Ivermectin–an antiviral drug for the COVID-19 pandemic?

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Abstract

The use of ivermectin for the treatment of COVID-19 infections has been a subject of significant interest and controversy. The drug has a history of off-label use for a variety of clinical disorders and has shown some potential as an antiviral drug in in vitro *studies and animal studies, and it has a relatively favorable safety profile. Multiple studies have been published examining the use of ivermectin against COVID-19. While several studies suggested it could be an effective therapeutic, most of these studies were insufficiently robust, had design flaws, or did not report any changes in important clinical outcomes, such as mortality. A smaller number of more robust studies did not support ivermectin use for COVID-19 treatment. Therefore, at present, ivermectin cannot be recommended for the treatment of COVID-19. While further studies may be warranted, this decision must be weighed against the possibility that this research may not alter current recommendations on the use of ivermectin in COVID-19 infections.*

Keywords: COVID-19, ivermectin, prophylaxis, hospitalization, respiratory failure, mortality

Introduction

The antiparasitic drug ivermectin has become a topic of interest and controversy during the COVID-19 pandemic. Its suggested use as a SARS-CoV-2 antiviral has highlighted issues regarding off-label pharmaceutical use, interpretation of clinical data, and the need to balance safety with the urgency for new therapeutics. Here we explore the studies on ivermectin as a SARS-CoV-2 antiviral drug and provide recommendations regarding ivermectin's role in the COVID-19 pandemic.

Background

Ivermectin is a macrocytic lactone and a derivative of naturally occurring ivermectins produced by *Streptomyces avermitilis*. It was isolated in 1974 as part of a drug development collaboration between the Kitasato Institute in Japan and the Merck, Sharpe, and Dohme laboratories in the United States. The effectiveness as an antiparasitic and favorable safety profile of ivermectin made it an ideal candidate for community-wide parasite treatment and eradication programs. By 1987, ivermectin had proven effectiveness against human parasites, namely onchocerciasis in Africa, intestinal (e.g., nondisseminated) strongyloidiasis due to *Strongyloides stercoralis*, and lymphatic filariasis.[1] Ivermectin is remarkably effective against parasites, with only a single dose often needed to eliminate microfilariae and prevent disease progression for one to two years.[2] In 1989, the World Health Organization (WHO) stated that ivermectin could be administered with limited supervision. Later, programs, such as the *Onchocerciasis* Elimination Programme in the Americas (1992), the African Programme for Onchocerciasis Control (1995), and the Global Programme to Eliminate Lymphatic Filariasis (1998), were launched using ivermectin (and other drugs) to combat parasitic diseases.[3] Ivermectin since then has

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been used to treat many infections, including ascariasis, demodicosis due to *Demodex folliculorum* and *Demodex brevis*, gnathostomiasis ascariasis, due to *Gnathostoma spinigerum*, hookworm-related cutaneous larva migrans, pediculosis, *Mansonella ozzardi* infection, *Mansonella streptocerca* infection, scabies due to *Sarcoptes scabiei*, trichuriasis due to *Trichuris trichiura*, and *Wucheria bancrofti* infection.[1] It has been very beneficial in resource-poor communities, and the African Programme for Onchocerciasis Control alone has prevented an estimated 17.4 million years of healthy life being lost from 1995 to 2014.[4] Presently, it is used annually in 250–300 million people,[5] many of them in resource-poor communities.

Mechanism of action, side effects, and uses

The antiparasitic mechanism of ivermectin is probably due to inhibition of glutamate-gated chloride ion channels found in muscles and nerves, effectively paralyzing adult parasites and inhibiting the release of egg or microfilaria.[6] Ivermectin also has inhibitory effects on other chloride channels, including γ-aminobutyric acid (GABA), which may potentiate its effect on glutamine chloride channels.[6] Despite this, ivermectin has a favorable safety profile in humans since GABA receptors are found only in the central nervous system (CNS)[7], and entry into the CNS is prevented by the blood-brain barrier.[8,9] Mutations in genes coding for blood-brain barrier pumps may make patients more susceptible to neurological toxicity. Side effects are generally minor and include headache, dizziness, muscle pain, nausea, fatigue, somnolence, and diarrhea.[1,10] Serious neurological effects are rare and have been associated with the treatment of specific parasites.[11] Ivermectin is not recommended for children under 5 years of age or weighing less than 5 kg or in pregnant or lactating women, due to concern that the developing blood brain barrier might allow passage of ivermectin into the CNS.

Ivermectin as an antiviral

In addition to its anthelmintic properties, ivermectin has antiviral properties and has activity against several RNA and DNA viruses, including yellow fever, Japanese encephalitis, dengue, West Nile, Venezuelan equine encephalitis, Zika, Chikungunya, HIV, and adenovirus,[6,12,13] likely through inhibition of NS3 helicase and nuclear pore IMPα/β1.[6,14] Ivermectin improved survival, improved clinical scores, reduced brain lesions, and decreased organ viral titers in mice infected with pseudorabies virus.[15] Ivermectin significantly reduced viral titers in sera and tissues in piglets infected with porcine circovirus type 2.[16] However, ivermectin did improve survival in mice infected with Zika virus despite activity *in vitro*.[17] A clinical trial using ivermectin to treat Dengue infection showed a statistically significant difference in patients with viral protein time to clearance (71.5 vs 95.8 hours, $p = 0.014$) and total clearance at discharge (72.0% vs 47.6%, $p = 0.001$), but there was no difference in viremia clearance.[18]

Additional uses

Ivermectin may have additional uses beyond its effect as an anthelmintic drug. It has been effective as a topical treatment for rosacea.[19] In an animal model of allergic asthma, mice treated with ivermectin had lower inflammatory cytokine levels and less secretion of IgE and IgG1.[20] Uses of ivermectin may extend to metabolic regulation, including lowering glucose and cholesterol and reducing lipid accumulation in the liver in mice.[21] Ivermectin has also been used as an insecticide.[22] Given this, ivermectin has been proposed as an antimalarial and as a vector control agent to eliminate malaria-carrying mosquitos.[23] It has direct effects against *Plasmodium falciparum*,[24–26] likely through inhibition of importin α/β.[23] Finally, ivermectin has been investigated as an anticancer drug.[27,28] Although there are no clinical trials to date with ivermectin as an anticancer agent, it does have effects on tumor cells *in vitro*[29–31] and in animal models.[32,33] Proposed antitumor mechanisms of action are varied and include induction of autophagy and apoptosis, interference with cellular signaling pathways (including Wnt/β-catenin and Ras/MAPK), RNA helicase inhibition, and angiogenesis inhibition.[27,28] Animal studies have reported effectiveness against breast,[34] colon,[35] and renal[33] cancers.

Ivermectin and adverse events

Ivermectin has a very favorable safety profile. A single 150 µg/kg dose can eliminate worm microfilariae and prevent new microfilariae for up to two years.[36] It is safe at single doses up to 800 µg/kg,[11] and a small study of 12 healthy volunteers noted no adverse events at a dose of 2000 µg/kg.[37] Side effects are generally minor and include headache, dizziness, muscle pain, nausea, fatigue, somnolence, and diarrhea.[1,10] Serious neurological effects are rare and have been associated with the treatment of specific parasites.[11] For example, treatment of filariasis can produce a transient immune response known as a Mazzotti reaction, likely due to the immune reaction to dead onchocerciasis microfilariae.[1] More serious reactions have been noted when patients were treated for loaitis, caused by the parasite *Loa loa*, and include encephalitis and death.[38,39] This may be due to microfilariae emboli in the brain in patients with high microfilariae loads.[40] It has been theorized this could be due to the prevalence of *mdr1* alleles.[41] Ivermectin is not recommended for children under 5 years of age or weighing less than 5 kg or for pregnant or lactating women. However, studies have demonstrated that ivermectin can be used safely to treat scabies in children, but more data are needed.[42] There is also some evidence that ivermectin can cause hematologic changes; studies have reported prolongation of the prothrombin time and reductions in factors II and VII levels. However, these changes did not cause any bleeding complications.[3] In meta-analyses reported by Navarro et al. and Chaccour et al., ivermectin was well tolerated at the doses of 400 µg/kg. Common adverse reactions noted were mainly dizziness, blurred vision, eye reactions, nausea, headache, and skin rash, which appeared to be dose-dependent.[43,75] Chandler described a series of 28 cases with severe neurological reactions after ivermectin treatment that could be due to variation in the MDR-1 gene, which may have allowed ivermectin to penetrate the central nervous system.[44]

Ivermectin and COVID-19

Discussions around ivermectin as a possible COVID-19 therapeutic began as the pandemic 2020 developed. An early study by Caly et al.[45] in June 2020 reported the effectiveness of ivermectin *in vitro* against COVID-19. This came at a time when there were few available treatments for COVID-19, no approved vaccines, and a heightened interest in finding potential new therapeutics that have low cost, availability, and a favorable side-effect profile. *In vitro* studies suggested that ivermectin acts by inhibiting the host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses use to suppress the host's antiviral response and to interfere with the spike protein S1, RNA-dependent RNA polymerase, and viral proteins, which may inhibit viral entry and replication.[46] Although ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell cultures, it requires administration of doses up to 100-fold higher to achieve antiviral efficacy that was detected *in vitro*.[47]

Despite this *in vitro* activity, multiple clinical trials have reported a clinical benefit for ivermectin in patients with these viruses.[48–52] Several clinical studies[53–55] and meta and systematic analyses[56–60] have also suggested that ivermectin may be an effective COVID-19 therapeutic or prophylactic drug. However, some of these studies have been criticized as being biased and having low methodological rigor adding to the confusion about if and how the drug should be used in this pandemic. There is also concern about people obtaining ivermectin illegally[61] and unsupervised use or use of veterinary formulations of ivermectin leading to adverse events.[62] At present, ivermectin and its use in COVID-19 continue to be a topic of interest, with 80 clinical trials listed by the NIH as completed or underway as of February 9, 2022 (available at clinicaltrials.gov). Nevertheless, the National Institutes of Health,[63] the World Health Organization,[64] and the Infectious Disease Society of America[65] have not supported using ivermectin to treat COVID-19 outside of clinical trials. A Cochrane analysis, considered a gold standard among meta and systematic analyses, by Popp et al. published in July 2021 is representative of the current state of ivermectin use and COVID-19 question; these authors concluded that the effectiveness of ivermectin to treat COVID-19 was uncertain and more high-quality research would be needed.[66] Here we endeavor to provide the current analysis of ivermectin clinical trials for COVID-19.

Studies in COVID-19 patients with mild infections

A randomized, double-blind, placebo-controlled IVERCOR-COVID-19 study was conducted in Corrientes, Argentina, between August 19, 2020, and February 22, 2021, in non-hospitalized patients. Primary outcomes of the study showed that 5.6% of patients in the ivermectin group required hospitalization compared to 8.4% of patients in the placebo group. The need for mechanical ventilation was 2% in the ivermectin arm vs. 1% in the placebo arm (P = 0.7), all-cause mortality was 2% in the ivermectin arm vs. 1% in the placebo arm (P = 0.7), and the occurrence of adverse effects was 18% in IVM arm vs. 21% in the placebo arm (P = 0.6). The study had some limitations since it enrolled fairly young patients with few comorbidities.[52]

A double-blind placebo-controlled randomized controlled trial (RCT) conducted in Columbia between July 15, 2020, and December 21, 2020, has shown that a five-day course of ivermectin 300 µg/kg per day given to patients with mild disease did not shorten the time to resolution of symptoms based on a 21-day follow-up period. Among 400 patients who were randomized, the median time to resolution of symptoms was 10 days in the ivermectin group compared to 12 days in the placebo group (hazard ratio [HR] for resolution of symptoms:1.07, 95% CI: 0.87–1.32]; p = 0.53 by log-rank test). By day 21, 82% in the ivermectin group and 79% in the placebo group had resolution of all symptoms.[51]

In an open-label, randomized parallel-group clinical trial, conducted in two tertiary care hospitals in Egypt at Tanta and Assiut University Hospitals between March 2020 and October 2020, 164 patients were randomized into two groups in which the treatment group received ivermectin 12 mg once daily for 3 days and the control group received the standard treatment protocol for 14 days. The main primary outcomes were mortality, the length of hospital stay, and the need for mechanical ventilation. Results showed no statistically significant difference in any of the primary endpoints between the 2 groups. The authors noted a trend in reduced hospital stay in the ivermectin group (8.82 ± 4.94 days) when compared to the control group (10.97 ± 5.28 days), but this was not statistically significant (p = 0.085).[55] A double-blind, parallel, randomized, placebo-controlled trial was conducted in a tertiary healthcare center in eastern India between August 1 and October 31, 2020, with adult patients with mild to moderate disease severity. Patients in the intervention arm received ivermectin 12 mg on days 1 and 2 post-enrollment, while the patients in the non-interventional arm received placebo tablets. Results showed no statistically significant difference between the 2 intervention arms for the primary endpoint, which was negative viral PCR on the 6th day (23.6% of the patients in the intervention arm versus 31.6% in the placebo arm; rate ratio [RR]: 0.8; 95% confidence interval [CI]: 0.4–1.4; p = 0.348). Nevertheless, 100% of the patients in the ivermectin group were successfully discharged compared to 93% of the patients in the placebo group; this difference was statistically significant (RR: 1.1; 95% CI: 1.0–1.2; p = 0.045).[67] In a RIVET-COV pilot, double-blind, randomized controlled trial conducted in India, hospitalized patients with mild-to-moderate COVID-19 were randomly assigned to receive ivermectin at either 12 mg or 24 mg doses or placebo in a 1:1:1 ratio. This study demonstrated that patients in two ivermectin groups had higher percent negative viral PCR compared to the placebo arm, but this did not reach statistical significance (ivermectin 24 mg, 47.5%; 12 mg arm, 35.0%; and placebo arm, 31.1%; p-value = 0.30). The decease in viral load on day 5 was similar in each arm.[68]

An open-label randomized clinical trial (ITECH) conducted in Malaysia enrolled patients who were 50 years and older with mild to moderate disease. Patients were randomized in a 1:1 ratio to receive either oral ivermectin plus standard of care (symptomatic therapy) (n = 241) or standard of care alone (n = 249). On analysis, 21.6% in the ivermectin group and 17.3% in the control group progressed to severe disease (relative risk [RR], 1.25; 95% CI: 0.87–1.80; P = 0.25). There were no significant differences between groups for secondary outcomes, including rates of mechanical ventilation, intensive care unit admission, 28-day in-hospital mortality, and adverse events.[58] In a randomized, double-blind, multicenter, phase II, clinical

trial conducted in Italy from July 2020 to May 2021, participants were randomly assigned to receive either placebo, single-dose ivermectin 600 µg/kg plus placebo for 5 days, or single-dose ivermectin 1200 µg/kg for 5 days. Primary outcomes were serious adverse drug reactions and changes in viral load on day 7. There was no significant difference in the reduction of viral load between the ivermectin and placebo arms. There were numerous mild to moderate adverse effects reported in all 3 groups, which mainly included eye symptoms, e.g., photophobia, photopsia, blurred vision, and vitreous floaters, symptoms related to the nervous system, e.g., headache, paresthesia, somnolence, gait disturbance, and fatigue, and GI symptoms, e.g., abdominal pain, nausea, vomiting, and diarrhea. A high dose of ivermectin (1,200 µg/kg) appeared to be safe but not well tolerated. Three out of four severe adverse events requiring hospitalization occured in the high dose of ivermectin 1200 µg/kg treatment arm, and one severe adverse event occurred in the dose of 600 µg/kg treatment arm. All events resolved with no reported sequelae.[69]

The TOGETHER trial conducted by Gilmar et al. was published in March 2022 and involved symptomatic SARS-CoV-2-positive adults recruited from 12 public health clinics in Brazil. The study found that 14.7% of the ivermectin group had a primary-outcome event (defined as hospitalization due to COVID-19 within 28 days after randomization or an emergency department visit due to the clinical worsening of COVID-19 within 28 days after randomization) as compared with 16.3% of the placebo group (RR: 0.90). There were no significant differences between the ivermectin group and the placebo group in viral clearance at day 7, risk of hospitalization for any cause, the time to hospitalization, the number of days in the hospital, time to clinical recovery, the risk of death, the time to death, number of days with mechanical ventilation, or outcome events (hospitalization or emergency department visit for COVID-19 within 28 days).[58]

Combination drug studies have also been performed. For example, an open-labeled RCT conducted by Choudhary et al. in Bangladesh from May–June 2020 enrolled asymptomatic, mild, and moderately symptomatic COVID-19 patients and compared two groups of patients who were on ivermectin 200 µg/kg single dose plus doxycycline 100 mg BID for ten days or hydroxychloroquine 400mg for the first day and then 200 mg BID plus azithromycin 500 mg daily for five days in the control group. The ivermectin-doxycycline combination had beneficial effects when compared to the hydroxychloroquine-azithromycin combination. The mean time to a negative PCR in the ivermectin-doxycycline combination was 8.93 ± 0.16 days compared to 9.33 ± 0.23 days in the hydroxychloroquine-azithromycin group ($p = 0.2314$). The ivermectin- doxycycline combination reached symptomatic recovery in 5.93 ± 1.29 days when compared to the hydroxychloroquine-azithromycin combination in 8.93 ± 1.9 days ($p = 0.07$).[70]

In a multicenter clinical study conducted in Iran with 180 patients with mild symptoms, patients with COVID-19 confirmed by PCR were enrolled and allocated into six arms, including hydroxychloroquine 200 mg twice per day, placebo plus hydroxychloroquine 200 mg twice per day, single-dose ivermectin (200 µg/kg), three low doses of ivermectin (200, 200, 200 µg/kg), single-dose ivermectin (400 µg/kg), and three high interval doses of ivermectin (400, 200, 200 µg/kg). The primary endpoint of this trial was all-cause mortality or clinical recovery. Study analysis reported a 15% reduction in mortality rate with a risk ratio of 0.18 in ivermectin-treated groups when compared to untreated groups. Parameters, such as CBC, CRP, ESR, and platelet counts, used to monitor clinical recovery showed favorable outcomes in the ivermectin arm when compared to the standard and placebo arms. Time of hospitalization and low oxygen saturation had significant differences among the six groups. However, the treatment arms and baseline disease severity were not assigned clearly, and interpretation of this data is therefore limited.[71] In a systematic review, meta-analysis, and trial sequential analysis done by Bryant et al. using ivermectin early in the clinical course reported a reduction in the number of patients progressing to severe disease and hence deaths associated with COVID-19 infection.[57] A randomized, double-blind, placebo-controlled trial conducted in 72 hospitalized patients in Dhaka et al. to determine the rapidity of viral clearance demonstrated that viral clearance in the 5-day ivermectin

group was significantly earlier than in the placebo group on days 7 and 14(HR: 4.1, 95% CI: 1.1–14.7; p = 0.03; HR: 2.7, 95% CI: 1.2–6.0; p = 0.02). The trend was similar for the ivermectin plus doxycycline group but this was not statistically significant (HR 2.3, 95% CI: 0.6–9.0; p = 0.22; HR 1.7, 95% CI: 0.8–4.0; p = 0.19).[72] Mohan-Padhy et al. carried out another meta-analysis of 4 studies with a total of 629 COVID-19 viral 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. The overall odds ratio (OR) of 0.53 (95% CI: 0.29–0.96) was reported for the primary outcome of all-cause mortality, which was statistically significant (p = 0.04). However, the interpretation of this study should be cautious since the quality of evidence is very low.[59]

Another multicenter case-control study that enrolled 280 hospitalized patients reported that ivermectin administered at a single dose of 150 µg/kg significantly reduced in-hospital mortality in those patients treated with the drug (1.4% ivermectin vs. 8.5% non-ivermectin; HR: 0.20, 95% CI: 0.11–0.37, p < 0.0001).[73,79] Chaccour et al. conducted a randomized, double-blind, placebo-controlled trial with 24 patients attending the emergency room of the Clínica Universidad de Navarra between July 31, 2020, and September 11, 2020, in Spain. Patients received a single dose of 400 µg/kg of ivermectin or placebo within 72 h of the onset of fever or cough. Results showed no difference in the proportion of patients with positive PCR at 7 days (RR: 0.92, 95% CI: 0.77–1.09; p = 1.0) but showed considerable reduction of self-reported symptoms like anosmia/hyposmia and cough and a tendency to lower viral loads and IgG titers.[74] A randomized, double-blind clinical trial was conducted from May 2020 to July 2020, in two referral tertiary hospitals in Mazandaran, Iran, with 69 patients with mild symptoms of COVID-19. Subjects who have received ivermectin showed improvement in clinical features, like dyspnea, cough, and lymphopenia, and in the mean duration of hospital stay when compared to control subjects.[75]

In one of the largest randomized double-blind studies conducted in Dhaka Medical College Hospital in Bangladesh by Mahmud et al. from June 1 to August 30, 2020, 556 patients were screened, 400 underwent randomization, 200 patients received an active drug (doxycycline plus ivermectin), and 200 patients received placebo. The trial showed profound effects on clinical outcomes with rates of early improvement (60.7% vs. 44.4% $P < 0.03$) and decreased rates of clinical deterioration (8.7% vs. 17.8%, $P < 0.02$).[76] In another randomized, dose-response, parallel-group study of ivermectin conducted by Babalola in Nigeria, 62 patients were randomized into receive 3 treatment groups: (A) ivermectin 6mg regime, (B) ivermectin 12 mg regime (given Q 84 hrs for 2 weeks), (C, control) Lopinavir/Ritonavir. Results showed a significant difference in viral clearance between both the low-dose and high-dose treatment groups and controls in a dose-dependent fashion (p = .0066). Ivermectin also tended to increase SPO_2% compared to controls (95% CI: 0.39–2.59; p = 0.073).[55]

Studies with ivermectin in patients with moderate to severe COVID-19 symptoms

A double-blind phase 2 study in Brazil in May 2020 to assess the effectiveness of chloroquine (CQ), hydroxychloroquine (HCQ), or ivermectin in severe forms of COVID-19, reported no differences among these arms in outcomes, including the need for supplemental oxygen (88% vs. 89% vs. 90%), ICU admission (28% vs. 22% vs. 21%), the mean number of days of supplemental oxygen, need for mechanical ventilation (24% vs. 21% vs. 21%), or mortality (23% vs. 21% vs. 22%).[47] In 24 COVID-19 subjects identified from patients referred by physicians or word-of-mouth in Los Angeles, CA, between August 2020 and February 2021 who refused hospitalization but had high-risk features, hypoxia, and untreated moderate to severe symptoms averaging 9 days, the authors administered a novel combination of ivermectin, doxycycline, zinc, and vitamin D. All subjects had symptom resolution (in 11 days on average) and improvement in oxygen saturation in 24 hours (87.4% to 93.1%; p = 0.001). There were no hospitalizations or deaths; these outcomes were better than controls matched from a CDC database (p < 0.002; p = 0.05, respectively).[77] In one of the largest retrospective trials (n = 280) conducted in hospitalized patients between March 15 and May

11, 2020, by Rajter et al. in Florida, the study reported decreased mortality in ivermectin-treated patients (15.0% vs. 25.2%, p = 0.03), especially in the subgroup of patients with severe pulmonary involvement (38.8% vs. 80.7%, p = 0.001).[78]

Transmission control (prophylaxis)

The short-term efficacy of oral ivermectin in prophylaxis has been studied by several research teams. A randomized controlled trial conducted by Shouman et al. at Zagazig University in Egypt reported that the administration of ivermectin at prophylactic doses of approximately 0.25 mg/kg twice daily on the day of the positive test and 72 hours later provided a statistically significant decrease in COVID-19 symptoms in household members during a two week follow up period (7.4% vs. 58.4%; $P < 0.001$).[54] Carvallo et al. performed a prospective observational trial in Argentina in which they gave healthy volunteers ivermectin and carrageenan, a seaweed extract, daily for 28 days and matched them to similarly healthy controls who did not take the medicines. None of the subjects receiving ivermectin and the carrageenan arm tested positive for SARS-COV-2, while 11.2% of patients in the control arm tested positive ($P < 0.001$).[80] The Carvallo IVERCAR protocol was also separately tested in a prospective RCT by the Health Ministry of Tucuman, Argentina; they found that in the 234 healthcare workers in the intervention group who took 12 mg once weekly, only 3.4% contracted COVID-19 versus 21.4% of controls (p < .0001).[79,80] A case-controlled study was conducted by Behera et al. on healthcare workers of AIIMS Bhubaneswar, India, from September to October 2020. Cases and controls were healthcare workers who tested positive and negative, respectively, for COVID-19 by RT-PCR. A two-dose ivermectin prophylaxis at a dose of 300 µg/kg taken with an interval of 72 hours between doses was associated with a 73% reduction in infection among 76 controls and 41 cases (AOR 0.27, 95% CI: 0.15–0.51).[81] Evidence supporting the efficacy of ivermectin as a prophylaxis agent was published in January 2021 by Hellwig et al. who collected data from countries that used prophylactic drug therapy for the treatment of other infections and found a lower incidence of COVID-19 in patients treated with ivermectin at 150–200 µg/kg doses (p < 0.05).[82]

Discussion

Currently, ivermectin has no approved indication for the treatment of COVID-19. Several public health organizations and medical associations, including the WHO,[74] AMA,[83] Merck,[84] FDA,[83] and the National Institutes of Health,[85] have released statements against the use of ivermectin in the treatment of COVID-19 except in clinical trials. These statements may change since ongoing clinical trials are working to obtain high-quality data regarding the efficacy of ivermectin as treatment for and as prophylaxis against COVID-19 infection.

The reviews conducted during an influx of misinformation regarding the efficacy of ivermectin, optimistic results from early non-peer-reviewed clinical trials, and *in vitro* studies have led to extensive off-label use of ivermectin by both clinicians and the general public. Investigations into the antiviral effects of ivermectin began long before the COVID-19 pandemic, with several projects assessing its *in vitro* efficacy against other RNA viruses, such as the Zika virus, dengue virus, and the West Nile virus. However, this does not guarantee the effectiveness of ivermectin against SARS-CoV-2. The pharmacokinetics of ivermectin for treating COVID-19 has been a contentious issue since the plasma inhibitory concentration of ivermectin for SARS-CoV-2 is high; thus, establishing an effective dose regimen without toxic effects in patients has been difficult. To replicate the efficacy observed *in vitro* studies, a high dose of ivermectin may be needed that is not safe for clinical use. In addition, a significant correlation between a cumulative ivermectin dose and patient outcome has not been observed.

Numerous clinical trials, observational studies (e.g., IVERCOR—COVID-19 trial, RIVET-COV pilot, ITECH, TOGETHER trial), and published research varying from pre-print trials and *in vitro* studies have investigated ivermectin efficacy and safety for short-term treatment and prophylaxis use in COVID-19 infection based on clinical setting and severity. The dose regimens that were used ranged from 0.2 mg/kg

single dose to 0.6 mg/kg for 5 days. The results from most of these trials were either inconclusive or did not establish a significant reduction in time to viral clearance, the duration of hospitalization, the requirement for mechanical ventilation, or the mortality rate based on moderate-quality RCT evidence[54–67] and meta-analyses of the observational studies. In clinical trials of high-risk patients with mild to moderate COVID-19, ivermectin treatment during early illness did not prevent progression to severe disease. Hence, randomized controlled trials did not support the use of ivermectin for patients with severe COVID-19. Due to significant heterogeneity in the data presented, these outcomes should be interpreted with caution.

Evaluating studies on ivermectin and COVID-19 can be challenging since these studies have used a variety of endpoints to determine effectiveness, including time to resolution of symptoms,[51,86] oxygen requirements,[71] progressions to severe disease,[57] viral clearance,[72] intensive care unit admission,[73] and mortality.[87] Study populations have also varied, often included relatively young patients with few comorbidities,[52,70] and the sample sizes ranged from 24 patients[77] to over 3500 patients. Medication dosing varied ranging from 100 µg/kg up to 400 µg/kg, with single-dose and multiple-dose regimens used in some studies.[86,87] Several studies have also examined ivermectin in combination with other drugs, such as azithromycin[86] and doxycycline.[72,87] The variation in study designs may be due to the urgency of COVID-19 research resulting in limited time to recruit multiple sites and centers. The differences in these studies makes it difficult to assess ivermectin systematically, and it cannot be recommended for the treatment of COVID-19 beyond the context of clinical trials. In addition, ivermectin use was associated with increased odds of adverse events based on the moderate quality of evidence from RCT.[14–18,72–75]

One of the reported limitations of ivermectin in infections is its potential to cause toxicity, and studies have shown that this concern can be eliminated by changing the formulation and pharmacokinetic properties. Smitt et al. showed in a study based on pharmacokinetic simulations that ivermectin may have limited therapeutic utility in controlling 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 available using approved dosing; thus, they proposed ivermectin inhalation therapy.[12,23–25] However, they did not consider the host immune response in humans. Therefore, a study based on concentration and the use of ivermectin as an inhalational agent is essential.

Several clinical studies[53–55] and meta and systematic analyses[56–60] have suggested that ivermectin may be effective in COVID-19 prophylaxis. However, some of these studies have been criticized as being biased and of low methodological rigor, adding to the confusion over if and how this drug should be used in the pandemic. Indeed, the 2021 Cochrane review found only 14 studies of sufficient quality to be included in their analysis.[66] Though many of these studies point to a potential role for ivermectin, more robust and uniform studies are needed before definitive recommendations can be given. Some of the studies that reported that ivermectin was effective against COVID-19 have been either retracted or were circulated before peer review on pre-print serverers and differed from the majority of evidence in other studies. Reasons for this are varied, but these studies continue to contribute to the diverse views on the role of ivermectin in COVID-19 infection.

From the overall review of the literature, we conclude that the role of ivermectin as a treatment for COVID-19 cannot be completely dismissed. Despite previous studies showing a lack of effectiveness of ivermectin as an antiviral drug for COVID-19, several studies are currently in progress. These studies may resolve conflicts or deficiencies in the data on COVID-19 and ivermectin and should satify the continued public interest in this drug. The interest in ivermectin as a COVID-19 therapeutic is not unreasonable due to its possible antiviral properties, the precedence off label use of pharmaceutics, and the need for new therapeutics during a public health crisis. However, more studies with small sample sizes are unlikely to answer needed questions about ivermectin in COVID-19 infection therapeutic and may contribute to poor allocation of resources and oversaturation of the literature with low-quality studies. Studies should measure important clinical endpoints, such as viral clearance, supplemental oxygen use, intensive care unit admission,

morbidity, and mortality. Studies of ivermectin in critically ill patients are limited, and the narrow therapeutic window for starting treatment may limit the use of this drug in these cases. However, the use of ivermectin in the early phase of the clinical course to reduce progression to severe disease should be considered. The safety of the drug at higher doses is not yet established. Due to its low cost and availability in developing countries, ivermectin might have a significant impact on the SARS-COV2 pandemic globally.

While usually safe, unregulated off-label use of this drug by professionals or by the public could be dangerous. Based on current evidence and lack of efficacy as a COVID-19 therapeutic, ivermectin is not recommended for use in the treatment of COVID-19. More investigations with large clinical trials comparing ivermectin and corticosteroids with current antiviral medications, such as nirmatrelvir-ritonavir, molnupiravir or remdesivir or monoclonal antibodies, in the early mild course of the disease process could provide important information in the near future. With the persistence of COVID-19 and the need for management strategies in infected patients, valid, high-quality evidence is needed to both improve patient outcomes and conserve hospital resources. These studies could provide more definitive answers regarding ivermectin's effectiveness as a COVID-19 treatment. Ultimately, any new evidence should be carefully and critically evaluated, and decisions regarding therapies should be based on the best evidence available.

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