EDITORIAL

Crying wolf in time of Corona: the strange case of ivermectin and hydroxychloroquine. Is the fear of failure withholding potential life-saving treatment from clinical use?

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1. Introduction

Since the beginning of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic, over a hundred million people contracted the virus, putting a high pressure over hospitals and healthcare systems.

Hydroxychloroquine, lopinavir/ritonavir and azithromycin have been extensively used attempting to prevent or cure Coronavirus Disease 2019 (COVID-19) during the first wave. However, during the last few months, large clinical trials demonstrated the lack of efficacy of the abovementioned treatments [1–3].

Ivermectin is widely used to treat roundworms and ectoparasites infestation, but also has antiviral effects against RNA viruses. COVID-19 drug repurposing research focused on its possible clinical use. Ivermectin was able to inhibit SARS-CoV-2 replication in monkey kidney cell culture [4]. While its empirical use grew in Latin America, more than 45 trials investigating ivermectin in COVID-19 are ongoing all over the world.

Aim of this research letter was to understand if the administration of ivermectin in COVID-19 patients can reduce mortality.

We performed a meta-analysis of randomized clinical trials (RCTs) investigating the impact of ivermectin on mortality in COVID-19. All randomized studies reporting mortality data – comprising both published and preprints manuscripts – were included in our analysis. Two investigators independently assessed the compliance to selection criteria, selected the studies for the final analysis, and extracted data with divergences finally resolved by consensus. We followed methods previously described in details [5]. Briefly, we used Review Manager (RevMan, Version 5.4. The Cochrane Collaboration, 2020), Mantel–Haenszel test and a fixed-effects model. The strength of the association between ivermectin administration and mortality was measured calculating the odds ratio. We focused on survival, as reported at the longest follow up available.

A total of 1323 patients were randomized in 7 RCTs performed in 6 countries. Four trials were multicentric. Ivermectin treatment resulted in a lower mortality when compared to placebo: 14/703 (2%) vs 57/620 (9%), \( P < 0.01, \) odds ratio 0.19 (0.10, 0.34), \( I^2 = 13\% \) (Fig. 1). The funnel plot was symmetrical at visual inspection. Findings were confirmed at the Influence analysis (removing one study at time).

All the mentioned RCTs included only hospitalized patients. Four trials were placebo-controlled. Ivermectin doses ranged between 12-24 mg for an average 60 kilograms subject. Duration of treatment ranged between 1 and 5 days, as reported in Table 1.

In the present meta-analysis of RCTs, administration of ivermectin reduced mortality among patients hospitalized for COVID-19. A possible rationale for these findings, other than a direct activity of ivermectin against SARS-CoV-2, [3] may involve Strongyloides hyperinfection, an uncommon complication of dexamethasone administration, [6] which is overprescribed worldwide in COVID-19 patients.

Ivermectin for the treatment of COVID-19 followed the opposite pathway of hydroxychloroquine: use of hydroxychloroquine was supported at first by medical agencies worldwide, and later proven ineffective by several RCTs including the RECOVERY Trial [1]. On the contrary, ivermectin was mostly neglected so far and only used in a few countries; nevertheless, scientific community is progressively building a body of randomized evidence which points in favor of its use. After the ruinous experience during the first wave, however, physicians became more “skeptical” and less prone to use...
Figure 1. Forest plot of studies reporting mortality on ivermectin versus control in COVID-19.

Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Author*</th>
<th>Country</th>
<th>Disease severity</th>
<th>Daily dose</th>
<th>Ivermectin treatment duration</th>
<th>Participating centres</th>
<th>Available at</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed S</td>
<td>Bangladesh</td>
<td>Mild</td>
<td>12 mg</td>
<td>5 days</td>
<td>1</td>
<td>Int J Infect Dis. 2020;103:214-216</td>
</tr>
<tr>
<td>Elgazzar A</td>
<td>Egypt</td>
<td>Mild to severe</td>
<td>400 mcg/kg (max 24 mg)</td>
<td>4 days</td>
<td>2</td>
<td>Preprint-doi.org/10.21203/rs.3.rs-100956/v1</td>
</tr>
<tr>
<td>Hashim HA</td>
<td>Iraq</td>
<td>Mild to severe</td>
<td>200 mcg/kg</td>
<td>2-3 days</td>
<td>2</td>
<td>Preprint-doi.org/10.1101/2020.10.26.20219345</td>
</tr>
<tr>
<td>Mahmud R</td>
<td>Bangladesh</td>
<td>Mild to moderate</td>
<td>12 mg</td>
<td>5 days</td>
<td>1</td>
<td>Clinicaltrials.gov - NCT04523831</td>
</tr>
<tr>
<td>Niaee MS</td>
<td>Iran</td>
<td>Mild to severe</td>
<td>200-400 mcg/kg</td>
<td>1-5 days</td>
<td>5</td>
<td>Preprint-doi.org/10.21203/rs.3.rs-109670/v1</td>
</tr>
<tr>
<td>Okumus N</td>
<td>Turkey</td>
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<td>200 mcg/kg</td>
<td>5 days</td>
<td>4</td>
<td>Clinicaltrials.gov-NCT04646109</td>
</tr>
<tr>
<td>Ravikirti RR</td>
<td>India</td>
<td>Mild to moderate</td>
<td>12 mg</td>
<td>2 days</td>
<td>1</td>
<td>Preprint-doi.org/10.1101/2021.01.05.21249310</td>
</tr>
</tbody>
</table>

* For data available at Clinicaltrials.gov, Responsible Party was indicated as author.

The authors declare they have no conflicts of interests.

References


