EXPERT REVIEW OF ANTI-INFECTIVE THERAPY
https://doi.org/10.1080/14787210.2021.1949984

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SYSTEMATIC REVIEW

The use of remdesivir for the management of patients with moderate-to-severe COVID-19: a systematic review

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ABSTRACT

Objective: We systematically reviewed the evidence of published original research to determine the role of remdesivir in the management of patients with COVID-19 and a moderate-to-severe course of illness.

Methods: A systematic search of articles was conducted in scientific databases, with the latest update in May 2021. This paper systematically reviewed the clinical evidence available (randomized controlled trials, compassionate use studies, and case reports) on the use of remdesivir for patients with moderate or severe COVID-19.

Results: A total of eleven studies were included: four studies based on compassionate use of remdesivir, three randomized, double-blind, placebo-controlled, multicentre trials, three randomized, open-label, phase III trials, and one case report. Clinical improvement and mortality rates in patients who used remdesivir varied across studies.

Conclusion: Given the current evidence, there is insufficient data to confidently recommend the use of remdesivir alone for the treatment of adult hospitalized patients with moderate-to-severe COVID-19. However, remdesivir may be considered along with an anti-inflammatory agent in patients with pneumonia, on oxygen support, provided there is close monitoring of clinical and laboratory parameters and adverse events.

ARTICLE HISTORY
Received 19 October 2020
Accepted 28 June 2021

KEYWORDS
Adverse events; critically ill; evidence-based medicine; remdesivir; SARS-CoV-2

1. Introduction

Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic since its first emergence in the city of Wuhan, China in December 2019 [1]. The pandemic has plummeted many parts of the world into a protracted economic, medical, and social crisis [2]. Patients with COVID-19 present with a wide spectrum of severity ranging from asymptomatic, to mild disease (i.e. absence of pneumonia or mild pneumonia), and to severe/critical life-threatening disease manifested as acute respiratory disease syndrome (ARDS) or multiorgan dysfunction [3–5]. Patients with severe illness typically present with dyspnea and low blood oxygen levels, requiring oxygen therapy or intensive respiratory support with mechanical ventilation [6]. Given the lethality of COVID-19 in which the case fatality rate ranged from approximately 1% to 12% [7], it is crucial to identify an effective treatment for patients with a severe course of illness, since oxygen supplementation and supportive care may not be sufficient to prevent deaths [8]. In addition, effective treatment is also required for patients with moderate course of illness to prevent further deterioration in their clinical progress.

The disease has garnered attention in the research and medical forefronts, and several candidate drugs have been evaluated for their effectiveness against SARS-CoV-2 infection; they include antimalarials (chloroquine and hydroxychloroquine), systemic corticosteroids (dexamethasone), convalescent plasma, protease inhibitors (lopinavir/ritonavir), interleukin-6 inhibitors (tocilizumab and sarilumab), and favipiravir, a broad-spectrum inhibitor of viral ribonucleic acid (RNA) polymerase [9–14]. However, there has been little or no success with almost all of these therapies in patients with COVID-19.

Remdesivir (GS-5734) is a broad-spectrum antiviral with activity against a range of RNA virus families including coronaviruses [15] and has been a strong contender in combating COVID-19. Remdesivir is an inhibitor of the viral RNA-dependent RNA polymerase, which demonstrates antiviral activity against the Middle East respiratory syndrome (MERS-CoV) and SARS-CoV [16]. *In vitro* testing of remdesivir during the early outbreak of COVID-19 in the Wuhan Institute of Virology has demonstrated its potential to inhibit SARS-CoV -2. Later, remdesivir has been reported to be successfully used

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Article highlights

- Remdesivir exhibited good in-vitro activity and is approved for use in patients with COVID-19.
- The evidence depicts mixed findings regarding the efficacy of remdesivir.
- The use of remdesivir with an anti-inflammatory agent (e.g. baricitinib) might be considered in hospitalized patients with moderate-to-severe COVID-19 to accelerate their recovery.

in a patient with COVID-19 in the United States of America (USA) in January 2020 [17]. Remdesivir which is an adenosine analog, exhibits antiviral activity by incorporating into nascent viral RNA chains, resulting in premature termination of RNA synthesis [18].

Due to its promising effects in preclinical models, the utilization of remdesivir for the treatment of patients with COVID-19 has been of huge interest. It is timely to evaluate the current evidence to assess the trade-off between efficacy and safety of remdesivir for patients with a moderate-to-severe course of COVID-19. Therefore, we aim to systematically review the evidence of published original research involving human subjects, including randomized controlled trials (RCTs), studies of individual compassionate use, and case reports, to determine the role of remdesivir in the management of COVID-19 patients with a moderate-to-severe course of illness.

2. Methods

2.1. Eligibility criteria

Studies were included if they were original studies, of any study design (case report, case series, non-randomized controlled trial, randomized controlled trial) and investigated the compassionate use of remdesivir or use of remdesivir in clinical trials, and reported outcomes related to clinical improvement and mortality in hospitalized, adult patients with moderate-to-severe COVID-19. Moderate illness was defined based on evidence of lower respiratory disease during clinical assessment or imaging, with oxygen saturation ≥94% on room air at sea level. Severe illness was defined based on the need for respiratory support (oxygen therapy, noninvasive or invasive ventilatory support), extracorporeal membrane oxygenation, or admission to intensive care unit (ICU).

Studies were excluded if there was no involvement of human subjects, if there was no identifiable information on the clinical severity of included participants with COVID-19, if there was involvement of pediatric patients or obstetric patients, and if there were no reported outcomes related to clinical improvement and mortality.

2.2. Search strategy and study selection process

A literature search was performed in August 2020, updated in January 2021 and again in May 2021, in the following electronic databases: PubMed (United States National Library of Medicine), Cochrane Central Register of Controlled Trials, and the World Health Organization (WHO) COVID-19 Database, to identify potential articles for inclusion. Google Scholar was also searched to identify articles not indexed in scientific databases. We also checked the reference lists of all potential studies identified to avoid omission of relevant studies.

Searches were constructed by using the search terms '2019-nCoV', 'COVID-19,' 'SARS-CoV-2,' 'remdesivir,' and 'GS-5734.' Searches were limited to 'adults (limit: 18+ years),' 'humans,' and '1 January 2020 up to 30 May 2021.' An initial screen of titles and abstracts was undertaken by the primary investigator (KT) to identify articles meeting the inclusion criteria. Subsequently, the full texts of the selected studies were retrieved. Two investigators (KT and CSK) independently assessed the full texts of possible articles for inclusion in this review to validate the results.

2.3. Data extraction

The study design, number of participants, study setting, disease severity, use of co-interventions, follow-up duration, participants' assessments, clinical and laboratory data, study endpoints, recovery or improvement rates, rates of adverse events, rates of discontinuation of treatment, and mortality rates, were extracted. The extracted data from all the included studies were subsequently collected and tabulated using a form developed by the primary investigator (KT) that was verified by the second investigator (CSK).

3. Results

3.1. Characteristics of included studies

Our search yielded 1876 unique records. After application of eligibility criteria and subsequent full-text examination, eleven studies were included in this review (Figure 1). Table 1 summarizes the findings of the included studies in chronological order. We included a total of four studies based on compassionate use of remdesivir [8,19–21], three randomized, double-blind, placebo-controlled, multicentre trials [22–25], three randomized, open-label, phase III trials [26–28], and one case report which we felt was of clinical interest [29]. Remdesivir was provided by its manufacturer, Gilead Sciences, and therapy was uniform across all studies for a total duration of 10 days (based on its efficacy established in an earlier study by Mulangu et al. [30]), i.e. 200 mg intravenous loading dose on day 1, followed by 100 mg daily administration from days 2 to 9; except the study by Goldman et al. {26]which compared the effectiveness of remdesivir as a 5-day or a 10-day course. the study by Aiswarya et al. [21] adjusted the dosing regimen for dialysis-dependent patients (2.5 mg/kg [dry weight] intravenously up to a maximum dose of 100 mg on day 1, 4 hours before the dialysis session, with subsequent doses up to a maximum of 6 doses given 4 hours before each dialysis session for 9 days to complete the 10-day duration). The trial by Spinner et al. [27] consisted of three arms where the effectiveness of remdesivir, each as a 5-day and a 10-day course, was compared with standard care. With an exception of the case report [29], the compassionate use study by

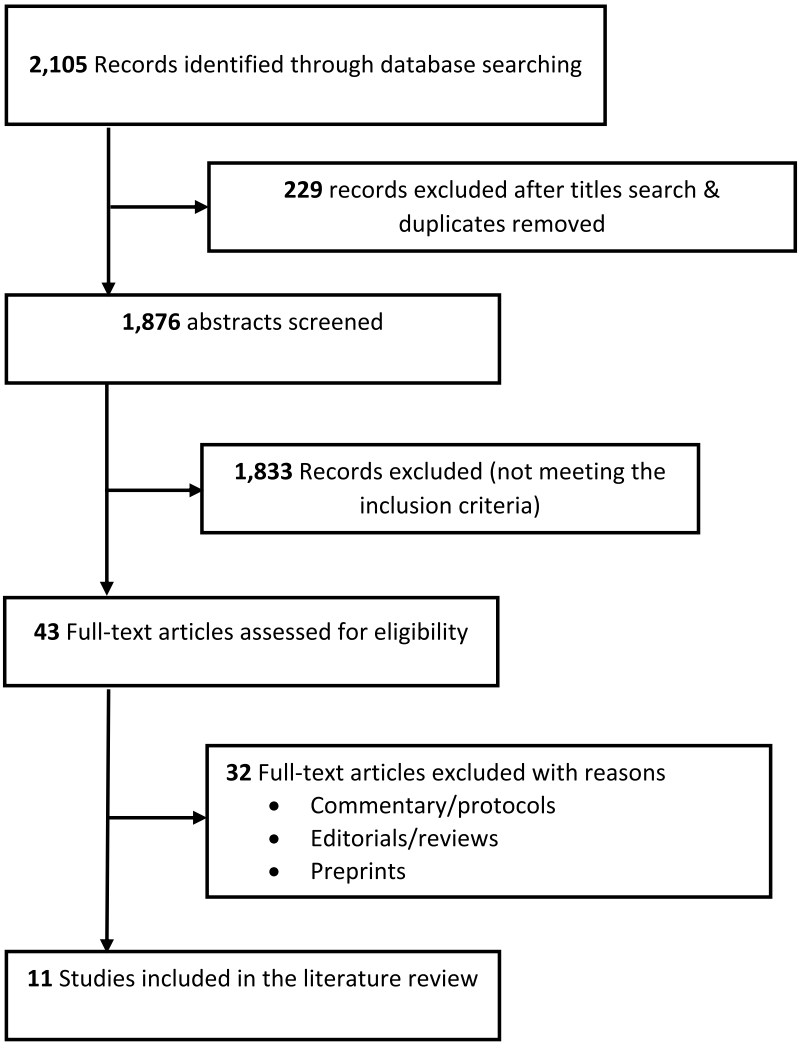

Figure 1. Study selection process.

Pasquini et al. [20], and the randomized, open-label multicentre trial by the WHO Solidarity Trial Consortium [28], all studies utilized an ordinal scale to evaluate the clinical improvement of patients based on a pre-specified point-decrease from baseline to discharge, albeit with varying scale interpretations across the included studies.

3.2. Clinical improvement with the use of remdesivir

The compassionate use study by Grein et al. [19] is the first to report the clinical benefits of remdesivir in patients with COVID-19. This study, which was sponsored by Gilead Sciences, the manufacturer of remdesivir, involved 53 hospitalized patients with COVID-19; details of the study population are presented in Table 1. The study reported that the overall cumulative incidence of improvement at day 28 was 84.0% (95% confidence interval (CI) 70–99%) and improvement was better among those receiving noninvasive ventilation or were younger than 50 years, compared to those receiving invasive ventilation or were 70 years and over, respectively. However, the authors reanalyzed the cumulative incidence of improvement at day 28 upon initiation of remdesivir using a competing-risk approach whereby death was deemed a treatment failure and reported cumulative incidence of improvement as 74.0% (95% CI 55–86%).

Antinori et al. [8] also reported a compassionate use study in Italy among 35 patients with COVID-19 in the ICU and 18 patients in the Infectious Diseases Ward (IDW) who had severe illness. All concomitant treatments were permitted except for lopinavir/ritonavir as per recommendation by Gilead Sciences. Rate of clinical improvement by day 28 was higher among patients admitted to IDW (88.2%) compared to patients admitted to the ICU (38.9%). Again, due to the nature of this study, it was not possible to include a control arm to preclude the possibility that patients may have improved regardless of any treatment. Furthermore, some patients (numbers not reported) had previously been administered with lopinavir/ritonavir and hydroxychloroquine before their inclusion in this study, and thus it was difficult to draw definitive conclusions due to such confounding factors.

In contrast to the aforementioned study, a compassionate use study by Pasquini et al. [20] reported possible mortality

Table 1. Summary of studies reviewed.

Authors (Country – Date)/ Sponsor	Study design, setting & period	Inclusion criteria, disease severity & use of other treatments	Intervention & follow-up duration	Study assessments, clinical and laboratory data & study endpoints	Ordinal scale used for recovery determination	Recovery/ improvement rates	Adverse event rates & discontinuation of treatment	Mortality rates
Grein et al. [19] (USA-10 April 2020) Sponsor: Gilead Sciences	Compassionate use, open-label study; hospitalized patients as follows: USA [23], Japan [9], Italy [12], Austria [1], France [4], Germany [2], Netherlands [1], Spain [1], and Canada [1]. Study period: 25 January 2020–7 March 2020	Gilead Sciences approved request for the following patients: Inclusion criteria: Hospitalized patients with confirmed SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction assay and either oxygen saturation of ≤94% while the patient breathing ambient air or if the patient needed oxygen support Disease severity: Severe COVID-19 Use of concomitant treatments: Not stated	Intervention: 10-day course of remdesivir: 200 mg intravenous loading dose on day 1, followed by 100 mg daily administration from day 2 to day 10 Follow-up duration: At least 28 days upon commencement of treatment or, until discharge or, until death	Day 1 to day 10: Change in oxygen-support requirements (low-flow oxygen, ambient air, nasal high-flow oxygen, noninvasive positive pressure ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation), discharge, adverse events (including those that led to discontinuation), serious adverse events and death. Laboratory values recorded for: Serum creatinine, ALT, and AST Day 11 to day 28: Additional follow-up information solicited through day 28 Clinical improvement parameters: Live discharge from hospital, a 2-point decrease from baseline of a modified ordinal scale as per the WHO R&D Blueprint group. Study endpoints: No pre-specified endpoints but incidence of key clinical events was quantified	6-point ordinal scale: 1: Not hospitalized 2: Hospitalized, not requiring supplemental oxygen 3: Hospitalized, requiring supplemental oxygen 4: Hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation or both 5: Hospitalized, requiring nasal invasive mechanical ventilation, ECMO, or both 6: Death	*Note: Data censored for deceased patients* Oxygen support 36/53 patients (68.0%) improved Ambient air & low-flow supplemental oxygen: All 12 patients improved Noninvasive oxygen support: 5 out of 7 improved Invasive mechanical ventilation: 17 out of 30 patients (57.0%) were extubated ECMO: 3 out of 4 patients (75.0%) stopped receiving it Improvement as per the ordinal scale or live discharge: Cumulative incidence of improvement at day 28 was 84.0% (95% CI 70–99). Less frequent among those receiving invasive ventilation than among those receiving noninvasive ventilation (HR 0.33; 95% CI 0.16–0.68) and among those aged 70 years and older (HR 0.29; 95% CI 0.11–0.74) when compared to those younger than 50 years.	*Note: Data censored for deceased patients* 32/53 patients (60.0%) reported most common adverse events with the following in ≥2 patients: increased hepatic enzymes [12], diarrhea [5], rash [4], renal impairment [4] and hypotension [4]. 12/53 (23.0%) had serious adverse events, with the following most common in ≥2 patients: multiple-organ-dysfunction syndrome, septic shock, acute kidney injury, hypotension. Discontinuation: 4 patients (8.0%) discontinued remdesivir because of preexisting renal failure [1], multiple organ failure [1], elevated aminotransferases [2], & maculopapular rash [1]	7 out of 53 patients (13.0%) died after completing remdesivir, which includes 6 of 34 (18.0%) receiving invasive ventilation and 1 of 19 (5.0%) receiving noninvasive oxygen support Overall mortality from date of admission was 0.56 per 100 hospitalization days (95% CI 0.14–0.97). Risk of death greater for those aged 70 years and over (HR compared to patients younger than 70 years, 11.34; 95% CI 1.36–94.17) & among those with higher serum creatinine at baseline (HR per mg per dL, 1.91; 95% CI 1.22–2.99). HR for patients with invasive ventilation compared to those with noninvasive oxygen support was 2.78 (95% CI 0.33–23.19).
Hillaker et al. [29] (USA-13 April 2020)	Case report; a previously healthy 40-year old man	Patient complaint: Presented to the emergency department on day 5 of illness, inability to tolerate orally and worsening body aches Patient history: Significant for anxiety and depression, obesity & hypercholesterolemia Disease severity: Not stated Use of concomitant treatments: Not stated, but patient previously took hydroxychloroquine & azithromycin for 5 days	Intervention: 200 mg IV remdesivir on day 9 of admission (day 13 of illness), followed by 100 mg daily administration for 9 days (10-day duration)	Clinical progress monitored; alanine transaminase and aspartate aminotransferase levels monitored	-	Patient continued to progress and tolerated weaning of aggressive mechanical ventilation On day 12 of admission (day 16 of illness), the patient was extubated; his oxygen saturations were stable requiring 2 to 3 L of oxygen via nasal cannula and maintained satisfactory oxygen saturation at room air on day 13 of admission (day 17 of illness), progressing toward discharge.	ALT and AST levels decreased	-

(*Continued*)

Table 1. (Continued).

Authors (Country – Date)/ Sponsor	Study design, setting & period	Inclusion criteria, disease severity & use of other treatments	Intervention & follow-up duration	Study assessments, clinical and laboratory data & study endpoints	Ordinal scale used for recovery determination	Recovery/ improvement rates	Adverse event rates & discontinuation of treatment	Mortality rates
Wang et al. [22] (China-29 April 2020)	Randomized, double-blind, placebo-controlled multicentre trial; 237 patients from 10 hospitals in Wuhan, China Study period: 6 February 2020–12 March 2020	Inclusion criteria: Men and non-pregnant women with COVID-19 aged ≥18 years and were RT-PCR positive for SARS CoV-2, had pneumonia (confirmed by chest imaging), oxygen saturation ≤94% on room air or ratio of arterial oxygen partial pressure of fractional inspired oxygen of ≤300 mmHg, and were within 12 days of symptom onset Patients of child-bearing age consented to taking contraceptive measures during the study period and for 7 days upon the last drug administration Disease severity: Severe COVID-19 Use of concomitant treatments: Permitted (including lopinavir/ritonavir)	Intervention: The interventional arm included 158 patients who received a 10-day course of remdesivir: 200 mg intravenous loading dose on day 1, followed by 100 mg daily administration from day 2 to day 10. The control arm included 79 patients who received the same volume of placebo infusions for 10 days Follow-up duration: 28 days upon randomization	Patients assessed daily by trained nurses who captured data of the 6-point ordinal scale & safety from day 0 to day 28. At baseline, upper & lower respiratory tract specimens were tested for detection of E-gene, RAN-dependent RNA polymerase gene and N-gene & samples on subsequent visits tested for E-gene Safety assessment: Daily monitoring of adverse events, clinical laboratory testing on days 1,3,7, &10, 12-lead electrocardiogram on days 1 & 14, daily vital signs measurements, nasophatyngeal or oropharyngeal swabs, expectorated sputa, and fecal or anal swab specimens collected on days 1,3,5,7,10,14,21 and 28 for viral RNA detection & quantification Clinical improvement parameters: 2-point reduction on admission status in 6-point ordinal scale or live discharge, whichever was first Study endpoints: Primary; Time to clinical improvement within 28 days of randomization Secondary; Proportions of patients in each category of the 6-point scale at days 7,14 & 28, all-cause mortality at day 28, the frequency of invasive mechanical ventilation, duration of oxygen therapy, duration of hospital admission, proportion of patients with nosocomial infection, proportions of patients with viral RNA detected & viral RNA load, adverse events, serious adverse events & premature discontinuation of remdesivir	6-point ordinal scale: 1: Discharged or having reached a discharge criterion, i.e. clinical recovery 2: Hospital admission but not requiring oxygen therapy 3: Hospital admission for oxygen therapy, but not requiring high-flow or noninvasive ventilation 4: Hospital admission for noninvasive ventilation or high-flow oxygen therapy 5: Hospital admission for extracorporeal membrane oxygenation or mechanical ventilation 6: Death	In the ITT population: Time to clinical improvement was not statistically significant in the remdesivir group to the placebo group: Median 21.0 days (IQR 13.0–28.0) in the remdesevir group vs. 23.0 days (IQR 15.0–28.0) in the placebo group; HR 1.23 (95% CI 0.87–1.75) In the per protocol population: Time to clinical improvement similar not statistically significant when both groups compared: Median 21.0 days (IQR 13.0–28.0) in the remdesivir group vs. 23.0 days (IQR 15.0–28.0) in the placebo group; HR 1.27 (95% CI 0.89–1.80) Clinical improvement rates for the remdesivir vs. placebo groups at day 14 (42 vs. 18) and day 28 (103 vs. 45) were not statistically significant in both groups	Adverse events were reported in 102 of 155 remdesivir patients (66.0%) and 50 of 78 placebo patients (64.0%). Most common adverse events in ≥2 patients in the remdesivir group: Constipation [22], hypoalbuminaemia [20], hypokalaemia [18], anemia [18], thrombocytopenia [16] & increased total bilirubin [15]. Most common adverse events in ≥ patients in the placebo group: Hypoalbuminaemia [12], constipation [12], anemia [12], hypokalaemia [11], increased aspartate aminotransferase [9], increased blood lipids [8] & increased total bilirubin [7]. Most common serious adverse events in ≥2 remdesivir vs. placebo patients: Respiratory failure or acute respiratory distress syndrome (16 vs. 6) & cardiopulmonary failure (8 vs. 7) Discontinuation: 18 (12.0%) from the remdesivir group and 4 (5.0%) from the placebo group discontinued due to serious adverse events	28-day mortality was similar in both groups; 22 (14.0% died in the remdesivir group vs. 10 (13.0%) in the placebo group; difference 1.1% (95% CI −8.1–10.3) For patients who used remdesivir within 10 days of symptom onset, 28-day mortality was not significantly different between both groups Patients with late use of remdesivir had a numerically higher 28-day mortality compared to the placebo group (12 vs. 3)

(*Continued*)

Table 1. (Continued).

Authors (Country – Date)/ Sponsor	Study design, setting & period	Inclusion criteria, disease severity & use of other treatments	Intervention & follow-up duration	Study assessments, clinical and laboratory data & study endpoints	Ordinal scale used for recovery determination	Recovery/ improvement rates	Adverse event rates & discontinuation of treatment	Mortality rates
Antinori et al. [8] (Italy- 11 May 2020)	Compassionate use, open-label study; 35 patients with pneumonia (18 in Intensive Care Unit- ICU & 17 in Infectious Diseases Ward- IDW) from Luigi Sacco Hospital, Milan, Italy Study period: 23 February 2020–20 March 2020	Inclusion criteria: Male or non-pregnant females aged ≥18 years, had SARS-Cov-2 infection who were RT-PCR positive, pneumonia confirmed by a chest X-ray or CT scan, were mechanically ventilated or had an oxygen saturation level of ≤94% on room air, or a National Early Warning Score (NEWS)2 of ≥4 Disease severity: Severe COVID-19 Use of concomitant treatments: Permitted to use existing treatment like hydroxychloroquine, but had to discontinue lopinavir/ritonavir as per Gilead Sciences recommendation	Intervention: 10-day course of remdesivir: 200 mg intravenous loading dose on day 1, followed by 100 mg daily administration from day 2 to day 10 Follow-up duration: 28 days upon administration	Clinical and laboratory data of all patients enrolled were collected daily until discharge, death or censoring (20 April 2020) In a subset of patients: Semi-quantitative RT-PCR test of nasopharyngeal swab carried out at baseline & during remdesivir treatment; 3 target genes were tested for: RNA-dependent RNA polymerase (RdRP), nucleocapsid protein (N) & envelope membrane protein (E). Viral load was also measured. Study endpoints: Primary; Change in patients hospitalization status on day 10 and day 28 of treatment (Assessed by the ordinal scale) Secondary; Safety, including adverse events which led to premature discontinuation	7-point ordinal scale: 1: Not hospitalized & capable of resuming normal activities 2: Not hospitalized by unable to resume normal activities 3: Hospitalized and not requiring oxygen supplementation 4: Hospitalized and requiring oxygen therapy 5: Hospitalized and requiring high-flow nasal oxygen therapy, noninvasive mechanical ventilation, or both 6: Intensive care unit hospitalization, requiring invasive mechanical or extra corporeal membrane oxygenation, or both 7: Deceased	Clinical improvement: By day 10 of treatment, 4 of the ICU patients (22.2%) showed improvement in hospitalization status; by day 28 of treatment, 38.9% of ICU patients improved (6 discharged and 1 weaned off ventilation) By day 10 of treatment, 6 of the IDW patients (35.3%) had improved hospitalization status, by day 28 of treatment, 88.2% of IDW patients had improved (14 discharged & 1 did not require oxygen supplementation)	Most frequent serious adverse event was grade 3–4 increase in transaminases in 15 (42.8%) of patients Most frequent adverse event leading to treatment discontinuation: acute kidney injury observed in 4 ICU patients (3 of whom died). Discontinuation: 22 (63.0%) completed the scheduled treatment, and 13 (9 in ICU and 4 in IDW) discontinued after a median of 5 doses due to early discharge (2, 2.9%), death (4, 11.4%) and toxicities (8, 22.8%).	By day 10 of treatment, 4 of the ICU patients (22.2%) had died; by day 28 of treatment, 44.4% of the ICU patients died By day 10 of treatment, 1 IDW patient died.
Aiswarya et al. [21] (India- 18 December 2020)	Compassionate use, open-label study; 48 dialysis-dependent patients from Institute of Nephrology, Madras Medical College, Chennai, India Study period: January 2020-September 2020	Inclusion criteria: All patients with CKD requiring hemodialysis who tested positive for SARS-CoV-2 infection from analysis of nasopharyngeal swab by RT-PCR and who received ≥1 dose of remdesivir Disease severity: Moderate-to-severe COVID-19 Use of concomitant treatments: Permitted to use LMWH, dexamethasone, and third-generation cephalosporin	Intervention: Intravenous 2.5 mg/kg (dry weight) remdesivir up to a maximum dose of 100 mg on day 1, 4 hours before the dialysis session; subsequent doses up to a maximum of 6 doses were given 4 hours before each dialysis session for 9 days (10-day duration)	Liver function tests were monitored daily, and further doses were withheld if there was ALT elevation ≥5 times the upper limit of normal or if ALT elevation was accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or prothrombin time international normalized ratio. Nasopharyngeal swabs for SARS-CoV-2 by RT-PCR were repeated every 72 hours after admission, until a negative result occurred. Study endpoints: No pre-specified endpoints	5-point ordinal scale: 0: No requirement for respiratory support 1: Use of simple face mask for oxygen delivery 2: Use of nonrebreathing mask for oxygen delivery 3: Use of high-flow nasal oxygen 4: Use of continuous positive airway pressure therapy	At the end of remdesivir therapy, 33 patients (68.8%) showed an improvement in oxygen requirement in the ordinal scale score	One patient had acute coronary syndrome 6 hours after the first dose of remdesivir and one patient had worsening of behavioral disorder after 15 hours of remdesivir initiation leading to withdrawal of the drug.	During hospitalization, 10 patients (20.8%) died; of the 10 patients, 7 patients had their remdesivir initiated less than 48 hours since admission while remaining 3 patients had their remdesivir initiated more than 48 hours since admission.

(*Continued*)

Table 1. (Continued).

Authors (Country – Date)/ Sponsor	Study design, setting & period	Inclusion criteria, disease severity & use of other treatments	Intervention & follow-up duration	Study assessments, clinical and laboratory data & study endpoints	Ordinal scale used for recovery determination	Recovery/ improvement rates	Adverse event rates & discontinuation of treatment	Mortality rates
Beigel et al. [23] (USA- 5 November 2020) Sponsor: National Institute of Allergy and Infectious Diseases and others Name of trial: Adaptive COVID-19 Treatment Trial (ACTT)	Double-blind, randomized, placebo-controlled trial; 1062 hospitalized patients from United States of America, Denmark, the United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan and Singapore. 541 patients in the remdesivir group & 521 in the placebo group Study period: 21 February 2020–19 April 2020	Inclusion criteria: ≥18 years with confirmed SARS-Cov-2 based on positive RT-PCR from any respiratory specimen collected within 72 hours of randomization, radiographic infiltrates of imaging studies, and peripheral oxygen saturation of ≤94% on room air or require supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation Women of childbearing potential agreed to use a study-specified contraception and participants practiced heterosexual abstinence Disease severity: Severity stratified, but 943 of 1063 (88.7%) had severe COVID-19 Use of concomitant treatments: Permitted but only as per respective standard of care for trial site hospitals. In the absence of written policies, experimental treatment or off-label use of any marketed medications were not permitted from day 1 to day 29 (although they could have been administered before the trial)	Intervention: 10-day course of remdesivir for the intervention arm: 200 mg intravenous loading dose on day 1, followed by 100 mg daily administration from day 2 to day 10, or until hospital discharge or death; matching placebo for the control arm, administered in the same schedule and same volume (normal saline used in some European sites due to shortage of matching placebo). All infusions were masked with an opaque bag & tubing covers Follow-up duration: 28 days upon administration	Patients assessed daily from day 1 to day 29 on the following parameters: Clinical status based on the 8-point ordinal category, the National Early Warning Score & serious adverse events, and grade 3 & 4 adverse events which represented an increase in severity from day 1, and any Grade 2 or higher suspected drug-related hypersensitivity reactions Study endpoints: Primary; Time to recovery, defined as the first day during 28 days of enrollment, on which patients satisfied the following categories: 1,2 or 3 on the ordinal scale. Secondary; Mortality at days 14 and 28 upon enrollment, and grade 3 and 4 adverse events and serious adverse events. Prespecified subgroups were defined according to sex & disease severity (ordinal scale at enrollment), age (18–39 years, 40–64 years, ≥65 years), duration of symptoms before randomization (≤10 days & >10 days)	8-point ordinal scale: 1: Not hospitalized, no limitations of activities 2: Not hospitalized, limitation of activities, home oxygen requirement, or both 3: Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used only if hospitalization was extended for infection-control reasons) 4: Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19-related or other medical conditions) 5: Hospitalized, requiring any supplemental oxygen 6: Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices 7: Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 8: Death	Clinical improvement: Patients in the remdesivir group had a shorter median recovery time of 10 days (CI 9–11) compared to the placebo group which had a median time of 15 days (CI 13–18); RR for recovery 1.29; 95% CI 1.12–1.49. Using a proportional odds model, patients with remdesivir were more likely than those receiving placebo to have clinical improvement at day 15 (OR 1.5; 95% CI 1.2–1.9), upon adjustment for actual disease severity. In the severe disease stratum (957 patients), median recovery time was 11 days compared to 18 days (RR for recovery 1.31; 95% CI 1.12–1.52). RR for recovery was largest for patients who had a baseline ordinal score of 5 (RR for recovery 1.45; 95% CI 1.18–1.79). For those receiving mechanical ventilation or extracorporeal membrane oxygenation at enrollment (baseline ordinal score of 7), RR for recovery was 0.98 (95% CI 0.70–1.36). When baseline ordinal score stratification was adjusted for overall effect, RR for recovery was 1.26 (95% CI 1.09–1.46). Patients who underwent randomization within the first 10 days after onset of symptoms had a RR for recovery of 1.37; 95% CI 1.14–1.64, while those with randomization more than 10 days from symptom onset had a RR 1.20; 95% CI 0.94–1.52. Patients in the remdesivir group had a shorter time to discharge or to a National Early Warning Score of 2 or lower compared to those in the placebo group (median 8 days vs. 12 days; HR 1.27; 95% CI 1.10–1.46). Initial length of hospital stay was shorter in the remdesivir than the placebo group (median 12 days vs. 17 days); 5% of patients were re-admitted from the remdesivir group, compared to 3% from the placebo group.	Serious adverse events occurred in 131 of 532 patients who took remdesivir (24.6%) and in 163 of 516 patients who took placebo (31.6%). Serious respiratory failures in 47 remdesivir patients (8.8%)- including acute respiratory failure requiring endotracheal intubation, and 80 placebo patients (15.5%). Grade 3 or 4 adverse events occurred on or before day 29 in 273 remdesivir patients (51.3%) and 295 placebo patients (57.2%); 41 events were judged to be due to remdesivir and 47 due to placebo. The most common adverse events in 5% of all patients include decreased hemoglobin level, decreased glomerular filtration rate, decreased lymphocyte count, anemia, respiratory failure, hyperglycemia, pyrexia, increased blood glucose level and increased blood creatinine level (incidence were similar in both groups).	Kaplan-Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15, and 11.4% with remdesivir and 15.2% with placebo by day 29 (HR 0.73, 95% CI: 0.52–1.03).

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Table 1. (Continued).

Authors (Country – Date)/ Sponsor	Study design, setting & period	Inclusion criteria, disease severity & use of other treatments	Intervention & follow-up duration	Study assessments, clinical and laboratory data & study endpoints	Ordinal scale used for recovery determination	Recovery/ improvement rates	Adverse event rates & discontinuation of treatment	Mortality rates
Goldman et al. [26] (USA- 27 May 2020) Sponsor: Gilead Sciences Name of trial: SIMPLE trial	Randomized, open-label, phase 3 trial; 397 patients from 55 hospitals in the United States of America, Italy, Spain, Germany, Hong Kong, Singapore, South Korea and Taiwan Study period: 6 March 2020– 26 March 2020	Inclusion criteria: Hospitalized patients aged ≥12 years who had SARS-CoV-2 infection (PCR assay- positive within 4 days before randomization), radiographic evidence of pulmonary infiltrates and either with oxygen saturation of ≤94% while breathing ambient air or were receiving supplemental oxygen. Patient receiving mechanical ventilation & extracorporeal membrane oxygenation and multiorgan failure at screening were excluded Disease severity: Severe COVID-19 Use of concomitant treatments: Supportive therapy continued at the discretion of the investigator Protocol amended to add an extension phase: Additional 5600 patients including those receiving mechanical ventilation (but results not reported in this paper)	Intervention: One arm included a treatment duration of 10 days, and the other for 5 days. Patients in both arms administered with 200 mg intravenous loading dose on day 1, followed by 100 mg daily administration from day 2 to day 10. Follow-up duration: 14 days upon administration of remdesivir	Patients assessed by physical examination and documentation of respiratory status, adverse events, and concomitant medications. Blood samples obtained for complete blood count and measurement of creatinine, blood glucose, total bilirubin and liver aminotransferases on days 1, 3, 5, 8, 10 and 14. Study endpoints: Primary; Clinical status assessed on day 14 on a 7-point ordinal scale Secondary; Proportion of patients with adverse events that occurred on or after the first dose of remdesivir for up to 30 days after the last dose, time to clinical improvement (defined as ≥2 points from baseline on the ordinal scale), time to recovery as an improvement from a baseline score of 2 to 5 to a score of 6 or 7, the time to modified recovery (defined as a baseline score improvement of 2 to 4 to a score of 5 to 7, or from a score of 5 to a score of 6 or 7), and death from any cause.	7-point ordinal scale: 7: Not hospitalized 6: Hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration) 5: Hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or unrelated o Co 4: Hospitalized, requiring low-flow supplemental oxygen 3: Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices 2: Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation 1: Death	Clinical improvement: 65.0% of patients in the remdesivir group who received a 5-day course showed an improvement of ≥2 points at day 14, compared to 54.0% of the patients who received a 10-day course. Upon adjustment of imbalances in baseline clinical status, those with the 10-day course had a distribution of clinical status at day 14 which was similar to those receiving a 5-day course ($p = 0.14$). Median duration of hospitalization among patients who were discharged ≥day 14 was 7 days (IQR 6–10) for the 5-day group and 8 days (IQR 5–10) for the 10-day group. Proportion of patients who recovered (those with a baseline score of 2 to 5 who improved to a score of 6 or 7): 64.0% of patients in the 5-day group compared to 54.0% in the 10-day group (−6.3% for a baseline-adjusted difference in proportions; 95% CI −15.4–2.8).	Those experiencing any adverse events were similar in both groups: 141 of 200 (70.0%) in the 5-day group vs. 145 of 197 (74.0%) in the 10-day group. The most common adverse events in the 5-day vs. the 10-day groups were: Nausea in 20 (10.0%) vs. 17 (9.0%), constipation in 13 (7.0%) for both, acute respiratory failure in 12 (6.0%) vs. 21 (11.0%), increased ALT levels in 11 (6.0%) vs. 15 (8.0%), and increased AST levels in 11 (6.0%) vs. 13 (7.0%). Those experiencing any serious adverse events: 42 of 200 (21.0%) in the 5-day group vs. 68 of 197 (35.0%) in the 10-day group. The most common serious adverse events in the 5-day vs. the 10-day groups were: acute respiratory failure in 10 (5.0%) vs. 18 (9.0%), respiratory failure in 5 (2.0%) vs. 10 (5.0%), and respiratory distress in 3 (2.0%) vs. 4 (2.0%). Discontinuation: 9 patients (4.0%) from the 5-day group and 20 patients (10.0%) from the 10-day group discontinued remdesivir due to adverse events.	For patients receiving mechanical ventilation or extracorporeal membrane oxygenation at day 5, 10 of 25 patients (40.0%) in the 5-day group died by day 14, compared to 7 of 41 patients (17.0%) in the 10-day group.
Pasquini et al. [20] (Italy- 24 June 2020)	Compassionate use, open-label study; 25 patients admitted in the ICU with severe respiratory failure from Pesaro Hospital, Italy Study period: 29 February 2020– 20 March 2020	Inclusion criteria: All patients aged ≥18 years, had SARS-CoV-2 infection who were RT-PCR positive and were mechanically ventilated Patients who died within the first 48 hours of admission to the ICU, and those with creatinine clearance <30 mL/min, serum levels of ALT or AST which were more than 5 times the upper limit of the normal range and those in need of inotropic support were excluded Disease severity: Severe COVID-19 Use of concomitant treatments: Upon commencing remdesivir treatment (Day 1), patients being treated with hydroxychloroquine and/or lopinavir/ritonavir were allowed to continue treatment with hydroxychloroquine but discontinued treatment with lopinavir/ritonavir.	Intervention: 10-day course of remdesivir: 200 mg intravenous loading dose on day 1, followed by 100 mg daily administration from day 2 to day 10 Follow-up duration: 28 days upon administration	Data collected from those treated included demographic data, any ongoing and previous medical conditions, clinical symptoms on onset, vital signs and laboratory data at ICU admission, the need for inotropic support and/or continuous veno-venous haemofiltration during ICU stay. Study endpoints: No pre-specified endpoints but outcomes of the study were focused on mortality rates.	-	Clinical improvement: Of 51 patients, 25 underwent treatment with remdesivir which 26 did not receive treatment (control). The sequential organ failure assessment (SOFA) score at ICU entry was higher for patients treated with remdesivir (5 vs. 4; $p = 0.037$). No other differences between both groups in terms of clinical or laboratory parameters. Tocilizumab was used more commonly among patients treated with remdesivir (28% vs. 7%, $p = 0.075$). Of the 25 patients treated with remdesivir, median time between treatment initiation to symptom onset was 18 [15–20] days, and time from ICU admission was 7 [4–8] days. At the end of the follow-up, 9 (17.6%) patients were discharged from the hospital.	20 patients completed the Day 10 therapy 25 patients (49%) required continuous renal replacement therapy due to kidney failure	5 (20%) patients died due to causes related to SARS-Cov-2 infection- median 5 [4–6] days upon initiation of remdesivir. At the end of the follow-up, 38 (74.5%) patients died and 4 (7.8%) patients were hospitalized but not mechanically ventilated. Mortality was significantly lower among those treated with remdesivir than among untreated patients (56.0% vs. 92.3%, $p < 0.001$). Death occurred at a median (IQR) of 17 (13–20 days) upon ICU admission in the remdesivir group and 10 [8–13] days in the untreated group. In multivariate analyses, the Charlson Comorbidity Index was the only factor associated with mortality (OR 1.184; 95% CI: 1.027–1.365; $p = 0.020$). In the multivariate analysis, remdesivir was the only factor associated with survival (OR 3.506; 95% CI: 1.768–6.954; $p < 0.001$). Treatment with remdesivir and tocilizumab were associated with better survival.

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Table 1. (Continued).

Authors (Country – Date)/ Sponsor	Study design, setting & period	Inclusion criteria, disease severity & use of other treatments	Intervention & follow-up duration	Study assessments, clinical and laboratory data & study endpoints	Ordinal scale used for recovery determination	Recovery/ improvement rates	Adverse event rates & discontinuation of treatment	Mortality rates
Spinner et al. [27] (USA- 15 September 2020) Sponsor: Gilead Sciences	Randomized, open-label multicentre trial; 584 patients from 105 hospitals in the United States, Europe and Asia 193 patients received a 10-day course of remdesivir, 191 patients received a 5-day course of remdesivir and 200 patients received standard care Study period: 15 March 2020–18 April 2020.	Inclusion criteria: Hospitalized patients with confirmed SARS-CoV-2 infection confirmed by RT-PCR upon 4 days of randomization and with moderate pneumonia defined as radiographic evidence of pulmonary infiltrates with oxygen saturation >94% on room air. Upon protocol amendment on March 15, the age eligibility was reduced from 18 years to 12 years, and minimum temperature requirement was eliminated. Patients with ALT or AST > 5 times the upper limit of normal or ClCr <50 mL/min were excluded. Disease severity: Moderate COVID-19 Use of concomitant treatments: The original protocol allowed use of other medications with presumptive activity against SARS-CoV-2 if use was considered 'local care.' This exception was not allowed however in a subsequent amendment (although some patients had already received other concurrent therapy).	Intervention: Patients randomized to the remdesivir group received: 200 mg intravenous loading dose on day 1, followed by 100 mg daily administration (for 5 days and 10 days, depending on the treatment arm). Those with severe increases in liver enzymes or decreases in ClCr<30 mL/min were discontinued on treatment. Follow-up duration: 28 days upon administration	Physical examination, respiratory status (including respiratory rate, type of oxygen supplementation, radiographic findings and blood oxygen saturation), concomitant medications and adverse events. Blood samples were obtained on days 1, 3, 5, 8, 10 and 14 for measurement of blood cell count, serum creatinine, glucose, total bilirubin, and liver transaminases. Self-reported fixed race and ethnicity groups were obtained for possible differences in disease severity and response to treatment. Clinical status was assessed daily from days 1 to 10, or until hospital discharge Study endpoints: Primary; Distribution of clinical status assessed on the 7-point scale on study day 11. Distribution of scores among patients treated with remdesivir should shift more toward higher values of the scale than those who received standard care, if remdesivir improves outcomes. Secondary; Proportion of patients who had adverse events throughout the study. Prespecified exploratory endpoints were time to recovery (improvement from baseline scores of 2–5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7); time to modified recovery (improvement from a baseline score of 2–4 to a score of 5–7, improvement from a baseline score of 5 to a score of 6–7, or improvement from a baseline score of 6 to 7); time to clinical improvement (≥2 point improvement from baseline); time to 1-point or larger improvement; and time to discontinuation of any oxygen support. Proportion of patients with these endpoints were also assessed on days 5, 7 and 11. Other exploratory endpoints included duration of different modes of respiratory support, duration of hospitalization, and all-cause mortality. Virological and pharmacokinetic measurements were limited at the time of study implementation (including SARS-CoV-2 RT-PCR measurements on days 5 and 10).	7-point ordinal scale: 7: Not hospitalized 6: Hospitalized, not requiring supplemental oxygen or ongoing medical care 5: Hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care (whether related or not to COVID-19) 4: Hospitalized, requiring low-flow supplemental oxygen 3: Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices 2: Hospitalized, requiring invasive mechanical ventilation or extra-corporeal membrane oxygenation 1: Death	On Day 11: Patients randomized to the 5-day remdesivir group has significantly higher odds of better clinical status distribution on the scale compared to standard care (OR 1.65; 95% CI: 1.09–2.48). The difference was not statistically significant for the 10-day group and standard care (p = 0.18 by the Wilcoxon rank sum test-proportional odds assumption not met for this comparison). No significant differences for any exploratory endpoints between the 5-day and 10-day groups and standard care. By day 14, clinical status of the 5-day and 10-day groups were significantly different than that of standard care (p = 0.3 for both groups). By day 28, clinical status remained significantly different in the 10-day group compared to the standard care group (p = 0.03).	51% patients in the 5-day group, 59% in the 10-day group and 47% in the standard care groups experienced adverse events. Difference in proportions between the 5-day group and standard care was not statistically significant (4.8%; 95% CI: −5.2 to 14.7%) but the difference between the 10-day group and standard care was statistically significant (12.0%; 95% CI: 1.6 to 21.8%). The more common adverse events in the remdesivir groups compared to standard care (occurred in >5% of participants in any treatment group) included hypokalemia [13 (7%) in the 10-day group, 10 (5%) in the 5-day group and 4 (2%) in the standard care group], nausea [18 (9%) in the 10-day group, 19 (10%) in the 5-day group, and 6 (3%) in the standard care group] and headache [10 (5%) in both the 10-day and 5-day groups and 5 (3%) in the standard care group]. Serious adverse events were less common in the remdesivir groups [10 (5%) in the 10-day group and 9 (5%) in the 5-day group) compared to the standard care group [18 (9%)], with differences of −4.3% (95% CI: −9.7 to 0.9) for the 5-day group vs. standard care, and −3.8% (95% CI: −9.3 to 1.4) for the 10-day group vs. standard care. Discontinuation due to adverse events: 8 (4%) in the 10-day group, 4 (2%) in the 5-day group and none in the standard care group.	All-cause mortality at day 28 for the 5-day group was 1% (95% CI: 0.0–2.6), 2% for the 10-day group (95% CI: 0.0–3.6) and 2% for standard care (95% CI: 0.1–4.1), using Kaplan-Meier estimates. All 9 deaths through day 28 (2 or 1% in the 5-day group, 3 or 2% in the 10-day group and 4 or 2% in the standard care group) occurred among those aged 64 years and older, and none were attributed to remdesivir treatment.

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Table 1. (Continued).

Authors (Country – Date)/ Sponsor	Study design, setting & period	Inclusion criteria, disease severity & use of other treatments	Intervention & follow-up duration	Study assessments, clinical and laboratory data & study endpoints	Ordinal scale used for recovery determination	Recovery/ improvement rates	Adverse event rates & discontinuation of treatment	Mortality rates
WHO Solidarity Trial Consortium [28] (Switzerland- 2 December 2020) Sponsor: World Health Organization (WHO) Name of trial: WHO Solidarity trial	Randomized, open-label multicentre trial; 11,330 patients from 405 hospitals in 30 countries 2750 patients assigned a 10-day course of remdesivir, 954 assigned hydroxychloroquine, 1411 assigned lopinavir (Without interferon), 2063 assigned interferon (which includes 651 to interferon and lopinavir), and 4088 with no trial drug Study period: March 2020- June 19 (hydroxychloroquine), July 4 (lopinavir), and October 16 (interferon regimens)	Inclusion criteria: Hospitalized patients with confirmed diagnosis of COVID-19, not known to receive any of the drugs under trial, no transfer within 72 hours, aged 18 years or older, and with no known contraindications to any of the trial drugs Disease severity: None specified	Intervention: Patients randomized to the remdesivir group received: 200 mg intravenous loading dose on day 0, followed by 100 mg daily administration until day 9. Those randomized to oral hydroxychloroquine (200 mg hydroxychloroquine with some patients on 155 mg hydroxychloroquine base and some on 155 mg chloroquine base) received 4 tablets at 0 hour and 6 respectively, and from hour 12, two tablets twice daily for 10 days. Patients randomized to the oral lopinavir (200 mg lopinavir plus 50 mg ritonavir) group was two tablets twice daily for 14 days; other formulations of lopinavir were not provided therefore patients on mechanical ventilation did not receive the trial lopinavir. Patients randomized to the interferon (44 µg subcutaneous interferon beta-1a) group comprised 3 doses over 6 days (at day of randomization, and days 3 and 6). If intravenous interferon was available, patients were administered with 10 µg interferon for 6 days. Follow-up duration: None specified (deaths recorded regardless if observed before or after day 28)	Patients were observed for suspected unexpected serious adverse reactions, deaths in hospital or discharges alive (which includes any documentation of respiratory support in the hospital), trial-drug timings, use on non-trial drugs, and probable causes of deaths. Study endpoints: In-hospital mortality (death during the original hospitalization; follow-up ceased at discharge)- regardless if death occurred before day 28. Secondary outcomes included initialization of mechanical ventilation, and hospitalization duration.	-	Ventilation time and time to discharge are reported as secondary outcomes. None of the trial drugs reduced initiation of ventilation. Ventilation was initiated in 295 remdesivir patients and 284 in its control, 75 in hydroxychloroquine patients and 66 in its control, 126 patients in lopinavir patients and 121 in its control, 209 interferon patients and 210 in its control	Active treatments ended within 14 days and deaths that occurred within these 14 days due to cardiac causes include 7 in remdesivir and 8 in its control, 4 in hydroxychloroquine and 2 in its control, 6 in lopinavir and 3 in its control, and 6 in interferon and 8 in its control. There were no reported deaths due to renal or hepatic disease.	There were 1253 deaths reported at median day 8 (IQR 4–14). The Kaplan-Meir 28-day mortality was reported at 12% (39% when already ventilated at randomization, and 10% if otherwise). The death rate ratios with numbers dead or randomized, with each drug vs. its control were: remdesivir RR 0.95 (95% CI 0.81–1.11; 301/2743 active vs. 303/2708); hydroxychloroquine RR 1.19 (95% CI 0.89–1.59; 104/947 vs. 84/906); lopinavir RR 1.00 (95% CI 0.79–1.25; 148/1399 vs. 146/1372); and interferon RR 1.16 (95% CI 0.96–1.39); 243/2050 vs. 216/2050).

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Table 1. (Continued).

Authors (Country – Date)/ Sponsor	Study design, setting & period	Inclusion criteria, disease severity & use of other treatments	Intervention & follow-up duration	Study assessments, clinical and laboratory data & study endpoints	Ordinal scale used for recovery determination	Recovery/ improvement rates	Adverse event rates & discontinuation of treatment	Mortality rates
Kalil et al. [24] (USA-11 December 2020) Sponsor: The National Institute of Allergy and Infectious Diseases	Double-blind, randomized, placebo-controlled trial; 1033 patients from 67 trial sites in 8 countries: USA (55), Singapore, Mexico, South Korea, Spain, Japan, United Kingdom, and Denmark. Patients were assigned in a 1:1 ratio; 515 patients were assigned to combination treatment (baricitinib and remdesivir) and 518 patients were assigned the control (placebo and remdesivir). Study period: May 2020-July 2020	Inclusion criteria: Participants aged 18 years or older, and with one of the following criteria: Radiographic infiltrates through imaging studies, $SpO_2 \leq 94\%$ on room air, or require mechanical ventilation, supplemental oxygen, or ECMO, confirmed RT-PCR collected <72 hours prior to randomization. There was no limit imposed on the duration of symptoms prior to enrollment. Disease severity: Mild/moderate (ordinal category 5 and 4, and those on low-flow oxygen device- 15 mL/min or less, including those without supplemental oxygen) and severe (ordinal category 7 and 6, including those on EMCO, invasive or noninvasive mechanical ventilation, or high flow oxygen devices). Use of concomitant treatments: Hospitals with written policies for COVID-19 treatment were allowed to receive them. In the absence of a policy, experimental treatment and off-label use of medications to treat COVID-19 was prohibited.	Intervention: Patients received remdesivir intravenously as a 200 mg loading dose on Day 1, followed by 100 mg maintenance dose until day 10. Baricitinib was given as a 4 mg daily dose, either orally (two 2 mg tablets) or via nasogastric tube for 14 days or until hospital discharge. However patients with a glomerular filtration rate of <60 mL/min received 2 mg of baricitinib. A matching oral placebo was administered as per the same schedule as the active drug.	Patients received standard supportive care at the trial sites. Prophylaxis for venous thromboembolism was recommended for all patients who did not have major contraindications. All patients were evaluated on Day 1, through day 29 of hospitalization. Study endpoints: Primary outcome was time to recovery, with day of recovery being the first day during the 28 days of enrollment in which a patient achieved category 1,2 or 3 on the ordinal scale. Secondary outcomes were clinical status at day 15, based upon the ordinal scale, time to improvement by one or two categories from the ordinal scale at baseline, clinical status assessed on days 3, 5, 8, 11, 15, 22 and 29, mean change in terms of the scale from days 1 to 3, 5, 8, 11, 15, 22 and 29, time to discharge or to a National Early Warning Score of 2 or less maintained for 24 hours, and other measures.	8-point ordinal scale 8: Death 7: Hospitalized, on mechanical ventilation or ECMO 6: Hospitalized, on noninvasive ventilation or high flow oxygen devices 5: Hospitalized, requiring supplemental oxygen 4: Hospitalized, not requiring supplemental oxygen – requiring ongoing medical care 3: Hospitalized, not requiring supplemental oxygen – no longer requires ongoing medical care 2: Not hospitalized, limitation on activities and/or requiring home oxygen 1: Not hospitalized, no limitations on activities	Patients with combination treatment recovered a median of 1 day sooner than patients who received remdesivir and placebo (median 7 days vs. 8 days; RR for recovery: 1.16; 95% CI 1.01–1.32; p = 0.03). Upon analyses based on stratification of disease severity at time of randomization (moderate vs. severe), the HR was 1.15 (95% CI 1.00–1.31; p = 0.047). Median time for recovery among those receiving noninvasive ventilation or high-flow oxygen (baseline score: 6) was 10 days (Combination group) and 18 days (control group); RR for recovery 1.51; 95% CI 1.10–2.08. RR for recovery among patients with glucocorticoids for clinical indications during the study was 1.06 (95% CI 0.75–1.48). Odds of improvement in clinical status at day 15 as per the ordinal scale was greater in the combination group than control group (OR for improvement 1.3; 95%CI: 1.0–1.6). Those with a baseline ordinal score of 6 with combination treatment were most likely to have clinical improvement at day 15 (OR 2.2; 95% CI: 1.4–3.6).	Grade 3 or 4 adverse events occurred in 207 patients (40.7%) for the combination group and 238 patients (46.8%) for the control group. Around 25 grade 3 or 4 adverse events were due to the combination group and 28 were due to the control group. Most common grade 3 or 4 adverse events that occurred in 5% of all patients included: anemia, hyperglycemia, acute kidney injury, and decreased lymphocyte count (incidence similar in both groups). Proportion of patients with serious or non-serious venous thromboembolism events were also similar in both groups (21 patients, 4.1% in the combination group and 16 patients, 3.1% in the control group). Serious adverse events in 81 patients (16.0%) in the combination group, with 6 events related to trial products; 107 patients (21.0%) in the control group with 5 events related to trial products; between-group difference was −5.0% (95% CI: −9.8 to −0.3; p = 0.03).	Kaplan-Meier estimates of mortality at day 28 upon randomization were 5.1% (95% CI: 3.5–7.6) for the combination group, and 7.8% (95% CI: 5.7–10.6) for the control group (HR for death 0.6, 95% CI: 0.39–1.09). The highest numerical difference in mortality among the combination and control group were for those with a baseline score of 5 (1.9% vs. 4.7%; HR 0.40, 95% CI: 0.14–1.14) or score of 6 (7.5% vs. 12.9%; HR 0.55, 95% CI: 0.22–1.38). Kaplan Meier estimates of mortality 14 days after randomization were 1.6% for the combination group and 3.0% in the control group (HR; 0.54, 95% CI: 0.23–1.28).

Table 2. Recommendations of use of remdesivir by drug-authorizing bodies across the globe.

Country/continent	Drug-authorizing organization	Recommendation date	Recommendations for use of remdesivir in COVID-19 patients	Actions taken to review the use of remdesivir
Australia	Therapeutic Goods Administration (TGA)	13 July 2020	The TGA has provisionally approved (maximum of six years) the use of remdesivir for use in Australian adults and adolescent patients who have severe COVID-19 symptoms and hospitalized (requiring oxygen or high-level support for breathing and within hospital care). Remdesivir is available in Australia (existing supplies), including those that were donated from Gilead to the National Medicines Stockpile which will be available for immediate use in coming weeks for appropriate patients [38].	This approval was based on remdesivir's preliminary clinical data and ability to reduce hospitalization time for those with sever COVID-19 and was reported to potentially reduce the strain on the healthcare system. Gilead Sciences will be able to apply for full registration when additional clinical data is available for further assessments by the TGA [38].
Europe	European Medicines Agency (EMA)	25 June 2020	The EMA has granted conditional marketing authorization for remdesivir in the treatment of COVID-19 for adults and adolescents aged 12 years and over who have pneumonia and require supplemental oxygen. Remdesivir is the first medication against COVID-19 to be recommended for authorization in the European Union [36].	The human medicines committee of the EMA has made this decision following a 'rolling review' of evidence on the use of remdesivir based on preliminary findings of the US National Institute of Allergy and Infectious Diseases (NIAID)'s global Phase III trial [20]. This type of review is intended to fasten the assessment of any promising investigational drug during public health emergencies [36].
The United States of America	U.S. Food and Drug Administration (US FDA)	15 June 2020	In May 2020, remdesivir was authorized for emergency use (EUA) in the treatment of suspected or laboratory-confirmed severe COVID-19 among hospitalized adults and children. This authorization allowed for remdesivir to be distributed and administered intravenously in the USA [6]. However following this recommendation on June 15, the FDA has warned health care professionals that administering remdesivir concomitantly with hydroxychloroquine or chloroquine phosphate may reduce the antiviral activity of remdesivir and is not recommended [42].	The initial approval in May 2020 was based on the preliminary findings of the trial conducted by the National Institutes of Health. This emergency use authorization (EUA) will be effective until termination or revision, or if the EUA is revoked based on not meeting statutory requirements given changing circumstances pertaining the use of remdesivir [6].
Singapore	Health Sciences Authority (HSA)	11 June 2020	The HSA has provided conditional approval for patients with an oxygen saturation ≤94%, and those who are in need of supplemental oxygen or intensive breathing support which includes invasive mechanical ventilation [41].	The review of remdesivir was expedited due to urgent public health needs during this pandemic. Gilead is required to obtain further safety data and monitor the use of remdesivir for this indication, as well as submit any ongoing clinical studies for continued safety and efficacy [41].
The United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)	27 May 2020	Remdesivir will be accessible to some adults and adolescents hospitalized with COVID-19 in the National Health Service (NHS). Remdesivir will be prioritized to patients who have the greatest likelihood of most benefit and if the patients meet specific clinical criteria to aid their recovery in the hospital [40].	The MHRA provided positive scientific opinions regarding remdesivir under the Early Access to Medicine Scheme (EAMS) [40].
Japan	Japanese Ministry of Health, Labor and Welfare (MHLW)	8 May 2020	Remdesivir has been approved for the treatment of patients with COVID-19 under the 'exceptional approval pathway' [37].	This approval was based on the preliminary findings of the US National Institute of Allergy and Infectious Diseases (NIAID)'s global Phase III trial [23] and Gilead's SIMPLE trial [26].

benefits with the use of remdesivir in critically ill patients with COVID-19. The study included 51 patients admitted into the ICUs receiving mechanical ventilation with confirmed SARS-CoV-2 infection, of which 25 were treated with remdesivir, while the remaining 26 did not have access to remdesivir. Concomitant therapy with hydroxychloroquine and tocilizumab was permitted, but not with lopinavir/ritonavir. Tocilizumab use was reported to be more commonly used among patients treated with remdesivir (28% versus 7%; p = 0.075). However, this study did not report outcomes related to clinical improvement.

Aiswarya et al. [21] investigated the compassionate use of remdesivir in 48 patients with end-stage renal disease (dialysis-dependent) and moderate-to-severe COVID-19. At the end of the remdesivir therapy, 33 patients (68.8%) showed an improvement in oxygen requirement in the ordinal scale score for respiratory support. This improvement was significant in patients requiring a lower modality of oxygen support (score 1–3) at admission. Patients on high-flow oxygen and noninvasive ventilation at the initiation of remdesivir therapy did not benefit. In addition, it was reported that early administration of remdesivir within 48 hours of hospital admission shortened the duration of hospitalization by a mean of 5.5 days (P = 0.001).

Hillaker et al. [29] described a case report of an otherwise healthy 40-year-old man with COVID-19. The patient showed good clinical progression upon administration of remdesivir, albeit previous administration of hydroxychloroquine and azithromycin to control symptoms while waiting for approval of compassionate remdesivir use. This case report suggested that late initiation of remdesivir could be effective in the treatment of patients with COVID-19.

Wang et al. [22] reported a randomized, double-blinded, placebo-controlled trial among 237 hospitalized patients with COVID-19, which was a continuation of their previous study [16] establishing promising *in-vitro* activity of remdesivir against SARS-CoV-2. The trial found that remdesivir did not significantly improve the time to clinical improvement (hazard ratio (HR) 1.23; 95% CI 0.87–1.75 in the intention-to-treat population and HR 1.27; 95% CI 0.89–1.80 in the per-protocol population), although it was numerically shorter for those treated with remdesivir within 10 days of symptom onset than those treated with placebo. Despite not statistically significant, the duration of use of invasive mechanical ventilation was also numerically shorter in the remdesivir group as opposed to the placebo group. It is important to note that their study permitted the use of concomitant therapy including lopinavir/ritonavir at baseline in 42 (18.0%) patients.

The US National Institute of Allergy and Infectious Diseases (NIAID)'s global Phase III trial by Beigel et al. [25] published their final report recently. This is a randomized, double-blinded, placebo-controlled trial which included 1,062 hospitalized patients with COVID-19; their preliminary findings had been reported previously [23]. The patients were stratified based on disease severity (mild/moderate and severe). Patients were permitted concomitant treatment as per the respective standard of care in trial sites. However, in the absence of concomitant treatment, experimental treatment and off-label use of marketed medications were not permitted. The authors reported an overall shorter recovery time (regardless of disease severity) among patients in the remdesivir group compared to those in the placebo group (a median of 10 days compared to 15 days; recovery risk ratio [RR] 1.29; 95% CI 1.12–1.49). Using a proportional odds model and upon adjustment for actual disease severity, patients with remdesivir were more likely than those receiving placebo to have clinical improvement at day 15 (odds ratio [OR] 1.5; 95% CI 1.2–1.9). In the severe disease stratum (957 patients), median recovery time was 11 days compared to 18 days (recovery RR 1.31; 95% CI 1.12–1.52). In the subgroup analysis, the reduced time to recovery was only statistically significant among patients who were on low-flow oxygen at baseline (ordinal score 5) (recovery RR 1.45; 95% CI 1.18–1.79). Among the subgroup of patients on mechanical ventilation or ECMO at baseline, there was no statistically significant difference on the time to recovery between remdesivir and placebo (recovery RR 0.98; 95% CI 0.70–1.36).

Goldman et al. [26] reported an open-label randomized phase III trial (sponsored by Gilead Sciences) to determine the shortest yet effective duration of treatment with remdesivir by comparing a 5-day course with a 10-day standard course (the SIMPLE trial). The study permitted concomitant supportive therapy at the discretion of the investigators. In their preliminary findings involving 397 hospitalized patients with severe COVID-19, the authors reported no significant differences in both groups after adjustment of imbalances in baseline clinical status. By day 14, clinical improvement of ≥2 points on the ordinal scale were reported in 64.0% and 54.0% of the patients in the 5-day and 10-day group, respectively. However, upon adjustment for clinical status at baseline, there was no significant difference in both groups (baseline-adjusted difference in proportions of −6.3%; 95% CI −15.4–2.8) (p = 0.14).

Spinner et al. [27] reported an open-label, three-arm, randomized phase III trial among hospitalized patients with moderate COVID-19 (i.e. hospitalized with evidence of pulmonary infiltrates and oxygen saturation >94% on room air). This trial investigated the effectiveness of remdesivir comparing a 5-day and a 10-day remdesivir course, with standard care at day 11 of treatment. Though initial study protocol was designed to evaluate the primary end-point of the proportion of patients discharged by day 14, the protocol was subsequently amended to modify the primary end-point to the assessment of clinical status on day 11 based on a 7-point ordinal scale. In addition, the trial initially permitted concomitant use of medications deemed as 'local care' but did not permit their use upon subsequent protocol amendment, although some patients previously had concurrent therapy. Patients in the 5-day remdesivir group had statistically significantly higher odds of better clinical status distribution on the 7-point scale by day 11 than those receiving standard care (OR 1.65; 95% CI 1.09–2.48). There was no significant difference in clinical status distribution between patients in the 10-day remdesivir group and the standard care group (p = 0.18). There were also no significant differences between the 5- or 10-day remdesivir groups and standard care group for any of the exploratory

end-points by day 11, including the time to 2-point or greater improvement in clinical status, time to 1-point or greater improvement in clinical status, time to recovery, time to modified recovery, and time to discontinuation of oxygen support. Subgroup analysis revealed no difference between the remdesivir group and placebo group in proportions of patients with 1-point or greater improvement in clinical status among the patients with supplemental low-flow oxygen therapy as well as those without supplemental low-flow oxygen therapy.

The open-label multicentre Solidarity trial by the WHO reported outcomes on in-hospital mortality, as well as the initiation of mechanical ventilation and hospital duration, with several investigational agents [28]. This study included 11,330 patients from 405 hospitals in 30 countries [28]. Trial drugs included remdesivir, hydroxychloroquine, lopinavir, and interferon, where a 10-day duration of remdesivir with a 200 mg intravenous loading dose, followed by a 9-day regimen of 100 mg was used; doses of other drugs are reported in the summary table. There were no placebos used in this study. None of the trial drugs, including remdesivir, reduced the requirement for ventilation for patients who were already on it. In addition, none of the trial drugs including remdesivir reduced duration of hospitalization.

Finally, the most recent findings from the clinical trials were reported by Kalil et al. [24] as part of a double-blind randomized, placebo-controlled, trial sponsored by The National Institute of Allergy and Infectious Diseases. Their trial included two arms where patients were assigned to either receive remdesivir and baricitinib, or remdesivir and a placebo; remdesivir dose was similar to the abovementioned studies, whereas baricitinib was administered as a 4 mg daily dose orally (two 2 mg tablets) or via a nasogastric tube for 14 days. If the glomerular filtration rate was <60 mL/min, the dose was halved to 2 mg daily. Given that this was a multicentre trial, they permitted the use of concomitant treatments if trial sites had written policies where off-label COVID-19 treatment was allowed; but in its absence, this was not permitted. Patients with combination treatment recovered a median of 1 day sooner than patients who received remdesivir and placebo (median 7 days vs. 8 days; recovery RR 1.16; 95% CI 1.01–1.32; p = 0.03). Odds of improvement in clinical status at day 15 as per the ordinal scale was greater in the combination group than the control group (OR for improvement 1.3; 95%CI: 1.0–1.6). Subgroup analyses based on stratification of disease severity (moderate vs. severe) at the time of randomization reported that combination of remdesivir and baricitinib significantly improved time to recovery for those with severe disease (recovery RR 1.32; 95% CI 1.00–1.75) but not for those with moderate disease (recovery RR 1.11; 95% CI 0.95–1.30). Median time for recovery among those receiving non-invasive ventilation or high-flow oxygen was 10 days in the combination group and 18 days in the control group (recovery RR 1.51; 95% CI 1.10–2.08).

3.3. Adverse events associated with remdesivir

Common adverse events observed in patients receiving remdesivir included hepatotoxicity (elevated serum levels of total bilirubin, aspartate aminotransferase, and alanine aminotransferase) [8,19,21–23], hypotension [19,23], diarrhea [19], rash [19], constipation [22,26], nausea [26,27], hypoalbuminemia [22], hypokalemia [22,27], anemia [22,23], thrombocytopenia [22], hyperglycemia [23] and headache [27]. Serious adverse events reported in patients using remdesivir included acute kidney injury (AKI [4.0% to 22.8%]; 49% of patients treated with remdesivir required continuous renal replacement therapy but the cause of kidney failure was not stated and could be due to multiorgan failure from COVID-19) [8,19,20,23], respiratory failure or ARDS (5.2% to 10.0%) [22,23,26], cardiopulmonary failure (5.0%) [22], multiple-organ dysfunction syndrome (4.0%) [19], septic shock (4.0%) [19] and hypotension (4.0%) [19]. Although hepatotoxicity and AKI have been reported as the most common adverse events associated with the use of remdesivir, it is challenging to establish causality as these adverse events can be attributed to the pathogenesis of COVID-19 itself [8,31]. In randomized controlled trials [22,23], common adverse events associated with the placebo group included hepatotoxicity (elevated serum levels of aspartate aminotransferase and total bilirubin) [22], hypotension [23], dyslipidemia [22], hypoalbuminemia [22], constipation [22], anemia [22], and hypokalemia [22]. Serious adverse events in the placebo group included respiratory failure or ARDS [22,23], cardiopulmonary failure [22], and AKI [23].

Adverse events could also be attributed to concomitant medications which were permitted in some studies [8,21–24,26]. In the trial by Kalil et al. [24] which included the addition of baricitinib in one arm, and the use of a placebo in another, serious adverse events that occurred in both arms included anemia, hyperglycemia, AKI, and decreased lymphocyte count; the proportion of patients with serious or non-serious venous thromboembolism were similar in both arms. The concomitant use of lopinavir/ritonavir with remdesivir in 18.0% of patients at baseline in the study by Wang et al. [22] and possibly in some or all of the patients in the study by Beigel et al. [23] (their study permitted concomitant therapies as per respective standard care for trial sites) could have resulted in hepatotoxicity; lopinavir/ritonavir is a potent inhibitor of the enzyme cytochrome P450 3A (CYP3A) and remdesivir is metabolized by CYP3A. Furthermore, hepatotoxicity, nausea, vomiting, and diarrhea are common adverse drug reactions associated with lopinavir/ritonavir [32].

Treatment discontinuation due to serious adverse events was another major limitation in the included studies. Remdesivir was discontinued in 4 patients (8.0%) in the study by Grein et al. [19], in 18 (12.0%) and 4 (5.0%) patients from the remdesivir and placebo groups, respectively, in the study by Wang et al. [22], in 4 ICU patients due to AKI and overall in 37.0% patients due to adverse events in the study by Antinori et al. [8], in 49 patients before day 10 in the study by Beigel et al. [23] and in 9 (4.0%) patients from the 5-day group and 20 (10.0%) patients from the 10-day group in the study by Goldman et al. [26]. In the study by Spinner et al., [27] remdesivir was discontinued in 8 (4%) patients in the 10-day group, 4 (2%) patients in the 5-day group, but none in the standard care group. Serious adverse events leading to discontinuation in patients receiving remdesivir included behavioral change

[21], respiratory failure or ARDS [22,23,26], cardiopulmonary failure [22], AKI [8,19,23], hypotension [23], multiple-organ failure [19], transaminitis [8,19,23], and maculopapular rash [19]. On the other hand, serious adverse events leading to discontinuation in the placebo group included respiratory failure or ARDS [22] and cardiopulmonary failure [22]. These data are available in detail in Table 1.

3.4. Mortality associated with remdesivir

Mortality rates in patients who used remdesivir varied across studies. The patient from the case report by Hillaker et al. [29] survived and were successfully discharged. The compassionate use study by Grein et al. reported that 7 of 53 patients (13.0%) died upon completion of remdesivir therapy, but their findings received some criticism from the research fraternity [19,33]. They claimed mortality rate should have been 22.0% based upon 7 patients who died but with a denominator of 32 (instead of 53) which represented the total number of patients who were discharged or had died, i.e. 25 and 7 patients, respectively [19,33]. The other compassionate use study by Antinori et al. reported that 3 of the 4 ICU patients who discontinued remdesivir due to AKI died and that 4 ICU patients (22.2%) who received remdesivir died by day 10 of treatment, and 8 ICU patients (44.4%) died by day 28 of treatment, while 1 IDW patient died by day 10 of treatment [8]. The compassionate use study by Aiswarya et al. [21] reported that 10 patients (20.8%) died during hospitalization; 7 patients had their remdesivir initiated less than 48 hours since admission while the remaining 3 patients had their remdesivir initiated more than 48 hours since admission.

The compassionate use study by Pasquini et al. [20] reported findings that were focused on mortality as an outcome. Survival analysis by Kaplan–Meier curves observed that the mortality rate was significantly lower among patients treated with remdesivir than in untreated patients (56.0% versus 92.3%; $p < 0.001$). In addition, multivariate analysis observed that treatment with remdesivir was the only factor associated with survival (odds ratio 3.506; 95% CI 1.768–6.954; $p < 0.001$). Nevertheless, it should be noted that there may be presence of selection bias in the study since patients with mild renal impairment or who received inotropic support had no access to remdesivir treatment. However, the authors argued that patient selection may not bias toward better outcomes since most of the ICU patients experienced clinical deterioration, resulting in death in 74.5% of included patients.

Mortality rates were not statistically significant between the two treatment groups in all three of the randomized, double-blinded, placebo-controlled trials by Wang et al. [22] (22 patients or 14.0% died in the remdesivir group vs. 10 or 13.0% in the placebo group; difference 1.1%; 95% CI −8.1–10.3), Beigel et al. [23] (HR for death 0.73; 95% CI 0.52–1.03), and Kalil et al. [24] (HR for death 0.60; 95% CI 0.39–1.09), respectively. Beigel et al. [23] reported that Kaplan–Meier estimates of 15-day and 29-day mortality were 6.7% and 11.9%, and 11.4% and 15.2%, in the remdesivir and placebo groups, respectively. However, among the subgroup of patients who were on oxygen supplementation but did not require high-flow oxygen or ventilatory support (either noninvasive or invasive), there was a statistically significant 29-day mortality benefit (4.0% versus 12.7%, HR 0.30, 95% CI 0.14-0.64). In the randomized, open-label, phase III trial by Goldman et al., [26] 16 of 200 patients (8.0%) in the 5-day group and 21 of 197 patients (10.7%) in the 10-day group died by day 14. The randomized, open-label trial by Spinner et al. [27] reported that all-cause mortality using Kaplan-Meier estimates at day 28 was 1% for the 5-day group (95% CI: 0.0–2.6), 2% for the 10-day group (95% CI: 0.0–3.6), and 2% for standard care (95% CI: 0.1–4.1). The Solidarity trial [28] by the WHO reported that remdesivir did not indefinitely reduce mortality (RR 0.95; 95% CI 0.81–1.11), even in the subgroup analyses.

4. Discussion

The use of remdesivir has garnered attention in the management of COVID-19 since March 2020 [34]. There was a variation in terms of eligibility of participants across studies in terms of dependence on oxygen support, which may not allow generalizability of results based on oxygen dependence level. A major confounder in some studies was the use of concomitant medications and prior therapies with potential effects against SARS-CoV-2, thus raising concerns about the conclusions made on the efficacy of remdesivir [8,20–27,29]. In addition, the use of an ordinal scale in most of the included studies is not ideal for demonstration of clinical improvement in patients with COVID-19 since decisions to discharge patients or to place patients on respiratory support, etc. may have been influenced by other considerations in addition to patients' clinical progress.

We included four compassionate use studies to present evidence in emergencies where all other therapeutic approaches were exhausted especially in both the studies by Antinori et al. [8] and Pasquini et al. [,20] respectively, during the outbreak in Italy. Although the study by Antinori et al. [8] was without a control group, a median recovery time of 12 days upon remdesivir administration and the recovery of higher number of patients outside the ICU suggested that remdesivir may be beneficial for patients with pneumonia who are not critically ill. The study by Grein et al. [19] had limitations including variation across trial sites for institutional treatment protocols and thresholds, small sample size, a lack of a placebo-controlled group, a lack of viral load data, and censored data for deceased patients. Although these limitations were acknowledged by the authors, the study received mixed reviews from the research and medical community [19,33]. Apart from the concerns mentioned above, the medical fraternity raised questions about the false-positive results implied by the authors with regard to the efficacy of remdesivir due to non-generalizability of the results to patients with severe COVID-19, since 12 of 53 patients were not receiving high-grade oxygen support. However, the authors maintained their stance on generalizing their results to patients with severe COVID-19, as their study population comprised hospitalized patients receiving supplemental oxygen or with hypoxia [33]. The study by Pasquini et al. [20] compared the

risk of mortality in hospitalized patients treated with remdesivir with their counterparts not treated with remdesivir, i.e. control group, and reported a higher mortality rate (74.5%) compared to other studies. The authors attributed the relatively high mortality rate to data collection during the initial 3 weeks of the pandemic when their ICU capacity was under extreme pressure. Their hospital was restructured to admit only patients who had confirmed SARS-CoV-2 infections with a fourfold increase in ICU beds, but with an unmet need of ventilators, specialized nurses, and doctors during the study period. Another limitation in the study was the exclusion of patients with mild renal impairment or those who commenced inotropic support, and therefore the possibility for selection bias. Nevertheless, the authors argued that since majority of the included patients with COVID-19 experienced clinical deterioration upon admission into ICU, patient selection in the remdesivir cohort may not lead to better clinical outcomes. The authors also reported late initiation of remdesivir at a median of 18 days upon symptom onset, although other studies [8,19] have not depicted better clinical outcomes with earlier initiation. The study by Aiswarya et al. [21] reported the safe compassionate use of remdesivir in dialysis-dependent patients (who had been excluded in clinical trials), and improvement in oxygen requirement was observed in patients requiring a lower modality of oxygen support at admission.

The case report [29] suggested positive outcomes in the use of remdesivir. However, given the low level of evidence associated with the nature of this study design, the findings cannot be generalized. This study was discussed in our paper as it was paramount in the initiation of larger studies (e.g. clinical trials) and the successful request to the US Food and Drug Administration (FDA) for remdesivir as an emergency investigational new drug (eIND) [21,29]. It is also important to acknowledge the difficulties associated with obtaining approval and the use of remdesivir in the case study by Hillaker et al. [29] which resulted in delayed treatment. The overwhelming request of remdesivir from the manufacturer put a strain on their supply and thus on 22 March 2020, the manufacturer halted their compassionate use program but committed to fulfilling the delivery of pre-approved requests [35]. However, Gilead Sciences is currently working closely with regulatory agencies globally to provide emergency access to remdesivir [6,36–38].

The randomized, double-blinded, placebo-controlled trials presented mixed findings [22,23]. It is important to note that the trial by Wang et al. [22] failed to achieve target enrollment due to marked reductions in new patients with COVID-19 in China and restrictions in terms of hospital bed availability, resulting in potentially insufficient power to detect significant differences between both groups. This study also aimed to assess the clinical benefits from the time of symptom onset to initiation of remdesivir, but failed to do so due to the limitations; otherwise, the findings may inform the optimal time to the initiation of remdesivir. Overall, the study found that remdesivir was well tolerated with no new safety concerns [22]. The data and safety monitoring board from the trial by Beigel et al. [23] allowed the results of their study to be unblinded to the trial team members which may have resulted in measurement bias. According to the authors, the publication of the paper on preliminary results was based on immediate importance for care of patients with COVID-19 within and outside the trial; they concluded that the use of remdesivir is indicated for hospitalized patients with COVID-19 who require supplemental oxygen therapy, in combination with other therapeutic approaches [23]. The final report presented consistent findings to the preliminary report, whereby a 10-day course of remdesivir was more effective than placebo in shortening the time to recovery among patients with COVID-19, especially those who were on low-flow oxygen at baseline [25]. Treatment with remdesivir may have prevented progression to a more serious form of respiratory disease, depicted by lower incidence of new oxygen use and lower proportion of patients with serious adverse events due to respiratory failure. New in the final report was that adjustment was made for glucocorticoid use, and that the benefits in terms of recovery persisted, suggesting that the benefit of glucocorticoids could be additive to remdesivir's benefit. They stated that treatment of patients with moderate-to-severe COVID-19 with an antiviral alone may not be sufficient given the high mortality rates despite the use of remdesivir.

This is where findings of the trial by Kalil et al. [24] which compared use of remdesivir and baricitinib vs. remdesivir and a placebo, are interesting to highlight. They reported that the use of remdesivir and baricitinib was superior compared to use of remdesivir alone, based on time to recovery given that the former significantly accelerated improvement in clinical status; this was the case for patients receiving noninvasive ventilation as well as high-flow oxygen. Serious adverse events were lower in incidence in the group that received baricitinib compared to those who received remdesivir alone. The authors also highlighted that dexamethasone, which has been recommended in clinical practice after the RECOVERY trial [14], has a longer half-life, and reduces inflammation via a broad-pathway approach and may be associated with immunosuppression, whereas baricitinib has a short half-life and reduces inflammation by acting on targeted critical pathways, with less immunosuppression.

In the open-label RCT by Goldman et al. [26], the authors reported that the trend toward better outcomes in patients treated with 5 days of remdesivir could be due to the fact that patients in the 10-day arm had more severe illness which necessitated mechanical ventilation with high-flow oxygen, which has been known to worsen the prognosis. An open-label design was used due to the unavailability of matched placebo vials which had been allocated to other trials. Since patients could be discharged when medically indicated and this precluded completion of the full 10-day course of remdesivir, only 44.0% of patients in the 10-day group completed their course. The authors also claimed that their results could not be extrapolated to patients with COVID-19 who are critically ill and receiving mechanical ventilation, given that only few patients in the trial were receiving mechanical ventilation prior to the initiation of remdesivir [26].

Similarly, the open-label nature in the RCT by Spinner et al. [27] was due to an insufficient number of placebo-containing vials to support this trial. Although the authors reported that

patients who received remdesivir for 5 days had significantly higher odds of better clinical status distribution 11 days after treatment initiation compared to those who received standard care, the effect size was of uncertain clinical importance. This could have been due to the open-label study design, whereby discharge decisions could have been influenced by the assigned duration for remdesivir treatment, which peaked upon the end of the dosing period (day 6 for the 5-day group and day 11 for the 10-day group) [27].

Finally, the Solidarity trial [28] by the WHO presents the recent evidence on the use of remdesivir, where remdesivir did not have a significant effect in hospitalized patients with COVID-19. None of the drugs including remdesivir effectively reduced in-hospital mortality overall and in any subgroups, neither did it reduce ventilation or duration of hospitalization. This was a large multicentre trial and adherence remained 94% to 96% midway through treatment, which included 2% to 6% on crossover. The study protocol did not specify disease severity, although subgroup analyses are provided elsewhere [28].

5. Conclusion

Given the current evidence, there is insufficient data to confidently recommend routine initiation of remdesivir alone for the treatment of hospitalized patients with moderate-to-severe COVID-19. However, remdesivir may be considered along with an anti-inflammatory agent (e.g. baricitinib) in adult or adolescent (≥12 years) patients with pneumonia and on oxygen support, provided there is close monitoring of clinical and laboratory parameters and adverse events upon administration of remdesivir. Most of the current evidence for remdesivir has emerged from its clinical use in patients with moderate-to-severe COVID-19 in a hospital setting or as emergency use in critically ill patients with COVID-19 and therefore, its use should be restricted in this patient population under close clinical supervision and monitoring. Ongoing clinical trials will provide better understanding of the role of remdesivir in improving outcomes in other subgroup of patients with COVID-19.

6. Expert opinion

Firstly, it is important to note that most of the national regulatory agencies across the world including the FDA in the USA, the European Medicines Agency (EMA) in Europe, the Therapeutic Goods and Administration (TGA) in Australia, the Japanese Ministry of Health, Labour and Welfare (MHLW) in Japan, the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom and the Health Sciences Authority (HSA) in Singapore have conditionally approved/approved the use of remdesivir in COVID-19 patients under specific conditions (Table 2) [6,37–41] (conditional approvals pending safety data) [35].

The inclusion of all RCTs available at the time of publication ensures highly credible evidence in concluding the effectiveness and safety of the use of remdesivir. Nevertheless, it should be highlighted that there is a lack of investigation on the impact of remdesivir on viral load in the RCTs reviewed in this paper. In addition, it is still not known with certainty that mechanically ventilated patients benefit from the use of remdesivir. At present, data on the effectiveness and safety of remdesivir alone is not compelling to allow for its routine use in hospitalized patients with moderate-to-severe COVID-19. However, the use of remdesivir with an anti-inflammatory agent (e.g. baricitinib) might be considered in hospitalized adults or adolescents with COVID-19 (☐12 years) with pneumonia and on oxygen support, in order to accelerate their recovery, provided that there is close monitoring of adverse events, and clinical and laboratory parameters upon administration of remdesivir. The initiation of remdesivir is considered optimal as soon as possible upon hospitalization and it is recommended for a 10-day duration, with a 200 mg intravenous loading dose on day 1, followed by a 100 mg daily administration [8,19–24,26–30].

The safety profile of remdesivir is not fully established at this stage as the suggestive incidence of adverse events and mortality may or may not be linked to its use. Therefore, careful monitoring is required and the following monitoring recommendations should be implemented [22,23,27]: daily monitoring of vital signs and blood pressure; clinical laboratory testing for hepatic, renal, blood, and lipid profiles every 3 days; and a 12-lead electrocardiogram upon 7 days of use.

There is insufficient evidence to conclusively recommend the use of remdesivir in pregnant women, children (<12 years), and older people (≥60 years) with multiple underlying comorbidities. However, Gilead Sciences has made a statement that compassionate use requests can be made exclusively for children (<12 years) and pregnant women with confirmed COVID-19 and with severe manifestations of the disease, if necessary [35]. Given the recent recommendation by the US FDA, remdesivir is not recommended to be concomitantly administered with hydroxychloroquine or chloroquine phosphate [42]. It is also important to consider that the manufacturer is moving toward an expanded access program for all future institutional use of remdesivir (with an exception of clinical trials), but the procedure of accessing remdesivir is expected to be similarly challenging to the individual compassionate use procedure [29,35]. Therefore, consideration must also be given to the accessibility of remdesivir, and arrangements for approvals to acquire remdesivir should be made as soon as possible if it is deemed potentially useful for patients based on respective hospital standards of care.

Results from other ongoing trials will further improve our current understanding on the role of remdesivir in patients with COVID-19. The second SIMPLE trial by Gilead Sciences which is a three-arm RCT aims to determine the efficacy and safety of remdesivir therapy for 5 and 10 days versus standard of care. In addition, their REMDECTA trial is being conducted and aims to determine the efficacy and safety of remdesivir in combination with an anti-inflammatory drug, tocilizumab [43]. The French Institute of Health and

Medical Research (INSERM) is conducting a study to evaluate remdesivir and other potential treatments based on a master protocol developed by the WHO [35]. When available, the results of these trials must be carefully considered and may shift the paradigm of treatment with remdesivir in hospitalized patients with moderate-to-severe COVID-19. Consideration should also be given to the recent development of dry powder remdesivir by researchers at the University of Texas [44]. This formulation can be considered for use in non-hospitalized COVID-19 patients, to increase accessibility to the drug. The dry powder inhalation will be deliverable at lower doses and allows for direct action in the lungs, which is the primary infection site for patients with respiratory symptoms.

Funding

This study was not funded.

Authors' contributions

KT drafted the manuscript, and KT, CSK, MAH, and SSH equally contributed to the revision of the manuscript in its final form. All authors read and approved the final manuscript.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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