Ivermectin in COVID-19 Related Critical Illness

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As the quest to define an anti-viral therapy for treatment of COVID-19 illness continues with little success, a new potential candidate has emerged.[1] A pre-clinical study, demonstrated that ivermectin, FDA approved as an anti-parasitic agent with an established safety profile, was able to reduce SARS-CoV-2 viral RNA by 5000-fold within 48 hours.[2] Importin (IMP) α/β1 30 is a heterodimer that binds to the SARS-CoV-2 cargo protein and moves it into the nucleus which reduces the host cell antiviral response. Ivermectin destabilizes the Impα/β1 heterodimer, prevents it from binding to the viral protein and thus, entering the nucleus.[2,3] Based on these promising *in-vitro* findings, we sought to evaluate the clinical usefulness of ivermectin in critically ill patients with COVID-19.

In an observational registry-based study from 169 hospitals across Asia (AS), Europe (EU), Africa (AF), North (NA) and South America (SA), we evaluated critically ill hospitalized patients diagnosed with COVID-19 with lung injury requiring mechanical ventilation, between January 1st 2020 and March 1st 2020. In this series of 1,970 patients, 1,609 survived hospitalization to discharge and 361 died (18.3%). We recorded 52 patients (AS-7, EU-21, AF-3, NA-14, SA-7) who received Ivermectin (150 mcg/Kg) once after mechanical ventilation was instituted. The indications for use of the drug were related to clinician preference and based on prior data on the broad antimicrobial and specifically antiviral effects of this agent.[1] Compared to 1,918 conventionally treated patients we observed a survival benefit for ivermectin (mortality rate 18.6% vs 7.7%; HR 0.18, 95% CI (0.07-0.48), log rank (Mantel-Cox) p<0.001; Figure 1). The hospital length of stay was 15.7 +/- 8.1 days vs 10.9 +/- 6.1 days, p<0.001 and intensive care unit length of stay 8.2 +/- 6.2 days vs 6.0 +/- 3.9 days, p<0.001 respectively.

In COVID-19 illness, critically ill patients with lung injury requiring mechanical ventilation may benefit from administration of Ivermectin. We noted a lower mortality and reduced healthcare resource use in those treated with ivermectin. These observations should not be considered definitive and allow for translation of a hypothesis from bench to bedside which will require confirmation in a controlled clinical trial setting.

References:

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3. Frieman, M., Yount, B., Heise, M., Kopecky-Bromberg, S.A., Palese, P., Baric, R.S., Severe acute respiratory syndrome coronavirus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane, J Virol, 81 (18) (2007), pp. 9812-9824.

Figure 1. Kaplan-Meier Analysis: Critically ill mechanically ventilated COVID-19 positive patients treated with(red) or without(blue) Ivermectin. HR 0.18, 95% CI (0.07-0.48), log rank (Mantel-Cox) p<0.001)
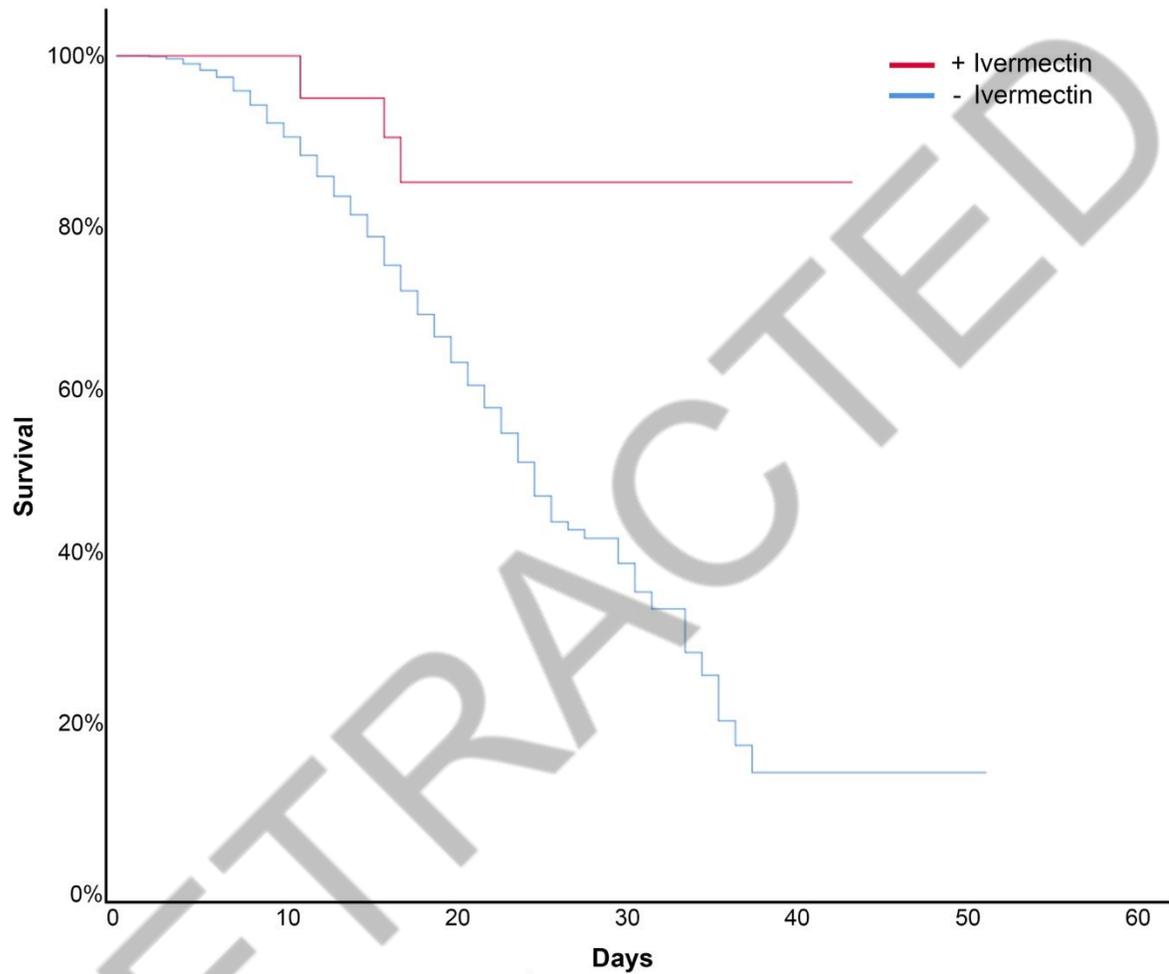
Number at Risk	0-10 days	11-20 days	21-30 days	31-40 days	41-50 days	51+ days
+ Ivermectin	52	7	1	1	1	0
- Ivermectin	1,918	883	140	19	3	1