Effectiveness and Safety of Remdesivir in Patients with COVID-19: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background: Remdesivir, a nucleoside analogue antiviral drug developed for Ebola, is approved by the US Food and Drug Administration for the treatment of COVID-19. However, the findings of randomised controlled trials (RCTs) and observational studies vary regarding the effectiveness of remdesivir. We aimed to comprehensively review the available evidence identify the effectiveness and safety of remdesivir in patients with COVID-19.

Methods: Seven databases (PubMed, Web of Science, Embase, Wanfang database, SinoMed, Chinese National Knowledge Infrastructure and Chinese Science Journal Database) were searched for literatures published until November 2020. Following the PRISMA flow diagram, we included RCTs and prospective observational studies that reported the effectiveness and safety of remdesivir in patients with COVID-19. With extracting study details, as well as patient characteristics and outcomes, data were meta-analyzed by using Review Manager software version 5.4.1. Meta-analyses were conducted with fixed-effect model or random-effect model to calculate risk ratio (RR).

Results: Four studies involving 2,279 patients were included in this meta-analysis. Compared with placebo, 10-day remdesivir was associated with significant increased clinical improvement on days 14 and 28 with RR 1.19 (95%CI 1.09-1.30) and RR 1.09 (95%CI 1.03-1.16). The clinical improvement of 5-day remdesivir was better than 10-day remdesivir on days 7 with RR 1.20 (95%CI 1.02-1.41), but the efficacy advantage of 5-day remdesivir disappeared on days 14 (RR 1.08; 95%CI 0.90-1.29). Remdesivir was associated with lower serious adverse events rates and grade 3 or 4 adverse events rates as compared with placebo with RR 0.75(95%CI 0.63-0.89) and RR 0.89(95%CI 0.80-0.99). Compared with 10-day remdesivir, 5-day remdesivir for patients with COVID-19 decreased the risk of serious adverse events rates and grade 3 or 4 adverse events rates with RR 0.65(95%CI 0.47-0.88) and RR 0.74 (95%CI 0.58-0.95).

Conclusions: Our meta-analysis suggested that remdesivir would increase clinical improvement conditions and decrease serious adverse events on patients with COVID-19. 5-day remdesivir had the similar clinical effectiveness and mortality with 10-day remdesivir, and had lower serious adverse events rate. Comprehensive considering the cost and benefit, 5-day remdesivir may be a better therapeutic option if available medical resources are limited.

Introduction

Since the first cases were reported in Wuhan, Hubei Province, China, infection with coronavirus disease 2019 (COVID-19) has become a worldwide pandemic^[1]. As of December 1, 2020, COVID-19, resulted in more than 60000000 laboratory and clinical confirmed cases, and more than 1400000 deaths globally^[2], is over whelming health care systems globally. Despite unprecedented global efforts during over the past year in the fight of the COVID-19 pandemic, an effective treatment has yet been validated.

There were 4284 clinical trials registered in Clinical Trials^[3]. Currently, several drugs including remdesivir, hydroxychloroquine, chloroquine, ritonavir + lopinavir, azithromycin and oseltamivir have been evaluated

for efficacy and/or safety in COVID-19 patients in randomized controlled trials (RCTs) in different countries^[4–7]. Remdesivir was identified as a promising therapeutic candidate for COVID-19^[5–7]. Remdesivir is a nucleoside analogue prodrug that has inhibitory effects on the replication of a broad range of viruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro^[8, 9]. The results reported by Beigel et al. showed that remdesivir provided moderate clinical benefit in the treatment of patients with COVID-19^[10]. However, another clinical trial found that remdesivir did not significantly improve the time to clinical improvement and mortality in patients with COVID-19 compared with control^[11].

In view of the conflicting results reported in the effect of remdesivir for patients with COVID-19, as such, the present study aimed to synthesize available remdesivir in COVID-19 among the clinical trials using meta-analyses, to summarize remdesivir efficacy, to pool adverse effects reported in the clinical trials, provide an evidence-based reference for the rational clinical use of remdesivir.

Methods

Search Strategy

Seven databases were systematically searched for eligible studies published up to November 2020: PubMed, Web of Science, Embase, Wanfang database, SinoMed, Chinese National Knowledge Infrastructure (CNKI) and Chinese Science Journal Database (VIP). The following key words were searched, which included: “COVID-19”, “COVID 19”, “SARS-CoV-2”, “SARS CoV 2”, “2019-nCoV”, “2019 nCoV”, “remdesivir”, “clinical trial” and “randomizes controlled trial”. This search strategy was further adapted to maximize the acquisition of all pertinent articles per each database searched. After exhausting the above-mentioned databases, snowballing from pertinent articles was rigorously performed to ensure that no relevant articles were overlooked. Finally, Clinical Trials Databases were reviewed as well. All identified articles were compiled using Endnote.

Eligibility Criteria

These eligible literatures comprised randomized controlled trials (RCTs) and prospective observational studies. To be included in the meta-analysis, studies had to report on (1) patients aged over 12 years old with COVID-19 (2) interventions: 10-days remdesivir arm versus 5-days remdesivir arm and 10-days remdesivir arm versus placebo. 10-days remdesivir arm included remdesivir IV with a loading dose of 200 mg on the first day followed by 100 mg once daily for additional 9 days, 5-days remdesivir arm involved remdesivir IV with a loading dose of 200 mg on day 1 followed by 4 days 100 mg once daily. Clinical outcomes of interest were required to be presented (no systematic review or meta-analysis). Two reviewers (Yao HB & Peng JR) assessed agreed upon each study for inclusion in this systematic review. All study designs were eligible for inclusion.

Exclusion Criteria

Studies were excluded if they were editorials, reviews, case reports, letters without original data, commentaries, or critiques. Manikin and simulation studies were excluded. Evaluation of full-text articles for analysis was performed by both reviewers, and any conflict arising over study inclusion was resolved by mutual consensus.

Outcomes

The primary outcome of interest included short-term clinical improvement (7 days), mid-term clinical improvement (14 days) and long-term clinical improvement (28 days).

Clinical improvement was defined as two-point reduction from the baseline ordinal severity scale score. Secondary outcomes included: (1) adverse events rates (2) serious adverse events rates (3) grade 3 or 4 adverse events rates (4) mortality. All included studies were screened for additional common outcomes for post hoc analysis.

Statistical Analysis

Data were meta-analyzed with Review Manager software version 5.4.1. Significance in all analyses was defined as $p < 0.05$. Chi-square test was considered for the heterogeneity testing. I^2 was calculated to evaluate the heterogeneity among studies^[12]: $I^2 < 25\%$ was considered as absence of heterogeneity (homogeneity); $25\% \leq I^2 < 50\%$, low heterogeneity; $50\% \leq I^2 < 75\%$, moderate heterogeneity; and $I^2 \geq 75\%$, substantial heterogeneity. A fixed-effect model was used to meta-analyze pooled data classified as homogeneous or of low heterogeneity. A random-effect model was used to meta-analyze data classified as of moderate or substantial heterogeneity.

Results

Literature search and included studies

After searching the seven databases and removing duplicates, 1318 potentially eligible articles were reviewed. After eliminating 859 articles based on the title and abstract, the remaining 459 were read in full text and 441 were excluded. 4 clinical trials studies^[10, 11, 13, 14] and 3 observational studies^[15–17] were finally included in the systematic review. The four studies involving 2,279 individuals were selected for meta-analysis, with follow-up period ranging from 14 days to 28 days. The flow chart was shown in Fig. 1. Details on the individual included studies are listed (see Additional file 1: Table S1).

Clinical improvement of short-term, mid-term and long-term

The meta-analysis of three studies ($n = 1,691$)^[10, 11, 13] showed that as compared with placebo, 10-day remdesivir was associated with significant increased clinical improvement on days 14 (mid-term) and 28 (long-term) with RR 1.19 (95%CI 1.09–1.30) and RR 1.09 (95%CI 1.03–1.16), while no-significant difference was found between 10-day remdesivir group and placebo on the short-term clinical improvement (day 7) by the pooled result of two studies (RR = 1.01; 95%CI 0.82–1.25). Among the 3 studies reporting clinical improvement between 10-day remdesivir treatment and placebo, no

heterogeneity was detected on days 7 ($I^2 = 0\%$; $p = 0.97$), 14 ($I^2 = 0\%$; $p = 0.68$) and 28 ($I^2 = 0\%$; $p = 0.94$), so fixed-effect models were used to meta-analyze the data (Fig. 2).

Two studies ($n = 781$)^[13, 14] investigated clinical improvement difference between 10-day remdesivir group and 5-day remdesivir group, the meta-analysis demonstrated that 5-day remdesivir had better short-term (day 7) clinical improvement than 10-day remdesivir group with RR 1.20 (95%CI 1.02–1.41), but the difference of long-term (day 14) clinical improvement between these two groups was not statistically significant (RR 1.08; 95%CI 0.90–1.29). Heterogeneity of these two studies was not significant on days 7 ($I^2 = 0\%$; $p = 0.55$), but moderate heterogeneity existed on days 14 ($I^2 = 69\%$; $p = 0.07$), so a random-effect model was used to meta-analyze the data (Fig. 3).

Adverse events rates

Three studies ($n = 1,865$)^[10, 11, 13] show adverse events rates of remdesivir arm was not significantly different as compared with placebo (RR = 1.02; 95%CI 0.87–1.20). Moderate heterogeneity was detected among included studies ($I^2 = 69\%$; $p = 0.04$), and a random-effect model was used to analyze the data (Fig. 4).

Two studies ($n = 781$)^[13, 14] observed the adverse events rates of 10-day remdesivir group and 5-day remdesivir group. The pooled result illustrated no significant difference existed between these two treatment groups (RR = 0.92; 95%CI 0.83–1.02). Heterogeneity was not significant between studies ($I^2 = 0\%$; $p = 0.41$), and a fixed-effect model was used for the data (Fig. 5).

Serious adverse events rates

As shown in Fig. 6, the meta-analysis result of three studies ($n = 1,865$)^[10, 11, 13] shown that the serious adverse events rate of remdesivir treatment was obviously lower than that of placebo, with significant difference (RR = 0.75; 95%CI 0.63–0.89). No heterogeneity was detected among three studies ($I^2 = 0\%$; $p = 0.56$), and a fixed-effect model was used to meta-analyze the data. As compared with 10-day remdesivir, 5-day remdesivir treatment reflected a lower serious adverse events rate (RR = 0.65; 95%CI 0.47–0.88) by the pooled result of two studies ($n = 781$)^[13, 14]. There was no heterogeneity between two studies ($I^2 = 0\%$; $p = 0.40$), and a fixed-effect model was used in this analysis (Fig. 7).

Grade 3 or 4 adverse events rates

The pooled result from three studies ($n = 1,865$)^[10, 11, 13] that reported the grade 3 or 4 adverse events rates of remdesivir and placebo indicated that COVID-19 patients who treated by remdesivir suffered significantly lower risk of grade 3 or 4 adverse events than patients of placebo group (RR = 0.89; 95%CI 0.80–0.99). No heterogeneity was detected ($I^2 = 0\%$; $p = 0.55$), so a fixed-effect model was used in this analysis (Fig. 8).

By the pooled result of two studies ($n = 781$)^[13, 14] with RR 0.74 (0.58–0.95), the difference of grade 3 or 4 adverse events rates between 10-day remdesivir and 5-day remdesivir was statistically significant. No heterogeneity was detected ($I^2 = 0\%$; $p = 0.60$), and a fixed-effect model was used (Fig. 9).

Mortality

As illustrated in Fig. 10, the mortality of remdesivir and placebo was similar with RR 0.78 (0.59–1.03), no heterogeneity was detected among three studies ($n = 1,882$)^[10, 11, 13] that investigated the mortality of remdesivir and placebo ($I^2 = 0\%$; $p = 0.59$). The mortality difference between 10-day remdesivir and 5-day remdesivir was also not statistically significant (RR = 0.74; 95%CI 0.41–1.33), in the view of no heterogeneity between included two studies ($n = 781$)^[13, 14], we used a fixed-effect model to analyze the data (Fig. 11).

Discussion

This is the most up-to-date systematic review and meta-analysis to compare the effectiveness and safety of 10-day remdesivir to 5-day remdesivir or placebo among hospitalized patients with confirmed COVID-19 infection and moderate or severe pneumonia. Hospitalized patients with COVID-19 who received 10-day remdesivir had greater clinical improvement and less serious adverse events than those who received placebo, however there was no difference in mortality or rate of all adverse events between remdesivir-treated and placebo-treated patients. Compared with 10-day remdesivir, 5-day remdesivir was associated with better clinical improvement in the early stage of clinical experiments and fewer serious adverse events, albeit the superiority in clinical improvement of 5-day remdesivir subsequently disappeared. The mortality and adverse events rates between 5-day remdesivir and 10-day remdesivir are similar.

Compared with other similar published works^[18–21], this meta-analysis did not limit the concerned outcome to clinical improvement, adverse events rates and mortality were also included in our analysis. Our findings in terms of clinical improvement corroborate the results of previous studies^[18–21] which demonstrated that hospitalized patients treated by remdesivir had better clinical improvement than those who treated by placebo. But different from the results of previous systematic reviews which indicated that 5-day remdesivir treatment might be superior to the 10-day treatment with regard to clinical improvement, although the 5-day remdesivir was associated with better short-term clinical improvement than 10-day, the long-term clinical improvement of 5-day remdesivir and 10-day remdesivir are similar. Consistent with another meta-analysis review, our study reflected that mortality and serious adverse events rate of patients treated by remdesivir were lower than those of patients treated by placebo. Limited literature explored the differences of mortality and adverse events rate between 10-day remdesivir arm and 5-day remdesivir arm, our research found that prolonged usage of remdesivir did not confer benefit to patients in mortality and adverse events rate, what is more, 5-day remdesivir might be more safety since the grade 3 or 4 adverse events rate and serious adverse events rate were lower in the 5-day therapy group than 10-day. Other three prospective observational studies^[15–17] also added to evidence that

remdesivir was associated with significantly greater clinical improvement and less adverse events versus placebo.

At present, there were only four RCT studies ^[10, 11, 13, 14] evaluated the safety and effectiveness of remdesivir for the treatment of patients with COVID-19. An open-label trial implemented by Goldman^[14] included two treatment arms of 10-day remdesivir and 5-day remdesivir, so the clinical benefit of remdesivir could not be properly assessed cause lacking of a placebo control group and open-label design. Furthermore, the follow-up duration of this trial^[14] was merely up to 14 days, no data were collected on longer-term effectiveness and safety. One study ^[11] conducted in Wuhan was terminated early as no sufficient patients were enrolled after the outbreak in Wuhan was well controlled. The power to detect differences in clinical outcomes reduced because the sample size did not reach its target number. Besides that, the effects of remdesivir may be obscured in this RCT^[11] because the concomitant use of corticosteroids in patient group might promote viral replication. The quality of Spinner's study^[13] may be affected by its open-label design, which potentially led to biases in decisions related to concomitant medication use and hospital discharge. The study of Beigel ^[10] was conducted in patients with a wide range of disease severity. This study was not powered to detect differences within subgroups.

Our meta-analysis has certain limitations. First, although there was no evidence of statistical heterogeneity and random effects model was choosing if statistical heterogeneity existed, some clinically meaningful heterogeneity between studies was highly likely (open-label, concomitant use, infection severity, and patient comorbidity). Secondly, given the inconsistency in clinical status measure and clinical improvement definition among different studies, the interpretation of the pooled results must be cautious. Thirdly, the included studies were not adequately designed to directly address the question of whether 5-day remdesivir exposure could positively affect treatment outcomes as compared with placebo. Only one study ^[13] provided direct evidence that patients randomized to the 5-day remdesivir group had significantly higher odds of a better clinical status compared with those randomized to standard care and the difference in adverse events proportions between these two groups was not statistically significant.

Conclusions

In conclusion, remdesivir in patients with COVID-19 was associated with better clinical improvement than placebo. The effectiveness of 5-day remdesivir and 10-day remdesivir were similar, even 5-day remdesivir had lower serious adverse events rate than 10-day remdesivir. Considering cost and benefit of the treatment for patients with COVID-19, 5-day remdesivir might be a better therapeutic option if available medical resources are limited. Further high-quality evidence supporting the effectiveness and safety of remdesivir in patients with COVID-19 is imperative.

Declarations

Authors' contributions

HBY, JRP and XMZ contributed equally to this work. HBY, JRP and XMZ collected the data, did the meta-analysis, performed the data statistical analysis, and drafted the manuscript. ZY, HY and XMT participated in the design and provided clinical aspects implications. YDL and MJW contributed to study supervision and revised the manuscript for important intellectual context. XDD reviewed and helped to revise the manuscript. All authors read and approved the final manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary files.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Competing interests

The authors have no existing or potential financial conflict with the content of this manuscript.

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Figures

Figure 1

The literature search and study selection flow diagram

Figure 2

Forest plot of clinical improvement rates between 10-day remdesivir group and placebo group

Figure 3

Forest plot of clinical improvement rates between 5-day remdesivir group and 10-day remdesivir group

Figure 4

Forest plot of adverse events rates between remdesivir group and placebo group

Figure 5

Forest plot of adverse events rates between 5-day remdesivir group and 10-day remdesivir group

Figure 6

Forest plot of serious adverse events rates between remdesivir group and placebo group

Figure 7

Forest plot of serious adverse events rates between 5-day remdesivir group and 10-day remdesivir group

Figure 8

Forest plot of grade 3 or 4 adverse events rates between remdesivir group and placebo group

Figure 9

Forest plot of grade 3 or 4 adverse events rates between 5-day remdesivir group and 10-day remdesivir group

Figure 10

Forest plot of mortality between remdesivir group and placebo group

Figure 11

Forest plot of mortality between 5-day remdesivir group and 10-day remdesivir group

Supplementary Files

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