Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial

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EDITORIAL NOTE:

25 October 2021: This study describes the results of a double-blind, randomized controlled trial for the use of ivermectin to treat mild to severe COVID-19 infection in 180 patients. The researchers indicated that the treatment resulted in reduced mortality, improved oxygen saturation, and improvement on a number of other clinical parameters. On 8 October 2021 and 9 October 2021, two articles were published by subject-matter experts outlining concerns about various aspects of the study and, in particular, calling into question the randomization of participants. The authors and publishing journal have been alerted to these issues, and this note will be updated with any new information related to the publication.

Abstract

Background: It appears that ivermectin can potentially act against COVID-19 infection. Today, it is an urgent need to evaluate the efficacy and safety of ivermectin. The effect of ivermectin therapy on mild to severe COVID-19 patients was investigated.

Methods: A 45-days randomized, double-blind, placebo-controlled, multicenter, phase 2 clinical trial was designed at five hospitals. A total number of 180 mild to severe hospitalized patients with confirmed PCR and chest image tests were enrolled. The radiographic findings, hospitalization and low O_2 saturation duration, and clinical outcomes such as mortality and variables of blood samples were analyzed using standard statistical analyses in SPSS (V20).

Results: Average age of the participants was 56 years (45-67) and 50% were women. The primary and secondary results showed significant changes between day zero and day five of admission (Δ 0/5) in terms of ΔALC5/0, ΔPLT5/0, ΔESR5/0, ΔCRP5/0, duration of low O_2 saturation, and duration of hospitalization (CI = 95%). Risk of mortality was also decreased significantly in the study groups.

Conclusion: Ivermectin as an adjunct reduced the rate of mortality, low O_2 duration, and duration of hospitalization in adult COVID 19 patients. The improvement of other clinical parameters showed that the ivermectin, with a wide margin of safety, had a high therapeutic effect on COVID-19.

Trial Registration: This trial was registered with the Iranian Registry of Clinical Trials website (registration ID IRCT20200408046987N1).

Introduction

The COVID-19 infection has become a pandemic since its first outbreak in Wuhan, China in 2019. This infection is caused by the novel COVID-19 and has created a difficult condition around the world. Thus, there is an important and urgent need to find proper treatments for an effective cure, decrease the virus carriage duration, and thus limit its transmission in society [1-3]. So far, different drugs such as Hydroxychloroquine (HCQ) [4,5], Azithromycin [6], and combination of them have been used against COVID-19. Several studies have demonstrated that chloroquine phosphate and chloroquine sulfate inhibit COVID-19 *in-vitro* [7-9]. In addition, Gautret et al. evaluated a combination of HCQ and azithromycin on COVID-19 infected cells *in-vitro*, and concluded that there was a considerable synergetic effect when the combination was used at doses which imitates the concentrations likely to be taken in humans [8]. Chloroquine, illustrated positive results in Chinese COVID-19 patients in clinical trials by alleviating fever, delaying disease progression, and management of COVID-19 disease (500mg twice per day for ten days) [8,10,11]. However, among the candidate treatments, only three main drugs including Remdesivir, Oseltamivir, and HCQ have been tested in large comparative studies [8,10-15]. Some of studies have shown that Lopinavir, Ritonavir, and Remdesivir have no clear influence on COVID-19 infection and they are associated with many adverse effects [13,16,17]. In addition, HCQ has demonstrated its efficacy in

reducing viral shedding durability [11], and improving patients' clinical status in observational or randomized clinical trials [12,18,19]. Ivermectin is an unexpensive FDA-approved anti-parasitic drug, known to have a wide-spectrum antiviral activity against a variety of viruses in *in-vitro* conditions. It inhibits the proliferation of COVID-19 in cell culture as well [6,20,21]. Moreover, ivermectin shows antiviral activity against some RNA viruses including Zika, dengue, yellow fever, West Nile, Hendra, Newcastle, Venezuelan equine encephalitis, chikungunya, Semliki Forest, Sindbis, Avian influenza A, Porcine Reproductive and Respiratory Syndrome, and HIV-1. Furthermore, there are some studies showing the antiviral effects of ivermectin against DNA viruses such as Equine herpes type 1, BK polyomavirus, pseudorabies, porcine circovirus 2, and bovine herpesvirus 1 [22]. Ivermectin may also act on the COVID-19 virus through three proposed mechanisms that result in reducing the load of the virus. These mechanisms includes: inhibition of nuclear import of host [23], interfering with the attachment of the spike to the human cell membrane [24,25], and inhibition of helicase activity [26]. Based on elementary data from Caly et al., Monash University in Australia, a strategy was designed including early PCR test or chest image to detect positive patients and adding ivermectin to the treatment regimen at different doses, to investigate its possible treatment efficacy on COVID-19 patient.

Materials And Methods

Study design

A randomized, double-blind, placebo-controlled, multicenter, phase 2 study was carried out to examine the effectiveness of oral ivermectin in hospitalized adults (age >18 years) with COVID-19. The trial was conducted at five hospitals (Velayat, Bu Ali, Taleghani, Razi, and Sina) in Qazvin and Khuzestan provinces of Iran. Ethical approval was in accordance with the ethical standards of the Helsinki Declaration (1964, amendment of 2008). The study protocol was approved by the medical ethics committee of Qazvin University of Medical Sciences (registration ID IR.QUMS.REC.1399.017).

Patient selection

Eligible patients with COVID-19 who met the following criteria were admitted: a) Age >18 years; b) signed the informed consent; c) clinical symptoms of suggestive of COVID-19 pneumonia: cough (with or without sputum), fever, pleuritic chest pain or dyspnea; d) mild to severe COVID-19 disease confirmed by chest computed tomography (CT) scan findings compatible with COVID-19 or positive real-time reverse transcription polymerase chain reaction (RT-PCR). Exclusion criteria included presence of severe immunosuppression (e.g., use of immune-suppressants and HIV positive), pregnant women, chronic kidney disease, malignancy, and indications that the patients were unable and/or unlikely to comprehend and/or follow the protocol. The primary endpoint of this trial was clinical recovery within 45 days of enrolment. Clinical recovery was defined as normal fever, respiratory rate, and oxygen saturation (>94) without oxygen therapy sustained for 24h. The patients would be discharged if this trend continued. During the process the criteria for discharge was changed over the course of study. Initially, patients with two successive negative nasopharyngeal samples based on PCR assay (CT value≥35) were separated.

The study sample size was estimated based on a test of equivalence[27]. Using a two-sided test level of 0.05 and a desired statistical power of 90% and under the assumption that each treatment arm would yield a 75 % success rate, the number of patients in the study was obtained equal to 163 patients. Assuming an availability rate of 35%, 30 patients were enrolled per treatment arm.

Interventions

The participants were randomly allocated to six arms including common regimen based on Iran health ministry (Hydroxychloroquine 200mg/kg twice per day), placebo plus common regime, single dose ivermectin (200mcg/Kg, 1 pill per day), three low interval doses of ivermectin (200, 200, 200 mcg/Kg , 3 pills in 1, 3 and 5 interval days), single dose ivermectin (400mcg/Kg, 2 pills per day), and three high interval doses of ivermectin (400, 200, 200 mcg/Kg, 4 pills in 1, 3 and 5 interval days).

Randomization and masking

Eligible patients were randomly allocated to either the standard, Placebo and the ivermectin arms. Randomization according to the severity of the disease was as follows: mild, moderate, and sever. The transposed block randomization sequence, including stratification, was prepared by a statistician not involved in the trial using Random Allocation Software. The patients in six treatment arms enrolment were randomized after calling the central randomization telephone number and receiving randomization information and confirmation. Each patient received the unique patient numbers that were to be used on all study medication containers, case report forms, and to identify all specimens. Pharmacia generated the randomization list and provided the list to the central randomization service.

Laboratory and radiographic tests

The patients systematically underwent an unenhanced chest low-dose computed tomography (LDCT) at reception or soon after, using a single CT machine (16 slice Model Neusof, China). All images were analyzed by expert chest radiologists and classified as compatible or not compatible with pneumonia. Images were considered as compatible with circumferential multifocal ground-glass opacities, vesicular consolidation, or crazy paving template. Novel Coronavirus RNA was recognized by real-time reverse transcription PCR [28]. Negative results for viral RNA detection were defined as a cycle threshold (CT) value≥35.

Treatment

All patients were treated according to “Iranian guideline of hospitalized COVID-19 patients’ management (version 5)”. This comprised oral hydroxychloroquine (HCQ) 200mg/kg twice per day as standard regimen and a heparin prophylaxis in combination with supplemental oxygen. Tablet of ivermectin (14 mg) and placebo were formulated in Alborz Darou pharmaceutical Co., Tehran, Iran. The Participants received drug after signing the consent letter. For all arms, radiographic findings, hospitalization time, clinical outcomes such as mortality, and clinical parameters such as account oxygen saturation testing

and blood sampling absolute lymphocyte count (ALC), C-reactive protein (CRP), white blood cells (WBC), lactate dehydrogenase (LDH), thrombocyte count (PLT), erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), and creatinine (Cr) were examined on days zero and five. Assessment of gas exchange requires knowledge of fractional inspired oxygen tension (FiO_2); unless the patient is breathing room air. Hence, all peripheral capillary oxygen saturation was measured in breathing room air at rest.

Statistical methods

The SPSS version 20 (SPSS®, Armonk, NY, USA) software was used for statistical analyses. Shapiro-Wilk test was used to evaluate normality of numerical variables. The quantitative variables were expressed as mean ± SD (standard deviation) or Median ± IQR (Inter Quartile Range). The difference values for each quantitative variable on days zero and five (Δ 0/5) were calculated to check recovery process of patients between groups. Pair T-test / Wilcoxon signed-rank test were used on inter-group comparison. The analysis of variance (ANOVA) was used to compare the mean scores of the groups. To compare the proportions, Pearson chi-square or Fisher's exact test was used. Analyses were based on non-missing data. P-value less than 0.05 was considered statistically significant.

Results

A clinical trial was started to determine the efficient dose of ivermectin for 45 days. A total of 180 patients with mild to severe infection, with positive PCR and chest image tests, hospitalized at Qazvin and Khuzestan provinces hospitals (five hospitals) were selected. The hospitalization term was from 1st of June to 15th of July 2020 (45 days) (Fig 1). Demographics (sex, age), Obesity, Severity on CT, PCR, Respiratory Rate (RR/min), Fever **(°C)**, Systolic and Diastolic Blood pressure (Bp;mmHg), Pulmonary Rate (PR /min) and Oxygen saturation (%) of the patients are reported in Table 1. The majority of patients had favorable outcomes and Mann-Whitney U Test and χ^2 test were used to analyze and compare the variables at the day one and five of admission (Δ 0/5). As reported in Table 2, complete blood count (CBC) evaluation of the patients among the standard and placebo and ivermectin treated (arms 3 to 6) showed that ivermectin had a good effect on blood biomarkers and improved other clinical parameters such as ALC, CRP, PLT , ESR , LDH, BUN, and Cr.

Patient care:

The majority of patients had desired consequence and were discharged from the hospitals. The results of preclinical consequences in Table 3 indicate a reduction in mortality rate in patients receiving ivermectin treatment to 0, 10, 0 and 3.3% for arms 1- 4 respectively, compared to the standard and placebo plus standard arms which was 16.7% and 20% respectively. Moreover, the decrease in hospitalization and low O_2 saturating terms was significant in ivermectin treated 1-4 arms compared to the two untreated controls (P=0.006 and P=0.025 respectively). The lowest mortality rate (0%), hospitalization duration (5days), and duration of low O_2 saturatin (2days) was observed arm 3 with single dose of 400mcg/kg ivermectin. Table 4 lists the risk of mortality for comparison between ivermectin

treated and untreated groups with CI: 95%. The estimation confirmed 15% reduction of the mortality with risk ratio of 0.18.

Discussion

Totally, 180 patients infected by COVID-19 virus were allocated to six arms and received single or interval doses of ivermectin. The positive effect of ivermectin therapy in patients receiving this drug was a reduction in mortality rate compared to the standard (16.7%) and placebo (20%) arms. The improvement of clinical manifestations of the patients was observed in all ivermectin groups in comparison with standard and placebo arms. From the beginning of the outbreak, various antiviral drugs such as Acyclovir, Ganciclovir, Oseltamivir and ribavirin have been tested. Unfortunately however, these drugs have not been effective in curing or alleviating the symptoms of COVID-19 [29]. Studies have shown that among the FDA-approved antiviral drugs, like ribavirin, Penciclovir, Nitazoxanide, Nafamostat and Remdesivir, the last two drugs are highly effective against novel coronavirus infection *in-vitro*[30]. Recently, ivermectin, another FDA-approved drug, was reported by Caly et al. to inhibit the *in-vitro* replication of novel Coronavirus. The results of this study showed that a single treatment of ivermectin was able to induce a 5000-folds reduction in the viral RNA 48hrs in cell culture[6]. As illustrated in Figure 2, the main *in vitro* proposed mechanism of activity of ivermectin hinders the viral load through inhibition of the interaction of importin α and β_1 proteins. Recently, a clinical trial reported lower mortality rates in hospitalized patients with COVID-19 who received ivermectin therapy [31]. Our clinical trial was designed with features such as double-blind, placebo-controlled, multicenter, open-label, phase 2/3, and randomized controlled trial. It is suggested by previous studies that the initial disease intensity assessment cannot rely only on clinical examination[11]. In this clinical trial, single and multiple oral doses (200mcg/Kg and 400 mcg/Kg) of ivermectin were added to the standard regimen of patients (treatment protocols of Iranian health ministry for COVID-19). At the time of writing the manuscript, the HCQ is stopped by world health organization (WHO) from all trials. As illustrated in Tables 2 and 3, the cure effect of ivermectin in different doses was confirmed by both laboratory and preclinical parameters. The results of ivermectin treated subgroups with the standard and placebo groups showed a difference between each subgroup and s,p groups. The combined effects of different-doses of ivermectin on patients' medication regimens shortened the duration hospitalization and low O_2 saturation. Promotion of other clinical parameters such as ALC, CRP, PLT, ESR, LDH, BUN and Cr showed that the ivermectin with a wide margin of safety had a higher therapeutic index and efficacy against COVID-19. One of the limitations of ivermectin in clinical utility is its potential to cause toxicity. Studies have shown that this defect can be eliminated by changing the formulation and pharmacokinetic properties. Therefore, a systematic design based on concentration of ivermectin is essential [32]. Schmith et al. showed in a study based on the pharmacokinetic simulations that ivermectin may have limited therapeutic utility on control COVID- 19. The reason is that the concentration of inhibitor required to act on the COVID-19 virus is much higher than the maximum plasma concentration by managing the approved dose [20,33]. Based on this limitation, they proposed ivermectin inhalation therapy; however, didn't consider the host immune

response in human. In addition, Caly et al. did not clarify if lower doses were effective or not. However, the antiviral properties of ivermectin have been demonstrated by targeting critical cellular process of the mammalian cell. Therefore, in line with our study, it is speculated that ivermectin administration, even at low doses, can reduce the loading of the virus in the early stages [34]. In addition to above explanations, sustainability of ivermectin in different tissues of animals and humans has been reported by various studies [35-37]. As mentioned in the introduction, it seems that the mechanisms of antiviral activity of ivermectin against various viruses is mediated via targeting importin α/β-mediated nuclear transport of HIV-1 integrase and NS5 polymerase; NS3 helicase; nuclear import of UL42; and nuclear localization signal-mediated nuclear import of Cap [38-41]. Although, at the time of the writing of this paper the HCQ was eliminated from the clinical care protocols of our clinical centers, we did the dose finding of ivermectin based on the standard care (HCQ) of Iranian ministry protocols at start. Based on findings, combined designs of ivermectin with other antiviral drugs appeared to have desirable results. In an unpublished study, the combination of ivermectin with HCQ was investigated [42]. As to the safety of using the high doses of ivermectin through this study, the flow-ups showed that there were no side effects such as nausea or skin rash during the trial. In a three arms phase 3 clinical trial, ivermectin was administered in two doses of 200 and 400 mcg/kg in patients with dengue fever. The main purpose of this trial was to evaluate safety of ivermectin in children and adult patients and the results showed that one daily dose of ivermectin treatment for three days was safe [43]. There have been several reports about drug treatments that have significantly affected viral load in COVID-19 patients. The novel coronavirus has several evolutionary phases, so that in the first clinical phase, including lower respiratory tract infection (LRTI) and upper respiratory tract infection (URTI) symptoms are associated with a high viral load and the incidence of early lung lesions on LDCT [44,45]. Here the focus of this study was to emphasize on the proper dose of ivermectin (single dose of 400mcg/Kg) that may reduce the viral load and affect both LRTI and URTI symptoms. However, for more efficacy of drug especially on URTI symptoms further studies are needed to experiment different combinations of immunological triggering agents such as corticosteroids on the mild to severe patients. Moreover, because of the direct impact of ivermectin on virus and as mentioned above and its sustainability in different organs specially the pulmonary tissue, further researched should be implemented to investigate the possible prophylactic effect of this drug against the first entrance of virus or after observation LRTI symptoms. Moreover, as listed in Tables 3 and 4, the lowest mortality rate was observed in arms 1-4 in comparison with 16.7% and 20% rates in the standard and placebo plus standard arms respectively. The risk base estimation with CI: 95% in Table 4 confirm 15% reduction of mortality or about 5.5 folds increase of the mortality rate in control groups. These results are in line with Rajter et al. [31] who reported a 40% drop in mortality of critical COVID-19 patients after oral administration of ivermectin at least in one dose (200mcg/Kg).

Limitations

The sample size was not large and the study was limited to the selected hospitals. Studies in areas with a maximum prevalence of COVID 19 and on patients with more diverse conditions such as body mass index over 40, different underlying diseases, or younger patients are needed. Without these limitations, a

stronger trial study could be carried out. Ongoing studies with larger sample sizes, using strategies to enhance the antiviral potency of ivermectin and its combination with other antivirals or higher-dose regimens, and focus on severe COVID-19 cases are recommended.

Declarations

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Abbas Allami: Writing - review & editing, Resources, Methodology , Supervision Physician , Project administration , Co-Coresspond .

Leila Zolghadr : Writing- original draft , Data curation , Design Figure 1(Mechanism of ivermectin inhibition on coronavirus) , Analysis Data.Chemistry of Medicine

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References

1. Lai C-C, Shih T-P, Ko W-C, Tang H-J, Hsueh P-R. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): the epidemic and the challenges. *International journal of antimicrobial agents.* 2020:105924.
2. Silva AAMd. On the possibility of interrupting the coronavirus (COVID-19) epidemic based on the best available scientific evidence. SciELO Public Health; 2020.
3. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *Jama.* 2020;323(13):1239-1242.
4. Yu B, Wang DW, Li C. Hydroxychloroquine application is associated with a decreased mortality in critically ill patients with COVID-19. *medRxiv.* 2020.
5. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. Paper presented at: Seminars in arthritis and rheumatism1993.
6. 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 research.* 2020:104787.
7. Andreani J, Le Bideau M, Duflot I, et al. In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. *Microbial pathogenesis.* 2020:104228.
8. Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel medicine and infectious disease.* 2020:101663.
9. Million M, Lagier J-C, Gautret P, et al. Full-length title: Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France. *Travel medicine and infectious disease.* 2020:101738.
10. Sturrock BR, Chevassut TJ. Chloroquine and COVID-19–a potential game changer? *Clinical Medicine.* 2020.

11. Lagier J-C, Million M, Gautret P, et al. Outcomes of 3,737 COVID-19 patients treated with hydroxychloroquine/azithromycin and other regimens in Marseille, France: A retrospective analysis. *Travel medicine and infectious disease.* 2020;36:101791.
12. Yu B, Li C, Chen P, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19. *Science China Life Sciences.* 2020:1-7.
13. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet.* 2020.
14. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *New England Journal of Medicine.* 2020.
15. Katzen J, Kohn R, Houk JL, Ison MG. Early oseltamivir after hospital admission is associated with shortened hospitalization: a 5-year analysis of oseltamivir timing and clinical outcomes. *Clinical Infectious Diseases.* 2019;69(1):52-58.
16. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine.* 2020.
17. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—preliminary report. *New England Journal of Medicine.* 2020.
18. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *MedRxiv.* 2020.
19. Huang M, Tang T, Pang P, et al. Treating COVID-19 with chloroquine. *Journal of molecular cell biology.* 2020;12(4):322-325.
20. Azeem S, Ashraf M, Rasheed MA, Anjum AA, Hameed R. Evaluation of cytotoxicity and antiviral activity of ivermectin against Newcastle disease virus. *Pakistan Journal of Pharmaceutical Sciences.* 2015;28(2).
21. Lundberg L, Pinkham C, Baer A, et al. Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. *Antiviral research.* 2013;100(3):662-672.
22. Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *The Journal of Antibiotics.* 2020:1-10.
23. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochemical Journal.* 2012;443(3):851-856.
24. Lehrer S, Rheinstein PH. Ivermectin Docks to the SARS-CoV-2 Spike Receptor-binding Domain Attached to ACE2. *In Vivo.* 2020;34(5):3023-3026.
25. de Oliveira OV, Rocha GB, Paluch AS, Costa LT. Repurposing approved drugs as inhibitors of SARS-CoV-2 S-protein from molecular modeling and virtual screening. *Journal of Biomolecular Structure and Dynamics.* 2020(just-accepted):1-14.

26. Mastrangelo E, Pezzullo M, De Burghgraeve T, et al. Ivermectin is a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. *Journal of Antimicrobial Chemotherapy.* 2012;67(8):1884-1894.
27. Wittes J. Sample size calculations for randomized controlled trials. *Epidemiologic reviews.* 2002;24(1):39-53.
28. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Eurosurveillance.* 2020;25(3):2000045.
29. Li H, Wang Y, Xu J, Cao B. Potential antiviral therapeutics for 2019 Novel Coronavirus. *Zhonghua jie he he hu xi za zhi= Zhonghua jiehe he huxi zazhi= Chinese journal of tuberculosis and respiratory diseases.* 2020;43:E002-E002.
30. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research.* 2020;30(3):269-271.
31. Rajter JC, Sherman M, Fatteh N, Vogel F, Sacks J, Rajter J-J. ICON (Ivermectin in COvid Nineteen) study: Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19. *medRxiv.* 2020.
32. Khan Sharun T, Aneesha V, Dhama K, Pawde AM, Pal A. Current therapeutic applications and pharmacokinetic modulations of ivermectin. *Veterinary world.* 2019;12(8):1204.
33. Anton R, Haas M, Arlett P, et al. Drug-induced progressive multifocal leukoencephalopathy in multiple sclerosis: European regulators' perspective. *Clinical Pharmacology & Therapeutics.* 2017;102(2):283-289.
34. Baraka O, Mahmoud B, Marschke C, Geary T, Homeida M, Williams J. Ivermectin distribution in the plasma and tissues of patients infected with Onchocerca volvulus. *European journal of clinical pharmacology.* 1996;50(5):407-410.
35. Lifschitz A, Virkel G, Sallovitz J, et al. Comparative distribution of ivermectin and doramectin to parasite location tissues in cattle. *Veterinary parasitology.* 2000;87(4):327-338.
36. Lespine A, Alvinerie M, Sutra J-F, Pors I, Chartier C. Influence of the route of administration on efficacy and tissue distribution of ivermectin in goat. *Veterinary parasitology.* 2005;128(3-4):251-260.
37. Sharun K, Dhama K, Patel SK, et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. BioMed Central; 2020.
38. Campbell W, Benz G. Ivermectin: a review of efficacy and safety. *Journal of Veterinary Pharmacology and Therapeutics.* 1984;7(1):1-16.
39. Barrows NJ, Campos RK, Powell ST, et al. A screen of FDA-approved drugs for inhibitors of Zika virus infection. *Cell host & microbe.* 2016;20(2):259-270.
40. Frieman M, Yount B, Heise M, Kopecky-Bromberg SA, Palese P, Baric RS. Severe acute respiratory syndrome coronavirus ORF6 antagonizes STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane. *Journal of virology.* 2007;81(18):9812-9824.

41. Wassenaar TM, Zou Y. 2019_nCoV/SARS-CoV-2: rapid classification of betacoronaviruses and identification of Traditional Chinese Medicine as potential origin of zoonotic coronaviruses. *Letters in Applied Microbiology.* 2020;70(5):342-348.
42. Patrì A, Fabbrocini G. Hydroxychloroquine and ivermectin: A synergistic combination for COVID-19 chemoprophylaxis and treatment? *Journal of the American Academy of Dermatology.* 2020;82(6):e221.
43. Yamasmith E, Avirutnan P, Mairiang D, Tanrumluk S, Suputtamongkol Y, Saleh-arong F. Efficacy and safety of ivermectin against dengue infection: a phase III, randomized, double-blind, placebo-controlled trial. Paper presented at: He 34th Annual Meeting the Royal College of Physicians of Thailand. Internal Medicine and One Health, Chonburi, Thailand2018.
44. Risch HA. Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis. *American Journal of Epidemiology.* 2020.
45. Singh AK, Singh A, Shaikh A, Singh R, Misra A. Chloroquine and hydroxychloroquine in the treatment of COVID-19 with or without diabetes: A systematic search and a narrative review with a special reference to India and other developing countries. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews.* 2020.

Tables

Table1: Baseline characteristics and demographic evaluation of patients enrolled in clinical trial

Median [interquartile range], n (%), S: common regimen, P: placebo plus common regime group, Arm1: Single dose ivermectin (200 mcg/Kg), Arm2: three dose ivermectin (200 mcg/Kg), Arm3: single dose ivermectin (400 mcg/Kg), Arm 4: three dose ivermectin (400, 200, 200 mcg/Kg).

Table2: Baseline characteristics and Complete blood Count (CBC) evaluation of patients enrolled in clinical trial.

median [interquartile range], n (%), S: common regimen , P: placebo plus common regime group, Arm1: Single dose ivermectin (200 mcg/Kg), Arm2: three dose ivermectin (200 mcg/Kg), Arm3: single dose ivermectin (400 mcg/Kg), Arm 4: three dose ivermectin (400, 200, 200 mcg/Kg). a. Mann-Whitney U Test, b. χ^2 test, Δ 0/5= Variable in 5th- Variable in admission day.

Table 3: Clinical Consequences occur in different arms of the study

		Group						
		Control groups (S +P)		Ivermectin Groups				
		S	P	Arm1	Arm2	Arm3	Arm4	Total
Sex	male	16 (53.3)	14 (46.7)	12 (40.0)	19 (63.3)	16 (53.3)	13 (43.3)	90 (50.0)
	female	14 (46.7)	16 (53.3)	18 (60.0)	11 (36.7)	14 (46.7)	17 (56.7)	90 (50.0)
Age (year)		55 [45 - 70]	58 [45 - 68]	61 [42 - 68]	53 [42 - 65]	54 [47 - 60]	54 [46 - 65]	56 [45 - 67]
BMI (Kg/m2)		26.0 [24.4]-27.6]	25 .6 [23.9 - 26.9]	26.1 [24.8 - 28.0]	26.4 [25.5 - 27.2]	27.7 [25.7 -32.6]	25.1 [23.9 -26.2]	26.0 [24.7 -27.4]
Severity on CT	negative	0 (0)	0 (0)	0 (0)	2 (6.7)	0 (0)	0 (0)	2 (1.1)
	mild	4 (13.3)	5 (16.7)	8 (26.7)	2 (6.7)	4 (13.3)	2 (6.7)	25 (13.9)
	mode	23 (76.7)	23 (76.7)	21 (70.0)	20 (66.7)	21 (70.0)	23 (76.7)	131 (72.8)
	sever	3 (10.0)	2 (6.7)	1 (3.3)	6 (20.0)	5 (16.7)	5 (16.7)	22 (12.2)
PCR	positive	18 (60.0)	14 (46.7)	23 (76.7)	23 (76.7)	29 (96.7)	21 (70.0)	128 (71.1)
	negative	12 (40.0)	16 (53.3)	7 (23.3)	7 (23.3)	1 (3.3)	9 (30.0)	52 (28.9)
RR (/ min)		28 [25 - 29]	28 [27 - 34]	28 [26 - 29]	30 [28 - 34]	22 [20 - 24]	29 [28 - 30]	28 [25 - 30]
Fever (°C)		36.8 [36.7 - 37.0]	36.8 [36.8 - 37.2]	36.8 [36.4 - 37.1]	36.8 [36.7 -37.2]	36.5 [36.5 - 36.8]	37.0 [36 - 37.2]	36.8 [36.5 - 37.1]
Systolic BP (mmHg)		110 [110 - 125]	112 [110 -135]	125 [110 -125]	110 [110 -125]	120 [110 - 120]	140 [120 - 160]	115 [110 -125]
Diastolic BP (mmHg)		80 [80 - 80]	80 [80 - 80]	80 [80 - 80]	80 [80 - 80]	75 [55 - 80]	80 [70 - 90]	80 [80 - 80]
PR (/min)		80 [75 - 85]	80 [72 - 85]	78 [75 - 85]	80 [78 - 95]	85 [80 - 93]	85 [78 -100]	80 [76 - 90]
O2 Sat (%)		89 [85 - 91]	88 [85 - 90]	90 [88 - 92]	88 [85 - 90]	91 [87 - 94]	89 [82 - 90]	89 [85 - 91]

	Group						
	Control groups (S +P)		Ivermectin Groups				
	S	P	Arm1	Arm2	Arm3	Arm4	Total
WBC (per µl)	8300 [5000 – 12000]	6600 [4600 - 400]	5750 [4400 – 7900]	5150 [4400 - 9200]	6300 [4800 - 7800]	5200 [4400 -7500]	6300 [4500 – 8850]
ΔWBC5/0	-300[-2500-800]	-350[-1200-900]	-200[1600-300]	150[-900-1000]	0[-1000-300]	650[-300-1800]	0 [-150-900]
p-value							0.217[a]
ALC (per µl)	1275 [770 - 1704]	1135 [783 1575]	1017.50 [792 1443]	1165.50 [816 - 1620]	1188 [888-1449]	1020 [561 - 600]	1124 [787 - 1584]
ΔALC5/0	78[-310-340]	58[-360-408]	357[5-625]	373[-38-565]	414[89-588]	316[-180-845]	288[-156-549]
p-value							<0.001*
PLT (per µl)	180 [164 - 227]	189 [154 245]	173 [133 - 205]	162 [121 - 217]	215 [175 256]	179 [141 - 237]	178 [149 – 227]
ΔPLT5/0	2[-11-27]	4[-27-28]	40.50[11-70]	39.50[10-74]	13[0-99]	30[8-61]	20[-3-59]
p-value							<0.001*
ESR (mm/h)	32 [13 - 56]	29 [17 - 38]	37 [24 - 50]	39 [25 - 53]	35 [20 - 70]	50 [36 - 59]	36 [20 - 56]
ΔESR5/0	-4.5[-13-1]	-2.5[-6-1]	-12.5[-18- -4]	-7[-16- -2]	-2[12-0]	-6[-11 -2]	-5[-14- -1]
p-value							0.015*
CRP (mg/dl)	28 [14 - 46]	27 [11 - 42]	20 [12 - 44]	39 [20 - 47]	25 [20 - 48]	34 [20 - 54]	29 [16 - 47]
ΔCRP5/0	-4.5[-18-4]	-2.50[-15-4]	-11.50[-29--3]	-19[-30 - -1]	-17[-36- -9]	-17[-29- -3]	-11[-26.50 - -1]
p-value							<0.001*
BUN (mg/dl)	19 [14 - 26]	23 [12 - 29]	19 [14 - 26]	14 [12 - 19]	14 [12 – 19]	15 [13 - 20]	17 [12 - 22]
ΔBUN5/0	-2.50[-7-2]	-2[-6-1]	-3.50[-8-1]	-2[-4- -1]	-1.50[-4.50-2]	1.50[-2-4]	-2[-5-2]
p-value							0.109
Cr (mg/dl)	1 [0.8 - 1.2]	[1.1 - [0.9 - 1.5]	1 [0.8 - 1.3]	0.9 [0.8 - 1.1]	0.9 [0.85 -1.05]	0.9 [0.8 - 1.2]	1 [0.8 - 1.2]
ΔCr5/0	-0.05[-0.2-0.1]	-0.1[-0.3-0.1]	-0.10[-0.2-0.1]	-0.05[-0.1-0.1]	0[-0.2-0]	-0.05[-0.2-0.1]	-0.1[-0.2-0.1]
p-value							0.64

Consequence		Group						
		Control groups (S +P)		Ivermectin Groups				
		S	P	Arm1	Arm2	Arm3	Arm4	P value
Tachypnea Off (day)		2 [2 - 3]	3 [2 - 4]	2 [1 - 3]	3 [2 - 4]	3 [3 - 5]	3 [3 - 5]	0.584
Fever Off (day)		0 [0 - 1]	0 [0 - 1]	0 [0 - 1]	0 [0 - 1]	1 [1 - 1]	1 [0 - 2]	0.102
Duration of low O2 Sat		3 [2 - 5]	4 [2 - 6]	2 [1 - 2]	3 [2 - 5]	2 [1 - 4]	5 [3 - 6]	0.025*
Duration on hospital stay (Day)		7 [7 - 9]	8 [6 - 11]	6 [5 - 7]	8 [6 - 9]	5 [4 - 7]	7 [6 - 10]	0.006*
Outcome1	**Alive**	25(83.3)	24 (80)	30 (100)	27 (90)	30(100)	29(96.7)	0.001*[b]
	Death	5 (16.7)	6 (20)	0 (0)	3 (10)	0 (0)	1 (3.3)	

a. Mann-Whitney U Test, b. χ^2 test, Δ 0/5= Variable in 5th- Variable in admission day, **S**: common regimen , **P**: placebo plus common regime group, **Arm1**: Single dose ivermectin (200 mcg/Kg), **Arm2:** three dose ivermectin (200 mcg/Kg), Arm3: single dose ivermectin (400 mcg/Kg), Arm 4: three dose ivermectin (400, 200, 200 mcg/Kg).

Table 4. Risk of mortality in study groups (estimates and 95% Confidence Intervals)

Point Estimates		Confidence Limits
Type	**Value**	**Lower, Upper**
Risk in Ivermectin groups	3.3%	1.0, 8.5
Risk in Control groups	18.3%	10.4, 30.1
Overall Risk	8.3%	5.0, 13.4
Risk Ratio	0.18	0.06, 0.55
Risk Difference	-15%	-25.3, -4.7°
Prevented fraction in Control groups	54.6%	23, 50
Prevented fraction in Ivermectin groups	81.8%	45.3, 94.0

Type: Taylor series, ° 95% confidence limits testing exclusion of 0 or 1, as indicated, P-values < 0.05 and confidence limits excluding null values (0,1, or [n]) are highlighted.

Figures

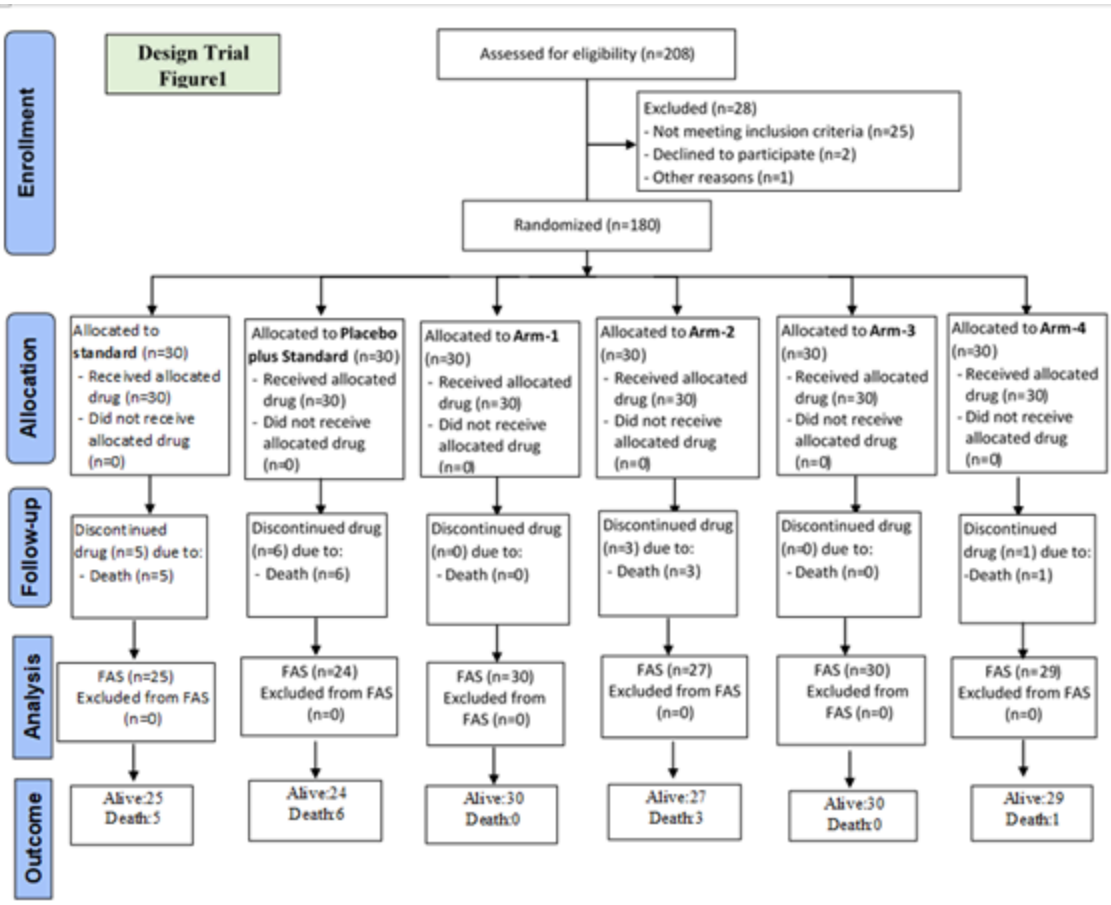

Figure 1

Design Trial

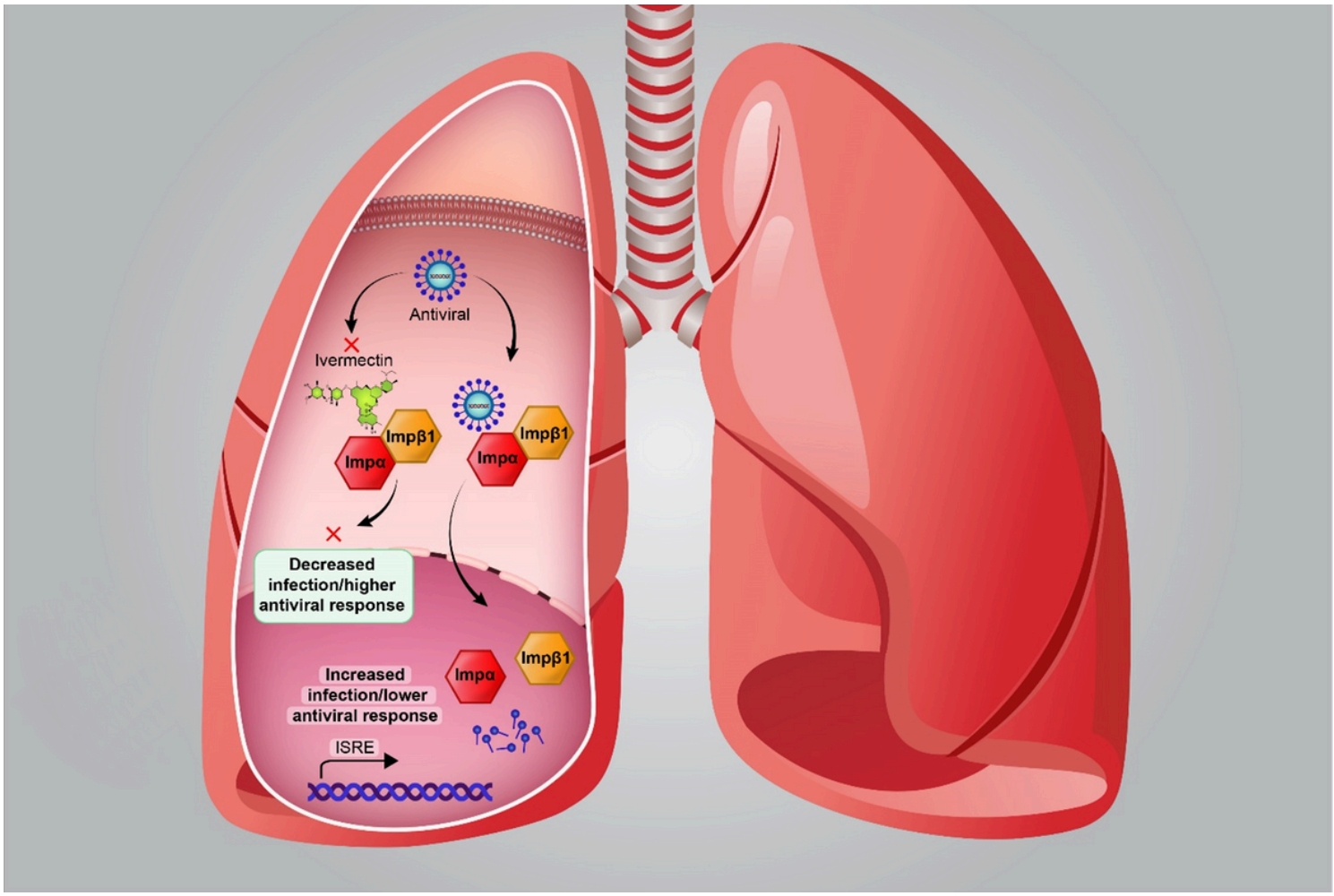

Figure 2

Mechanism of ivermectin inhibition on coronavirus (Designed by the researcher)