Evaluation of Ivermectin as an Effective Prophylactic, and for Treatment in Hospitalized Patients with COVID-19

by

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Executive Summary

- Whereas vaccines are effective at preventing disease, alternative treatments are urgently required for patients already infected with the SARS-CoV-2 virus (the virus that causes COVID-19). To date, this has relied on keeping patients alive while they build up their own immunity to fight the disease.
- In a proof of concept *in-vitro* study, it was shown that the drug ivermectin inhibits the replication of SARS-CoV-2.
- Subsequently, clinical studies in over 22 countries using TaqMan RT-PCR have demonstrated that the replication of the virus was indeed reduced with ivermectin treatment correlating with improvements in the patient's medical condition.
- Shorter hospitalization and lower mortality rates were observed in patients treated with ivermectin when compared to the placebo group.
- Ivermectin was shown in clinical trials to be effective at preventing COVID-19 when administered prophylactically to human subjects.
- Ivermectin has been prescribed to roughly 3.7 billion people around the world for over 40 years, with a proven safety record.

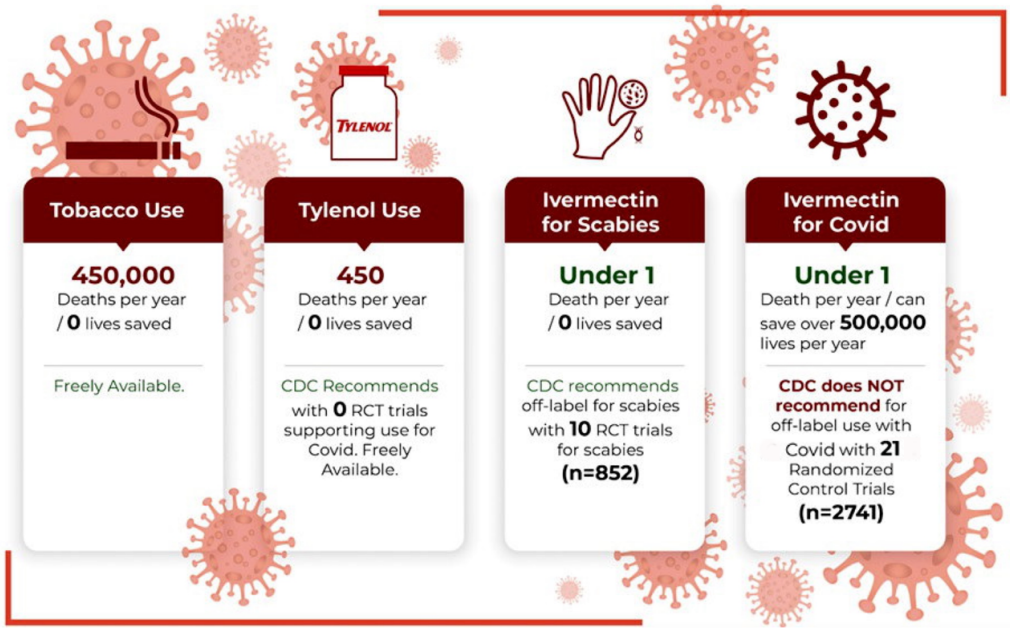

Figure 1. Various products outlining the number of deaths per year versus lives saved or estimated that could be saved in the U.S. Extracted from the Front Line COVID-19 Critical Care Alliance (FLCCC) website: https://covid19criticalcare.com/network-support/the-flccc-alliance/

The author would like our readers to be aware of the following letter issued by the FDA titled: "Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans": https://www.fda.gov/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-COVID-19-humans

Also, The Health Canada Directive - Health products that make false or misleading claims to prevent, treat or cure COVID-19 may put your health at risk: https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/72659a-eng.php

Introduction

The causative agent of the current COVID-19 pandemic is a single stranded positive sense RNA virus that is closely related to the severe acute respiratory syndrome coronavirus (SARS-CoV).

Whereas vaccines are effective at preventing disease (Andre *et al.,* 2008), nothing is better at fighting disease than utilizing a person's own immune system. However, once someone is already infected with the pathogen, a vaccine would be of no value. Therefore, alternative treatments are urgently required for patients already infected with SARS-CoV-2. To date, this has consisted on keeping patients alive while they build up their own immunity to the disease. Health Canada has not authorized any drugs to prevent, treat or cure COVID-19 in patients, with the exception of Veklury (remdesivir) from Gilead Sciences Canada Inc., to treat COVID-19 in patients (at a cost of approximately $3000 per treatment) with pneumonia requiring supplemental oxygen (Health Canada, 2020). The World Health Organization, however, does not recommend the use of Veklury based on their analyses (https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-COVID-19-patients).

Consequently, there is a serious gap that needs to be filled in order to cost effectively treat patients infected with SARS-CoV-2. In this briefing, we recommend that ivermectin (Figure 1) should be considered as a suitable candidate to "fill the treatment gap" for early out-patient treatment for COVID-19, as well as a prophylactic, while the public are being vaccinated.

Ivermectin - Proof of Concept

In a report by Caly *et al.* (2020), it was demonstrated using TaqMan RT-PCR that ivermectin effectively inhibited replication of the SARS-CoV-2 *in vitro* by blocking the ability of the host cell IMPα/β1 protein complex to bind to the coronavirus cargo protein in the cytoplasm, thereby preventing it from going through the nuclear pore complex (NPC) and entering the nucleus (Figure 2). It is within the nucleus of cells that the RNA genome of the SARS-CoV-2 is replicated.

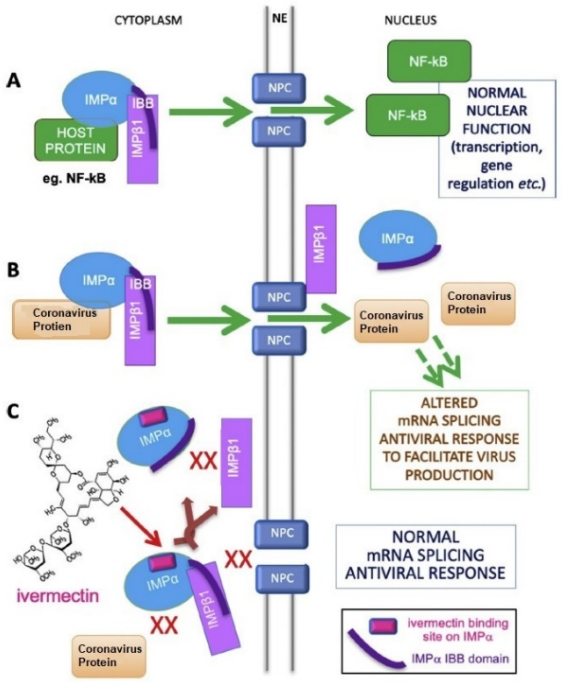

Figure 2. Schematic of ivermectin's proposed antiviral action on COVID-19. Modified from Jans & Wagstaff (2021).

The authors noted a 93–99.8% decrease in viral RNA levels for ivermectin versus control treatments at 24 hours both in the released and cell-associated viral RNA. Likewise, they reported that by 48 hours there was a >5000-fold decrease of viral RNA, indicating that ivermectin treatment resulted in the effective loss of essentially all viral material by 48 hours. Consistent with this, no further reduction in viral RNA was observed at 72 hours. Under the conditions tested, the ivermectin concentration that inhibited viral replication by 50% (IC50) was determined to be approximately 2 µM.

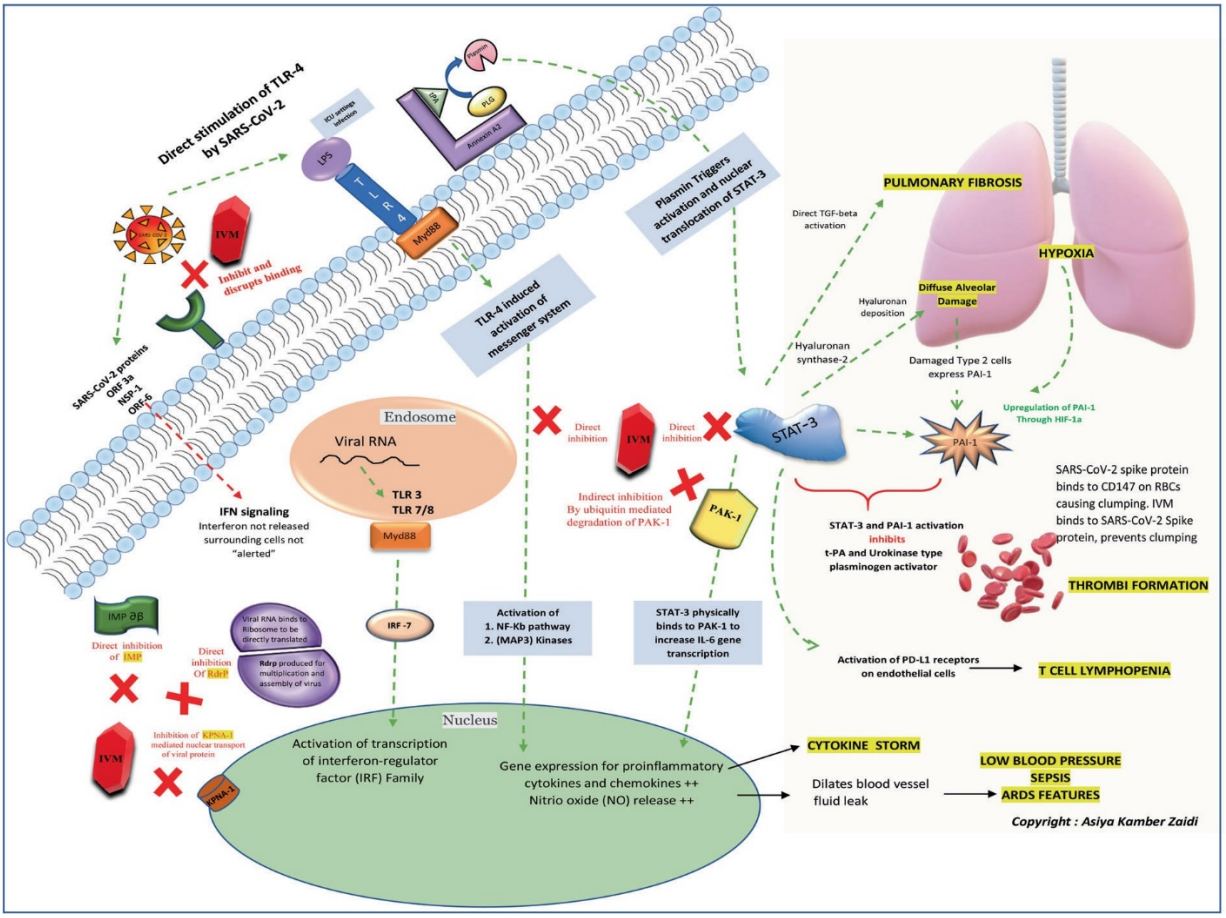

Figure 3. A schematic of the key cellular and biomolecular interactions between Ivermectin, host cell, and SARS-CoV-2 in COVID-19 pathogenesis and prevention of complications. Extracted from: Zaidi & Dehgani-Mobaraki (2021).

A recent review by Zaidi & Dehgani-Mobaraki (2021) has documented that in addition to the effects of ivermectin on SARS-CoV-2 replication by interaction with host proteins, it can also interfere with entry of the virus and affect the inflammatory response. Therefore, ivermectin is highly effective during the viral replication and inflammatory phases of the disease.

Ivermectin has an established safety profile for human use and is approved both by the US FDA and Health Canada. It has been used for a number of treatments since the 1980s, including treatments for intestinal infections, lice, scabies, and river blindness. Now that this drug has been found to inhibit SARS-CoV-2 replication *in vitro*, it was not surprising that clinical trials have been subsequently initiated throughout the world in particular countries that have a lot of experience in its use.

Ivermectin – Clinical Trial Data

Currently there are over 70 clinical trials worldwide evaluating the clinical benefit of ivermectin to treat or prevent COVID-19. Recent meta-analyses of many of these clinical trials support a 56% (Hill *et al.,* 2021) to 86% (Bryant *et al.*, 2021) reduction in mortality with ivermectin. However, these trials include variations in dosing regimens, combination therapies, and prophylactic protocols (Jans & Wagstaff, 2021). Because a single small clinal trial does not provide enough data to provide a definitive conclusion, meta-analysis using data from a number of clinical trials of ivermectin to treat COVID-19 infection will be described.

Meta-analysis of ivermectin clinical trials to treat COVID-19 infection

Ivermectin, a widely available generic drug, is currently re-purposed for the treatment of patients with SARS-CoV-2, being evaluated in clinical trials throughout the world. So, the first question we have to ask is: Do we have enough clinical evidence to support the worldwide approval of ivermectin to treat COVID-19? Although data from a single clinical trial may be considered unsuitable by Health Canada, the combined data from all of the available clinical trials to date should be large enough to reliably assess clinical efficacy of ivermectin, and that is where the meta-analysis of the available clinical trials comes in. The second question is: What are going to be our end-points?

For patients infected with SARS-CoV-2 it would be:

1. PCR test negativity
2. Clinical recovery
3. Hospitalisation and intensive critical care
4. Survival

For the subjects involved to assess the prophylactic properties of ivermectin, it would be the number of people subsequently infected with SARS-CoV-2 as a percentage of the total. Comparing the ivermectin treated with the control group.

Besides the meta-analyses performed by Bryant *et al.* (2021) and Hill *et al.* (2021), yet another recent meta-analysis was performed by the Front Line COVID-19 Critical Care Alliance (FLCCC) using data from 23 studies to determine the effectiveness of ivermectin to treat patients infected with SARS-CoV-2 (Kory *et al.*, 2021).

This report was successfully submitted to the US National Institute of Health (NIH) for consideration and their conclusions as they appear in the report are as follows:

"The FLCCC recommendation is based on the following set of conclusions derived from the existing data, which will be comprehensively reviewed below:

1) Since 2012, multiple *in vitro* studies have demonstrated that ivermectin inhibits the replication of many viruses, including influenza, Zika, Dengue and others (Mastrangelo *et al*., 2012; Wagstaff *et al*., 2012; Tay *et al*., 2013; Götz *et al*., 2016; Varghese *et al.*, 2016; Atkinson *et al.,* 2018; Lv *et al*., 2018; King *et al*., 2020; Yang *et al*., 2020).

2) Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue via several observed and proposed mechanisms (Caly *et al.*, 2020a).

3) Ivermectin has potent anti-inflammatory properties with *in vitro* data demonstrating profound inhibition of both cytokine production and transcription of nuclear factor-κB (NF-κB), the most potent mediator of inflammation (Zhang *et al*., 2008; Ci *et al*., 2009; Zhang *et al.,* 2009).

4) Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses (Arevalo *et al*., 2020; de Melo *et al*., 2020).

5) Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients (Bernigaud *et al*., 2020; Carvallo *et al.,* 2020b; Hellwig and Maia, 2020; Shouman, 2020; Behera *et al*., 2021).

6) Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms (Carvallo *et al.,* 2020a; Gorial *et al.,* 2020; Khan *et al.,* 2020; Mahmud, 2020; Morgenstern *et al*., 2020; Alam *et al*., 2020).

7) Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients (Hashim *et al.,* 2020; Khan *et al*., 2020; Niaee *et al*., 2020; Portmann-Baracco *et al*., 2020; Rajter *et al.,* 2020; Spoorthi *et al.,* 2020).

8) Ivermectin reduces mortality in critically ill patients with COVID-19 (Hashim *et al*., 2020; Rajter *et al.,* 2020).

9) Ivermectin leads to striking reductions in case-fatality rates in regions with widespread use (Chamie, 2020).

10) The safety, availability, and cost of ivermectin is nearly unparalleled given its near nil drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered (Kircik *et al*., 2016).

11) The World Health Organization has long included ivermectin on its "List of Essential Medicines" (https://www.who.int/publications/i/item/WHOMVPEMPIAU201907)

Data from the meta-analysis report referenced in this briefing, were recently presented to the NIH. On 14th January 2021, the NIH Treatment Guidelines Panel has now upgraded their recommendation on ivermectin on the use of ivermectin for COVID-19. The NIH are making it an option for use in the treatment of patients with COVID-19. In addition, the meta-analysis report performed by the FLCCC has been published by the American Journal of Therapeutics entitled: "FLCCC meta-analysis evidencing promise of ivermectin as treatment for COVID-19".

What is the status in Canada regarding treatment of patients with COVID-19?

As stated above, the only drug that Health Canada has authorized with conditions is remdesivir for the treatment of patients with COVID-19. On November 20, 2020, the WHO issued a statement recommending against the use of remdesivir in COVID-19 patients, due to the observed lack of efficacy (World Health Organization, 2020). Despite this, Canada continues to use remdesivir as a treatment for those with severe late-stage COVID-19.

Closing Remarks

Having reviewed the scientific literature, my colleagues and I at the Canadian Covid Care Alliance have come to the conclusion that the data are such that we in Canada should include ivermectin for early out-patient treatment for COVID-19. Multiple clinical trials from different countries support the use of ivermectin both in the early and late stages of the disease. The principal investigators of these studies were acting in good faith with no financial interests by the institutions carrying them out. The data from these trials are available for consideration (Kory, *et al.*, 2021), and there are clinical trials world-wide that are still on-going. Ivermectin has a proven safety record with over 40 years of use, it is readily available and is off-patent and therefore is a cheap therapy. Safely is not an issue, since ivermectin has already been approved for human use both in the USA and Canada for several other diseases. Ivermectin has never been withdrawn from the market for safety reasons. The dosages proposed (refer to Treatment Protocols available from the CCCA) for the treatment of COVID-19 for prophylaxis and out-patients are more than covered based upon the data from the Phase 1 ascending dose study in the NDA submission (US FDA, 2008), and published in a peer reviewed publication (Guzzo *et al*., 2002).

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Further information may be obtained from the following websites:

Front Line COVID-19 Critical Care Alliance: www.flccc.net

Trial SiteNews: https://trialsitenews.com/?s=Ivermectin

British Ivermectin Recommendation Development (BIRD): https://bird-group.org/the-bird-recommendation-on-the-use-of-ivermectin-for-COVID-19/

Medical Education Network (MedNet): https://www.mednet.ca/en/report/oma-district-11-physicians-lounge-virtual-sessio.html