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Effects of Ivermectin in Patients With COVID-19: A Multicenter, Double-blind, Randomized, Controlled Clinical Trial

Leila Shahbaznejad, MD,[1] Alireza Davoudi, MD,[2] Gohar Eslami, PharmD,[3] John S. Markowitz, PharmD,[4] Mohammad Reza Navaeifar, MD,[1] Fatemeh Hosseinzadeh, MSc,[1] Faeze Sadat Movahedi, MSc,[5] and Mohammad Sadegh Rezai, MD[1,*]

[1]Pediatric Infectious Diseases Research Center, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran
[2]Antimicrobial Resistance Research Center, Department of Infectious Diseases, Communicable Diseases Institute, Mazandaran University of Medical Sciences, Sari, Iran
[3]Department of Clinical Pharmacy, Faculty of Pharmacy, Cardiovascular Research Center, Mazandaran University of Medical Sciences, Sari, Iran
[4]Department of Pharmacotherapy and Translational Research, Center for Pharmacogenomics and Precision Medicine, University of Florida, Gainesville, Florida
[5]Student Research Committee, Mazandaran University of Medical Sciences, Sari, Iran
*Address correspondence to: Mohammad Sadegh Rezai, MD, Pediatric Infectious Diseases Research Center, Bouali Hospital, Pasdaran Boulevard, Sari, Iran. Postal code: 4815838477.

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Abstract

Purpose

Given the coronavirus disease 2019 (COVID-19) pandemic, there is a global urgency to discover an effective treatment for patients withthis disease. This study aimed to evaluate the effects of the widely used antiparasitic drug ivermectin on outcomes in patients with COVID-19.

Methods

In this randomized, double-blind clinical trial, patients with COVID-19 admitted to 2 referral tertiary hospitals in Mazandaran, Iran, were randomly divided into 2 groups: intervention and control. In addition to standard treatment for COVID-19, the intervention group received a single weight-based

dose (0.2 mg/kg) of ivermectin; the control group received the standard of care. Demographic, clinical, laboratory, and imaging data from participants were recorded at baseline. Patients were assessed daily for symptoms and disease progression. The primary clinical outcome measures were the durations of hospital stay, fever, dyspnea, and cough; and overall clinical improvement.

Findings

Sixty-nine patients were enrolled (mean [SD] ages: ivermectin, 47.63 [22.20] years; control, 45.18 [23.11] years; $P = 0.65$). Eighteen patients (51.4%) in the ivermectin group and 18 (52.9%) in control group were male ($P = 0.90$). The mean durations of dyspnea were 2.6 (0.4) days in the ivermectin group and 3.8 (0.4) days in the control group ($P = 0.048$). Also, persistent cough lasted for 3.1 (0.4) days in the ivermectin group compared to 4.8 (0.4) days in control group (P$P = 0.019$). The mean durations of hospital stay were 7.1 (0.5) days versus 8.4 (0.6) days in the ivermectin and control groups, respectively ($P = 0.016$). Also, the frequency of lymphopenia decreased to 14.3% in the ivermectin group and did not change in the control group ($P = 0.007$).

Implications

A single dose of ivermectin was well-tolerated in symptomatic patients with COVID-19, and important clinical features of COVID-19 were improved with ivermectin use, including dyspnea, cough, and lymphopenia. Further studies with larger sample sizes, different drug dosages, dosing intervals and durations, especially in different stages of the disease, may be useful in understanding the potential clinical benefits ivermectin. Iranian Registry of Clinical Trials identifier: IRCT20111224008507N3.

Keywords: clinical trial, cough, COVID-19, dyspnea, ivermectin, lymphopenia

Introduction

Coronavirus disease 2019 (COVID-19) was declared a global pandemic following its first outbreak in Wuhan, China, in December 2019.[1, 2] As of January 2021, more than tens of millions have been infected, with >1 million reported COVID-19–related deaths worldwide.[3] Therefore, it is essential to develop effective treatment modalities for this public health emergency.[2] There are a number of ongoing clinical trials related to COVID-19, involving a wide array of medications, including interferon alfa, lopinavir/ritonavir, chloroquine and hydroxychloroquine, ribavirin, and umifenovir, among others. Effective medications such as remdesivir and dexamethasone have been introduced for COVID-19 treatment, but they have been associated with adverse events and should be applied in multiple doses over several days and during hospitalization.[4, 5]

Ivermectin has been suggested as a potential COVID-19 treatment.[6] It is a US Food and Drug Administration (FDA)-approved broad-spectrum antiparasitic agent, widely utilized in the treatment and control of several tropical diseases, including strongyloidiasis and onchocerciasis.[7, 8] Moreover, ivermectin has antimicrobial, anticancer, and antiviral properties and may hold potential in the treatment of associated diseases.[7, 8, 9] First commercialized in 1981, ivermectin has a low cost, high efficacy, established tolerability, and marked helminth tropism, leading to its inclusion in the 21st World Health Organization Model List of Essential Medicines.[10]

Ivermectin causes hyperpolarization and paralysis of the infecting organism and leads to the immunomodulation of the host response.[11] It has been suggested that the nuclear transport-inhibitory activity of ivermectin may be effective against severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2).[8] Considering the potential effects of ivermectin on viral replication, its

efficacy may be greatest when it is used in the first stages of the disease.[12] An effective antiviral therapy for SARS-CoV-2, if administered early in infection, may be useful for reducing the viral load, preventing the progression of the disease, and limiting person-to-person transmission.[13]

Due to a lack of supporting clinical evidence, especially human studies on ivermectin, clinical trials are necessary on a larger scale. Therefore, many clinical studies are underway to provide more information in this area, and few studies have been published (unpublished observations, Rajter et al, 2020).[11, 14, 15] This study reports the effects of ivermectin on outcomes in hospitalized patients with COVID-19 in a double-blind randomized clinical trial.

Participants and Methods

Study Design

This multicenter, prospective, randomized, double-blind, controlled clinical trial was conducted in patients with COVID-19 (age, >5 years; weight >15 kg), who were hospitalized in 1 of 2 tertiary hospitals affiliated with the Mazandaran University of Medical Sciences, Sari, Iran. The diagnostic criteria for COVID-19 included any of the following: (1) positive result on COVID-19 reverse-transcription polymerase chain reaction; (2) clinical symptoms of COVID-19, with a history of contact with a patient with COVID-19; and/or (3) abnormalities on chest computed tomography (CT) compatible with COVID-19 (ground-glass opacity, halo sign, reversed halo sign, and patchy infiltration).[16]

The exclusion criteria were as follows: a history of chronic liver and/or renal disease; receipt of treatment with warfarin, an angiotensin-converting enzyme inhibitor, or a angiotensin II receptor antagonist; and acquired immunodeficiency. Pregnant or breast-feeding women were also excluded from the study.

Randomization and Masking

The patients were randomly divided into 2 groups (ivermectin and control) by a simple randomization method using a table of random numbers. The total sample size consisted of 70 patients, 35 participants per group. Neither the participants nor the evaluators were aware of the randomization process or group allocation. After patients were admitted to the hospital and provided written informed consent, a package containing oral medications was given to the patients in both groups.

Dosing

In addition to supportive medical treatment for COVID-19 according to the national protocols of Iran at the time of this study (hydroxychloroquine and/or lopinavir/ritonavir) in the control group, the intervention group received a single oral dose (0.2 mg/kg) of ivermectin utilizing 3-mg oral tablets,* or a multiple thereof,[17] on the first day of admission, at the following weight-based doses: 15 to 24 kg, 3 mg; 25 to 30 kg, 6 mg; 36 to 50 kg, 9 mg; 51 to 80 kg, 12 mg; and >80 kg, 0.2 mg/kg. All of the participants received appropriate antibiotics and/or supplemental oxygen as indicated.

Measures

Demographic, clinical, laboratory, and imaging data from all participants were recorded at baseline on the first day of admission. Also, the patients were evaluated regarding the severity of the disease, and patients with moderate to severe COVID-19 who needed hospitalization were enrolled the study.

The severe form of the disease was defined as tachypnea (respiratory rate of ≥24 breaths/min), need for mechanical ventilation, need for supplemental oxygen, and oxygen saturation of <94% in the ambient air.[18] Other patients were considered as having moderate disease.

Patients were assessed once daily by nurses, using a checklist that included the primary outcome variables: clinical symptoms including fever, chills, sore throat, cough, dyspnea, loss of appetite, abdominal pain, dizziness, insomnia, itching, joint pain, joint swelling, headache, nausea, vomiting, diarrhea, malaise, conjunctivitis, tachycardia, wheezing, rhonchi, retraction, hypotension, rash, and other symptoms, from baseline until discharge. Moreover, respiratory rate, oxygen saturation, complete blood count with differential, erythrocyte sedimentation rate, sodium, potassium, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, and creatine phosphokinase were measured. The laboratory measurements were repeated after 48 hours.

Additionally, a chest CT was obtained prior to the intervention. Patients were evaluated in terms of disease progression or any new symptoms, daily for 7 days. The need for supplemental oxygen, route of oxygen administration, invasive mechanical ventilation, and other outcomes were also recorded. Moreover, potential drug-induced adverse events, including wheezing, itching, skin rash, edema, and hypotension, were assessed daily.

Outcomes

The primary outcome was clinical improvement after baseline, defined as resolving a patient's baseline status on persistent and continuous cough (persistent cough for >1 hour, or ≥3 coughing episodes in 24 hours, that interferes with activities of daily living and the ability to work) and tachypnea in addition to increasing oxygen saturation to >94%.

Other secondary outcomes included the time to improvement of chief symptoms; hospitalization duration; duration of supplemental oxygen with noninvasive ventilation; and the prevalences of mortality, drug-induced adverse events, and changes in assessed laboratory values over time.

Ethical Considerations

The ethics committee of Mazandaran University of Medical Sciences approved the study protocol (protocol no. IR.MAZUMS.REC.1399.057; Iranian Registry of Clinical Trials identifier, IRCT20111224008507N3). Written informed consent was obtained from all participants and parents of minor children prior to enrollment. The trial was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 20.0 (IBM, Armonk, NY). Means (SD) were used for reporting quantitative data, and frequency and percentage, for qualitative variables. For comparison of differences between intervention and control group, *t* test and χ^2 tests were used. The Kaplan-Meier Breslow method was used for estimating the duration of hospitalization and symptoms in both groups. A *P* value of <0.05 was considered as statistically significant.

Results

The patient-recruitment process was initiated on May 23, 2020, and ended on July 31, 2020 (date of enrollment of the last patient). Seventy COVID-19–positive patients were enrolled in the study; 1 patient from the control group withdrew (Figure). The patients' age ranged between 5 and 86 years.

Also, the mean (SD) ages of the intervention and control groups were 47.63 (22.20) and 45.18 (23.20) years, respectively ($P = 0.65$). Nine (13%) patients were <18 years of age (4 in the ivermectin group and 5 in the control group; $P = 0.68$). Eighteen patients (51.4%) in the ivermectin group and 18 patients (52.9%) in the control group were male ($P = 0.9$). Table I presents the patients' demographic and clinical characteristics at baseline. No significant difference was found between the 2 groups regarding the duration of symptoms before admission, place of residence, or comorbidities. The percentages of patients prescribed of antibiotics, hydroxychloroquine, and lopinavir/ritonavir were not significantly different between the 2 groups.

Figure

Study flow.

Table I

Demographic characteristics and symptoms of the patients in both groups.

	Total (n=69) n (%)	Intervention (n=35)	Control (n=34)	p-value
Age				
< 18 years	9 (13.0)	4 (11.4)	5 (14.7)	0.68
≥18 years	60 (87.0)	31 (88.6)	29 (85.3)	
Gender				
Female	33 (47.8)	17 (48.6)	16 (47.1)	0.90
Male	36 (52.2)	18 (51.4)	18 (52.9)	
Habitat				
Urban	52 (75.4)	25 (71.4)	27 (79.4)	0.41
Rural	17 (24.6)	10 (28.6)	7 (20.6)	
Underlying disease	38 (55.1)	22 (62.9)	16 (47.1)	0.64
RT-PCR*				
Positive	16 (64.0)	11 (64.7)	5 (62.5)	0.91
Negative	9 (36.0)	6 (35.3)	3 (35.7)	
Need Ventilator	3 (4.3)	2 (5.7)	1 (2.9)	1.000[e]
Severe COVID-19	31 (44.9)	13 (37.1)	18 (52.9)	0.19
Symptoms				
Dyspnea	53 (76.8)	27 (77.1)	26 (76.5)	0.94
Persistent cough	50 (72.5)	26 (74.3)	24 (70.6)	0.73
Fever	40 (57.8)	17 (48.6)	23 (67.6)	0.10
Loss of appetite	37 (53.6)	23 (65.7)	14 (41.2)	**0.04**
Chills	33 (47.8)	14 (40.0)	19 (55.9)	0.18
Myalgia	32 (46.4)	16 (45.7)	16 (47.1)	1.00
Headache	26 (37.7)	17 (48.6)	9 (26.5)	0.05
Nausea	24 (34.8)	14 (40.0)	10 (29.4)	0.35
Abdominal pain	14 (20.3)	9 (25.7)	5 (14.7)	0.25
Vomiting	14 (20.3)	7 (20.0)	7 (20.6)	0.95
Vertigo	13 (18.8)	9 (25.7)	4 (11.8)	0.13
Insomnia	12 (17.4)	10 (28.6)	2 (5.9)	**0.01**
Diarrhea	11 (15.9)	5 (14.3)	6 (17/6)	0.70
Rales	10 (14.5)	8 (22.9)	2 (5.9)	**0.04**
Arthralgia	9 (13.0)	8 (22.8)	1 (2.9)	**0.02e**
Sore throat	8 (11.6)	6 (17.1)	2 (5.9)	0.25[e]
Weakness	8 (11.6)	6 (17.1)	2 (5.9)	0.25[e]
Tachypnea	8 (11.6)	4 (11.4)	4 (11.8)	1.00[e]
Sweating	6 (8.7)	5 (14.3)	1 (2.9)	0.19[e]

	Total (n=69) n (%)	Intervention (n=35)	Control (n=34)	p-value
Chest pain	4 (5.8)	3 (8.6)	1 (2.9)	0.61[e]
Hypotension	3 (4.3)	1 (2.9)	2 (5.9)	0.61[e]
Conjunctivitis	2 (2.9)	1 (2.9)	1 (2.9)	1.00[e]
Wheezing	1 (1.4)	1 (2.9)	0	1.00[e]
Skin rash	1 (1.4)	1 (2.9)	0	1.00[e]
Retraction	1 (1.4)	0	1 (2.9)	0.49[e]
Age (years) Mean±SD (Min, Max)	46.43±22.51 (5, 86)	47.63±22.20 (5.5, 85.0)	45.18±23.11 (5.0, 86.0)	0.65
Duration of symptoms before admission (days) Mean±SD (Min, Max)	6.29±3.23 (1, 15)	6.21±3.60 (1, 15)	6.38±2.86 (2, 15)	0.72

*PCR was performed for 25 patients.

[e] Exact p-value.

On admission, 13 patients (37.1%) in the intervention group and 18 patients (52.9%) in the control group presented with severe disease ($P = 0.19$). Overall, 53 patients (76.8%) had dyspnea on admission, 50 (72.5%) had persistent cough, 40 (57.8%) had fever, and 37 (53.6%) experienced loss of appetite. The frequencies of symptoms and signs at baseline were not significantly different between the 2 groups, except for loss of appetite, insomnia, rales, and arthralgia, which were higher in the intervention group (Table I). Also, the 2 groups were similar in terms of baseline laboratory markers and rate of positive reverse-transcription polymerase chain reaction. COVID-19–compatible abnormalities were found on chest CT in all patients, except for 1 patient with normal chest CT in the control group.

Following admission, the mean durations of symptoms in the ivermectin and control groups were 4.2 (0.3) and 5.2 (0.3) days, respectively ($P = 0.023$). The mean durations of dyspnea were 2.4 (1.7) days in the ivermectin group and 3.7 (2.1) days in the control group ($P = 0.02$). Also, persistent cough continued for 3.1 (1.8) days in the ivermectin group versus 4.8 (2.0) days in the control group ($P < 0.001$). The mean lengths of hospital stay were 6.9 (3.1) and 8.3 (3.3) days in the ivermectin and control groups, respectively ($P = 0.01$). Table II presents the durations of clinical recovery, symptoms, and hospital stay in the 2 groups in detail.

Table II

Durations of hospital stay and symptoms with ivermectin versus standard of care (control) in patients with moderate to severe COVID-19. Data are given in days.

Parameter	Ivermectin (n = 35)			Control (n = 34)			*P*
	Mean (SD) (95% CI)	Median (SE) (95% CI)	IQR	Mean (SD) (95% CI)	Median (SE) (95% CI)	IQR	
Duration of hospital stay	7.1 (0.5) (6.1–8.1)	6.0 (0.5) (5.1–7.0)	5.0–8.0	8.4 (0.6) (7.2–9.5)	7.0 (0.4) (6.2–7.8)	7.0–10.0	0.016
Duration of symptoms	4.2 (0.3) (3.6–4.8)	4.0 (0.4) (3.2–4.8)	3.0–5.0	5.2 (0.3) (4.6–5.8)	5.0 (0.5) (4.0–6.0)	4.0–7.0	0.023
Fever	1.7 (0.3) (1.2–2.2)	–	–	2.0 (0.3) (1.2–2.5)	–	–	0.495
Chills	1.4 (0.3) (0.8–1.9)	–	–	1.3 (0.1) (1.2–1.6)	–	–	0.474
Cough	3.1 (0.4) (2.7–4.1)	3.0 (0.5) (2.0–4.0)	2.0–5.0	4.8 (0.4) (4.0–5.6)	5.0 (0.4) (4.3–5.7)	4.0–7.0	0.019
Dyspnea	2.6 (0.4) (2.0–3.3)	2.0 (0.3) (1.2–2.6)	1.0–3.0	3.8 (0.4) (3.0–4.6)	3.0 (0.4) (2.3–3.7)	2.0–6.0	0.048
Loss of appetite	2.7 (0.3) (2.1–3.3)	2.0 (0.2) (1.5–2.5)	2.0–4.0	3.1 (0.4) (2.2–3.9)	2.0 (0.4) (1.2–2.9)	4.0–2.0	0.603
Abdominal pain	2.6 (0.5) (1.6–3.6)	2.0 (1.1) (0.0–4.1)	1.0–4.0	2.3 (0.5) (1.4–3.1)	2.0 (0.3) (1.4–2.6)	1.0–2.0	0.783
Headache	3.1 (0.5) (2.1–4.0)	2.0 (0.9) (0.3–3.7)	1.0–5.0	2.3 (0.4) (1.5–3.1)	2.0 (0.4) (1.2–2.8)	1.0–3.0	0.427
Nausea	2.7 (0.4) (1.9–3,6)	2.0 (0.4) (1.3–2.7)	2.0–4.0	2.7 (0.5) (1.7–3.6)	2.0 (0.7) (0.6–3.4)	1.0–3.0	0.818
Myalgia	2.3 (0.4) (1.5–3.0)	2.0 (0.4) (1.3–2.7)	1.0–3.0	2.4 (0.3) (1.9–2.9)	2.0 (0.3) (1.5–2.5)	2.0–3.0	0.468

IQR = interquartile range.

Ten patients (28.6%) in the ivermectin group and 9 patients (26.5) in the control group required supplemental oxygen ($P = 0.84$) (Table III). Three patients underwent invasive mechanical ventilation (2 in the ivermectin group and 1 in the control group). In the ivermectin group, a 78-year-old woman with a history of diabetes mellitus and heart failure died. She was critically ill at the time of admission and died within the first 24 hours.

Table III

Comparison of the needs for oxygen and medications, including antibiotics, with ivermectin versus standard of care (control) in patients with moderate to severe COVID-19. Data are given as number (%) of patients.

Outcome	All Patients (N = 69)	Intervention (n = 35)	Control (n = 34)	*P*
Oxygen needed	19 (27.5)	10 (28.6)	9 (26.5)	0.84
Medication given				
Lopinavir/ritonavir	55 (79.71)	27 (77.14)	28 (82.35)	1.00[e]
Chloroquine	52 (75.36)	23 (65.71)	29 (85.29)	0.13
Oseltamivir	0	0	0	–
Ribavirin	0	0	0	–
Antibiotics				
Ceftriaxone	44 (63.77)	21 (0.60)	23 (67.65)	0.33
Azithromycin	40 (57.97)	23 (65.71)	17 (0.50)	0.21
Meropenem	10 (14.49)	7 (0.20)	3 (8.82)	0.20
Vancomycin	4 (5.80)	2 (5.71)	2 (5.82)	1.00[e]
Total	62 (89.86)	32 (91.43)	30 (88.24)	0.24[e]

[e]Exact. Sig.

The laboratory test results were not significantly different between the 2 groups on admission (Table IV). Although lymphopenia was detected in 7 (22.6%) and 13 (40.6%) patients in the intervention and control groups on admission, 2 days after the intervention, the frequency of lymphopenia decreased to 3 (14.3%) in the ivermectin group and did not change in the control group (13; 52.0%) ($P = 0.007$).

Table IV

Laboratory test results at baseline and admission day 2 in patients with moderate to severe COVID-19 receiving treatment with ivermectin versus standard of care (control).

Time Point/ Laboratory Test	IQR			Anomalies	No. (%) of Patients			
	Intervention (n = 35)	Control (n = 34)	*P*		All Patients (N = 69)	Intervention (n = 35)	Control (n = 34)	*P*
Baseline								
WBCs, cells × 10^3/μL*	4.70–12.35	4.60–7.95	0.11	Leukopenia (≤4 cells × 10^3/μL)	8 (12.3)	4 (12.1)	4 (12.5)	1.00[e]
				Leukocytosis (≥15 cells × 10^3/μL)	4 (6.2)	3 (9.4)	1 (3.0)	0.35[e]
Lymphocytes, cells × 10^3/μL	1.13–2.51	0.09–2.25	0.14	Lymphopenia (<1 cells × 10^3/μL)	20 (31.7)	7 (22.6)	13 (40.6)	0.12
Hb, mg/dL	9.93–13.55	10.75–13.20	0.97	Hb <10 mg/dL	14 (21.5)	8 (25.0)	6 (18.2)	0.50
Platelets, cells × 10^3/μL	172.75–293.00	125.75–212.75	0.01	Thrombocytopenia (<150 cells × 10^3/μL)	30 (46.2)	18 (54.5)	12 (37.5)	0.16
				Thrombocytosis (≥450 cells × 10^3/μL)	2 (3.1)	1 (3.1)	1 (3.1)	1.00[e]
ESR, mm/h	14.50–58.00	15.75–59.50	0.94	ESR >30 mm/h	11 (44.0)	7 (53.8)	4 (33.3	0.30
LDH, U/L	450–750	425–707	0.71	LDH >500 U/L	26 (61.9)	15 (65.2)	11 (57.9)	0.62
CPK, IU/L	65.75–209.25	62.25–206.50	0.81	CPK >200 IU/L	11 (27.5)	5 (25.0)	6 (30.0)	0.72
ALT, IU/L	19–65	21–59	0.64	ALT >45 IU/L	11 (36.7)	5 (33.3)	6 (40.0)	0.70
AST, IU/L	25–60	22–69	0.78	AST >45 IU/L	10 (33.3)	5 (33.3)	5 (33.3)	1.00
BUN, mg/dL	19.75–30.25	20.00–33.75	0.47	BUN >40 mg/dL	5 (8.3)	0	5 (16.7)	0.05[e]
Cr, mg/dL	0.78–1.12	0.70–1.20	0.89	Cr >1.5 mg/dL	2 (3.4)	0	2 (6.9)	0.49[e]
K, mmol/L	4.00–4.60	3.80–4.50	0.03	K >5.5 mmol/L	0	0	0	–

Time Point/ Laboratory Test	IQR			Anomalies	No. (%) of Patients			
	Intervention (n = 35)	Control (n = 34)	*P*		All Patients (N = 69)	Intervention (n = 35)	Control (n = 34)	*P*
Na, mEq/L	135.00–140.00	136.00–140.00	0.52	Na <125 mEq/L	0	0	0	–
CRP, mg/L	NA	NA	–	CRP ≥10 mg/L	40 (57.97)	18 (51.43)	22 (64.71)	0.89
Admission day 2								
WBCs, cells × 10^3/μL*	4.98–8.80	4.60–6.75	0.06	Leukopenia (≤4 cells × 10^3/μL)	6 (12.2)	3 (12.5)	3 (12.0)	1.00[e]
				Leukocytosis (≥15 cells × 10^3/μL)	1 (2.0)	1 (4.2)	0	0.49[e]
Lymphocytes, cells × 10^3/μL	1.36–2.31	0.09–1.99	<0.001	Lymphopenia (<1 cells × 10^3/μL)	16 (34.8)	3 (14.3)	13 (52.0)	0.007
Hb, mg/dL	9.63–12.92	9.90–12.70	0.64	Hb <10 mg/dL	15 (30.6)	8 (33.3)	7 (28.0)	0.68
Platelets, cells × 10^3/μL	173.0–280.5	133.5–218.0	0.05	Thrombocytopenia (<150 cells × 10^3/μL)	12 (25.5)	4 (18.2)	8 (32.0)	0.27
				Thrombocytosis (≥450 cells × 10^3/μL)	1 (2.1)	1 (4.5)	0	0.468[e]
ESR, mm/h	10.25–77.25	24.00–56.50	0.96	ESR >30 mm/h	14 (60.9)	5 (50.0)	9 (69.2)	0.34
LDH, U/L	276–690	482–680	0.21	LDH >500 U/L	12 (60.0)	2 (28.6)	10 (76.9)	0.06[e]
ALT, IU/L	16.00–36.00	20.75–71.25	0.13	ALT >45 IU/L	7 (22.6)	2 (13.3)	5 (31.3)	0.39[e]
AST, IU/L	18.0–34.0	22.0–48.5	0.09	AST >45 IU/L	6 (18.8)	2 (13.3)	4 (23.5)	0.65[e]
BUN, mg/dL	13.00–34.50	20.00–64.25	0.40	BUN >40 mg/dL	4 (19.0)	2 (15.4)	2 (25.0)	0.61[e]

Time Point/ Laboratory Test	IQR			Anomalies	No. (%) of Patients			
	Intervention (n = 35)	Control (n = 34)	*P*		All Patients (N = 69)	Intervention (n = 35)	Control (n = 34)	*P*
Cr, mg/dL	0.70–1.04	0.90–1.90	0.22	Cr >1.5 mg/dL	3 (13.6)	1 (6.7)	2 (28.6)	0.22[e]
CRP	NA	NA	–	CRP ≥10 mg/L	12 (17.39)	9 (25.71)	3 (8.82)	0.34[e]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CPK = creatine phosphokinase; Cr = creatinine; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; Hb = hemoglobin; IQR = interquartile range; K = potassium; LDH = lactate dehydrogenase; NA = not available; Na = sodium; WBCs = white blood cells.

[e]Exact. sig.

No potential adverse events, including wheezing, itching, skin rash, edema, hypotension or liver toxicity were observed in the patients of either group.

Discussion

To date, few therapies have shown adequate efficacy in the treatment of COVID-19. This study evaluated the effects of ivermectin in patients with COVID-19. With spread of the COVID-19 pandemic, researchers have attempted to find drugs that can be potentially effective in treating this disease.[13] In this study, both groups were matched with regard to age, sex, severity of disease, and comorbidities. Most of the participants were middle-aged, and the male-to-female ratio was almost 1:1. Given that this study was performed in hospitalized patients and the intervention included a single oral dose of ivermectin, the likelihood of missing participants was very low.

Based on the results of the current study, we found significant effects of ivermectin on parameters including hospital stay, dyspnea (as an easily assessed symptom), cough, and lymphopenia. Although in *in vitro* studies the dose of ivermectin needed for inducing antiviral effects was higher than the approved usual dose in humans, in animal models the concentration of ivermectin in the lung tissues was found to be 3-fold higher than the plasma concentration.[7] Some patients with COVID-19 develop dyspnea, which can progress rapidly to acute respiratory distress syndrome and even death.[19, 20] Cough, fever, and dyspnea are the most common symptoms in the clinical presentation of COVID-19[21] and can represent progression of the disease.[22]

In the present study, shorter times to significant improvement in clinical symptoms and a shorter duration of hospital stay were detected in the ivermectin group. In a study by Gorial et al (unpublished observations, 2020), the mean length of hospital stay was significantly less in ivermectin group compared with that in the controls (7.6 [2.7] vs 13.2 [5.9] days; $P = 0.00005$). Rajter et al (unpublished observations, 2020) did not observe a significant difference in lengths of hospital stay between the ivermectin and control groups, and patients received 1 dose of ivermectin at any time during the hospitalization. A possible explanation could have been a delay in prescribing ivermectin due to a lag in obtaining the required results from repeated COVID-19 testing. There have been trials on the efficacy of other drugs, such as remdesivir, dexamethasone, and lopinavir/ritonavir, in the treatment of patients with COVID-19.[5, 18, 23, 24, 25] In a study by Wang et al,[24] no improvement was achieved in the remdesivir group, while in a study by Beigel et al[18] remdesivir treatment for 10 days was associated with a shorter length of hospital stay, clinical improvement by day 15, and a median recovery time of 10 days, but serious adverse events occurred

in 24.6% patients in the remdesivir group. A similar study of lopinavir/ritonavir reported adverse gastrointestinal effects in the intervention group compared to standard-of-care controls.[25] In a study from the RECOVERY Collaborative Group,[5] the use of oral or IV dexamethasone for up to 10 days was associated with a lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen supplementation alone compared with those receiving no respiratory support. Although remdesivir was approved for use in the treatment of COVID-19 by the FDA, it is not specific for it. Despite ivermectin having several advantageous characteristics, including single-dose administration, oral formulation, and associations with a shorter recovery time and no adverse events in hospitalized adults with COVID-19, it needs further investigations to be considered for approval as a COVID-19–specific treatment.

In the current study, 2 days after the intervention, ivermectin was associated with a significantly decreased frequency of lymphopenia. The potential mechanisms of lymphopenia in patients with COVID-19 include lymphocyte apoptosis; destruction of lymphatic organs, such as thymus and spleen, directly by the virus; lymphocyte apoptosis by disturbed inflammatory cytokines; and inhibition of lymphocytes following metabolic disorders, such as hyperlactic acidemia.[26, 27] A low lymphocyte count is consistently associated with severe COVID-19.[28] In other words, lymphopenia can be used as a marker of poor prognosis in COVID-19, especially in younger patients.[26, 29] Therefore, an increased lymphocyte count is a valuable finding of the present study, which may be considered in the treatment of patients with COVID-19.

In the present study, ivermectin was prescribed in combination with hydroxychloroquine, azithromycin, and antivirals such as lopinavir/ritonavir. Lopinavir/ritonavir, a potent inhibitor of cytochrome P-450, which is the main metabolic pathway of ivermectin,[7] may enhance the toxicity of ivermectin when used in combination with it. The risks for adverse events with such combinations are very low,[30] and no adverse events were associated ivermectin use in the present study. No adverse events associated with ivermectin use were reported in other similar studies (unpublished observations, Rajter et al, 2020; unpublished observations, Gorial et al, 2020).[15] However, other studies have reported adverse events associated with hydroxychloroquine, including prolonged QT interval, irreversible retinal damage, myopathy, and neuropathy, as well as the adverse events associated with lopinavir/ritonavir, such as hypertriglyceridemia and hypercholesterolemia.[11, 24, 25] In the study by Beigel et al,[18] 52 patients discontinued remdesivir treatment before day 10 because of an adverse event, and serious adverse events occurred in 24.6% of the patients.

Although several doses and treatment durations of ivermectin are recommended, this study used a single dose of 0.2 mg/kg to achieve clinical improvement. Ahmed et al[14] studied the effects of ivermectin alone (12 mg once daily for 5 days) or in combination with doxycycline (12 mg ivermectin single dose and 200 mg stat doxycycline on day 1, followed by doxycycline 100 mg q12h for 4 days) compared with placebo; time to virologic clearance was less in the 5-day ivermectin treatment arm versus the placebo group. Therefore, a treatment regimen with ivermectin can be considered due to its lower cost, availability, oral route of administration, and fewer associated adverse events in comparison with other available drugs.[11] Although remdesivir has been associated with few adverse events in clinical trials, it has not been not approved by the FDA for administration in children under 12 years of age.[23, 31]

There are some concerns regarding the neurotoxicity of ivermectin, as the drug targets glutamate-gated chlorine channels in invertebrates and may cross-react with GABA-gated chlorine channels in mammalians.[32] This concern is diminished with regard to an intact blood–brain barrier, while in a hyperinflammatory state in patients with severe COVID-19, this barrier may become permeable and the drug may penetrate the CNS.[7] Therefore, in patients with severe disease, ivermectin should be prescribed with extreme caution. For this reason, in the present study, a single dose of the drug was used on the first admission day, before progression of the disease to CNS involvement.

This study had a number of limitations. First, the sample size was small, and the effects of the drug on mortality could not be evaluated. Therefore, further studies with larger sample sizes are warranted. A further limitation of this study was the assessment of patients with moderate to severe disease who required hospitalization. Regarding the mechanism of action of this drug, its application during the first days of symptom onset may be associated with higher clinical response. Although benefits of ivermectin were apparent in this study, due to the small sample size, further studies with larger sample sizes; different drug dosages, dosing intervals, and treatment durations; and especially in patients with different severity of disease are needed for generalization of the findings on effects and optimization.

Conclusions

Based on the findings from the present study, a single weight-based dose (0.2 mg/kg) of ivermectin could improve important clinical symptoms in patients with COVID-19, such as dyspnea, cough, and lymphopenia. This drug was well tolerated, with a good tolerability profile and few adverse events with oral administration.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

Author Contributions

L.S. and M.S.R. contributed to study conception and design. L.S., A.D., and M.S.R. contributed to data collection and patient sampling. M.R.N. and F.H. contributed to drafting and editing the manuscript. F.S.M. performed the statistical analysis. L.S., J.S.M., F.H., and M.S.R. revised the manuscript. G.E. and M.S.R. provided study supervision. J.S.M. assisted in the drafting and editing of the manuscript. All of the authors read and approved the submitted manuscript.

Consent for Publication

Written informed consent was obtained from the patients or their parents prior to manuscript submission for their personal or clinical details in addition to any identifying images to be published in this study. The data from the patients of this study have not been reported in any other submission.

Availability of Data and Material

All data generated or analyzed during this study were included in this published article. For additional data, please contact the corresponding author.

Footnotes

*Distributed by Europhartech (Lempdes, France).

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