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Review Article

Ivermectin in Covid-19: Important and Timely Updates for Family Medicine Physicians

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ABSTRACT

Ivermectin is not approved by the United States (US) Food and Drug Administration (FDA) for the treatment or prevention of COVID-19. Nonetheless, ivermectin prescriptions increased 11-fold from 3589 per week pre-COVID-19 to 39,102 by early 2021. In recent polls, 85% of the public trust their family medicine physicians as a source of reliable information on COVID-19 vaccinations. Ivermectin is FDA approved to treat intestinal strongyloidiasis and onchocerciasis orally, as well as ectoparasites and skin conditions topically. Possible side effects include skin rash, nausea, vomiting, diarrhea, stomach pain, facial or limb swelling, dizziness, seizures, confusion, hypotension, and liver injury. The United States (US) National Institutes of Health, World Health Organization, US FDA and European Medicines Agency have all advised against ivermectin for treatment or prevention of COVID-19 outside randomized trials. To do more good than harm in COVID-19 requires concerted efforts by competent and compassionate family medicine physicians who are deservedly the most trusted by the US public. In the US today, widespread vaccinations, masking, social distancing, crowd avoidance and frequent hand and face washing are remarkably effective and safe options. For ivermectin in COVID-19, family medicine physicians should reassure all patients that if a sufficient totality of evidence emerges, then this drug can be considered a therapeutic innovation and regulatory authorities will approve the drug. Thus, we strongly recommend that family physicians exert all reasonable efforts to increase vaccinations and have a moratorium on the prescription of ivermectin for COVID-19.

Keywords: COVID-19; Olfactory dysfunction; Ivermectin; Prescription moratorium

LITERATURE REVIEW

Ivermectin is not approved by the United States (US) Food and Drug Administration (FDA) for the treatment or prevention of COVID-19 [1]. Nonetheless, ivermectin prescriptions increased 11-fold from 3589 per week pre-COVID-19 to 39,102 by early 2021. In recent polls, 85% of the public trust their family medicine physicians as a source of reliable information on COVID-19 vaccinations [2,3].

In this Special Communication we strongly recommend to family medicine physicians a moratorium on the prescription of ivermectin for the treatment or prevention of COVID-19. Family medicine physicians face many clinical challenges including that patients with continued opposition to the vaccine and reluctance to resume masking and social distancing often prefer prescription of unproven drugs to proven health and safety measures. We believe that competent and compassionate family medicine physicians should continue to exert all efforts to educate their patients that masking, social distancing, crowd avoidance, and frequent hand washing reduce the risks of COVID-19, especially in unvaccinated patients, but also among those who have already received the vaccine [4].

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Ivermectin is approved by the United States (US) Food and Drug Administration (FDA) to treat intestinal strongyloidiasis and onchocerciasis orally, as well as ectoparasites and skin conditions topically. Possible side effects include skin rash, nausea, vomiting, diarrhea, stomach pain, facial or limb swelling, dizziness, seizures, confusion, hypotension, and liver injury. At present, there are data from basic research and some inconsistent clinical observations that contribute to the formulation of the hypothesis of efficacy in COVID-19.These include in vitro studies showing that ivermectin produces a 99% reduction in the COVID-19 viral load within 48-72 hours [5]. 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, however, there are no published peer reviewed randomized trials of sufficient size, dose, and duration to reliably test the hypothesis.

As of August 1, 2021, the >616 thousand deaths from COVID-19 in the US exceed those from World War I, II, and Vietnam combined. These lives lost are exceeded only by casualties from the Civil War and Spanish influenza [6]. COVID-19 cases and deaths had been plummeting into June 2021, but now are increasing rapidly in all 50 US states. These trends are also alarming because respiratory virus infections are characteristically uncommon during the summer. In Australia, currently in winter, rapidly rising numbers of infections with low immunization rates have led to mandatory shutdowns [7]. 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 vaccine is so effective and safe, these trends largely reflect the "vaccine hesitancy" of nearly 1/3 of the US population. Suboptimal vaccination rates in the US and low rates worldwide have fueled the emergence and rapid spread of the Delta variant. This strain accounts for <83% of new US cases. Delta is far more contagious with suggestions of possible worse infections and perhaps even some resistance to vaccines [8]. Unless vaccination rates increase in the US and worldwide it is very likely that new vaccine resistant strains will emerge [9].

As regards ivermectin in the treatment of COVID-19, two major scientific bodies, namely the US National Institutes of Health (NIH) and the World Health Organization (WHO) have recently reviewed the available data which included some small randomized trials among both inpatients and outpatients [10,11]. Both organizations recommended that the drug should only be prescribed to patients enrolled in randomized trials. With respect to ivermectin in the prevention of COVID-19, the WHO has not opined but an NIH Advisory Board concluded that there is insufficient evidence to recommend either for or against the use of ivermectin in COVID-19 [12]. This independent group further reaffirmed that recommendations should be based on a totality of evidence that includes well-designed and conducted randomized trials. Finally, two major regulatory authorities, the US FDA and the European Medicines Agency advised against the use of ivermectin for the treatment or prevention of COVID-19 outside randomized trials [13].

Family medicine physicians should not prescribe a drug of unproven benefit and safety for COVID-19. This would be especially tragic if patients were to take ivermectin instead of being vaccinated. Last years, millions of US patients were prescribed hydroxychloroquine, based, in part, on an Emergency Use Authorization (EUA) by the FDA [14]. Since that time, data from randomized trials of treatment and prevention have demonstrated a lack of efficacy and possible harm for hydroxychloroquine the treatment and prevention of COVID-19 [15].

Among patients with "vaccine hesitancy," 59% worry about side effects and 53% believe that the vaccine is too new. 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 most effective and safest therapeutic innovation for COVID-19 and is currently supported by EUA from the FDA. In this regard, we applaud the US FDA for accelerating its final approval process. We believe final FDA approval may help to achieve the urgently needed further increases in vaccination rates which will lead to decreases in cases and deaths from COVID-19.

With respect to ivermectin in COVID-19, when the totality of evidence is complete, health care 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. When the totality of evidence is incomplete, however, it is appropriate for family medicine physicians to remain uncertain [16,17]. At present, family medicine physicians should reassure their trusting patients that if a sufficient totality of evidence emerges then this drug can be considered a therapeutic innovation and regulatory authorities will approve the drug.

To do more good than harm requires competent and compassionate family medicine physicians to refrain from prescribing ivermectin at all and, especially as an alternative to vaccination against COVID-19. The moratorium on the prescriptions by family medicine physicians of ivermectin to treat or prevent COVID-19 should remain until there emerges reliable data from randomized trials of sufficient size, dose, and duration.

The prescription of a drug of unproven benefit by family medicine physicians for COVID-19 is far less attractive than before the advent of the remarkably efficacious and safe vaccines. Further, ivermectin has no proven efficacy but does have side effects.

CONCLUSION

To do more good than harm in COVID-19 requires concerted efforts by competent and compassionate family medicine physicians who are deservedly the most trusted by the US public. In the US today, widespread vaccinations, masking, social distancing, crowd avoidance and frequent hand and face washing are remarkably effective and safe options. For ivermectin in COVID-19, family medicine physicians should reassure all patients that if a sufficient totality of evidence

emerges, then this drug can be considered a therapeutic innovation and regulatory authorities will approve the drug. Thus, we strongly recommend that family physicians exert all reasonable efforts to increase vaccinations and have a moratorium on the prescription of ivermectin for COVID-19.

CONFLICTS OF INTEREST

Dr. Molnar, Dr. Lau, Ms. Berges, Mr. Masa, Dr. Solano, Dr. Alter, Dr. Clayton, and Professors Shih and Maki have no disclosures. Professor Hennekens reports that he serves as an independent scientist in an advisory role to investigators and sponsors as Chair of data monitoring committees for Amgen, British Heart Foundation, Cadila, Canadian Institutes of Health Research, DalCor, and Regeneron; to the Collaborative Institutional Training Initiative (CITI), legal counsel for Pfizer, the United States Food and Drug Administration, and UpToDate; receives royalties for authorship or editorship of 3 textbooks and as co-inventor on patents for inflammatory markers and cardiovascular disease that are held by Brigham and Women's Hospital; has an investment management relationship with the West-Bacon Group within SunTrust Investment Services, which has discretionary investment authority; does not own any common or preferred stock in any pharmaceutical or medical device company.

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