Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients

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Abstract

Ivermectin has recently shown efficacy against SARS-CoV-2 in-vitro. We retrospectively reviewed severe COVID-19 patients receiving standard doses of ivermectin and we compared clinical and microbiological outcomes with a similar group of patients not receiving ivermectin. No differences were found between groups. We recommend the evaluation of high-doses of ivermectin in randomized trials against SARS-CoV-2.

Introduction

Several months after the beginning of the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), few therapeutic agents have proven their efficacy in human clinical trials [1, 2]. Several repurposed drugs with antiviral effect have been tested outside the scope of the initial approved medical use, such as lopinavir/ritonavir, hydroxychloroquine or azithromycin [3]. Researchers in Australia have shown ivermectin (IVM) to be active against SARS-CoV-2 in cell cultures by drastically reducing viral RNA at 48h [4]. The concentrations tested in these in-vitro assays are equivalent to more than 50-fold the normal $C_{\text{max}}$ achieved with a standard single dose of IVM 200 $\mu$g/kg, raising concerns about the effective dose of IVM for treating SARS-CoV-2 infection in humans and its tolerability [5]. The hypothesis of our study was that standard doses of IVM to treat strongyloidiasis (200$\mu$g/kg single dose) were not efficacious to treat patients with SARS-CoV-2 pneumonia. We evaluated clinical and microbiological outcomes of 13 patients with confirmed SARS-CoV-2 severe infection receiving standard doses of IVM in comparison with a similar group of patients not receiving IVM.

Methods

For this retrospective study, we identified hospitalized patients diagnosed with SARS-CoV-2 infection receiving IVM between March 10th and 30th 2020 in Hospital Clinic in Barcelona, Spain. Patients from countries endemic for Strongyloides stercoralis receiving immunosuppressant drugs such as corticosteroids or tocilizumab for COVID-19 were empirically treated with IVM 200$\mu$g/kg, single dose, following standard hospital procedures based on international guidelines.
recommendations (IVM group) [6]. Once identified, an equal number of COVID-19 patients with similar baseline characteristics and immunosuppressive treatment but not receiving IVM (non-IVM group) were selected as a comparator group.

Patients diagnosed with SARS-CoV-2 infection were admitted and quarantined in the ward during the study period. Diagnosis of COVID-19 was performed with IgM and IgG antibodies rapid diagnostic test (VivaDiag™ COVID-19 IgM/IgG Rapid Test) and/or polymerase chain reaction (PCR) assay in nasopharyngeal swab samples. A full biochemistry and haematology profile including C-reactive protein, D-dimer and ferritin and a chest X-ray was performed to all patients at hospitalization. Nasopharyngeal swab was repeated for standard control 6–12 days after the beginning of the antiviral treatment.

Data were obtained as part of standard care, to create a fully anonymized database. Categorical variables were expressed as absolute frequency and percentage and compared with chi-square test or Fisher’s exact test. Continuous variables were expressed as median and inter-quartile range (IQR) and compared with Mann-Whitney-Wilcoxon test. The statistical analysis was carried out using Stata 15 (StataCorp.2017).

This study was approved by the Ethics Committee of Hospital Clinic of Barcelona (HCB/2020/0475), who waived the requirement for informed consent, due to the retrospective nature of the study.

**Results**

During the study period a total of 13 severe COVID-19 patients receiving immunosuppressant therapy were treated with IVM at 200 μg/kg, single dose. In the IVM group, 5 (38.5%) patients were treated with tocilizumab, 3 (23.1%) with high doses of steroids, 3 (23.1%) with both tocilizumab and steroids, and 2 (15.3%) with tocilizumab, steroids and anakinra. Five patients required admission to an ICU. IVM was administered a median of 12 (IQR 8–18) days after the initiation of symptoms. In the non-IVM group, six (46.2%) patients were treated with tocilizumab and steroids, 2 (15.3%) with anakinra and steroids, 2 (15.3%) with tocilizumab, 2 (15.3%) with high doses of steroids and 1 with siltuximab.

Following hospital protocols at that moment, all patients received hydroxychloroquine and azithromycin. All patients in the control group and 12 up to the 13 patients in the IVM group were also treated with lopinavir/ritonavir. One patient in the IVM group did not receive lopinavir/ritonavir due to diarrhea. Two patients in the IVM group and one in the control group were also treated with remdesivir and one patient in the IVM group and two in the control group received beta-interferon. Comparison of baseline characteristics, clinical presentation, treatment and outcomes between COVID-19 patients treated with and without IVM is shown in Table 1. Although no significant differences in baseline characteristics were observed

| Baseline characteristics | No IVM (n = 13) | IVM (n = 13) | p-value |
|--------------------------|----------------|-------------|---------|
| Sex (female)             | 5 (38.5)       | 4 (30.8)    | 1.000   |
| Age                      | 54 [48–58]     | 43 [41–49]  | 0.117   |
| Origin                   |                |             | 0.006   |
| • Europe                 | 7 (53.8)       | 0 (0)       |         |
| • South-America          | 5 (38.5)       | 10 (76.9)   |         |
| • Asia                   | 1 (7.7)        | 3 (23.1)    |         |

(Continued)
Table 1. (Continued)

|                        | No IVM (n = 13) | IVM (n = 13) | p-value |
|------------------------|----------------|--------------|---------|
| **Comorbidities**      |                |              |         |
| Cough                  | 10 (76.9)      | 11 (84.6)    | 0.001   |
| Diapedema             | 11 (84.6)      | 8 (61.5)     | 0.012   |
| Fever                  | 13 (100)       | 13 (100)     | –       |
| Abdominal symptoms     | 6 (46.1)       | 4 (30.8)     | 0.672   |
| Days before admition   | 7 [6–9]        | 7 [5–9]      | 0.172   |
| **Radiological pattern** |              |              |        |
| • Interstitial pattern | 2 (15.4)       | 5 (38.5)     | 0.013   |
| • Patchy infiltrates   | 5 (38.5)       | 6 (46.1)     | –       |
| • Mixed pattern        | 6 (46.1)       | 2 (15.4)     | –       |
| CRP                    | 12.05 [6.48–21.72] | 14.22 [8.37–20.68] | 0.644   |
| LDH                    | 426 [333–501]  | 383 [301–418] | 0.317   |
| D-dimer                | 500 [400–800]  | 500 [400–1000]| 0.836   |
| Ferritin               | 1243 [654.25–2259.75] | 1101 [477.5–1434.5] | 0.751   |
| Lymphocytes            | 800 [500–900]  | 900 [500–1200]| 0.279   |
| NLR                    | 11.2 [6.9–13.4] | 4.9 [2.5–10.0] | 0.016   |
| Eosinphils             | 0 [0–200]      | –            | –       |
| **Pharmacological treatment** |             |              |        |
| Antiviral agents       | 13 (100)       | 12 (92.3)    | 0.753   |
| IS treatment           | 13 (100)       | 13 (100)     | –       |
| Steroids               | 10 (76.9)      | 8 (61.5)     | 0.018   |
| Days until steroids treatment | 9 [8–13] | 8.5 [6.75–10.75] | 0.512   |
| **Anti-IL treatment**  |                |              |         |
| • Anti IL-6 (tocilizumab, siltuximab) | 9 (69.2) | 10 (76.9) | 0.001   |
| • Anti IL-1 (anakinra) | 2 (15.4)       | 2 (15.4)     | 1.000   |
| Days until anti-IL treatment | 9 [7.5–13.5] | 9.5 [7.5–13.5] | 0.671   |
| **Supportive treatment** |              |              |         |
| Maximum FiO2           | 60 [23–60]     | 40 [23–60]   | 0.529   |
| NIV/HFNC               | 4 (30.8)       | 2 (15.4)     | 0.645   |
| ETI + MV               | 5 (38.5)       | 3 (23.1)     | 0.671   |
| Admission to ICU       | 9 (69.2)       | 5 (38.5)     | 0.238   |
| **Outcomes**           |                |              |         |
| Other severe adverse events | 4 (30.8) | 3 (23.1) | 1.000   |
| Positive PCR 3–5 days after IVM² | 4 (30.8) | 5 (38.5) | 1.000   |
| Days to naso-pharyngeal swab³ | 19 [15–21] | 15 [12–21] | 0.382   |
| CRP³                   | 0.4 [0.4–2.57] | 0.4 [0.5–2.2] | 0.368   |
| LDH³                   | 300 [277–374]  | 266 [246.7–327.2] | 0.097   |
| D-dimer³               | 1600 [1300–4300] | 850 [600–4275] | 0.351   |
| Ferritin³              | 1263 [771–1785.5] | 816 [414–1031] | 0.172   |
| Lymphocytes³           | 1100 [700–1300] | 1400 [875–1800] | 0.369   |
| NLR³                   | 8.38 [3.55–13.75] | 3.22 [1.92–9.35] | 0.201   |
| Eosinphils³           | 100 [0–100]    | 100 [0–125]  | 0.821   |
| Improvement 8 days after IVM³ | 10 (76.9) | 9 (69.2) | 0.001   |
| Localization 8 days after IVM³ | 100 [0–100] | 100 [0–125] | 0.821   |
| • Discharged           | 6 (46.1)       | 7 (53.8)     | 1.000   |
| • Hospitalized         | 4 (30.8)       | 4 (30.8)     | –       |

(Continued)
between groups, a higher proportion of patients in the IVM group required admission to an intensive care unit (ICU) (69% vs 38% in the non-IVM group) (Table 1).

No relevant differences in microbiological or clinical outcomes were observed between groups. SARS-CoV-2 PCR from nasopharyngeal swabs performed between 3 and 5 days after ivermectin treatment resulted positive in 5 out of 13 patients in the IVM group (38.5%), and 4/13 in the non-IVM group (30.8%, \(p\text{-value} > 0.999\)). A remarkable clinical improvement was observed in 9 (69.2%) participants receiving IVM and in 10 (76.9%) of the non-IVM group, with no differences between groups (\(p\text{-value} > 0.999\)), eight to eleven days after IVM treatment (or equivalent time in the non-IVM group).

**Discussion**

In our retrospective study, a single dose of 200 \(\mu g/kg\) of IVM did not improve clinical and microbiological outcomes of patients with severe COVID-19, compared to a similar group of patients not receiving IVM. Although IVM may lack of in-vivo effect against SARS-CoV2, in our study the drug was given at late stages of the infection (median 12 days after the beginning of symptoms) and, most importantly, all patients received a standard (200 \(\mu g/kg\)) single dose of the drug, which could be below the IC50 values \([4, 5]\) for SARS-CoV-2 infection.

In the last years, high doses of IVM have been evaluated for the treatment of soil-transmitted helminths \([7–10]\) and as a new vector control tool to reduce malaria transmission in malaria endemic areas \([11]\). Recent studies have evaluated doses up to 800 \(\mu g/kg\), given in single dose or three consecutive days \([9, 11, 12]\), showing a good safety profile both in adult and paediatric populations. Subjective ocular problems such as transitory blurred vision appeared, but no severe adverse events were reported with these high doses \([11, 12]\).

These findings, including a recent meta-analysis of the safety of high doses of ivermectin \([7]\), add evidence of the safety of IVM at doses up to 800 \(\mu g/kg\), which has a safety profile comparable to lower doses of 200 or 400 \(\mu g/kg\). Moreover, the results of the meta-analysis do not suggest an increased number of adverse events with increasing doses of IVM. The maximum doses of IVM given to study participants have been published in a study with a limited number of participants, in which doses up to 2000 \(\mu g/kg\) were received by 12 participants, showing a similar rate of adverse events than those receiving placebo \([13]\). However, the antiviral efficacy of these high doses of IVM should be still evaluated in clinical studies, since some authors have

|       | No IVM (n = 13) | IVM (n = 13) | \(p\text{-value}\) |
|-------|----------------|-------------|------------------|
| ICU   | 3 (23.1)       | 2 (15.4)    | \(p\text{-value}\) |

\(N\) (% or median [p25-p75]).

\((a)\) \(p\) values from Fisher’s exact test.

\((b)\) Days between symptoms initiation and admission to hospital.

\((c)\) Nasopharyngeal swab performed between 3 and 5 days after ivermectin treatment (or equivalent time in the non-IVM group).

\((d)\) 8–11 days after IVM treatment (or equivalent time in the non-IVM group).

\((e)\) Other adverse events in patients not receiving IVM: organizing pneumonia (1), acute kidney injury requiring hemodialysis (1), pancreatitis (1) and catheter bacteremia (1). Other adverse events in patients receiving IVM: organizing pneumonia (1), pulmonary embolism (1) and Strongyloides infection (1).

CRP: C-reactive protein. ETI+MV: endotracheal intubation + mechanical ventilation. FiO2: Fraction of inspired oxygen. ICU: intensive care unit. IS: immunosuppressant treatment. IL: interleukin. IVM: ivermectin. LDH: lactate dehydrogenase. NIV/HFNC: Non-invasive ventilation / high flow nasal cannula. NLR: Neutrophil-to-lymphocyte ratio. PCR: polymerase chain reaction.

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recently suggested that in vitro inhibitory concentrations of 5μmol/L (those needed for a total eradication of SARS-CoV-2 in in vitro studies) would not be attainable even using high doses of ivermectin (2000ug/kg) [4, 14].

The study has some limitations. Given the retrospective design of the study, possible confounding factors could bias the results of the study, which was addressed by a careful selection of a matched control group. Potential differences between groups might not be detected due to the small sample size and the lack of a quantitative evaluation of the viral response. Activity of some antiviral treatments received cannot be excluded. However, no differences between both study groups should be expected given that antivirial regimens between groups were similar. Another limitation of the study was that disease status at baseline could not be confirmed by PCR in all patients. Nevertheless, all patients presented with symptoms, signs, blood test alterations and radiological findings compatible with COVID-19. Median of time between symptoms onset and hospital admission for patients who were not diagnosed by PCR was 6 days (range 2–9), which was not different to the median of time of those patients diagnosed by PCR.

Finally, in light of the presented results, it is unlikely that the widespread use of IVM at standard doses may have an impact in decreasing the mobility related with COVID-19. We suggest the evaluation of high-doses of IVM in randomized clinical trials to test the efficacy of IVM in COVID-19 patients, especially in early stages of the disease.

Author Contributions

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References

1. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19—Preliminary Report. New Engl J Med. 2020. https://doi.org/10.1056/NEJMoa2021436 PMID: 32678530

2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—preliminary report. New Engl J Med. 2020. May 22. https://doi.org/10.1056/NEJMoa2007764 PMID: 32445440

3. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020. https://doi.org/10.1001/jama.2020.6019 PMID: 32282022

4. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020.104787. https://doi.org/10.1016/j.antiviral.2020.104787 PMID: 32251768

5. Chaccour C, Hamman F, Ramón-García S, Rabinovich NR. Ivermectin and Novel Coronavirus Disease (COVID-19): Keeping Rigor in Times of Urgency. Am J Trop Med Hyg. 2020,00(0):1–2.

6. Requena-Méndez A, Buonfrate D, Gomez-Junyent J, Zammarchi L, Bisoffi Z, Muñoz J. Evidence-Based Guidelines for Screening and Management of Strongyloidiasis in Non-Endemic Countries. Am J Trop Med Hyg. 2017; 97(3):645–652. https://doi.org/10.4269/ajtmh.16-0923 PMID: 28749768
7. Navarro M, Camprubí D, Requena-Méndez A, et al. Safety of high-dose ivermectin: a systematic review and meta-analysis. J Antimicrob Chemother. 2020; 75(4):827–834. https://doi.org/10.1093/jac/dkz524 PMID: 31960060

8. Muñoz J, Ballester RM, Antonijoan RM, et al. Safety and pharmacokinetic profile of fixed-dose ivermectin with an innovative 18mg tablet in healthy adult volunteers. PLoS Negl Trop Dis. 2018; 12(1): e0006020. https://doi.org/10.1371/journal.pntd.0006020 PMID: 29346388

9. Wimmersberger D, Coulibaly JT, Schulz JD, et al. Efficacy and safety of ivermectin against Trichuris tri-chiura in preschool-aged and school-aged children: a randomized controlled dose-finding trial. Clin Infect Dis 2018; 67: 1247–55. https://doi.org/10.1093/cid/ciy246 PMID: 29617737

10. Buonfrate D, Salas-Coronas J, Muñoz J, et al. Multiple-dose versus single-dose ivermectin for Strongyloides stercoralis infection (Strong Treat 1 to 4): a multicentre, open-label, phase 3, randomised controlled superiority trial. Lancet Infect Dis. 2019; 19(11):1181–1190. https://doi.org/10.1016/S1473-3099(19)30289-0 PMID: 31558376

11. Smit MR, Ochomo EO, Aljajyussi G, et al. Human Direct Skin Feeding Versus Membrane Feeding to Assess the Mosquitocidal Efficacy of High-Dose Ivermectin (IVERMAL Trial). Clin Infect Dis. 2019; 69 (7):1112–1119. https://doi.org/10.1093/cid/ciy1063 PMID: 30590537

12. Kamgno J, Gardon J, Gardon-Wendel N, et al. Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. Trans R Soc Trop Med Hyg 2004; 98: 496–504. https://doi.org/10.1016/j.trstmh.2003.10.018 PMID: 15186939

13. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol 2002; 42: 1122–33. https://doi.org/10.1177/009127002401382731 PMID: 12362927

14. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from a pharmacokinetic point of view; antiviral levels are not likely attainable with known dosing regimens. Biotechnology & Biotechnological Equipment, 34:1, 469–474, https://doi.org/10.1080/13102818.2020.1775118