Title

Targeting vascular leakage using imatinib in patients with severe COVID-19

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Introduction: Vascular leak is a condition that complicates a variety of clinical conditions. Despite high mortality rates of this complication, there is currently no drug to target vascular leak. Coronavirus disease 2019 (COVID-19) is often complicated by hypoxemic respiratory failure, resulting from widespread capillary leak and alveolar oedema. The kinase inhibitor imatinib may protect the endothelial barrier and reverses pulmonary capillary leak.

Methods: We performed a randomized, double-blind, placebo-controlled trial in 16 centres in the Netherlands. Hospitalized COVID-19 patients requiring supplemental oxygen were treated with oral imatinib (800mg loading dose, followed by 400mg *daily* for 9 days) or placebo on top of standard care. The primary outcome was time to liberation from ventilation and supplemental oxygen for more than 48 hours while being alive during a 28-day period. In addition, we report short (28 days) and long term (90days) clinical outcome, as well as ventilation and gas exchange parameters during the first 14 days of ICU admission.

Results: 385 patients (median age 64 (range 28-93) years) received at least one dose of study medication, and were included in the analysis. There was no difference in the time to liberation from ventilation and supplemental oxygen (unadjusted hazard ratio [HR] 0.95; 95% confidence interval [CI] 0.76-1.20). At 28 days, mortality was 9% in the imatinib group, compared to 17% in the placebo group (unadjusted HR 0.51, 95% CI 0.27-0.95; adjusted HR 0.52, 95% CI 0.26-1.05). At 90 days, mortality was 8% in the imatinib group, compared to 14% in the placebo group (unadjusted HR 0.53 (95% CI 0.29-0.94), adjusted HR 0·52, 95% CI 0.28-0.99). After 90 days the median duration of invasive mechanical ventilation was 7 days in the imatinib group versus 12 days in the placebo group (p=0.026). The number of ventilator-free days was 84 in the imatinib group versus 64 in the placebo group (p=0·036). Treatment with imatinib resulted in faster clinical improvement at an 8-point ordinal scale, paralleled by faster improvement in oxygenation status.

Conclusion: Although no effect on the primary endpoint was observed, imatinib treatment resulted in a significant reduction in mortality and the duration of mechanical ventilation, most likely via improving oxygenation status. These data suggest that imatinib may predominantly benefit patients with more severe forms of COVID-19 and alveolocapillary injury, and provides first clinical evidence for a beneficial effect of imatinib. Further studies are required to validate these findings.

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