



COMMENTARY

Ivermectin in COVID-19: The Case for a Moratorium on Prescriptions

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Abstract

In treatment or prevention of COVID-19, ivermectin is not approved by the United States (US) Food and Drug Administration (FDA). Nonetheless, in the US, prescriptions of ivermectin by healthcare providers have increased > tenfold from 3589 per week pre-COVID-19 to 39,102. Ivermectin is FDA approved for animals to treat parasites and for humans to treat intestinal strongyloidiasis and onchocerciasis orally, and ectoparasites and skin conditions topically. It is not a benign drug, with reported side effects including cutaneous, gastrointestinal, and cardiovascular symptoms. The evidence to support ivermectin to treat or prevent COVID-19 includes some basic research and inconsistent clinical observations that contribute to the formulation of a hypothesis of efficacy in COVID-19. At present, data from peer-reviewed published randomized trials of sufficient size, dose, and duration to reliably test the hypothesis of the most plausible small to moderate benefits on clinically relevant endpoints are sparse. In addition to the US FDA, the US National Institutes of Health, World Health Organization, and European Medicines Agency have all advised against ivermectin for treatment or prevention of COVID-19 outside of randomized trials. For ivermectin in treatment or prevention of COVID-19, healthcare providers should reassure all patients that if sufficient evidence were to emerge, then this drug could be considered a therapeutic innovation and regulatory authorities would approve the drug. In the meanwhile, we strongly recommend a moratorium on the prescription of ivermectin for the treatment or prevention of COVID-19 except in randomized trials to provide the most reliable test of the hypothesis.

Keywords Ivermectin · COVID-19 · Therapeutic innovation · Regulatory science · Prescription moratorium · Randomized trials

Text

The general public of the United States (US) should be informed that, with respect to therapeutic innovation, there is a process for development of drugs for a specific indication for application to receive permission to market for other

diseases. As regards regulatory science, there is an orderly and unbiased process to achieve regulatory approval.

In treatment or prevention of COVID-19, ivermectin is neither approved nor authorized by the United States (US) Food and Drug Administration (FDA) [1]. Nonetheless and without reliable evidence of benefit, in the US, prescriptions of ivermectin by healthcare providers have increased > tenfold from 3589 per week pre-COVID-19 to 39,102 [2]. In this Commentary we review the peer-reviewed published evidence and strongly recommend a moratorium on the prescription of ivermectin for the treatment or prevention of COVID-19.

Ivermectin is FDA approved for animals to treat parasites and for humans to treat intestinal strongyloidiasis and onchocerciasis orally, and ectoparasites and skin conditions topically. It is not a benign drug, with reported side effects including cutaneous, gastrointestinal, and cardiovascular symptoms. Specifically, skin rash, nausea,

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vomiting, diarrhea, stomach pain, hypotension, dizziness, and seizures have been reported. [1] The evidence to support the use of ivermectin in the treatment and prevention of COVID-19 includes some basic research and inconsistent clinical observations that contribute to the formulation of a hypothesis of efficacy in COVID-19. In basic research, *in vitro* studies show that ivermectin produces a 99% reduction in the COVID-19 viral load within 48–72 h [3]. In addition, some, but not all, uncontrolled clinical observations of small sample size, useful to formulate but not test the hypothesis, are compatible with both therapeutic and preventive benefits of ivermectin in COVID-19. At present, data from peer-reviewed published randomized trials of sufficient size, dose, and duration to reliably test the hypothesis of small to moderate benefits on clinically relevant endpoints are sparse [1, 4–7]. In a recently reported trial from Dhaka, Bangladesh, 400 patients were randomized to ivermectin plus doxycycline or placebo, of which 363 completed the treatment and follow-up. There was a significant reduction in the primary prespecified outcome of duration from days of treatment to recovery, [8] In another recently reported trial from Cali, Colombia 400 patients were randomized in the primary analysis, of which 398 completed the treatment and follow-up. There was no significant reduction in the primary prespecified outcome of time to resolution of symptoms [9]. Both authors from opposite sides of the globe cautioned that more randomized data are necessary from trials of larger sample sizes. In addition to the US FDA, the US National Institutes of Health (NIH), [4, 5] World Health Organization (WHO), [6] and European Medicines Agency (EMA) [7] have all advised against ivermectin for treatment or prevention of COVID-19 outside randomized trials.

Doing more good than harm in COVID-19 requires concerted efforts by competent and compassionate healthcare providers, who are the most trusted, to communicate with their patients the therapeutic and preventive measures of proven benefit [10]. At present, for treatment of COVID-19, the US FDA has approved dexamethasone and remdesivir and has issued an Emergency Use Authorization (EUA) for monoclonal antibodies. [11] In prevention, there is an even more urgent need for mitigation and containment of COVID-19 in the US and worldwide. The preventive measures of proven benefit include more widespread vaccinations, [12] as well as masking, social distancing, crowd avoidance, and frequent hand and face washing [13]. In the treatment and prevention of COVID-19, ivermectin has no proven efficacy but has proven side effects. The prescription of a drug of unproven benefit for COVID-19 is far less attractive today than it may have been before. At present, there are remarkably efficacious and safe preventive measures, especially vaccinations and masking. In addition, there are also therapeutic innovations of proven benefit [11].

As of November 6, 2021, the over 750 thousand deaths from COVID-19 in the US [14] exceed those from World War I, II, and Vietnam combined. These lives lost are exceeded only by casualties from the Civil War [13]. COVID-19 cases and deaths had been plummeting into June 2021, spiked in all 50 US states in September 2021, and had been trending down until a November 2021 uptick. These trends are particularly alarming because respiratory virus infections are characteristically less common during the summer. In Australia, in winter, rapidly rising numbers of infections with low immunization rates have led to mandatory shutdowns [15]. Some hospitals have longer lines of patients severely ill with COVID-19 wanting a bed in intensive care units than healthy individuals wanting vaccinations. Since the vaccines are so effective and safe, these trends largely reflect the “vaccine hesitancy” of nearly 1/3 of the US population [13]. Suboptimal vaccination rates in the US and low rates worldwide have fueled the emergence and rapid spread of the Delta variant [14]. At this time Delta was responsible for > 99% of all the US cases [16] and is far more contagious than previous strains. There are also indications of worse infections and perhaps even some resistance to current vaccines. Unless vaccination rates increase in the US and worldwide more dramatically, it is very likely that new vaccine resistant strains will emerge, especially the recently discovered Omicron variant [16].

For ivermectin in treatment of COVID-19, on February 4, 2021, Merck, the manufacturer, stated that they believe that the available data do not support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information [17]. Most recently, on July 28, in a meta-analysis of 14 trials, the Cochrane Collaboration concluded that the currently available evidence does not support the use of ivermectin for treatment or prevention of COVID-19 [18]. Further, the NIH [4] and WHO [6] have recently reviewed available data which included some small randomized trials among both inpatients and outpatients. Both organizations recommend that the drug should only be prescribed to patients enrolled in randomized trials. With respect to ivermectin in prevention of COVID-19, an NIH Advisory Board [5] concluded that there is insufficient evidence to recommend either for or against the use of ivermectin in COVID-19. WHO has not provided an opinion but two major regulatory authorities, the US FDA [1] and EMA [7] have advised against the use of ivermectin for treatment or prevention of COVID-19 outside randomized trials.

It would be unfortunate and create avoidable morbidity and mortality if healthcare providers were to prescribe a drug of unproven benefit and safety for COVID-19, such as ivermectin, to patients as an alternative to vaccinations. For example, last year, millions of US patients were prescribed hydroxychloroquine, based, in part, on a EUA by the FDA

[19]. Since that time, the EUA has been withdrawn, and randomized trials have demonstrated a lack of efficacy and possible harm from hydroxychloroquine for treatment or prevention of COVID-19 [19]. Healthcare providers should be aware that the US and Brazil have high rates of prescriptions for both ivermectin and hydroxychloroquine. The US has been and remains the epicenter of the pandemic, and Brazil has the third most cases and second most deaths worldwide [14].

In recent polls, 85% of Americans trust their healthcare provider to provide reliable information about COVID-19 [8]. Healthcare providers should continue to exert all efforts to educate their patients about their own personal benefits as well as those to their families, friends, and society of vaccinations [1] and masking. Among patients with “vaccine hesitancy,” 59% worry about side effects and 53% believe that the vaccine is too new [3]. Family medicine physicians can provide reassurance about these issues to increase the acceptance of the COVID-19 vaccines as well as to discourage use of drugs without proven benefit such as ivermectin. In the US today, widespread vaccination is the safest and most effective therapeutic innovation for COVID-19 and is fully approved by the FDA. We applaud the US FDA for accelerating its approval process, which may help achieve urgently needed further increases in vaccination rates which will lead to decreases in cases and deaths from COVID-19.

When a sufficient totality of evidence becomes available, healthcare providers can make rational decisions for individual patients and policy makers can approve and promote a drug or novel application to improve health of the general public. For ivermectin, until such evidence emerges, it is appropriate for healthcare providers to remain uncertain. Until such evidence emerges, healthcare providers should redouble efforts to support vaccinations and masking [19, 20].

Doing more good than harm requires competent and compassionate healthcare providers to refrain from prescribing ivermectin in treatment or prevention of COVID-19 to their trusting patients, especially as an alternative to vaccination and other therapeutic innovations. Towards this end, healthcare providers should reassure all their patients of the robust and unbiased means in the US to achieve therapeutic innovations that can then be considered for approval by regulatory science. We believe a moratorium on prescriptions by healthcare providers of ivermectin to treat or prevent COVID-19 should remain in effect until such a time that more reliable data emerge from randomized trials of sufficient size, dose, and duration.

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Data Availability

All authors had access to the data and a role in writing the manuscript.

Declarations

Conflict of interest

Dr. Molnar, Dr. Lau, Ms. Berges, Mr. Masa, Dr. Solano, Dr. Alter, Dr. Clayton, and Professors Shih and Maki have no disclosures.

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