



Remdesivir in Coronavirus Disease 2019 (COVID-19) treatment: a review of evidence

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Abstract

COVID-19 is an infectious disease caused by a novel β -coronavirus, belonging to the same subgenus as the Severe Acute Respiratory Syndrome (SARS) virus. Remdesivir, an investigational broad-spectrum antiviral agent has previously demonstrated *in vitro* activity against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and *in vivo* efficacy against other related coronaviruses in animal models. Its safety profile has been tested in a compassionate use setting for patients with COVID-19. The current therapeutic studies demonstrate clinical effectiveness of remdesivir in COVID-19 patients by shortening time to clinical recovery, and hospital stay. In this review, we critically analyze the current evidence of remdesivir against COVID-19 and dissect the aspects over its safety and efficacy. Based on existing data, remdesivir can be regarded as a potential therapeutic agent against COVID-19. Further large-scale, randomized placebo-controlled clinical trials are, however, awaited to validate these findings.

Keywords COVID-19 · SAR-CoV-2 · Remdesivir · Hui Xian Jaime Lin and Sanda Cho shared the first authorship

Introduction

In December 2019, the novel Coronavirus Disease 2019 (COVID-19) was first identified as a new emerging infectious disease in China. It has rapidly spread across the globe, and was declared a global health emergency by the World Health Organization (WHO) on 30th January 2020 [1]. To date, many countries are still struggling to contain the spread of this virus. As of 2nd November 2020, there are among

218 countries affected, 46.8 million infections and over 1.2 million deaths reported worldwide [2]. These numbers continue to rise daily.

COVID-19 is caused by a novel β -coronavirus, a ribonucleic acid (RNA) virus which belongs to the same subgenus as the Severe Acute Respiratory Syndrome (SARS) virus [3]. It has, therefore, been designated Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses [3]. SARS-CoV-2 shares 79% of the sequence homology with SARS-CoV and more distantly (50% of sequence homology) with the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [4]. These are two Coronaviruses that had caused severe acute respiratory syndrome outbreaks in China in 2002/2003 and in Saudi Arabia in 2012, respectively [5].

The clinical course of COVID-19 ranges from asymptomatic infection or mild respiratory symptoms to severe or life-threatening pneumonia and death. With no definitive curative treatment insight, and high mortality rate in vulnerable populations, health authorities have sought to re-stratify risks, and focus on the repurposing of available drugs to develop timely and cost-effective therapeutic strategies, targeting the hospitalized and critically ill. Several

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antiviral/antimalarial agents such as remdesivir, ritonavir/lopinavir combination, hydroxychloroquine, chloroquine; and immuno-modulating therapies such as tocilizumab, sarilumab, lenzilumab, eculizumab, ravulizumab, convalescent plasma, and interferon are currently being evaluated in randomized controlled trials (RCT) in many countries to evaluate their efficacy and safety in the treatment of COVID-19.

Remdesivir was touted as a potential candidate drug for the treatment of COVID-19. Recent studies have shown promising results and have been regarded as a ‘molecule of hope’ for the treatment of COVID-19 [6]. On the 22nd October 2020, remdesivir became the first United States Food and Drug Administration (FDA) approved drug for the treatment of hospitalized COVID-19 patients [7]. Our objective is to review and summarize the most current evidence of the antiviral properties of remdesivir, its safety profile and efficacy in COVID-19 patients. We will also briefly discuss other experimental treatments that are available in the literature.

Remdesivir as an anti-viral agent: in vitro and in vivo studies

Remdesivir, also named as GS-5734 is an adenosine analogue with a broad-spectrum antiviral activity against RNA viruses [8]. It is a prodrug that requires metabolism by the host cell to its active form, GS-441524, that interferes with viral RNA-dependent RNA polymerase (RdRp) enzyme causing a delay in chain termination, arresting RNA synthesis and viral replication [8].

In vitro, remdesivir has been shown to inhibit viral replication in both MERS-CoV and SARS-CoV [9]. Sheahan et al. measured intracellular genomic and subgenomic viral

RNA via quantitative reverse transcriptase polymerase chain reaction in remdesivir-treated human airway epithelial cell line [9]. A dose dependent reduction for both SARS-CoV and MERS-CoV was demonstrated, which is consistent with titer reduction [9].

Similarly, in mouse models of SARS-CoV infection, prophylactic or early administration of remdesivir lowered viral load and reduced SAR-CoV-associated pulmonary pathology of denuding bronchiolitis, perivascular inflammatory infiltrates and intra-alveolar edema, and prevented deterioration in pulmonary function [9]. Interestingly, therapeutic remdesivir treatment in SARS-CoV after virus replication and lung epithelial cell damage had peaked did not alter disease severity or mortality, despite a significant reduction in SARS-CoV lung viral titre [9].

These findings are consistent with studies on non-human primates (rhesus macaque model). A reduction in lung viral load was observed in both prophylactic and therapeutic treatment groups [10]. Respiratory rate of animals treated prophylactically with remdesivir remained normal throughout the study; however, 83% of those treated therapeutically developed increased heart rate [10]. Pulmonary pathology was absent in the prophylactic treated group [10]. Gross lung lesions were observed in 83% of the animals treated therapeutically with remdesivir, the total lung area affected was, however, significantly smaller than that compared to control animals [10].

Evidence from the above in vitro and in vivo studies of SARS-CoV and MERS-CoV (refer to Table 1 and Table 2) suggest that prophylactic treatment with remdesivir inhibit viral replication, prevent clinical disease and changes in pulmonary pathology [9–12]. The clinical benefit

Table 1 Summary of IC₅₀/IC₉₀ or EC₅₀/EC₉₀ values determined by infectious viral titre from in vitro and animal studies, respectively

Study	Component	Virus	Cell line	EC ₅₀ /EC ₉₀ (determined by infectious viral titre)
Sheahan et al. (2017) [9]	Remdesivir	MERS-CoV	Calu3 2B4	IC ₅₀ = 0.025 μM
	Remdesivir	MERS-CoV	*HAE	IC ₅₀ = 0.074 μM
	Remdesivir	SARS-CoV	*HAE	IC ₅₀ = 0.069 μM
Wang et al. (2020) [11]	Remdesivir	SARS-CoV-2	Vero E6	EC ₅₀ = 0.77 μM EC ₉₀ = 1.76 μM
Pruijssers et al. (2020) [12]	Remdesivir	SARS-CoV-2	Calu3 2B4	EC ₅₀ = 0.28 μM EC ₉₀ = 2.48 μM
	Remdesivir	SARS-CoV-2	Vero E6	EC ₅₀ = 1.65 μM EC ₉₀ = 2.40 μM
	Remdesivir	SARS-CoV-2	*HAE	IC ₅₀ = 0.010 μM IC ₉₀ = 0.009 μM
	GS-441524 [^]	SARS-CoV-2	Vero E6	EC ₅₀ = 0.47 μM EC ₉₀ = 0.71 μM
	GS-441524 [^]	SARS-CoV-2	Calu3 2B4	EC ₅₀ = 0.62 μM EC ₉₀ = 1.34 μM

*HAE = Primary human airway epithelial

[^]GS-441524 is the main plasma metabolite of the antiviral prodrug remdesivir

Table 2 Summary of IC50/IC90 or EC50/EC90 values determined by qRT-qPCR from in vitro and animal studies, respectively

Study	Component	Virus	Cell line	EC50/EC90 (determined by qRT-qPCR)
Pruijssers AJ et al. (2020) [12]	Remdesivir	SARS- COV-2	Vero E6	EC 50 = 1.49 μ M EC 90 = 3.03 μ M
	Remdesivir	SARS-COV-2	Calu3 2B4 cells	EC 50 = 0.60 μ M EC 90 = 1.28 μ M
	GS-441524 [^]	SARS- COV-2	Vero E6	EC 50 = 0.47 μ M EC 90 = 0.80 μ M
	GS-441524 [^]	SARS-COV-2	Calu3 2B4 cells	EC 50 = 1.09 μ M EC 90 = 1.37 μ M

*HAE=Primary human airway epithelial

[^]GS-441524 is the main plasma metabolite of the antiviral prodrug remdesivir

of therapeutic remdesivir treatment, however, is less clear. Although there is an appreciable reduction in viral load, the reduction in severity and disease progression remains unclear.

Remdesivir in the clinical setting

Remdesivir was first identified as an investigational drug to treat Ebola virus disease during the West African outbreak in 2013–2016. Although remdesivir appeared promising in preclinical studies, it did not meet efficacy and safety endpoints in a clinical trial. A randomized controlled trial (RCT) by Mulangu et al. of 681 patients with acute Ebola virus infection demonstrated remdesivir to be less effective than other monoclonal antibody therapies [13]. The study was also terminated prematurely because of high case fatality rate of 53% in the remdesivir group compared to other competitive Ebola drugs [13]. The higher fatality rate could be explained by the virology of Ebola. The Ebola virus is a RNA virus with tropism to antigen presenting cells of lymph nodes, hepatocytes and endothelium [14]. Clinical manifestation include non-specific viral syndrome followed by gastrointestinal manifestations. A proportion of patients progress to a systemic inflammatory phase with hemorrhagic complications that is associated with high mortality [14]. Furthermore, Ebola virus disease predominantly affects resource poor countries with limited supportive care, likely contributing to the higher fatality rate (Tables 1, 2).

The first case report of remdesivir use in COVID-19 originated from the United States. This is a previously well 35-year-old gentleman with history of hypertriglyceridemia, who was admitted for monitoring and isolation [15]. He remained stable for the first 6 days of his admission. His illness progressed with persistent fevers and requirement of oxygen supplementation. Remdesivir was administered as a trial on day 7 of admission (day 11 of illness) with significant clinical improvement over the next 24 h [15]. Subsequent to the case report, small cohort [16] and prospective

[17] studies on compassionate use of remdesivir suggests improvement in oxygen requirement, ability to wean off ventilatory support and improved clinical outcomes (refer to Table 3). Both of these studies were limited by their small sample size, and lack of a comparator group. The study by Grein et al. was further limited by lack of viral titers to measure direct anti-viral efficacy.

In more recent months, evidence from RCTs have begun to surface. The first randomized double-blinded, placebo-controlled multicentre trial was conducted by Wang et al. in Hubei, China [18]. A total of 236 patients were enrolled in this study with a randomization of 2:1 to receive remdesivir or placebo, respectively. 8 patients in the remdesivir group and 2 patients in the control group were excluded from the per-protocol analysis as they did not commence or completed less than 5 days of treatment [18]. The primary clinical endpoint was time to clinical improvement within 28 days after randomization, based on a six-point ordinal scale [18]. Time to clinical improvement, though not significant, was shorter in the remdesivir-treated group (median 21 days vs 23 days) compared to control group [18]. 28-day mortality was similar in both groups with 14% mortality in the remdesivir and 13% in the control group [18]. No significant differences were observed in the duration of oxygen requirement, length of hospital stay, days from randomisation to discharge, and days from randomisation to death in both groups [18]. SARS-CoV-2 RNA viral load were similar in both remdesivir and control groups from onset of symptoms to start of study treatment [18]. Over time, viral load decreased similarly in both groups [18]. This study remains inconclusive, as study recruitment was halted before target enrollment was achieved, due to declining incidence of COVID-19 in China, resulting in poor statistical power.

Another randomized, open-labeled phase 3 multi-center trial (SIMPLE-Severe trial) was conducted in multiple countries (United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan) to evaluate the safety and efficacy of different dosing regimens of remdesivir (5 days

Table 3 Case report and therapeutic studies with remdesivir in COVID-19 patients

Authors	Study design	Population	Intervention	Outcomes measured
Holshue ML et al. [11]	First case report	1 patient	Remdesivir initiated on day 11 of illness	Clinical condition and oxygen status
Grein J et al. [12]	Cohort study, multi-center	53 patients with oxygen saturation of $\leq 94\%$ on ambient air or on oxygen support.	10-day course of remdesivir*	Incidence of key clinical events, including changes in oxygen support requirements, hospital discharge, and reported adverse events, and death
Antinori S et al. [13]	Prospective open-label study	35 patients on mechanical ventilation or with an oxygen saturation level of $\leq 94\%$ on air or a National Early Warning Score 2 of ≥ 4	10-day course of remdesivir*	Change in clinical status based on a 7-category ordinal scale (1 = not hospitalized, resuming normal daily activities; 7 = deceased)
Wang Y et al. [14]	First randomize, double-blind, placebo-controlled clinical trial	237 patients with an interval from symptom onset to enrollment of ≤ 12 days, oxygen saturation of $\leq 94\%$ on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤ 30 mm Hg, and radiologically confirmed pneumonia	Randomly assigned in a 2:1 ratio to remdesivir* or the same volume of placebo infusions for 10 days	Time to clinical improvement up to day 28, on a six-point ordinal scale of clinical status (1 = discharged to 6 = death) or discharged alive from hospital
Goldman, JD et al. [15] SIMPLE-Severe trial	Randomized, open-label, multi-center	397 patients with radiographic evidence of pulmonary infiltrates and either had oxygen saturation of $\leq 94\%$ on room air or on supplemental oxygen	Randomly assigned in a 1:1 ratio to receive intravenous treatment with remdesivir# for 5 days or 10 days.	Clinical status on day 14 on a 7-point ordinal scale (1 = death; and 7 = not hospitalized)
Spinner CD et al. [17] SIMPLE-Moderate Trial	Randomized, open-label, multi-center	596 hospitalized patients with moderate COVID-19 pneumonia (defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation $> 94\%$ on room air)	Randomly assigned in a 1:1 ratio to receive a 10-day course of remdesivir, a 5-day course of remdesivir, or standard care	Clinical status on day 11 on a 7-point ordinal scale (1 = death; and 7 = discharge)
Beigel et al. [18] ACTT-1 Trial	Double-blind, randomized, placebo-controlled trial	1062 adult hospitalized patients with evidence of lower respiratory tract involvement	Randomly assigned to a 1:1 ratio to receive remdesivir* for 10 days or placebo	Time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only
WHO [23]	Multinational randomized, open-control study	11266 adult hospitalized patients	Randomized in equal proportions between local standard-of-care, remdesivir, hydroxychloroquine, lopinavir-ritonavir and interferon	In-hospital mortality

*Remdesivir treatment schedule of intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day from day 2 to day 10

#Remdesivir treatment schedule of intravenous loading dose 200 mg of remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent 4 or 9 days

Table 4 Candidate therapies for COVID-19

Class	Availability	Mechanism of action	Clinical data
<i>Antivirals</i>			
Lopinavir–ritonavir	FDA approved for HIV infection	Protease inhibitor	Small RCT failed to show clinical benefit [47] WHO solidarity trial failed to show benefit in mortality, initiation of ventilation or hospitalisation duration [23]
Hydroxy-chloroquine	FDA approved for lupus, malaria, rheumatoid arthritis	Inhibition of endosomal acidification, glycosylation of host receptors and proteolytic processing	Several RCTs have not shown a clinical benefit for hydroxychloroquine [48–52] WHO solidarity trial failed to show benefit in mortality, initiation of ventilation or hospitalisation duration [23]
Favipiravir	Investigational	Inhibits RNA polymerase and halt viral replication	Small RCT showed no improved clinical recovery at day 7, clinical symptoms of cough and fever was shorter [31]
<i>Immune-based agents</i>			
Tocilizumab, sarilumab	FDA approved for some autoimmune diseases and cytokine release syndrome	Interleukin-6 inhibitors	RCTs did not show benefit in clinical status, and preventing intubation or death [37–39]
Interferon beta-1a	FDA approved for relapsing multiple sclerosis	Immunomodulation	Small RCTs show unclear evidence [53–55] WHO solidarity trial failed to show benefit in mortality, initiation of ventilation or hospitalisation duration [23]
Ravulizumab, eculizumab	FDA approved for adult patients with paroxysmal nocturnal hemoglobinuria	Immunomodulation: complement C5 inhibitor	RCT in progress [42–43]
Lenzilumab	Investigational	Immunomodulation: monoclonal antibody against granulocyte macrophage colony-stimulating factor	Small study showed clinical improvement, and improved inflammatory markers such as C reactive protein and IL-6 [41]
Convalescent plasma therapy	Investigational	Passive immunotherapy	Insufficient data from adequately powered RCT to evaluate the efficacy and safety [56–61]

All classes of drug in Table 4 have clinical trials in progress to further evaluate their efficacy and safety in COVID-19

vs 10 days) in patients with severe COVID-19 [19]. 397 patients were randomized in a 1:1 ratio to receive intravenous remdesivir for either 5 or 10 days [19]. The primary efficacy endpoint was clinical status assessed on day 14 on a 7-point ordinal scale [19]. At day 14, 64% of patients who received a 5-day course of remdesivir showed clinical improvement, as compared with 54% of patients who received a 10-day course [19]. After adjusting for baseline clinical status, there was no difference in clinical improvement at day 14 between the groups [19]. Among patients discharged on or before day 14, the median duration of hospitalization was similar in both the groups (7 days for the 5-day group and 8 days for the 10-day group) [19]. There was also no significant difference demonstrated in the number of hospital discharges and mortality, although numerically there were more discharges in the 5-day treatment group (60% vs 52%), and lower mortality (8% vs 11%) [19]. Post hoc analysis did not demonstrate any improved outcomes with remdesivir treatment beyond 5 days among patients who were receiving non-invasive ventilation, any supplemental oxygen, or breathing ambient air [19]. In multivariate analysis, duration of clinical improvement was shorter in patients that were younger than 65 years old, of a black or white race, did not require supplemental oxygen or only required low-flow oxygen, were not on a biologic treatment and recruitment was outside Italy [19]. Efficacy of remdesivir cannot be determined in this study as it lacks a placebo control group. Although numerically, there is a trend towards better outcomes in the 5-day remdesivir-treated group, the authors have acknowledged several possible reasons. The 10-day remdesivir treatment group included a significantly higher proportion of patients with more severe COVID-19 disease, requiring invasive mechanical ventilation and high-flow oxygen [19]. Furthermore, there is a higher percentage of men in the 10-day remdesivir group [19]. Males with COVID-19 have been shown to have worse outcomes [20]. An expansion phase of the study was recently added and will include 180 trial sites worldwide and aims to enroll a further 5600 patients, including those on mechanical ventilation.

A second SIMPLE trial (SIMPLE-Moderate) was conducted to assess the safety and efficacy of standard care vs 5-day and 10-day intravenous remdesivir treatment in patients with moderate COVID-19 infection [21]. 596 patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir, a 5-day course of remdesivir, or standard care [21]. The primary end point was clinical status on day 11 on a 7-point ordinal scale [21]. On day 11, patients in the 5-day remdesivir group had significantly higher odds of a better clinical status distribution than those receiving standard care (odds ratio, 1.65; 95% CI 1.09–2.48; $P=0.02$) [21]. The clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different ($p=0.18$) [21].

The National Institute of Allergy and Infectious Diseases funded ACTT-1 trial conducted a large international study of 1062 patients from 60 trial sites and 13 subsites in the United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1) [22]. Patients were randomized in a 1:1 ratio to receive remdesivir for 10 days or placebo [22]. The primary outcome was the time to recovery assessed on the eight-category ordinal scale [22]. Results showed that remdesivir treatment shortened recovery time by 5 days (median 10 days vs 15 days, $P<0.001$) [22]. Furthermore, at day 15, the odds of recovery according to the ordinal scale score were higher in the remdesivir group compared to the placebo group (odds ratio for improvement, 1.50; 95% CI 1.2–1.9; $p=0.001$) [22]. Although numerically, mortality rate by day 15 was lower in the remdesivir group, this was not significant (6.7% vs 11.9%, hazard ratio for death, 0.55; 95% CI 0.36–0.83) [22].

Subgroup analysis showed remdesivir was most beneficial in patients receiving supplemental oxygen, but not in those receiving high-flow oxygen, non-invasive or mechanical ventilation [22]. Furthermore, benefit of remdesivir was only seen in patients with ≤ 10 days of symptoms, and not seen in patients with > 10 days of symptoms [22].

More recently, WHO Solidarity Trial Consortium released their trial results. This is a large multinational randomized, open-control study involving over 11,000 hospitalized patients with COVID-19 from 405 hospitals across 30 countries [23]. Remdesivir was one of four available active treatment options (remdesivir, lopinavir/ritonavir, hydroxychloroquine, and interferon beta-1a). The primary outcome was to assess effects on in-hospital mortality in all COVID-19 patients, and secondary outcomes were initiation of ventilation and hospitalization duration [23]. All four interventions failed to show benefit in mortality, initiation of ventilation or hospitalisation duration [23]. One limitation of this study is the lack of data on the duration of symptoms prior to the initiation of remdesivir. Since remdesivir is likely to be beneficial in the early viral replication phase rather than the inflammatory phase, it is possible that remdesivir was administered in the later stage of COVID-19 disease that is characterized by dysregulated host immune response. These findings, therefore, should not be interpreted that remdesivir has no role in the treatment of COVID-19.

While remdesivir has been associated with higher mortality in Ebola viral disease, this has not been observed in COVID-19, possibly due to early diagnosis and treatment initiation. Given the mechanism of action of remdesivir as an antiviral that halts viral replication, these trial findings support the use of remdesivir in the early active viral replication phase in COVID-19 PCR-positive patients. If patients progress from the viral replication phase to the inflammatory phase of infection, such as patients with ARDS requiring

mechanical ventilation, remdesivir is not effective and anti-inflammatory drugs may be beneficial. Choice of therapeutics, therefore, may depend on the disease phase, where remdesivir may have a significant role in the early viral replication phase to reduce disease progression.

Safety profile of remdesivir in COVID-19

Being an investigational drug, safety data on remdesivir are limited. Initial safety profile of remdesivir was evaluated in phase 1 clinical trial for the treatment of Ebola virus disease [25]. In this study, remdesivir demonstrated a linear pharmacokinetics within the dose range of 3 mg and 225 mg, with an intracellular half-life of more than 35 h [25]. This dose range was well tolerated with no evidence of hepatic or renal toxicity [25]. Multiple doses of remdesivir, however, resulted in reversible hepatocellular enzyme elevations [25].

More recent studies from COVID-19 disease provided further insight into the safety of remdesivir. Observational study from the compassionate use of remdesivir in the treatment of severe COVID-19 showed that majority (60%) of patients reported adverse events (AE), with 23% being serious adverse events (SAEs) [16]. All SAEs, however occurred in patients requiring invasive ventilation [16]. These SAEs include multi-organ failure, septic shock, acute kidney injury, and hypotension [16]. Other commonly reported AEs include liver derangement, diarrhea, rash, renal impairment, and hypotension, which also occurred more frequently in patients requiring invasive ventilation [16]. 8% of patients discontinued treatment with remdesivir prematurely, as its use was attributed to one for the following: worsening of preexisting renal failure, multi-organ failure, elevated hepatic enzymes, and maculopapular rash [16]. These AEs described in this study are also commonly experienced in patients with severe COVID-19 disease. Given the lack of a control group, conclusive evidence on the safety of remdesivir cannot be made.

In the most recent and largest ACTT-1 trial, results showed no evidence of significant harm with remdesivir treatment. SAE occurred in 24.6% of patients in the remdesivir group, and 31.6% of patients in the placebo group [22]. No deaths were found to be associated with the use of remdesivir treatment [22]. The most common SAE in the remdesivir group compared to the placebo group were: (i) respiratory failure (7.3% vs 12.8%); (ii) hypoxia or respiratory distress (1.9% vs 2.9%); (iii) acute kidney injury or a reduction in estimated glomerular filtration rate (eGFR) (2.6% vs 3.3%); (iv) septic shock (1.5% vs 2.9%); and (v) cardiac arrest (1.9% vs 1.4%) [18]. Non-serious adverse events (AEs) occurred in 51.9% of patients in the remdesivir group and 57.2% in the placebo group [22]. The most common non-serious AE in the remdesivir group compared to the placebo group were (i) anemia or decreased hemoglobin

(16.5% vs 21.7%); (ii) acute kidney injury, a reduction in eGFR or creatinine clearance, or a rise in blood creatinine (16.0% vs 20.3%); (iii) fever (7.1% vs 6.2%), (iv) hyperglycemia or a raised blood glucose level (13.7% vs 11.8%); and (v) elevated aminotransferase levels (6.0% vs 10.7%) [22].

Clinical trials evaluating different dosing regimens did not demonstrate any difference in AEs among groups. Overall, 70% of patients in the 5-day remdesivir group and 74% of patients in the 10-day group experienced AEs [21]. SAE occurred in 21% in the 5-day group and 35% in the 10-day group [21]. SAEs were, however, significantly increased in the 10-day group after adjusting for baseline clinical status [21]. Consistent with other studies, majority of the SAEs occurred in patients receiving mechanical ventilation or non-invasive ventilation or high-flow oxygen [21]. The most common SAEs were acute respiratory failure (9% 10 days vs 5% 5 days) and respiratory failure (5% 10 days vs 2% 5 days) [21].

Overall, data from clinical trials demonstrated no significant harm with remdesivir. The AEs described are similar between all studies and may suggest that these common AEs could be a result of COVID-19 severity rather than remdesivir treatment.

Current therapeutic pipelines for COVID-19 infection

One other investigational drug is also currently being evaluated for its use in COVID-19. Favipiravir is another RNA polymerase inhibitor that hinders viral replication. Its efficacy and safety profile were mostly obtained from preclinical data with influenza and Ebola virus disease [26–30]. Clinical evidence for the use of favipiravir in COVID-19 is limited. A prospective, multicentre RCT of 240 COVID-19 patients was randomized in a 1:1 ratio to receive either favipiravir or arbidol [31]. Favipiravir did not significantly improve the clinical recovery rate at day 7 [31]. No difference was observed in the requirement for supplemental oxygen or non-invasive mechanical ventilation [31]. Duration of febrile illness and cough, however, was significantly shorter in the favipiravir group [31]. To better evaluate the efficacy of favipiravir in the treatment of COVID-19, RCTs with a placebo control group will need to be conducted.

The anti-cytokines and immune-modulatory agents are also being evaluated for their use in severe COVID-19 disease. Pro-inflammatory cytokines, such as interleukin (IL)-2, IL-6, IL-7, IL10, granulocyte colony-stimulating factor, interferon- γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , and tumour necrosis factor- α have been implicated in the underlying pathophysiology of a dysregulated host hyperinflammatory response in severe COVID-19 disease

[32–34]. There are ongoing clinical trials evaluating the treatment options for this dysregulated host hyperinflammation targeting the inflammatory cascade. Earlier case studies from China suggest that IL-6 may be the predominant mediator of this dysregulated immune response [35]. Peak IL-6 level is associated with severity of pulmonary complications [36]; hence, monoclonal antibodies against IL-6 could reduce inflammatory response and improve clinical outcomes.

Tocilizumab, an IL-6 receptor antagonist, has been used in a small case series of 21 patients with severe COVID-19 with promising evidence [37]. Clinical improvement in respiratory function was evidenced by the reduction in oxygen requirement, and interval reduction in lung opacity on CT imaging [37]. A significant reduction in the percentage of lymphocytes and C reactive protein levels was also observed after tocilizumab treatment [37]. No SAE or AE was reported in this study [37]. In more recent RCTs, tocilizumab did not show benefit in clinical status [38], or in the prevention of intubation or death in moderately ill-hospitalized patients with Covid-19 [39].

Other immune-modulatory agents that are being investigated for the management of patients with dysregulated host hyperinflammatory response include humanized monoclonal antibody against circulating granulocyte macrophage colony-stimulating factor [40, 41] (lenzilumab) and humanized monoclonal antibodies that inhibit the late stage of complement cascade (ravulizumab [42], and eculizumab [43]).

Convalescent plasma therapy, though limited in experience and evidence, is regarded as one possible treatment of COVID-19. It is increasingly being used to urgently counter the COVID-19-associated mortality [44]. The hypothesis is that convalescent plasma of SARS-CoV patients carries antibodies against coronavirus, which may lead to phagocytosis or direct neutralization of the virus. In a study during the SARS pandemic in 2003, 80 SARS patients were given convalescent plasma [45]. 41% of patients who were treated with convalescent plasma in the first 14 days of illness were discharged by day 22 [45]. The mortality rates, however, were no different in the group who received treatment before or after 14 days of illness [45]. It is difficult to make any conclusion from this study due to several limitations. These included a non-randomized study with no placebo group for comparison, variability of antibody dosing, and lack of long-term follow-up for risk of infusion-related infections.

It has been suggested, however, that empiric usage of convalescent plasma may be detrimental in some patients as “antibody-dependent enhancement (ADE)” may lead to a more severe infection later [44]. The risk of ADE is thought to occur in a patient with pre-existing antibodies. These antibodies may cross-react, and enhance infection against another virus, or a subtype of the same virus [44].

Conclusion

In depth understanding of the emerging data related to COVID-19 is crucial to curb this pandemic. At present, remdesivir remains an investigational drug for the treatment of COVID-19. Although it is associated with shorter hospital length of stay, and a more rapid clinical convalescence, no mortality benefit has been demonstrated. These results do not provide clear evidence on the efficacy and safety of remdesivir against COVID-19. It has been suggested that remdesivir is unlikely to achieve adequate concentration in lung tissues through intravenous infusion alone because of its low tissue distribution and poor lung penetration [46]. A proposed combination of pulmonary and intravenous administration of remdesivir has been suggested for a more effective strategy for the treatment of COVID-19 [46].

With the lack of available effective treatment options to date, it is reasonable to trial remdesivir treatment in patients with severe COVID-19 disease. Larger, multi-center RCTs with a placebo control group, however, is required to confirm the efficacy and safety of remdesivir before it can be considered as a ‘standard’ anti-viral treatment for COVID-19.

To further clarify the role of remdesivir across the clinical spectrum of COVID-19, studies comparing different treatment strategies and/or administration routes including combination of antiviral therapy with immune-modulatory agents particularly in severe COVID-19 disease are warranted.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest nor affiliations with or financial involvement with any commercial organisations.

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