



# What is the role of remdesivir in patients with COVID-19?

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## **Purpose of review**

COVID-19 represents an unprecedented public health crisis caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The antiviral remdesivir is one component of treating COVID-19. Unfortunately, the trials evaluating remdesivir have reported mixed results, leading to uncertainty on when to use remdesivir. This review discusses the trials evaluating the efficacy of remdesivir for COVID-19 and other supporting data to help inform the role of remdesivir in patients with COVID-19.

## **Recent findings**

Since the start of the pandemic, there have been four randomized trials of remdesivir in treating patients hospitalized with COVID-19. More recently, extensive observational studies have provided supportive data.

## **Summary**

The majority of trials evaluating remdesivir suggest that remdesivir is effective in the treatment of patients hospitalized with COVID-19. Although there may be a benefit in some subgroups more than others, there is insufficient data to make definitive statements about benefits or lack of benefits in particular groups. Remdesivir has demonstrated clinical benefits such as decreased time in the hospital, lower progression to mechanical ventilation, and decreased utilization of other hospital resources; it is unclear if it reduces mortality, but one randomized controlled trial suggested possible survival benefits. Based on the data available, remdesivir has been approved (or authorized for early use) in 48 countries.

## **Keywords**

Adaptive COVID-19 Treatment Trial, ordinal scale, severe acute respiratory syndrome coronavirus 2, Simple trial, Solidarity

## **INTRODUCTION**

COVID-19 represents an unprecedented public health crisis, exceeding 170 million cases and 3.5 million deaths. Early in the outbreak, before a declaration of a pandemic, remdesivir was proposed as a putative antiviral and advanced to clinical trials based on prior human experience in other viral infections and preclinical data with other coronaviruses. Four randomized efficacy trials evaluated the efficacy of remdesivir. Two of these trials were unblinded and had other significant design issues limiting the interpretability. One blinded trial stopped early due to relatively few COVID-19 patients. The one remaining blinded treatment trial had design and sample size issues, leading some to question the results. In optimal circumstances, additional trials would be conducted to help inform on the efficacy of remdesivir. However, given the public health crises of COVID-19, additional efficacy trials are unlikely. Therefore, a detailed understanding of

these four studies, supporting observational studies, preclinical data, and interpretations by regulatory authorities, is critical to understand the totality of data supporting remdesivir.

## **REMDESIVIR**

Remdesivir, a prodrug, undergoes rapid intracellular conversion and triphosphorylation to the pharmacologically active nucleoside form [1]. The nucleoside acts as an analog of adenosine triphosphate (ATP) and competes with the endogenous ATP for

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## KEY POINTS

- The totality of the data suggests that remdesivir is effective in the treatment of coronavirus disease 2019 (COVID-19).
- The largest and most consistent benefit is in hospitalized patients on no oxygen, low-flow, or high-flow oxygen, but benefits in mechanical ventilation cannot be excluded.
- Based on assessment of all available data, remdesivir has been approved or authorized for use in the treatment of COVID-19 in 48 countries.

incorporation into viral RNA via RNA-dependent RNA polymerase (RdRp). Remdesivir was discovered from research programs beginning in 2009 by Gilead Science looking for treatments of hepatitis C (HCV) and respiratory syncytial virus (RSV) [2].

Remdesivir inhibits a diverse group of RNA viruses, including filoviruses (e.g., Ebola, Sudan, Marburg), paramyxoviruses (e.g., RSV, Nipah, Hendra), and pathogenic coronaviruses [3–5]. Studies in human airway epithelial cell assays demonstrated that remdesivir inhibits replication of coronaviruses, including Middle East respiratory syndrome-related coronavirus (MERS-CoV) [6]. In mouse infection models, remdesivir had therapeutic efficacy against severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and MERS-CoV [6,7]. In a nonhuman primate study, remdesivir treatment initiated 12 h post-inoculation with MERS-CoV provided clinical benefit with reduced clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions. [8,9]. This preclinical data, combined with clinical experience using remdesivir in the treatment of Ebola [10], led to this compound selected early to treat viral pneumonia due to the emergence of SARS-CoV-2 in China [11,12].

## CLINICAL STUDIES

Four randomized efficacy trials evaluated the efficacy of remdesivir (Table 1). The first trial implemented in response to the SARS-CoV-2 outbreak was in Hubei, China. Wang *et al.* [13] conducted a randomized, double-blind, multicenter, placebo-controlled trial of 237 hospitalized adults at ten hospitals with laboratory-confirmed SARS-CoV-2 infection, with severe disease (oxygen saturation  $\leq 94\%$  and radiologically confirmed pneumonia). Remdesivir was administered as a 200-mg loading dose on day 1, followed by a 100-mg daily maintenance dose on days 2 through 10. The primary endpoint was time to clinical improvement, defined as decline (improvement) of two levels on a six-point ordinal scale (from 1 = discharged to 6 = death) or hospital discharge. This trial started February 6, 2020, and ended enrollment on March 12, 2020. The median time from symptom onset to starting study treatment was 10 days (interquartile range [IQR], 9–12 days). The study was terminated before attaining the prespecified sample size ‘because the outbreak of coronavirus disease 2019 (COVID-19) was brought under control in China’. In the 237 participants enrolled, the time to clinical improvement was 21 days in the remdesivir group compared to 23 in the placebo group (hazard ratio [HR] 1.23, 95% confidence interval [CI] 0.87–1.75). Patients receiving treatment within 10 days of symptoms demonstrated greater efficacy (median 18.0 days [IQR 12.0–28.0] vs. 23.0 days [15.0–28.0]; HR 1.52 [0.95–2.43]). This trial assumed a large treatment effect (HR 1.4) would be seen, and randomization was allocated 2:1. Hence, it is unlikely that this trial, even if fully enrolled, was powered to detect a difference of outcomes attributable to remdesivir.

The Adaptive COVID-19 Treatment Trial (ACTT) was the second trial implemented for evaluating remdesivir in the treatment of COVID-19 [14<sup>\*\*\*</sup>]. ACTT was also a randomized, blinded placebo-controlled trial. This trial enrolled 1062 hospitalized adults with COVID-19 and evidence of lower

**Table 1.** Characteristics of key remdesivir efficacy trials

Trial	Study size	Randomized	Blinded	Control	Primary endpoint
Wang <i>et al.</i> [13]	237	Yes	Yes	Placebo + SOC	Time to two-point improvement on ordinal score
ACTT [14 <sup>***</sup> ]	1062	Yes	Yes	Placebo + SOC	Time to recovery (hospital discharge or resolution of active medical issues)
SIMPLE-Moderate [15]	596	Yes	No	SOC	Clinical status on day 11
Solidarity [16]	5475 (remdesivir arm)	Yes, to acceptable arms	No	SOC	Mortality

ACTT, Adaptive COVID-19 Treatment Trial; SOC, Standard of Care.

respiratory tract infection between February 21, 2020, and April 19, 2020. Remdesivir was administered as a 200-mg loading dose on day 1, followed by a 100-mg daily maintenance dose on days 2 through 10 or until hospital discharge or death. Overall, the baseline characteristics are balanced between the two groups. The placebo group had higher severity of illness as measure by ordinal score (mechanical ventilation 24.2% in remdesivir group compared to 29.6% in placebo). However, other metrics such as baseline National Early warning score (NEWS) were more balanced (5.7 compared to 6.1). Before initiation of the study drug, the median duration of symptoms was 9 days in both groups (IQR 6–12 days). Median time to recovery defined as being discharged or still hospitalized but no longer requiring medical care, the primary endpoint, was shorter with remdesivir than with placebo (10 vs. 15 days; RR 1.29, 95% CI 1.12–1.49) [14<sup>\*\*\*</sup>]. The benefit of remdesivir was more significant when it was given earlier in the illness. Patients who received remdesivir within the first 10 days of symptom onset had a rate ratio for recovery of 1.37 (95% CI 1.14–1.64); in comparison, patients who received remdesivir more than 10 days after the onset of symptoms had a rate ratio for recovery of 1.20 (95% CI 0.94–1.52). The rate ratio of recovery for patients who began remdesivir within 6 days from symptom onset was 1.92 (95% CI 1.41–2.60). Those with the more moderate disease (no oxygen or low flow oxygen) had better outcomes (HR 1.29 and 1.45, respectively) than those with severe or critical disease (high flow oxygen HR 1.09; mechanical ventilation, HR 0.98).

The ACTT trial changed the primary endpoint after the study was started when 7% of subjects were enrolled. The original primary endpoint was the clinical status on day 15. Early in the pandemic, there was insufficient to understand the protracted course of SARS-CoV-2. As data emerged from China, there was concern that the original endpoint was too early to detect differences. Clinical status on day 15 was then made the key secondary endpoint. The final analysis also shows benefit by this endpoint – odd ratio (odds of a better clinical status on the ordinal scale) 1.5 (1.2, 1.9) [14<sup>\*\*\*</sup>]. Remdesivir was associated with a lower incidence of new oxygen use among those who had not been receiving oxygen at baseline (36% vs. 44%), fewer days of subsequent oxygen use for patients receiving oxygen at enrollment (13 days vs. 21 days), lower progression to mechanical ventilation (13% vs. 23%), and a shorter subsequent duration of mechanical ventilation or extracorporeal membrane oxygenation for those receiving these interventions at baseline (17 days vs. 20 days).

The Simple-Moderate trial was an open-label trial of 584 hospitalized adults with moderate

COVID-19 (pneumonia and room-air oxygen saturation > 94%) who were randomized to receive remdesivir for either 5 or 10 days or standard treatment (no remdesivir) [15]. This trial enrolled patients between March 15, 2020, and April 18, 2020. Patients who received remdesivir for 5 days, but not those who received it for 10 days, were more likely to improve their clinical status on day 11 than those who received standard treatment (odds ratio 1.65; 95% CI 1.09–2.48) [15]. This trial only enrolled those not requiring any supplemental oxygen at baseline, while a parallel study randomizing to two active arms and no control enrolled the sicker population. There were differences in how patients were treated depending on the treatment arm, with an increase in hospital discharges occurring shortly after completing the assigned duration of treatment.

The Solidarity trial, sponsored by the World Health Organization, enrolled 11 266 hospitalized adults with COVID-19 randomized to receive one of four treatments: remdesivir, hydroxychloroquine, lopinavir/ritonavir, or interferon beta. Controls were the local standard of care [16]. This trial enrolled participants from March 22, 2020, to October 4, 2020. At least one manufacturer providing product for this trial has suggested it was primarily a way to provide access to remdesivir [17<sup>\*</sup>]. There was no predefined sample size. An interim analysis found that none of the drugs affected in-hospital mortality, the primary outcome, or on initiation of ventilation or duration of hospital stay. For the remdesivir component, the mortality was 12.5% for the remdesivir treated arm vs. 12.7% for the control. Investigators were allowed to choose among acceptable treatments. Participants with the more severe disease were more likely to be assigned to the remdesivir arm than other arms (control arm mortality for remdesivir analysis was 12.7% compared to 8.9% for hydroxychloroquine analysis).

## **SUBGROUPS BASED ON THE SEVERITY OF ILLNESS**

Although the totality of data suggests that remdesivir has some clinical benefit, some severity subgroups may benefit more from remdesivir. None of the four randomized trials were designed to assess subgroup efficacy, and only two reported results by subgroups. Neither of these adjusted for multiple comparisons. One other trial only enrolled one subgroup. The remaining study did not report by subgroups. So, definitive statements cannot be made about efficacy (or definitive statements about lack of efficacy) in any given subgroup. Each trial also had a unique endpoint, so comparison across

**Table 2.** Subgroup efficacy by subgroups

Trial	Endpoint	No oxygen	Low-standard flow oxygen	High flow oxygen	NAME	Mechanical ventilation
Wang <i>et al.</i> [13]	Time to two-point improvement	NT		Not reported by subgroups		
ACTT [14 <sup>***</sup> ]	Time to recovery (higher HR is better)	H.R.: 1.29 (0.91–1.83)	H.R.: 1.45 (1.18–1.79)	HR: 1.09 (0.76–1.57)		HR: 0.98 (0.70–1.36)
SIMPLE-Moderate [15]	Clinical Status on day 11 (higher is better)	OR: 1.65 (1.09–2.48)		NT		
Solidarity [16]	Mortality (lower H.R. is better)	HR: 0.90 (2.0% vs. 2.1%)	HR: 0.85 (12.2% vs. 13.8%)			HR: 1.2 (43.0% vs. 37.8%)

This population was not part of the trial population evaluated in the trial.

ACTT, Adaptive COVID-19 Treatment Trial; HR, hazard ratio; NT, not tested; OR, odds ratio.

trials is challenging (Table 2). The limited data would suggest that the group most likely to benefit from remdesivir is low flow or standard flow oxygen, but the 95% CI of all subgroups overlapped, which indicates that benefits cannot be excluded from any subgroup.

## MORTALITY

No studies have conclusively shown a mortality benefit with treatment with remdesivir. Only one trial, Solidarity, was large enough to evaluate mortality, and that study did not show any difference [16]. The ACTT trial was suggestive of mortality benefit at both 14 and 28 days, but was not powered to assess mortality differences [14<sup>\*\*\*</sup>]. When broken down by the subgroups of clinical status at study enrollment and looking across studies, those patients not on oxygen or low flow oxygen had a hazard ratio of less than 1 in every study (Table 3). There is likely some small benefit to mortality, most evident in the lower severity of illness. However, there seems to be minimal benefit on high flow oxygen or invasive or noninvasive mechanical ventilation.

## DURATION OF THERAPY

Simple-Severe was an open-label trial of 397 hospitalized adults with severe COVID-19 (pneumonia and oxygen saturation of  $\leq 94\%$  or requiring supplemental oxygen) randomized to receive remdesivir for either 5 or 10 days (there was no nontreated group). Overall, baseline characteristics were comparable between the two groups. The median duration of symptoms before initiation of remdesivir was 8 days in the 5-day group and 9 days in the 10-day group. Clinical improvement of  $\geq 2$  points on a 7-point ordinal scale on day 14, the primary endpoint, occurred in 64% of patients treated with remdesivir for 5 days compared to 54% of those treated for ten days ( $P=0.12$ ) [18<sup>\*\*\*</sup>]. All-cause mortality at day 28 was 12% in the 5-day treatment group vs. 14% in the 10-day treatment group [18<sup>\*\*\*</sup>].

## OBSERVATIONAL STUDIES

Observational studies are helpful to frame real-world data compared to the randomized trials above. Using a US nationwide database, survival for adults hospitalized with COVID-19 from August to November 2020 on high-flow/noninvasive or low-

**Table 3.** Mortality in remdesivir efficacy trials

	Trial	No oxygen	Low-standard flow oxygen	High flow oxygen	NIMV	Mechanical ventilation
Mortality	Wang <i>et al.</i> [13]	NT	HR: 0.82 (8.5% vs. 10.3%)	HR: 1.4 (37.9% vs. 30.0%)		
	ACTT [14 <sup>***</sup> ]	HR: 0.82 (4.1% vs. 4.8%)	HR: 0.30 (4.0% vs. 12.7%)	HR: 1.02 (21.2% vs. 20.4%)		HR: 1.13 (21.9% vs. 19.3%)
	SIMPLE-Moderate [15]	HR: 0.64 (1.3% vs. 2.0%)	NT	NT	NT	NT
	Solidarity [16]	HR: 0.90 (2.0% vs. 2.1%)	HR: 0.85 (12.2% vs. 13.8%)		HR: 1.2 (43.0% vs. 37.8%)	

This population was not part of the trial population evaluated in the trial.

ACTT, Adaptive COVID-19 Treatment Trial; HR, hazard ratio; NT, not tested; NIMV, non-invasive mechanical ventilation.

flow O<sub>2</sub> treated with remdesivir ( $N=19\,589$ ) was compared to those who did not receive remdesivir ( $N=8703$ ). After adjusting for baseline and clinical covariates, those treated with remdesivir had a significantly lower risk of 14-day mortality (low flow oxygen HR 0.68 (0.60–0.77), high flow oxygen 0.81 (0.70–0.93) [19]. A separate analysis assessed mortality after COVID-19 using US-based claims data. Those treated with remdesivir ( $N=9271$ ) had a reduced risk of death (HR=0.79) compared to matched controls ( $N=9271$ ). Those treated also had a significantly greater likelihood of discharge by day 28, compared with controls. These findings were most pronounced in patients with lower oxygen requirements at baseline, but the benefit was across all groups, including those on mechanical ventilation [20].

## PREGNANCY AND LACTATION

There is currently limited information on the use of remdesivir during pregnancy and lactation. Pregnant women were excluded from the four pivotal trials, and no other clinical trials have been conducted in this population. There are ongoing natural history trials [21]. No adverse effects on embryofetal (rats and rabbits) or pre/postnatal (rats) development were observed in rats and rabbits at non-toxic doses in pregnant animals [22]. A case series of 67 pregnant patients who received remdesivir through the compassionate use program demonstrated that 93% recovered within 28 days [23]. Pregnant women not requiring invasive ventilation at baseline had the highest rates of recovery (98%) and shortest median time to recovery (5 days); among those women, 98% recovered, and 95% were discharged. Treatment with remdesivir was well tolerated; no new safety signals were detected among pregnant patients. The NIH Guidelines note that treatment should not be withheld from pregnant women because of theoretical concerns related to the safety of therapeutic agents in pregnancy [24]. Therefore, remdesivir should be given to pregnant women hospitalized with COVID-19.

## RENAL DYSFUNCTION

Prior clinical studies have excluded patients with estimated glomerular filtration rate (eGFR) values of <30 ml/min per 1.73 m<sup>2</sup> and those requiring renal replacement therapy. Available data from published controlled trials in COVID-19 do not demonstrate an increased risk of renal-associated adverse events in patients who received remdesivir compared to placebo [13,14<sup>\*\*\*</sup>]. Concerns of using remdesivir in patients with renal dysfunction may arise from the

presence of the excipient sulfobutylether- $\beta$ -cyclodextrin (SBECD). The American Society of Nephrology suggests that patients without underlying liver disease who are expected to undergo continuous or intermittent dialysis or those with acute kidney injury expected to be transient may safely receive remdesivir [25].

## HOW REMDESIVIR IMPROVES OUTCOMES

To understand if remdesivir improves outcomes, it is helpful to understand how remdesivir improves outcomes. The clinical course of patients with COVID-19 can be followed daily over time, and these pathways of improvement or deterioration can be evaluated using a competing risks analysis. Of the pivotal studies, only the ACTT trial had daily assessments to inform how remdesivir modifies the course of the illness/hospitalization. In one such analysis, using ACTT data and following clinical severity as measured by ordinal score, remdesivir works primarily by decreasing clinical deterioration (HR 0.65; 95% CI 0.51–0.83) rather than accelerating clinical improvement (HR 1.00; 95% CI 0.84–1.18) (Fintzi, 2020 in press). This model may also explain why the combination of remdesivir with anti-inflammatory agents like baricitinib may improve outcomes [26] – remdesivir decreases viral replication to stop additional insult (deterioration), and anti-inflammatory agents target the immune response to improve recovery.

## REGULATORY AUTHORITIES

Remdesivir has been approved or authorized for temporary use in the treatment of COVID-19 in 48 countries – Argentina, Australia, Brazil, Canada, European Union (30 countries including Iceland, Norway), Great Britain, Hong Kong, India, Iraq, Israel, Japan, Jordan, Lebanon, Russia, Singapore, South Korea, Switzerland, Taiwan, United Arab Emirates, United States [27]. The governing regulatory agencies are independent, and the approval suggests that in their review, the totality of the data suggests that remdesivir is likely to be beneficial in the treatment of COVID-19.

## CONCLUSION

The totality of the data suggests that remdesivir is effective in the treatment of COVID-19. Although some subgroups may benefit some subgroups more than others, none of the studies were designed and powered to answer this critical question definitively. There appears to be a consistent benefit in hospitalized patients on no oxygen, low-flow, or high-flow oxygen. Those on mechanical ventilation may not have the

same magnitude of benefit from remdesivir alone. However, the current anti-inflammatory strategies essential to treating critical COVID-19 (dexamethasone or other agents such as baricitinib and tocilizumab) were not used in most remdesivir trials.

It is unclear if remdesivir improves mortality. None of the randomized studies conclusively demonstrated an improvement in mortality, though observational studies with much larger sample sizes did. Additionally, decreased time in the hospital, lower progression to mechanical ventilation, and decreased utilization of other hospital resources are meaningful to an individual and essential to healthcare systems that are often stretched thin during the pandemic.

Navigating a field of mixed results is always challenging for any clinician. Not all the trials demonstrated benefit. The one trial that evaluated only mortality failed to demonstrate benefit. Larger studies are supposed to instill more confidence in the results. However, when larger studies are coupled with more uncertainty from design limitations, they do not clarify the situation. The objective review and subsequent approval (or early use authorization) by regulatory authorities in 48 countries support the assessment based on current data that remdesivir is effective in treating COVID-19.

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### Conflicts of interest

The author has no financial conflict of interest. The author helped implement and was the lead author for the ACTT study of remdesivir and recognizes a bias towards that study in assessing the benefit of remdesivir. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does any mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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