Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Correspondence

Ivermectin for Coronavirus Disease 2019: Yet to Be Well Evaluated Before Clinical Use

To the Editor,

We read with great interest the recent article by Shahbaznejad et al[1] regarding the effectiveness of ivermectin for coronavirus disease 2019 (COVID-19). In this randomized, double-blind clinical trial, 35 patients were treated with ivermectin, and 34 patients were included as controls. The authors concluded that a single ivermectin dose successfully improved major clinical COVID-19 manifestations, such as dyspnea, cough, and lymphopenia, without apparent adverse effects, and shortened the hospitalization length of stay. However, we found several points regarding the study design that need to be addressed.

First, the age of the study participants is a concerning issue. The mean (SD) ages of patients in the ivermectin and control groups were 47.63 (22.20) years and 45.18 (23.20) years, respectively, with no significant differences between the 2 groups. Considering the small number of patients and the wide age range, the ages would not be normally distributed. Thus, the Mann-Whitney *U* test, not the *t* test, should have been applied. Alternatively, the data should have been proved to be normally distributed. Because the age of the patients ranged from 5 to 86 years, there was a large variation in the participant populations. In general, therapeutic effectiveness of any drugs is different among children, adults, and older individuals. Especially for COVID-19, it is well known that age greatly affects the differences of clinical presentations and prognoses; children are mostly asymptomatic, whereas middle-aged and older patients possibly manifest more symptoms with increased risk of mortality.[2] Therefore, evaluating clinical data without age stratification can cause various biases, which should be avoided.

Second, ivermectin administration timing should also be noted. As the authors stated, ivermectin potentially inhibits the proliferation of severe acute respiratory syndrome coronavirus 2,[3] reducing the viral load. Thus, the drug should be administered as early as possible.[4] However, in the study, the mean duration of symptoms before administration appeared to be approximately 6 days in both groups, which may be rather late for ivermectin administration. Moreover, the dates of treatment from disease onset varied greatly in this study, ranging from 1 to 15 days. Thus, the patients for whom ivermectin therapy was initiated in the late phase of the disease would not benefit from the treatment.

Third, a definite COVID-19 diagnosis should usually be based on the positive result of reverse transcription–polymerase chain reaction testing. However, only 25 of 69 patients (36.2%) underwent such examination, and 9 patients with negative reverse transcription–polymerase chain reaction test results seemed to have been included in this study. On the basis of this, we are skeptical about the inclusion criteria and patient backgrounds of the study.

Furthermore, we wondered how the sample size of the study was calculated before starting this trial. Too much univariate analysis can lead to multiplicity concerns, and to avoid this, the authors should have recruited more patients such that multivariate analysis could be applied. In particular, the patients received various medications (lopinavir/ritonavir, chloroquine, oseltamivir, ribavirin, and antibiotics) for COVID-19 treatment, which should have been statistically adjusted.

In light of the aforementioned concerns, in our opinion, the article does not adequately address the efficacy of ivermectin in patients with COVID-19. Ivermectin is an inexpensive agent that can save lives in developing countries; however, a well-designed clinical trial is warranted before its clinical application.

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REFERENCES

1. Shahbaznejad L, Davoudi A, Eslami G, et al. Effects of Ivermectin In Patients With COVID-19: a multicenter, double-blind, randomized, controlled clinical trial. *Clin Ther*. 2021.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) Outbreak in China. *JAMA*. 2020;323:1239–1242.
3. 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;178.
4. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther*. 2020;14:58–60.

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