Should remdesivir be used in the treatment of COVID-19?

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This rapid review summarizes the available evidence on the efficacy and safety of remdesivir in treating patients with COVID-19. This may change as new evidence emerges.

KEY FINDINGS

Based on pooled published results of two randomized controlled clinical trials, remdesivir showed modest benefit in clinical improvement among patients with severe/hospitalized COVID-19 infection. Data suggest there might be benefit on mortality but needs more studies to strengthen the conclusion.

- Remdesivir is an experimental drug that is currently not approved in any country for any disease indication.
- It is a nucleotide analogue that inhibits RNA-dependent RNA polymerases.
- Based on the pooled results of two randomized trials involving 1296 patients with severe/hospitalized COVID-19 which evaluated outcomes at day 28 , remdesivir was able to accelerate the time to clinical improvement by as much as 3 days (Mean Difference: -2.80, 95%CI: -4.92, -0.68) and increase the recovery rate (Rate Ratio 1.30, 95%CI: 1.12, 1.51). The risk ratio for the 14-day mortality rate showed a trend towards benefit in favor of remdesivir (RR: 0.64 (95%CI: 0.44,0.94). However, it did not show a clear effect on mortality based on the hazard ratio (HR 0.78, 95%CI: 0.56 , 1.07).
- It is relatively safe based on the lesser incidence of adverse events reported in the remdesivir group compared to the placebo group.
- US NIH recommends the use of remdesivir in patients with severe COVID-19 but does not recommend its use among mild and moderate cases outside of a clinical trial.
- There are 9 ongoing randomized controlled clinical trials.

RESULTS

Characteristics of Included Studies

As of May 24,2020, we found two published randomized controlled clinical studies (n=1299) on remdesivir and its effect on severe COVID-19 patients.

The Adaptive COVID-19 Treatment Trial, or ACTT[1] (NCT04280705) published the preliminary results of their study. The study sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) was a multicenter adaptive, double blind randomized controlled study carried out in the United States, Denmark, the United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore. The study was designed to achieve a power of 85% with at least 400 recoveries. A total of 1063 hospitalized COVID-19 patients were randomized (RDV n=541 and placebo n=522).

A randomized controlled double blinded multicenter study (NCT04257656) [2] was conducted among patients in Wuhan, Hubei province, China. Enrollment in this study was stopped early due to lack of eligible patients. It involved 237 patients with confirmed severe SARS-COV-2 infection where 158 patients were assigned to the RDV group and 79 patients were assigned to the placebo group.

In both studies, remdesivir was administered intravenously as a 200 mg loading dose on day 1, followed by 100 mg dose once daily for the next 9 days or until discharge. Patients who had ALT (alanine transferase) or AST (aspartate aminotransferase) > 5x upper normal limit, severe renal impairment based on GFR or on dialysis, and pregnant/breastfeeding women were excluded.

Effectiveness Outcomes

Clinical improvement

In the ACTT, improvement meant discharge from hospitalization, no or slight limitation of activities, or no requirement for supplemental oxygen/medical care. In the RCT by Wang et al, improvement meant alive at time of discharge or a decrease of 2 levels in a 6-point ordinal scale. Despite this difference, there was low heterogeneity in the pooled results.

The meta-analysis of the two included studies (n=1296) showed that remdesivir had a modest benefit in clinical improvement among patients with severe COVID-19.

Pooled estimate of the studies showed that more patients improved in the remdesivir group compared to the placebo group. Although statistically significant, the magnitude of the effect is small (RR 1.17, 95%CI: 1.07, 1.29). See Figure 1.

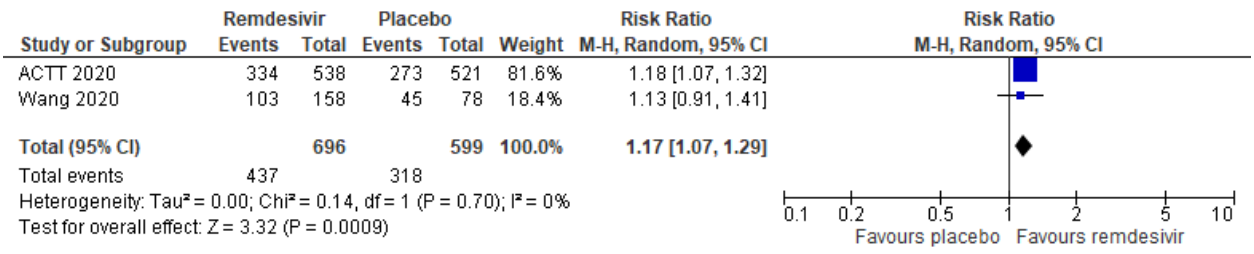

Figure 1. Proportion of patients who clinically improved

The patients in the remdesivir group improved faster than patients in the placebo group by approximately 3 days (MD -2.80 95%CI: -4.92, -0.68). It was statistically significant and with minimal heterogeneity (P=0.37, I2=0%). See Figure 2.

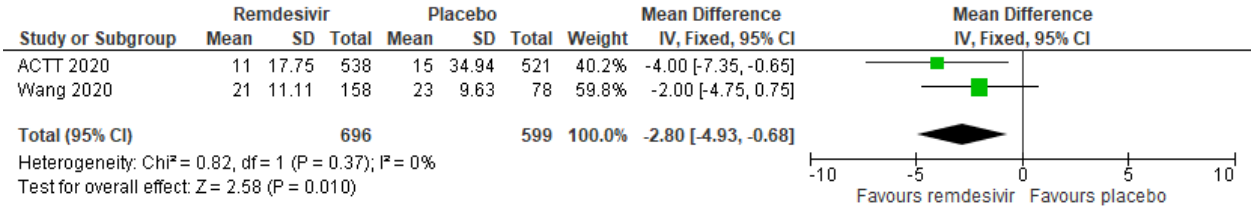

Figure 2. Mean difference (MD) in days to clinical improvement

The remdesivir group also had a statistically significant higher rate of clinical improvement compared to the placebo group (Rate Ratio 1.30, 95%CI: 1.12, 1.51). See Figure 3.

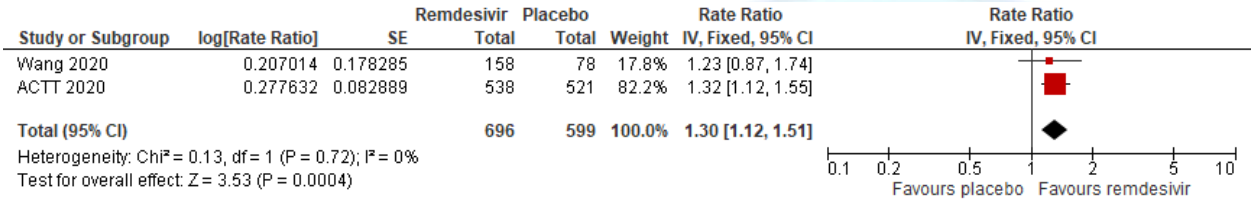

Figure 3. Forest plot on the rate to clinical improvement

Mortality

The 14-day mortality rate is lower in the remdesivir group in ACTT while rates in the RCT by Wang were similar in the 2 groups. Pooling these results, the risk ratio shows that remdesivir group has a lesser risk for mortality at day 14 compared to the placebo group (RR: 0.64 (95%CI: 0.44,0.94)).

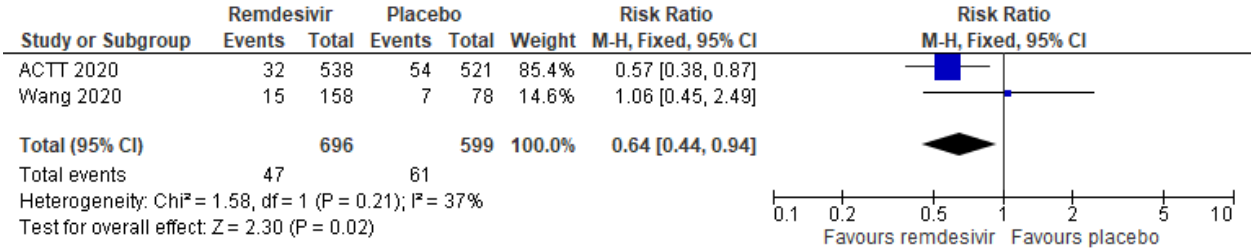

Figure 4. 14-day mortality

Based on the hazard ratio reported in the 2 studies, the pooled mortality rate was lower in the RDV arm but the difference with placebo was not statistically significant (HR 0.78, 95%CI: 0.56 , 1.07). It should be noted that 301 participants (28%) in the ACTT-1 study have yet to complete the 28-day observation period and whose outcome may still change the result.

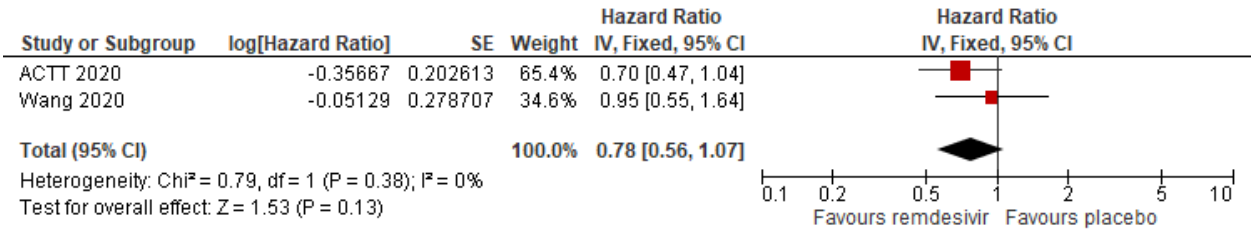

Figure 5. Mortality rate

Safety Outcomes

In the ACTT, the proportion of patients who discontinued the study due to serious adverse events (SAE) other than death was similar in both groups (7%). More SAEs were reported in patients taking the placebo (n=141, 27.0%) compared to the remdesivir group (n=114, 21.1%). The higher rate of SAE in the placebo group was mostly due to respiratory failure/acute respiratory failure (10.3% vs. 6.8%), viral pneumonia (1.3% vs. 0.6%), and use of mechanical ventilation (1.0% vs. 0.2%). Grade 3[1] (incapacitating) or grade 4[1] (life-threatening) adverse events were reported more frequently in the placebo group (33.0% vs. 28.8%). Non-serious adverse events were also higher in the placebo group (33% vs. 28.8%) and included anemia/ decreased hemoglobin, hyperglycemia/increased blood glucose level, and increased AST/ALT levels.

In the study of Wang et al [2], 12% of patients in the RDV group discontinued treatment due to adverse events such as respiratory failure, acute respiratory distress, secondary infection, and cardiopulmonary failure vs. 5% in the placebo group. There was no significant difference in other adverse events between the 2 groups. Common adverse events in the remdesivir group include constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin. More serious adverse events were noted in the placebo group.

Serious adverse events were reported for 12 patients (23%) in the case series of Grein et al [3] and included multiple organ dysfunction syndrome, septic shock, AKI, and hypotension. Worsening of renal failure, elevated aminotransferases, and multi-organ failure led to discontinuation in 4 patients (8%).

Ongoing Studies

Currently there are 9 clinical studies on remdesivir summarized in Table 2. Two studies in China (RCT by Wang NCT04252664 and NCT04257656) have been suspended/terminated due to lack of eligible patients (i.e. hospitalized /severe cases) in the wake of the epidemic being controlled in the area.

Three studies allow enrollment of patients > 12 years old. Patients who are pregnant, breastfeeding, or have positive pregnancy tests will be excluded.

Recommendations from Other Guidelines

WHO interim guidance does not recommend any specific anti-viral or biologic agents and only recommends symptomatic treatment for patients with COVID-19.[4] The Philippine Society for Microbiology and Infectious Diseases interim guidance states that remdesivir can be considered as compassionate use for moderate and severe cases when available.[5] Surviving Sepsis Campaign guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19) does not have a recommendation at this time due to insufficient evidence.[6]

[1] ACTT protocol 20-0006 ver.1 18Feb2020

The US NIH COVID-19 treatment guidelines panel recommends the use of remdesivir for the treatment of COVID-19 in hospitalized patients with severe disease, defined as SpO2 ≤94% on ambient air (at sea level), requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation. (Moderate strength of recommendation). The recommendation is based on the results of ACTT earlier mentioned. The panel, however, does not recommend its use among mild and moderate cases of COVID-19 outside of a clinical trial (Strong recommendation).[7] At the moment, the US FDA has not approved the use of remdesivir but is available through a US FDA emergency use authorization.

In the Initial Guidance on Use of Antivirals for Children with COVID-19 [8] the panel acknowledged the ongoing clinical studies among patients > 12 years of age and recommended remdesivir as the preferred agent in the context of a clinical trial among critically ill or severely immunocompromised children. This recommendation was made in the context of possible, yet unproven, potential for benefit vs. generally acceptable potential risks which can be tracked and monitored under the compassionate use program of the manufacturer. Additional statements include consideration of using hydroxychloroquine (loading dose followed by daily intake for 5 days) ” in particular for patients who are not candidates for remdesivir, when remdesivir is not available, or while awaiting delivery of remdesivir from the manufacturer, preferably as part of a clinical trial if available”.

CONCLUSION

Remdesivir is an experimental drug that is currently not approved in any country for any disease indication. Based on a meta-analysis of 2 published randomized clinical trials, remdesivir showed modest benefit in clinical improvement on day 28 among hospitalized patients with COVID-19 infection.. Remdesivir was able to accelerate clinical improvement by 3 days. The current data suggest benefit in terms of mortality that but needs further studies to strengthen the conclusion. The results of the ACTT may still change pending the outcomes of the last remaining participants.

The drug is contraindicated for patients with liver and renal impairment. It is relatively safe based on the lesser incidence of adverse events reported in the remdesivir group compared to the placebo group. The US CDC recommended its use among severe COVID-19 infection but not among mild and moderate cases

Declaration of Conflict of Interest

I. Cabaluna do not have relevant conflict of interest.
C. Larracas is a Medical Director at LivaNova PLC, a former employee of Abbott Vascular (a division of Abbott Labs), and is a stockholder at Abbott, Abbvie, and LivaNova.

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Table 1. Characteristics of included studies

No.	Trial ID	Title/Author	Study design	Country	Number of patients	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings	Premature discontinuation due to adverse events
1	NCT04280705	Remdesivir for the Treatment of Covid-19 (ACTT) — Preliminary Report/ Beigel et al	Adaptive, randomized double blind controlled trial	United States, Denmark, the United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore	N=1059	Severe COVID-19 patients defined as confirmed cases with radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), clinical assessment of illness (evidence of rales/crackles on exam) and SpO2 ≤ 94% on room air, or requiring mechanical ventilation and/or supplemental oxygen. Concomitant treatment with other medications for RDV were not allowed.	Remdesivir, given IV 200 mg on the first and 100 mg daily on the next succeeding 9 days	Placebo	Time to recovery Mortality Adverse events	There was a significant difference in the time to recovery among patients taking remdesivir compared to placebo. There was a tendency towards benefit with regards to mortality based on the pooled risk ratio. However, no significant difference was observed in the mortality rate based on the hazard ratio.	Discontinuation due to SAE other than death was similar in both groups (7.0% RDV vs. 7.1 % placebo).
2	NCT04257656	Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial / Wang et al	Randomized double blind controlled trial	China	N=237	Severe infection was defined as had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset. . Concomitant treatment with other medications for RDV was allowed.	Remdesivir, given IV 200 mg on the first and 100 mg daily on the next succeeding 9 days.	Placebo	Time to clinical improvement Mortality Viral load Adverse events	There were no significant differences noted in all other secondary outcomes namely, proportions of patients in each category of the six-point scale at day 7, 14, and 28 after randomization, all-cause mortality at day 28, frequency of invasive mechanical ventilation, duration of oxygen therapy, duration of hospital admission and proportion of patients with nosocomial	12% of patients in the RDV group discontinued treatment due to adverse events such as respiratory failure, acute respiratory distress, secondary infection, and cardiopulmonary failure vs. 5% in the placebo group.

										infection. The computed RR for mortality at day 28 is 1.08 (95%CI 0.54 – 2.18). The viral load tested from naso-/oropharyngeal swabs and expectorated sputum were likewise not different in the 2 groups through day 28.	

Table 2. Characteristics of ongoing clinical trials

URL/ Clinical trial identification	Title	Trial Design	Estimated Sample Size	Status	Study Results	Conditions	Interventions	Primary outcome	Locations	Expected Completion date	Sponsor
http://www.isrctn.com/ISRCTN83971151	Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients	Randomized open label		Recruiting	No Results Available	COVID-19|SARS-CoV-2 adult > 18	Local standard of care alone OR local standard of care plus one of Remdesivir, Chloroquine or HC OR L/R OR + L/R interferon-beta	All cause death	International	March 2021	WHO
https://ClinicalTrials.gov/show/NCT04252664	A Trial of Remdesivir in Adults With Mild and Moderate COVID-19	Randomized quadruple-masked	308	Suspended	No Results Available	COVID-19|SARS-CoV-2 adult ≥ 18	Remdesivir vs. placebo	Day 28: Time to clinical recovery	China	April 27, 2020	IIR
https://ClinicalTrials.gov/show/NCT04292899	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Severe Coronavirus Disease (COVID-19) or SIMPLE 1 trial.	Randomized open label	6000 397 in the RCT phase; 5600 in the expansion phase	Recruiting	Results for RCT arm available, pending publication [13]	COVID-19 children > 12 yrs; adults	Remdesivir 5-day vs. 10-day course	Day 14 odds ratio clinical improvement based on a 7-point scale	USA, EU, UK, Asia	May 2020	Gilead

https://ClinicalTrials.gov/show/NCT04292730	Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to SoC Treatment (SIMPLE 2 Trial)	Randomized open label	1600	Recruiting	No Results Available	COVID-19 children > 12 yrs; adults	Remdesivir 5 vs. 10-day course	Day 14 odds ratio clinical improvement based on a 7-point scale	USA, EU, UK, Asia	May 2020	Gilead
https://ClinicalTrials.gov/show/NCT04257656	A Trial of Remdesivir in Adults With Severe COVID-19	Randomized quadruple-masked	237	Terminated	Results published [**Error! Reference source not found.**]	COVID-19|Remdesivir|SARS-CoV-2	Remdesivir vs. placebo	Day 28 clinical improvement based on a 6-point scale	China	May 1, 2020	IIR
https://ClinicalTrials.gov/show/NCT04321616	The (Norwegian) NOR Solidarity Multicenter Trial on the Efficacy of Different Anti-viral Drugs in SARS-CoV-2 Infected Patients	Randomized open label	700	Recruiting	No Results Available	SARS-CoV Infection|COVID 19|Acute Respiratory Distress Syndrome ARDS > 18	Hydroxychloroquine vs. Remdesivir 10-day vs. Standard of Care	3 weeks in-hospital mortality	Norway	November 2020	IIR

https://ClinicalTrials.gov/show/NCT04280705	Adaptive COVID-19 Treatment Trial or NIAID ACTT-1 trial	Randomized double blind	1059	completed enrollment.	Preliminary results published [13]	Corona Virus Infection adult	Remdesivir vs. placebo	Day 28 Time to recovery	USA, Japan, Korea, Singapore, Germany, UK, Denmark, Greece, Mexico, Spain	April 2, 2023	NIAID
https://ClinicalTrials.gov/show/NCT04315948	Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy)	Randomized open label	3100	Recruiting	No Results Available	Corona Virus Infection adult	Remdesivir 10-day vs. L/R vs. L/R+ Interferon Beta-1a vs. HC vs. Standard of care	Day 15 clinical improvement based on a 7-point scale	France	March 2023	IIR
https://ClinicalTrials.gov/show/NCT04349410	The Fleming [FMTVDM] Directed CoVid-19 Treatment Protocol	Randomized Factorial assignment	500	Enrolling by invitation	No Results Available	CoVid 19 Positive (children adult)	11 treatment arms consisting of: HC, Azithromycin; Doxycycline, Clindamycin, Primaquine - low dose, Primaquine - high dose; Remdesivir; Tocilizumab; Methylprednisolone; Interferon-Alpha2B; Losartan; Convalescent Serum	Improvement in FMTVDM Measurement with nuclear imaging. [Time Frame: 72 hours	USA	Nov. 11, 2020	Camelot Foundation
FMTVDM: Fleming Method for Tissue and Vascular Differentiation and Metabolism ; HC: Hydroxychloroquine; IIR: Investigator Initiated Research;; L/R Lopinavir/ritonavir; NIAID: National Institute of Allergy and Infectious Diseases; NR : not reported											