Wang Y et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. April 2020. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext. Accessed May 3, 2020.

BACKGROUND – THE STUDY QUESTION?		
Background	• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified as a novel respiratory virus in Wuhan, China in December 2019. This has led to over 3.5 million cases and 247,000 deaths worldwide as of May 3, 2020. Although several approved and investigational drugs have shown antiviral activity against SARS-CoV-2 *in vitro*, there are conflicting data about safety and efficacy of these agents in humans. There are currently no FDA-approved therapies to treat SARS-CoV-2 and data are conflicting regarding antiviral therapies effective in treating severely ill patients with COVID-19. • Remdesivir (GS-5734, RDV) is an intravenous nucleoside analogue prodrug with broad-spectrum antiviral activity, including filoviruses, paramyxoviruses, and coronaviruses. It has been shown to have antiviral and clinical effects in animal models for SARS-CoV-1 and MERS infections, as well as inhibiting SARS-CoV-2 replication in human and nasal bronchial airway epithelial cells.[1-4] It is currently available via clinical trials, compassionate use for pediatric or pregnant patients, and was granted FDA Emergency Use Authorization (EUA) status on May 1, 2020.	
Previous trials	• A compassionate use study of 53 severe COVID-19 patients demonstrated clinical improvement in 68% of patients with higher rates of clinical improvement in patients who were on low-flow oxygen or ambient air at baseline. However, this was a small sample size without a control group and 8 patients could not be analyzed for the primary outcome.[5]	
Why this study?	• There are limited and conflicting data regarding potential therapies to treat COVID-19. This is the first randomized, double-blind, placebo-controlled trial assessing remdesivir for severe COVID-19 patients.	
Null Hypothesis	• There is no difference in clinical efficacy or safety between severe adult COVID-19 patients who received RDV compared to patients who did not.	
GENERAL STUDY OVERVIEW		
	Summary	Critique
Funding	• Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing Science and Technology Project	• Not involved in study design, enrollment, or data analysis
Trial design	• Randomized, placebo-controlled, double-blind trial • Randomized 2:1 (RDV: placebo), stratified by level of respiratory support	• 2:1 design aids in ensuring enrollment given later study timeline for disease and event/power calculations • Stratified by respiratory support to determine if affects results
Objectives	• To assess the safety and effectiveness of RDV in adult patients (≥18 years) admitted with severe COVID-19	
Enrollment	• Ten hospitals in Wuhan, Hubei, China from Feb 6,2020 to March 12, 2020	• Multi-center study in the epicenter of the disease • Did not discuss number of patients from each hospital
METHODS		
Inclusion criteria	• Adult men and non-pregnant women (≥18 years) • PCR-confirmed COVID-19 with pneumonia demonstrated on chest imaging • O_2 saturation ≤94% on room air or PaO_2/FiO_2 ratio ≤300 mm Hg • Within 12 days of symptom onset	• Inclusion of severe patient population, but required earlier symptom onset presentation • Patients were allowed to receive other potential COVID-19 therapy (e.g. lopinavir-ritonavir, interferon-alfa-2b) • No time requirement from either positive PCR test or admission to randomization

Exclusion criteria	• Pregnancy or breast feeding • Hepatic cirrhosis; alanine aminotransferase or aspartate amino transferase >5x ULN • Known severe renal impairment (estimated GFR <30 mL/min per 1.73 m^2) or receipt of continuous renal replacement therapy, hemodialysis, or peritoneal dialysis • Possibility of transfer to a non-study hospital within 72 hours • Enrollment into an investigational treatment study for COVID-19 in the 30 days before screening	• No discussion of avoiding other hepatotoxic agents (e.g. acetaminophen)
Interventions	• IV RDV 200 mg on day 1 followed by 100 mg on days 2-10 • Placebo (same volume) for total of 10 days	
Monitoring	• Assessment once daily by trained nurses using diary cards to capture scale data and safety from day 0 to day 28 or death • Safety assessment included daily monitoring for adverse events, clinical lab testing (days 1,3,7, and 10), 12-lead EKG (days 1 and 14) and daily vital sign measurements • Clinical data were recorded on paper case record forms and then double entered into electronic database and validated by trial staff • Naso or oropharyngeal swabs (expectorated sputum as available) and fecal or anal swab specimens were collected on days 1,3,5,7,10,14,21, and 28 for viral RNA detection and quantification	• Multiple checks for inputting clinical and safety assessments • No evaluation of patients once discharged

Primary Endpoints	• Time to clinical improvement within 28 days of randomization: two-point reduction in patients' admission status on six-point ordinal scale , or live discharge from the hospital (whichever occurred first)
	  • 6=Death
	  • 5=Hospital admission for ECMO or mechanical ventilation
	  • 4=Hospital admission for non-invasive ventilation or high-flow oxygen
	  • 3=Hospital admission for oxygen, but not high-flow or non-invasive ventilation
	  • 2=Hospital admission but not requiring oxygen
	  • 1=Discharged or having reached discharge criteria
		• Use of clinical scale at three specified time points
		• Clinical improvement scale modified from other clinical trial designs (combined two outpatient strata into one, so not evaluating quality of life or oxygen support on outpatient basis)

Secondary Endpoints	• 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 • Proportion of patients with nosocomial infection	• Evaluation of clinical improvement at different time points • Also assessed virologic load and clearance over time

Statistical analyses	• Original design required 325 events across both groups to provide 80% power under a one-sided type I error of 2.5% if hazard ratio (HR) of RDV to placebo was 1.4 (time to clinical improvement of 6 days vs. 21 days) • Assumption of 80% event rate and 10% dropout rate required 453 patients total with interim analysis after 240 patients • Primary efficacy analysis in intention-to-treat (ITT) population portrayed by Kaplan-Meier plot	• All data analyzed using SAS software • Patients censored at day 28 if no clinical improvement or death before day 28 • Subgroup analyses for those receiving treatment $\leq$10 days vs. >10 days after symptom onset, time to clinical deterioration, and for viral RNA load at study entry (did not include study site as subgroup)
RESULTS		
Enrollment	• 158 remdesivir and 79 placebo assigned (one in placebo withdrew consent) so 158 and 78 patients included in ITT population	• Small patient enrollment given control of disease and on basis of termination criteria, so study terminated early (no interim analysis) • Statistical power reduced from 80% to 58% • Low drop-out rate
Baseline characteristics	• Median age of 65 years (IQR 65-71), 56% men (RDV) and 65% (placebo) • Most common comorbidity in each group was hypertension, followed by diabetes and coronary artery disease • 70% had normal WBC at baseline, but were lymphopenic • 18% received lopinavir-ritonavir, 80% antibiotics, and 40% steroids at baseline • Most patients were at category 3 at baseline • More patients in RDV group had hypertension, respiratory rate >24 breaths/min, and later time (>10 days) from symptom onset to randomization, while more patients in the placebo group received interferon alfa-2b	• Imbalance between groups that may have biased RDV patients to worse clinical outcomes • 30% of patients received lopinavir-ritonavir either at baseline or during study and >90% received antibiotics before and after enrollment. This was not different by treatment group. • Majority of patients received steroids during treatment course, which may have promoted viral replication • Very few critically ill patients at baseline (18% requiring hi-flow or non-invasive ventilation in RDV group vs. 12% in placebo; only 1 patient in placebo on ECMO or intubated) • Only 19% of 196 with data available had undetectable viral RNA at baseline
Primary Outcome	• Time to clinical improvement was not significantly different between groups (median 21 days [IQR 13.0–28.0] in the RDV group vs 23 days [15.0–28.0]; HR 1.23 [95% CI 0.87–1.75]) • Similar results in per-protocol population • Patients receiving RDV within 10 days of symptom onset had numerically faster time to clinical improvement (median 18 days [IQR 12.0-28.0] vs 23 days [15.0-28.0]; HR 1.52 [0.95-2.43)	• Did not discuss duration of antiviral or adjunctive therapy • Although numerically faster time to improvement of those who received RDV within 10 days of symptom onset, not statistically significant

Secondary Outcomes	• 28-day mortality was similar between groups (14% vs. 13%), but was numerically higher for the placebo group in patients who received RDV within 10 days after symptom-onset (later presentation had numerically higher mortality in RDV patients). • Clinical improvement similar at 14 days and 28 days, but numerically higher in RDV group vs. placebo • No difference in duration of mechanical ventilation (numerically shorter in RDV group), length of oxygen support, hospital length of stay, days from randomization to discharge, days from randomization to death and distribution of six-category scale at day 7, 14, and 28	• Possible benefit if RDV administered earlier in disease process, but not statistically significant • Prolonged length of stay in both groups (25 days RDV and 24 days placebo) • Slow transition over time from category 3 to categories 1 and 2 • By day 28, 61% with live discharge in RDV group vs. 58% in placebo group with 15% deaths in RDV group and 13% in placebo group • Numerically shorter duration of mechanical ventilation (7 vs 15.5 days) in RDV group not statistically significant likely due to small number of participants overall requiring ventilation
Other Clinical events	• Viral load decreased similarly over time between groups and there was no difference when stratified by interval from symptom onset to study treatment • Adverse events were reported in 65% of patients in both groups (constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, increased total bilirubin) • More serious adverse events in placebo group, but more patients in RDV group stopping study drug (5% due to respiratory failures or ARDS)	• Over 60% in each group experienced adverse effect, mostly unrelated to study drug treatment

AUTHORS' CONCLUSIONS

- Remdesivir did not significantly improve time to clinical improvement, mortality, or time to virus clearance in patients with severe COVID-19 when compared to placebo
- Study was not sufficiently powered to detect clinical endpoints, due to public health interventions controlling the epidemic in Wuhan and inability to continue enrollment
- Remdesivir was well tolerated with no new safety concerns identified
- Future studies evaluating earlier start of therapy and higher-dose regimens with possible combination of other antiviral regimens are needed

GENERALIZABILITY/CRITIQUE/DISCUSSION

- First randomized controlled trial evaluating remdesivir in severe COVID-19 patients with relevant subgroup analyses
- Less critically ill patient population that were treated later in the disease course, so unclear of benefit in those who require more respiratory support
- Unclear benefit with adjunctive antiviral therapy and high proportion of patients receiving steroids even though low number in ICU requiring ECMO or invasive mechanical ventilation at baseline
- Unable to detect differences in outcomes given insufficient power, but data do not demonstrate benefit with remdesivir over placebo
- Unable to assess whether earlier treatment may provide clinical benefit as unable to reach target enrollment, but data describe possibility of clinical benefit if remdesivir given earlier in disease process
- An ongoing NIH adaptive clinical trial (ACTT) released preliminary results (n=1063 patients) demonstrating 31% faster time to recovery than those who received placebo ($p<0.001$). The median time to recovery was 11 days for the RDV group compared to 15 days in the placebo group. Results also suggest a survival benefit with a mortality rate of 8% for RDV vs. 11.6% for placebo ($p=0.059$).[6]
- Gilead announced preliminary results from an open-label Phase 3 SIMPLE trial evaluating 5- vs. 10-days of RDV in severe COVID-19 patients. Results demonstrated similar efficacy between the 10-day and 5-day treatment course on day 14 (OR: 0.75 [95% 0.51-1.12]). Time to clinical improvement for 50% of patients was 10 days in the 5-day group vs. 11 days in the 10-day treatment group. Sixty percent in the 5-day and 52% in the 10-day groups were discharged by day 14 and 65% in the 5-day vs. 54% in the 10-day achieved clinical recovery by day 14. Patients who received RDV within 10 days of symptom onset had improved outcomes. RDV was well tolerated overall with about 10% discontinuing the drug (3% of patients discontinued due to elevated liver tests.). However, there was no placebo group for comparison of these results.[7]
- Based on the above discussion, remdesivir may be useful in less critically ill patients without respiratory support if administered earlier in the disease; results from ongoing RCTs are needed to determine this

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