Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe COVID-19. *N Engl J Med*. May 27, 2020 [Epub Ahead of Print]. DOI:10.1056/NEJMoa2015301

BACKGROUND – THE STUDY QUESTION?	
Background	• Remdesivir is a prodrug of an adenosine analogue with demonstrated antiviral activity against many RNA virus families, including SARS-CoV-2 which causes coronavirus disease that was found in 2019 (COVID-19). • A preliminary report of the ACTT-1 trial which was a placebo controlled, adaptive design, randomized controlled trial, demonstrated that a 10 day course of remdesivir could shorten the duration of symptoms of COVID-19 by 4 days ($p<0.001$). • "A shorter course of treatment without a loss of efficacy could reduce hospital stays and extend the limited supply of remdesivir available."
Previous trials	• Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. *JAMA.* 2020. • Mulangu S, Dodd LE, Davey RT, Jr., et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. *N Engl J Med.* 2019;381(24):2293-2303. • Grein J, Ohmagari N, Shin D, et al. Compassionate Use of Remdesivir for Patients with Severe COVID-19. *N Engl J Med*. April 10, 2020. [Epub Ahead of Print]. DOI: 10.1056/NEJMoa2007016 • Wang T, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial. *Lancet.* April 29, 2020. [Epub Ahead of Print]. DOI: 10.1016/S0140-6736(20)31022-9 • Biegel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of COVID-19 – Preliminary Report. *N Engl J Med*. May 22, 2020. [Epub Ahead of Print]. DOI: 10.1056/NEJMoa2007764
Why this study?	• This open-label, randomized, multicenter trial seeks to identify if a shorter duration of remdesivir could extend the limited supply of the drug and decrease total hospital stay in patients with SARS-CoV-2.
Null Hypothesis	• No significant difference in clinical outcomes of patients who received 5 vs 10 days of remdesivir

GENERAL STUDY OVERVIEW		
	Summary	Critique
Funding	• Funded by Gilead Sciences; GS-US-540-5773 ClinicalTrials.gov number, NCT04292899.	• Funded and written by the drug company. This is expected for a new agent but is important to remember when assessing for bias.
Trial design	• Randomized, open-label, multi-center, phase 3 trial	• Not placebo controlled so cannot assess efficacy of remdesivir itself. • Open-label design could lead to bias. • Lack of stratification by disease severity led to an imbalance of patient distribution. Due to this, they did a comparative analysis by baseline status later on. • Multiple amendments to the study design decreases the integrity of the results typically associated with randomized controlled trials.
Objectives	• To "evaluate the efficacy and safety of treatment with remdesivir for 5 or 10 days in patients with severe Covid-19 disease."	• N/A
Enrollment	• 55 hospitals in the United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan between March 6 and March 26, 2020.	• This was a large trial that enrolled across multiple countries. This could increase generalizability globally but it also can introduce differences in care across different sites. Distribution

		across sites/ nations was not provided which impacts generalizability to a particular practice area.
METHODS		
Inclusion criteria	• Lower age limit for eligibility was reduced from 18 years to 12 years on March 15th • Positive SARS-CoV-2 PCR within 4 days of randomization • Radiographic evidence of pulmonary infiltrates • Either (1) SpO2 of ≤ 94% on room air or (2) receiving supplemental oxygen • Axillary temperature of 36.6°C at screening was eliminated on March 15th	• Study design amendments here seem reasonable and not overwhelmingly concerning. I agree with the removal of a temperature cut off as more data has come out to show that it is not reliable to identify patients with COVID-19. • Due to the purpose of the study being for severe COVID-19, it makes sense to have inclusion criteria with evidence of pulmonary disease. However, it might decrease the efficacy of the drug by initiating therapy too late in the disease course. This is a theoretical concern based on the mechanism of action and did not impact results in ACTT-1.
Exclusion criteria	• Patients who were receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening were initially excluded. However, the March 15th amendment added an extension phase for a mechanically ventilated cohort. The results of which are not incorporated here. • Patients with signs of multi-organ failure at screening. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 5 times the upper limit of the normal range at baseline • Estimated creatinine clearance (Cockcroft–Gault) of less than 50 mL per minute. • Patients receiving agents with COVID-19 activity within 24 hours of trial initiation.	• For a trial comparing the appropriate duration of therapy in severe COVID-19, it is odd that they chose to exclude patients that required invasive mechanical ventilation upon screening. This could be why they later amended the study to include a mechanically ventilated cohort. • The exclusion criteria related to LFTs are reasonable based on the safety data from when it was studied for Ebola. • From a science perspective, it is appreciated that the study did not allow for confounding treatment with agents active against COVID-19. The implications for practice are yet to be determined.

Interventions	• 1:1 Randomization to one of the following arms:
	  ○ Remdesivir 200mg IV on day 1 then 100mg IV once daily for days 2 – 5.
	  ○ Remdesivir 200mg IV on day 1 then 100mg IV once daily for days 2 – 10.
		• Lack of stratification by diseases severity led to balanced baseline demographics but imbalances in baseline disease characteristics. This could lead to skewed results.

Primary Endpoints	• Clinical status at day 14 based on a 7-point ordinal scale. • (1) death; (2) hospitalized, receiving invasive mechanical ventilation or ECMO; (3) hospitalized, receiving noninvasive ventilation or high-flow oxygen devices; (4) hospitalized, requiring low-flow supplemental oxygen; (5) hospitalized, not requiring supplemental oxygen but receiving ongoing medical care; (6) hospitalized, requiring neither supplemental oxygen nor ongoing medical care; and (7) not hospitalized.	• The March 15th amendment included a change in the primary endpoint of the study. The authors indicate that the change of a primary endpoint of temperature resolution at day 14 to clinical assessment on a 7-point ordinal scale at day 14 was due to evolving information about the virus. • The new primary endpoint is more consistent with other studies including the WHO blueprint for study design for COVID-19. The change also provides a more clinically meaningful endpoint. • Be advised that this ordinal scale is the inverse of the ACTT-1 study and many other studies which could lead to confusion as study information is analyzed for practice.

Secondary Endpoints	• 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.
	• Exploratory end points:
	  ○ Time to clinical improvement (a 2-point change from baseline on the ordinal scale)
	  ○ The time to recovery (An improvement from a baseline score of 2 to 5 to a score of 6 or 7)
	  ○ The time to modified recovery (an improvement from a baseline score of 2 to 4 to a score of 5 to 7 or from a score of 5 to a score of 6 or 7)
	  ○ Death from any cause
		• Clinical status was assessed on a 7-point ordinal scale. Subjective data could be biased based on diagnostician or patient.
		• Given the statistical information below, it is appropriate to label most of the secondary endpoints as exploratory end points.

Statistical analyses	• "A sample size of 400 patients (200 in each group) provided greater than 85% power to detect an odds ratio for improvement of 1.75, using a two-sided significance level of 0.05" • "The conclusion would be that 10 days of treatment was superior to 5 days of treatment if the lower bound of the two-sided 95% confidence interval of the odds ratio (10 days to 5 days) on day 14 was greater than 1" • For time-to-event end points (such as the time to clinical improvement, the time to recovery, and the time to modified recovery), the hazard ratio and its 95% confidence interval were estimated from a cause-specific proportional-hazards model • Only the primary endpoint was adjusted for multiplicity • A post hoc analysis was utilized to derive if a subgroup might have greater benefit from 5 days of therapy	• Power threshold is appropriate • Despite not having patients stratified by disease severity, they did do a comparative analysis by enrollment clinical ordinal scale. • It is unfortunate that the study did not correct for multiple statistical calculations increasing the chance for error in all secondary outcomes. The exploratory end points are not reliable for application to practice but may draw further study interests. • Post-hoc analyses are not encouraged as they were not incorporated in the original power calculations and increase the risk of introducing error.
RESULTS		
Enrollment	• 397 of the 408 patients screened initiated therapy. • 5 days of therapy: 200 patients • 10 days of therapy: 197 patients • Despite excluding patients that needed invasive mechanical ventilation, 13 patients were intubated in between the time of study enrollment and initiation of therapy or had a study protocol deviation. Nine of these patients were in the 10 day arm	• The study did not reach their target sample size of 400 patients and therefore is not powered to say that no difference truly exists. They only missed the cut off by 3 patients and they targeted a power of 85% when the community largely accepts a power of 80%. Therefore, this will likely be a controversial topic when applied to practice. • Having more patients in the 10-day arm that were initiated on invasive mechanical ventilation before initiating therapy could be a potential confounder, especially since the sample size is limited.

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<td>Baseline characteristics</td>
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Demographic characteristics

Median age was 61 (50-71)
Predominately white (70-71%)
Black patients made up 10 – 12% of the patients
Predominately male (60-68%)
Median BMI was 29 (25-34)
Diabetes occurred in ~22%, hypertension in 50%
Median CrCl was ~105 mL/min (80-140)

<table>
<tr><th>Disease Characteristic</th><th>5 – Day Group (n = 200)</th><th>10 – Day Group (n = 197)</th></tr>
<tr><td>Median Duration of Hospitalization before 1st dose</td><td>2 (1 – 3)</td><td>2 (1 – 3)</td></tr>
<tr><td>Median Duration of Symptoms before 1st dose</td><td>8 (5 – 11)</td><td>9 (6 – 12)</td></tr>
<tr><td>Ordinal scare 2 (invasive ventilation or ECMO)</td><td>4 (2%)</td><td>9 (5%)</td></tr>
<tr><td>Ordinal scale 3 (noninvasive ventilation or high flow O2)</td><td>49 (24%)</td><td>60 (30%)</td></tr>
<tr><td>Ordinal scale 4 (low flow O2)</td><td>113 (56%)</td><td>107 (54%)</td></tr>
<tr><td>Ordinal scale 5 (no O2 required)</td><td>34 (17%)</td><td>21 (11%)</td></tr>
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General demographic data were well balanced between the treatment arms which highlights the importance of randomization.
The patient population was a little younger than the highest risk age group of ≥ 65 years and had a very low proportion of minorities that have been associated with poor outcomes from COVID-19. The incidence of coexisting comorbidities was also lower than expected. The patient demographics in this study do not represent the highest risk category for severe COVID-19 and decreases the applicability of the results.
The baseline disease state characteristics were not stratified and ended up skewed with the 10- day arm having a numerical increase in patients with an ordinal scale of 2 or 3. This potentially biases the results to look less favorable for the 10- day arm and more favorable for the 5- day arm.
While about the same duration of symptoms before the first dose of remdesivir (~9 days) between the study arms, this may be too late in the disease presentation to initiate therapy. Given remdesivir’s mechanism of action, it is logical that it would have a greater impact if initiated sooner.

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<td>Monitoring</td>
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“Patients were assessed by physical examination and by documentation of 1) respiratory status, 2) adverse events, and 3) concomitant medications. On trial days 1, 3, 5, 8, 10, and 14, blood samples were obtained for complete blood count creatinine, glucose, total bilirubin, and liver aminotransferases.”
“The clinical status of patients was assessed daily on a 7-point ordinal scale from day 1 through 14 or until discharge. The worst (i.e., the lowest) score from each day was recorded.”
Adverse events were those that “occurred on or after the first dose of remdesivir for up to 30 days after the last dose”

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A clinical follow up of 14 days does not seem adequate for patients with severe COVID-19 as it often takes considerable time for them to recover. It would have been nice if clinical follow up, in addition to ADRs was followed for 30 days, or even 3 months.
SARS-CoV-2 viral load results were not available during or after treatment. This would have been an interesting objective measure to add to the study that would assess differences in viral clearance between treatment durations.

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<td>Primary Outcome</td>
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There was no statistically significant difference (p = 0.14) in clinical status at day 14 between the treatment arms even when adjusted for baseline clinical status.

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Purists will argue that the trial is not powered to determine that no difference truly exists while practical implications (see stats section above) will suggest that there really is no difference between 5 and 10 days of therapy with remdesivir.

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<td>Secondary Outcomes</td>
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• <u>Safety:</u>
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<tr><th>Select ADRs</th><th>5-Day Group</th><th>10-Day Group</th></tr>
<tr><td>Any ADR</td><td>141 (70%)</td><td>145 (74%)</td></tr>
<tr><td>Nausea</td><td>20 (10%)</td><td>17 (9%)</td></tr>
<tr><td>Acute respiratory failure</td><td>12 (6%)</td><td>21 (11%)</td></tr>
<tr><td>AKI</td><td>4 (2%)</td><td>15 (8%)</td></tr>
<tr><td>Any Serious ADR</td><td>42 (21%)</td><td>68 (35%)</td></tr>
<tr><td>Acute respiratory failure</td><td>10 (5%)</td><td>18 (9%)</td></tr>
<tr><td>Respiratory failure</td><td>5 (2%)</td><td>10 (5%)</td></tr>
<tr><td>Septic shock</td><td>2 (1%)</td><td>5 (3%)</td></tr>
<tr><td>Any grade 3 or higher lab abnormality</td><td>53/ 195 (27%)</td><td>64/ 191 (34%)</td></tr>
<tr><td>Grade 4 CrCl reductions</td><td>3%</td><td>12%</td></tr>
<tr><td>Mortality</td><td>16 (8%)</td><td>21 (11%)</td></tr>
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• <u>Clinical Outcomes:</u>
• Clinical improvement at day 14: 64% vs 54% for 5 vs 10 day arms
• Recovery at day 14: 64% vs 54% for 5 vs 10 day arms
• Modified recovery at day 14: 70% vs 59% for 5 vs 10 day arms.

• <u>Exploratory Outcomes:</u>
• Median time to clinical improvement was 10 vs 11 days in the 5 vs 10-day arms. The baseline adj difference was 0.79 (0.61 – 1.01)
• Median time to recovery was 10 vs 11 days in the 5 vs 10-day arms
• Median time to modified recovery was 9 vs 10 days in the 5 vs 10-day arms.
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• The most common serious adverse events in the 10- day arm are consistent with disease progression and having a patient population with a higher baseline acuity. Otherwise they seem well balanced and largely what is expected from remdesivir, such as an increase in LFTs. One notable difference was the numerically higher rate of AKI in the 10-day group but it is unclear if associated with a longer duration of the drug or high acuity disease states that may lead to an AKI (ex: septic shock).
• The study was not powered to determine that no difference exists as it did not reach its target sample size for the primary outcome though that will be debated by some. In addition, it was not designed to determine if there was a difference in secondary and exploratory outcomes and the results are likely skewed by the variation in baseline disease severity between the treatment arms. Despite this, most of the secondary and exploratory outcomes were similar.
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<td>Other Clinical events</td>
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• “only 44% of patients in the 10-day treatment group completed the full course of therapy”. Up to 35% of patients in the 10-day arm were discharged early.
• Discharge rates were higher in the overall population among patients who had symptoms < 10 days before receiving remdesivir (62%) vs. symptoms ≥ 10 or more days (49%).
• “Post hoc analysis to determine whether any subpopulation might have benefitted from receiving more than 5 days of therapy with remdesivir”. “Patients receiving mechanical ventilation or ECMO at day 5, 40% (10 of 25) in the 5-day group had died by day 14, as compared with 17% (7 of 41) in the 10-day group.”
• “In multivariate analysis, characteristics associated with shorter time to clinical improvement were an age of less than 65 years, black and white race, a baseline oxygen requirement of low-flow oxygen or ambient air, no use of a biologic medication, and enrollment outside Italy.”
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• While there was no difference in the distribution of clinical outcomes on the ordinal scale at day 14, it could be confounded by almost half of the patients in the 10-day arm not completing therapy. This increases the implication that five days may be okay for the general in-patient with COVID-19.
• While post-hoc analyses are not encouraged, the difference in mortality outcomes for patients on invasive mechanical ventilation or ECMO is notably in support of a 10-day course of therapy. This has significant implications for practice as more data are being studied such as the final results of ACTT-1.
• The epidemiologic characteristics associated with clinical improvement are mostly consistent with other studies with the exception of black race. Given the small number of black patients in the trial, this could be an error of not being powered enough.
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AUTHORS' CONCLUSIONS

- The authors concluded that there was no difference in treatment outcomes between 5-day and 10-day treatment course of remdesivir in patients who did not require mechanical ventilation at baseline.

GENERALIZABILITY/CRITIQUE/DISCUSSION

- This article is a bit challenging to interpret as there are notable implications for bias in the study design including an open-label design, lack of stratification for disease severity, multiple protocol amendments that make it more like an adaptive trial, statistics that are limited to the primary outcome, a relatively short follow up period of only 14 days, and a focus on severe COVID-19 where the patient already has pneumonia and presumably (though this was not provided) a higher viral burden. Some of these are due to initial study design and some are due to the heroic effort of conducting a randomized controlled trial in the middle of a pandemic from a virus that we are still learning.
- The generalizability of the results of this study is limited. There was not data provided on the distribution of patients by site or nation and the demographics were not consistent with patients that fall into the highest risk category though they were close.
- In addition, the study is hurt by the differences in patient populations between the treatment arms. Not only does the 10-day arm have higher baseline disease characteristics which could potentially skew the data, but 44% of the patients in the 10-day arm didn't finish the full course of therapy. The 10-day arm had a median duration of therapy of 9 days but the interquartile range was 5 to 10 meaning that we could be comparing patients that received 5 days of therapy in both arms and that is why there was no difference in clinical outcomes.
- While this study has a high risk of type 2 error because it was not powered to say that no difference exists, the fact that a third of the patients in the 10-day arm were discharged early is reassuring that there may not be a difference in 5 vs 10 days of treatment. This is not proven by this study but it is a reasonable interpretation of the results for this specific patient population.
- There also appears to be some safety advantages with 5-days of therapy vs 10 days with a high incidence of adverse events noted in the 10 day arm
- One of the more compelling findings was the mortality rate among individuals who were receiving mechanical ventilation or ECMO. At day 5 40% (10 of 25) in the 5-day group died by day 14 vs 17% (7 of 41) in the 10-day group. Although this was a post-hoc analysis, the numbers are clinically significant and warrant continuing treatment in these patients for 10 days.
- Given the limited supply of remdesivir available during this pandemic, 5-days of therapy in patients that do not require invasive mechanical ventilation/ECMO that are responding to therapy seems like an appropriate way to prioritize healthcare resources. The results of this trial cannot be extrapolated to high-risk groups such as those that have invasive mechanical ventilation/ ECMO and immunocompromising conditions given the small sample size. While preliminary results from ACTT-1 suggest that remdesivir may not be helpful for these high risk groups, many were still in the follow up phase of the trial. The final results of ACTT-1 and the extended cohort of this trial will likely provide more guidance on the role of remdesivir in patients with invasive mechanical ventilation/ ECMO and immunocompromising conditions. Until then, it may be reasonable to extend therapy in these patients to 10 days.

CITATIONS

1. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe COVID-19. *N Engl J Med*. May 27, 2020 [Epub Ahead of Print]. DOI:10.1056/NEJMoa2015301
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