Ivermectin & Orthomolecular Medicine Combination Therapy for COVID-19: Successful Clinical Protocols and A Case Study

Jose Luis Abreu, PhD

Abstract. The objective of this study is to provide information that can be useful in the global analyses of data related to the research in the treatment of COVID-19. The protocol for this case study was followed by a person with an asthmatic condition for 10 consecutive days. The protocol was integrated by: Ivermectin: 18 mg the first day. 12 mg daily the following days, except when the headache was intense the patient was given an extra 12 mg dosage (It occurred for three days). Ibuprofen: 400 mg every 8 hours. Doxycycline: 100 mg daily. Aspirin: 100 mg daily. Zinc: 50 mg daily. Vitamin D3: 5,000 IU daily. Vitamin C: 3 grams daily. Two cups per day of Artemisia annua infusion with lemon. The outcome in this case was successful.

Keywords: Ivermectin, COVID-19, Artemisia annua, Orthomolecular Medicine, Coronavirus.

Resumen. El objetivo de este estudio es aportar información que pueda ser útil en los análisis globales de datos relacionados con la investigación en el tratamiento de COVID-19. El protocolo para este caso de estudio se aplicó durante 10 días consecutivos a una persona de condición asmática. El protocolo estuvo integrado por: Ivermectina: 18 mg el primer día. 12 mg los días siguientes, excepto cuando el dolor de cabeza era intenso, el paciente recibió una dosis adicional de 12 mg (ocurrió durante tres días). Ibuprofeno: 400 mg cada 8 horas. Doxiciclina: 100 mg al día. Aspirina: 100 mg al día. Zinc: 50 mg al día. Vitamina D3: 5,000 UI diarias. Vitamina C: 3 gramos diarios. Dos tazas al día de infusión de Artemisia annua con limón. El resultado en este caso fue exitoso.

Palabras claves: Ivermectina, COVID-19, Artemisia annua, Medicina Ortomolecular, Coronavirus.

Introduction

It is well known in research methodology that a case study research paper examines a person, place, event, phenomenon, or other type of subject of analysis in order to extrapolate key themes and results that help predict future trends, illuminate previously hidden issues that can be applied to practice, and/or provide means for understanding an important research problem with greater clarity. This case study reports the successful utilization of Ivermectin as a combination therapy, in which a 30 old years woman, with an asthmatic condition was treated for COVID-19.

The case consisted in the application of a combination therapy integrated by Ivermectin, Artemisia annua, Doxycycline, Orthomolecular Nutrients, Ibuprofen and Aspirin.

The objective of this report is to provide information that can be useful in the global analyses of data related to the research in the treatment of COVID-19. At the present time, The National Institutes of Health in the United States are administrating 36 Clinical Trials related to the utilization of Ivermectin in the treatment of COVID-19.

Research Background

Ivermectin (IVM): Tolerated Doses

According to Scheim (2020), the potential for enhanced clinical benefits for COVID-19 with higher or more frequent dosing of IVM has been considered in the context of a hypothesized biological mechanism. Yet this potential is feasible given the proportionality of IVM plasma levels to oral dose up to 1.7 mg/kg, and the linear or in some case more robust correlation of response to dose in some studies of antiviral agents. The safety of IVM at doses up to 2,000 µg per kg, ten times the dose of 200 µg/kg as used in a Florida clinical study, allows such latitude for dose escalation. This standard dose of 200 µg/kg is taken, for example, once to three times per year for river blindness or twice, a week apart, for scabies. Since 1987, 1.3 billion treatments for river blindness at 200 µg/kg have been provided worldwide. In addition, much higher doses of IVM have proven equally safe. In one clinical study at fixed doses, the highest at 120 mg (up to 2,000 µg/kg) taken once or at 180 mg (up to 3,000 µg/kg) taken in split doses over one week, IVM was generally well tolerated, with no difference in adverse events between placebo and these highest doses (Guzzo et al, 2002; Lankas & Gordon, 1989; Gieschke et al, 1999; Shen et al, 2011; CDC, 2020; Badhan et al, 2018; Lawrence et al, 2015 in Scheim 2020).

Scheim (2020) has explained that likewise IVM was well tolerated at a single dose of 800 µg/kg, at 1,600 µg/kg over 12 weeks and at 1,600 µg/kg over 13 days. An oral dose of IVM of up to 1,400 µg/kg over one month is recommended by the US-CDC as a treatment option for crusted scabies. A meta-analysis of clinical experience with IVM found no significant differences in frequency or intensity of adverse events with doses up to 800 µg/kg vs. standard doses. Also, long-term follow-up studies of IVM use in elderly populations at doses up to 400 µg/kg found no deaths. The safety of IVM as noted

in humans and other mammals derives from the shielding by the blood brain barrier of the central nervous system, the most potentially vulnerable tissue, from penetration by IVM. However, since the blood brain barrier may be at risk for being compromised in some cases of COVID-19, the most aggressive dose range of 1,000-2,000 µg/kg of IVM that would appear safe for normal subjects may not be appropriate for patients with this disease (Awadzi et al, 1995; Costa & Diazgranados, 1994; Awadzi et al, 1999; CDC, 2020; Navarro et al, 2020; Alexander et al, 1998; del Giudice et al, 1999; Guzzo et al, 2002; Scott, 2008; Juarez, Schcolnik-Cabrera & Dueñas-Gonzalez, 2018; Wu et al, 2020 in Scheim, 2020).

Monash University

Researchers from Biomedicine Discovery Institute (BDI) at Monash University in Australia have found that the anti-parasitic drug called Ivermectin could kill the novel coronavirus, SARS-CoV-2, within 48 hours in a laboratory setting. Monash University, in alliance with the Peter Doherty Institute of Infection and Immunity (Doherty Institute), led the study. Ivermectin holds the US Food and Drug Administration (FDA) approval as an anti-parasitic medicine. In-vitro, the drug demonstrated activity against different viruses including HIV, dengue, influenza and Zika. According to findings from the latest study, a single dose of the drug could stop SARS-CoV-2 growing in cell culture within two days. Monash Biomedicine Discovery Institute scientist Dr Kylie Wagstaff said: “We found that even a single dose could essentially remove all viral RNA by 48 hours and that even at 24 hours there was a really significant reduction in it.” (Pharmaceutical-Technology, 2020).

Caly et al (2020) reported that Ivermectin, an FDA-approved anti-parasitic previously shown to have broad-spectrum anti-viral activity in vitro, is an inhibitor of the causative virus (SARS-CoV-2), with a single addition to Vero-hSLAM cells 2h post infection with SARS-CoV-2 able to effect ~5000-fold reduction in viral RNA at 48 h. Ivermectin therefore justifies further investigation for potential benefits in humans.

Caly et al (2020) highlighted the following points:

- Ivermectin is an inhibitor of the COVID-19 causative virus (SARS-CoV-2) in vitro.
- A single treatment able to effect ~5000-fold reduction in virus at 48 h in cell culture.

- Ivermectin is FDA-approved for parasitic infections, and therefore has a potential for repurposing.
- Ivermectin is widely available, due to its inclusion on the WHO model list of essential medicines.

The Bangladesh Protocol

Prof. Mohammed Tarek Alam, Professor and Head of Department of Medicine, Bangladesh Medical College, was the lead author of this protocol. Alam et al (2020) carried out a prospective study in which a combination of **Ivermectin and Doxycycline** was evaluated therapeutically to treat COVID-19 patients. 100 COVID-19 patients were enrolled in the study with a predefined inclusion and exclusion criteria. RT- PCR of the SERS-CoV-2 were done at designated government hospitals. The clinical features and response to treatment were recorded according to a dedicated protocol.

They were given a combination treatment of Ivermectin and Doxycycline along with supportive medical treatment. The dose of Ivermectin was 0.2 mg/kg single dose. Doxycycline 100 mg daily was given to patients for 10 days (Alam et al, 2020).

This observational study, consisting of 64 males and 36 females was conducted from April to May 2020 in Bangladesh Medical College. The oldest patient was 84 years and the youngest one was 8 years with most patients between the ages of 21 to 40 years. Patients were divided in 3 groups: Mild (73), Moderate (20) and Severe (7), based on their symptoms. From the severe patients, three had fever more than 103 degrees Fahrenheit for seven days with severe cough and lung infiltrates, three had severe loose motion and one had uncontrolled diabetes. Out of the rest, 20 patients had moderate symptoms of mild fever (100 degrees Fahrenheit) and mild cough. Moreover, 73 had mild symptoms of malaise, sore throat, loss of smell, loss of taste, and body ache. Fifty percent symptomatic improvement of mild to moderate patients was seen between the 3rd to 5th day after starting treatment. All 7 severe patients' symptoms subsided by 50 percent by the 7 th day of treatment. Retesting was done between 4 to 18 days of starting medication. Twenty-five patients underwent retesting between the 4th to 8th days, 51 between the 9th to 13th days and 24 between the 14th to 18th days from starting medication. All the patients tested negative. None needed intensive care admission and no deaths were reported. No toxicity was seen with the drug at any point of time (Alam et al, 2020).

Broward County (South Florida) Protocol

Rajter et al (2020), at the Broward Health Medical Center, followed on a retrospective cohort study of consecutive patients hospitalized at four Broward Health hospitals in South Florida with confirmed SARS-CoV-2. 280 patients with confirmed SARS-CoV-2 infection (mean age 59.6 years [standard deviation 17.9], 45.4% female), of whom 173 were treated with Ivermectin and 107 were usual care reviewed. 27 identified patients were not reviewed due to multiple admissions, lack of confirmed COVID results during hospitalization, age less than 18, pregnancy, or incarceration. Exposure: Patients were categorized into two treatment groups based on whether they received at least one oral dose of Ivermectin at 200 micrograms/kilogram at any time during the hospitalization in addition to usual clinical care. Treatment decisions were at the discretion of the treating physicians. Rajter et al (2020) concluded that Ivermectin was associated with lower mortality during treatment of COVID-19, especially in patients who required higher inspired oxygen or ventilatory support. The authors suggested that these findings should be further evaluated with randomized controlled trials.

Dr. Camargo Protocol

Dr. Antonio Camargo, Scientific Director of the Institute ONKOS, conducted a study on the use of high doses of Ivermectin: in the treatment of infection by SARS-CoV2 (COVID-19), as a case of molecular resolution. He presented his experience and personal testimony about the use of Ivermectin to treat himself. In his case, the treatment protocol, considering the high viral load presented in the molecular test, augured a prognosis quite reserved and critical. Departing from this delicate situation, the protocol was formulated as follows: 60 mg of Ivermectin for 4 days, followed by 30 mg for 3 days, for a total of 330 mg in 7 days (Camargo, 2020).

Three days after starting treatment with 60 mg dose of Ivermectin daily, and after testing, it was observed that the viral load was completely negative, indicating complete disappearance of the pathogen after 3 days of treatment with this medicine (Camargo, 2020).

In this regard, sub-doses of Ivermectin should not be used, since this can cause the false impression of achieving an effect. In any case, it deserves to bet on the maximum tolerated and suggested doses in order to eradicate the virus effectively and achieve rapid rates of cure (Camargo, 2020).

Camargo (2020) explained that it is therefore worth to note that studies carried out by Aránzazu Gonzáles Canga et.al (2010), demonstrated a remarkable safety with doses higher than those suggested, thus, using doses of 1000ug / kg for 3 days, for example, no adverse effects were noted, even with additional doses of 200ug / Kg there were no problems, highlighting that the drug's metabolism is widely distributed, mainly in hepatic peroxisomes

With his own study (Case Report), Camargo assures that he has evidence that Ivermectin represents so far the most powerful and effective "coronicidal" agent that exists for the rapid treatment and attack of the pathogen, therefore he maintains that the application deserves to be massive in the face of the threat of the pandemic, since its use is simple to apply and far superior in terms of safety and toxicological profile compared to other drugs.

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)

Academy of Advanced Medical Education

Vora et al (2020) reported that a group of senior doctors with vast experience in the management of COVID-19 got together on 19th July'20 under the leadership of Prof Dr V. K. Arora, Prof. Dr D. Behera, Prof. Dr Suryakant Tripathy, Dr. MohanKumar Thekkinkattil, Dr. Agam Vora, Dr. Vasant Nagvekar, Lt Gen (Rtd) Dr. B.N.B.M Prasad, Dr. K.S. Satish, Dr. V.K.Singh, Dr. Mangesh Tiwaskar, Dr. Parthiv Mehta, Dr. P. Sarat Singh, Dr. Narayana Pradeep, Dr. Rahul Mayekar and Dr. Bhupesh Dewan, under the auspices of Academy of Advanced Medical Education. Many of the attending doctors shared their personal experience of using Ivermectin successfully with very good results in their patients. The group, at the end of the discussion, proposed the following consensus statement:

"Ivermectin in the dose of 12 mg BD alone or in combination with other therapy for 5 to 7 days may be considered as safe therapeutic option for mild moderate or severe cases of COVID-19 infection. It is cost effective especially when the other drugs are very costly & not easily available".

However, the group strongly feels the urgent need for a well-designed randomized control trial & proposes judicious use of Ivermectin for COVID-19 treatment.

Dr. Borody's Ivermectin Proposal

News Corp media is the latest major media to report on the proposal of Professor Thomas Borody. This gastroenterologist received credit for developing the world's first peptic ulcers cure, saving many

lives in the process. What is his proposal? Make Ivermectin available for at least those economically disadvantaged individuals–without health care access (vulnerable people)–infected with COVID-19 as the drug in real-world usage has evidenced safety and efficacy in an endeavor to reduce the severity and duration of the novel coronavirus. Professor Borody stepped up to publicly declare this need despite a great majority of health authorities that do not think much on this topic. A few clinical trials have been completed (Bangladesh and Iraq), but because they have been on the smaller scale and TrialSite suspects (and this is just a speculation), because they originate out of low-and middle-income countries (LMICs) health regulators and research elites in richer countries are not paying attention. A real-world, observational off label initiative was deemed successful in Broward County U.S., but no medical journals are willing to consider a review of the findings. Borody broadcasted his concerns due to the complete lack of intellectual curiosity exhibited by a majority of the world's leading research agencies and health authorities (TrialSite, 2020).

In the meantime, Shannon Molloy from News Australia was given the green light to write about Ivermectin. TrialSite emphasizes this because a good many highly respected journalists working for major media will not, at least up until this point, benefit from such a decision. The Sydney-based doctor, Borody, now urges health authorities to consider an Ivermectin plan for at least A) low-and middle-income countries and B) the underdeveloped areas within developed countries (TrialSite, 2020).

Molloy reports that Borody believes the "answer to Australia's COVID-19 crisis" is what was termed the Australian combination of **Ivermectin, Doxycycline, and Zinc**. Borody, a well-established and prominent figure suggests at least in Australia: A) these medicines are already approved by authorities and proven safe and B) they do not need to go through any more preclinical research, or for that matter clinical trials unless they are to be combined in a capsule (TrialSite, 2020).

Dr. Borody is the Study Director of a Clinical Trial of Combination Therapy to Treat COVID-19 Infection. Patients in this trial will undergo treatment for 10 days with either a combination of therapies or placebo. They will then be followed for 6 months. The intervention therapy is: Ivermectin, Doxycycline Hcl, Zinc, Vitamin D3, Vitamin C.

Prophylactic Protocol with Ivermectin for Exposed Persons

Aguirre and Trujillo (2020) explain that Pre-exposure Prophylaxis (PrEP) consists of people at high risk of contracting COVID-19 taking medications periodically to prevent the virus from establishing in the mucosa and spreading through the body. When taken weekly or every 2 weeks, they have observed that it has a high effectiveness in preventing contracting COVID-19. PrEP becomes less effective when it is taken every 30 to 45 days. In people who have been using PrEP, Ivermectin reduces the risk of contracting the virus by approximately 99% when taken weekly, and by 94% if taken every 2 weeks (every 14 days). In people who are not exposed to places with High Viral Load it could be justified to give doses every 14 days, since in them PrEP would reduce the risk of contracting the virus by 97% if taken every 14 days, and it is reduced by approximately 89% when taken monthly.

Aguirre and Trujillo (2020) has proposed the following protocol for prophylaxis with Ivermectin:

Dose= 0.2 mg. per kg of weight. 2nd dose in 1 week. Then repeat dose every 2 weeks.
People in places in which they are exposed to high viral load (hospitals, markets, terminals and the like) and their "contacts" which are males >50 years and women >75 years repeat the dose every week (7 days).

Shouman (2020) proposed the use of Ivermectin as a Prophylactic Option in Asymptomatic Family Close Contacts with Patients of COVID-19, in a clinical trial. He is evaluating two doses (12 mg) 72 hours apart in 340 participants.

Action Mechanism of Ivermectin

Gupta, Sahoo and Singh (2020) have reported that in recent times, the antiviral function of Ivermectin has been discovered, which appears to be intriguing. Already its effectiveness against certain flavivirus (dengue fever, Japanese encephalitis and tick-borne encephalitis virus) and chikungunya virus has been demonstrated in vitro. Since then the same activity has been assessed in numerous other viral infections. Off lately its potency has been recognized in eliminating coronavirus in vitro. The exact mechanism to which this effect can be attributed to is yet to be validated, but the speculated method is inhibition of importin α/β1 mediated transport of viral proteins in and out of the nucleus. Importins, a type of karyopherins, exemplify a major class of soluble transport receptors which are involved in nucleo-cytoplasmic transit of various substrates. The speculated inhibitory action of Ivermectin on

importin α/β1 mediated transport system explains the role of Ivermectin in eliminating Covid-19 (Mastrangelo et al, 2012; Varghese et al, 2016; Tessier et al, 2019; Oka &Yoneda, 2018; in Gupta, Sahoo and Singh, 2020).

In a single in vitro study, the efficacy of Ivermectin against coronavirus has been demonstrated by Caly et al. (2020). The in vitro potency of Ivermectin against Covid-19 virus is a testimony that this drug can be utilized to manage those patients who have been infected with SARS-CoV-2. It seems that if compared with the other pharmacotherapeutic options for the management of Covid-19 infection, Ivermectin may prove to have leverage over them. Furthermore, the treatment regimen with Ivermectin may turn out to be more cost-effective. Considering these merits, it becomes imperative that clinical trials with Ivermectin be conducted (Gupta, Sahoo and Singh, 2020).

International Society for Orthomolecular Medicine (ISOM)

Yanagisawa (2020) is convinced that "Protecting Population Immunity" in a healthy community is the way forward for human beings. During and post-pandemic health management is an important key. By reviewing lifestyle, in addition to optimum diet, exercise, sleep, good mental health, and taking nutrients (vitamin C, vitamin D, zinc, selenium, magnesium, etc.) necessary to prevent viral infection, people will have a good healthy immune system. In this community, COVID-19 infections can be asymptomatic or with mild symptoms. People in this community can protect their weakened older people and those with disease by surrounding them. This is "Protecting Population Immunity". "Protecting Population Immunity" is not only effective against COVID-19 but also pandemics caused by the emergence of new viruses. Moreover, this strategy is realistic, practical, immediate, safe, and inexpensive. The ISOM and related societies and colleagues will promote to make their communities healthier, with the slogan of "Protecting Population Immunity".

The International Society for Orthomolecular Medicine has promoted the following daily protocol:

- Vitamin C: 3 grams or more
- Vitamin D3: 2,000 IU daily
- Zinc: 20 mg daily
- Selenium: 100 mcg daily
- Magnesium: 400 mg daily

Protective Effect of Aspirin on COVID-19 Patients (PEAC)

Cai Yue (2020) has explained that COVID-19 has a high infection rate and mortality, and serious complications such as heart injury that cannot be ignored. Cardiac dysfunction occurs in COVID-19 patients, but the law and mechanism of cardiac dysfunction remains unclear. The occurrence of progressive inflammatory factor storm and coagulation dysfunction in severe and fatal cases of Novel Coronavirus Pneumonia (NCP) points out a new direction for reducing the incidence of severe and critically ill patients, shortening the length of duration in severe and critically ill patients and reducing the incidence of complications of cardiovascular diseases. Aspirin has the triple effects of inhibiting virus replication, anticoagulant and anti-inflammatory, but it has not received attention in the treatment and prevention of NCP. Although Aspirin is not commonly used in the guidelines for the treatment of NCP, it was widely used in the treatment and prevention of a variety of human diseases after its first synthesis in 1898. Subsequently, aspirin has been confirmed to have antiviral effect on multiple levels. Moreover, one study has confirmed that aspirin can inhibit virus replication by inhibiting prostaglandin E2 (PGE2) in macrophages and upregulation of type I interferon production. Subsequently, pharmacological studies have found that aspirin as an anti-inflammatory and analgesic drug by inhibiting cox-oxidase (COX). Under certain conditions, the platelet is the main contributor of innate immune response, studies have found dynamic neutrophil and platelet aggregation in the lung injury model. Cai Yue (2020) suggested an intervention treatment of 100 mg/day of aspirin in a clinical trial.

In summary, the early use of aspirin in COVID-19 patients, which has the effects of inhibiting virus replication, anti-platelet aggregation, anti-inflammatory and anti-lung injury, is expected to reduce the incidence of severe and critical patients, shorten the length of hospital duration and reduce the incidence of cardiovascular complications (Cai Yue, 2020).

Ibuprofen

As fever is one of the most common symptoms of COVID-19, antipyretic medications, including ibuprofen, play an important role in controlling patients' symptoms.

On 14 March 2020, during the emergence of the COVID-19 outbreak, the French Minister of Health published a recommendation to avoid the use of anti-inflammatory medications like ibuprofen or cortisone, claiming it could aggravate infections. Though no reference was provided, the statement

may stem from a report published by the French Agency for the Safety of Health Products, concerning 400 cases of severe infections that were linked temporally to ibuprofen administration. Adding to these concerns, recent in vitro work has supported the hypothesis that pathogenic coronaviruses have a high affinity to the angiotensin converting enzyme 2 (ACE2) receptor, and that ACE2 production as well as the ACE 2 receptor expression, can be increased by ibuprofen.

The public statement prompted a global debate about the safety of ibuprofen as an antipyretic treatment for individuals with confirmed or even suspected COVID-19 during the current pandemic. Several national health agencies worldwide, including the WHO, have responded with official statements emphasizing that no evidence supports these claims. Nevertheless, some authorities, erring on the side of caution while awaiting clinical data, have suggested that paracetamol should be considered the recommended first-line antipyretic, with ibuprofen reserved for individuals who are unable to tolerate paracetamol.

In a recent study, Rinott et al (2020) aimed to evaluate whether ibuprofen administration to individuals with COVID-19 was associated with worse clinical outcomes, compared with paracetamol or no antipyretic. In this retrospective cohort study of 403 individuals with COVID-19 admitted to Shamir Medical Centre in central Israel, Rinott et al (2020) did not observe an increased risk for mortality or the need for respiratory support in patients treated with ibuprofen. Among patients with fever, no excess mortality or need for respiratory support was observed in those who chose to use ibuprofen exclusively. In fact, the need for respiratory support was higher in the paracetamol group with borderline significance. In this cohort of COVID-19 patients, ibuprofen use was not associated with worse clinical outcomes, compared with paracetamol or no antipyretic.

A Note on Artemisia annua

In this section it is suggested to consult the book ¨Artemisia Annua Research: Antiviral Properties¨ by Abreu (2020). Here is the book description:

“There is strong scientific evidence that suggests viruses can be fought with Artemisia annua, especially in the early stages of a disease. In this book, the antiviral qualities of Artemisia annua are illustrated with the presentation of several research studies, showing its pharmacological potential”.

Arnold (2020) is the Principal Investigator of a Clinical Trial in phase II for rapid efficacy and toxicity assessment of multiple therapies immediately after COVID19 positive testing in high-risk individuals. Therapies include stand-alone or combination treatment with Hydroxychloroquine, Azithromycin, Ivermectin, Camostat mesilate, Artemesia annua. The hypothesis of this study is that the addition of agents that inhibit viral entry or replication of SARS-CoV-2 virus replication in will be devoid of additional moderate to severe toxicities, will prevent clinical deterioration, and will improve viral clearance in high risk individuals.

Method: Case Study

This case report was carried out under the medical prescriptions and follow up of Medicine Doctor Ezequiel Jose Castro Ortiz (Treating Physician).

Andreina, my daughter, is a young married woman, 30 years old with an asthmatic condition who lives in Monterrey, Mexico. She works at a State Preparatory Educational Institution. On the 8th day of the onset of symptoms, after testing positive with COVID-19, she took a 1st dose of 18 mg, at around 7 pm. During that day, the symptoms were severe headache, severe fatigue and a severe breathing problem. Next day in the morning she reported that all the symptoms had disappeared. However, on the third day of treatment the symptoms reappeared but in a very mild way until they disappeared almost completely at day 9th of treatment (Table 2).

This patient was classified as: a) Moderate case with asthmatic risk factors and b) With rapid response to treatment (15 hours) / Moderate viral load.

Table 2. Timeline for the symptoms and for the application of the protocol (Year 2020)

Date	Symptoms and Observations
August 01 to August 05	Mild fatigue and mild breathing problem
August 06	Severe headache, severe fatigue and severe breathing problem.
August 07	Severe headache, severe fatigue and severe breathing problem.
August 08	Severe headache, severe fatigue and severe breathing problem. **Tested positive for COVID-19**. **Initiated protocol at 7 pm.**
August 09	Headache disappeared. Fatigue disappeared. Normal breathing.

August 10	Mild headache in the morning and mild headache at night.
August 11	Mild headache in the morning and intensive headache at night. Loss of sense of smell and taste.
August 12	Mild headache in the morning and intensive headache at night. Loss of sense of smell and taste.
August 13	Mild headache in the morning and intensive headache at night. Nasal congestion. Loss of sense of smell and taste.
August 14	Mild headache in the morning and intensive headache at night. Nasal congestion. Loss of sense of smell and taste.
August 15	Mild headache in the morning and mild headache at night. Nasal congestion. Loss of sense of smell and taste.
August 16	Mild headache in the morning and mild headache at night. Nasal congestion disappeared. Loss of sense of smell and taste.
August 17	Most of the symptoms disappeared. Recovered sense of smell and taste by 60%. **The protocol is finished.**
August 21	**Tested negative for COVID-19.** The patient is back to a normal life and work.
August 30	The patient recovered completely the sense of smell and taste

The Protocol

Ivermectin: 18 mg the first day. 12 mg daily the following days, except when the headache was intense the patient was given an extra 12 mg dosage (It occurred for three days). The total treatment was for 10 consecutive days. (Several references and clinical trials).

Ibuprofen: 400 mg every 8 hours for 10 days (Rinott et al, 2020).

Doxycycline: 100 mg every 24 hours for 10 days (Alam et al, 2020)

Aspirin: 100 mg daily for 10 days (Cai Yue, 2020)

Zinc: 50 mg daily for 10 days (Yanagisawa, 2020)

Vitamin D3: 5,000 IU for 10 days (Yanagisawa, 2020)

Vitamin C: 5 grams for 10 days (Yanagisawa, 2020)

Artemisia annua infusion with lemon: Two cups per day (Abreu, 2020; Arnold, 2020)

Final Remarks

Andreina lives with her husband in a separate house from her parents America and Jose Luis (that is me), and her brother Jose Luis Jr. At the beginning of the viral cycle on August 01 (Saturday) all of us spent time together without keeping social distance. On August 6th (Thursday), Andreina was feeling real sick, thus she came to our house so that we could take care of her. At this time, I was suspecting it could be COVID-19. That day, before her arrival, I decided, by my own decision, to take the minimum dose of Ivermectin (12 mg) for four consecutive days. On August 8th (Saturday) Andreina was given the test and then, the next day, we were officially informed that she was positive with COVID-19. She initiated treatment On August 8th (Saturday) after the first test. The very same day, her mother, and her brother initiated a preventive treatment with Ivermectin taking a minimum dose daily for three consecutive days. On August 21, one day before my birthday, Andreina, America and I resulted negatives with the COVID19 test. Andreina presented formation of antibodies and negative for the viral presence. My wife America and I did not showed antibodies in the results of the test. It was like we were never in contact with the virus. Our son did not take the test, but he has never shown any symptoms. Andreina recovered complete sense of smell and taste on August 30th.

It is very important not to follow an Ivermectin Protocol (or any other protocol) without the guidance and prescription of a qualified Medicine Doctor.

References

Abreu, Jose Luis. 2020. Artemisia Annua Research: Antiviral Properties. ASIN: B089SMMJNL Spenta University Mexico (June 7, 2020)

Agam Vora, V.K. Arora, D. Behera, Surya Kant Tripathy. 2020. White paper on Ivermectin as a potential therapy for COVID-19. Indian Journal of Tuberculosis. Volume 67, Issue 3, July 2020, Pages 448-451

Aguirre Chang, Gustavo and Trujillo Figueredo, Aurora Natividad. 2020. COVID-19: Profilaxis Pre-exposición con Ivermectina para Personas Expuestas. DO - 10.13140/RG.2.2.20012.69763 https://www.researchgate.net/publication/343615584_COVID-19_Profilaxis_Pre-exposicion_con_Ivermectina_para_Personas_Expuestas

Aguirre Chang, Gustavo. 2020. Inclusión de La Ivermectina en la Primera Línea de Acción Terapéutica para COVID-19. National University of San Marcos, Lima, Peru. https://www.researchgate.net/

Alexander ND, Bockarie MJ, Kastens WA, et al. Absence of Ivermectin-associated excess deaths. Trans R Soc Trop Med Hyg. 1998;92(3):342.

Aránzazu González-Canga et al. 2010. Safety of Ivermectin: toxicity and adverse reactions in several mammal species. Rev.MVZ Córdoba 15(2):2127-2135, 2010.

Arnold, Susanne. 2020. University of Kentucky. The National Institutes of Health. Novel Agents for Treatment of High-risk COVID-19 Positive Patients. https://clinicaltrials.gov/ct2/show/NCT04374019?term=Ivermectin&cond=COVID19&draw=2&rank=33#studydesc

Awadzi K, Attah SK, Addy ET, et al. The effects of high-dose Ivermectin regimens on Onchocerca volvulus in onchocerciasis patients. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1999;93(2):189-194.

Awadzi K, Opoku NO, Addy ET, et al. The chemotherapy of onchocerciasis. XIX: The clinical and laboratory tolerance of high dose Ivermectin. Trop Med Parasitol. 1995;46(2):131-137.

Badhan R, Zakaria Z, Olafuyi O. The Repurposing of Ivermectin for Malaria: A Prospective Pharmacokinetics-Based Virtual Clinical Trials Assessment of Dosing Regimen Options. Journal of Pharmaceutical Sciences. 2018;107(8):2236-2250.

Cai Yue. 2020. Protective Effect of Aspirin on COVID-19 Patients (PEAC). Xijing Hospital. https://clinicaltrials.gov/ct2/show/NCT04365309

Caly, L., Druce, J., Catton, M., Jans, D. & Wagstaff, K. 2020. The FDA-approved drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Research. Volume 178, June 2020, 104787

Camargo, Antonio. 2020. La Ivermectina: Altas dosis en el tratamiento de infección por SARS-CoV2 (COVID-19): Un caso de resolución molecular. http://www.onkos.pe/category/estudios

Centers for Disease Control and Prevention (CDC). Prescription medication for the treatment of scabies. http://www.cdc.gov/parasites/scabies/health_professionals/meds.html. Accessed May 18, 2020.

Costa JL, Diazgranados JA. Ivermectin for spasticity in spinal-cord injury. Lancet. 1994;343(8899):739.

Del Giudice P, Marty P, Gari-Toussaint M, et al. Ivermectin in elderly patients. Arch Dermatol. 1999;135(3):351-352.

Dhyuti Gupta, Ajaya Kumar Sahoo, Alok Singh. 2020. Letter to the editor Ivermectin: potential candidate for the treatment of Covid-19. The Brazilian Journal of Infectious Diseases

E. Rinott, E. Kozer, Y. Shapira, A. Bar-Haim, and I. Youngster. Ibuprofen use and clinical outcomes in COVID-19 patients. Clin Microbiol Infect. 2020 Sep; 26(9): 1259.e5–1259.e7.

Gieschke R, Fotteler B, Buss N, et al. Relationships Between Exposure to Saquinavir Monotherapy and Antiviral Response in HIV-Positive Patients. Clinical Pharmacokinetics. 1999;37(1):75-86. Table VI.

Gobierno de Mexico. 2020. https://coronavirus.gob.mx/

Gupta, D. et al. Ivermectin: potential candidate for the treatment of COVID19. Braz J Infect Dis. 2020.

Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of Ivermectin in healthy adult subjects. J Clin Pharmacol. 2002;42(10):1122-1133.

Juarez M, Schcolnik-Cabrera A, Dueñas-Gonzalez A. The multitargeted drug Ivermectin: from an antiparasitic agent to a repositioned cancer drug. Am J Cancer Res. 2018;8(2):317-331.

Juliana Cepelowicz Rajter, Michael Sherman, Naaz Fatteh, Fabio Vogel, Jamie Sacks, Jean-Jacques Rajter, 2020. COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv. ICON (Ivermectin in COVID Nineteen) study: Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19. https://www.medrxiv.org/content/10.1101/2020.06.06.20124461v2

Lankas GR, Gordon LR. Toxicology. In: Campbell WC, ed. Ivermectin and Abamectin. New York, NY: Springer New York; 1989:89-112.

Lawrence J, Sodahlon YK, Ogoussan KT, et al. Growth, Challenges, and Solutions over 25 Years of Mectizan and the Impact on Onchocerciasis Control. PLoS Negl Trop Dis. 2015;9(5):e0003507.

Mastrangelo E, Pezzullo M, Burghgraeve TD, et al. Ivermectinia a potent inhibitor of flavivirus replication specifically targeting NS3 helicase activity: new prospects for an old drug. J Antimicrob Chemother. 2012;67: 1884–94.

MT Alam, R Murshed, E Bhiuyan, S Saber, RF Alam, RC Robin. 2020. Journal of Bangladesh College of Physicians and Surgeons Vol. 38, COVID-19 (Supplement Issue), July 2020.

Navarro M, Camprubí D, Requena-Méndez A, et al. Safety of high-dose Ivermectin: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy. 2020;75(4):827-834.

Oka M, Yoneda Y. Importin: functions as a nuclear transport factor and beyond. Proc Jpn Acad Ser B: Phys Bio Sci. 2018; 94:259–74, http://dx.doi.org/10.2183/pjab.94.018

Pharmaceutical-Technology. 2020. Study finds anti-parasitic drug could kill coronavirus in 48 hours. https://www.pharmaceutical-technology.com/news/study-Ivermectin-kills-coronavirus/

Scheim, David. 2020. Ivermectin for COVID-19 Treatment: Clinical Response at Quasi-Threshold Doses Via Hypothesized Alleviation of CD147-Mediated Vascular Occlusion (June 26, 2020). Available at SSRN: https://ssrn.com/abstract=3636557

Scott N. Ivermectin Toxicity. In: Silverstein D, K H, eds. Small animal critical care medicine. St. Louis: Saunders Elsevier; 2008:392-394.

Shen L, Rabi SA, Sedaghat AR, et al. A Critical Subset Model Provides a Conceptual Basis for the High Antiviral Activity of Major HIV Drugs. Science Translational Medicine. 2011;3(91):91ra63. Figure 2

Shouman, Waheed. 2020. Prophylactic Ivermectin in COVID-19 Contacts. Zagazig University. https://clinicaltrials.gov/ct2/show/NCT04422561

Tessier TM, Dodge MJ, et al. Viral appropriation: laying claim to host nuclear transport machinery. Cells. 2019; 8:1–23.

Varghese FS, Kaukinen P, Gläsker S, et al. Discovery of berberine, abamectin and ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Res. 2016; 126:117–24, http://dx.doi.org/10.1016/j.antiviral.2015.12.012.

Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun. 2020: S0889-1591(0820)30357-30353.

Yanagisawa, Atsuo. 2020. Editorial: Protecting Population Immunity. Journal of Orthomolecular Medicine. volume 35, number 1. June 2020.

Dr. Jose Luis Abreu is an independent researcher in the field of Phytochemistry & Pharmacognosy. He is also a Research-Professor in another field of science at FACPYA-Universidad Autónoma de Nuevo León and Spenta University Mexico. This case study was funded with his own personal resources. There is not conflict of interest in this publication.

Email: spentamexico@gmail.com

Dr. Ezequiel Jose Castro Ortiz was the consulted Physician during the application of the protocol (Treating Physician)

Email: drecastro@live.com
