

Ivermectin as a treatment option for COVID-19

Introduction

1. Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become the forefront of global public health. Since the first reported case in Wuhan, China on December 31, 2019, there have over 225 million confirmed cases and 4.6 million deaths.
2. Ivermectin (IVM) is a commonly used antiparasitic with a favorable safety profile. There has been an increasing buzz for its use in COVID-19 treatment because of an in vitro study that showed effectiveness against the virus at extremely high concentrations.
3. Numerous studies have since been conducted to determine the safety and efficacy of IVM with doses ranging from 100-200 mcg/kg as a single dose up to 5 doses.
 - a. This opens the question of what dose/regimen should be studied to achieve the desired concentration in humans.

Pharmacology	
<u>Ivermectin</u>	
Proposed Mechanisms of Action	<ul style="list-style-type: none"> • Inhibition of nuclear transport mediated by the importin $\alpha/\beta 1$ heterodimer, responsible for the translocation of various viral species proteins. • Variety of anti-inflammatory effects • Competitive binding of ivermectin with the viral S protein
PK/PD	<ul style="list-style-type: none"> • Onset: ~4 hours to peak concentrations • Half-life: 18 hours • Distribution: High liposolubility, is widely distributed in the body • Metabolism: Hepatic via CYP3A4
Adverse Effects	<ul style="list-style-type: none"> • Pruritis, lymphadenitis, fever, and GI distress
Comment	<ul style="list-style-type: none"> • Administer on empty stomach with water (package insert) • Administering with a fatty meal may increase absorption • Dosing for COVID-19 has not been confirmed by rigorous clinical literature and need to further testing to recommend a dose and duration of therapy • The dosing regimen has not been confirmed in the literature and various doses and durations of therapy has been utilized

Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Glorial et al, 2020	Pilot trial N= 87	<ul style="list-style-type: none"> Ivermectin 200 mcg/kg x 1 +usual care Hydroxychloroquine/azithromycin 	<ul style="list-style-type: none"> All patients who received ivermectin were cured compared with 97% of patients who did not receive ivermectin The mean duration of hospitalization was shorter in the ivermectin group than in the control group
Chacar et al, 2020	Open label, RCT N= 50	<ul style="list-style-type: none"> Ivermectin 3 doses (12mg stat, 12mg 12h later, 12mg at 24h) Standard care (symptomatic treatment) 	<ul style="list-style-type: none"> At day 7 of observation 64% of patients receiving IVM were symptom free compared to 60% in the control group; no significant difference
Krolewiecki et al, 2020	RCT N= 45	<ul style="list-style-type: none"> Ivermectin at 0.6 mg/kg/day for 5 days Standard of care alone 	<ul style="list-style-type: none"> There was no difference in viral load reduction between groups. There was a significant difference in reduction found in patients with higher median plasma IVM levels. The mean ivermectin plasma concentration levels also showed a positive correlation with viral decay rate
Rajter et al, 2021	Retrospective, cohort study N= 280	<ul style="list-style-type: none"> Ivermectin (0.2-mg/kg dose) + usual care Usual care alone at the time (hydroxychloroquine and/or azithromycin) 	<ul style="list-style-type: none"> Overall mortality was lower in the ivermectin group than in the group not treated with ivermectin Overall mortality in the matched cohort also was lower in the ivermectin group
Ahmed et al, 2021	RCT N= 72	<ul style="list-style-type: none"> Ivermectin 12 mg Qday x 5 days Ivermectin 12-mg oral x 1+ doxycycline Placebo 	<ul style="list-style-type: none"> There was a significant difference in mean time to viral clearance between 5 days IVM vs placebo, but not with IVM + doxycycline
Lopez-Medina et al, 2021	RCT N=398	<ul style="list-style-type: none"> Ivermectin (300 mcg/kg Qday x 5 Placebo 	<ul style="list-style-type: none"> Ivermectin treatment did not significantly improve time to resolution of symptoms in patients with mild COVID-19
Chaccour et al, 2021	RCT N=12	<ul style="list-style-type: none"> Ivermectin 400 mcg/kg x 1 Placebo 	<ul style="list-style-type: none"> No difference in the proportion of PCR-positive patients between the ivermectin group and placebo group at day 7 (100% of pts in both groups still had positive PCR)
Gonzalez et al, 2021	RCT N=106	<ul style="list-style-type: none"> Hydroxychloroquine <ul style="list-style-type: none"> 400 mg x 1, then 200 mg every 12 hours for another 4 days Ivermectin <ul style="list-style-type: none"> < 80 kg=12 mg Qday x 5 > 80 kg= 18 mg Qday x 5 Placebo PO Qday x 5 	<ul style="list-style-type: none"> No differences in outcome were detected between the treatment groups Duration of hospital stay was 7d, 6d, 5d for hydroxychloroquine, ivermectin, and placebo respectively
Mohan et al, 2021	RCT N=125	<ul style="list-style-type: none"> Ivermectin 12 mg (~200 µg/kg) Ivermectin 24 mg (~400 µg/kg) Placebo 	<ul style="list-style-type: none"> There was no significant difference in RT-PCR negative test on day 5 between the 3 groups There was no significant difference in the viral load in the three arms, either at baseline or at day 5 of enrolment, or in the decline of viral load between the ivermectin and placebo arms at day 5

Conclusions

- **Currently, there are no recommendations on the use of ivermectin in COVID-19 outside of clinical trials**
- Some studies suggest there is a benefit in COVID positive patients that receive ivermectin, however, multiple studies were not peer-reviewed and have significant methodological flaws that need to be confirmed in well designed clinical trials and published in peer-reviewed journals
- There are also studies that suggest there is no benefit in adding ivermectin to usual care in COVID positive patients
- No studies showed significant adverse effects with the use of ivermectin
- There is not enough evidence to recommend for or against the use of ivermectin for the treatment of COVID-19

References

1. Micromedex [Electronic version]. Greenwood Village, CO: Truven Health Analytics. Retrieved January 17, 2021, from <http://www.micromedexsolutions.com/>
2. Gorial FI, Mashhadani S, Sayaly HM, Dakhil BD, AlMashhadani MM, Aljabory AM, et al. Effectiveness of ivermectin as add-on therapy in COVID-19 management (pilot trial). medrxiv.org/content/10.1101/2020.07.07.20145979v1 (first received 8 July 2020). [DOI: 10.1101/2020.07.07.20145979]
3. Chachar AZ, Khan KA, Asif M, Tanveer K, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-CoV-2/COVID-19 patients. International Journal of Sciences 2020;9:31-5. [DOI: 10.18483/ijSci.2378]
4. Krolewiecki A, Lifschitz A, Moragas M, Travacio M, Valentini R, Alonso D, et al. Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial. ssrn.com/abstract=3714649 (first received 11 November 2020). [DOI: 10.2139/ssrn.3714649]
5. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. ICON (Ivermectin in COvid Nineteen) study: use of ivermectin is associated with lower mortality in hospitalized patients with COVID19. medrxiv.org/content/10.1101/2020.06.06.20124461v2 (first received 10 June 2020). [DOI: 10.1101/2020.06.06.20124461]
6. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International Journal of Infectious Diseases 2020;103:214-6. [DOI: 10.1016/j.ijid.2020.11.191] [PMID: 33278625]
7. López-Medina E, López P, Hurtado IC, Dávalos DM, Ramirez O, Martínez E, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. JAMA 2021;325(14):1426-35. [DOI: 10.1001/jama.2021.3071] [PMID: 33662102]
8. Chaccour C, Casellas A, Blanco-Di Matteo A, Pineda I, Fernandez-Montero A, Ruiz-Castillo P, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with mild COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. researchsquare.com/article/rs-116547/v1 (first received 7 December 2020). [DOI: 10.21203/rs.3.rs-116547/v1]
9. Gonzalez BJ, González Gámez M, Enciso EA, Maldonado RJ, Palacios HP, Dueñas Campos S, et al. Efficacy and safety of ivermectin and hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. medrxiv.org/content/early/2021/02/23/2021.02.18.21252037 (first received 23 February 2021). [DOI: 10.1101/2021.02.18.21252037]
10. Mohan A, Tiwari P, Suri T, Mittal S, Patel A, Jain A, et al. Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial. researchsquare.com/article/rs-191648/v1 (first received 2 February 2021). [DOI: 10.21203/rs.3.rs-191648/v1]