Ivermectin

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Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies.¹ For these indications, ivermectin has been widely used and is generally well-tolerated.¹,² Ivermectin is not approved by the FDA for the treatment of any viral infection.

Proposed Mechanism of Action and Rationale for Use in Patients With COVID-19

Reports from in vitro studies suggest that ivermectin acts by inhibiting host importin alpha/beta-1 nuclear transport proteins, which are part of a key intracellular transport process.³⁴ Viruses hijack the process and enhance infection by suppressing the host’s antiviral response. In addition, ivermectin docking may interfere with SARS-CoV-2 spike protein attachment to the human cell membrane.⁵ Some studies of ivermectin have also reported potential anti-inflammatory properties, which have been postulated to be beneficial in people with COVID-19.⁶-⁸

Ivermectin has been shown to inhibit replication of SARS-CoV-2 in cell cultures.⁹ However, pharmacokinetic and pharmacodynamic studies suggest that achieving the plasma concentrations necessary for the antiviral efficacy detected in vitro would require administration of doses up to 100-fold higher than those approved for use in humans.¹⁰,¹¹ Although ivermectin appears to accumulate in lung tissue, predicted systemic plasma and lung tissue concentrations are much lower than 2 µM, the half-maximal inhibitory concentration (IC₅₀) observed in vitro for ivermectin against SARS-CoV-2.¹²-¹⁵ Subcutaneous administration of ivermectin 400 µg/kg had no effect on SARS-CoV-2 viral loads in hamsters.¹⁶ However, there was a reduction in olfactory deficit (measured using a food-finding test) and a reduction in the interleukin (IL)-6:IL-10 ratio in lung tissues.

The safety and efficacy of ivermectin for the prevention and treatment of COVID-19 have been evaluated in clinical trials and observational cohorts. Summaries of the studies that informed The COVID-19 Treatment Guidelines Panel’s (the Panel) recommendation can be found in Table 7b. The Panel reviewed additional studies, but these studies are not summarized in Table 7b because they have study design limitations or results that make them less definitive and informative.

Recommendation

• The Panel recommends against the use of ivermectin for the treatment of COVID-19, except in clinical trials (AIIa).

Rationale

The results of several randomized trials and retrospective cohort studies of ivermectin use in patients with COVID-19 have been published in peer-reviewed journals or have been made available as manuscripts ahead of peer review. Most of these studies, especially studies completed earlier in the pandemic, had incomplete information and significant methodological limitations, which made excluding common causes of bias difficult. Many of these studies have not been peer reviewed, and some have now been retracted.

The Panel’s recommendation is primarily informed by recently published randomized controlled trials.¹⁷-²⁰ The primary outcomes of these trials showed that the use of ivermectin for the treatment of COVID-19 had no clinical benefit. In TOGETHER, an adaptive platform trial conducted in Brazil, there

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was no apparent difference between the ivermectin and placebo arms for the primary outcome of risk of emergency department visits or hospitalization (14.7% vs. 16.4%). Also, there was no statistically significant difference between the ivermectin and placebo arms in mortality (3.1% vs. 3.5%).

I-TECH, an open-label trial conducted in Malaysia, found no difference between the ivermectin and standard of care arms (21.6% vs. 17.3%) for the primary outcome of risk of progression to severe disease. The ivermectin arm had a lower risk of mortality than the standard of care arm (1.2% vs. 4.0%), but this difference was not statistically significant.

The study populations of both the TOGETHER and I-TECH trials were patients with mild to moderate disease, and the number of deaths was low (as expected). In these randomized trials, completely excluding an effect of ivermectin is difficult, because the trials were not powered to detect differences in secondary outcomes, such as death. However, data from these trials do not provide evidence that the use of ivermectin benefited the treatment of COVID-19.

Comparisons of the efficacy of ivermectin for the treatment of COVID-19 are complicated by the large variability of doses and durations of treatment used in the studies. There have been concerns that doses in early trials were too low and durations of treatment were too short. However, the higher doses (300 μg/kg–400 μg/kg per day for up to 3–5 days) used in the more recent TOGETHER and I-TECH trials did not demonstrate clinical benefit.

Although there have been many ivermectin studies, only a few trials have been adequately powered, well-designed, and well-conducted. More recent clinical trials address the limitations of earlier studies but fail to show clear evidence that ivermectin reduces time to recovery or prevents COVID-19 disease progression. For this reason, and because several medications now have demonstrated clinical benefit for the treatment of COVID-19, the Panel recommends against the use of ivermectin for the treatment of COVID-19, except in a clinical trial (AIIa). Additional adequately powered, well-designed, and well-conducted trials are needed to evaluate the effect of ivermectin on COVID-19. The Panel will continue to review emerging data on ivermectin use, including the results from 2 large, ongoing randomized controlled trials.

See Table 7b for summaries of the key studies that informed the Panel’s recommendation.

### Monitoring, Adverse Effects, and Drug-Drug Interactions

- Adverse effects of ivermectin may include dizziness, pruritus, nausea, or diarrhea.\(^{21}\)
- Neurological adverse effects have been reported with the use of ivermectin for the treatment of onchocerciasis and other parasitic diseases, but it is not clear whether these adverse effects were caused by ivermectin or the underlying conditions.\(^{22}\)
- Ivermectin is a minor cytochrome P450 3A4 substrate and a p-glycoprotein substrate.
- Ivermectin is generally given with water on an empty stomach; however, administering ivermectin with food increases its bioavailability.
- The FDA first issued a warning in April 2020 that ivermectin intended for use in animals should not be used to treat COVID-19 in humans. This warning was updated and reiterated in 2021.

### Clinical Trials

Several clinical trials evaluating the use of ivermectin for the treatment of COVID-19 are currently underway or in development. Please see ClinicalTrials.gov for the latest information.
References


