Original Article

Ivermectin as a possible treatment for COVID-19: a review of the 2022 protocols

Ivermectina como um possível tratamento para COVID-19: uma revisão dos protocolos de 2022

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Abstract

Ivermectin is a safe and effective drug in humans and has been approved for use in numerous parasitic infections for over 50 years. In addition, many studies have already shown its antiviral activity. Ivermectin is generally well tolerated, with no indication of central nervous system-associated toxicity at doses up to 10 times the highest FDA-approved dose of 200 µg/kg. The in vitro results of ivermectin for reducing SARS-CoV-2 viral load are promising and show that Ivermectin kills SARS-CoV-2 within 48 hours. A hypothesized mechanism of action for this drug is a likely inhibition of IMPα/β1-mediated nuclear import of viral proteins as demonstrated for other RNA viruses. However, controlled and randomized studies are needed to prove its effectiveness in COVID-19 in humans. In a single in vivo study with published results, patients confirmed to be infected with SARS-CoV-2 received at least one dose of ivermectin at any time during hospitalization. The use of ivermectin was associated with lower mortality during treatment with COVID-19, especially in patients who required increased inspired oxygen or ventilatory support. Additionally, 81 studies with the clinical use of ivermectin in humans are being carried out worldwide according to ClinicalTrials.gov. However, none of these data has been published so far. However, private and public entities in Brazil have been adopting this drug in their protocols as prophylaxis and in the initial phase of the disease. In addition, ivermectin has been used in mass treatment to prevent onchocerciasis and lymphatic filariasis in sub-Saharan Africa for many years. Surprisingly, this region has the lowest proportional mortality rate among the continents, despite the increasing numbers of infected people released by the World Health Organization.

Keywords: SARS-CoV-2, ivermectin, antiparasitic, antiviral, COVID-19.

Resumo

A ivermectina é um fármaco seguro e eficaz em seres humanos e é aprovado para uso em inúmeras infecções parasitárias há mais de 50 anos. Além disso, muitos estudos já evidenciaram sua atividade antiviral. A ivermectina é geralmente bem tolerada, sem indicação de toxicidade associada ao sistema nervoso central para doses até 10 vezes a dose mais alta, aprovada pelo FDA (Food and Drug Administration), de 200 µg/kg. Os resultados *in vitro* da ivermectina para redução da carga viral do SARS-CoV-2 são promissores e mostram que a Ivermectina mata o SARS-CoV-2 dentro de 48 horas. Uma hipótese de mecanismo de ação para esta droga é uma provável inibição da importação nuclear de proteínas virais mediada por IMPα / β1 como demonstrado para outros vírus de RNA. No entanto, estudos controlados e randomizados são necessários para comprovar sua eficácia na COVID-19 em humanos. Em um único estudo *in vivo* com resultados publicados, pacientes confirmadamente infectados por SARS-CoV-2 receberam pelo menos uma dose de ivermectina em qualquer momento durante a hospitalização. A utilização da ivermectina foi associada a menor mortalidade durante o tratamento com COVID-19, especialmente em pacientes que necessitaram de maior oxigênio inspirado ou suporte ventilatório. Adicionalmente, 81 estudos com o uso clínico da ivermectina em humanos estão sendo realizados em todo o mundo segundo o site ClinicalTrials. gov. Porém, nenhum destes teve seus dados publicados até o momento. No entanto, entidades privadas e públicas no Brasil vêm adotando este medicamento em seus protocolos como profilaxia e na fase inicial da doença. Além disto, a ivermectina é utilizada no tratamento em massa na prevenção da oncocercose e filariose linfática na África subsaariana há muitos anos. Surpreendentemente, esta região possui o menor índice de mortalidade proporcional entre os continentes, apesar dos números crescentes de contaminados divulgados pela Organização Mundial da Saúde.

Palavras-chave: SARS-CoV-2, ivermectina, antiparasitário, antiviral, COVID-19.

1. Introduction

The COVID-19 (Corona Virus Disease - 2019) pandemic represents a serious threat to global public health and local economies, in addition to being a public health emergency of international concern (Walker et al., 2020). Although there is a commercially available vaccine against SARS-CoV-2 (Cascella et al., 2020), there are still symptoms that can worsen health status when a patient is affected by the virus. Since the beginning of the epidemic in China, ways of treatment have been sought to eliminate the SARS-CoV-2 (Severe acute respiratory syndrome coronavirus 2 of the genus Betacoronavirus) or to alleviate the symptoms and severity of COVID-19, these searches increased after the pandemic state (Cascella et al., 2020).

Thus far, in only a single *in vitro* study, the efficacy of ivermectin against the coronavirus has been demonstrated. This study by Caly et al. (2020) collaborative led by the Biomedicine Discovery Institute (BDI) of Monash University, Melbourne, Australia, with the Peter Doherty Institute of Infection and Immunity (Doherty Institute), showed that Ivermectin, an antiparasitic drug already available worldwide kills the virus within 48 hours (Caly et al., 2020). Ivermectin (Figure 1) is a mixture of two semi-synthetic analogues of *Streptomyces avermitilis* fermentation products (Chaccour et al., 2017). It has been in widespread use in veterinary medicine since 1981 and its use has been extended to humans from 1987. Since this year, nearly 3.7 billion treatments have been given worldwide, primarily for mass drug administration campaigns (MDA) for onchocerciasis (river blindness) and lymphatic filariasis (elephantiasis) in sub-Saharan Africa (Daley, 2015; King, 2020; Richards et al., 2020). Currently, ivermectin is approved for use in humans in several countries (Australia, France, Japan, Netherlands, USA, Brazil, among others) to treat onchocerciasis, lymphatic filariasis, strongyloidiasis and/or scabies (González Canga et al., 2008).

It has also been hypothesized that combination therapy using hydroxychloroquine and ivermectin might exert a synergistic inhibitory effect on SARS-CoV-2. In this combination, hydroxychloroquine acts by inhibiting the entry of SARS-CoV-2 into host cells, while ivermectin further increases antiviral activity by inhibiting viral replication (Patrì and Fabbrocini, 2020).
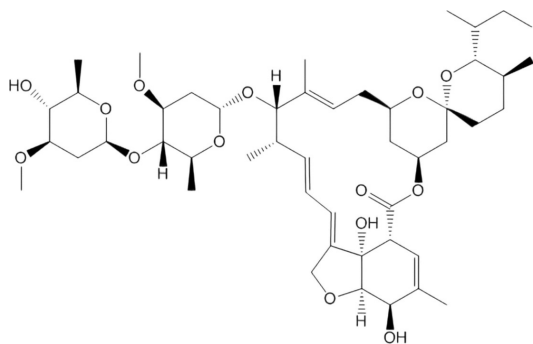

Figure 1. Chemical structure of ivermectin, the 22,23-dihydro derivative of a macrocyclic lactone avermectin B1. Source: Sharun et al. (2020).

2. Development

In Brazil, the generic drug Ivermectin (ANVISA Registration No. 1558401840033-01/16/2012) is intended for the treatment of: intestinal strongyloidiasis: infection caused by the nematode parasite *Strongyloides stercoralis*; onchocerciasis: infection caused by the nematode parasite *Onchocerca volvulus*; filariasis: infection caused by *Wuchereria bancrofti* parasite; ascariasis: infection caused by the parasite *Ascaris lumbricoides*; scabies: skin infestation caused by the mite *Sarcoptes scabiei* and pediculosis: dermatosis caused by *Pediculus humanus capitis* (ANVISA, 2021). It is also an endectocide, a drug capable of killing arthropods that feed on a treated individual, including *Anopheles* spp. mosquitoes (Chaccour et al., 2017). Ivermectin blocks synaptic transmission in invertebrates, binding to glutamate-dependent chlorine channels in nerves and muscles, leading to hyperpolarization, paralysis and death of invertebrates, including mosquitoes (Merck & Co., 2009). In mammals, ivermectin acts as an allosteric agonist at the $GABA_A$ receptor, another member of the Cys-loop family of ligand-dependent ion channels. These receptors are located on neurons in many regions of the central nervous system (including the cerebral cortex, limbic system and thalamus) and increase chloride conductivity, resulting in hyperpolarization and less formation of action potentials (Ménez et al., 2012). In vertebrates, $GABA_A$ is an important inhibitory transmitter. The net effect of $GABA_A$ receptor stimulation is central nervous depression, which defines the syndrome of ivermectin toxicity in vertebrates (Chaccour et al., 2017). *In vitro* and *in vivo* studies of ivermectin against numerous viruses over the last 50 years can be found in the work of Heidary and Gharebaghi (2020).

The predominant isoform responsible for the biotransformation of ivermectin in the human liver is cytochrome P-4503A4, converting the drug into at least 10 metabolites, most of them hydroxylated and demethylated derivatives (Zeng et al., 1998). In plasma, radioactive metabolites were reported following oral administration of ivermectin in healthy volunteers (Fink and Porras, 1989; González Canga et al., 2008).

The rapid response of ivermectin against COVID-19 is consistent with reporting its absorption into the blood and distributed into body tissues to peak levels typically within 4-8 hours after oral dosing. A mean elimination half-life of ivermectin of approximately 12-18 hours has been observed after oral administration in humans (Chaccour et al., 2017; Crump, 2017). But the half-life of the main metabolites of ivermectin is four times longer. Its significant biological effects have been manifested in humans, from many days to a month after a single dose (Baraka et al., 1996; Chaccour et al., 2017; Guzzo et al., 2002). It was suggested by Edwards et al. (1988) that the kinetics of ivermectin was somewhat disconnected from its pharmacodynamics (antiparasitic events persisting for several months after a single dose of the drug). No differences in elimination half-life were detected between healthy and onchocerciatic patients (Baraka et al., 1996).

The pharmacokinetic parameters obtained after oral administration of ivermectin in humans can be seen in Table 1.

Long-term animal studies have not been performed to assess the carcinogenic potential of ivermectin. Ivermectin did not show signs of genotoxicity in the *Salmonella typhimurium* reverse mutation assay to verify microbial mutagenicity *in vitro* with *Salmonella* spp., varieties TA1535, TA1537, TA98 and TA100, with and without activation of the rat liver enzyme system, as well as in cytotoxicity and mutagenicity using mouse lymphoma lineage L5178Y and in DNA synthesis assay with human fibroblasts. Ivermectin has been shown to be teratogenic in mice, rats and rabbits when administered in repeated doses of 0.2; 8.1 and 4.5 times the maximum recommended human dose, respectively (based on mg/m²/day). Teratogenicity was characterized in the three species tested by cleft palate. Deformation of the forepaws in rabbits was also observed. These effects were only obtained at doses equal to or close to toxic levels for pregnant females. Therefore, ivermectin does not appear to be selectively toxic to the developing fetus. Ivermectin had no adverse effects on rat fertility in repeat dose studies up to three times the maximum recommended human dose of 200 µg/kg (based on mg/m²/day) (ANVISA, [s.d.]).

Ivermectin was generally well tolerated, with no indication of Central Nervous System (CNS) associated toxicity at doses up to 10 times the highest FDA-approved dose of 200 µg/kg (Guzzo et al., 2002). Pharmacokinetic studies in healthy volunteers have suggested that single doses of up to 120 mg of ivermectin may be safe and well tolerated (Guzzo et al., 2002). Single doses of ivermectin up to 800 µg/kg are well tolerated according to Awadzi et al. (1995).

In the study by Oosting et al. (1995) investigated whether reduced absorption of ivermectin could explain the fact that some patients severely infected with onchocerciasis and had few adverse effects after treatment with ivermectin, although the occurrence and extent of adverse reactions were related to the intensity of infection. Also according to this study, there was no adverse reaction observed in plasma concentration after administration of a single oral dose of 150 µg/kg. There are no reports of drug interactions with ivermectin; however, it should be administered with caution to patients using drugs that depress the CNS (ANVISA, 2021).

This drug is also contraindicated for use by patients with hypersensitivity to ivermectin or other components of this drug, patients with meningitis or other conditions of the central nervous system that may affect the blood-brain barrier, due to its effects on GABA-ergic receptors in the brain and for children under 15kg or under 5 years old (ANVISA, 2021).

The recommendations for elderly patients on the use of ivermectin are similar to those for adult patients. And as there is still not enough clinical data regarding

Table 1. Pharmacokinetic parameters obtained after oral administration of ivermectin in humans.

Reference dose	Dose	Absorption			Elimination	
		C_{max} (ng·mL⁻¹)	t_{max} (h)	$t_{1/2(abs)}$ (h)	$t_{1/2}$ (h)	Cl (1 kg⁻¹·dia⁻¹)
Healthy individuals						
9[a]	12 mg (tablet)	–	–	–	12	–
8[a]	6 mg (tablet)	23.1	4.3	0.5	12.6	4.28
8[a]	12 mg (tablet)	30.4	10.3	2.5	13.4	4.03
9[a]	6 mg (tablet)	20.2	4.7	1.4	11.1	7.57
9[a]	12 mg (tablet)	23.5	5.3	1.4	21.1	6.53
9[a]	18 mg (tablet)	31.2	5.1	1.7	16.7	10.6
11	12 mg (solution)	81	3.6	–	–	–
11	12 mg (tablet)	50	3.4	–	–	–
11	12 mg (capsule)	46	3.6	–	–	–
12	150 µg/kg	54.4	4.9	–	36.6	–
13	150 µg/kg	37.9	–	–	–	–
14	150 µg/kg	33.8	–	–	–	4.70 (♂) 8.40 (♀)
Onchocerciasis patients						
12	150 µg/kg	52.2	5.2	–	35.0	–
15	150 µg/kg	39	5.6	–	16	–
16	6 mg (tablet)	38.2	4.7	–	54,5	3.1
17	150 µg/kg				19.9	–

Unknown data; C_{max} maximum plasma concentration; t_{max} maximum time to reach C_{max}; $t_{1/2}$abs half-life of absorption; $t_{1/2}$ elimination half-life; $t_{1/2}$; C_l total body clearance. [a]One-compartment model.
Source: Adapted from González Canga et al. (2008).

the treatment of children under 5 years old or weighing less than 15kg, the use of this drug by patients in this age group should not be carried out. Safety and efficacy in children under 15 kg or under 5 years of age have not been established (ANVISA, 2021).

A first systematic review and meta-analysis focused on six published studies to address whether inadvertent ingestion of ivermectin during pregnancy results in abnormal birth outcomes (Nicolas et al., 2020). Five of the six studies were retrospective case-control studies of women who gave birth within 40 weeks of an mass drug administration (MDA) program that compared abnormal birth outcomes (stillbirths, miscarriages, and congenital anomalies) between women who took ivermectin and those who did not receive the drug. The authors concluded that current evidence does not support the safety of ivermectin during pregnancy and recommend that it continue to exclude pregnant women from treatment during MDA programs. Another interpretation is that the risk of adverse events associated with exposure to ivermectin in pregnancy is sufficiently low to warrant a randomized, multicenter trial to administer ivermectin to infected pregnant women (King, 2020). Ivermectin is excreted in breast milk at low concentrations. Treatment of mothers planning to breastfeed should only be done when the risk of delaying the mother's treatment outweighs the possible risk to the infant (ANVISA, 2021).

Another systematic literature review and meta-analysis on the safety and doses of ivermectin was conducted by Navarro et al. (2020). Clinical trials reporting data on doses ≥200 and ≥400 µg/kg were included. Although in this review the safety of ivermectin at high doses appears to be comparable to standard doses, the authors state that

there is insufficient data to support a recommendation for its use at doses higher than those approved.

2.1. In vitro studies with ivermectin against COVID-19

An article published in the journal Antiviral Research showed that ivermectin inhibits the replication of SARS-CoV-2 in vitro (Caly et al., 2020). This collaborative study was led by the Biomedicine Discovery Institute (BDI) at Monash University in Melbourne, Australia, in conjunction with the Peter Doherty Institute for Infection and Immunity (Doherty Institute). To test the antiviral activity of ivermectin against SARS-CoV-2, Vero-hSLAM cells were infected with SARS-CoV-2 (isolated Australia / VIC01 / 2020 at an MOI of 0.1) and after 2h ivermectin was added (5 µM). The supernatant and cell granules were collected on days 0-3 and analyzed for RNA replication of the new coronavirus by polymerase chain reaction - reverse transcriptase (qRT-PCR) techniques in real time. DMSO was used as a control and drug diluting agent. As a result, after 24 hours, there was a 93% reduction in viral RNA present in the supernatant (indicating released virions) from ivermectin-treated samples. After 48 h the reduction was approximately 5,000-fold in viral RNA. The authors hypothesize a possible mechanism of action inhibition of the nuclear import of viral proteins mediated by IMPα / β1 as shown for other RNA viruses; the confirmation of this mechanism in the case of SARS-CoV-2 and the identification of the SARS-CoV-2 and/or impacted host component(s) is an important focus of future work in the authors' laboratory (Figure 2). The authors now want to find out whether the dosage that is possible to use in humans will be effective.
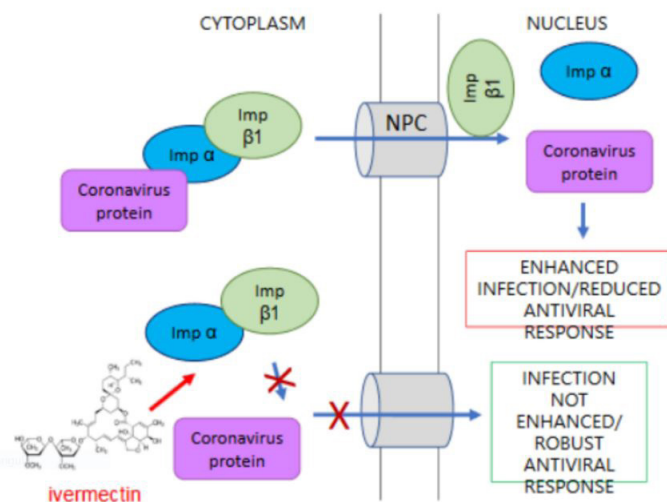

Figure 2. Ivermectin is a potent inhibitor of the clinical isolate SARS-CoV-2 237 Australia / VIC01 / 2020. Schematic diagram of the antiviral action proposed by ivermectin on coronaviruses. IMPα / β1 binds to the coronavirus cargo protein in the cytoplasm (upper part) and translocates it through the nuclear pore complex (NPC) to the nucleus where the complex breaks down and the viral load can reduce the antiviral response of the host cell, leading to infection. Ivermectin binds to and destabilizes the Impα / β1 heterodimer, thereby preventing Impα / β1 from binding to the viral (lower) protein and preventing it from entering the nucleus. This likely results in reduced inhibition of antiviral responses, leading to a normal and more efficient antiviral response. Source: Caly et al. (2020).

Finally, the authors conclude that the results obtained in their research, combined with a known safety profile, demonstrate that ivermectin has potential and needs further studies to confirm its possible antiviral effect SARS-CoV-2 and as a possible treatment of COVID- 19, for that, controlled clinical trials must be carried out (Caly et al., 2020).

2.2. In vivo studies with ivermectin against COVID-19

The main objective of the protocol performed by Chaccour et al. (2020) is to determine the efficacy of a single dose of ivermectin, administered to 24 patients with low-risk, non-severe COVID-19 within the first 48 hours after symptom onset, to reduce the proportion of patients with SARS-CoV- RNA 2 detectable by polymerase chain reaction (PCR) test of the nasopharyngeal swab on the seventh day after treatment (Chaccour et al., 2020). This SARS-CoV-2 Ivermectin Navarra-ISGlobal (SAINT) trial is being conducted in a single center (at the University of Navarre, Spain), double-blind, randomized, placebo-controlled, with two parallel arms. Participants will be randomized to receive a single 400 µg/kg dose of ivermectin or placebo, and the number of patients in the treatment and placebo groups will be the same (1:1 ratio). All recruited patients completed the study within 28 days (mean age 26 years; 12 [50%] women; 100% had symptoms at enrollment, 70% reported headache, 62% reported fever, 50% general malaise, and 25% cough). On day 7 there was no difference in the proportion of PCR positive patients The ivermectin group had non-statistically significant lower viral loads on day 4 (p = 0.24 for the E gene; p = 0.18 for the N gene) and at day 7 (p=0.16 for the E gene; p=0·18 for the N gene) post-treatment, as well as lower IgG titers on day 21 post-treatment (p=0.24). Patients in the ivermectin group recovered earlier from hyposmia/anosmia (76 vs 158 patient-days; p < 0.001) (Chaccour et al., 2021).

Rajter et al. (2020) published a study to determine whether ivermectin is associated with a lower mortality rate in patients hospitalized with COVID-19. Two hundred and eighty patients with confirmed SARS-CoV-2 infection participated in the survey, with a mean age of 59.6 years, of which 173 were treated with ivermectin and 107 patients were treated with usual health care. Patients were categorized into two treatment groups based on whether they received at least one dose of ivermectin at any time during hospitalization. Univariate analysis showed lower mortality in the ivermectin group (25.2% versus 15.0%). Mortality was also lower among the 75 patients with severe lung disease treated with ivermectin (38.8% vs 80.7%), but there was no significant difference in successful extubation rates (36.1% vs 15.4%). In summary, ivermectin was associated with lower mortality during treatment with COVID-19, especially in patients who required increased inspired oxygen or ventilatory support. However, the authors suggested that these findings should be evaluated with randomized clinical trials. In an analysis of 15 studies conducted in 2021, Bryant et al. (2021) found in 2438 subjects that ivermectin reduced the risk of death compared to placebo. This result was confirmed in a sequential test analysis using the same DerSimonian-Laird method that supported the unadjusted analysis. This was also robust against a sequential test analysis using the Biggerstaff-Tweedie method. Evidence found that ivermectin prophylaxis reduced COVID-19 infection by an average of 86%. The results also provided evidence that the use of ivermectin for inpatients contributed to the absence of mechanical ventilation. Serious adverse events were rare among trials of ivermectin treatment.

In 2021, Krolewiecki et al. (2021) performed a trial to assess the high-dose antiviral activity of ivermectin in 45 hospitalized patients with COVID-19 randomized in a 2:1 ratio to standard of care plus oral ivermectin at 0.6 mg/kg/day for 5 days versus standard care in 4 hospitals in Argentina. Eligible patients were adults with SARS-CoV-2 infection confirmed by RT-PCR within 5 days of symptom onset. The primary endpoint was the difference in viral load in respiratory secretions between positive confirmation and day 5 by quantitative RT-PCR. Plasma IVM concentrations were measured.

Eighty one studies with the clinical use of ivermectin in humans are being carried out with data yet to be published. These protocols were registered until March 13, 2022, on the website clinicaltrials.gov (U.S. National Library of Medicine, 2022). Of these, 6 studies have already been completed (Table 2), 26 are recruiting volunteers, 49 have not yet started recruiting (2 of these in Brazil). In addition, numerous protocols that are not on the clinicaltrails.gov list were registered with the National Research Ethics Commission (CONEP) for studies in Brazil using ivermectin (CONEP, 2020).

2.3. Protocols for the use of ivermectin against COVID-19 in Brazil

In Brazil, the private service network through its health plans provides its patients with a protocol for the use of ivermectin in the initial stage of the disease, even if this drug is not yet in the official protocol of the Brazilian government (Unimed, 2020a e 2020b.The dosage routinely used is 12 mg VO in a single dose or for 2 days (Nunes and Lima, 2020) and already established in some protocols in Brazil (Bezerra et al., 2020; AGORARN, 2020).

Some municipalities in Brazil are purchasing doses of ivermectin and distributing it to residents as a prophylactic treatment (Brasil, 2020a, b; Rupp, 2020; UFC, 2020; Vilanova and Baía, 2020). In Itajaí, a medium-sized city in Santa Catarina, southern Brazil, 9,000 residents received the drug ivermectin with prophylactic treatment by COVID-19, through a medical prescription or signature of the citizen and responsible physician in the Informed Consent Form. This drug was included in the protocol of the Municipal Health Department for prevention and treatment in the fight against COVID-19 in this municipality, according to Decree No. 11,940/2020 (Brasil, 2020a).

2.4. Bulk ivermectin administration versus COVID-19 WHO data

As stated earlier, ivermectin is used in mass treatment to prevent two ancient scourges that have plagued sub-Saharan Africa for centuries - elephantiasis and river blindness. For this region of Africa with lower health infrastructure conditions,

Table 2. Clinical trial protocols registered until March 13, 2022 in clinicatrials.gov, using ivermectin alone or in associations that have already been completed but not yet completed, and protocols that will be used in Brazil.

clinicaltrials.gov Identifier/ Status	Title/Number of participants	Medication	Location
NCT04343092/ Concluted	Efficacy of Ivermectin as Add on Therapy in COVID19 Patients/100	• Ivermectin 12 mg/0.2 mg weekly/kg (single dose = 2 tablets of 6 mg/weekly) + Hydroxychloroquine 400 mg/day + Azithromycin 500 mg daily • Without intervention: Hydroxychloroquine 400 mg / day + azithromycin 500 mg daily	General Directorate of Medical City Bagdad, Baghdad, Iraq
NCT04434144/ Concluted	A Comparative Study on Ivermectin and Hydroxychloroquine on the COVID19 Patients in Bangladesh/116	• A group: • -Ivermectin 200μgm/kg single dose + Doxycycline 100mg twice daily for 10 days • Group B: • -Hydroxychloroquine 400mg on the first day and then 200mg twice a day for 9 days + azithromycin 500mg daily for 5 days	Chakoria Upazilla Health Complex Cox's Bazar, Bangladesh
NCT04431466/ Concluted	A Study to Compare the Efficacy and Safety of Different Doses of Ivermectin for COVID-19/64	• Ivermectin 100mcg / kg PO single dose • 100mcg / kg PO on the first day, followed by 100mcg / kg PO after 72h • Ivermectin 200mcg / kg PO single dose • 200mcg / kg PO on the first day, followed by 200mcg / kg PO after 72h	University Hospital of the Federal University of São Carlos (HU-UFSCar) São Carlos, São Paulo, Brazil
NCT04446429/ Concluted	Anti-Androgen Treatment for COVID-19/254	• Ivermectin 200 mcg/kg q.d (1 time a day) + azithromycin 500 mg q.d + Dutasteride 0.5 mg q.d. • Ivermectin 200 mcg/kg q.d + azithromycin 500 mg q.d.	Corpometria Institute Brasilia, Brazil
CTRI/2022/01/039235 / Recruting	A clinical trial to study the effects of several commercially available drugs in patients with mild COVID-19/3000	• 200 mg Artesunate and 540 mg Amodiaquine daily (i.e.two tablets of 100 mg of artesunate and 270 mg of amodiaquine) for 3 days and Ivermectin tablets 0.4 mg/kg body weight for 5 days	Indian Council of Medical Research, India
ACTRN12621001535864 / Recruting	A pilot randomized placebo-controlled double-blind trial of single dose oral Ivermectin for post-exposure prophylaxis of SARS-CoV-2/40	• Single dose of ivermectin 200ug/kg orally or matching placebo tablets. The trial will recruit participants who have, in the preceding 72 hours, had close contact with a person infectious with SARS-CoV-2.	Monash University, Australia
IRCT20200818048444N3 / Recruting	Ivermectine effect in treatment of patients with COVID-19 disease/25	• Intervention group: 3 doses of oral ivermectin 200 μg / kg once daily for 3 doses	Imam Reza Hospital, East Azarbaijan

Source: Clinicaltrials.gov (2022).

a high mortality rate due to COVID-19 contamination was expected. However, figures released by the WHO (2020a) show the African continent with the lowest proportional mortality rate among the continents, despite the growing numbers of notified contaminated. It is necessary to analyze whether the mass use of ivermectin contributed or not to the reduction of these indices.

In addition, mass administration of ivermectin with co-administration of azithromycin was offered to the entire population of Choiseul Province, Solomon Islands, and from that population two sets of ten villages were randomly selected for monitoring, one at baseline and one at 12 months from onset (Romani et al., 2019). According to the WHO, so far no deaths have been reported due to

COVID-19 contamination in this location (Nicolas et al., 2020; WHO, 2020a, b).

3. Conclusion

The exact mechanism of action of ivermectin against SAR-CoV-2 is not yet known. And although many studies present its application, some of them have a series of methodological limitations that make it difficult to analyze the data, interpret the results of the work, in addition to making comparisons between them difficult. Much of the current evidence on the use of this drug to treat patients with COVID-19 is inconclusive and lacks further research advances, including new adequate and structured clinical trials. It is noteworthy that private and public protocols in Brazil already use ivermectin based on clinical data from the municipalities, at a dose of 12 mg orally in a single dose or with a repeated dose within 24 hours or 12 mg for 3 days, in the first symptoms of the disease or even as a prophylactic use.

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