A Randomized Controlled Trial of Combined Ivermectin and Zinc Sulfate versus Combined Hydroxychloroquine, Darunavir/Ritonavir, and Zinc Sulfate among Adult Patients with Asymptomatic or Mild Coronavirus-19 Infection

Sireethorn Nimitvilai, Yupin Suputtamongkol, Ussanee Poolvivatchaikarn, Dechatorn Rassamekulthana, Nuttawut Rongkiettechakorn, Anek Mungaomklang, Susan Assanasae, Ekkarat Wongsawat, Chompunuch Boonarkart, Waritta Sawawdee

Department of Medicine, Nakhon Pathom Hospital, Nakhon Pathom, Departments of *Medicine and *Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, **The Golden Jubilee Medical Center, Faculty of Medicine Siriraj Hospital, Office of Disease Prevention and Control Region 4 Saraburi, Ministry of Public Health, Bangkok, *Department of Medical Sciences, Genomic Medicine and Innovation Support, Ministry of Public Health, Nonthaburi, Thailand

Abstract

Introduction: Ivermectin, hydroxychloroquine (HQ), and darunavir/ritonavir are widely prescribed as an oral treatment for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection despite their uncertainty of clinical benefit. The objective is to determine the safety and the efficacies of two treatment regimens against SARS-CoV-2 infection. Methods: We conducted an open-labeled, randomized, controlled trial to compare the efficacy between a 3-day course of once-daily high-dose oral ivermectin plus zinc sulfate (Group A) and a combination of HQ, darunavir/ritonavir, and zinc sulfate (HQ + antiretroviral, Group B) for 5 days in asymptomatic or mild SARS-CoV-2 infection. The study period was between December 2020 and April 2021. Results: Overall, 113 patients were randomized and analyzed (57 patients in Group A and 56 patients in Group B). The median duration to achieve virological outcome of either undetected or cycle threshold (Ct) for N gene of SARS-CoV-2 by real-time polymerase chain reaction was 6 days (95% confidence interval [CI] 5.3–6.7) versus 7 days (95% CI: 5.4–8.6) in Group A and Group B, respectively ($P = 0.419$) in the modified intention-to-treat population. All patients were discharged from hospital quarantine as planned. Two patients in Group A and one patient in Group B were considered clinically worsening and received 10 days of favipiravir treatment. There was no serious adverse event found in both groups. Conclusion: We demonstrated that both treatment regimens were safe, but both treatment regimens had no virological or clinical benefit. Based on this result and current data, there is no supporting evidence for the clinical benefit of ivermectin for coronavirus-19.

Keywords: Coronavirus-19, darunavir/ritonavir, hydroxychloroquine, ivermectin

INTRODUCTION

The outbreak of coronavirus-19 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused an ongoing burden on health-care systems worldwide. Both the asymptomatic and symptomatic patients had similar viral loads. Published data showed that the transmission from asymptomatic or mild infection is very high. The administration of an effective oral antiviral therapy would be useful for transmission blocking or reducing onward transmission by these population. In addition, early treatment of these patients may prevent progression to severe COVID-19. However, an effective treatment option is not yet available for SARS-CoV-2 infection.

Ivermectin is a safe and widely used antiparasitic drug with known in vitro efficacy against several single-strain RNA viruses, including SARS-CoV-2. Ivermectin has been...
evaluated as a potential treatment and/or prevention for COVID-19, as well as being used off-label in many parts of the world. However, based on the pharmacokinetic report, with the routine antiparasitic dose of ivermectin (0.15 mg/kg–0.2 mg/kg body weight), its inhibitory action on SARS-CoV-2 replication is practically not attainable in humans.[4] Currently, ivermectin dose (0.1 mg/kg–24 mg fixed dose) and duration (single dose through 1 week) that were used for the treatment of COVID-19 varied from study to study.[5] Based on our previous published data on ivermectin used in adult patients with dengue infection in Thailand[6] and unpublished data on pharmacokinetic of ivermectin among this population, 0.6 mg/kg body weight per day for 3 days could be effective for the treatment of SARS-CoV-2 infection.

Combination of hydroxychloroquine (HQ) and antiretroviral (ARV) drugs such as lopinavir/ritonavir or darunavir/ritonavir was used for the treatment of COVID-19 in 2020 and is currently being used in some countries, despite the published report that they show no benefit.[7–9] Here, we reported a randomized controlled trial of a high dose of ivermectin combined with zinc sulfate versus a combination of HQ, darunavir/ritonavir, and zinc sulfate for the treatment of asymptomatic or mild COVID-19 infection.

Methods

This was an open-labeled, randomized, controlled trial of a once-daily dose of ivermectin (0.6 mg/kg body weight) for 3 consecutive days and the combination of HQ and darunavir/ritonavir for 5 days. The trial enrolled 118 adult patients at three hospitals in Thailand: Siriraj Hospital and the Golden Jubilee Medical Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, and Nakhon Pathom Hospital, Nakhon Pathom Province, Thailand. The period of recruitment and follow-up of participants was between December 2020 and April 2021.

Patients

Patients were eligible if they were 18 years of age or older with a confirmed diagnosis of COVID-19 by real-time polymerase chain reaction (RT-PCR) detection of SARS-CoV-2 specific genes (Allplex 2019-nCoV Assay, Seegene, Korea) who were asymptomatic, or axillary temperature of <38°C, normal chest radiography, and oxygen saturation at room air of more than 95%. Patients were excluded if they were HIV infected, pregnant, lactating, taking warfarin, receiving immunosuppressive therapy for other chronic disorders, or had a history of hypersensitivity to ivermectin or HQ or darunavir/ritonavir. All patients provided written informed consent.

Randomization and interventions

After informed consent was received, baseline medical history and physical examinations were completed in standard case record forms, and baseline laboratory investigations were performed. Patients were randomly assigned to either Group A or Group B according to a computer-generated sequence of random numbers in blocks of 4. The treatment allocations were kept in sealed envelopes, which were not opened until after enrollment in the study. Group A was treated with oral ivermectin (Atlantic Laboratory Ltd, Bangkok, Thailand) 0.6 mg/kg body weight once daily, plus oral zinc sulfate 200 mg twice daily for 3 days. The ivermectin was given with a meal after baseline blood sample collection. Treatment of Group B composed of a combination of HQ (200 mg) plus darunavir/ritonavir (ARV, 400/100 mg) and zinc sulfate (Zn, 200 mg) twice daily for 5 days. The study pharmacist prepared treatment packs for each patient, according to the randomization group, for dispensation in sequential order after patients were recruited. YS, SN, UP, DR, and NR were responsible for enrolling the participants; YS and SN were responsible for ensuring that the correct sequence of study codes, and therefore the treatment allocation, was followed. All virological tests were done at the Molecular Laboratory, Faculty of Medical Technology and Allied Health, Mahidol University, and all samples were labeled with the study code. Thus, all laboratory personnel who performed virological tests were blinded for the treatment allocation.

The condition of all inpatients was reviewed daily until discharge for the assessment of clinical progress and drug-related adverse event (AEs). Patients were discharged from the hospital after 10 to 14 days of hospital quarantine. They were asked to come back for follow-up at 1–2 weeks after discharge from the hospital.

Study measurements

Nasopharyngeal (NP) samples were collected in 2 ml viral transport media (VTM) before study medication was administered, 5–7 days after treatment, at discharge, and at 1–2 week follow-up. Total nucleic acid extraction was performed using a viral RNA mini kit (QIAGEN, Hilden, Germany), and was recovered using 60 µL of elusion buffer. RT-PCR assay targeting the three genes including receptor domain-binding protein gene, enveloped protein (E), and nucleocapsid (N) genes of SARS-CoV-2 was performed (Allplex 2019-nCoV Assay, Seegene, Korea). The cycle threshold (Ct) value of these genes was recorded.

Eighty microliters of the remaining samples was inoculated into cell culture.[10] Vero E6 cell line (American Type Culture Collection certificate revocation list-1586, Manassas, US) was cultured in Dulbecco’s Modified Eagle’s Medium (DMEM; Gibco, Grand Island, US) with 10% fetal bovine serum (FBS, Gibco, Grand Island, USA) and 1% Penicillin-Streptomycin (Pen/Strep; Gibco, Grand Island, USA) for 1 h. Then, 100 µL of DMEM with 2% FBS was added and incubated at 37°C in 5% CO₂. Vero cells were seeded on 96-well plates at a density of 1.5 × 10⁴ cells/well 24 h prior. After 7 incubation days, if the cytopathic effect was microscopically detected, then SARS-CoV-2 antigen detection was confirmed by immunofluorescence assay, using SARS-CoV/SARS-CoV-2 nucleocapsid rabbit monoclonal antibody (Sino Biological).[11] In brief, suspected SARS-CoV-2-infected Vero E6 cells were washed by phosphate-buffered saline (PBS) and fixed by 80%
acetone at 4°C for 1 h. Fixed cells were washed three times using PBS with 0.03% Triton X (Sigma, St. Louis, US), then were blocked by 3% bovine serum albumin (Sigma, St. Louis, US) in PBS for 30 min at room temperature. Hundred-fold diluted SARS-CoV/SARS-CoV-2 nucleocapsid rabbit monoclonal antibody (Sino Biological, Beijing, China) was added and incubated at 37°C for 1 h. After incubation, three-time washing was performed, then 250-fold diluted Alexa Fluor 488 conjugated goat anti-rabbit IgG (Invitrogen) and 5,000-fold diluted Hoechst 33342 (Invitrogen, Eugene, US) were added and incubated for 1 h at 37°C. After three-time washing, cells were fixed by 1% paraformaldehyde, then were observed under inverted fluorescent microscopy.

SARS-CoV-2 variants were determined by whole-genome sequencing using Illumina COVID Seq Test. Briefly, viral RNA was purified from 300 μl of NP samples using Chemagik Viral DNA/RNA 300 Kit H96 (cat. CMG-1033-S) on PerkinElmer Chemagic 360 Instrument according to the manufacturer’s instruction. All RNA samples were quality controlled by RT-PCR. The RNA with Ct values <30 was used for library preparation according to the manufacturer’s instruction (Illumina Covid Seq RUO Kits Reference Guide 1000000126053 v06). The sequencing was done on the Next Seq 550 system. Variant calling was accomplished by Illumina DRAGEN COVID Lineage analysis v. 3.5.3 software on illumine base space. All virological tests were performed by technicians that were not involved in the enrollment and management of cases; thus, they were blinded to the interventions.

Statistical analysis and sample size calculation

We assumed that an antiviral treatment was effective against viral replication during the first phase of illness, and patients developed immune responses against this virus after 1 week of infection. Although RT-PCR cannot reflect the presence of an infectious virus, a high Ct value was considered a marker for undetected the live virus. Thus, we compared the time from initiation of the study medication to RT-PCR Ct value of >30 or undetected between the two treatment groups. Thus, the sample size of this study was calculated from an assumption that the proportion of patients with this virological outcome was 40% and 70% in the combined HQ, darunavir/ritonavir, and zinc sulfate group and combined ivermectin and zinc sulfate respectively, with a two-sided significant level of 0.05 and 80% power, and 20% loss to follow-up, we calculated that 40 patients with RT-PCR positive per group would be needed.

Baseline demographic data and clinical and laboratory results between the study groups were compared with Chi-square test, Fisher’s exact test, and the nonparametric Mann–Whitney test as appropriate. The comparison of time to reduction of SARS-CoV-2 detection by RT-PCR to Ct >30 after the treatment was displayed using Kaplan–Meier curves with statistical comparison by a log-rank test. Other outcomes were compared between treatment group using Fisher’s exact test or Mann–Whitney test as appropriate.

RESULTS

Of the 164 adult patients with SARS-CoV-2 infection who underwent screening, 118 patients were randomized (58 patients in Group A and 60 patients in Group B, respectively). Two patients were withdrawn from the study due to randomization because exclusion criteria were detected in one patient in Group B and incorrect study drug administered leading to protocol deviation in another patient in Group A. Two patients in Group B withdrew informed consent and did not complete the treatment due to AEs, and baseline NP sample was missing in the third patient in this Group B. Thus, there were 57 patients in Group A and 56 patients in Group B in the modified intention-to-treat analysis [Figure 1]. Demographic data and baseline information of both study groups are shown in Table 1. After enrollment, we did not perform RT-PCR and culture of four patients (two patients in each Group) because their first follow-up NP swab was missing from the VTM. The per-protocol analysis included those who had detectable SARS-CoV-2 RNA at enrollment or detectable RNA at follow-up if baseline RNA was undetected, completed the treatment, and had follow-up NP samplings after treatment (42 patients in Group A and 38 patients in Group B) [Figure 1]. Most patients in this study were infected with B.1.36.16 variant. B.1.1.7 was identified in seven patients who enrolled in April 2021.

Virological outcomes

Viral isolation

Overall SARS-CoV-2 was isolated from NP samples from 18 patients (10 in Group A and 8 in Group B, with a mean ± standard deviation Ct for N gene 22.54 ± 2.76, minimum Ct of 13.99, and maximum Ct of 35.99 for N gene detection) at baseline, including two patients (one patient in each group) who were excluded from the study after randomization. None of these patients had a positive culture after treatment. However, the SARS-CoV-2 was isolated from NP sample of 2 more patients in Group A after treatment. The first patient, who was previously healthy and was asymptomatic on admission, developed mild symptoms of cough during the hospital quarantine. She admitted with the Ct of 32, 20.05, and 22.11 for N gene detection at baseline, 10 days, and 12 days after that. The SAR-CoV-2 was also isolated from her NP sample taken on day 12. Another patient presented with a mild symptom of cough 1 day prior to admission, her symptoms resolved on day 7 of the hospital quarantine. The Ct for N-gene of this patient was 33.39, 28.49, and 36.46 at baseline, 6 days after enrollment (when the virus was isolated), and 9 days after enrollment, respectively.

Real-time-polymerase chain reaction outcome

At baseline, RT-PCR results were undetected in 29 patients (13 patients in Group A and 16 patients in Group B) [Figure 1]. The distribution of Ct for N gene at baseline varied widely but similar in distribution among the two study groups (P = 0.139). The median duration to achieve the virological outcome of either undetected or Ct of more than 30 of SARS-CoV-2 RNA by RT-PCR was 6 days (95% Confidence interval [CI]: 5.3 – 6.7) versus 7 days (95% CI:
population, the median duration to achieve virological outcome was 7 days (95% CI: 5.9 – 8.1) versus 8 days (95% CI: 7.1 – 8.8) in Group A and Group B, respectively (P = 0.207). Kaplan–Meier plots compared the proportion of patients with this virological outcome among modified intention-to-treat analysis population and per-protocol analysis population [Figures 2 and 3, respectively].

### Clinical outcome

All patients were discharged between 10 and 14 days of hospital quarantine as planned. Two patients in Group A and one patient in Group B were considered as clinically worsening and received 10 days of favipiravir treatment. One of them (Group A) developed pneumonia after completed 3 days of ivermectin and zinc sulfate treatment. He received 10 days of favipiravir and oral dexamethasone. Another patient in Group A (who had SARs-CoV-2 isolated, with the Ct for N gene of 24.6 at baseline) received favipiravir due to persistent fever during hospital quarantine. These two patients were infected with alpha (B.1.1.7) SARS-CoV-2 variant. Another patient in Group B developed pneumonia after admission and received favipiravir after 4 days of combined HQ + ARV + Zn treatment. He recovered eventfully and discharged after 12 days of admission. This patient was infected with B.1.36.16 SARS-CoV-2 variant.

AE was assessed in all randomized patients up to 28-day follow-up. Overall, 14 AEs occurred in both treatment groups (four patients in Group A and ten patients in Group B, P = 0.235). Two patients in Group B withdrew their informed consent due to AE, one patient developed generalized maculopapular rash and another patient developed persistent vomiting despite antiemetic treatment. In Group A, AEs included transient watery diarrhea, nausea, and transient blurred of vision. In Group B, AEs included watery diarrhea.
detected in three patients, and nausea, feeling unwell detected in one each. Rising of AST/ALT to 1.5 times and 5 times of upper normal limit was found in two patients and one patient in Group A and Group B, respectively.

**DISCUSSION**

All patients in this study were either asymptomatic or mild SARS-CoV-2 infection. Most infections were caused by the B.1.36.16 variant which was the main variants causing the epidemic in Thailand during the study.[16] Their baseline Ct values for N gene varied widely and approximately one-fourth of RT-PCR results were negative at enrollment. The SARS-CoV-2 viral load is inversely proportional to the Ct values, and a high value of Ct indicates a lower infectivity risk, as it depicts a low concentration of viral RNA material.[12-14] The high Ct at enrollment found at baseline was associated with a convalescent stage in most patients. It was also associated with the incubation period in two patients in Group A, whose SARS-CoV-2 was isolated after ivermectin treatment.

In designing this clinical trial, we hypothesized that early treatment with a combination of 3-day once-daily high-dose oral ivermectin[17] and zinc sulfate[18,19] could accelerate SARS-CoV-2 clearance from the upper respiratory tract of patients with asymptomatic or mild infection compared to the control group. We did not demonstrate any significant difference in virological outcomes between the two treatment groups. The interpretation of these results could be that both regimens were equally effective or ineffective. The evidence supportive for the effectiveness included a low rate of worsening or progression of infection in both groups (two patients in Group A and one patient in Group B). However, there was no clear evidence of antiviral effects for the control arm. The current published data did not support that HQ or chloroquine and/or darunavir/ritonavir was effective against COVID-19.[7-9] In addition, the finding that SARS-CoV-2 was isolated from two patients after ivermectin treatment was strong evidence that ivermectin had no antiviral effect in these cases. Thus, the lack of benefit for ivermectin found in this study most likely indicated that it had no antiviral effects.

Our results are supported by various recently published studies. Results from the IVERCOR-COVID-19 trial,[20] which was a randomized, double-blinded, placebo-controlled trial evaluating 2 days of ivermectin versus placebo in 501 patients with mild infection in Argentina also showed no significant clinical benefit of ivermectin. Another ongoing clinical study, the “TOGETHER” trial,[21] randomized over 2100 outpatients with COVID-19 infection in Brazil to either fluvoxamine, ivermectin, or placebo. The initial results of this study showed that there is no clinical benefit of HQ, and lopinavir/ritonavir for COVID-19, and the latest results presented in August 2021 showed that only oral fluvoxamine, not ivermectin, had a statistically significant reduction in the risk of hospitalization when compared to placebo. As a result, the current evidence has led to the National Institutes of Health’s decision that there is insufficient evidence for ivermectin treatment in COVID-19.[22]

Although the laboratory outcomes were determined by blinded laboratory personnel, the duration for achieving virological outcomes could be imprecise because two-third of the patients were asymptomatic. Other limitations of this study included small sample size and no placebo-controlled group. Meta-analysis of small sample size but well-controlled studies should provide evidence for potential efficacies of ivermectin. However, Hill et al. recently retracted their published meta-analysis[23] and re-submitted excluding clinical trials that the published analysis...
was based on due to unreliable data found in the preprint study reporting that ivermectin treatment was associated with a significant reduction of COVID-19 deaths. Thus, it is crucial that data from all clinical trials are assessed comprehensively to identify any indication of fraud or misconduct.

The clinical benefit of both fluvoxamine andinhaled budesonide is shown in two well-designed randomized controlled trials with large sample size and less biases compared to previous clinical trials of repurposed drugs for COVID-19. For example, results from the clinical trial, PRINCIPLE, reported that early treatment withinhaled budesonide shortened recovery time by 3 days compared to standard care in patients with COVID-19 who were treated at home.

**Conclusion**

This randomized controlled trial observes two-combination drug treatment regimens for early SARS-CoV-2 infection. We demonstrated that both treatment regimens were safe but had no virological or clinical benefit. Based on this result and current data, there is no supporting evidence for the clinical benefit of ivermectin for COVID-19.

**Research quality and ethics statement**

The authors followed applicable EQUATOR Network (http://www.equator-network.org/) guidelines during this research project. This study was approved by the appropriate Institutional Review Board of all study sites, the Council of Architecture (COA 323/2563), and (COA 002/2021). The trial was registered with ClinicalTrials.gov (NCT02045069).

**Financial support and sponsorship**

This work was funded by Health Systems Research Institute, Thailand (Grant Number 63-067). Y. S. has been supported by a Siriraj Chalermprakiat Grant, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 2020;382:1177-9.
2. Baek YJ, Lee YJ, Yoon JS, Sohn Y, Cho Y, Kim MH, et al. Duration of culturable SARS-CoV-2 within different specimens among mild and severe COVID-19 patients: A longitudinal study. J Infect 2021;83:e29-31.
3. 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.
4. Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view: Antiviral levels are not likely attainable with known dosing regimens. Biotechnol Biotechnol Equip 2020;34:469-74.
5. Hill A, Garratt A, Levi J, Falconer J, Ellis L, McCann K, et al. Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection. Open Forum Infect Dis 2021;8:ofab358.
6. Suputamongkol Y, Avirutnan P, Mairiang D, Angkasewinchai N, Niwattayakul K, Yamasmit E, et al. Ivermectin accelerates circulating nonstructural protein 1 (NS1) clearance in adult dengue patients: A combined phase 2/3 randomized double-blind placebo controlled trial. Clin Infect Dis 2021;72:e586-93.
7. Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: Open label, randomised controlled trial. BMJ 2020;369:m1849.
8. Bakaidsi BM, He F, Souho T, Lamboni L, Ullah MW, Boni BO, et al. Prevention and treatment of COVID-19: Focus on interferons, chloroquine/hydroxychloroquine, azithromycin, and vaccine. Biomed Pharmacother 2021;133:111008.
9. Osborne V, Davies M, Lane S, Evans A, Denyer J, Dandha S, et al. Lopinavir–ritonavir in the treatment of COVID-19: A dynamic systematic benefit-risk assessment. Drug Saf 2020;43:809-21.
10. Araujo DB, Machado RR, Amgarten DE, Malta FM, de Araujo GG, Monteiro CO, et al. SARS-CoV-2 isolation from the first reported patients in Brazil and establishment of a coordinated task network. Mem Inst Oswaldo Cruz 2020;115:e200342.
11. Terry JS, Anderson LB, Scherman MS, McAlister CE, Perera R, Schountz T, et al. Development of a SARS-CoV-2 nucleocapsid specific monoclonal antibody. Virology 2021;558:28-37.
12. Rabaan AA, Tirupathi R, Sule AA, Aldali J, Mutair AA, Alhumaid S, et al. Viral dynamics and real-time RT-PCR Ct values correlation with disease severity in COVID-19. Diagnostics (Basel) 2021;11:1091.
13. Jefferson T, Spencer EA, Braysey J, Heneghan C. Viral cultures for COVID-19 infectious potential assessment – A systematic review. Clin Infect Dis 2021;73: e3884–e3899
14. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill 2020;25:2001483.
15. Fleiss JL, Tytun A, Ury HK. A simple approximation for calculating sample sizes for comparing independent proportions. Biometrics 1980;36:343-6.
16. Yap PS, Tan TS, Chan YF, Tee KK, Kamurazaman A, Teh CS. An overview of the genetic variations of the SARS-CoV-2 genomes isolated in Southeast Asian countries. J Microbiol Biotechnol 2020;30:962-6.
17. Kinde RB, Owens L. A systematic review of experimental evidence for antiviral effects of ivermectin and an in silico analysis of ivermectin’s possible mode of action against SARS-CoV-2. Fundam Clin Pharmacol 2021;35:260-76.
18. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 2010;6:e1001176.
19. Elgarzzar A, Eltaweel A, Youssef SA, Hany B, Hafes M, Moussa H. Antiviral Res 2020;178:104787.
20. Reis G, Silva E, Silva D, Thabane M, Milagres AC, Ferreira TS, et al. Effect of Early Treatment with Ivermectin among Patients with COVID-19. N Engl J Med 2020 Mar 30. doi: 10.1056/NEJMoa2115869. Epub ahead of print. PMID: 35353979.
21. National Institutes of Health. Ivermectin. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ivermectin/. [Last updated on 2021 Feb].
22. Hill A, Garratt A, Levi J, Falconer J, Ellis L, McCann K, et al. Erratum: Expression of concern: “Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection”. Open Forum Infect Dis 2021;8:ofab394.
23. Elgarzzar A, Altaweel YA, Youssif SA, Hany B, Hafes M, Moussa H. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. Res Sq 2020. [doi: 10.21203/rs.3rs-100956/v3].
24. Elgarzzar A, Altaweel YA, Youssif SA, Hany B, Moussa H. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. Res Sq 2020. [doi: 10.21203/rs.3rs-100956/v3].
25. Counsilman AA, Mouawia H, Fawaz M, Hassain H, Salami A, Bazzal AA, et al. Effects of a single dose of ivermectin on viral and clinical outcomes in asymptomatic SARS-CoV-2 infected subjects: A pilot clinical trial in Lebanon. Viruses 2021;13:989.
26. Yu LM, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): A randomised, controlled, open-label, adaptive platform trial. Lancet 2021;398:843-55.