

The safety, tolerability and mortality reduction efficacy of remdesivir; based on randomized clinical trials, observational and case studies reported safety outcomes: an updated systematic review and meta-analysis

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Abstract

Introduction: Remdesivir, an experimental antiviral drug has shown to inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), both *in vitro* and *in vivo*. The present systematic review and meta-analysis were performed to quantify the safety and tolerability of remdesivir, based on safety outcome findings from randomized controlled trials, observational studies and case reports of remdesivir in coronavirus disease 2019 (COVID-19) patients.

Methods: We have performed a systematic search in the PubMed, Google Scholar and Cochrane Library using specific keywords such as 'COVID-19' OR 'SARS CoV-2' AND 'Remdesivir'. The study endpoints include total adverse events (AEs), serious adverse events (SAEs), grade 3 and grade 4 AEs, mortality and drug tolerability. Statistical analysis was carried out by using Revman 5.4 software.

Results: Total 15 studies were included for systematic review, but only 5 randomized clinical trials (RCTs) ($n = 13,622$) were included for meta-analysis. Visual inspection of the forest plots for remdesivir 10-day *versus* placebo and remdesivir 10-day *versus* 5-day groups revealed that there is a significant difference in SAEs [10-day remdesivir *versus* control (odds ratio [OR] = 0.55, 0.40–0.74) $p = 0.0001$; $I^2 = 0\%$; 10-day remdesivir *versus* 5-day remdesivir (OR = 0.56, 0.38–0.84) $p = 0.005$; $I^2 = 13\%$]. In grade 4 AEs, there is a significant difference in 10-day remdesivir *versus* control (OR = 0.32, 0.19–0.54) $p = 0.0001$; $I^2 = 0\%$, but not in comparison to 5-day remdesivir (OR = 0.95, 0.59–1.54) $p = 0.85$; $I^2 = 0\%$. But there is no significant difference in grade 3 AEs [remdesivir 10 day *versus* control (OR = 0.81, 0.59–1.11) $p = 0.19$; $I^2 = 0\%$; 10-day remdesivir *versus* 5-day remdesivir (OR = 1.24, 0.86–1.80) $p = 0.25$; $I^2 = 0\%$], in total AEs [remdesivir 10 day *versus* control (OR = 1.07, 0.66–1.75) $p = 0.77$; $I^2 = 79\%$; remdesivir 10 day *versus* 5 day (OR = 1.08, 0.70–1.68) $p = 0.73$; $I^2 = 54\%$], in mortality [10-day remdesivir *versus* control (OR = 0.93, 0.80–1.08) $p = 0.32$; $I^2 = 0\%$; 10-day remdesivir *versus* 5-day remdesivir (OR = 1.39, 0.73–2.62) $p = 0.32$; $I^2 = 0\%$] and tolerability [remdesivir 10 day *versus* control (OR = 1.05, 0.51–2.18) $p = 0.89$; $I^2 = 65\%$, 10-day remdesivir *versus* 5-day remdesivir (OR = 0.86, 0.18–4.01) $p = 0.85$; $I^2 = 78\%$].

Discussion & Conclusion: Ten-day remdesivir was a safe antiviral agent but not tolerable over control in the hospitalized COVID-19 patients with a need of administration cautiousness for grade 3 AEs. There was no added benefit of 10- or 5-day remdesivir in reducing mortality over placebo. To avoid SAEs, we suggest for prior monitoring of liver function tests (LFT), renal function tests (RFT), complete blood count (CBC) and serum electrolytes for those with preexisting hepatic and renal impairments and patients receiving concomitant hepatotoxic or nephrotoxic drugs. Furthermore, a number of RCTs of remdesivir in COVID-19 patients are suggested.

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Plain Language Summary

- Ten-day remdesivir is a safe antiviral drug with common adverse events in comparison to placebo.
- The rate of serious adverse events and grade 3 adverse events were significantly lower in 10-day remdesivir in comparison to placebo/5-day remdesivir.
- There was no significant difference in the rate of tolerability and mortality reduction in 10-day remdesivir over placebo/5-day remdesivir.
- There were no new safety signals reported in vulnerable populations, paediatric, pregnant and lactating women.

Keywords: remdesivir, COVID-19, mortality, safety, tolerability

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Introduction

In the year 2019, a novel coronavirus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. Now it became a pandemic and it was named as COVID-19, which stands for coronavirus disease 2019 by the World Health Organization (WHO).¹ The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-n CoV.

Remdesivir (GS-5734) is a novel experimental nucleotide analogue that was invented by Gilead life sciences for the treatment of Ebola virus disease (EVD) in the year 2016.^{2,3} Remdesivir has shown activity against SARS-CoV-2 *in vitro*⁴⁻⁶ and related coronaviruses, including severe acute respiratory syndrome (SARS-CoV-1) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV) as well, both *in vitro* and in animal studies.⁷⁻⁹ It has demonstrated prophylactic and restorative viability in nonclinical models of these coronaviruses. Being a phosphoramidite prodrug, it gets metabolized to an analogue of adenosine triphosphate (ATP) by intracellular kinases that inhibit viral RNA-dependent RNA polymerase (RdRp) because of its close structural similarity with the later enzyme.^{4,5,10} After its administration, it has decreased lung viral load and along with improvement in clinical symptoms of COVID-19 including respiratory function.⁷ Furthermore, it was also found that its efficacy is higher than combined interferon beta plus lopinavir-ritonavir combination in the experimental animal models of MERS-CoV infections.⁷

Remdesivir has issued an emergency use authorization by the US Food and Drug Administration

(USFDA) for hospitalized adults and children with severe COVID-19 [saturation of peripheral oxygen (SpO_2) \leq 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)].¹¹ In the European Union (EU), it has been given conditional marketing authorization for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen.¹²

The approved current dose regimen of remdesivir for COVID-19 was calculated from available *in vitro* data and bridging the PK data with the rhesus monkey experience to humans.^{6,13} For an adult, remdesivir dose is 200 mg intravenously (IV) on the first day, diluted in normal saline (0.9%) or 5% dextrose as a loading dose to be given over 60 min, followed by 100 mg diluted over 60 min daily for the next 9 days in patients on mechanical ventilation or ECMO and 5-day use in other patients (with extension to 10 days if there is no clinical improvement).¹³

The present systematic review and meta-analysis were performed to review and quantify the safety and tolerability of remdesivir, based on measured outcomes which are total adverse events (AEs), serious adverse events (SAEs), grade 3 and 4 AEs, mortality rate and tolerability from the available clinical trials, observational studies and case studies of remdesivir for the treatment of COVID-19.

Methodology

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and

Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.

Eligibility criteria for inclusion of studies

We employed the population, intervention, comparison, outcome and study design (PICOS) framework for the inclusion of studies. The randomized or nonrandomized interventional studies assessing the safety of remdesivir with or without concomitant medications compared with placebo/any other treatment/another dose of the same drug/no comparator (in case of single-arm) in patients who diagnosed with COVID-19 were included in this review. Review articles, duplicate studies and studies with no original information about remdesivir therapy were excluded. *In vitro* and animal studies were also excluded. Observational studies, meeting abstracts, case reports and case series were included in the systematic review.

Data sources and literature search

A literature search was performed in MEDLINE (PubMed), Google Scholar and the Cochrane Library using a comprehensive search strategy from inception to mid-September 2020. We also looked into the references of the included papers for more relevant studies. We employed all the Medical Subject Headings (MeSH) terms and keywords for 'COVID-19' OR 'SARS-CoV-2' AND 'Remdesivir' which were obtained from the databases and previous studies. We have restricted it to only clinical trials, randomized controlled trials, observational studies and case series. Publication year were limited to 1 year. The reference list of all included studies and a snowball search in Google were performed for any additional relevant articles.

Study selection and data abstraction

The retrieved studies from databases were screened for their title and abstracts followed by the full text in accordance with the predefined inclusion and exclusion criteria. The highly irrelevant studies only were excluded during the title/abstract screening. A well-defined data extraction sheet was employed for the data abstraction which includes the characteristics of studies, participants, intervention, comparator and outcomes. Two independent authors were involved in study

selection and data extraction, and any disagreements were resolved through consensus or by a discussion with another reviewer (KVS/SC). Figure 1 summarizes the design that we have used to report the study results in line with the PRISMA-P 2015 guidelines.

Quality assessment

The Cochrane risk of the bias assessment tool and Newcastle-Ottawa was used to assess the methodological quality of the included randomized clinical trials (RCTs) and observational studies. Two independent reviewers were involved in study selection and data extraction to limit the bias, and any disagreements were resolved through consensus or by a discussion with another reviewer (KCA and SC). Cochrane's risk of bias tool was used to assess the quality of the articles based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete outcome data, selective report and other biases. Then, the risk of bias summary graph was successfully generated as Figures 2 and 3 show.

Data analysis

Results of the final studies were reported separately in a narrative way. Measured outcomes were 'Total adverse events, serious adverse events, Grade 3 and 4 adverse events', 'tolerability', 'mortality rates' and 'time to clinical improvement'. Statistical analyses were performed using the 'Review Manager 5.4' version. A meta-analysis of categorical data was analysed, pooled the estimates and presented as odds ratio (OR) along with their 95% confidence intervals (CIs).

Heterogeneity testing

Owing to the natures of studies, substantial heterogeneity was expected, and a random-effects meta-analysis was done with the estimate of heterogeneity being taken from an inverse-variance model (DerSimonian and Laird, 1986). Heterogeneity was identified through Cochran's Q test and I^2 statistics. Heterogeneity was considered as significant if value of $p < 0.05$ and $I^2 > 50\%$. Subgroup analysis was conducted according to the study design.

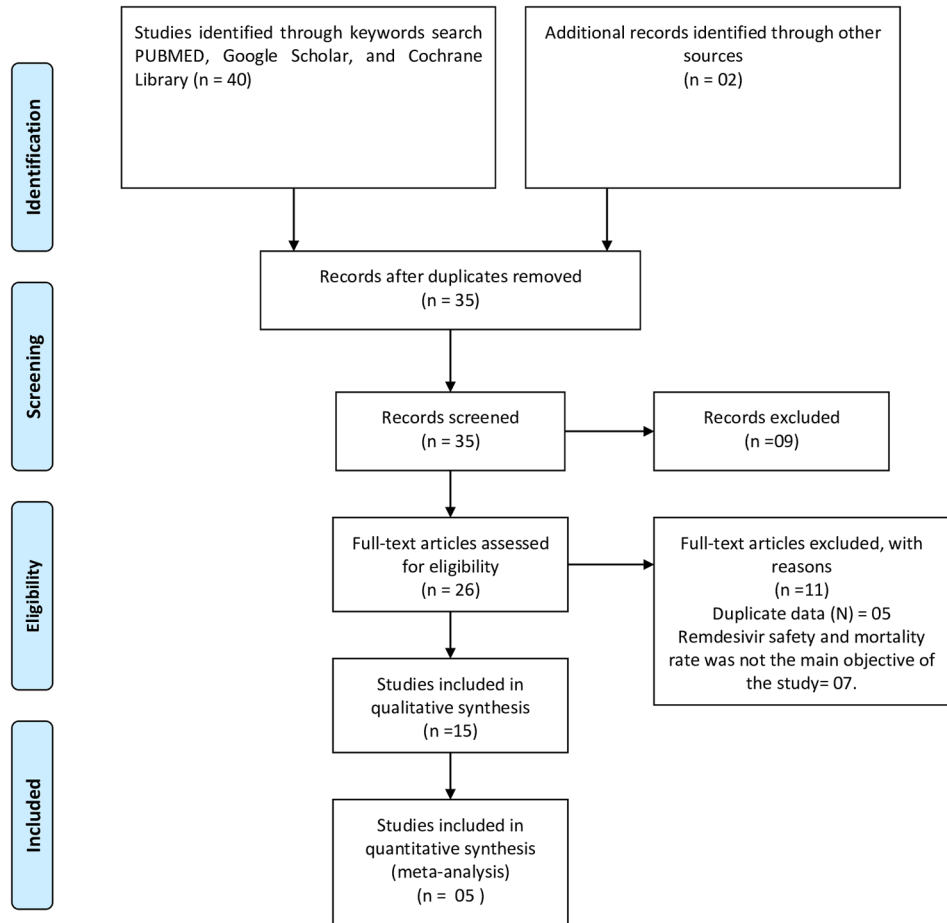


Figure 1. Remdesivir study selection PRISMA 2009 flow diagram.

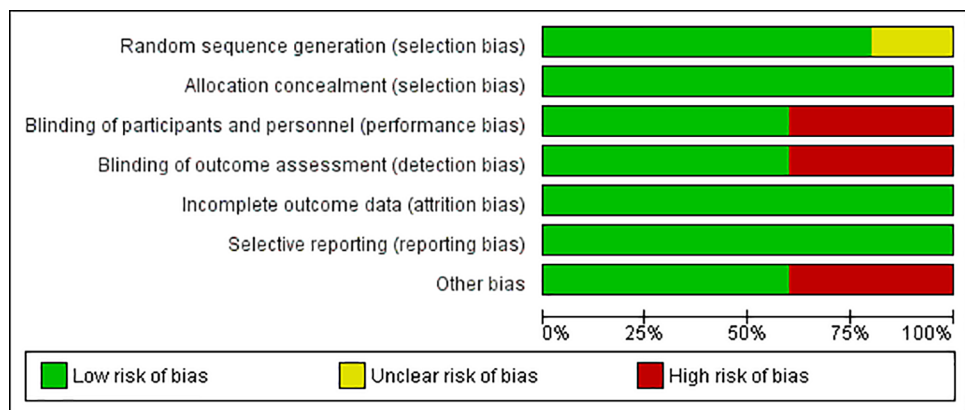


Figure 2. Risk of bias graph.

Publication bias

Publication bias was planned to visualize through funnel plot and statistically by Egger’s and Begg’s test. However, it was not possible due to an insufficient number of included studies (less than 10).

Results

Description of studies

After screening the databases, a total of 33 records were identified. In addition, another two studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Beigel et al., 2020	+	+	+	+	+	+	-
Goldman et al., 2020	+	+	-	-	+	+	+
Spinner et al., 2020	+	+	-	-	+	+	+
Wang et al., 2020	+	+	+	+	+	+	-
WHO Solidarity Trial Consortium et al., 2020	?	+	+	+	+	+	+

Figure 3. Risk of bias summary.

were taken from other resources. A total of 14 studies matched our inclusion and exclusion criteria (Figure 1). A total of five RCTs ($n = 7726$) were included in the meta-analysis. Further nine studies (non-RCTs) met the inclusion criteria for safety outcome data: four observational cohort studies ($n = 264$) and five case series ($n = 9$) (Figure 1). The dosage of remdesivir in five trials was as follows: a loading dose of 200-mg intravenous dose in the first day followed by a once-daily 100-mg intravenous dose from the second day up to 10 or 5 days.^{14–18} There are three comparators namely 10-day remdesivir and placebo, 10-day remdesivir and 5-day remdesivir. The 10-day remdesivir was administered IV as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose daily on days 2 through 10 or until hospital discharge or death. Five-day remdesivir arm includes treatment with 200-mg remdesivir on day 1 followed by 4 days 100 mg once daily. A placebo was administered in the same schedule and the same volume as the active drug.¹⁹

Randomized controlled trails

The study of Spinner and colleagues had three arms (5- and 10-day remdesivir and control), while the studies of Beigel and colleagues, Wang and colleagues and WHO Solidarity Trial Consortium and colleagues had two arms (10-day remdesivir and control) and the study of Goldman and colleagues had two arms (5- and 10-day remdesivir).^{14–18}

A multinational, randomized, placebo-controlled trial (NCT04280705) study named National Institute of Allergy and Infectious Diseases adaptive COVID-19 treatment trial (NIAID ACTT-1) has been conducted by Beigel and colleagues, in 1062 (remdesivir: 538; placebo: 521) COVID-19-positive patients with lung involvement evidence. All the patients were randomly assigned in a 1:1 ratio to receive either 10 days of remdesivir or a placebo. Dose and route of intervention drugs administered were 200 mg of remdesivir IV on day 1 followed by 100 mg from day 2 to 10, in a single daily infusion, or the same volume of

placebo infusions for a total of 10 days. Efficacy, safety, tolerability and mortality findings were announced.

A double-blind randomized controlled trial (NCT04257656) by Wang and colleagues assessed the effectiveness and safety of remdesivir in 237 admitted severe COVID-19 pneumonia adult (aged ≥ 18 years) patients. All enrolled patients were randomly assigned to receive remdesivir (200 mg on day 1 followed by 100 mg from day 2 to 10 in a single daily infusion) and control (same volume of placebo infusions for a total of 10 days). Study findings assessed include efficacy, safety, tolerability and rate of mortality in both the groups.¹⁴

An open-label phase 3 randomized trial called SIMPLE (NCT04292899) has been conducted in 408 hospitalized COVID-19 patients with oxygen saturation of 94% or less and radiological evidence of severe pneumonia. Out of 408, only 402 were enrolled and underwent randomization, and among them, only 397 patients were initiated with treatment. Remdesivir was given in the following two different groups: 5 days ($N = 200$) and 10 days ($N = 197$), respectively. The dose of remdesivir administered was 200 mg on day 1 followed by 100 mg IV once daily for the remaining days (4 or 9 days). Safety outcome findings described include total AEs, SAEs, total deaths and drug discontinuation due to SAEs.¹⁵

Another randomized, open-label trial of remdesivir was conducted in 584 hospitalized patients with confirmed SARS-CoV-2 infection and moderate COVID-19 pneumonia. Patients were randomized to 10-day group ($n = 197$), 5-day group ($n = 199$) and standard of care group ($n = 200$). Remdesivir group received 200 mg of remdesivir IV on day 1, followed by 100 mg of remdesivir once daily for the subsequent days, infused over 30–60 min. Safety findings released which include total AEs, SAEs, total deaths and drug discontinuation due to SAEs.¹⁶

Recently, the largest open-label randomized controlled trial of four COVID-19 repurposed drugs including remdesivir conducted by the WHO announced its findings. The trial has been conducted in 11,330 hospitalized adult COVID-19 patients at 405 hospitals in 30 countries. Among them, remdesivir has been administered to around 2750 included patients. The primary outcome was in-hospital mortality (regardless of whether

death occurred before or after day 28) and secondary outcomes were initiation of mechanical ventilation and duration of hospitalization, but safety outcomes were not assessed.¹⁷

Observational and case series studies

Safety findings of an open-label observational study in 53 COVID-19 patients, who have received 10-day remdesivir on a compassionate use basis: Among 53, a total of 60% (32) of patients reported AEs. The most common AEs reported include increased hepatic enzymes (22%), diarrhoea, rash, renal impairment and hypotension.¹⁸

Safety findings of another prospective (compassionate), open-label study of remdesivir in 48 patients (35 patients received remdesivir out of 48) with SARS-CoV-2 pneumonia and aged 18 years and older (undergoing mechanical ventilation or with an oxygen saturation level of $\leq 94\%$ in the air or a National Early Warning Score 2 of ≥ 4) have been released out and the most common AE reported was hepatotoxicity.²⁰

In a case series of five COVID-19 patients, who have required intensive care unit (ICU) admission due to acute respiratory distress syndrome (ARDS) and were treated with remdesivir, AEs such as maculopapular rash, elevated transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] levels and renal failure were reported in four of the five patients.²¹

Another 77-year-old COVID-19 female patient with a history of hypertension and hyperlipidaemia received recommended dose of remdesivir. However, within 2 days after administering remdesivir, the patient had shown worsening of renal function followed by multiorgan failure.²²

Safety findings of a compassionate use study of remdesivir in 86 pregnant women (67 pregnant and 19 postpartum days 0–3) presented in a virtual COVID-19 Conference (held 10–11 July 2020) have shown that no new AEs were observed.²³

A 35-year-old COVID-19-positive pregnant (22 weeks and 2 days of gestation) woman showed no new AEs, except mild hepatic transaminase elevations.²⁴

In acute EVD trial [The PAmoja TuLinde Maisha(PALM)] 3% of pregnant women and 26% of children have been administered remdesivir without any serious adverse events. Furthermore, there were no reports of foetal toxicity in some pregnant women with Ebola and Marburg virus disease and is being used to treat on a compassionate use basis, even in pregnant patients with severe COVID-19.²

Safety results of a prospective compassionate open-label study of remdesivir in COVID-19 children presented in a virtual COVID-19 Conference (held on 10–11 July 2020) showed that most of the 77 children with severe COVID-19 improved with remdesivir, and no new safety signals were observed.²⁵

A case report of a COVID-19 paediatric patient, who has received remdesivir under the compassionate use programme, has shown no new AEs except mildly elevated transaminases.²⁶

Another 5-year-old COVID-19 child with precursor B-cell acute lymphoblastic leukaemia tolerated remdesivir well without any AEs except elevation in ALT on the third day.²⁷

An open-label, single-arm phase 2/3 trial (CARAVAN) of remdesivir was initiated in June 2020 to assess safety, tolerability, pharmacokinetics and efficacy in children with moderate-to-severe COVID-19 (birth to age 18 years). Results are awaited.²⁸

Quality assessment

Among included trials, two trials (Goldman and colleagues, and Spinner and colleagues, WHO Solidarity Consortium and colleagues) were carried out in an open-label manner and other biases were also detected in two studies (Beigel and colleagues and Wang and colleagues). Risk of bias assessment of four prospective studies (Antinori and colleagues, Grein and colleagues, Burwick and colleagues and Chiotos and colleagues) with Newcastle–Ottawa scale reported medium quality as all these studies inadequately reported information regarding lack of control group and insufficiency of follow-up time which are also other sources of bias in these studies (Figures 2 and 3).

Meta-analysis outcomes results

Remdesivir: 10 day versus placebo or standard of care and remdesivir 10 day versus 5-day remdesivir treatment

Total AEs: Among included trials, four trials ($n = 2279$) (Beigel and colleagues, Spinner and colleagues, Wang and colleagues and Goldman and colleagues) reported on the number of patients with total AEs, and the final analysis findings revealed that there is no significant difference in total AEs in both remdesivir 10-day treatment group *versus* control (OR = 1.07, 0.66–1.75) $p = 0.77$; $I^2 = 79\%$, and remdesivir 10-day treatment group *versus* 5-day treatment groups (OR = 1.08, 0.70–1.68) $p = 0.73$; $I^2 = 54\%$ (Figure 4).

SAEs: Four trials ($n = 2279$) (Beigel and colleagues, Spinner and colleagues, Wang and colleagues and Goldman and colleagues) reported on the number of patients with SAEs. Total 136 out of 1285 patients who have been treated with remdesivir 10 days experienced SAEs compared with 196 out of 1187 patients in the control group. There is a significant reduction in SAEs in both 10-day remdesivir group *versus* control group (OR = 0.55, 0.40–0.74) $p = 0.0001$; $I^2 = 0\%$, and 10-day remdesivir group *versus* 5-day remdesivir group (OR = 0.56, 0.38–0.84) $p = 0.005$; $I^2 = 13\%$ (Figure 5). Overall, 10-day remdesivir treatment reduced frequency of SAEs by 9.5% compared with the control.

Grade 3 AEs: Four trials ($n = 2279$) (Beigel and colleagues, Spinner and colleagues, Wang and colleagues and Goldman and colleagues) have reported on the number of patients with grade 3 AEs, and the final analysis findings revealed that there is no significant difference in grade 3 AEs in 10-day remdesivir treatment group *versus* control group (OR = 0.81, 0.59–1.11) $p = 0.19$; $I^2 = 0\%$, and 10-day remdesivir group *versus* 5-day remdesivir group (OR = 1.24, 0.86–1.80) $p = 0.25$; $I^2 = 0\%$ (Figure 6).

Grade 4 AEs: Four trials ($n = 2276$) (Beigel and colleagues, Spinner and colleagues, Wang and colleagues and Goldman and colleagues) have reported on the number of patients with grade 4 AEs, and the final analysis findings revealed that there is a significant difference in grade 4 AEs in

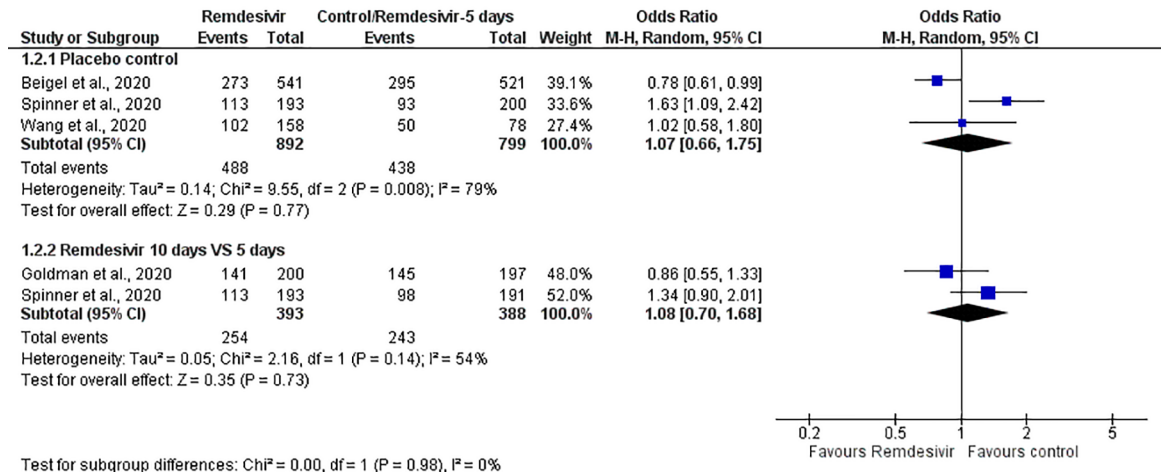


Figure 4. Total adverse events.

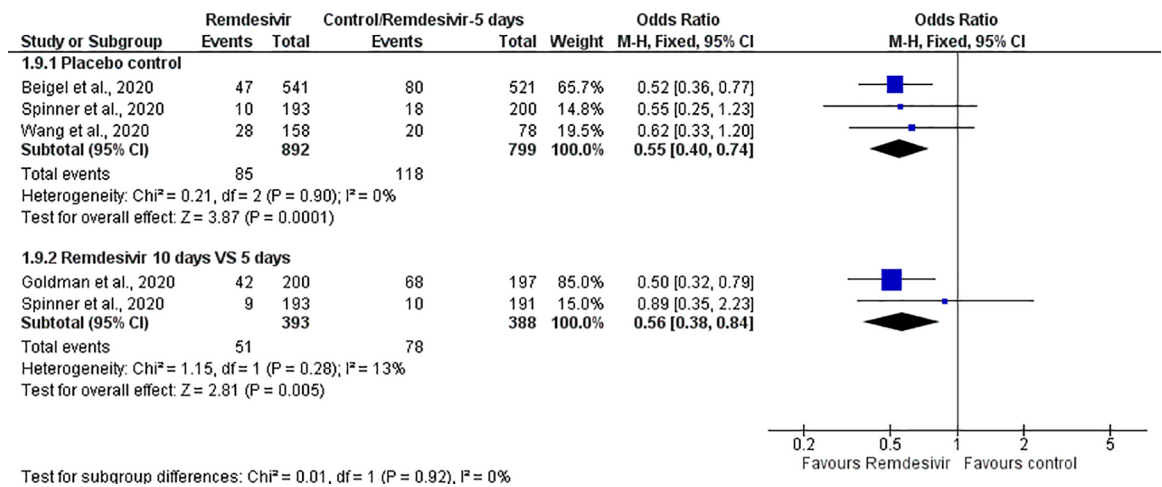


Figure 5. Serious adverse events.

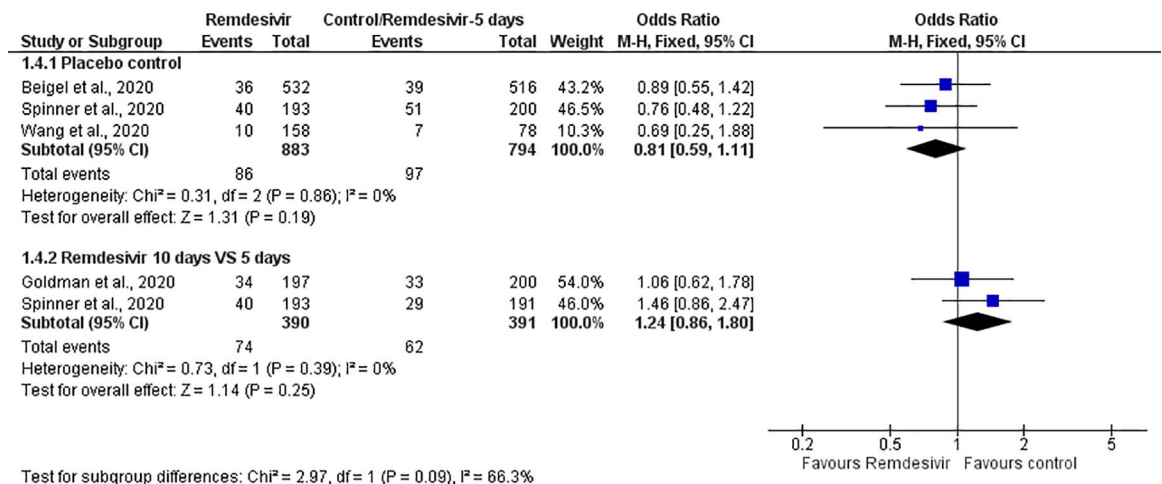


Figure 6. Grade 3 Adverse Events.

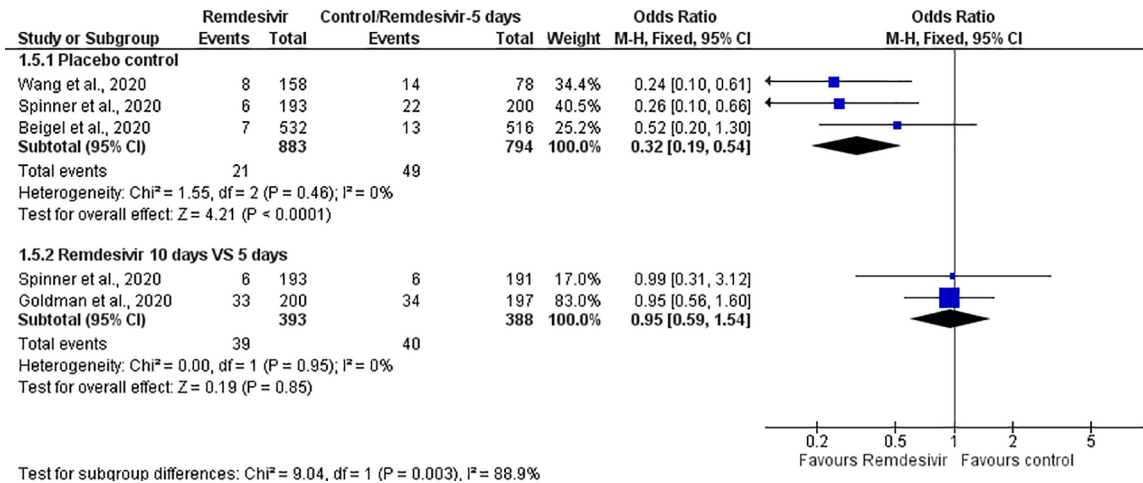


Figure 7. Grade 4 Adverse Events.

10-day remdesivir group *versus* control group (OR = 0.32, 0.19–0.54) $p = 0.0001$; $I^2 = 0\%$, but there is no significant difference in 10-day remdesivir group *versus* 5-day remdesivir group (OR = 0.95, 0.59–1.54) $p = 0.85$; $I^2 = 0\%$ (Figure 7).

Tolerability: Four trials ($n = 2279$) (Beigel and colleagues, Spinner and colleagues, Wang and colleagues and Goldman and colleagues) have reported on the number of patients who discontinued the treatment drug (intolerance). Findings of analysis revealed that there is no significant difference between 10-day remdesivir treatment group *versus* control group (OR = 1.05, 0.51–2.18) $p = 0.89$; $I^2 = 65\%$, and 10-day remdesivir group *versus* 5-day remdesivir group (OR = 0.86, 0.18–4.01) $p = 0.85$; $I^2 = 78\%$ (Figure 8).

Mortality: All the five trials ($n = 7726$) (Beigel and colleagues, Spinner and colleagues, Wang and colleagues, Goldman and colleagues and WHO Solidarity Consortium and colleagues) have reported on the mortality rate, and the final analysis was done between remdesivir *versus* control (385 *versus* 394) and remdesivir 10-day *versus* 5-day treatment (24 *versus* 18). ACTT-1 trial (Biegel and colleagues) reported on 15- and 29-day mortality; Wang and colleagues, WHO Solidarity Trial Consortium and colleagues and Spinner and colleagues trials reported on 28-day mortality; and Goldman JD and colleagues reported on 14-day mortality. Final analysis findings revealed that there is no significant reduction

of mortality in both, patients who have received 10-day remdesivir group compared with the control group (OR = 0.93, 0.80–1.08) $p = 0.32$; $I^2 = 0\%$, and 10-day remdesivir group compared with the 5-day remdesivir group (OR = 1.39, 0.73–2.62) $p = 0.32$; $I^2 = 0\%$ (Figure 9).

Discussion

Evaluation of safety, tolerability and mortality reducing the efficacy of a newer drug-like remdesivir based on the real-world safety data from clinical trials, observational studies and case reports is helpful to understand and to use the newer drug more safely in the clinical treatment of COVID-19 patients. In the present systematic review and meta-analysis (five RCTs) of remdesivir safety, tolerability and mortality reducing efficacy over placebo and 10-day remdesivir over 5-day remdesivir treatment in COVID-19 patients, it was shown remdesivir 10-day treatment is safe and tolerable with common AEs when administered IV in various RCTs, cohort studies and case series studies over placebo and 5-day remdesivir treatment.^{14–28} Ten-day remdesivir treatment has shown significantly less number of SAEs over the placebo and/or 5 day. Remdesivir when compared with the placebo and/or 5-day treatment group, there was no significant difference in total AEs and grade 3 and 4 AEs. Overall, remdesivir is a safe drug for the treatment of COVID-19, with mild AEs. However, there was no significant reduction or difference in mortality and tolerability as well. In addition, there were no new AEs reported in the

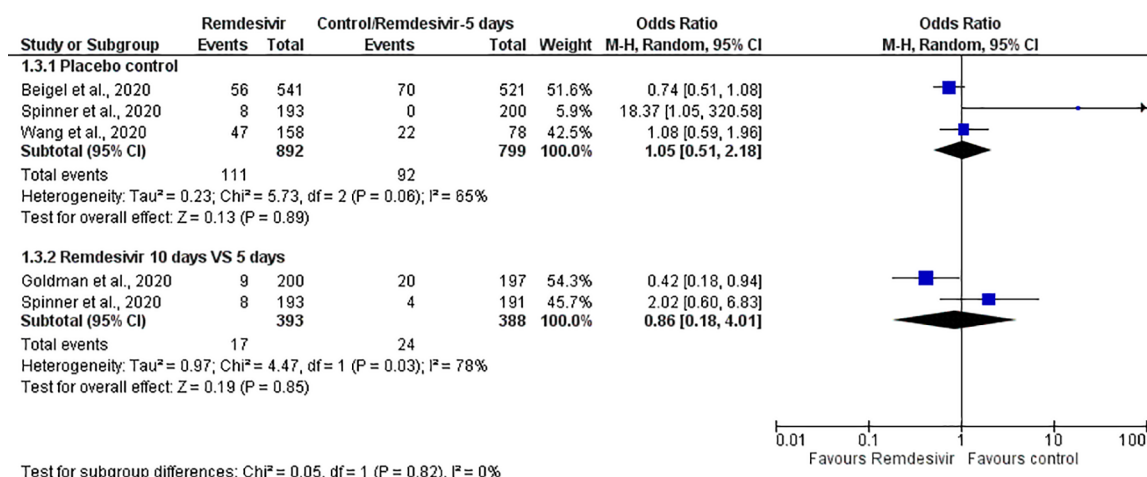


Figure 8. Tolerability.

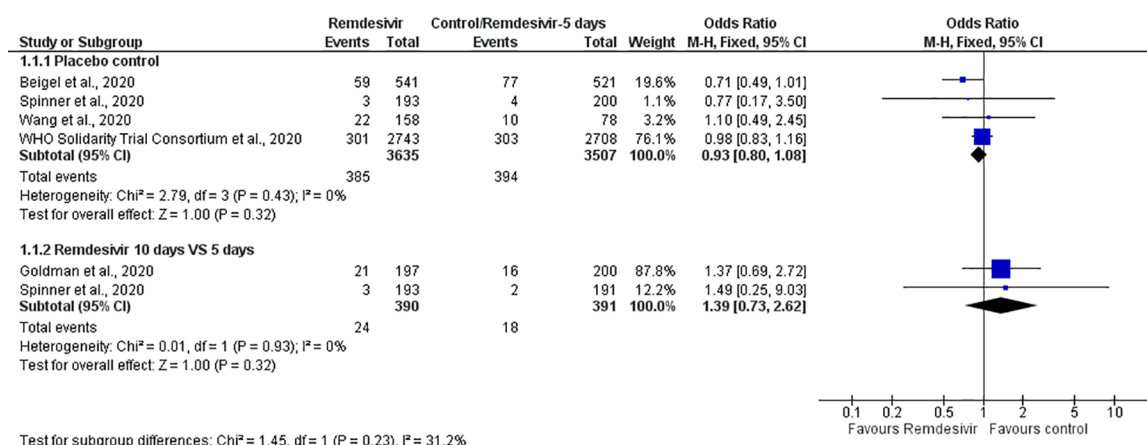


Figure 9. Mortality.

special vulnerable population like pregnant, postpartum women and paediatric patients as well.¹³ Although remdesivir was recommended to use in these vulnerable COVID-19 patients on an emergency basis, there is much dearth of safety data in this special population.²⁹ It is because there were no clinical trials that have included this vulnerable population. Hence, unless required, based on clinical severity and emergency, remdesivir should be avoided, especially in pregnant women. Lactating mothers should use remdesivir with careful infant monitoring or discontinue breastfeeding and abstain from treatment with remdesivir, until the availability of more clinical trials.²⁹

Based on the available evidence till now, most common AEs observed from remdesivir administration

include nausea, vomiting, respiratory failure or acute respiratory distress syndrome, delirium, headache, anaemia, hematuria, hypernatremia, acute kidney injury, renal impairment, elevated serum creatinine, rash, fever, diarrhoea, constipation, hyperglycemia, elevated transaminase enzymes (ALT and AST), prothrombin time (PT), ecchymosis, constipation, hypotension, atrial fibrillation, multiorgan dysfunction syndrome, infusion-related reactions, phlebitis, diaphoresis shivering and gastric haemorrhage.^{2,14–28} The rate of occurrence of these common AEs was mostly similar between remdesivir and placebo. Remdesivir was discontinued in the COVID-19 patients due to SAEs including gastrointestinal symptoms, elevated aminotransferases and worsened renal function with elevated serum creatinine and cardiopulmonary status.

Renal toxicity abnormalities due to remdesivir were not seen in the preclinical toxicological studies. Owing to the limited aqueous solubility of remdesivir, it is prepared in a cyclodextrin solubilizing agent, sulfobutylether- β -cyclodextrin sodium (SBECD), and it accumulates in individuals with moderate or severe renal impairment. Hence, before administering remdesivir, it is very essential to know the initial estimated glomerular filtration rate (eGFR). Thus, remdesivir is not recommended in adults and paediatric patients (older than 28 days) with an eGFR less than 30 ml/min (per 1.73 m² in young adults) or in the full-term neonates (at least 7 days and \leq 28 days old) with serum creatinine greater than or equal to 1 mg/dl unless the potential benefit outweighs the risk. Even discontinuation of the drug is required if eGFR falls to greater than or equal to 50% from baseline.³⁰ Because urine is found to have 49% of its metabolite GS-441524, in renal compromised patients, it may lead to increased plasma concentration of the metabolite GS-441524. Until today, there were no clinical studies in patients with renal impairment. Given the short duration of therapy and the low concentration of the cyclodextrin vehicle, the risks in patients with renal impairment may be relatively low.³¹

Hepatic abnormalities were not observed in the preclinical toxicology studies of remdesivir. However, in RCTs, observational studies and case studies have revealed abnormal hepatic function tests in patients who have received remdesivir, including children and pregnant and lactating women.^{2,14-26,32,33} But given the potential benefits outweigh the potential risk ratio, no dose modification is currently recommended in COVID-19 patients, although it is not recommended in patients with elevated ALTs greater than 5 times upper limit of normal (ULN) or more or if the increase in ALT is accompanied by signs or symptoms of hepatic inflammation or increasing conjugated bilirubin, alkaline phosphatase or an international normalized ratio (INR) and along with other hepatotoxic drugs.³⁴ Generally, after administration of remdesivir, it is rapidly cleaved by hydrolases; thus, the effect of hepatic impairment on remdesivir plasma levels is likely low.³¹⁻³³ Therefore, elevated liver enzymes are not a contraindication to enrol patients with COVID-19 in trials for investigational therapies. Elevated liver biochemistries have been commonly observed in clinical trials, but the elevations had not been greater than 10 times the

baseline values.³²⁻³⁵ See Table 1 for details about study design, participants and measured outcomes in the included studies.

Overall, remdesivir is absolutely contraindicated in patients (adults and paediatric) who have hypersensitivity to remdesivir, in patients with an eGFR $<$ 30 ml/min per 1.73 m² unless the potential benefit outweighs the risk, patients with elevated ALTs ($>$ 5 times the ULN) or severe hepatic dysfunction and pregnant and breastfeeding women. Furthermore, remdesivir is also contraindicated to be used with concomitant drugs such as vasopressors, which may lead to end-organ failure, and with hydroxychloroquine and chloroquine to avoid drug interactions, which may lead to decreased activation of remdesivir into active compound.^{12,36}

A systematic review and meta-analysis of remdesivir efficacy and safety have shown significantly higher adverse drug events (ADEs) in the 10-day arm of remdesivir compared with the control. In the control, the elevation of ALT and AST, and the decreased creatinine clearance (grade 3 or 4) were also numerically higher. In our findings, it was revealed that there was a significant difference in grade 3 ADEs also in the 10-day remdesivir group in comparison to the control group, but there is no difference in 10-day remdesivir over 5-day remdesivir treatment. They have also reported that SAEs were significantly lower with an absolute difference of 6% in the 10-day remdesivir arm compared with the control, whereas in our study, 10-day remdesivir treatment has shown fewer SAEs than placebo with an absolute difference of 9.5% in comparison to the control. They have also shown similar results on the mortality that there was no significant difference between remdesivir 10-day treatment and placebo or between the 5- and 10-day treatment.³⁷

There were some limitations in our systematic review and meta-analysis. The total number of RCTs available were less in number with less number of participants ($n = 2342$). Although remdesivir was administered in the recommended dose by some cohort studies, but the control arm was not used in the latter studies.^{14,15} Pooling the data of the original articles was impossible due to heterogeneity in study design and reported outcomes, but the reported results have enabled us to compare the differences observed in the results of these studies. Overall, more high-quality RCTs

Table 1. Details about study design, participants and measured outcomes in the included studies.

S. no.	Type of study	Patient characteristics	Interventions	Outcomes	References
1	Clinical trial (NCT04280705)	Total 1042 (remdesivir: 541; placebo: 521) COVID-19 hospitalized adult patients with evidence of lower respiratory tract involvement. The median age: 58.9 ± 15.0 years. Male: 684 (64.4%); female: 375 (35.41%).	Remdesivir: 200-mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days). Placebo: Same volume of placebo for 10 days.	Total non-SAEs observed: remdesivir group: 131 [24.6%]; placebo group: 163 [31.6%]; 295 [57.2]. Total SAEs observed: remdesivir: 131 [24.6%]; placebo: 163 [31.6%]. Serious respiratory failure AEs: Remdesivir: 47 (8.8%); placebo: 80 (15.5%) Grade 3 or 4 SAEs: Remdesivir: 273 (51.3%); placebo: 295 (57.2%) Most common non-SAEs: Decreased eGFR or increased serum creatinine [40 (7.4%) versus 38 (7.3%)]; anaemia [43 (7.9%) versus 47 (9.0%)]; pyrexia [27 (5.0%) versus 17 (3.3%)]; hyperglycemia [22 (4.1%) versus 17 (3.3%)]; increased ALT, AST or both [22 (4.1%) versus 31 (5.9%)] in the placebo group. Mortality: Day 15: remdesivir: 6.7%; placebo: 11.9% (HR, 0.73; 95% CI, 0.52–1.03); Day 29: remdesivir: 11.4%; placebo: 15.2% (HR, 0.73; 95% CI, 0.52–1.03). Patients who were on oxygen supplementation but did not require high-flow oxygen or ventilator support: Remdesivir: 4%; placebo: 12.7% (HR, 0.30; 95% CI, 0.14–0.64)	Beigel et al. ¹⁹
2	Clinical trial (NCT04257456)	Total COVID-19-positive adults (n) = 237 (hospital admitted aged ≥18 years), and oxygen saturation of ≥94% or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤300 mmHg and radiologically confirmed pneumonia (remdesivir = 158; placebo = 79). Mean age: 66 (57–73) versus 64 (53–70) years. Sex: Male: 89 (56%) versus 51 (65); female: 69 (44%) versus 27 (35)	Remdesivir: intravenous remdesivir (200 mg on day 1 followed by 100 mg on day 2–10 in single daily infusions). Placebo: Same volume of placebo infusion for 10 days.	Total AEs observed: remdesivir: 102 (66%) (control: 64%). Common AEs reported in the remdesivir group: nausea [5%], constipation [14%], hypalbuminaemia [13%], hypokalemia [12%], increased blood glucose [7%], increased AST [5%], blood lipids [6%], anaemia [12%], rash [7%], thrombocytopenia [10%] and increased total bilirubin [10%]. SAEs: Total 18% [28] SAEs were reported in the remdesivir group [26% (20) in the placebo group]. Grade 3 or 4 AEs: remdesivir 13 (8%); control: 11 (14%). Drug discontinuation: 12% discontinued the treatment drug (placebo: 5%) due to SAEs [5%: acute respiratory distress syndrome; 3%: secondary infection, 2%: cardiopulmonary failure, 1%: nausea, rash, ileus, loss of appetite, increased ALT, bilirubin and AKI]. Mortality: By day 28, remdesivir: 22 (14%); placebo: 10 (13%); hazard ratio, 1.1% (–81 to 10.3).	Wang et al. ¹⁴
3	Clinical trial (NCT04292899)	Total number of COVID-19 patients (n) = 397 (SARS-CoV-2 confirmed hospitalized patients with confirmed oxygen saturation of 94% or less while they were breathing ambient air, and radiologic evidence of pneumonia) (5-day remdesivir: 200; 10-day remdesivir: 197). The median age: 61 (50–69) versus 62 (60–71) years. Sex: Male 120 (60) versus 133 (68) Female: 80 (40) versus 62 (32)	Remdesivir: 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days.	Total AEs: 5-day treatment group: 141 (70%); 10-day group: 145 (74%). Percentage of patients experiencing AEs: 52% in the 5-day group and 55% in the 10-day group. Most common AEs reported in more than 5% of patients: 5-day: 10%; 10-day: 9%; SOC: 3%. Acute respiratory failure: 5-day: 6% / 10-day: 11%. Increased ALT: 5-day: 6% / 10-day: 8%. Constipation: 5-day: 7% / 10-day: 7%. SAEs: 5-day group: 21% (respiratory failure 5% versus 2%); 10-day group: 35% (acute respiratory failure 9% versus 5%). Grade 3 or higher AEs: 27% of patients in the 5-day group and 34% of patients in the 10-day group. Grade 4 creatinine clearance reductions: 12% of patients in the 10-day group and 3% in the 5-day group (in the patients who were on mechanical ventilation). Discontinuation of the treatment: 5-day group: 4%; 10-day group: 10%.	Goldman et al. ¹⁵

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Table 1. (continued)

S.no.	Type of study	Patient characteristics	Interventions	Outcomes	References
4	Clinical trial (NCT04292730)	Total number of COVID-19 patients (n) = 596 (hospitalized moderate COVID-19 pneumonia, pulmonary infiltrates and room-air oxygen saturation >94%). Patients were randomized in a 1:1:1 ratio: 10-day remdesivir (n = 197), 5-day remdesivir (n = 199), Standard care (n = 200). Median age: 56 versus 58 versus 58 Sex: Male: 118 versus 114 versus 125. Female: 75 versus 77 versus 75.	Remdesivir: intravenous remdesivir 200 mg on day 1 followed by 100 mg/day for remaining duration (4 and 9 days). Standard of care: For the duration of 10 days.	Total AEs observed: 5-day group: 51%; 10-day group: 59%; Standard of care group: 47%. Most common AEs observed in the remdesivir groups: Nausea (5-day: 10% / 10-day: 9% / SOC: 3%), diarrhoea (5-day: 5% / 10-day: 5% / SOC: 7%) and headache (5-day: 5% / 10-day: 5% / SOC: 3%). SAEs: 5- and 10-day group: 5%; SOC: 9%. Grade \geq 3 AEs: 5-day group: 10%; 10-day group: 12%; SOC group: 10%. Mortality: 5-day remdesivir group: 2 (1%); 10-day remdesivir group: 3 (2%) Standard care group: 4 (2%)	Spinner et al. ¹⁶
5	Open-label, randomized trial	Total number of COVID-19 patients: 11,330. Remdesivir versus its control (n): 2743 versus 2708.	Remdesivir: intravenously 200 mg on day 0 and 100 mg on days 1 through 9. Control: same volume of placebo for 10 days.	Primary outcomes: In-hospital mortality, regardless of whether death occurred before or after day 28. Secondary outcomes: The initiation of mechanical ventilation and hospitalization duration. Death: 301 of 2743 patients who have received remdesivir and in 303 of 2708 in patients who have received control (rate ratio, 0.95; 95% confidence interval (CI), 0.81–1.11; p = 0.50).	WHO Solidarity Trial Consortium et al. ¹⁷
6	Prospective (compassionate use), open-label study	Total number of COVID-19 patients (n) = 53 (oxygen saturation of 94% or less or who were receiving oxygen support.) The median age: 64 (48–71) years. Male: 40 (75%). Female: 13 (25%)	10-day remdesivir: intravenous 200 mg on day 1, followed by 100 mg daily for the remaining 9 days of treatment.	Total patients reported AEs = 32 (60%) Most common AEs: Increased hepatic enzymes (22%), diarrhoea 5 (9%), rash 4 (8%), renal impairment 4 (8%) and hypotension 4 (8%). Total SAEs reported: 12 (23%) of patients who were on mechanical ventilation (multiorgan dysfunction syndromes, septic shock, AKI and hypotension). Drug discontinuation: 5 (8%) patients [worsening of preexisting renal failure: 1, multiple organ failure: 1, elevated amino-transferases: 2 (3%), maculopapular rash: 1].	Grein et al. ¹⁸
7	Prospective (compassionate use), open-label study	Total number of COVID-19 patients (n) = 48 (COVID-19 pneumonia patients undergoing mechanical ventilation or with an oxygen saturation level of \leq 94% in air or a national early warning score 2 of \geq 4)	Remdesivir (M): 35. An intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day from days 2 to 10.	Most common AE reported: hepatotoxicity: Grade 3–4 increase in transaminase levels: 42.8%; Increased total bilirubin levels: 20% AKI: 22%; rash: 5% The most frequent AE leading to treatment drug discontinued due to: AKI (4 patients (3 patients died)). Discontinued in another 3 patients due to elevated transaminase levels (grade 3–4), and in another one patient due to serious maculopapular rash.	Antinori et al. ²⁰
8	Prospective (compassionate use), open-label study	Total 86 severe COVID-19 women [pregnant women (n = 67) and postpartum women (n = 19)]	Intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day from days 2 to 10.	Grade 1 and 2 abnormal hepatic enzyme elevation: 27%; pregnant and 38% postpartum women. Grade 3 ALT level elevation: 9% pregnant women and 5% postpartum women. Grade 3 AST elevations: only 5% pregnant women and 1% postpartum women. Grade 4 elevations: Nil in either group. Grade3 elevations in serum creatinine: Pregnant women: 2%; postpartum women: 11% Grade 4 serum creatinine elevations: pregnant women: 55; postpartum women: nil.	Burwick et al. ²³ Available at: https://cattandee.abstractsonline.com/meeting/9307/Presentation/3944 .

(continued)

Table 1. (continued)

S. no.	Type of study	Patient characteristics	Interventions	Outcomes	References
9	Prospective (compassionate), open-label study	Total 77 children (age: 0–17 years) with severe COVID-19.	Intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day from days 2 to 10.	No new safety signals observed. Only 8% of patients those receiving invasive mechanical ventilation ($n = 39$) had serious ADEs while remaining ($n = 38$) patients had 4% ADE. Grade 1 or 2 abnormal elevations of hepatic transaminases (ALT, AST), and serum creatinine were also observed ($<5 \times \text{ULN}$). Grade 3 or 4 elevations were very less. Total no. of patients discontinued the remdesivir due to SAEs = 5	Chiotos <i>et al.</i> ²⁵ Available at https://cattandee.com/ meeting/9307/ Presentation/3946.
10	Case study	COVID-19-positive paediatric (12 years old) patient.	Intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day from days 2 to 6.	No new adverse events were reported, discontinued remdesivir 6 days after due to mild elevated transaminases.	Patel <i>et al.</i> ²⁴
11	Case study	A 77-year-old COVID-19 female patient with a history of hypertension and hyperlipidaemia.	Intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day from days 2 to 10.	Within 2 days after starting remdesivir, the patient's renal function has been worsened followed by multiorgan dysfunction (MOD)	Douedi and Miskoff ²²
12	Case study	Total five COVID-19 patients.	Intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day for a maximum duration of 14 days.	Maculopapular rash, elevated transaminase levels and renal failure (in 4 of the 5 patients).	Dubert <i>et al.</i> ²¹
13	Case study	A 35-year-old COVID-19-positive pregnant (22 weeks and 2 days of gestation) woman	Intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day from days 2 to 10.	Mild elevation in hepatic transaminases	Anderson <i>et al.</i> ²⁶

ADEs, adverse drug events; AEs, adverse events; AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SAEs, serious adverse events; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ULN, upper limit of normal; WHO, World Health Organization.

should be performed to address the efficacy and safety of these drugs in the treatment of COVID-19.

Conclusion

We conclude that remdesivir is a safe antiviral drug for hospitalized COVID-19 patients, though the number of available trials is very less in number. We prior monitoring liver function tests (LFT), renal function tests (RFT), complete blood count (CBC) and serum electrolytes for those with preexisting hepatic and renal impairments and for those who is receiving concomitant hepatotoxic or nephrotoxic drugs to avoid severe AEs. We suggest for furthermore number of randomized controlled trials in a large number of COVID-19 patients.

Author contributions

SC helped in conception of idea, drafting and critical revision. KCA, SNG, SP and RP helped in drafting and editing. VK and BS helped in critical inputs and revision. All authors helped in review and final approval.

Conflict of interest statement

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