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A Journal Club Article Review on the Study: Remdesivir in Adults with Severe COVID-19: A Randomised, Double-Blind, Placebo-Controlled, Multicentre Trial. Wang *et al.*, 2020

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Abstract: ***The study reported the results of the first of its kind placebo controlled randomised trial of Remdesivir in patients with severe COVID-19.The references used were recent and looked at other articles where Remdesivir was used whether in vivo or for compassionate use which gave some background to the study. In the above title study, the randomised controlled trials (RCTs) conceptual framework was carried out, that is; assigning patients equally to the two different treatment groups. This trials has unequal ratio as 2:1 and such unequal allocations need justification, but the rationale was not stated in this publication. Such a randomisation needs to overcome scientific and ethical problems and should always publicly declare why unequal randomisation was chosen which was not done in this study. The statistics are not simple to design and power correctly they are complex statistical concerns, and harder for non-experts to assess the statistical validity of the design. The study found that i.v. Remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of virus and adverse effects in patients with COVID-19 compared with placebo, though this outcomes may be affected by the unequal distribution of Comorbidities amongst the groups, gender disparity and limited Pharmacokinetics knowledge of Remdesivir in the severely ill COVID-19 patients. This study shows that Remdesivir in vivo has no clinical significance on the management of severely illCOVID-19 patients.***

Keywords: Comorbidities, COVID-19, Journal club, Randomised controlled trials, Remdesivir, Clinical improvement

1. Description of the Study

The Lancet is a weekly peer-reviewed general medical journal. It is among the world's oldest and best-known general medical journals first published in 1823. *The Lancet* is a world leading medical journal with a Journal Impact Factor of 59·102® (2018 Journal Citation Reports®, Clarivate Analytics 2019) and are currently ranked second out of 160 journals in the Medicine, General & Internal subject category. The study reported the results of the first of its kind a placebo controlled randomised trial of in patients with severe COVID-19.This trial was registered with ClinicalTrials.gov, NCT04257656.No. The research objectives were not stated anywhere in the article. The journal clearly stated that all authors who represented the 10 hospitals used in the study contributed to the conducting of the trial. Specific authors were involved in various aspects of data handling, analysis and manuscript writing.

2. Literature Review Evaluation

This paper provides the first peer reviewed, scrutable, multicentre, randomised trial of Remdesivir, and for patients with COVID-19 in hospital (but not necessarily intensive care), fails to demonstrate a clinically meaningful improvement. This is despite a plausible mechanism of action and in vitro evidence of its antiviral efficacy. news of its findings were largely eclipsed by the widely publicised, but as yet unpublished positive results of an interim safety analysis of the similarly designed, but larger, US National Institute of Health (NIH) funded multicentre trial (Adaptive COVID-19 Treatment Trial; ACTT), which were released to the press on the same day as this trial was published in the Lancet (29 April).The literature review for this study does take into account other drug trials in COVID-19 Management although some of those drug trials have been inconclusive so it needs an updated review although recent, more findings about COVID-19 are being churned out daily.

3. Conceptual Framework

The concept for this work was a randomized controlled trial which ensured that patients were randomly assigned to either a treatment group or a placebo group in other to assure that any documented effects in the treatment group are indeed due to the treatment and not to chance. An unequal randomization formula (2:1) was adopted probably to encourage more people to consent to the study because of the higher chance of being placed in a treatment group rather than the placebo group. (Brody, 2016;Tal, 2011). Appropriately, a statistician was employed to carry out the randomization which means both the participants and the researchers are not aware of the group a patient is placed in (double-blind study).

4. Sample and Sampling Methods

In Wang *et al's* trial, 237 hospitalised patients with PCR-confirmed COVID-19 at 10 sites in Wuhan, China, were randomly assigned in a 2:1 ratio to receive either Remdesivir 200mg intravenously on day 1 followed by 100mg IV daily on day 2-10, or placebo. (Wang *et al.*,

2020)Patients had symptom onset within 12 days, radiographic features of pneumonia, and an oxygen saturation of <94% on room air, or a P:F ratio of <300mmHg. Patients who were pregnant, or with liver dysfunction or severe renal impairment were excluded. Inclusion/exclusion criteria were specified. Patient's recruitment could not reach their target enrolment. The used population was less than the projected or anticipated population; hence the report could not be generalized due to the small size of population. (Wang *et al.,* 2020). Frequent use of corticosteroids in the patient group might have promoted viral reported prolongation of the detection of viral RNA, not infectious virus. There is no answer to whether longer treatment course and higher dose of Remdesivir would be beneficial in patients with severed COVID-19.This trials has unequal ratio as 2:1 and such unequal allocations need justification, but the rationale was not stated in this publication. (Dumville *et al*., 2006).

5. Method and Design

The study setting was ten hospitals in Wuhan, Hubei, China where adults admitted to hospital with laboratory-confirmed SARS-CoV-2 (COVID-19) infection between February 06 and March 12, 2020 were recruited. All patients of child-bearing age were made to adopt effective contraceptive measures during and for ≥ 7 days after the last study drug administration. The design was a Investigator-initiated, individually randomised, placebo-controlled, double-blind trial and the patients were randomly assigned (2:1) to: Remdesivir group (who received intravenous Remdesivir 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) and placebo group (who received 200 mg placebo infusion on day 1 followed by 100 mg on days 2-10). (Wang *et al.,* 2020). Randomisation was stratified according to level of respiratory support viz.: (1) no oxygen support or oxygen support with nasal duct or mask; or (2) high-flow oxygen, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation. The Outcomes measures were clinical endpoint i.e. time to clinical improvement within 28 days after randomization, then safety outcomes i.e. treatment-emergent adverse events, serious adverse events, and premature discontinuations of study drug (Wang *et al.,* 2020). The method and design was appropriate although allocating more patients to the arm with a high drop-out rate allowed greater power for a "per-protocol" analysis and will not interfere with an intention-to-treat (ITT) analysis.

6. Statistical Analysis

The selected statistical tests were appropriate for the data obtained and the study objectives. Comparative analysis between the Remdesivir and Placebo treatment groups did not show any statistically significant difference in time to clinical improvement. Thus, suggesting that the use of Remdesivir in patients with severe COVID-19 would not yield significant clinical benefits. For the same power a trial that is randomised 2:1 needs 12% more patients and a 3:1 randomisation scheme requires 33% more patients.

7. Results and Interpretations

The study found that i.v. Remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of virus and adverse effects in patients with COVID-19 compared with placebo, though this outcomes may be affected by the unequal distribution of Comorbidities (Cheng *et al.,* 2020) amongst the groups, gender disparity and limited Pharmacokinetics knowledge of Remdesivir in the severely ill COVID-19 patients (Jorgensen *et al., 2*020; Wang *et al.,* 2020). The median age of participants was 65, and this age bracket predisposes to co-mobidities. When compared with a previous study (Grein *et al.,* 2020), the study population was less ill and was treated somewhat earlier in their disease course. This is contrary to Beigel *et al.,* 2020 preliminary results which concluded that Remdesivir was superior to placebo in shortening the time to recovery in severely ill adults hospitalized with COVID-19. The study could not reach their target enrolment because of the public health strategies put in place in China which resulted in fewer hospitalized patients by Mid-March. Thus, the sampled population was less than the projected or anticipated population which meant that the statistical power had to be reduced. The result is therefore, not generalizable due to the small size of the population.

8. Clinical Significance and Implications

Clinical researches are geared toward therapy fundamental to generate new knowledge and validate therapies. The evaluation of researches findings is crucial to clinical decision making and to help comply the principles of evidence based-practice. (Armijo-Olive, 2018; Armijo-Olive *et al.,* 2011).From the study, the results shows that the dose of Remdesivir was adequately tolerated by all the participants but the clinical outcomes in terms of improve time for clinical improvement, mortality, and clearance time for the virus, remdesivir did not show any significant advantage over the placebo.

9. Conclusion

The experimental drug-Remdesivir did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19, nonetheless, clinically meaningful differences and numerical reductions in some clinical parameters cannot be excluded. The place of ongoing studies is encouraged to promote better understanding of the intervention effect in larger sample sizes of severely ill COVID-19 patients.

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Authors Abbreviations

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Description of the Study: AJ/UUI
Literature Evaluation: CI/KN/EU
Conceptual Framework: EO/JE/ABM
Sample and sampling methods: OAP/AOF/IS
Method and Design: KG/IOU
Analysis: UIE/YJD
Results and Interpretation: EGP/OOI/VCA
Clinical Significance: AAE/ASC/KNM
Abstract: EGP/AJ
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