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Remdesivir has questionable efficacy in patients with severe COVID-19 receiving high-flow oxygen

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Remdesivir has questionable efficacy in patients with severe COVID-19 receiving high-flow oxygen

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ABSTRACT A clinical decision report using:

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med*. 2020;383:1813-1826. <https://doi.org/10.1056/NEJMoa2007764>

for a patient with severe COVID-19.

Keywords: *remdesivir, COVID-19*

Clinical-Social Context

Mrs. Bagchi (pseudonym) is a 60-year-old woman who arrived to the emergency department in August of 2020 by ambulance in acute respiratory distress less than 24 hours after being discharged from a local hospital where she tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and was treated for symptoms related to the disease.

During her prior admission, she received two doses of methylprednisolone 40 milligrams and did not require supplemental oxygen therapy. According to hospital records, she was discharged in stable condition and at her baseline respiratory function. However, shortly after arriving home from the hospital, she become short of breath, tachypneic, and agitated, prompting her son to call emergency medical services. When they arrived at the patient's home, her oxygen saturation was in the 60s and respiratory rate in the 40s.

In the emergency department, the blood pressure was 124/91 mmHg, the heart rate 129 beats per minute, the respiratory rate 36 breaths per minute, and the oxygen saturation (SpO₂) 83% while the patient was receiving supplemental oxygen through a nonrebreather mask at a rate of 15 liters per minute. Nucleic acid testing was positive for SARS-CoV-2. Radiography of the chest revealed diffuse bilateral ground glass opacities. A diagnosis of acute respiratory distress syndrome due to coronavirus disease of 2019 (COVID-19) was made. The patient's illness was classified as severe based on having an SpO₂ <94% on room air, a respiratory rate >30 breaths per minute, and lung infiltrates >50%.¹

The patient was started on intravenous doses of vancomycin 1750 milligrams per day, cefepime 2 grams per day, and dexamethasone 6 milligrams per day and she was switched to high-flow supplemental oxygen therapy at a rate of 40 liters per minute and 100% fraction of inspired oxygen (FiO₂). Per the treatment guidelines for COVID-19 at this hospital, the patient qualified for antiviral therapy with remdesivir, a viral RNA polymerase inhibitor. The care team and the patient were thus posed with the decision of whether to pursue this novel therapy.

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A translator was consulted to discuss the use of remdesivir and obtain additional medical and social history, as the patient only speaks Bengali. She had difficulty conversing with the translator due to her shortness of breath and preferred the team speak directly with her son who is fluent in both Bengali and English. She also permitted him to make any and all decisions regarding her care, adding that he oversees her medical care and usually speaks with the doctor. According to her son, Mrs. Bagchi's symptoms began seven days prior with malaise, cough, and fever. Her past medical history includes type II diabetes mellitus, hypertension, hyperlipidemia, and hypothyroidism. The son was hesitant to disclose the patient's social history, asking why it was immediately relevant to her care. After the team addressed these concerns, he did disclose that she lives with her husband and two adult children and has no formal education or history of employment. She does not smoke tobacco or electronic cigarettes, drink alcohol, or use illicit drugs.

Mrs. Bagchi's son consented to the use of remdesivir after the risks, benefits, and alternatives of the medication were explained in detail. In his words, he wanted the team "to do whatever you think is best for my mother" and had no further questions about the medication.

Clinical Question

Does remdesivir improve recovery time and reduce mortality compared to the current standard of care in patients with severe COVID-19 receiving high-flow supplemental oxygen?

Research Article

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med.* 2020;383:1813-1826. <https://doi.org/10.1056/NEJMoa2007764> ²

Description of Related Literature

A search on PubMed in October of 2020 using the key phrases "remdesivir" and "covid-19" and restricting the article type search parameters to clinical trial, meta-analysis, and randomized control trial yielded nine results.

Three articles were eliminated from consideration based on abstract alone. One article was a foreign paper not available in the English language.³ Another article described protocol for a trial that had not been completed.⁴ The third article described the safety, tolerability, and pharmacokinetics of remdesivir without clinical outcomes data.⁵

One study was excluded from consideration on the basis of being a descriptive study without a designated control group.⁶ Two articles were meta-analyses and therefore did not meet inclusion criteria of this paper (ie, randomized, placebo-controlled trials). One of the meta-analyses compiled data from four randomized trials and demonstrated that the rate of clinical improvement was significantly higher in patients who received remdesivir compared to standard of care.⁷ The other meta-analysis failed to demonstrate a difference between remdesivir versus placebo on all-cause mortality or nonserious adverse events, but showed evidence of a beneficial effect of remdesivir on serious adverse events.⁸

Two additional studies were identified by reviewing the references of the aforementioned meta-analyses. One study was a randomized trial that found no difference in clinical outcomes between patients who received a 5-day versus 10-day course of remdesivir.⁹ However, with no placebo control, the benefit of remdesivir compared to standard of care could not be determined. The other study was an announcement of results from an ongoing phase 3 trial.¹⁰ This study was excluded from consideration as the findings were preliminary and had not been published at the time they were reviewed.

Two articles were randomized, placebo-controlled trials. A multicenter trial of 237 patients across 10 hospitals in Hubei, China found that remdesivir did not significantly improve clinical status, mortality, or time to clearance of the virus compared to placebo in patients with severe COVID-19.¹¹ However, the study was limited by insufficient power due premature termination of enrollment. Another randomized control trial investigated whether remdesivir improved clinical status on day 11 of hospitalization in patients

with moderate COVID-19, defined as oxygen saturation >94% and pulmonary infiltrates.¹² The study found that patients receiving a 5-day course of remdesivir had a statistically significant improvement in clinical status compared with standard of care. Patients receiving a 10-day course of remdesivir, however, did not. This article had limited application to our clinical question, as it only included patients with moderate COVID-19 whereas our patient would be classified as severe (ie, oxygen saturation <94% on room air). Additionally, the trial implemented an open-label design which has inherently high susceptibility to bias.

A large, multicenter, double-blind, randomized, placebo-controlled trial by Beigel et al. was ultimately selected to answer the clinical question.² With a total 1062 patients enrolled, the trial included a larger and more diverse study population than any other study to date. Importantly, results were stratified and presented based on multiple subgroups, including race, ethnicity, geographic location, age, sex, symptom duration, and baseline need for various levels supplemental oxygen therapy, which allowed for detailed consideration of how the results applied to our patient. The Food and Drug Administration's (FDA) decision to expand Emergency Use Authorization for remdesivir to hospitalized patients with mild or moderate COVID-19 was based on data from this study and therefore speaks to the paper's relevance and the impact it had on the COVID-19 treatment landscape at the time a decision was made.¹³

The overall body of literature investigating the efficacy of remdesivir for the treatment of COVID-19 receives a level B strength of recommendation per the SORT criteria due to the limited number of randomized control trials and the conflicting findings presented by these studies.¹⁴

Critical Appraisal

Beigel et al. is a double-blind, randomized, placebo-controlled trial that investigated the efficacy of remdesivir for the treatment of hospitalized patients with COVID-19. The primary outcome of the study was time to recovery.

A total of 1114 patients were assessed for eligibility. Inclusion criteria included evidence of lower respiratory tract infection (eg, radiographic infiltrates, SpO₂ ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation) and laboratory-confirmed SARS-CoV-2 infection. Exclusion criteria included having aminotransferase levels >5 times the upper limit of normal, impaired renal function, allergy to study products, being pregnant or breastfeeding, and anticipated discharge or transfer from the hospital. 28 patients were excluded after applying inclusion and exclusion criteria and 24 patients were eligible, but were not enrolled. Ultimately, 1062 patients underwent 1:1 randomization to receive remdesivir (541) or placebo (521).

The treatment group received 200-mg loading dose of remdesivir on day 1, followed by a 100-mg maintenance dose for the next 9 days. The control group received a placebo of the same volume and frequency as remdesivir. Both remdesivir and the placebo were indistinguishable from one another in order to maintain blinding. Additionally, all patients received supportive care according to the standard of care at each hospital site. Off-label or experimental COVID-19 treatments were prohibited, except at sites where these treatments had already been adopted as the standard of care and were reflected in a written policy or guideline of the hospital. Variability in the standard of care between the 60 trial was sites was not controlled for and is an inherent limitation of the multicenter study design due to potential confounding and effect-modification. 66 patients in the remdesivir group and 70 patients in the placebo group discontinued their participation due to an adverse event or voluntary withdrawal. The similar rate of discontinuation in both groups likely minimized attrition bias and its impact on outcomes.

Patients who received remdesivir had a shorter time to recovery (median, 10 days vs. 15 days; rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001). No significant difference was detected in all-cause mortality by day 29 (11.4% with remdesivir vs. 15.2% with placebo; hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events occurred in 24.6% (131/532) of patients who received remdesivir and 31.6% (163/516) of patients who received placebo. The investigators deemed 41 adverse events to be related to remdesivir and 47 to the placebo. No deaths were considered by the investigators to be related to the intervention.

Of note, the primary outcome was changed after enrollment had begun from a comparison on clinical status on day 15 to recovery time up to day 29. According to the authors, little was known about the natural history of COVID-19 when the trial was designed, and the change was made after new data were published on the protracted course of the disease. The decision to modify the primary outcome is an important consideration when interpreting the findings of this study, but it is also understandable given the



novelty of the disease. Nevertheless, Beigel et al., a level 1 quality study per the strength of recommendation taxonomy (SORT)¹⁴, implemented compelling methodology and successfully recruited a large, multinational population to evaluate an emerging therapeutic for the treatment of COVID-19.

Clinical Application

The findings of Beigel et al. support the use of remdesivir as a viable COVID-19 adjuvant therapy to reduce recovery time. However, these findings do not hold up if subgroup analysis is applied to our patient.

Subgroup analysis of race and age as it applies to Mrs. Bagchi does not demonstrate a statistically significant recovery rate ratio compared to control. Based on the study's classification system, our patient is Asian (recovery rate 1.36; 95% CI, 0.74 to 2.47) and age 40 to <65 years-old (recovery rate 1.19; 95% CI, 0.98 to 1.44). However, it is important to note that only 52 patients of Asian ethnicity were included in this study and the confidence interval for this subgroup is relatively large, suggesting that it may be underpowered.

The study demonstrated that remdesivir resulted in a faster recovery time if given within 10 days from the onset of symptoms. Per our conversation with Mrs. Bagchi's son, her symptoms started seven days prior to admission, which means that she was within this crucial 10-day window for receiving treatment. However, her clinical presentation was quite severe and required the use of intensive high-flow supplemental oxygen therapy at 100% FiO₂ and a rate of 40 liters per minute. Based on these clinical characteristics, she would receive a baseline ordinal score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation) per the study's 8-category scoring system for clinical status. This subgroup did not demonstrate a faster recovery rate compared to control (1.09; 95% CI, 0.76 - 1.57). Furthermore, treatment guidelines for the use of remdesivir at the hospital where Mrs. Bagchi was being treated recommends a 5-day course rather than the 10-day course studied in Beigel et al. This introduces further uncertainty as to whether the results of this trial can be applied to our patient.

It should be noted that a translator was employed into the care of this patient. Doctors are expected to have cultural competence when providing care and it is entirely possible that having the son make decisions and "doing what the doctor thinks best" is a cultural norm given the culture of origin for Mrs. Bagchi.

New Knowledge Related to Clinical Decision Science

Remdesivir is a novel medication for COVID-19 and potential side effects have not been studied extensively. According to the FDA's emergency use authorization, hepatotoxicity is a major side effect that requires routine monitoring of liver enzymes. Therefore, the use of remdesivir must be carefully considered for each patient and proper consent protocol followed due to the potential for unknown adverse medication reactions and known hepatotoxicity. This brings up the important ethical and clinical question of whether remdesivir should have been given to our patient. Remdesivir did not show a statistically significant recovery time benefit for many subgroups that apply to our patient including age, race, and clinical status. This discrepancy illustrates the importance of using a patient-specific approach when considering research literature to make treatment decisions. Although a quick look at this study's abstract would suggest that remdesivir should be given to reduce recovery time, a thorough investigation of the study's findings reveal that this therapy would likely provide little benefit to our patient and potentially do harm due to known and unknown side effects.

Thematic issues for Clinical Decision Science that are highlighted in this article include 1) the need to make clinical decisions in the absence of high quality evidence with an established standard of care; 2) Clinical Decision making in a setting where the available evidence is evolving; and 3) using the inclusion metrics and outcome metrics by the clinical researchers to anticipate how the individual patient may respond to the treatment being studied.

The utility of Clinical Decision Reports is to guide exploration of how decisions are made. Passive decisions—decisions without thoughtfulness and intent—should be avoided.



Conflict Of Interest Statement

This author, their immediate family, and any research foundation with which they are affiliated did not receive any financial payments or other benefits from any commercial entity related to the subject of this article.

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