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Correspondence

Response to Letter Regarding Article, "Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-Blind, Randomized, Controlled Clinical Trial"

Dear Dr. Jhaveri

We thank Drs Otsuka and Hagiya for expanding our point regarding the effect of ivermectin on coronavirus disease 2019 (COVID-19) from our recent multicenter, double-blind randomized controlled trial in their letter entitled, "Ivermectin for Coronavirus Disease 2019: Yet to Be Well Evaluated Before Clinical Use.[1] The authors mainly offer the following points.

1. "Considering the small number of patients and the wide age range, the ages would not be normally distributed. Thus, the Mann-Whitney *U* test and not the *t* test should have been applied. Alternatively, the data distribution should have been normal. 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. Therefore, evaluating clinical data without age stratification can cause various biases, which should be avoided."

2. Ivermectin administration timing should also be noted. As the authors stated, ivermectin potentially inhibits the nuclear transport of severe acute respiratory syndrome coronavirus 2,[3] suppressing viral replication and reducing the viral load. Thus, the drug should be administered as early as possible. 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."

3. "A definite COVID-19 diagnosis should usually be based on the positive result of reverse transcription–polymerase chain reaction testing."

4. "Furthermore, we wondered how the sample size of the study was calculated before starting this trial. … "In particular, the patients received various medications (lopinavir/ritonavir, chloroquine, oseltamivir, ribavirin, and antibiotics) for COVID-19 treatment, which should have been statistically adjusted."

To the first point, the results of our analysis indicated that the age distribution was normal ($P > 0.05$). Therefore, performing the *t* test rather than the Mann-Whitney *U* test was an appropriate choice. The result of the normality test are given in the Table 1.

To the second point, ivermectin was prescribed for the patients once they were admitted to the hospital. Because the peak viral load of patients with Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus infections occurs at approximately 7 to 10 days after symptom onset,[2] severe acute respiratory syndrome coronavirus 2 appears to continue replicating nearly 3 weeks after clinical disease onset.[2,3] In most patients in our study, admission occurred before the first week of symptoms; therefore, ivermectin was administered during the replication period. Accordingly, the patients would benefit from the treatment in this period.

To the third point, the diagnostic criteria for COVID-19 in this study included any of the following: (1) positive reverse transcription–polymerase chain reaction (RT-PCR) result for COVID-19, (2) clinical concerns of COVID-19 with a history of contact with a person with COVID-19 patient, or (3) abnormalities in chest computed tomography compatible with COVID-19 (ground-glass opacity, halo sign, reversed halo sign, and patchy infiltration). These criteria were based on the report of Bernheim et al.[4] Those patients who did not undergo RT-PCR testing or

had negative RT-PCR results were probable COVID-19 cases based on other diagnostic criteria and spiral chest computed tomography and were thus included in the study.

To address the fourth point, at the time of performing this clinical trial, no published article was available to the investigators, and this study was one of the first clinical trials conducted assessing the use of ivermectin in patients with COVID-19. In the absence of published information, we calculated the sample size based on the following formula and the unpublished study by Gorial et al[5]:

$$n = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 (s_1^2 + s_2^2)}{(\mu_1 - \mu_2)^2} = 16 \approx 20 \text{ cases in each group and we increased the size to 35 cases in each group.}$$

$\alpha = 0.05 \ \mu_1 = 6.72 \ S_1 = 2.75$

Power $(1-\beta) = 0.95 \ \mu_2 = 13.22 \ S_2 = 5.90$

At this time, we are performing a larger double-blind placebo-controlled clinical trial on 1000 cases admitted with COVID-19.

Regarding the last comment, although both groups received different medications, they all followed a similar treatment protocol based on national COVID-19 committee guidelines in Iran at the time. Therefore, they were considered to be statistically adjusted. Finally, although the evidence generated from our preliminary study suggested efficacy of ivermectin in patients with COVID-19, as we stated in the original article, "Further studies with larger sample sizes are warranted."

DISCLOSURES

Leila Shahbaznejad, MD
Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

Alireza Davoudi, MD
Antimicrobial Resistance Research Center, Department of Infectious Diseases, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran

Gohar Eslami, PharmD
Department of Clinical Pharmacy, Faculty of Pharmacy, Cardiovascular Research Center, Mazandaran University of Medical Sciences, Sari, Iran

John S. Markowitz, PharmD
Department of Pharmacotherapy and Translational Research, Center for Pharmacogenomics and Precision Medicine, University of Florida, Gainesville, Florida

Table 1. Tests of normality.

Group	Kolmogorov-Smirnov Test[*]			Shapiro-Wilk Test		
	Statistic	df	P	Statistic	df	P
Ivermectin	0.109	34	0.200[†]	0.952	34	0.144
Control	0.089	33	0.200[†]	0.964	33	0.338

[*] Lilliefors significance correction.
[†] This is a lower bound of the true significance.

Mohammad Reza Navaeifar, MD, Fatemeh Hosseinzadeh, MSc
Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of
Medical Sciences, Sari, Iran

Faeze Sadat Movahedi, Sc
Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran

Mohammad Sadegh Rezai, MD
Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of
Medical Sciences, Sari, Iran

E-mail address: drmsrezaii@yahoo.com

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