The COVID-19 Treatment Guidelines Panel's Statement on the Use of Ivermectin for the Treatment of COVID-19

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Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.

Rationale

Ivermectin is an antiparasitic drug that is approved by the Food and Drug Administration (FDA) for the treatment of onchocerciasis and strongyloidiasis. Ivermectin is not FDA-approved for the treatment of any viral infection. In general, the drug is well tolerated. It is currently being evaluated as a potential treatment for COVID-19.

Antiviral and Anti-Inflammatory Effects of Ivermectin

Reports from in vitro studies suggest that ivermectin acts by inhibiting the host importin alfa/beta-1 nuclear transport proteins, which are part of a key intracellular transport process that viruses hijack to enhance infection by suppressing the host antiviral response.[1,2] In addition, ivermectin docking in vitro may interfere with the attachment of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein to the human cell membrane.[3]

Ivermectin has been shown to inhibit the replication of SARS-CoV-2 in cell culture. However, pharmacokinetic and pharmacodynamic studies suggest that ivermectin doses up to 100-fold higher than those approved for use in humans would be required to achieve the plasma concentrations necessary to duplicate the drug's antiviral efficacy in vitro.[4,5] Even though ivermectin appears to accumulate in lung tissue, with the doses used in most clinical trials, predicted systemic plasma and lung tissue concentrations are much lower than 2 μM, the half-maximal inhibitory concentration (IC_{50}) against SARS-CoV-2 in vitro.[6,7]

Ivermectin demonstrates potential anti-inflammatory properties in some in vitro studies,[8,9] properties which have been postulated to be beneficial in the treatment of COVID-19.[10]

Clinical Data

Since the last revision of the Ivermectin section of the Guidelines, 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 made available as preliminary, non-peer-reviewed reports. Some clinical studies showed no benefits or worsening of disease after ivermectin use,[11-14] whereas others reported shorter time to resolution of disease manifestations attributed to COVID-19,[15-18] greater reduction in inflammatory markers,[16,17] shorter time to viral clearance,[11,16] or lower mortality rates in patients who received ivermectin than in patients who received comparator drugs or placebo.[11,16,18]

However, most of the studies reported to date had incomplete information and significant methodological limitations, which make it difficult to exclude common causes of bias. The missing information and limitations include the following:

- The sample size of most of the trials was small.
- Various doses and schedules of ivermectin were used.
- Some of the randomized controlled trials were open-label studies in which neither the participants nor the investigators were blinded to the treatment arms.
- In addition to ivermectin or the comparator drug, patients also received various concomitant medications (e.g., doxycycline, hydroxychloroquine, azithromycin, zinc, corticosteroids), confounding assessment of the true efficacy or safety of ivermectin.
- The severity of COVID-19 in the study participants was not always well described.
- The study outcome measures were not always clearly defined.

Because of these limitations, the Panel cannot draw definitive conclusions about the clinical efficacy or safety of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.

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