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International Journal of Infectious Diseases 103 (2021) 214–216

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

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

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ARTICLE INFO

Article history:
Received 24 November 2020
Accepted 26 November 2020

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

ABSTRACT

Ivermectin, a US Food and Drug Administration-approved anti-parasitic agent, was found to inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in vitro. A randomized, double-blind, placebo-controlled trial was conducted to determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients. The trial included 72 hospitalized patients in Dhaka, Bangladesh, who were assigned to one of three groups: oral ivermectin alone (12 mg once daily for 5 days), oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days), and a placebo control group. Clinical symptoms of fever, cough, and sore throat were comparable among the three groups. Virological clearance was earlier in the 5-day ivermectin treatment arm when compared to the placebo group (9.7 days vs 12.7 days; $p = 0.02$), but this was not the case for 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 adult patients with mild COVID-19. Larger trials will be needed to confirm these preliminary findings.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic of the highest priority (Johns Hopkins University of Medicine, 2020). Eighty-one percent of cases are categorized as mild, for whom symptomatic management at home and monitoring of clinical deterioration is recommended (Centers for Disease Control and Prevention, 2020). 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 (Caly et al., 2020). Recent virtual drug screening identified doxycycline as a potential inhibitor of SARS-CoV-2 papain-like protease (Wu et al., 2020). An observational study in which patients were treated with a single-dose of ivermectin and multiple doses of doxycycline for the treatment of COVID-19 yielded considerable improvements in symptoms and the viral response (Alam et al., 2020). 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 (Rajter et al., 2020). Further studies are needed to verify these findings. This need is further underscored by the observation that SARS-CoV-2 multiplies rapidly in the respiratory tract and that evidence from animal models shows three-fold higher levels of ivermectin in pulmonary tissue than in the plasma at 1 week after oral dosing (Chiu and Lu, 1989; Lespine et al., 2005). This pilot study was performed to evaluate the rapidity of viral clearance and safety of a 5-day course of ivermectin or a single-dose of ivermectin + a 5-day course of doxycycline in the treatment of mild COVID-19 in adults.

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

Methods

A randomized, double-blind, placebo-controlled trial was conducted to determine the rapidity of viral clearance and safety of ivermectin among adult SARS-CoV-2 patients. The trial included 72 hospitalized patients in Dhaka, Bangladesh, who were assigned to one of three groups: oral ivermectin alone (12 mg once daily for 5 days), oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days), and a placebo control group. Inclusion criteria were age 18–65 years; admitted to hospital within the last 7 days; presence of a fever (≥37.5 °C), cough, and/or sore throat; diagnosed positive for SARS-CoV-2 by real-time reverse transcription PCR (rRT-PCR). Patients were excluded if they were allergic to ivermectin or doxycycline, or if there was the potential for a drug–drug interaction with ivermectin or doxycycline; had chronic illnesses (e.g., ischemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease); had received ivermectin and/or doxycycline in the last 7 days; were pregnant or lactating; or had participated in any other clinical trial within the last month.

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

Venous blood was collected for blood parameters on enrolment and on day 4 (complete blood count, creatinine, alanine aminotransferase, Random Blood Sugar). A chest X-ray and ECG were assessed on enrolment and on day 3. Blood biomarkers were measured on enrolment and on day 7 (C-reactive protein (CRP), ferritin, lactose dehydrogenase (LDH), and procalcitonin). RNA was tested for SARS-CoV-2 by rRT-PCR targeting ORF1ab- and N-gene specific primers and probes following the protocol of the Chinese Center for Disease Control and Prevention; subjected to amplification (iTaq Universal Probes One-Step Kit; Bio-Rad Laboratories, Inc., Hercules, CA, USA) in a Bio-Rad CFX96 Real-Time PCR Detection System (Bio-Rad Laboratories, Inc., Hercules CA, USA). A positive case had a cycle threshold (Ct) value of <40. Other information collected included demographic data and details of any co-morbidity, medication use, and previous hospitalization as part of the medical history. Data were entered into SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA).

The primary endpoints were the time required for virological clearance (a negative rRT-PCR result on nasopharyngeal swab), and remission of fever (≥37.5 °C) and cough within 7 days. Secondary outcomes included failure to maintain an SpO_2 >93% despite oxygenation and days on oxygen support, the duration of hospitalization, and all-cause mortality. Drug safety outcomes recorded were adverse events that occurred during treatment and post treatment, and the discontinuation of the study drug during the trial.

Results

Study descriptors

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

The mean duration of hospitalization after treatment was 9.7 days (95% confidence interval (CI) 8.1–11.0 days) in the placebo group, 10.1 days (95% CI 8.5–11.8 days) in the ivermectin + doxycycline group, and 9.6 days (95% CI 7.7–11.7 days) in the ivermectin alone group ($p = 0.93$). None of the patients enrolled required oxygen or had serious adverse drug events recorded. The mean values of the blood biomarkers (CRP, LDH, procalcitonin, and ferritin) dropped from baseline 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 group, and 77.3% (17/22) in the 5-day ivermectin group were recorded as having a fever, among whom 84.2% (16/19), 94.1% (16/17), and 100% (17/17), respectively, were afebrile on day 7. Similarly, 65.2% (15/23) in the placebo group, 82.6% (19/23) in the ivermectin + doxycycline group, and 81.8% (18/22) in the 5-day ivermectin group had a cough on enrolment. On 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 on day 7, the sore throat had subsided in 75% (3/4), 33.3% (1/3), and 75% (3/4) of patients, respectively. Of note, these changes were not statistically significant for fever ($p = 0.35$ and $p = 0.09$), cough ($p = 0.18$ and $p = 0.23$), or sore throat ($p = 0.35$ and $p = 0.09$) 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 days (95% CI 7.8–11.8 days) for the 5-day ivermectin arm ($p = 0.02$), 11.5 days (95% CI 9.8–13.2 days) for the ivermectin + doxycycline ($p = 0.27$) arm, and 12.7 days (95% CI 11.3–14.2 days) for the placebo group. Kaplan–Meier survival analysis revealed that the proportion of patients at risk of SARS-CoV-2 was significantly reduced in the 5-day ivermectin group (Figure 1, below). Virological clearance in the 5-day ivermectin group was significantly earlier compared to the placebo group on days 7 and 14 (hazard ratio (HR) 4.1, 95% CI 1.1–14.7 ($p = 0.03$) and HR 2.7, 95% CI 1.2–6.0 ($p = 0.02$)). The trend was similar for the ivermectin + doxycycline group on days 7 and 14, but this was not statistically significant (HR 2.3, 95% CI 0.6–9.0 ($p = 0.22$) and HR 1.7, 95% CI 0.8–4.0 ($p = 0.19$)).

Discussion

The drugs ivermectin and doxycycline are commonly used in the developing world and have been found to be safe and effective in treating both parasitic and bacterial infections. The drugs are affordable (the full 5-day cost ranges from US$ 0.60 to US$ 1.80 for 5-day ivermectin) and readily available in Bangladesh, and thus are a highly attractive alternative for treating COVID-19 patients. The aim of this study was 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 the 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 that early intervention with this agent may limit viral replication within the host. In the 5-day ivermectin group, there was a significant drop in CRP and LDH by day 7, which are indicators of disease severity. It is noteworthy that the viral nucleic acid Ct value (indicator of viral load) dropped significantly compared to the placebo group on day 7

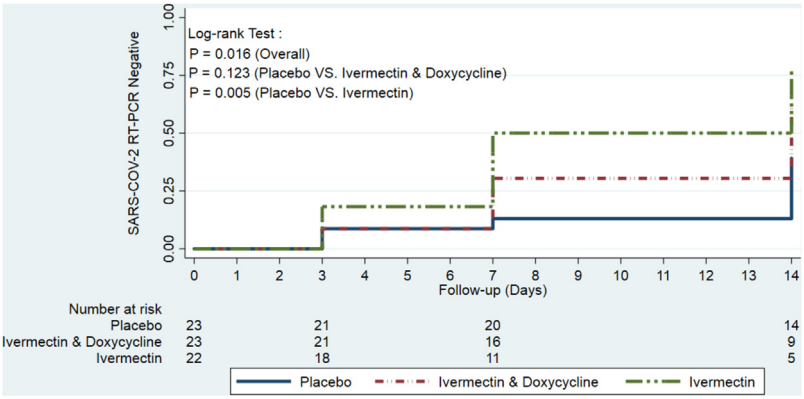

Figure 1. Cumulative viral recovery estimates in the overall study population.

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 draw any solid conclusions, the results provide evidence of the potential benefit of early intervention with the drug ivermectin for the treatment of adult patients diagnosed with mild COVID-19. First, early intervention promoted faster viral clearance during disease onset, which might have prevented significant immune system involvement and hastened the 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.

Funding source

This work was supported by 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 the Directorate General of Drug Administration, Government of Bangladesh. Written informed consent was obtained from all patients.

Declaration of interests

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

Conflicts of interest

The authors have no conflicts of interest to declare.

Author contributions

JDC, AGR, WAK, KZ, JS, conceived and designed the study. RY, MAH, AK, SA, MMK, CSP, MSH, MR, and ABA made substantial contributions in reviewing the design of the study and acquiring the data. SA, MMK, MSH, and ABA coordinated sample collection and oversaw data collection. MR and MKS conducted and analysed the laboratory results. MSH analysed the data and WAK, SA, MMK, CSP and MSH interpreted the data. WAK and SA conducted the literature review and drafted the manuscript. MMK, MSH, and ABA contributed by revising the manuscript critically for important intellectual content. JDC, AGR, WAK, KZ, JS, MSF, MR, RY, MAH, and AK critically reviewed the manuscript. All authors contributed to final approval of the version to be submitted.

Author agreement

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

Acknowledgements

We would like to express our sincere appreciation and gratitude to the hospital staff who helped to coordinate the trial and 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.

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