11 days (95% CI, 9 to 12)†† 15 days (95% CI, 13 to 19)	Test arm Control arm	7.1%¶ 11.9%¶	Test arm Control arm	156/541 (28.8%) 172/522 (33%)	Test arm Control arm	114/541 (21%) 141/522 (27%)
Jason D. Goldman, et al.	Total 5-day arm 10-day arm	n=236 n=129 (65%) n=107 (54%)	-	5-day arm 10-day arm	10 days (IQR, 6 to 18)‡ 11 days (IQR, 7 to unknown)‡	Total 5-day arm 10-day arm	n=37 n=16 (8%) n=21 (11%)	Total 5-day arm 10-day arm	n=286 n=141 (70%) n=145 (74%)	Total 5-day arm 10-day arm	n=110 n=42 (21%) n=68 (35%)

Abbreviations: IQR-interquartile range, C.I-confidence interval

† Clinical improvement has been defined as improvement in the category of oxygen support in Grein's study, improvement in 7-category ordinal score till 28th day in Antinori's study till day 28, 2 points in 6-point ordinal scale in Wang's study, being discharged or hospitalized only for infection-control reasons in Beigel's study, and 2 points in 7-category ordinal scale in Goldman's study.

* In Antinori, et al. and Wang, et al.'s studies measured by day 28. In Beigel et al. and Goldman, et al.'s studies measured by day 14.

¶ Kaplan-Meier estimation of the mortality rate is reported here for Beigel, et al.'s study.

** cumulative frequency of adverse events was not reported but events in 6 patients in group1 and 2 patients in group 2 led to drug discontinuation.

‡ = median day of 50% cumulative incidence of clinical improvement was reported as time to improvement in the study of Goldman et al.

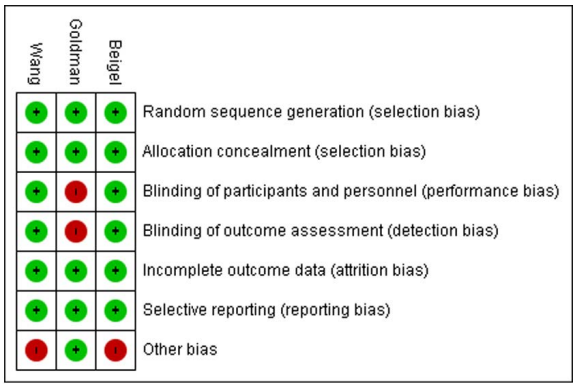

Fig. 2. Risk of bias assessment of RCTs with Cochrane Collaboration's Risk of Bias 2.0 tool for RCTs (ROB-2)

of 17 ward patients completed the 10-day course of Remdesivir therapy. ICU patients had lower clinical improvement rate (38.9% vs. 88.2%) by day 28. The mean duration of viral load conversion in 22 patients with negative PCR tests was 12 days (IQR 9.25-16.75). The most common severe adverse events observed were elevation of the liver enzymes (42.8%) and acute kidney injury (22.8%).

Mortality. As shown in Fig. 3, mortality rates were higher in cohort studies compared to RCTs. It suggested lower mortality rates in controlled situations of RCTs compared to real-world situations in cohort studies. Besides, the efficacy of Remdesivir in reducing 28-day mortality rate was not significantly lower than its efficacy in reducing 14-day mortality rate (Fig. 4). Forest plot of mortality rates in placebo-control and 10-day vs. 5-day studies is presented in Fig. 1.

Clinical improvement. As shown in Fig. 5, in contrast to mortality rates, improvement rates in RCTs and cohorts were not significantly different. As seen in the mortality rate, the efficacy of Remdesivir in increasing the improvement rate was not significantly different by day 14 and 28 (Fig. 6). Fig. 2 shows improvement rates in the placebo-control and 10-day vs. 5-day studies.

Time to clinical improvement. Fig. 7. shows the effects of Remdesivir in reducing the time to clinical improvement. It was revealed that 5-day regimen can reduce the time to clinical improvement compared to placebo; also, continuing Remdesivir for another 5 days can even cause more decrease in the time to improvement than 5-day regimen.

All adverse events. The patients who received 10-day Remdesivir therapy showed lower adverse events compared to the placebo-control group. Besides, the patients who had undergone 5-day Remdesivir regimen experienced a lower adverse event rate than the 10-day group. However, both of the above comparisons did not show significant differences between the two groups. Furthermore, superiority of the 5-day arm to the placebo arm is not notable due to the remarkable overlap between 95% C.I of the odds ratio (Fig. 8). Forest plot of all adverse event rates in RCTs and cohort studies is presented in Fig. 3.

Severe adverse events. 10-day regimen showed lower severe adverse events rate than the placebo-control group. In addition, 5-day regimen group had lower adverse event rate compared to the 10-day group. In contrast to all adverse events, superiority of the 5-day regimen to the 10-day regimen and 10-day regimen to the placebo group are significant for severe adverse events (Fig. 9). Fig. 4 shows severe adverse event rates in the RCTs and cohort studies.

Table 3. Risk of bias assessment in two cohort studies with Newcastle–Ottawa scale

Author	Selection				Comparability	Outcome			Total
	Representativeness	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration		Assessment of outcome	Follow-up	Adequacy of follow-up	
Antinori	C	NA	A*	A*	B*	A*	A*	A*	6
Grein	C	NA	A*	A*	B*	A*	A*	C	5

Abbreviation: NA – Not Available

A, B, C, D are the answers to each questions of the Newcastle–Ottawa scale. A star (*) is given to answer A of all questions and answer B of questions 1, 3, 5, 6, 8. The stars are count to produce a total score. In general, a study with greater total score has lesser risk of bias.

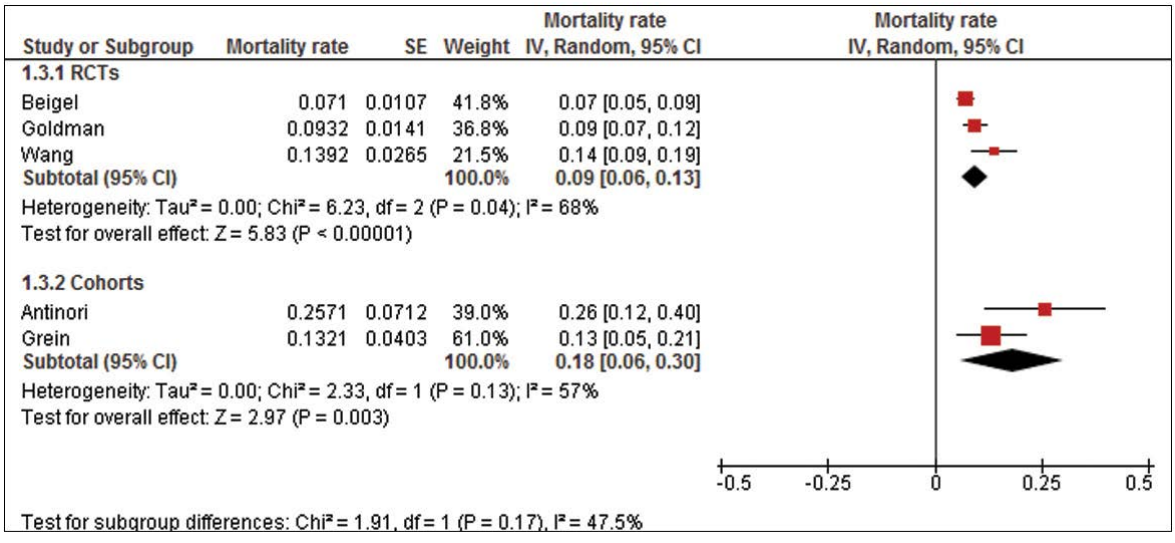

Fig. 3. Forest plot of mortality rates in placebo-control and 10-day vs. 5-day studies

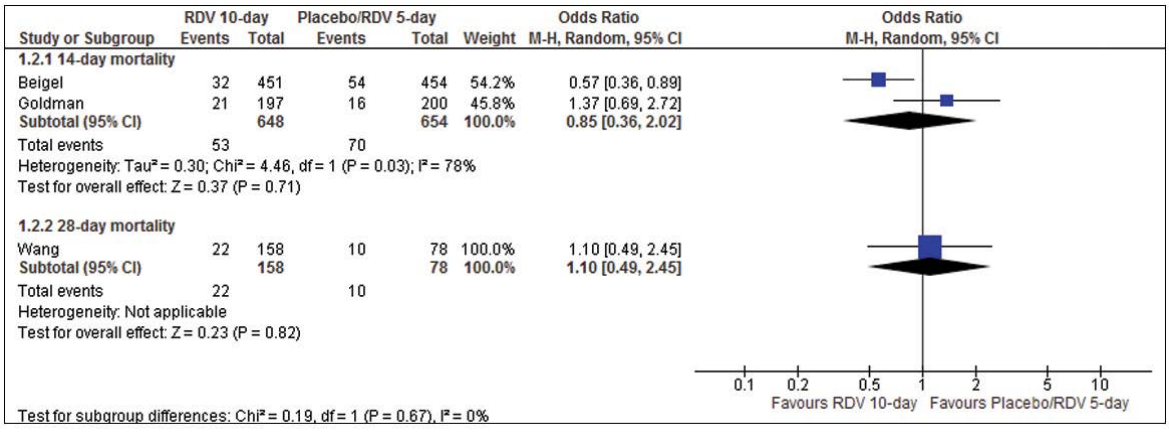

Fig. 4. Forest plot of 14-day vs. 28-day mortality rates in RCTs

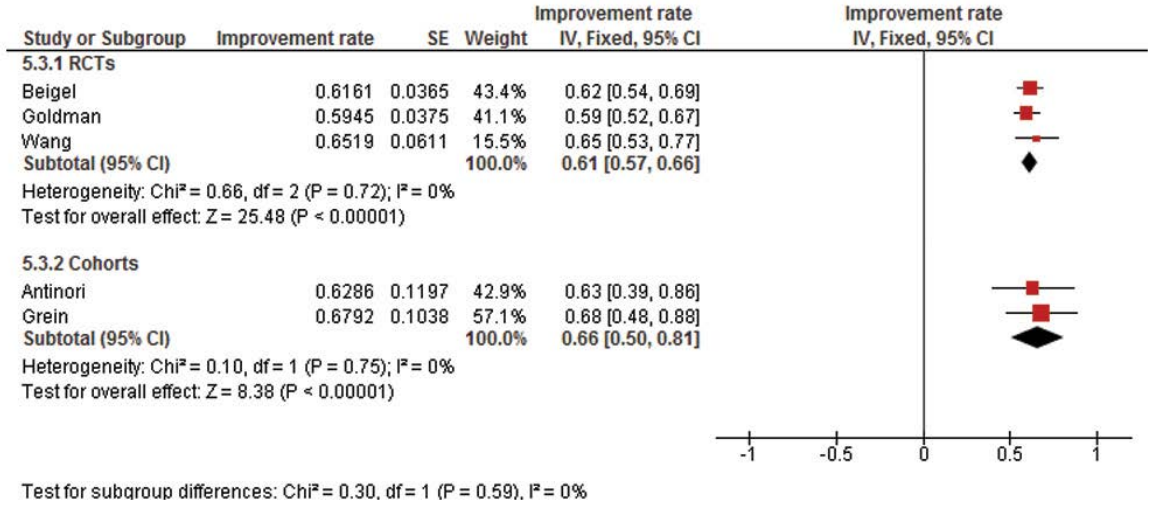

Fig. 5. Forest plot of mortality rates in the placebo-control and 10-day vs. 5-day studies

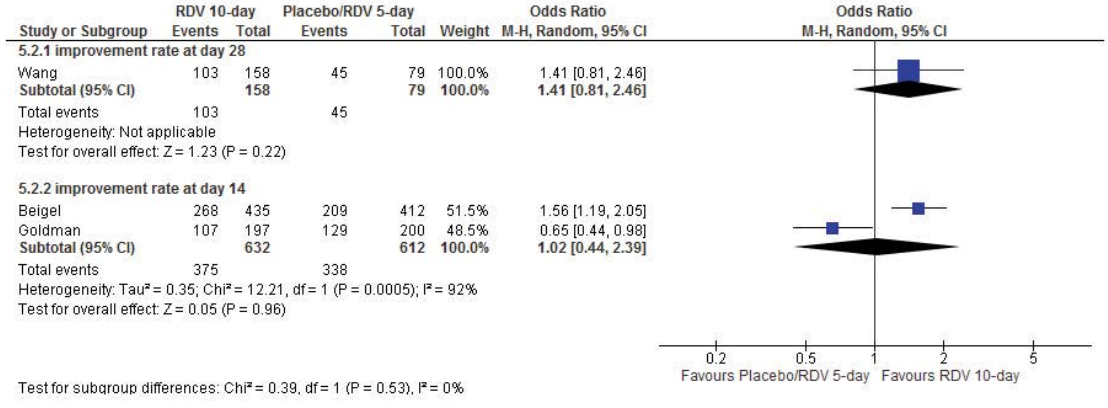

Fig. 6. Forest plot of 14-day vs. 28-day improvement rates in RCTs

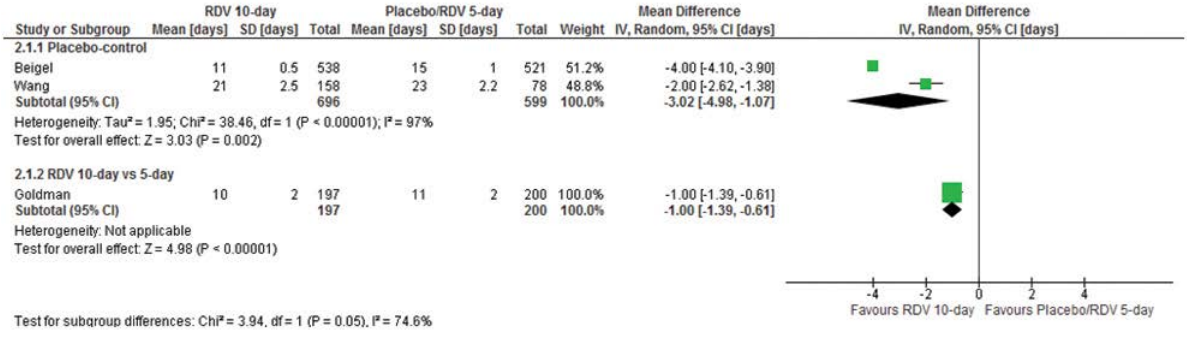

Fig. 7. Forest plot of the time to clinical improvement rates in placebo-control and 10-day vs. 5-day RCTs

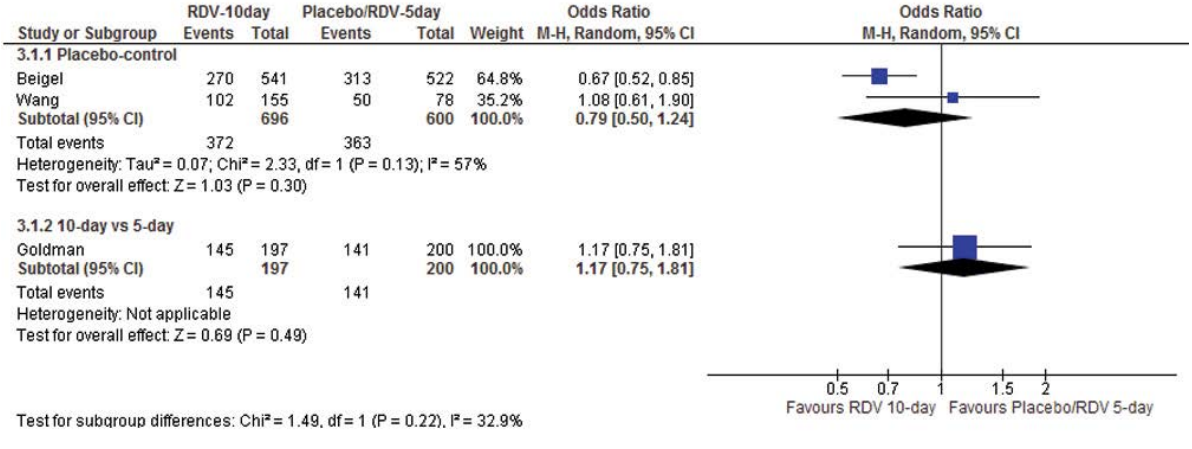

Fig. 8. Forest plot of all adverse event rates in the placebo-control and 10-day vs. 5-day RCTs

DISCUSSION

After searching for all the manuscripts which had evaluated the use of Remdesivir in the clinical management of COVID-19, we identified 3 RCTs and 2 cohort studies. Unfortunately, the heterogeneity in the study design and definition of clinical outcomes, as well as controversial study results, make it hard to establish a solid conclusion regarding the clinical efficacy of Remdesivir. ACTT reported that Remde-

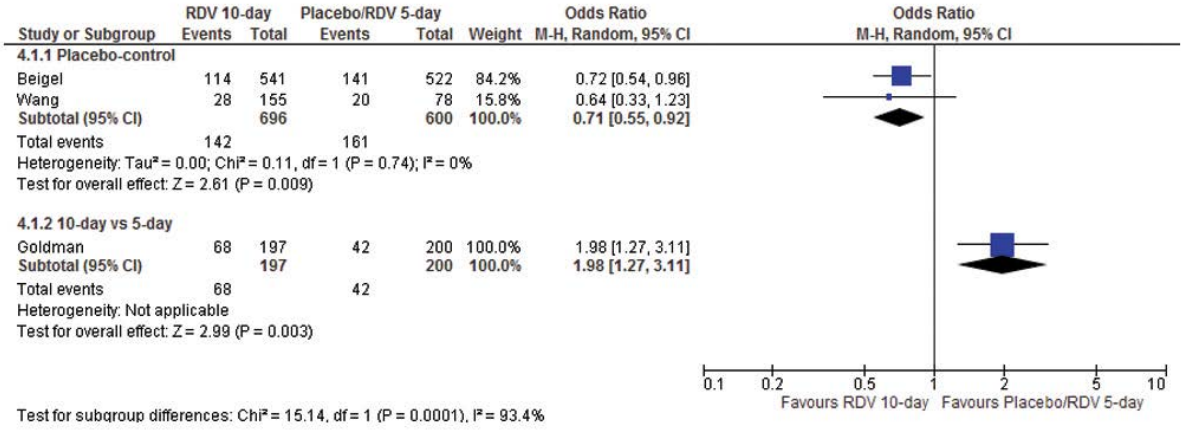

Fig. 9. Forest plot of severe adverse event rates in the placebo-control and 10-day vs. 5-day RCTs

sivir was useful in reducing the time to recovery in patients with COVID-19 pneumonia (17). On the other side, Wang et al. failed to show a significant benefit associated with the use of Remdesivir in terms of clinical outcomes (19). In this regard, Goldman et al.'s study revealed that 5-day and 10-day Remdesivir therapy did not show a significant difference in the terms of clinical outcomes (18). Finally, it is suggested in 2 cohort studies that the use of Remdesivir may improve the clinical outcomes; however, their results must be interpreted carefully considering the lack of a control group and incomplete understanding of the natural course of the virus (15, 16).

To date, Beigel et al. have published the largest RCT evaluating the use of Remdesivir in patients with lower respiratory tract involvement (17). Large sample size and a well-designed study protocol are the strengths of this study. The Remdesivir group was superior to the placebo group in reducing the time to recovery and increasing the rate of recovery. Based on this study, administration of Remdesivir is safe; however, patients with severe renal impairments were excluded in this study.

The report of an RCT in 10 hospitals in China demonstrates no benefit in clinical outcomes in using Remdesivir for treatment of COVID-19 patients with lower respiratory tract involvement (19). However, the inability to recruit the predetermined study population resulted in reduction of the study power from 80% to 58%, as Wang et al. stated in the manuscript. Furthermore, the imbalances in baseline characteristics of Remdesivir and placebo groups were also a source of error in this study. Low study power and higher severity of illness in the Remdesivir arm both decrease the probability of detecting the efficacy of Remdesivir. For example, a separate analysis in a subgroup of patients with less than 10 days from the symptom onset to the start of treatment showed lesser time to clinical improvement (hazard ratio (HR) for clinical improvement, 1.52; 95% CI, 0.95 to 2.43) and faster rate of sputum viral load reduction in the Remdesivir group (0.0672). The mentioned outcomes could be statistically significant if this study had higher power and was able to detect smaller effects. As a whole, this study was not in favor of using Remdesivir to treat COVID-19 patients although there was an underestimation towards the efficacy of Remdesivir.

Goldman et al.'s study showed that 5-day and 10-day courses of Remdesivir therapy did not have a significant difference (18). Patients receiving mechanical ventilation or extracorporeal membrane oxygenation were not enrolled in this study. Therefore, fewer patients with severe disease were evaluated in this study. Unlike the 2 other RCTs, assessing the efficacy of Remdesivir is impossible due to the lack of the placebo control group. Baseline clinical characteristics of the patients in the two arms were different because of the lack of stratification. After adjustment of baseline imbalances, both 5-day and 10-day groups showed nearly the same outcomes. However, severe adverse events were more prevalent in the 10-day group. Furthermore, in the patients who required invasive mechanical ventilation after receiving Remdesivir for 5 days, continuation of therapy for another 5 days was associated with lower mortality rate. Due to the shortage of Remdesivir supply (20), lack of difference between the outcomes of these 2 regimes helps us to treat more patients with severe conditions.

Grein et al. stated that Remdesivir may be useful

in treating severe COVID-19 patients (15). 64% of the patients needed invasive mechanical ventilation and the sample was correctly labeled as severe. This study showed that clinical improvement in milder cases was higher than that of more severe cases. It prompts the need for earlier recognition and initiation of treatment before the disease advances to severe stages. However, the results may be confounded by several reasons. First, receiving previous treatment and differences in the length of Remdesivir therapy might affect the final results. Second, lack of a control group for comparison of the results makes it difficult to understand whether the reported improvement rate is due to Remdesivir or not. Third, authors in this study considered death as a censoring event. Reanalysis of the data for correcting this error showed that the improvement rate estimated by Kaplan-Meier analysis falls from 84% to 70%. Lastly, 32 patients were discharged or died by the end of this study which by reducing the denominator from 53, increases mortality rate from 13% to 22% (21).

A study of Remdesivir therapy on 35 ICU and ward patients showed that ward patients benefited more from Remdesivir therapy than ICU patients and experienced fewer adverse events. Also, this study reminds the higher efficacy of Remdesivir therapy in patients with less severe disease.

When we considered mortality as the outcome of interest, effectiveness of Remdesivir in treating COVID-19 patients was higher than its efficacy; however, this superiority was not observed when the improvement rate was chosen as the target outcome. Besides, as mentioned previously, the efficacy of Remdesivir in reducing the mortality rate and increasing the improvement rate by days 28 and 14 is not much different. Therefore, we suggest that most benefits from Remdesivir therapy appear in the first 14 days from the start of the treatment, and final conditions of the patients are mostly determined by day 14. Also, we found that extending Remdesivir treatment to 10 days led to faster clinical improvement.

All adverse event rates were not significantly different among the 10-day arm, 5-day arm and placebo groups. However, severe adverse event rates were lower in the 5-day group compared to the 10-day group; also, the 10-day group showed fewer severe adverse events compared to the placebo group.

It is difficult to answer the question regarding the efficacy of using Remdesivir in severe COVID-19 patients. So far, there are only 2 studies which have compared the efficacy of Remdesivir in the test arm and placebo control arm, and the results of these two studies were controversial. Beigel et al.'s study results were in favor of using Remdesivir, while Wang et al.'s study could not reveal a significant superiority over Remdesivir therapy. We think that Remdesivir can be considered as a choice, especially in patients without invasive mechanical ventilation (17) or in those with less duration of illness (19). The previous studies revealed that Remdesivir was beneficial; however, the magnitude of this benefit is not large enough to make Remdesivir monotherapy an ultimate treatment. Further RCT studies with similar study designs and larger sample sizes evaluating the efficacy of Remdesivir as a monotherapy and in combination with other choices should be conducted. Moreover, assessing the efficacy of Remdesivir in patients with different clinical subgroups and duration of symptoms is required for optimizing the selection of patients.

Our study has three major limitations. Firstly, only five articles were eligible to enter our study, and at least three of them (15, 16, 19) did not have enough sample sizes in different clinical subgroups. Therefore, comparing these subgroups regarding the efficacy of Remdesivir was not incontrovertible. Second, pooling the data of the original articles was impossible due to heterogeneity in the study design and reported outcomes. However, critical review of the study settings and methods and their associations with the reported results have enable us to compare the differences observed in the results of these studies. Third, lack of a control arm in 2 cohort studies (15, 16) and differences in baseline characteristics between the test and control arms in the 2 RCTs (17, 19) made it difficult to suggest a conclusive statement for the efficacy of Remdesivir in treating COVID-19.

CONCLUSION

Based on the current evidence, 5-day course of Remdesivir therapy in COVID-19 patients is probably efficacious and safe. Remdesivir efficacy differs in different disease severity subgroups, and hospitalized patients without invasive mechanical ventilation benefit the most from Remdesivir. Treatment can be extended to 10 days if satisfactory improvement is not achieved by day 5. Most benefits from Remdesivir therapy take place in the first 14 days, and the

patients' conditions usually do not change dramatically in the next 14 days. More studies are needed to explore the efficacy of Remdesivir monotherapy or combination therapy in different disease severity subgroups.

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