

Journal Pre-proof

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PII: S0300-2896(20)30288-X

DOI: <https://doi.org/doi:10.1016/j.arbres.2020.08.007>

Reference: ARBRES 2607

To appear in: *Archivos de Bronconeumología*

Received Date: 6 August 2020

Accepted Date: 28 August 2020

Please cite this article as: Khan MSI, Khan MSI, Debnath CR, Nath PN, Mahtab MA, Nabeka H, Matsuda S, Akbar SMF, Ivermectin treatment may improve the prognosis of patients with COVID-19, *Archivos de Bronconeumología* (2020), doi: <https://doi.org/10.1016/j.arbres.2020.08.007>

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Article type: Scientific letter

Ivermectin treatment may improve the prognosis of patients with COVID-19

El tratamiento con ivermectina puede mejorar el pronóstico de los pacientes con COVID-19

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Declaration of interest statement: All author have nothing to disclose

Funding sources: None

IRB approval status: Hospital approval and patient consents were taken

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Highlights

- COVID-19 patients receiving ivermectin became SARS-CoV-2 negative more quickly

- Fewer ivermectin-treated patients developed respiratory distress
- Ivermectin-treated COVID-19 patients had shorter hospital stays
- Ivermectin is associated with a lower mortality rate in COVID-19 patients

To the Editor:

The pandemic coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been spread rapidly worldwide with considerable morbidity and mortality. COVID-19 patients have various clinical presentations: asymptomatic, exhibit mild flu-like symptoms, be severely ill or death.^{1,2} In addition to elder age and comorbidities, higher levels of D-dimer and C-reactive protein (CRP) and lower levels of lymphocyte and eosinophil as well as a cytokine storm are associated with disease severity in COVID-19 patients.³⁻⁶ The virus load may be a main determinant underlying the pathological diversity in COVID-19 patients.^{1,2,6} Thus, an effective antiviral treatment is essential to improve the prognosis of patients with COVID-19.⁷ In the absence of specific anti-SARS-CoV-2 agents, various drugs with antiviral potential are now used to contain the virus in COVID-19 patients. Ivermectin, a US FDA-approved anthelmintic, has garnered enormous interest for treating COVID-19 as it is safe and cheap and has strong antiviral activities against broad ranges of viruses including SARS-CoV-2 *in vitro*.⁸⁻¹⁰ Despite the widespread use of ivermectin, to our knowledge, there is currently no published clinical reports of ivermectin in COVID-19 patients. Here, we assessed the clinical efficacy of ivermectin in COVID-19 patients.

This retrospective study enrolled a total of 325 consecutive patients with SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) of nasal swabs in SK hospital, a unit dedicated to COVID-19 at Mymensingh Medical College Hospital (MMCH), Mymensingh, Bangladesh, from April to June 2020. Of these, the present study included 248 adult COVID-19 patients free from any other serious pathological conditions: 115 received ivermectin plus standard care (SC), while 133 received only SC. Remaining 77 patients who were under 18 years of age or transferred from other facilities and received different management approaches including partial hospital stays or treated with different therapeutic agents prior to hospital admission were excluded from the analysis. The two groups were compared in terms of time to SARS-CoV-2 negativity, disease progression (develop pneumonia to severe respiratory distress), duration of hospital stays, and mortality rate. Ivermectin was given once at dose of 12 mg within 24-h after hospital admission. SC was provided as required and included antipyretics for fever, anti-histamines for cough, and antibiotics to control secondary infection. The study was approved by MMCH and informed consent was obtained from all patients or their relatives before starting treatment. Categorical variables are shown as frequencies and percentages and continuous variables as the median and interquartile range (IQR). Differences with 95% confidence intervals (CI) were computed to show the level of certainty. Paired *t*-tests or Pearson Chi-square test were used to analyze statistical differences. All calculations were performed using SAS, version 9.4 (Cary, NC, USA).

The median age of the patients was 35 (IQR 30–43) years and 60% were men. Table 1 summarizes the demographics and clinical presentations of the two groups. At the time of

admission, all patients had comparatively mild/moderate disease with cough, headache, sore throat, anosmia, breathing difficulty, and pneumonia in different proportions. Some patients in both groups had underlying comorbidities like hypertension, diabetes mellitus, asthma, and hyperlipidemia. About 13% of the patients were current smokers. Also, about 58% had higher D-dimer and C-reactive protein levels, 51% had lymphopenia, and 47% had eosinopenia. However, at the time of admission, there were no significant differences in the patient profiles, presenting symptoms, comorbidities and hemato-biochemical parameters of the two treatment groups (Table 1).

The treatment did not produce any aberrant symptoms related to ivermectin use. None of the ivermectin-treated patients showed progressive pathology, such as pneumonia or cardiovascular complications (Table 1). On the other hand, 9.8% patient developed pneumonia and 1.5% had ischemic stroke those were not received ivermectin. Significantly fewer ivermectin-treated patients required oxygen inhalation (9.6% vs. 45.9), developed respiratory distress (2.6% vs. 15.8%), or needed antibiotic treatment (15.7% vs. 60.2%) and intensive care management (0.9% vs. 8.3%). Interestingly, the patients receiving ivermectin became SARS-CoV-2 negative more quickly (median 4 vs. 15 days; 95% CI, 8.97–10.59; $P<0.001$). The ivermectin-treated patients also had shorter hospital stays (median 9 vs. 15 days; 95% CI, 5.09–7.51; $P<0.001$). Furthermore, the mortality rate was significantly lower in the ivermectin group than SC (0.9% vs. 6.8%; $P<0.05$; Table 1). Of the ivermectin-treated patients, 61 were randomly assigned for follow-up assessment 10 and 20 days after discharge; none of them were reported any complications.

After SARS-CoV-2 infection, the disease generally progresses within 1 week of symptom onset due to uncontrolled viral replication in the upper respiratory tract,^{2,6,11,12} followed by immune anomalies, and a cytokine storm.^{2,5,6} Thus, an effective antiviral therapy capable of blocking viral replication at the earliest time after infection may prevent disease progression. This study shows that ivermectin is safe in COVID-19 patients and efficient at rapidly clearing SARS-CoV-2 from nasal swabs (median 4 days). This was much shorter than in the COVID-19 patients receiving only SC (15 days) or receiving a combination of three antiviral drugs (7~12 days¹³). Furthermore, in terms of developing respiratory distress leading to ICU admission and the final outcome (discharge/death), we observed a significant clinical benefit of ivermectin in COVID-19 patients. In fact, with ivermectin, we observed quick hospital discharge (median 9 days) in 114 out of 115 patients; the remaining patient arrived with advanced disease.

Ivermectin induced rapid virological clearance that we observed in this study indicating that the preclinical efficacy of the drug against SARS-CoV-2⁹ may be mirrored in patients. Such rapid clearing of SARS-CoV-2 (median 4 days); this is much shorter than the median duration (20 days) of viral shedding in patients with COVID-19,¹⁴ indicate that ivermectin could limit the viral spreading. Collectively, the present findings suggest that ivermectin induced rapid SARS-CoV-2 clearance could reduce COVID-19 disease progression and community transmission.

Although ivermectin is an anti-parasitic, its anti-viral capacities are known in both animals and human. In fact, ivermectin has been previously shown to exert antiviral activity *in vitro* against various viruses including dengue fever virus, zika virus, west Nile virus,

Venezuelan equine encephalitis virus, influenza virus, and SARS-CoV-2.^{8,9} It acts at different viral protein binding sites, reducing viral replication. Although we are not sure of the mechanisms underlying the antiviral potential of ivermectin in COVID-19 patients, the blockage of the transport of viral proteins from the cytosol to the nucleus may be one mechanism. Elucidation of the mechanisms of action of ivermectin in terms of its antiviral properties and arrest of disease progression, especially the down-regulation of pneumonia, remain to be elucidated.

In conclusion, in addition to rapid SARS-CoV-2 clearance, ivermectin seems to control the course of the disease in patients with COVID-19. As of early August 2020, the numbers of COVID-19 patients are increasing worldwide; the rise is especially marked in Latin American and South Asian countries.¹⁵ Containment strategies and patient management vary by country. Appropriate rapid management of those who are asymptomatic-to-mildly/moderately symptomatic (about 90% of all patients) is essential to prevent disease progression and community spread. Therefore, given the urgent need to manage the COVID-19 patients with a safe, cheap and widely available drug, the present findings suggest that ivermectin can be considered as a first-line treatment for containing SARS-CoV-2 to prevent severe irreversible respiratory complications and community transmission. A multicenter, double-blind, drug-controlled study will strengthen our findings.

Table 1. Profiles, treatment approaches, clinical developments and final outcomes of SARS-CoV-2-positive patients receiving or not receiving ivermectin*

Variables	Ivermectin (n = 115)	No Ivermectin (n = 133)	Difference (95% CI)	P-value
Characteristics of patients				
Age, median (IQR)–years	34.0 (30.0–42.0)	35.0 (30.0–45.0)	1.6 (-0.87 – 4.07)	0.223
Age group				
18–50– no. (%)	108 (94)	125 (94)		0.213
≥ 51–no. (%)	7 (6)	8(6)		0.148
Sex				
Female–no. (%)	35 (30.4)	64 (48.1)		<0.01
Male–no. (%)	80 (69.6)	69 (51.9)		0.367
Preexisting conditions				
Hypertension – no. (%)	14 (12.2)	16 (12.0)		0.715
Diabetes mellitus – no. (%)	19 (16.5)	16 (12.0)		0.612
Hypertension plus diabetes mellitus – no. (%)	10 (8.7)	15 (11.3)		0.317
Hyperlipidemia – no. (%)	4 (3.5)	8 (6.0)		0.248
Asthma – no. (%)	10 (15.0)	13 (9.8)		0.531
Inhaler using – no. (%)	10 (15.0)	12 (9.0)		0.669
Currently smoking – no. (%)	14 (12.2)	18 (13.5)		0.479
Presenting symptoms				
Fever – no. (%)	66 (57.4)	70 (52.6)		0.731
Cough – no. (%)	70 (60.9)	80 (60.2)		0.414
Fever plus cough – no. (%)	40 (34.8)	35 (26.3)		0.563
Sore throat – no. (%)	17 (14.8)	13 (9.8)		0.465
Runny nose – no. (%)	5 (4.3)	5 (3.8)		1.000
Shortness of breath – no. (%)	18 (15.7)	18 (13.5)		1.000
Pneumonia	4 (3.5)	3 (2.3)		0.562
Headache – no. (%)	39 (33.9)	56 (42.1)		0.081
Loose motion – no. (%)	13 (11.3)	14 (10.5)		0.847
Anosmia – no. (%)	5 (4.3)	9 (6.8)		0.285
Body temperature, median (IQR) – °F	100 (99.0 – 101.4)	100 (99.0 – 101.5)	0.0 (-0.39 – 0.39)	0.890
≤99.4 – no. (%)	50 (43.5)	64 (48.1)		0.189
≥ 99.5 – no. (%)	65 (56.5)	69 (51.9)		0.729
Heart rate, median (IQR) – beats/min	90 (86–94)	90 (85–94)	0.9 (-0.41 – 2.21)	0.155
Respiratory rate, median (IQR) – breaths/min	24 (22–25)	24 (22–26)	0.5 (-0.20 – 1.20)	0.236
Oxygen saturation, median (IQR) – %	97 (96–99)	98 (96–99)	0.3 (-0.29 – 0.89)	0.318
≤94 – no. (%)	14 (12.2)	12 (9.0)		0.694

Continued Table 1

Variables	Ivermectin (n = 115)	No Ivermectin (n = 133)	Difference (95% CI)	P-value
Baseline hemato-biochemical profiles[#]				
D-dimer (µg/mL), median (IQR)	0.54 (0.38–0.69)	0.54 (0.42–0.69)	0.01 (0.06–0.08)	0.758
> 0.5 – no. (%)	67 (58.3)	76 (57.1)		0.858
Lactate dehydrogenase (U/L), median (IQR)	230 (167–291)	249 (187–294)	13.41 (-2.91–29.72)	0.106
> 280 – no. (%)	35 (21.74)	47 (35.3)		0.413
C-reactive protein (mg/L), median (IQR)	13.9 (6.1–23.8)	13.7 (5.7–23.2)	0.32 (-3.01–3.65)	0.849
> 10.0 – no. (%)	65 (56.5)	79 (59.4)		0.646
Lymphocyte count per mm ³ , median (IQR)	2.07 (1.2–2.49)	1.94 (1.19–2.41)	0.03 (0.14–0.21)	0.712
< 2.0 – no. (%)	57 (49.6)	70 (52.6)		0.630
Eosinophils count per mm ³ , median (IQR)	0.04 (0.00–0.10)	0.04 (0.01–0.15)	0.00 (-0.03–0.04)	0.806
< 0.02 – no. (%)	47 (40.9)	54 (40.6)		0.964
Treatments approaches				
Ivermectin – no. (%)	115 (100)	-		
Antipyretic drug – no. (%)	66 (57.8)	70 (52.6)		0.731
Antihistamine drug – no. (%)	70 (60.9)	80 (60.2)		0.414
Antibiotic – no. (%)	18 (15.7)	80(60.2)		<0.001
Required oxygen inhalation – no. (%)	11 (9.6)	61 (45.9)		<0.001
Disease progression				
Developed moderate respiratory distress – no. (%)	3 (2.6)	21 (15.8)		<0.001
Developed pneumonia – no. (%)	-	13 (9.8)		
Ischemic stroke – no. (%)	-	2 (1.5)		
Required intensive care management – no. (%)	1 (0.9)	11 (8.3)		<0.001
Clinical outcomes				
Duration of viral clearance, median (IQR) – day	4 (4–6)	15 (12–17)	9.78 (8.97–10.59)	<0.001
Duration of hospital stay, median (IQR) – day	9 (7–10)	15 (12–19)	6.3 (5.09–7.51)	<0.001
Recovered and discharged – no. (%)	114 (99.1)	124 (92.2)		0.516
Death – no. (%)	1 (0.9)	9 (6.8)		<0.05

* The values of presenting symptoms at hospital admission are shown based on available data. [#] D-dimer normal value ≤ 0.05 µg/mL; Lactate dehydrogenase normal range 135–280 U/L; C-reactive protein normal value ≤ 10.0 mg/L; Lymphocyte normal range 1.50–4.00 x 10⁹/L; Eosinophil normal range 0.20–0.50 x 10⁹/L. SARS-CoV-2, severe acute respiratory syndrome coronavirus; CI, confidence interval; IQR, interquartile range.

References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020;10.1001/jama.2020.12839. doi:10.1001/jama.2020.12839
2. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature*. 2020;581(7809):465-469. doi:10.1038/s41586-020-2196-x
3. Posso M, Comas M, Román M, et al. Comorbidities and Mortality in Patients With COVID-19 Aged 60 Years and Older in a University Hospital in Spain. *Arch Bronconeumol*. 2020;S0300-2896(20)30215-5. doi:10.1016/j.arbres.2020.06.012
4. Xie G, Ding F, Han L, Yin D, Lu H, Zhang M. The role of peripheral blood eosinophil counts in COVID-19 patients. *Allergy*. 2020;10.1111/all.14465. doi:10.1111/all.14465
5. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. *Allergy*. 2020;75:1564-1581. doi:10.1111/all.14364
6. Shi D, Wu W, Wang Q, et al. Clinical characteristics and factors associated with long-term viral excretion in patients with SARS-CoV-2 infection: a single center 28-day study. *J Infect Dis*. 2020;jiaa388. doi:10.1093/infdis/jiaa388

7. Wu J, Li W, Shi X, et al. Early antiviral treatment contributes to alleviate the severity and improve the prognosis of patients with novel coronavirus disease (COVID-19). *J Intern Med.* 2020;**288**:128-138. doi:10.1111/joim.13063
8. Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot (Tokyo).* 2020;**73**:593-602. doi:10.1038/s41429-020-0336-z
9. 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**:104787. doi:10.1016/j.antiviral.2020.104787
10. Portmann-Baracco A, Bryce-Alberti M, Accinelli RA. Antiviral and Anti-Inflammatory Properties of Ivermectin and Its Potential Use in Covid-19. *Arch Bronconeumol.* 2020;S0300-2896(20)30212-X. doi:10.1016/j.arbres.2020.06.011
11. Yu X, Sun S, Shi Y, Wang H, Zhao R, Sheng J. SARS-CoV-2 viral load in sputum correlates with risk of COVID-19 progression. *Crit Care.* 2020;**24**:170. doi:10.1186/s13054-020-02893-8
12. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ.* 2020;**369**:m1443. doi:10.1136/bmj.m1443

13. Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet*. 2020;**395**:1695-1704. doi:10.1016/S0140-6736(20)31042-4
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;**395**:1054-1062. doi:10.1016/S0140-6736(20)30566-3
15. WHO. Coronavirus disease (COVID-19) Situation Report – 197 on August 04, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200804-covid-19-sitrep-197.pdf?sfvrsn=94f7a01d_2_2 (Accessed 05 August 2020).