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Title: A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19.

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Introduction & Aims:

This randomized, controlled, single-centre, open-label trial studied the efficacy and safety of lopinavir–ritonavir in hospitalized adults with Covid-19.

Design and Methods:

199 patients were randomised to receive either standard care alone or lopinavir–ritonavir in addition to standard care. Inclusion criteria: Patients who had a positive RT-PCR assay for SARS-CoV-2, pneumonia on chest imaging and oxygen saturation of ≤ 94% on room air or a PaO2/FiO2 ratio of ≤ 300. The primary end point for efficacy was the time to clinical improvement outlined as discharge from the hospital or an improvement of two points on an ordinal scale. Secondary outcomes included mortality at day 2 and rate of adverse events.

Results:

The initial intention-to-treat analysis found that lopinavir–ritonavir was not associated with a difference in the time to clinical improvement (hazard ratio,1.31;95% confidence interval [CI],0.95 to 1.80) or mortality (19.2%vs.25.0%;95% CI,−17.3 to 5.7).

A modified intention-to-treat analysis, excluding 3 patients who died prior to receiving lopinavir–ritonavir, demonstrated a reduction in median time to clinical improvement by 1 day compared to standard care (hazard ratio,1.39;95% CI,1.00 to 1.91).

Conclusion:

No benefit was demonstrated with lopinavir–ritonavir treatment of severe COVID-19 beyond standard care.

Strengths:

This trial was performed at a crucial time to provide the first experimental data in the use of anti-virals in severe COVID-19. Accuracy was optimised using clear, objective inclusion criteria. Heterogenous distribution of patients regarding duration and severity of illness and need for respiratory support at enrolment further strengthens this study. Additionally, the choice of an intention-to-treat analysis reduces results bias and type 1 errors and provides a more accurate evaluation of effectiveness in the real world[1].

Limitations:

Given the modest sample size this trial was statistically unpowered to demonstrate this outcome. The trial was not blinded which could have resulted in a bias in patient assessment or in clinical decision-making. An additional limitation includes the use of concomitant pharmacologic interventions. 35.7% of those in the standard-care group received glucocorticoids versus 33.0% in the treatment group. Given the limited data on corticosteroids in COVID-19, this is an important confounder[2].

Interpretation, applicability, and future direction:

COVID-19 represents a major cause of morbidity and mortality in Ireland and worldwide. This trial alone will not significantly change practice in Ireland however it provides important safety data and forms the basis of further research.

This RCT demonstrated no benefit for the primary endpoint beyond standard care in the initial analysis however the modified intention-to-treat analysis demonstrated a reduction in time to clinical improvement of 1 day. Even this modest advantage could significantly affect the availability of limited resources.

A post hoc subgroup analysis suggests that commencement of lopinavir–ritonavir within 12 days of symptom onset reduces mortality. This finding is consistent with anti-viral studies demonstrating the benefit of earlier time-to-treat in influenza[3] and SARS[4].

The lower incidence of severe complications including acute kidney injury, bacterial infection and need for mechanical ventilation for respiratory failure in the lopinavir-ritonavir arm prompts further study of lopinavir-ritonavir and COVID-19 related complications.

Given that there is no approved treatment for Covid-19, this study supports continuing to consider this affordable and widely available drug as a treatment option for Covid-19 until the RECOVERY and the WHO SOLIDARITY trial data is available.

References:

1. McCoy CE. Understanding the Intention-to-treat Principle in Randomized Controlled Trials. *West J Emerg Med*. 2017;18(6):1075-1078. doi:10.5811/westjem.2017.8.35985

2. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020;395:473-475.
3. Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: a 5-year analysis of oseltamivir timing and clinical outcomes. Clin Infect Dis 2019;69:52-58.
4. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J 2003;9:399-406.