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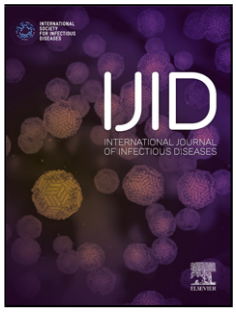

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PII: S1201-9712(20)32506-6

DOI: https://doi.org/10.1016/j.ijid.2020.11.191

Reference: IJID 4901

To appear in: *International Journal of Infectious Diseases*

Received Date: 24 November 2020

Accepted Date: 26 November 2020

Please cite this article as: { doi: https://doi.org/

A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness

Sabeena Ahmed[1], Mohammad Mahbubul Karim[1], Allen G. Ross[1], Mohammad Sharif Hossain[1], John D. Clemens[1], Mariya Kibtiya Sumiya[1], Ching Swe Phru[1], Mustafizur Rahman[1], Khalequ Zaman[1], Jyoti Somani[2], Rubina Yasmin[3], Mohammad Abul Hasnat[4] Ahmedul Kabir[5], Asma Binte Aziz[1], Wasif Ali Khan[1,†]

[1] International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), Dhaka, Bangladesh;

[2] Division of Infectious Diseases, Department of Medicine, National University Hospital, Singapore;

[3] Mugda Medical College and Hospital, Dhaka, Bangladesh;

[4] Kurmitola General Hospital, Dhaka, Bangladesh;

[5] Dhaka Medical College & Hospital, Dhaka, Bangladesh.

†*Corresponding author*

Dr. Wasif Ali Khan

E-mail: wakhan@icddrb.org

Highlights

- Ivermectin, an FDA-approved anti-parasitic agent, was found to be an inhibitor of SARS-CoV-2 replication in the laboratory.
- Ivermectin may be effective for the treatment of early-onset mild Covid-19 in adult patients. Early viral clearance of SARS-CoV-2 was observed in treated patients.

- Remission of fever, cough and sore throat did not differ between those treated with or without ivermectin. No severe adverse event observed with the longer duration of ivermectin use.
- Larger trials will be needed to confirm these preliminary findings.

Abstract

Ivermectin, an FDA-approved anti-parasitic agent, was found *in vitro* to inhibit SARS-CoV-2 replication. To determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients we conducted a randomized, double-blind, placebo-controlled trial of oral ivermectin alone (12mg once daily for 5 days) or in combination with doxycycline (12mg ivermectin single dose and 200mg stat doxycycline day-1 followed by 100mg 12hrly for next 4 days) compared with placebo among 72 hospitalized patients in Dhaka, Bangladesh. Clinical symptoms of fever, cough and sore throat were comparable among the three treatment arms. Virological clearance was earlier in the 5-day ivermectin treatment arm versus the placebo group (9.7 days vs. 12.7 days; P =0.02); but not with the ivermectin + doxycycline arm (11.5 days; P=0.27). There were no severe adverse drug events recorded in the study. A 5-day course of ivermectin was found to be safe and effective in treating mild COVID-19 adult patients. Larger trials will be needed to confirm these preliminary findings.

Keywords: Ivermectin; Doxycycline; COVID-19, SARS-CoV-2; Bangladesh

Introduction

COVID-19, caused by the novel Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), has become a global pandemic of the highest priority.[1] Eighty-one percent of the cases are categorized as mild for whom symptomatic management at home and monitoring of clinical deterioration is recommended.[2] Despite providing symptomatic management, a therapeutic drug that would limit the course of infection is greatly needed.

Ivermectin, a popular anti-parasitic drug, acts on SARS-CoV-2 by preventing viral proteins from entering the host cell nucleus.[3] Recent virtual drug screening identified doxycycline as a potential inhibitor of SARS-CoV-2 papain-like protease.[4] An observational study with a single-dose of ivermectin with a multi-dose of doxycycline for the treatment of COVID-19 yielded considerable improvement of symptoms and viral response.[5] A recent retrospective study found that hospitalized patients given ivermectin with other treatments (e.g., azithromycin and hydroxychloroquine) had a lower mortality than those who did not receive ivermectin.[6] Further studies are needed to verify these findings. This need is further underscored by the observations that SARS-CoV-2 rapidly multiplies in the respiratory tract and that evidence from animal models shows 3-fold higher levels of ivermectin in pulmonary tissue than in the plasma one week after oral dosing.[7,8] In this pilot study we evaluated the rapidity of viral clearance and safety of a 5-day course of ivermectin or a single-dose of ivermectin with a 5-day course of doxycycline in the treatment of mild COVID-19 in adults.

Methods

To determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients we conducted a randomized, double-blind, placebo-controlled trial of oral ivermectin alone (12mg once daily for 5 days) or in combination with doxycycline (12mg ivermectin single dose and 200mg stat doxycycline day-1 followed by 100mg 12hrly for next 4 days) compared with placebo among 72 hospitalized patients in Dhaka, Bangladesh. Inclusion criteria were: age 18-65 years; admitted to hospital within the last 7 days; with either fever (≥37.5^{o}C); cough or sore throat; and diagnosed positive for SARS-CoV-2 by rRT-PCR. The patients were excluded if they were allergic to or had a potential drug-drug interaction for ivermectin or doxycycline; had chronic illnesses (e.g., ischemic heath disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease); received ivermectin and/or doxycycline in the last 7 days; were pregnant or lactating; or participated in any other clinical trial within the last month.

Patients were physically examined for COVID-19 related symptoms and their vital signs (e.g., temperature, blood pressure, pulse rate, oxygen saturation, respiratory rate) were recorded. Nasopharyngeal swabs were obtained to confirm the presence of SARS-CoV-2 using rRT-PCR on the day of enrolment, and then on day 3, 7, and 14. After day 14, patients were followed-up weekly until found test negative.

Venous blood was collected for blood parameters (CBC, Creatinine, SGPT, RBS) on enrolment and on day 4; chest X-ray and ECG were assessed on enrolment and on day 3. Blood biomarkers (C-Reactive Protein (CRP), Ferritin, Lactose dehydrogenase (LDH) and Procalcitonin) were measured on enrolment and day 7. RNA was tested for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction (rRT-PCR) targeting ORF1ab- and N-gene specific

primers and probes following protocol of Chinese Center for Disease Control and Prevention; subjected to amplification (iTaq universal probes one-step Kit, Bio-Rad Laboratories, Inc. California, USA) in a Bio-Rad CFX96™ Real-Time PCR Detection System (Bio-Rad Laboratories, Inc. California, USA). A positive case had the Cycle Threshold value (Ct-value) less than 40. Other information was collected on demographics, co-morbidity, medication use, and previous hospitalization as part of the medical history. Data were entered using SPSS Version 17.0 for Windows, (SPSS, Chicago, IL).

The primary endpoints were the time required for virological clearance (a negative rRT-PCR result on nasopharyngeal swab); remission of fever (≥37.5^{o}C) and cough within 7 days. Secondary outcomes included patients failing to maintain an SpO2 >93% despite oxygenation and days on oxygen support; duration of hospitalization; and all-cause mortality. Drug safety outcomes recorded were adverse events that occurred during treatment, post treatment, and the discontinuation of the study drug during the trial.

Results

Study descriptors

A total of 72 (24 per arm) out of 113 patients who consented were enrolled in the trial. One patient from each of the ivermectin+doxycycline and placebo group and two patients in the 5-day ivermectin arm withdrew their consent during the study due to family obligations and unwillingness to test further. The pretreatment characteristics (demographics, clinical history, co-morbidity and laboratory values) were comparable among the three treatment groups. The mean age was 42 years, with 54% being female and ill on average 3.83 days before assessment.

The mean duration of hospitalization after treatment was 9.7 (Confidence interval (CI)= 8.1 - 11.0), 10.1 (CI= 8.5 - 11.8) and 9.6 (CI= 7.7 - 11.7) days in the placebo, ivermectin+doxycycline and ivermectin alone arms respectively (P =0.93). None of the patient enrolled required oxygen or had serious adverse drug events recorded. The mean values of the blood-biomarkers (CRP, LDH, Procalcitonin and Ferritin) dropped from base-line to day 7 in all three groups and these changes were significant for CRP (P=0.02) and LDH (P=0.01) in the 5-day ivermectin arm and for LDH in the placebo group (P=0.01).

At enrolment, 82.6% (19/23) of patients in the placebo group, 73.9% (17/23) in the ivermectin+doxycycline arm and 77.3% (17/22) in 5-day ivermectin group were recorded having fever and among them 84.2% (16/19), 94.1% (16/17) and 100% (17/17) were afebrile at day 7 respectively. Similarly, 65.2% (15/23), 82.6% (19/23) and 81.8 (18/22) had cough on enrolment in the placebo group, the ivermectin+doxycycline arm, and in the 5-day ivermectin group respectively. At day-7 this dropped to 40% (9/15), 63.2% (7/19) and 61.1% (7/18) respectively for cough. Sore throat was present at enrolment in 17.4% (4/23), 13% (3/23) and 18.2% (4/22) of patients in the placebo group, ivermectin+doxycycline group, and 5-day ivermectin group respectively and at day 7, sore throat subsided in 75% (3/4), 33.3% (1/3) and 75% (3/4) patients respectively. It is noteworthy that these changes were not statistically significant for fever (p=0.35 and 0.09), cough (p=0.18 and 0.23) or sore throat (p=0.35 and 0.09) in the ivermectin+doxycycline and the 5-day ivermectin groups when compared with placebo.

Viral clearance

The mean duration to viral clearance was 9.7 (CI= 7.8 - 11.8) days, 11.5 (CI= 9.8 - 13.2) and 12.7 days (CI= 11.3 - 14.2) for the 5-day ivermectin arm (P=0.02), ivermectin+doxycycline (P=0.27) arm and the placebo group respectively. Kaplan-Meier survival analysis revealed that the proportion of patients at risk for SARS-CoV-2 was significantly reduced in the 5-day ivermectin group (Figure, below). At day 7 and 14 virological clearance in the 5-day ivermectin group was significantly earlier compared to placebo [Hazard Ratio (HR) =4.1; Confidence Interval (CI) = 1.1 - 14.7; p=0.03 versus HR=2.7; CI= 1.2 - 6.0; p=0.02]. This trend was similar with the ivermectin + doxycycline group on day 7 and 14 but not statistically significant (HR=2.3; CI= 0.6 - 9.0; p=0.22 versus HR=1.7; CI= 0.8 - 4.0; p=0.19).

Discussion

The drugs ivermectin and doxycycline are commonly used in the developing world and found to be safe and effective in treating both parasitic and bacterial infections. The drugs are affordable (the full 5-day cost ranges from $.60-$1.8 USD for 5-day ivermectin) and readily available in Bangladesh thus are a highly attractive alternative for treating COVID-19 patients. Our study aimed to investigate the role of ivermectin alone or in combination with doxycycline in the treatment of adult COVID-19 patients presenting with mild symptoms. It was hoped that treatment early in the course of infection would decrease viral load, shorten the duration of illness, and halt transmission.

A 5-day course of ivermectin resulted in an earlier clearance of the virus compared to placebo (P=0.005) thus indicating early intervention with such an agent may limit viral replication within the host. In the 5-day ivermectin group there was significant drop of CRP and LDH by day-7

which are indicators of disease severity. It is noteworthy that the viral nucleic acid cycle threshold value (indicator of viral load) significantly dropped compared to the placebo group on day-7 and day-14. In the absence of co-morbidity, a 5-day course of ivermectin treatment showed faster SARS-CoV-2 virus clearance compared to the placebo arm (9 vs.13 days; P = 0.02).

Although the study sample was too small (n=72) to make any solid conclusions, the results provide evidence of the potential benefit of the early intervention with the drug ivermectin for the treatment of adult patients diagnosed with mild SARS-CoV-2. First, early intervention promoted faster viral clearance during disease onset which might have prevented significant immune-system involvement and speed recovery. Secondly, early intervention reduced the viral load faster, thus may help block disease transmission in the general population. A larger randomized controlled clinical trial of ivermectin treatment appears to be warranted to validate these important findings.

Author Agreement

All authors have seen and approved the final version of the manuscript being submitted. The article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

Author Contributions

JDC, AGR, WAK, KZ, JS, MSF conceived concept and designed the study. RY, MAH, AK, SA, MMK, MSH MR and ABA made substantial contributions in reviewing design of the study

and acquisition of data. SA, MMK, MSH. ABA coordinated sample collection and oversaw data collection. MR and MKS conducted and analyzed laboratory results. MSH analyzed the data and WAK, SA, MMK, MSH interpreted. WAK and SA conducted the literature review and drafted the manuscript. MMK, MSH and ABA contributed by revising it critically for important intellectual content. JDC, AGR, WAK, KZ, JS, MSF, MR, RY, MAH, AK critically reviewed the manuscript. All authors contributed to final approval of the version to be submitted.

Funding source

This work was supported by the Beximco Pharmaceutical Limited, Bangladesh.

Ethical Review

The trial was approved by the institutional review board (Research Review Committee and Ethical Review Committee) of icddr,b and subsequently by the National Ethics Review Committee of Bangladesh Medical Research Council and Clinical Trial Advisory Committee of Directorate General of Drug Administration, Govt. of Bangladesh. Written informed consent was obtained from all patients.

Conflicts of interest

The authors have no conflicts of interest to declare.

Declaration of interests

The authors declare that there is no known competing financial interests or personal relationships that could have appeared to influence the work described in this paper.

Acknowledgement

We like to express our sincere appreciation and gratitude to the hospital staff who helped to coordinate the trial, to the patients who participated. This research study was funded by Beximco Pharmaceutical Limited (BPL), Bangladesh. icddr,b acknowledges with gratitude the commitment of BPL to its research efforts. icddr,b is also grateful to the Governments of Bangladesh, Canada, Sweden and the UK for providing core/unrestricted support.

References

1. Johns Hopkins University of Medicine COVID-19

   COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (Available from: https://coronavirus.jhu.edu/map.html [accessed 17.11.2020]
2. Centers for Disease Control and Prevention. Interim Clinical Guidance for Management of Patients with Confirmed 2019 Novel Coronavirus (2019-nCoV) Infection, Updated March 7, 2020. 2020 [Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html [accessed 17.11.2020]
3. Caly, L., J. D. Druce, M. G. Catton, D. A. Jans and K. M. Wagstaff. (2020, Apr 3). "The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro." Antiviral Res, from https://www.ncbi.nlm.nih.gov/pubmed/32251768 (Caly et al. 2020)
4. Wu C., Liu Y., Yang Y. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm Sin B. 2020 doi: 10.1016/j.apsb.2020.02.008
5. Alam, M. T., Murshed, R., Bhiuyan, E., Saber, S., Alam, R., & Robin, R. (2020). A Case Series of 100 COVID-19 Positive Patients Treated with Combination of Ivermectin and Doxycycline. *Journal of Bangladesh College of Physicians and Surgeons*, *38*, 10-15. https://doi.org/10.3329/jbcps.v38i0.47512
6. Rajter J.C., Sherman M.S., Fatteh N., Vogel F., Sacks J., Rajter J.-.J. ICON (Ivermectin in COvid Nineteen) study: use of ivermectin is associated with lower mortality in hospitalised patients with COVID-19. medRxiv. 2020 2020.06.06.20124461.

7. Lespine A, Alvinerie M, Sutra JF, Pors I, Chartier C, 2005. Influence of the route of administration on efficacy and tissue distribution of ivermectin in goat. Vet Parasitol 128: 251–260.
8. Chiu SH, Lu AY, 1989. Metabolism and tissue residues. Campbell WC, ed. Ivermectin and Abamectin. New York, NY: Springer-Verlag, 131–143.

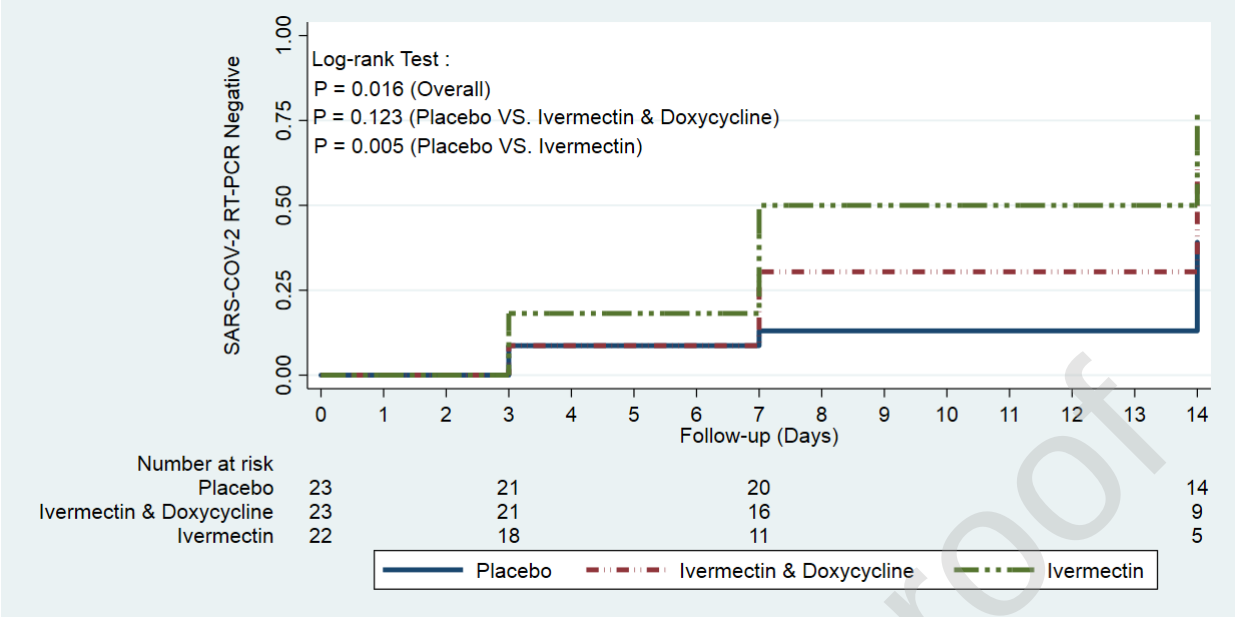

Figure: Cumulative viral recovery estimates in the overall study population.