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Potential use of ivermectin for the treatment and profilaxis of SARS-CoV-2 infection: Efficacy of ivermectin for SARS-CoV-2

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Abstract

Currently no treatment has been proven to be efficacious for patients with early or mild COVID-19. Although most patients present mild or moderate symptoms, up to 5-10% may have a poor disease progression, so there is an urgent need for effective drugs, which can be administered even before the onset of severe symptoms, i.e. when the course of the disease is more modifiable. In addition to the antiparasitic effect of the drug, ivermectin also appears to possess an antibacterial effect, as well as antiviral activity. This is the reason why it is thought that ivermectin could be also effective in the treatment and prophylaxis of SARS-CoV-2 infection, with a good safety profile. The review of the scientific literature published to date seems to indicate that there is sufficient evidence to recommend treatment with ivermectin in patients with COVID-19 especially in the early stages of the disease.

Introduction

Ivermectin is a macrocyclic lactone with a broad-spectrum antiparasitic pharmacological activity [1]. It is the safest and most effective semi-synthetic derivative of the entire avermectin class. Marketed since 1981, its low cost, high efficacy and safety, and the marked helminth tropism (therefore with almost no impact on human biochemistry) have led to the inclusion of the drug in the 21st World Health Organization List of Essential Medicines [2].

In addition to the antiparasitic effect, it also appears to have an antibacterial effect [3], and antiviral and anticarcinogenic activity [4], and it is particularly useful for treating certain chronic diseases [5].

Regarding the function as an antiviral agent, the efficacy has been demonstrated against several viruses, both *in vitro* and *in vivo*. One of the most important mechanisms by which ivermectin performs its function, considers the drug an inhibitor of nuclear transport mediated by the imported heterodimer α/β1, which is responsible for the translocation of the proteins of several viral species (HIV-1, SV40), and such translocation is in turn, essential for viral replication [6,7]. This inhibition appears to affect a considerable number of RNA viruses. It has recently been shown that ivermectin inhibits the replication of the SARS-CoV-2 virus *in vitro* [8,9], although it is not clear how this occurs. However, since the causal agent of COVID-19 is an RNA virus, the interference with the same proteins and molecular processes described above can reasonably be expected. However, these studies were conducted at concentrations substantially higher than expected in the plasma and lungs of humans who receive the approved dose of ivermectin. Pharmacokinetic and pharmacodynamic studies suggest that in order to achieve the plasma concentrations required for *in vitro* antiviral efficacy, it would be necessary to administer doses up to 100 times higher than those approved for human use [10,11]. However, increasing the dose/kg of body weight may be a strategy to increase efficacy, although the risk of toxicity may be increased [10].

Currently, there is a noteworthy absence of treatments proven to be efficacious for patients with early or mild infection, so interventions that can be administered early during the course of infection to prevent disease progression and longer-term complications are urgently needed [12]. Although most patients present mild or moderate symptoms, up to 5-10% may have a bad disease progression, so there is an urgent need for effective drugs [13], which can be administered even before the appearance of severe symptoms, i.e. when the course of the disease is more modifiable. In fact, it is known that the earlier the antiviral therapies are started, the greater the benefits for patients, in both influenza [14] and SARS infections [15].

Given the need to find an effective drug that can mitigate the harmful consequences of COVID-19, a large number of studies are being carried out in order to assess the effectiveness of different existing drugs, including ivermectin, with promising results.

This narrative review summarizes and outlines the evidence-based effectiveness and safety of ivermectin in patients with SARS-CoV-2 infection, recommending the drug for the treatment of COVID-19 specially in the early stages of the disease.

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Methodology

A literature search was conducted on MEDLINE, The Cochrane Library and EMBASE databases with the following search strategy "COVID-19 treatment" or "ivermectin treatment for COVID-19" or "ivermectin treatment for SARS-CoV2 infection". No restrictions were applied to the search. In order to identify unpublished studies, a search was also conducted on clinical trial registration platforms such as, Clinicaltrials.org.

In order to facilitate the review, the retrieved articles were organized in the following four main topics: a) short-term efficacy in the treatment of the disease, b) long-term efficacy in the treatment of patients with post-acute symptoms of COVID-19, c) efficacy in the prophylaxis of the disease, and finally, c) safety of ivermectin. The results of the studies reviewed are presented as a narrative review.

Results

Short-term efficacy of ivermectin in the treatment of patients with COVID-19

By short-term or early treatment of the disease, we refer to the treatment administered immediately or soon after symptoms appear.

Very recently, the WHO has commissioned a meta-analysis [16] to assess the clinical efficacy of ivermectin through the ACC Accelerator Program. The meta-analysis included 11 randomized controlled trials (RCTs) conducted on a total of 1,452 RT-PCR positive patients (both, inpatients and outpatients), with mild to severe COVID-19 symptoms. The efficacy of ivermectin was assessed at doses of 200-600 μg/kg in a 1-7 day treatment schedule and an increase in survival of 83% (95% Confidence Interval (CI): 65%-92%) was observed in patients treated with ivermectin, p<0.0001. Additionally, a reduction in hospital stay from 18 days (standard deviation- SD 8) to 6 (SD 8) days, p<0.001, and a reduction in the time for the negativization of PCR testing from 12 (SD 4) days to 6(SD 1) days p<0.001, in patients with no ivermectin treatment and in patients treated with ivermectin, respectively, were also calculated. Furthermore, the effect was shown to be dose dependent, being greater for a 5-day pattern *versus* a single-dose administration [16].

A real-time meta-analysis of 33 studies [17] conducted over a total sample of 10,132 patients with COVID-19 disease, assessing 15 RCTs, 12 observational retrospective studies and 6 observational prospective studies, described that all the studies included in the analysis reported positive effects. According to the results of the meta-analysis, treatment at an earlier stage of the disease (<=5 days after the onset of symptoms) is more successful, with an estimated 84% reduction in the measured effects (fever, death, no virological cure, no resolution of symptoms, need for ventilation, need for hospitalization, etc.) using a random-effects meta-analysis, relative risk (RR) 0.16 [0.08-0.32] [17]. It should be noted that, 100% of the 15 randomized controlled trials (RCTs) included in the meta-analysis also report positive effects, with an estimated reduction in the effect measure of 74%, RR 0.26 [0.15-0.47]. Generally, antiviral drugs are only considered effective when used at the early stages of the infection, e.g., within 36-48 hours for oseltamivir, with longer delays not being effective [18,19].

In another meta-analysis conducted by Mohan-Padhy, *et al.* [20], which included 4 studies and a total of 629 COVID-19 RT-PCR positive patients, to assess the therapeutic potential of ivermectin at a standard dose of 200 μg/kg for the treatment of COVID-19 as an adjuvant therapy to the standard care, an overall Odds Ratio (OR) of 0.53 (95% CI: 0.29 to 0.96) was reported for the primary outcome of all-cause mortality which was statistically significant (p=0.04) [20].

In a multicenter case-control study [21] of 280 hospitalized patients, ivermectin administered in a single dose of 150 μg/kg to patients diagnosed with SARS-CoV-2 infection, achieved a significant reduction in intrahospital mortality in those patients treated with the drug (1.4% versus 8.5% (ivermectin *versus* non-ivermectin; Hazard Ratio (HR) 0.20, 95% CI: 0.11 to 0.37, p<0.0001) [21]. These results are very similar to those obtained by Cepelowicz-Rajter, *et al.* [22], in a retrospective study comparing the efficacy of two therapeutic strategies (at least one dose of ivermectin + hydroxychloroquine and/or azithromycin *versus* hydroxychloroquine and/or azithromycin). In the group of patients who received ivermectin at a dose of 200 μg/kg, a reduction in mortality was observed (15.0% versus 25.2%, OR 0.52, 95% CI: 0.29 to 0.96, p=0.03). In the same study, the subgroup of patients with severe lung disease showed an even lower mortality (38.8% *versus* 80.7%, OR 0.15, 95% CI: 0.05-0.47, p=0.001) [22].

In both studies described above, the standard dose was administered (i.e., 150-200 μg/kg for most filarial infections and *S. stercoralis* and up to 400 μg/kg for *Wuchereria bancrofti* infections) [23,24], which contrasts with the very high doses of ivermectin employed in the *in vitro* experiment conducted by Caly, *et al.* [8] with COVID-19-infected cell lines, indicating that it appears that standard doses might also be effective in reducing mortality.

In another interventional study conducted by Isho, *et al.* [25], in 30 hospitalized patients with mild to moderate COVID-19, no difference was observed in the percentage of cured patients among those treated with 200 μg/kg in a single dose of ivermectin at the admission day + hydroxychloroquine + azithromycin and those treated with hydroxychloroquine + azithromycin, but there was a difference in the length of hospital stay (7.62 ± 2.75 versus 13.22 ± 5.90 days, p=0.00005) and no adverse effects were observed [25].

Gómez-Hernández, *et al.* (26), observed in a retrospective cohort of 325 patients diagnosed with SARS-CoV-2 infection, that disease progression was better in patients treated with ivermectin at a single dose of 12mg within 24-h after hospital admission (lower incidence of respiratory distress: 3 patients (2.5%) *versus* 21 patients (15.8%) p<0.001) and lower need for intensive care: 1 patient (0.9%) versus 11 patients (8.3%) p<0.001) [26]. Furthermore, the length of hospital stay was also lower in the group treated with ivermectin plus standard care (9 (7-10) days) compared to standard care alone (15 (12-19) days) (p<0.001) [26].

In another retrospective study that evaluated the mortality of 3,099 patients with a definitive or highly probable diagnosis of infection due to COVID-19 (both inpatients and outpatients) treated with ivermectin, a mortality-rate of 1.3% was found, which contrasts with the world average mortality-rate of 2.2% [27]. Ivermectin dosage varied depending on the type of patient; outpatients were administered ivermectin at 400 μg/kg, orally in a single dose in the Emergency Service, and azithromycin 500mg PO per day for 5 days, and hospitalized patients were administered ivermectin orally at 300 μg/kg, at days 1 and 2, and the dose was repeated on days 6 and 7. Patients were given azithromycin 500mg PO daily, for 7 days.

The routine prophylactic administration of ivermectin in Peru starting from May 2020 was also associated with a reduction in mortality due to SARS-CoV-2 [28]. Hashim, *et al.* in a randomized controlled study conducted on 70 COVID-19 patients treated orally

with 200ug/kg of ivermectin per day for 2-3 days along with 100mg of oral doxycycline twice per day for 5-10 days in addition to the standard therapy, also observed a reduction in recovery time and a reduction in mortality in severe patients treated with doxycycline and ivermectin [29].

A non-randomized intervention evaluating the efficacy of ivermectin combined with azithromycin and cholecalciferol treatment, showed that the recovery-rate was 100% in patients treated with the drug at the early stages of the disease [30].

The results of the clinical trial carried out by Chaccour, *et al.* [31], in 24 patients who received a single dose of 400 μg/kg of ivermectin or placebo, have recently been published. No difference was found in the proportion of patients with positive PCR at 7 days (RR 0.92, 95% CI: 0.77 to 1.09, p = 1.0). Patients in the ivermectin group had fewer days of symptoms as compared to those in the placebo group (171 versus 255 patient-days). The observed difference was mainly due to two symptoms, anosmia/hyposmia and cough. There was no difference in the days of fever, malaise, headache, or nasal congestion between the two groups. In contrast, the ivermectin group presented more days of gastrointestinal symptoms (21 versus 6) and less days of respiratory difficulty (3 versus 15) [31].

Long-term efficacy of ivermectin in the treatment of patients with post-acute symptoms of COVID-19

It is estimated that between 10 to 45% of people who become ill with COVID-19 will present with symptoms after the acute stage of the disease [32]. In a study carried out by Aguirre, *et al.* 33 patients with subacute symptoms of COVID-19 between weeks 4 and 12 from the onset of symptoms, who received 2 consecutive daily doses of ivermectin 200 - 400 μg/kg depending on the severity of the symptoms, an improvement of symptoms (total or partial) was observed in 94% of patients, and a total improvement in 87.9% of them. Patients whose main symptoms were musculoskeletal, such as fatigue due to muscle weakness, diminished muscle strength and myalgia (muscle pain) were excluded from the study. If any symptoms were present after the second dose (12.1% of patients), 2 additional doses were administered, reaching a 94% of success in the complete resolution of the symptoms after the fourth dose [32].

In another study carried out by the same authors, 21 adult patients with persistent symptoms of anosmia or hyposmia received ivermectin at a dose of 200 μg/kg of body weight per day for 2 days. If symptoms did not disappear after the second day of ivermectin treatment, patients received two more doses of 400 μg/kg (in days 5 and 6). Among the 21 adult patients with persistent anosmia or hyposmia treated with ivermectin, 66.7% had an overall clinical improvement after the two first days of ivermectin treatment, and this percentage increased to 85.7% after 2 more doses of ivermectin and acetylsalicylic acid for 5 days [33].

Efficacy of ivermectin for infection prophylaxis

The scientific literature provides evidence regarding the use of ivermectin as a prophylactic agent. We searched for studies in which the medication was regularly taken following different schedules in order to prevent or minimize SARS-CoV-2 infection. We found a real-time meta-analysis of 10 studies showing high effectiveness for the prophylactic use of ivermectin, which reported a 90% reduction in the risk of acquiring the disease on a sample of 3,663 patients RR 0.10 (0.04 to 0.23) [17]. The meta-analysis included 3 RCTs and 7 observational studies (4 retrospective and 3 prospective). The results regarding prophylaxis remain very similar when only the three RCTs included in the meta-analysis were taken into consideration, showing a 91% reduction in the risk of a COVID-19 case (RR 0.09 (0.06 to 0.23)). Further, one of the studies included in the meta-analysis also investigated the risk of death as the main outcome measure reporting a 99% improvement (RR 0.01 (0.00 to 0.10)) [34].

On the other hand, it has been observed that those countries with prophylactic administration of drugs on a routine basis have less incidence of COVID-19. Thus, a study conducted by Hellwig, *et al.* collecting data from countries that use prophylactic drug therapy for the treatment of other infections, detected a lower incidence of COVID-19 in patients treated with ivermectin at 150-200 μg/kg doses ($p<0.05$) [35], without observing any remarkable difference between doses. This could be partly due to the relatively short half-life of ivermectin and the little added effect of higher doses [36,37]. Additionally, the hypothesis of activation of alternative routes when lower doses are employed should be also considered [35].

In addition, it is interesting to note that the prophylactic administration of ivermectin at a weekly single dose of 200 μg/kg up to 8 weeks in 74 people (residents and workers in nursing homes) produced IgG titers for SARS-CoV-2 of 5 to 10 times higher than the standard titers in 85% of cases, showing that the workers included in the study had come into contact with the virus, asymptomatically, but their immune system was able to produce antibodies against SARS-CoV-2 [38,39].

Safety

The safety of ivermectin at high doses (>400 μg/kg) appears to be comparable to standard doses (<=400 μg/kg) according to a meta-analysis of RCTs conducted by Navarro, *et al.* [39] (OR 1.16, 95% CI: 0.89 to 1.52). The severity of adverse reactions was similar in both dosage groups and was mild or moderate in almost 100% of the cases. Only one study reported a severe anaphylactic reaction in the standard dose group and a prolongation of QTc (corrected QT interval) in the high dose group [39]. Among the studies included in the meta-analysis only one study on onchocerciasis (river blindness) treatment showed an increase in eye reactions (transient blurred vision, itching, eye pain, dyschromatopsia) (IR-incidence ratio 2.797, 95% CI 1.226 to 6.377) [40]. These observations are in agreement with the side effects reported by other research groups [11,41,42].

In the clinical trial carried out by Chaccour, *et al.* [31], in which 12 patients were given a single dose of 400 μg/Kg of ivermectin and 12 patients were given a placebo, the patients in the ivermectin group reported more patient-days of dizziness (7 versus 1) and blurred vision (24 versus 1), although it should be taken into account that the blurred vision was reported in a single patient [31].

Generally, ivermectin is well tolerated causing mainly dizziness, nausea, headache, skin rash, and appears to be dose-dependent [43,44]. Since the approval of the drug in the 1980s, the drug has been distributed for the treatment of river blindness (onchocerciasis) through the Mectizan program, administering more than 3 billion treatments over the last 30 years, with an excellent safety profile. Most adverse reactions are mild, transient and associated with the death of the parasite rather than the drug itself [45]. Despite this, Chandler [46] described a series of 28 cases with severe neurological reactions after ivermectin treatment outside the onchocerciasis-endemic areas. One of the possible causes may be a variation of the MDR-1 gene, which may have allowed ivermectin to penetrate the central nervous system [46].

Ivermectin has affinity for glutamate-gated chloride channels, which are only present in invertebrates. Mammals only express a similar channel that could potentially cross-react with ivermectin, but such channels are only expressed in the central nervous system and are protected by the blood-brain barrier thanks to the P glycoprotein, a product of the MDR-1 gene, in humans [47]. This protein is located in the endothelium of the brain capillaries and has the function of eliminating substances or toxins found on the plasmatic membranes before they penetrate the cell, or to eliminate toxic substances that have managed to enter the cellular cytoplasm [48].

Discussion

The scientific evidence reviewed in this manuscript seems to clearly indicate that ivermectin is effective in the short--term treatment and prophylaxis of COVID-19. The debate now focuses on selecting an effective dose with the best safety profile and lowest possible toxicity. The doses used across the different studies reviewed range from 150-800μg/kg, administered as a single dose or in a 1-7 days schedule. According to the scientific evidence available, the standard dose (150-400 μg/kg depending on the indication) could be effective and has a lower probability of causing adverse reactions, especially at eye level [45]. In relation to the dosing schedule, it appears that a multi-day pattern would produce better results than the single dose [16].

It should be noted that the high quality evidence from meta-analyses of randomized controlled trials [16] is also corroborated by other studies (i.e., observational studies) reviewed in this article. Evidence shows that non-RCT trials can also provide reliable results [49]. The authors showed that the results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment compared to RCTs. So far, no individual clinical trial conducted to date is large enough to clearly establish the efficacy of ivermectin for the treatment of COVID-19. Nevertheless, the meta-analysis of 11 RCTs conducted by Hills and colleagues [16] includes a sample of 1,452 patients with COVID-19, providing stronger evidence on the efficacy of the drug. In one month time, the results of two big RCTs will be available, which will increase the pooled sample size to 3,000 patients, the same evidence-base used for the approval of Remdesivir. Two possible limitations should be also noted: firstly, that there is a possibility of publication bias, by which only studies reporting positive results in relation to the ivermectin treatment would be published and secondly, that several clinical trials included in the meta-analysis are open-labelled and therefore, the potential investigator bias cannot be ruled out.

With the available evidence, the Frontline COVID-19 Critical Care Alliance (FLCCC) recommends the use of ivermectin in both prophylaxis and treatment of COVID-19 [50]. It should be noted that very recently the American NIH (National Institutes of Health) has upgraded the recommendation and has issued a statement on the use of ivermectin within the COVID-19 Treatment Guidelines [51]. Despite, the NIH Guidelines do not recommend either for or against the use of ivermectin for the treatment of COVID-19, they now allow treatment of COVID-19 patients with ivermectin in the U.S.A. It should be noted that the results of the recent systematic review of RCTs commissioned by WHO have not been taken into consideration by the Guideline Panel. The Health Ministries of India, Macedonia, Bulgaria and several South American countries have already approved the use of ivermectin for the treatment of COVID-19.

Several clinical trials are underway to further evaluate the efficacy of ivermectin in the management of SARS-CoV-2 infection using different dosing patterns. Further investigations should be conducted in order to explore the above mentioned aspect, by means of carrying out well-designed studies that would allow the assessment of the efficacy and safety at low and high doses, following different dosing schedules. Such studies should make a special emphasis on the incidence of ocular and neurological adverse reactions and should also identify the profile of patients where these adverse reactions occur most frequently.

Evidence regarding the effectiveness of ivermectin for the treatment of persistent COVID-19 symptoms is provided by two prospective observational studies conducted in 33 and 21 adult patients with post-acute symptoms of COVID-19, respectively [32,33]. Nevertheless, it is important to point out that the studies mentioned above have serious methodological limitations. Firstly, both studies lack a control group and have very small sample sizes. Secondly, the assessment of the main outcome measures was subjective and has not been clearly specified in the published papers. Therefore, the evidence in favor of the treatment with ivermectin for long-term COVID-19 is very weak due to the serious limitations of the studies conducted by Aguirre-Chang and co-workers. Given the high number of patients with persistent COVID-19 symptoms, further investigations should be carried out in order to unequivocally prove the effectiveness of ivermectin in long haulers. In this regard it is crucially important to carry out well designed controlled clinical studies.

Given the significant upsurge in cases of SARS-CoV-2 infection that has occurred in recent months, the widespread use of ivermectin could potentially play a crucial role in reducing in transmission-rates, as well as decreasing short- and long-term morbidity and mortality in mild, moderate and even severe phases of the disease [50]. In this regard, it has been shown that treatment with ivermectin could produce IgG titers for SARS-CoV-2 around 5 to 10 times higher as compared to the titrations of untreated patients in 85% of people who had come into contact with the virus asymptomatically [37,38].

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Conflict of interest

Authors declare no conflict of interest.

References

1. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, et al. (2008) The pharmacokinetics and interactions of ivermectin in humans--a mini-review. *AAPS J* 10: 42-46. [Crossref]

2. WHO (2019) World Health Organization model list of essential medicines: 21st list 2019. World Health Organization, Geneva.

3. Lim LE, Vilchèze C, Ng C, Jacobs WR, Ramón-García S, et al. (2013) Anthelmintic avermectins kill Mycobacterium tuberculosis, including multidrug-resistant clinical strains. *Antimicrob Agents Chemother* 57: 1040-1046. [Crossref]

4. Juarez M, Schcolnik-Cabrera A, Dueñas-Gonzalez A (2018) Review The multitargeted drug ivermectin: from an antiparasitic agent to a repositioned cancer drug. *Am J Cancer Res* 8: 317-331. [Crossref]

5. Ventre E, Rozières A, Lenief V, Albert F, Rossio P, et al. (2017) Topical ivermectin improves allergic skin inflammation. *Allergy* 72: 1212-1221. [Crossref]

6. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA (2012) Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J* 443: 851-856. [Crossref]

7. Şimşek Yavuz S, Ünal S (2020) Antiviral treatment of COVID-19. *Turk J Med Sci* 50: 611-619. [Crossref]

8. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM (2020) The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 3: 104787. [Crossref]

9. Ketkar H, Yang L, Wormser GP, Wang P (2019) Lack of efficacy of ivermectin for prevention of a lethal Zika virus infection in a murine system. *Diagn Microbiol Infect Dis* 95: 38-40. [Crossref]

10. Chaccour C, Hammann F, Ramon-Garcia S, Rabinovich NR (2020) Ivermectin and COVID-19: keeping rigor in times of urgency. *Am J Trop Med Hyg* 102: 1156-1157. [Crossref]

11. Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, et al. (2002) Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol* 42: 1122-1133. [Crossref]

12. Kim PS, Read SW, Fauci AS (2020) Therapy for Early COVID-19: A Critical Need. *JAMA* 324: 2149-2150. [Crossref]

13. WHO (2020) "Solidarity" clinical trial for COVID-19 treatments, World Health Organization.

14. Uyeki TM, Bernstein HH, Bradley JS, Englund JA (2019) File TM Clinical practice guidelines by the infectious diseases society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenzaa. *Clin Infect Dis* 68: e1-e47. [Crossref]

15. Chan KS (2003) Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med* 9: 399-406. [Crossref]

16. https://www.researchsquare.com/article/rs-148845/v1

17. https://ivmmeta.com/

18. McLean HQ, Belongia EA, Kieke BA, Meece JK, Fry AM (2015) Impact of Late Oseltamivir Treatment on Influenza Symptoms in the Outpatient Setting: Results of a Randomized Trial. *Open Forum Infect Dis* 2: ofv100. [Crossref]

19. Treanor JJ, Hayden FG, Vrooman PS, Barbarsh R, Bettis R, et al. (2000) Efficacy and Safety of the Oral Neuraminidase Inhibitor Oseltamivir in Treating Acute Influenza: A Randomized Controlled Trial. *JAMA* 283: 1016-1024. [Crossref]

20. Mohan- Padhy B, Ranjan-Mohanty R, Das S, Ranjan-Meher B (2020) Therapeutic potential of ivermectin as add on treatment in COVID 19: A systematic review and meta –analysis. *J Pharm Pharm Sci* 23: 462-469. [Crossref]

21. Patel AN, Desai SS, Grainger DW, Mehra MR (2020) Usefulness of Ivermectin in COVID-19 Illness.

22. Cepelowicz-Rajter J, Sherman MS, Fatteh N, Vogel F, Sacks J, et al. (2020) ICON (Ivermectin in COvid Nineteen) Study: Use of Ivermectin Is Associated with Lower Mortality in Hospitalized Patients with COVID-19. *Chest* (In press).

23. Tisch DJ, Michael E, Kazura JW (2005) Mass chemotherapy options to control lymphatic filariasis: a systematic review. *Lancet Infect Dis* 5: 514-523. [Crossref]

24. Chaccour C, Rabinovich NR (2017) Ivermectin to reduce malaria transmission. Considerations regarding regulatory and policy pathways. *Malar J* 16: 162. [Crossref]

25. Isho F, Mashhadani S, Sayaly H, Dakhil B, Almashhadani M, et al. (2020) Effectiveness of Ivermectin as add-on Therapy in COVID-19 Management (Pilot Trial) (preprint). *MedRxiv*.

26. Gómez-Hernández MT, Novoa NM, Antúnez P, Jiménez MF (2020) Ivermectin Treatment May Improve the Prognosis of Patients With COVID-19. *Arch Bronconeumol* 56: 816-830. [Crossref]

27. Morgenstern J, Redondo JN, De León A, Canela JM, Torres N, et al. (2020) The use of compassionate Ivermectin in the management of symptomatic outpatients and hospitalized patients with clinical diagnosis of COVID-19 at the Medical Center Bournigal and the Medical Center Punta Cana, Rescue Group, Dominican Republic, from may 1 to august 10, 2020. *BMJ Yale*.

28. Juan C (2020) Real-World Evidence: The Case of Peru. Causality between Ivermectin and COVID-19 Infection Fatality Rate.

29. Hashim HA, Maulood MF, Rasheed AW, Fatak DF, Kabah KK, et al. (2020) Abdulamir. Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq (preprint). *MedRxiv*.

30. Espitia-Hernandez G, Munguia L, Diaz-Chiguer D, Lopez-Elizalde R, Jimenez-Ponce F (2020) Effects of Ivermectin-azithromycin-cholecalciferol combined therapy on COVID-19 infected patients: A proof of concept study. *Biomed Res* 31: 129-133.

31. Chaccour C, Casellas A, Blanco Di-Matteo A, Pineda I, Fernández-Montero A, et al. (2021) 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. (In press).

32. Chaccour C (2021) The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. (In Press).

33. Aguirre-Chang G, Saavedra E, Yui M, Trujillo- Figueredo A (2020) post-acute or persistent covid-19: treatment with ivermectin and acetylsalicylic acid of patients with the persistent symptom of anosmia or hyposmia.

34. Bernigaud C, Guillemot D, Ahmed-Belkacem A, Grimaldi-Bensouda L, Lespine A, el al. (2020) Ivermectin benefit: from scabies to COVID-19, an example of serendipity. *Annals of Dermatology and Venereology* 147: A194.

35. Hellwig MD, Maia A (2021) A COVID-19 prophylaxis? [published online ahead Lower incidence associated with prophylactic administration of ivermectin. *Int J Antimicrob Agents* 57: 106248. [Crossref]

36. Carballo HE, Hirsch RE (2020) Ivermectin and Herd Immunity in SARS COV2 Pandemic from Local Experience to Broader Possibility. *Clin Immunol Res* 4: 1-2.

37. Hirsch-Roberto R, Carvallo-Hector E (2020) Covid 19 and Ivermectin Prevention and Treatment Update. *J Inf Dis Trav Med* 4: 000S1-007.

38. Fink DW, Porras AG (1989) Pharmacokinetics of ivermectin in animals and humans. In: Campbell WC, editor. Ivermectin and abamectin. Springer; New York, NY, pp. 113-130.

39. Navarro M, Camprubí D, Requena-Méndez A, Buonfrate D, Giorli G, et al. (2020) Safety of high-dose ivermectin: a systematic review and meta-analysis. *J Antimicrob Chemother* 75: 827-834. [Crossref]

40. Kamgno J, Gardon J, Gardon-Wendel N, Demanga-Ngangue, Duke BO, et al. (2004) Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. *Trans R Soc Trop Med Hyg* 98: 496-504. [Crossref]

41. Awadzi K, Opoku NO, Addy ET, Quartey BT (1995) The chemotherapy of onchocerciasis. XIX: the clinical and laboratory tolerance of high dose ivermectin. *Trop Med Parasito* 46: 131-137. [Crossref]

42. Awadzi K, Attah SK, Addy ET, Opoku NO, Quartey BT (1999) The effects of highdose ivermectin regimens on Onchocerca volvulus in onchocerciasis patients. *Trans R Soc Trop Med Hyg* 93: 189-194. [Crossref]

43. Ottesen EA, Campbell WC (1994) Ivermectin in human medicine. *J Antimicrob Chemother* 34: 195-203. [Crossref]

44. Duthaler U, Suenderhauf C, Karlsson MO, Hussner J, Meyer Zu Schwabedissen H, et al. (2019) Population pharmacokinetics of oral ivermectin in venous plasma and dried blood spots in healthy volunteers. *Br J Clin Pharmacol* 85: 626-633. [Crossref]

45. https://www.isglobal.org/healthisglobal/-/custom-blog-portlet/questions-and-answers-about-ivermectin-and-covid-19/2877257/

46. Chandler RE (2018) Serious Neurological Adverse Events after Ivermectin-Do They Occur beyond the Indication of Onchocerciasis? *Am J Trop Med Hyg* 98: 382-388. [Crossref]

47. Garrigues A, Nugier J, Orlowski S, Ezan E (2002) A high-throughput screening microplate test for the interaction of drugs with P-glycoprotein. *Anal Biochem* 305: 106-114. [Crossref]

48. Schinkel AH, Mayer U, Wagenaar E, Mol CA, van Deemter L, et al. (1997) Normal viability and altered pharmacokinetics in mice lacking mdr1-type (drug-transporting) P-glycoproteins. *Proc Natl Acad Sci U S A* 94: 4028-4033. [Crossref]

49. Concato J, Nirav S, Horwitz RI (2000) Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 342: 1887-1892. [Crossref]

50. Marik P (2020) An overview of the MATH+ and I-MASK+ Protocols A Guide to the Management of COVID-19. *FLCCC Alliance* pp: 1-50.

51. https://www.covid19treatmentguidelines.nih.gov/