DEM Journal Club

# Article Appraisal

**Article:** Remdesivir in Adults with Severe COVID-19: A Randomized Double-Blind, Placebo-Controlled, Multicenter Trial

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## Background and Study Objective(s):

Remdesivir is a nucleoside analogue that blocks viral RNA replication. It has been minimally studied as treatment for COVID-19 in humans. This study aimed to explore whether remdesivir administration to admitted patients was associated with improved clinical and laboratory outcomes.

## Study Design:

In this randomized trial at 10 hospitals in Hubei, China, reserarchers enrolled admitted patients with confirmed COVID-19 on PCR and who had signs of respiratory distress into the trial and randomized them in a 2:1 manner to a 10-day course of remdesivir vs. placebo. Inclusion criteria: adult male/nonpregnant inpatients with RT/PCR confirmed COVID-19, pneumonia on chest x-ray, SpO2 <94% on room air or a P:F < 300, and presenting within 12 days of symptom onset. Exclusion criteria: Pregnant/breastfeeding, hepatic cirrhosis, elevated liver enzymes, renal failure, involved in previous COVID drug trials (but allowed other drugs to be used), transfer within 72h to non-participating hospital.

Intervention: 10-day course of remdesivir (200mg on day 1 followed by 100mg/day for days 2-10). The authors did not constrain the patient treatment in hospital otherwise and all other therapies were allowed, including other experimental COVID-19 medications.

The primary outcome of interest was the time to clinical improvement within 28 days after randomization, defined as a 2-point reduction in a prespecified clinical severity scale (1-discharged, 2-admitted, 3-supplemental O2, 4-high flow O2, 5-ECMO or intubated, 6-death). This was determined by daily surveys of patients by research staff.

The authors also had 11 secondary outcomes, including clinical (mortality, duration of O2), laboratory (eg. Viral load, proportion of patients with positive viral RNA), and safety (adverse events, premature discontinuation) outcomes. To monitor safety, the authors recorded daily vital signs and regular bloodwork and viral swabs as well as ECGs.

The initial design anticipated a time-to-clinical improvement of 21 days in the placebo group and 15 days in the intervention group (hazard ratio 1.4) required 325 events in both groups. The design also included an interim

analysis of 453 patients, and an interim analysis of 240 patients, although the latter would substantially decrease the power of the study to detect a true difference

### Results:

The study was terminated early due to public health measures in Wuhan that effectively halted new cases of COVID after the authors had enrolled 255 patients. Of the 255 patients enrolled, 237 underwent randomization with 158 assigned to the remdesivir group. The majority of the remaining patients underwent the study (1 withdrew consent, 3 did not start treatment, and 7 did not complete a 10-day course). This reduced study power from 80% to 58%.

Baseline characteristics of the two groups appeared similar, with the intervention group having a greater proportion of comorbidities and slightly longer duration of illness. Both groups had similar rates of ancillary treatments (ie steroids) as well as similar rates of inotrope use, renal replacement therapy, and antibiotic usage.

There was no significant difference in the primary outcome (HR 1.23, 95% CI 0.87-1.75). In a post-hoc analysis, broadening the definition of "improvement" to a 1-point improvement on the clinical scale resulted in no significant difference (HR 1.34, 95% CI 0.96 to 1.86).

There was no difference in secondary outcomes, including all-cause mortality, frequency of invasive mechanical ventilation, duration of oxygen therapy, duration of admission, proportion of patients with positive viral swabs, viral load, adverse events, and serious adverse events.

### Validity of Results:

Although a well-designed study, internal validity is compromised by the lack of power, and a non-significant result in an underpowered study ensures the results cannot be interpreted meaningfully. Due to likely ethnocultural differences, it may be challenging to extrapolate the results elsewhere; for example, patients of Asian descent have a lower incidence of thrombotic events. Furthermore, management of this illness has changed and invasive ventialition is now discouraged as early therapy.

### Generalizability of Results:

Lack of significance in an underpowered study is difficult to apply to a general or local population.

### The Bottom Line:

We applaud Wang et al. for their rigorously designed study under pandemic conditions to investigate a new medication with promising in vivo and in vitro findings. However, this study was underpowered to detect a difference, and no outcomes had a significant outcome, making the results of this study non-interpreble. Any trends in the data may be hypothesis-generating for future studies.