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IVERMECTIN FOR THE PREVENTION OF COVID-19

So…WHO is telling the Truth?

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Abstract. The World Health Organization (WHO) has emphasized that to date, there is no specific medicine recommended to prevent or treat the new coronavirus. This documentary research is reporting that several prestigious scientists and physicians around the globe, with hard evidence and successful research results in their hands, are recommending Ivermectin as a preventive treatment. This study discusses the case for Ivermectin as a proven preventive treatment for COVID 19. So…WHO is telling the truth?

Keywords. COVID-19, Coronavirus, Ivermectin, COVID-19 Prophylaxis, COVID-19 Treatment, WHO.

INTRODUCTION

For the World Health Organization, to date, there is no specific medicine recommended to prevent or treat the new coronavirus. However, those infected with the virus should receive appropriate care to relieve and treat symptoms, and those with severe illness should receive optimized supportive care. Some specific treatments are under investigation and will be tested through clinical trials. WHO is helping to accelerate research and development efforts with a range or partners (WHO, 2020).

Currently there are no FDA-approved medicines specifically for COVID-19. However, the FDA has granted emergency use authorizations for some medicines to be used for certain patients hospitalized with COVID-19. The National Institutes of Health provides more information about treatment options (FDA,2020).

IVERMECTIN

Ivermectin is a Food and Drug Administration (FDA)-approved antiparasitic drug that is used to treat several neglected tropical diseases, including onchocerciasis, helminthiases, and scabies. It is also being evaluated for its potential to reduce the rate of malaria transmission by killing mosquitoes that feed on treated humans and livestock. For these indications,

Ivermectin has been widely used and has demonstrated an excellent safety profile (NIH, 2020).

Ivermectin, approved by the US Food and Drug Administration for parasitic infections, has received renewed attention in the last eight years due to its apparent exciting potential as an antiviral. It was identified in a high-throughput chemical screen as inhibiting recognition of the nuclear localizing Human Immunodeficiency Virus-1 (HIV-1) integrase protein by the host heterodimeric importin (IMP) α/β1 complex, and has since been shown to bind directly to IMPα to induce conformational changes that prevent its normal function in mediating nuclear import of key viral and host proteins. Excitingly, cell culture experiments show robust antiviral action towards HIV-1, dengue virus (DENV), Zika virus, West Nile virus, Venezuelan equine encephalitis virus, Chikungunya virus, Pseudorabies virus, adenovirus, and SARS-CoV-2 (COVID-19). Phase III human clinical trials have been completed for DENV, and more that 50 trials currently in progress worldwide for SARS-CoV-2 (Jans and Wagstaff, 2020).

This study discusses the case for Ivermectin as a preventive treatment for SARS-CoV-2.

Mechanism of Action for the treatment of COVID-19

Ivermectin has been shown to inhibit the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in cell cultures. Ivermectin acts by inhibiting the host importin alpha/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. Ivermectin is therefore a host-directed agent, which is likely the basis for its broad-spectrum activity *in vitro* against the viruses that cause dengue, Zika, HIV, and yellow fever profile (NIH, 2020).

Wagstaff et al (2012) have explained that the movement of proteins between the cytoplasm and nucleus mediated by the importin superfamily of proteins is essential to many cellular processes, including differentiation and development, and is critical to disease states such as viral disease and oncogenesis. They developed a high-throughput screen to identify specific and general inhibitors of protein nuclear import, from which Ivermectin was identified as a

potential inhibitor of importin α/β-mediated transport. In their study, they characterized in detail the nuclear transport inhibitory properties of Ivermectin, demonstrating that it is a broad-spectrum inhibitor of importin α/β nuclear import, with no effect on a range of other nuclear import pathways, including that mediated by importin β1 alone. Importantly, they established for the first time that Ivermectin has potent antiviral activity towards both HIV-1 and dengue virus, both of which are strongly reliant on importin α/β nuclear import, with respect to the HIV-1 integrase and NS5 (nonstructural protein 5) polymerase proteins respectively. Ivermectin would appear to be an invaluable tool for the study of protein nuclear import, as well as the basis for the development of antiviral agents.

Ivermectin has the capacity to modulate the immune response. An uncontrolled immune response is partly responsible for the pathophysiology of COVID-19. It exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway, it may inhibit LPS-induced production of inflammatory cytokines by blocking NF-kappaB and MAP-kinase in RAW 264.7 cells (Xinxin C, 2009).

Lehrer & Rheinstein (2020) carried out a docking study to determine if Ivermectin might be able to attach to the SARS-CoV-2 spike receptor-binding domain bound with ACE2. They concluded that the Ivermectin docking that they identified may interfere with the attachment of the spike to the human cell membrane.

Other potential mechanisms of action include inhibition of the viral enzyme used to unwind its RNA, the helicase, for which it seems Ivermectin may be effective at much lower concentrations. Interaction with the Nicotinic Acetylcholine receptor that may cause immunomodulation or reduce the expression of ACE-II, the receptor used by the virus to enter the cells (Chaccour, 2020).

WHAT SHOULD BE KNOWN ABOUT CLINICAL TRIALS

Clinical trials are research studies performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention. They are the primary way that researchers find out if a

new treatment, like a new drug or diet or medical device (for example, a pacemaker) is safe and effective in people. Often a clinical trial is used to learn if a new treatment is more effective and/or has less harmful side effects than the standard treatment.

Other clinical trials test ways to find a disease early, sometimes before there are symptoms. Still others test ways to prevent a health problem. A clinical trial may also look at how to make life better for people living with a life-threatening disease or a chronic health problem. Clinical trials sometimes study the role of caregivers or support groups.

Before the U.S. Food and Drug Administration (FDA) approves a clinical trial to begin, scientists perform laboratory tests and studies in animals to test a potential therapy's safety and efficacy. If these studies show favorable results, the FDA gives approval for the intervention to be tested in humans.

The Phases of Clinical Trials

Clinical trials advance through four phases to test a treatment, find the appropriate dosage, and look for side effects. If, after the first three phases, researchers find a drug or other intervention to be safe and effective, the FDA approves it for clinical use and continues to monitor its effects (NIH, 2020).

Clinical trials of drugs are usually described based on their phase. The FDA typically requires Phase I, II, and III trials to be conducted to determine if the drug can be approved for use (NIH, 2020).

Phase 0 trials are optional first-in-human trials. Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (typically 10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs). For a test drug, the trial documents the absorption, distribution, metabolization, and removal (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected (The Lancet, 2009).

NIH (2020) has established the following classification:

A Phase I trial tests an experimental treatment on a small group of often healthy people (20 to 80) to judge its safety and side effects and to find the correct drug dosage.

A Phase II trial uses more people (100 to 300). While the emphasis in Phase I is on safety, the emphasis in Phase II is on effectiveness. This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. These trials also continue to study safety, including short-term side effects. This phase can last several years.

A Phase III trial gathers more information about safety and effectiveness, studying different populations and different dosages, using the drug in combination with other drugs. The number of subjects usually ranges from several hundred to about 3,000 people. If the FDA agrees that the trial results are positive, it will approve the experimental drug or device.

A Phase IV trial for drugs or devices takes place after the FDA approves their use. A device or drug's effectiveness and safety are monitored in large, diverse populations. Sometimes, the side effects of a drug may not become clear until more people have taken it over a longer period of time.

On average, it takes at least ten years for a new drug to complete the journey from initial discovery to market, and clinical trials take six to seven years. Thus, it can be hypothesized that clinical bureaucracy might be killing a lot of people.

COVID-19 TREATMENT GUIDELINES

The National Institutes of Health (NIH) (2020) have informed that a COVID-19 Treatment Guidelines Panel (the Panel) was appointed based on their clinical experience and expertise in patient management, translational and clinical science, and/or development of treatment guidelines. It is important to mention that NIH has stressed that the rated treatment recommendations in the Guidelines should not be considered mandates. The choice of what to do or not to do for an individual patient is ultimately decided by the patient with their provider.

PREVENTION AND PROPHYLAXIS OF COVID-19 INFECTION

Pre-exposure prophylaxis (PrEP) is a term used to describe the use of medications used to prevent the spread of disease in people who have not yet been exposed to a disease-causing agent, usually a virus. The term typically refers to the specific use of antiviral drugs (NIH, 2020).

Post-exposure prophylaxis, also known as post-exposure prevention (PEP), is any preventive medical treatment started after exposure to a pathogen in order to prevent the infection from occurring.

The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of any agents for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pre-exposure prophylaxis (PrEP), except in a clinical trial (NIH, 2020).

Rationale by NIH (2020)

At present, there is no known agent that can be administered before exposure to SARS-CoV-2 (i.e., as PrEP) to prevent infection. Clinical trials are investigating several agents, including emtricitabine plus tenofovir alafenamide or tenofovir disoproxil fumarate, hydroxychloroquine, and supplements such as zinc, vitamin C, and vitamin D. Studies of monoclonal antibodies that target SARS-CoV-2 are in development. The Panel **recommends against** the use of any agents for SARS-CoV-2 post-exposure prophylaxis (PEP), except in a clinical trial (NIH, 2020).

Rationale by NIH (2020)

At present, there is no known agent that can be administered after exposure to SARS-CoV-2 infection (i.e., as PEP) to prevent infection. Potential options for PEP that are currently under investigation include chloroquine, hydroxychloroquine, lopinavir/ritonavir, nitazoxanide, vitamin super B-complex, and vitamin D. Other post-exposure preventive strategies that are in development include the use of SARS-CoV-2 monoclonal antibodies and convalescent plasma (NIH, 2020).

BUREAUCRACY, COSTS AND NOT ENOUGH PROFITS

The path a drug travels from a lab to our medicine cabinet is very long, and every drug takes a unique route. Often, a drug is developed to treat a specific disease. An important use of a drug may also be discovered by accident (FDA, 2020). On average, it takes at least ten years for a new medicine to complete the journey from initial discovery to the marketplace, with clinical trials alone taking six to seven years on average. The average cost to research and develop each successful drug is estimated to be $2.6 billion (Phrma, 2015).

Patent on a drug holds a lot of importance to the company manufacturing the drug. It means that the company holds exclusive rights to sell the drug (or formulation) throughout the world with no competition for more than 10 years. This encourages the company to market the drug, sell it at a higher price, and reap all the profits for more than a decade. The problem for the company arises when the drug, which has contributed to a large pie of profits, is going off-patent. This means that it will face a lot of competition from generic substitutes, which will have a huge impact on its sales (London School of Economics and Political Science, 2007; Harvard Kennedy School, 2010).

Ethics or No Ethics, and Patents

During the time a prescription drug company has a patented product; it has a monopoly on the benefits the prescription drug offers to consumers. When a company has a monopoly on its product it is free from market competition and can therefore charge whatever price the market will pay (Hoen, 2003 in Bodem, 2020). This price is usually the most profitable price as few companies will choose do charge less on the basis that they want to help people who need their medicines for a better, healthier life. This is somewhat of a downside to the patent system in that those who are receiving the newly marketed drugs are only those who can afford them (Bodem, 2020).

There is a conflict between companies who have rights to make profits on innovative new drugs and those who wish to direct companies to innovate new pharmaceuticals for developing countries. (Hoen, 2003 in Bodem, 2020) The amount of new medicines developed

over the last 25 years is approximately 1.400. Only 1% of these new medicines have been for tropical diseases, such as new malaria drugs, that kill thousands of people every year. (Hoen, 2003 in Bodem, 2020) Developing world's diseases do not represent a profitable venture for pharmaceutical companies and that is why innovative drugs for the people of the developing world are not being developed. (Hoen, 2003 in Bodem, 2020).

Some even say that the patent system is a fault for the lack of prescription drugs available to developing countries. (Sterchx, 2005 in Bodem, 2020) Also, that the patent system is the main contributing factor to the lack of essential drugs in developing countries because the patent system raised drug prices and provides less choice of sources of drugs. Some would even call the patent system inhuman, as poor people in developing counties are dying because they cannot afford to buy prescriptions drugs they need and the fact that these prices are necessary to ensure pharmaceutical research and development is an unacceptable excuse. (Sterchx, 2005 in Bodem, 2020) Insuring that sick people have access to the prescriptions that they need should be the goal and because the current patent system does not achieve this for the men, women, and children of developing countries some think that the patent system should be redone and changed so that these people do have access to the prescriptions drugs that they need. (Sterchx, 2005 in Bodem, 2020).

There has been a debate. Is it really the patents given to pharmaceutical companies and the subsequent expensive prescriptions the reason developing countries do not have the prescription medications they need, or is it public policy in developing countries that is to blame? This issue may have to be resolved through politics and government intervention (Bodem, 2020).

Patent expiration leads to the marketing and sales of generic equivalents to the previously patented prescription drugs. This patent expiration represents a loss in profits for pharmaceutical companies who may try to encourage customers to switch to a new and better equivalent of the previously patented prescription. The generic drug companies have benefited recently from the Hatch-Waxman Act that allows them to put their generics on the market without having to go through costly testing, only proving that their generic is the same as the previously patented brand-name prescription drug (Bodem, 2020).

Ivermectin has been off patent since 1996 when Merck's patent on Ivermectin expired (WHO, 2020). Here emerges a reasonable question: Is this the reason for which the pharmaceutical industry is not that interested in Ivermectin for the potential treatment of COVOD 19?

ZAGAZIG UNIVERSITY PREVENTIVE PROTOCOL

Shouman (2020) from Zagazig University, recently completed a randomized, open label, interventional trial titled "Use of Ivermectin as Prophylactic Option in Asymptomatic Family Close Contact for Patient with COVID-19." Targeting 340 participants, this study was completed in late August. The research included a total of 304 participated, 203 participants in the Ivermectin group and 101 in the control group. The goal of this investigation was to determine whether Ivermectin could serve as a prophylactic treatment and included a 14-day follow-up period involving a diagnosis for symptoms of COVID-19. The findings revealed that Ivermectin demonstrates statistically significant benefits for use as a prophylaxis to prevent symptomatic COVID-19 infection in individuals that have been exposed to close family members diagnosed with COVID-19 (Shouman, 2020; TrialSite News, 2020).

The study confirmed the hypothesis that Ivermectin in fact possesses an antiviral effect and demonstrates efficacy in preventing the development of symptomatic infection for those individuals that have come in close contact to family members diagnosed with COVID-19. These findings have not been peer reviewed nor published in any medical journals. The study wasn't' blinded, the sample size wasn't that large, etc. Moreover, the study was conducted in Egypt and hence any findings are not necessarily relevant for other food and drug jurisdictions, such as those in the United States (FDA), European Union (EMA), and the UK (MHRA) etc. On the other hand, an accumulation of observational, case series and even randomized controlled study data points (completed in Iraq and Bangladesh) increasingly weigh toward possible benefit for Ivermectin as a low cost, highly available consideration inhibiting COVID-19, particularly in low-to middle-income countries (LMICs). The drug has already been in wide use in LMICs for tropical parasites for decades. Regulatory authorities and national research units should at least be open to reviewing the data, rather than exhibiting indifference (TrialSite News, 2020).

Overview

This study is one of over 30 such clinical trials that investigate the drug repurposing of an FDA approved antiparasitic drug called Ivermectin. Based on the severity of the COVID-19 pandemic, a number of low-LMICs such as Egypt are assessing possible reuse of drugs that may help reduce the severity of the pandemic. Shouman (2020) in the study protocol highlights the importance of considering "drug re-purposing" as a "widely used method for rapid response in the face of epidemic." An underlying premise: solely focusing on advanced, expensive and complex new investigational drugs "de novo medicines" at the expense of also experimenting with well known, approved drugs "may not be the perfect rationale" with a rapidly rising death toll.

Rational for Ivermectin

Based on the study protocol, Shouman (2020) notes the use of FDA approved Ivermectin. Known for a wide spectrum of antiviral activity, however only under in vitro condition. Ivermectin can inhibit the nuclear import of host and viral proteins, the evidence has revealed that it can limit infection by some RNA viruses such as influenza, dengue, and West Nile viruses. Dr. Shouman (2020) has suggested that the antiparasitic medication can act against the DNA virus pseudorabies virus (PRV) both in vitro and in vivo. And, of course, much like the rest of the world that has accepted Ivermectin, the rational for this study: the University of Monash findings that Ivermectin is in fact an inhibitor of the SARS-CoV-2, "with a single addition to Vero-hSLAM cells 2 h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 hours."

The Research Question

Sponsored by Zagazig University, the researchers pursued the answer as to whether oral Ivermectin can prevent symptomatic COVID-19 infection in family close contacts with patients diagnosed as having the disease by RT-PCR. In a study of a few hundred subjects:

Can Ivermectin in fact demonstrate an antiviral effect and actually prevent the development of symptomatic infection in family close contracts with patients already diagnosed as positive? (TrialSite News, 2020).

Objective

This study sought to determine if Ivermectin could serve as a prophylactic for those individuals who had been exposed to someone in their household that was tested positive for COVID-19. To participate, the subject had to be between the ages of 16 and 70, healthy and confirm that a family member was infected with SARS-CoV-2, the virus behind COVID-19. The study excluded any pregnant or lactating individuals or those with a known hypersensitivity to Ivermectin. Also excluded were any subjects that previously were infected with COVID-19 or evidenced any symptoms suggestive of the condition (Shouman, 2020; TrialSite News, 2020).

Intervention

All documented asymptomatic family contacts, starting on day of diagnosis of their index case received the study drug based on body weight as follows:

Weight	Dosage
40-60 kg	15 mg
60-80 kg	18 mg
>80 kg	24 mg

The subject was given one dose at day one (diagnosis day); repeated once at day 3. Shouman (2020) claims that based on relevant literature, a subject can receive 600 mcg per Kg of Ivermectin daily for 3 days without side effect (Smit et al, 2019 and Navarro et al, 2020).

Dr. Shouman and the Zagazig University study team followed the subjects for two weeks after the diagnosis.

Summary of Findings

The Zagazig University results revealed that out of 203 subjects in the Ivermectin arm 15 contacts (7.4%) developed COVID-19 as compared to 59 (58.4%) in the non-intervention arm. Note, all the subjects were symptomatic based on the study protocol, again here. The difference between the Ivermectin arm and the non-intervention arm was "highly significant" (Shouman, 2020).

Shouman (2020) reported that the median (range) day for the development of the disease was 2 (2-6) in Ivermectin group and 4 (2-10) in the non-intervention group with a significant difference.

Interestingly, within the first 3 days in the Ivermectin group, ten (10) contacts (66.6%) developed symptoms while none developed after 6 days. While in the non-intervention arm, 25 (42.3%) developed symptoms in the first 3 days and continued to the 10 days (Shouman, 2020).

Shouman (2020) depicted the so-called "Protection Rates" of Ivermectin versus the non-intervention arm and breakdown by a number of categories such as severity index (mild, moderate, severe) and various demographics. TrialSite (2020) summarized that the overall "Protection Rate" was calculated as 92.6% for the intervention (Ivermectin) group and 41.6% for the non-intervention arm. When breaking this comparison down by demographic overwhelmingly Ivermectin reveals statistically significant benefits according to the Zagazig University investigator analysis.

Ivermectin Role in Preventing SARS-CoV-2 Infection

According to Shouman (2020) Ivermectin played a prominent role in preventing SARS-Cov-2 infection. Based on the data analysis, the protection was not compromised by gender or comorbidities in the multivariate model.

Side Effects

In 11 or 5.4% of the contacts side effects were reported. These included the following: diarrhea (1.5%), nausea (1%), fatigue (1%), sleepiness (0.5%), abdominal pain (0.5%), heartburn (0.5%), tingling and numbness (0.5%) and lastly burning sensation (0.5%) (Shouman, 2020).

IVER.CAR PROTOCOL

Carvallo et al (2020) found out that the combined use of Iota-Carrageenan and Ivermectin in the prophylaxis of health workers showed an effectiveness of one hundred percent, among those who received a preventive treatment.

1,195 Health Agents from different Assistance Centers voluntarily participated in the IVER.CAR protocol between June 1 and August 10, 2020, distributed in four assistance centers in Ezeiza, Caseros and Cañuelas. Of the 1,195 Health Agents who participated in the trial, 788 received IVER.CAR, while 407 did not. In the group that did not receive IVER.CAR, 237 infections (58%) were verified. On the contrary, in the group that received IVER.CAR, no infections were recorded (Carvallo et al, 2020).

In this protocol, medication was given for mild, moderate and severe cases:

- In the mild ones, Ivermectin was given at a dose of 200 micrograms per kilogram of weight and aspirin to prevent hypercoagulability.
- In moderate cases, the dose of Ivermectin was 400 micrograms and, in addition to aspirin, injectable dexamethasone, an anti-inflammatory drug, was added to prevent hyperinflammation in the lungs.
- In severe cases, the Ivermectin dose was increased to 600 micrograms, aspirin was replaced by enoxaparin, and dexamethasone was maintained.
- In all cases, Ivermectin is given once a week, while the other drugs are given daily. The idea with Ivermectin is not to totally eliminate the virus, with the aim of generating antibodies, in the manner of a vaccine produced by the body itself.

Carvallo (2020) explained that the duration of the treatment is 30 days on average. The cost of this treatment is estimated at 15 dollars per day.

In this protocol, intended for healthy hospital staff, a nasal spray and some oral drops are administered to protect the nose and mouth. The nasal spray has carrageenan, a product derived from red algae that acts as an emulsifier, widely used in pharmaceuticals and cosmetics. Carrageenan has a virucidal effect, which is why it is present in long-life milk as a natural preservative. Both Ivermectin and carrageenan are highly concentrated in the salivary glands, generating an antisepsis in the droplets of saliva. Therefore, the healthy patient could be quite protected and the asymptomatic one would cease to be infectious (Carvallo, 2020).

Intervention:

- Ivermectin drops (6 mg / ml, each 100 ml of solution contains 0.6 g of Ivermectin).
- Carrageenan spray (each 100 ml, 0.9 g of sodium chloride and 0.17 g of carrageenan).

Dosage scheme: one shot of the iota-carrageenan spray in each nostril and 4 shots of the spray in the oral cavity. Then apply 1 drop of Ivermectin oral solution on the tongue. Observation: Avoid food and liquid intake 1 hour before and 1 hour after treatment. Carry out this dosing scheme 5 times a day, repeating the scheme.

The proposed prophylactic treatment consists of the application of Ivermectin over a carrageenan solution, 5 times a day, for a period of 14 days.

Procedure:

- Apply one pulverization of iota-carrageenan spray in each nostril and 4 pulverizations of the spray in the oral cavity (under the tongue, one on each side and one in the oropharyngeal area)
- Apply 1 drop of Ivermectin oral solution on the tongue.
- Carry out this dosing scheme 5 times a day, repeating the scheme every 4 hours. The last dosage schedule of the day should be done prior to nighttime rest, in this case you should

not wait for the 4-hour period with respect to the previous dose. Avoid the intake of food and liquids 1 hour before and 1 hour after each treatment.

- Perform the full treatment for 14 days.
- Perform standard care routine at the same time.

Optimization of the IVER.CAR Prophylaxis Protocol

It is open to all Hospital Health Agents. The nasal spray will be applied to both nostrils and both cheeks, four times a day. Ivermectin will be taken at a rate of 12 mg (2 tablets or 60 drops) once a week and will be repeated up to 10 weeks (Carvallo, 2020).

Treatment of Prophylaxis with Ivermectin and the "Vaccine Effect"

If the incubation period of COVID 19 is 5 to 6 days, and the effect of a single dose of Ivermectin is maintained for 3 to 4 days (which implies a reduction of the inoculum to 5% of the original, too little to cause disease but enough to develop immunity due to antibody generation), the repetition of the single dose in periods sequential and for a limited time pre-established, would confer the host a level of acceptable immunity against infection, thus generating a "vaccine effect".

GUSTAVO AGUIRRE CHANG PROTOCOL

Aguirre (2020) explains that at a local level in Peru, although to date there are not many documented cases, the Fatality Rate has been 0% and it was also observed that in 100% of the cases treated with Ivermectin there is an improvement in the disease and resolution of the fever within 48 hours of starting the treatment.

At the local level, in the City of Lima, some Doctors individually began to give treatment with Ivermectin since mid-April 2020. Based on to the studies and experiences mentioned, a group of Physicians graduated from Class 83 of the Faculty of Medicine of San Fernando of the UNMSM, all with more than 27 years of professional experience, they reviewed the safety of the use of Ivermectin. It was a consensus that no major adverse effects have been

reported and that these are rare and mild. It was then proceeded to elaborate a Ivermectin Treatment Scheme for COVID-19 (Table 1) (Aguirre, 2020).

In mild cases you have that, within 8 hours, after the 1st dose, the patient starts to show a decrease in fever, malaise, dyspnea, and any symptoms of COVID-19. In these cases, it is estimated that the viral load has been low and it helps with the reduction of the viral load. In Moderate and Severe cases, the decrease in fever, malaise, and dyspnea occurs within 12 to 48 hours. In case the answer is only partial after 2 doses of Ivermectin, viral load is estimated to be high. In severe and critical cases, it has been observed that there is an improvement between 65 to 85% within 48 hours, being necessary in some cases to give more doses for more days (Aguirre, 2020).

Table 1. Gustavo Aguirre Chang Protocol

Severity	**Dosage**
Mild	12 mg in a single dose (for patients with 80 Kg, more than 80 Kg give 18 mg)
Moderate	12 mg per day, for 2 days (for patients with 80 Kg, more than 80 Kg give 18 mg)
Severe	Day 1. 24 mg Day 2. 12 mg Day 3. No treatment Day 4. If symptoms persist, give 1-2 additional doses Day 7. If symptoms persist, give 1-2 additional doses
	Note: Usual average dose: 200 mcg/kg

Reference: Aguirre (2020)

Dr. Landrito Protocol

Dr. Allan A. Landrito (2020) has been a practicing as an Integrative Medical Doctor since 2005. He is connected with the City Health Department of Muntinlupa (Philippines), and serving in his capacity as a front-liner in that institution. He has successful experiences in handling COIVID-19 patients giving intravenous Vitamin C and DMSO. He always gives Ivermectin 15mg to adult patients and I he has seen that symptomatic swab-positive patients are responding to this. It usually takes 3-4 days and then he is surprised that patients improve.

The recommended dose of Dr. Landrito for prevention is one capsule (15 mg) as a single dose for adults. It may be repeated every three weeks.

ONGOING RESEARCH

1. Effectiveness and Safety of Ivermectin for the Prevention of Covid-19 Infection in Colombian Health Personnel

This clinical trial is sponsored by the Pontificia Universidad Javeriana, Cali, Valle Del Cauca, Colombia. The objective is to determine the effectiveness and safety of the administration of Ivermectin at a dose of 200 mcg/kg once a week for 7 weeks in a prophylactic treatment against SARS COV-2 infection in 500 Colombian health workers during the COVID-19 pandemic (Clinical Trials 1, 2020).

It will be performed a randomized, multicenter, triple-masked, placebo-controlled clinical experiment to determine the relative risk of SARS COV-2 infection, seroconversion, and clinically presenting disease. In addition, the relative risk of requiring hospitalization or entering the intensive care unit was evaluated in doctors, nurses, respiratory therapists and assistants who have direct contact with patients with COVID-19. After being exposed to Ivermectin prophylaxis or placebo for seven weeks, the results will be measured at eight weeks, with interim analyses to monitor the safety of the participating subjects.

Intervention Treatment:

Oral administration of Ivermectin 200 mcg/kg every week for seven weeks

2. Comparative Study of Hydroxychloroquine and Ivermectin in COVID-19 Prophylaxis

The study is an open-blind, randomized trial that will be conducted by the Federal University of Ceará (UFC) Fortaleza, Ceará, Brazil, in 400 asymptomatic professionals working in areas of high exposure and high risk of transmission of SARS-COV-2 (Clinical Trials 2, 2020).

Front-line healthcare workers can become infected in the management of patients with COVID-19; the high viral load in the atmosphere, and infected medical equipment are sources for the spread of SARS-CoV-2. If prevention and control measures are not in place, these healthcare workers are at great risk of infection and become the inadvertent carriers to patients who are in hospital for other diseases. Nowadays a question that has not yet been clarified by science has been arises: is hydroxychloroquine associated with zinc compared to Ivermectin associated with zinc effective as a prophylaxis for asymptomatic professionals involved in the treatment of suspected or confirmed case of COVID-19?

Intervention Treatment:

(1) Hydroxychloroquine. Oral hydroxychloroquine 400 mg twice a day on day 1, one 400 mg tablet on day 2, 3, 4, and 5, followed by one 400 mg tablets every 05 days until day 50th associated with 66 mg of zinc sulfate. (2) Ivermectin. Oral Ivermectin dosage guidelines based on participant body weight, once on day for 2 consecutive days. This dose schedule should be repeated every 14 days for 45 days associated with 20 milligrams twice on day of active zinc.

3. A Preventive Treatment for Migrant Workers at High-risk of Covid-19

This is an interventional randomized study with the enrollment of 5000 participants, conducted by the National University Hospital at Singapore (Clinical Trials 3, 2020).

Patients are known to shed viruses despite mild or no symptoms, making it essential that a collective approach against COVID-19 incorporate active pharmacological treatment to prevent or mitigate virus pathogenesis prior to its potential evolution to cause respiratory distress. To date, clinical trials have focused on the treatment of hospitalized patients diagnosed with COVID-19; only few have examined the clinical benefits of pharmacological agents despite few compelling in vitro data.

The relatively high transmission of COVID-19 in a closed dormitory environment of migrant workers in Singapore presents a real-life scenario where a prophylaxis treatment could reduce the impact of the disease. In Singapore, there are well grounded concerns an excess in cases could pose the possibility of strain in healthcare system and mentally drain her workers. The availability of an effective prophylaxis treatment is highly desirable to potentially reduce this burden. Data from the current study could also have implications on how future outbreaks in high-density areas should be managed, especially when residents are subjected to quarantine and isolation.

Intervention treatment:

- Hydroxychloroquine Sulfate tablet 400 mg loading dose, followed by 200 mg daily for 42 days
- Ivermectin tablet 12 mg single dose
- Zinc tablet 80 mg for 42 days
- Vitamin C 500 mg daily for 42 days
- Povidone-iodine throat spray (3 times daily) for 42 days

4. Ivermectin Nasal Spray for COVID19 Patients

Tanta University (Egypt) will be conducting an interventional randomized study with the participation of 60 people. The hypothesis is that, since COVID-19 has shown to be particularly damaging to the respiratory system, using inhaled forms of Ivermectin will deliver the drug directly to the infection site and make it a treatment option (Clinical Trials, 2020).

Intervention treatment:

- Ivermectin nasal spray one ml in each nostril two times daily
- Ivermectin administered orally (one tablet 6 mg three times daily) for 72 hours plus the standard care of COVID-19 cases.

5. Ivermectin to Prevent Hospitalizations in COVID-19 (IVERCORCOVID19)

It is a single-center, prospective, randomized, double-blind, placebo-controlled study carried out by the Ministry of Public Health of the Province of Corrientes, Argentina, in coordination with the Corrientes Institute of Cardiology "Juana F. Cabral". 500 patients who meet all the inclusion criteria and none of the exclusion criteria are randomized via the web system to receive placebo or Ivermectin. The need for hospitalization in patients with COVID-19 is assessed as the primary end point. As secondary end points are evaluated: time to hospitalization (in days); use of invasive mechanical ventilation; time to invasive mechanical ventilation (in days); dialysis; all-cause mortality; negative of the swab at 3 ± 1 days and 12 ± 2 days after entering the study and Ivermectin safety.

Intervention Treatment:

The dose of Ivermectin in patients who are randomized to the active substance depends on the weight of the patient:

More than 48 kg and less than 80 kg: Two tablets of 6 mg each (12 mg in total) at the time of inclusion and the same dose at 24 hours.

More than 80 kg and less than 110 kg: Three tablets of 6 mg each (18 mg in total) at the time of inclusion and the same dose at 24 hours.

More than 110 Kg: Four tablets of 6 mg each (24 mg in total) at the time of inclusion and the same dose at 24 hours. Patients will receive the tablet from the branch to which they were randomized only at the time of inclusion and 24 hours after the first dose.

6. Clinical Trial on Ivermectin for the early Treatment of COVID-19

IRCCS Sacro Cuore Don Calabria Hospital is an accredited Italian provider in the Veneto region that accommodates about 30,000 patients per year, includes 968 beds and employs approximately 1,712. The regional provider has come together with Mario Negri Institute for Pharmacological Research, a nonprofit research institute dedicated to clinical and biomedical research, to conduct the 'COVER trial', a 102 patient, prospective, multi-center, randomized, double-blind trial to assess efficacy and safety of Ivermectin for the treatment of initial infection with SARS-CoV-2 infection. Led by infectious and tropical disease expert Dr. Zeno Bisoffi, the study will be conducted through August with final reports planned for October 2020. The study will span regions of Italy and Spain (TrialSite News, 2020).

This is a randomized, double-blind, multi centre phase II, proof of concept, dose finding clinical trial on Ivermectin for the early treatment of COVID-19, sponsored by IRCCS Sacro Cuore Don Calabria di Negrar and Istituto Di Ricerche Farmacologiche Mario Negri (Clinical Trials 5, 2020).

The main objectives of this clinical trial are:

- To define if Ivermectin, administered at dosage of 600 μg/kg or 1200 μg/kg QD for five consecutive days is safe in patients with initial, asymptomatic or oligosymptomatic SARS_CoV-2 infection,
- To define if Ivermectin, administered at the dosage(s) found to be safe decreases the viral load of SARS-CoV-2 at Day 7.

The secondary objectives are to assess:

- The temporal profile of viral load at baseline, day 7, 14 and 30
- The time to clinical cure (for symptomatic patients)
- the proportion of patients with virological clearance at day 14 and 30.
- The hospitalization rate.
- The COVID-19 Severity Score at day 14 and 30

Intervention Treatment:

Arm a: Placebo.

Arm b: Patients will be administered a single oral daily dose of approximately 600 μg/Kg of Ivermectin for 5 consecutive days.

Arm c: Patients will be administered a single oral daily dose of approximately 1200 μg/kg of Ivermectin daily at empty stomach with water for 5 consecutive days.

In Italy, the sites include the following:

IRCCS Sacro Cuore Don Calabria Hospital (Negrar Verona)

- Policlinico S. Orsola (Bologna)
- Ospedale Luigi Sacco (Milan)
- Ospedale di Rovereto (Rovereto)
- Ospedale Amedeo di Savoia (Turin)

While in Spain the following sites are involved:

- Hospital Clinic/IS Global (Barcelona)
- Hospital La Paz-Carlos III (Madrid)

IVERMECTIN IN THE NEWS

Several South Florida doctors are using an anti-parasitic drug for lice and pinworms to treat COVID-19 patients. The drug has not been given the green light to treat the novel coronavirus, although trials are underway, and the National Institutes of Health recommends against using it that way (Goodhue, 2020).

Despite the skepticism and the red flag, a Florida Keys physician who runs three clinics along the island chain says more than a dozen of his patients have recovered after getting doses of Ivermectin. Dr. Bruce Boros of Key West said he has been giving it to COVID patients for

months and said they are encouraged by the results. Despite this, the national medical researchers are not on board. The National Institutes of Health's COVID-19 Treatment Guidelines Panel two has recommended against using Ivermectin, first approved as an anti-parasitic drug in 1975, to treat the coronavirus outside of clinical trials (Goodhue, 2020).

The U.S. Food and Drug Administration posted on its website in May that the use of Ivermectin to treat or prevent COVID-19 "should be avoided as its benefits and safety for these purposes have not been established. Data from clinical trials are necessary for us to determine whether Ivermectin is safe and effective in treating or preventing COVID-10." The FDA also warned against self-medicating with invermectin that is prescribed for veterinary purposes. It is used as a prophylactic against heartworm (Goodhue, 2020).

The NIH, in its recommendation against prescribing Ivermectin as a COVID treatment, mentioned a Broward County doctor's study, saying the document lacked enough information to conclude the drug was a significant factor in the sampled patients' recoveries. "The limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using Ivermectin to treat patients with COVID-19," the NIH statement reads (Goodhue, 2020).

Despite what some consider its promise in treating COVID-19, not only in South Florida, but in India, Bangladesh, Peru and Colombia, many doctors and pharmacists globally have warned against prescribing Ivermectin until more peer-reviewed clinical trials are conducted (Goodhue, 2020).

Broward Hospital Approval

Broward Health has approved the anti-parasite drug for its "portfolio" of medications its doctors can use to treat COVID-19 after one of its physicians theorized dozens of his patients beginning in April recovered after taking it. They think of it as helping stop the viral replication early in the process (Goodhue, 2020).

However, even proponents of the drug stress it is not a cure, and years of peer-reviewed clinical trials will likely be needed to conclude if Ivermectin was truly instrumental in patients' recoveries, or if they would have gotten better without taking it (Goodhue, 2020).

Florida Keys Treatment

Dr. Bruce Boros, a cardiologist who owns and operates all three of the Keys' Advanced Urgent Care clinics, was one of the earliest healthcare professionals along the island chain to sound the alarm about the dangers of the novel coronavirus, urging social distancing and mask-wearing (Goodhue, 2020).

He was also a vocal proponent of the highway checkpoints that went up in late March to keep tourists outside the Keys in what turned out to be a successful effort to stop the disease from spreading throughout the archipelago. Soon after the checkpoints came down June 1, COVID-19 cases spiked in the Keys. By July, there were hundreds of cases. One of those ill with the virus earlier this summer was Kyle Carter, a 45-year-old music promoter living in Key West (Goodhue, 2020).

Carter stands six feet, four inches and weighs around 290. He has had several surgeries in his life but is otherwise healthy. For about three days, he felt like he had the flu. By Day 5, he had a fever of more than 103 degrees. Five days later, he had a bad cough and trouble breathing. On the 11th day of the illness, Dr. Boros' staff X-rayed his lungs and the right one was filled with fluid. He tested positive for COVID-19 and had developed viral pneumonia. Boros told him about Ivermectin, which he had been reading about as a possible treatment for COVID and asked him if he wanted to try it. He did. Carter was on the verge of having to go on a ventilator, which he said is when most deaths occur (Goodhue, 2020).

Intervention Treatment. Starting around 4 p.m. that day, Dr. Boros gave Carter a large dose of Ivermectin, **18 3-milligram pills over the next four hours (a total of 54 mg). Carter took nine pills at first (27 mg), five more (15 mg) about two hours later**, **and the rest of the dose early the next morning (12 mg)**. Boros was worried at first about how much to give Carter since there are no established guidelines about using the drug to treat COVID.

But he was more concerned about how fast his patient's condition was deteriorating (Goodhue, 2020).

Within 12 hours Carter started to feel better. Twenty-four hours later, he was out of the hospital and his symptoms went away. Dr. Boros believes in Ivermectin's effectiveness so much that he gives it to all his patients showing signs of COVID-19, especially since the drug has few known negative side effects. And, more importantly, the sooner patients start treatment, the better the outcome. That is because COVID-19 is a virus that is built on ribonucleic acid, which allows it to quickly reproduce itself inside the human body. Boros and other advocates of Ivermectin believe the drug stops the RNA replication of the virus. Boros is not the only, and not the first inSouth Florida to treat patients with Ivermectin (Goodhue, 2020).

Shashikanth Manikappa

Shashikanth Manikappa, a specialist cardiac anaesthetist working at Monash Health in Melbourne, Australia, addressed a media conference in Kalaburagi on September 14, 2020. Elaborating on the effective methods being followed for treating COVID-19 across the globe, he has strongly advised what he termed Quadruple Therapy involving four medicines — Ivermectin, Doxycycline, Zinc and Vitamin D3 — as a preventive as well as treating method.

Manikappa (2020) said that the use of Ivermectin would be more effective than that of Hydroxychloroquine which was widely being used worldwide, right from the outbreak of the pandemic. Referring to a pre-official release of a randomized controlled trial using Ivermectin in three doses in primary contacts of COVID-19, he reported that 93 % of primary contacts who received Ivermectin did not develop any symptoms and 58 % of primary contacts who did not receive Ivermectin did progress to have symptoms of the pandemic.

Quadruple Therapy includes Ivermectin 12 mg one dose, Doxycycline 100 mg once a day for four days, Zinc 50 mg once a day for four days and Vitamin D3 once a week. Ivermectin, Doxycycline and Zinc are to be repeated every 14 days and Vitamin D3 every week with blood levels monitored. The synergistic effect of these medicine acts to prevent viral

multiplication and also stop the virus from entering human cells. Thomas Borody, an Australian gastroenterologist who is known for curing peptic ulcers with triple antibiotic therapy, has revealed that one block in South America that received Ivermectin combination prophylaxis did not contract coronavirus infection while others did (Manikappa, 2020).

On the side effects, Manikappa (2020) explained that Ivermectin was being used in 3.7 billion people for intestinal parasites and was found to be safe. “These are not new medicine. They are already in use for treating different ailments and are found to be safe. They can be prescribed by any doctor to control the pandemic. He informed that the Indian Council of Medical Research (ICMR) had, though late, come up with new guidelines recommending Ivermectin. District Kannada Vaidya Sahitya Parishat president S.S. Gubb and joint secretary Shashishekhar Reddy were present at the media conference.

Kitasato University Hospital

The word on Ivermectin as a potential approach to therapeutically countering COVID-19 is now getting out there—this time with Nikkei Asian Review. TrialSite News (2020) has followed the progression of the off-label approach of this anti-parasite drug carefully. Most recently, University of Kentucky announced that the common, cheap drug would be used in a clinical trial. Now a Japanese media offers updates including the fact that Kitasato University is in discussions with Merck’s Japanese subsidiary to consider a clinical trial there.

Kitasato University Hospital announced plans for testing Ivermectin, which is widely used against parasite-borne infectious diseases. The university's Distinguished Emeritus Professor, Omura Satoshi, won a Nobel prize for discovering a compound that led to the development of Ivermectin. The university hospital says the trial will involve 240 COVID-19 patients aged 20 or over with mild to moderate symptoms. They will be divided into two groups. One will be given Ivermectin, and the other will receive a placebo.

The hospital plans to compare changes in their symptoms to assess the drug's efficacy and safety. The operator of the university, the Kitasato Institute, says experiments using cells have shown Ivermectin works in inhibiting the proliferation of the coronavirus.

The Toronto Nursing Home Case

This notorious case has been reported by health practitioner Dr Jennifer Hibberd. This report can be watched on the Hibberd Health Coronavirus Covid-19 Pandemic Series transmitted by YouTube Channel.

To treat an outbreak of scabies, a nursing home in Toronto happened to administer the drug Ivermectin to its patients just before the coronavirus outbreak started. In late Feb 2020 or early March, they gave higher doses of Ivermectin to patients on the fourth floor of their building, where the scabies outbreak occurred, and in lower doses to patients on the third floor. They did not give Ivermectin to staff. Then when the coronavirus outbreak came to their facility, the patients on the fourth floor had no cases of COVID-19, the patients on the third floor (who had a lower dose of Ivermectin) had a few mild cases, and the fourth floor had the most infected staff.

It was noticed that healthier, younger, staff on the fourth floor had the most cases of COVID-19, while the very patients for whom they were caring, who were old and sick with other diseases had no cases. The difference: the patients on the fourth floor had the strong dose of Ivermectin.

Unexpectedly, Dr. Jennifer Hibberd was blocked from getting information from the nursing home when it was told to stop communicating any of this information to the public. For some unknown reason, the institution did not want the potential of an effective and inexpensive therapeutic, Ivermectin, to go public.

FINAL REMARKS

It was found that Ivermectin, originally introduced as an anthelmintic, to be an effective, safe and an affordable therapeutic option for prevention of COVID-19. It has potential to convert

RT-PCR negative quickly. It can be used across the severity of COVID-19 especially in preventive and early viremic phase. It can be combined with other molecules of interest, like hydroxychloroquine, azithromycin, doxycycline, zinc. Ivermectin is affordable, easily available, and safe without any major side effects. Right now many lives in the world are at stake. Something to be considered when choosing the right treatment is that many renowned scientists propose Ivermectin, a strong antiviral drug as a therapeutic option in the prevention of COVID-19.

Finally, WHO is telling the truth? It is a big challenge to answer this delicate question. First, look at the available scientific evidence by yourself and also accompanied by an honest and qualified Physician, then it is up to everyone (Doctors and Patients) to make the right responsible choices.

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