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Editorial

Why Are We Still Talking about Ivermectin? Editorial Note on Stone et al. Changes in SpO2 on Room Air for 34 Severe COVID-19 Patients after Ivermectin-Based Combination Treatment

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In this issue of *Biologics*, we publish an article describing a surprising clinical effect of the anti-helminthic drug ivermectin on patients with COVID-19 [1]. The authors report a dramatic increase in the arterial oxygen saturation (SpO2) following the administration of ivermectin. All patients were maintained on room air. The result was clear and highly significant. From the results reported in this study, we can only speculate as to the mechanism or the clinical effect.

The general consensus based on the outcomes of well-designed clinical trials, has established that ivermectin does not affect the outcome of COVID-19, whether administered early in the infection or after hospitalization, and its use is not recommended [2–7]. We emphasize that the results published here do not constitute a recommendation for the use of ivermectin. However, persistent reports have also emerged pointing to the clinical efficacy of ivermectin in COVID-19, particularly in countries where a high burden of parasitemia may also exist [8–13]. A recently reported controlled trial from Nigeria also showed a rapid rise in SpO2 following ivermectin administration in COVID-19, and ivermectin treatment was also associated with a better outcome [12] The current study was performed under field conditions in Zimbabwe, and has several flaws that include having no control group nor randomization, no follow-up regarding outcomes, and the coadministration of doxycycline and zinc. Thus, we are unable to determine if the treatment had any effect on the course and outcome of COVID-19 in these patients, nor does it give us any indication of the mechanism. The combination of medications makes it impossible to attribute the observed effect on SpO2 to ivermectin, as opposed to either of the other components.

Despite the flaws in the study, the observation of a marked increase in SpO2 within 12 h of ivermectin treatment cannot be ignored, especially since similar results have been reported elsewhere. What mechanism can possibly account for these findings? A direct antiviral effect cannot be ruled out. Caly et al. report a direct inhibition of SARS-CoV-2 replication at concentrations of 1–10 μM [14]. However, given the lack of efficacy of ivermectin in lowering viral loads in well-monitored trials, this seems unlikely. In considering the populations under study in both this and the Nigerian report, we must note that these were patients who likely carried a burden of helminthic and other microbial parasites. Reports of the clinical efficacy of ivermectin in COVID-19 have most frequently arisen in similar patient settings. Is it possible that the anti-parasitic effect of ivermectin is responsible for the observed increase in SpO2? This could be a direct effect, caused by eliminating the physiologic burden that the parasitic infestation places upon the host. Or it may be an indirect effect of treating the parasitic infection, causing a physiologic response akin to the immune reconstitution inflammatory (IRIS) syndrome or the Jarisch-Herxheimer reaction [15,16]. Such responses generally have negative, although transient, effects. However, it is also possible that an adrenergic response could result in bronchodilation and improved SpO2.

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Citation: Pincus, S.H. Why Are We Still Talking about Ivermectin? Editorial Note on Stone et al. Changes in SpO2 on Room Air for 34 Severe COVID-19 Patients after Ivermectin-Based Combination Treatment. *Biologics* **2022**, *2*, 211–212. https://doi.org/10.3390/biologics2030016

Received: 25 August 2022
Accepted: 27 August 2022
Published: 31 August 2022

In support of this notion is the elevated heart rate illustrated in Figure 4 of the publication. These of course are only speculations, but point to testable hypotheses.

The publication of this article should in no way be taken as an endorsement of the clinical use of ivermectin. Rather we hope to encourage further research into the mechanism(s) underlying the surprising observations of this group [1] and others [12], that ivermectin induces a rapid and substantial increase in SpO2 in COVID-19 patients on room air, and to determine if treating parasitic infections with ivermectin may improve the outcome in COVID-19.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Stone, J.C.; Nadarkwa, P.; Scheim, D.E.; Dancis, B.M.; Dancis, J.; Gill, M.G.; Aldous, C. Changes in SpO2 on Room Air for 34 Severe COVID-19 Patients after Ivermectin-based Combination Treatment: 62% Normalization within 24 hours. *Biologics* **2022**, *2*, 15. [CrossRef]
2. Bramante, C.T.; Huling, J.D.; Tignanelli, C.J.; Buse, J.B.; Liebovitz, D.M.; Nicklas, J.M.; Cohen, K.; Puskarich, M.A.; Belani, H.K.; Proper, J.L.; et al. Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for COVID-19. *N. Engl. J. Med.* **2022**, *387*, 599–610. [CrossRef]
3. Reis, G.; Silva, E.; Silva, D.C.M.; Thabane, L.; Milagres, A.C.; Ferreira, T.S.; Dos Santos, C.V.Q.; Campos, V.H.S.; Nogueira, A.M.R.; de Almeida, A.; et al. Effect of Early Treatment with Ivermectin among Patients with COVID-19. *N. Engl. J. Med.* **2022**, *386*, 1721–1731. [CrossRef] [PubMed]
4. World Health Organization. Therapeutics and COVID-19: Living Guideline. Available online: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.4 (accessed on 18 August 2022).
5. Abdool Karim, S.S.; Devnarain, N. Time to Stop Using Ineffective COVID-19 Drugs. *N. Engl. J. Med.* **2022**, *387*, 654–655. [CrossRef]
6. Lim, S.C.L.; Hor, C.P.; Tay, K.H.; Mat Jelani, A.; Tan, W.H.; Ker, H.B.; Chow, T.S.; Zaid, M.; Cheah, W.K.; Lim, H.H.; et al. Efficacy of Ivermectin Treatment on Disease Progression among Adults with Mild to Moderate COVID-19 and Comorbidities: The I-TECH Randomized Clinical Trial. *JAMA Intern. Med.* **2022**, *182*, 426–435. [CrossRef] [PubMed]
7. Shafiee, A.; Teymouri Athar, M.M.; Kohandel Gargari, O.; Jafarabady, K.; Siahvoshi, S.; Mozhgani, S.H. Ivermectin under scrutiny: A systematic review and meta-analysis of efficacy and possible sources of controversies in COVID-19 patients. *Virol. J.* **2022**, *19*, 102. [CrossRef] [PubMed]
8. Okumus, N.; Demirturk, N.; Cetinkaya, R.A.; Guner, R.; Avci, I.Y.; Orhan, S.; Konya, P.; Saylan, B.; Karalezli, A.; Yamanel, L.; et al. Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. *BMC Infect. Dis.* **2021**, *21*, 411. [CrossRef] [PubMed]
9. Mahmud, R.; Rahman, M.M.; Alam, I.; Ahmed, K.G.U.; Kabir, A.; Sayeed, S.; Rassel, M.A.; Monayem, F.B.; Islam, M.S.; Islam, M.M.; et al. Ivermectin in combination with doxycycline for treating COVID-19 symptoms: A randomized trial. *J. Int. Med. Res.* **2021**, *49*, 3000605211013550. [CrossRef] [PubMed]
10. Babalola, O.E.; Ndanusa, Y.A.; Ajayi, A.A.; Ogedengbe, J.O.; Thairu, Y.; Omede, O. A Randomized Controlled Trial of Ivermectin Monotherapy versus Hydroxychloroquine, Ivermectin, and Azithromycin Combination Therapy in COVID-19 Patients in Nigeria. *J. Infect. Dis. Epidemiol.* **2021**, *7*. [CrossRef]
11. Omede, O.; Ogedengbe, J.O.; Ndanusa, Y.; Ajayi, A.A.; Babalola, O.E.; Thairu, Y. A Comparison of Ivermectin and Non Ivermectin Based Regimen for COVID-19 in Abuja: Effects on Virus Clearance, Days-to-discharge and Mortality. *J. Phar. Res. Int.* **2022**, 1–19. [CrossRef]
12. Babalola, O.E.; Ajayi, A.A.; Thairu, Y.; Ndanusa, Y.A.; Ogedengbe, J.O.; Omede, O. Ivermectin is Associated with Increase in SpO2 in Hypoxemic SARS-CoV-2 Patients: Pharmacodynamic Profile and Correlates. *J. Clin. Chem. Lab. Med.* **2022**, *5*, 1–9. [CrossRef]
13. Ahmed, S.; Karim, M.M.; Ross, A.G.; Hossain, M.S.; Clemens, J.D.; Sumiya, M.K.; Phru, C.S.; Rahman, M.; Zaman, K.; Somani, J.; et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int. J. Infect. Dis.* **2021**, *103*, 214–216. [CrossRef] [PubMed]
14. Caly, L.; Druce, J.D.; Catton, M.G.; Jans, D.A.; Wagstaff, K.M. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir. Res.* **2020**, *178*, 104787. [CrossRef] [PubMed]
15. French, M.A. HIV/AIDS: Immune reconstitution inflammatory syndrome: A reappraisal. *Clin. Infect. Dis.* **2009**, *48*, 101–107. [CrossRef] [PubMed]
16. Butler, T. The Jarisch-Herxheimer Reaction after Antibiotic Treatment of Spirochetal Infections: A Review of Recent Cases and Our Understanding of Pathogenesis. *Am. J. Trop. Med. Hyg.* **2017**, *96*, 46–52. [CrossRef] [PubMed]