Research protocol for reproposing of ivermectin in the treatment of mild stage patients with corona virus disease (COVID-19) in Primary Health Care Centers

Study: Protocol for reproposing of ivermectin in the treatment of mild stage patients with COVID-19

Conceptual description: Treatment in mild stages of COVID-19 disease (ambulatory patients) for diminution of viral load and for stop or reverse the progression to develop moderate or severe stages of the disease.

Protocol Date: October 2020

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Place of development: Centros B.A.F.S* – Primary Health Care Centers (C.A.P.S. and Policlinics)
*B.A.F.S. Center where is applied the protocol designed by de Ministry of Public Health for active search of feverish and symptomatic patients COVID-19

Management Authority: Health Research Directorate of Ministry of Public Health (SIPROSA). Virgen de bMerced st. 189 – 1th floor. Postal Code: 4000 – San Miguel de Tucumán.

Protocol summary

In Tucumán, at October 2020, the situation of pandemic is in its fase of community transmission with a prevalence rate of 2750/100.000 people for the last SE of the month. This presentation is proposing an observational study for applied ivermectin as a treatment in mild stages of COVID-196 disease (mild outpatients) for diminution of viral load and for stop or reverse the progression to develop moderate or severe stages of the disease

Total number of voluntary patients enrolled, included the outpatient population with mild stages of COVID-19, will be attended by health personal of Primary Health Care Centers of SIPROSA. The inclusion criteria shall correspond to patients with COVID-19 with symptoms classified for mild stage of the disease, male and female, from the age group considered active occupationally (16-60 years) with or without preexistent pathologies.

After informing participants in detail about the purpose of study, informed consent will be required. Weekly telephone contacts will be established to evaluate the clinical development of patients and his state of health, additionally to the clinical examination. This will make it possible to act on any warning signs.

Objective: To evaluate the use of ivermectin in patients with COVID-19 disease in mild stages, for diminution of viral load and for stop or reverse the progression to develop moderate or severe stages of the disease.

Population: Will be constituted by individuals with positive COVID-19 diagnosis by RT-PCR test with symptomatology, which meets the inclusion criteria. Patients will be classified depending on their symptomatology according to the 10-point clinical progression scale recommended by the World Health Organization.

Eligibility criteria:

Inclusion

1. > 18 years of either sex
2. Outpatients infected with SARSCoV-2 confirmed by RT-PCR test
3. Female in fertile age with negative pregnant test.
4. Which meet symptoms of mild cases definition

MINOR CRITERIA	Mild Stage
Fever < 38,5° Isolated diarrheic episodes. Hyposmia o hypogeusia. Mild desaturation (between 96% and 93%). Dyspnea. Polyarthralgia, persistent headache. Abdominal pain. Erythema, nonspecific rash	Presence of 2 o + Symptoms

Exclusion:

1. Hypersensitivity or known allergy to ivermectin
2. Pregnant or lactate
3. Kids or adolescent < 18 years
4. Patients with neurological pathology
5. Patients with renal insufficiency
6. Patients with hepatic insufficiency
7. Weight < 40 kg.
8. Patients with concomitant use of drugs that act on receptors. GABA, barbiturates, benzodiazepines
9. Patients which doesn't completed/signed an informed consent
10. Patients who took ivermectin previously (30 days) or another protocol treatment for mild COVID-19

Intervention: 4 doses of 24 mg of ivermectin divided into four doses every 7 days. This consists of 4 tablets 6 mg each to be administered in patients, it is recommended with 2 (two) hours of fasting before and 2 (two) hours of fasting (without food intake) after taking the drug. Post-intervention control consists of a remote monitoring every 7 days for 14 days after taking.

Total Duration of the Study: Intervention Period Visit 1 / week 1 enrollment and delivery of doses for the first 14 days. Visit 2: delivery of doses and collection of clinical record; Post Intervention Follow-up Period: 15 days. If the patient presents symptoms of progression or worsening of the disease, he will automatically be assisted by the medical staff of the effector centers, complying with the care regulations and recommendations that are available in the Ministry of Health for this purpose.

Theoretical foundation

At the end of December 2019, the incidence of atypical pneumonia of unknown cause was reported in Wuhan, China. Since then a successive series of spreads have generated on a global scale what would be the COVID-19 pandemic, which represents the largest global public health crisis of this generation's, and potentially since the 1918 pandemic influenza outbreak.

PCR (Polymerase Chain Reaction) studies found a corona virus, which was > 85% similar to a SARS-CoV of bats (bat-SL-CoVZC45). This species, initially named nCOV19 and later renamed SARS-CoV-2 due to its structural similarity to the homonymous species quickly spread. The first cases were slow to be made public - inexplicable delays, in terms of international health cooperation - which meant an irrecoverable loss of time in containing the epidemic. The early association identified between SARS-CoV with SARS-CoV-2 was supported by analyzes made later on the protein S, that characterizes these two viruses, where an important similarity in these transmembrane structures was made clear. The only significantly different portion is a furin-binding domain in the SARS-CoV-2 protein S, which has been speculated, could expand the tropism or increase transmission of the virus, compared to SARS-CoV of 2003. On the other hand, one of the most conserved portions of the protein is the receptor-binding domain (RBD), which has a similar affinity to angiotensin-converting enzyme type 2 (ACE2) in comparison with SARS-CoV.

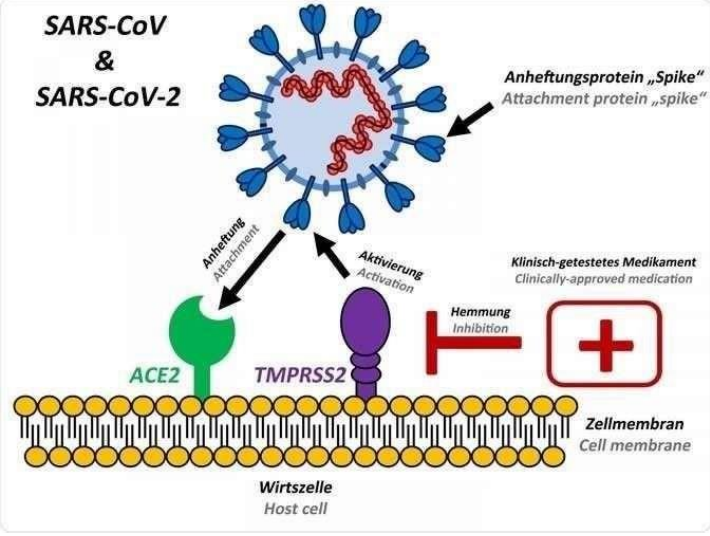
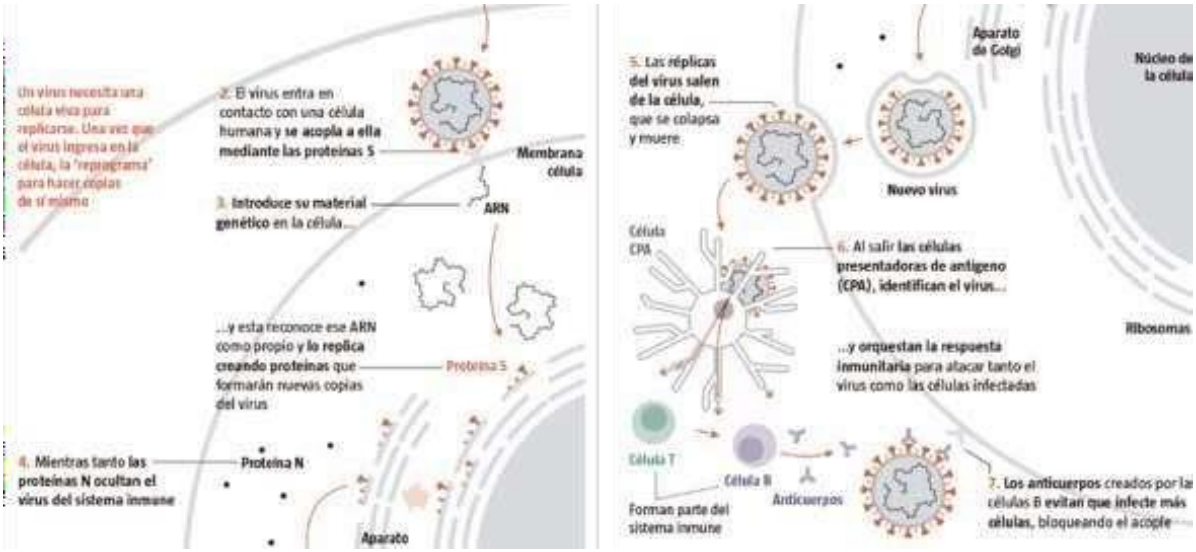


FIG. 1: STRUCTURE OF COVID 1 SARS-CoV2 is an enveloped virus (100-160 nm) that contains RNA Single-stranded attached to a nucleoprotein (protein N), within a capsid composed of matrix proteins (protein M). The envelope possesses spine-shaped glycoproteins (protein S) that bind to the cellular receptor ACE2 in humans and generate neutralizing antibodies.

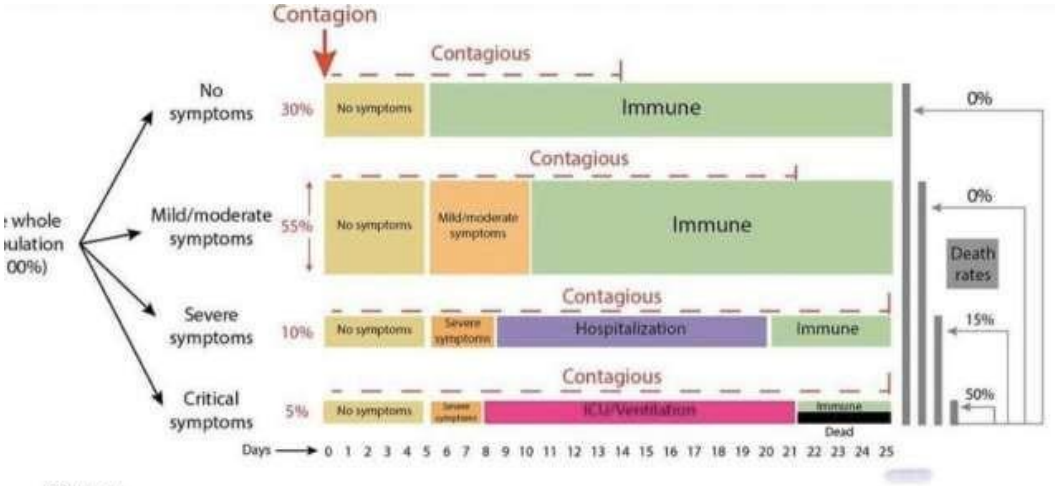
FIG. 2: VIRAL ACCESS AND ACTION MECHANISMS



This functional receptor is found in tissues, including lung alveolar epithelium, arterial and venous endothelium, smooth muscle, renal tubular epithelium, and small intestine epithelium, largely explaining the clinical presentation of patients with COVID-19. The incubation period of the virus has been calculated at 5.1 days (95% CI, 4.5 to 5.8 days), and it is said that 97.5% of patients will have symptoms at 11 days (95% CI 8.2 to 15.6 days). A mortality of 5.7% has been calculated. The average COVID patient presents with fever (78%), cough (60-79%), and myalgia or fatigue (35.8-44%); 55% develop dyspnea, which appears on average 8 days after the onset of symptoms.

Evidence suggests that a subset of patients with severe forms of COVID 19 may have a syndrome known as a cytokine storm. A cytokine profile that resembles SHLH is associated with the severity of COVID-19 disease, characterized by an increase in interleukin (IL) -2, IL-7, granulocyte colony stimulating factor, protein 10 inducible by interferon-γ, monocyte chemo-attractant protein 1, macrophage inflammatory protein 1 -α, and tumor necrosis factor-α. Mortality predictors from a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin (mean 1297.6 mg / ml in non-survivors vs. 614.0 mg / ml in survivors; $p < 0.001$) and IL-6 ($p < 0.0001$), suggesting that mortality could be due to viral hyper inflammation. Nevertheless, cases have been reported where tissue and organ involvement was found whose concentration of ECA2 receptors is very dissimilar (myocardium, brain). In all of them, the common denominator was small vessel thrombosis, as observed in entities such as catastrophic antiphospholipid Syndrome (SAC) and Disseminated Intravascular Coagulation (DIC).

FIG. 3: CLINICAL EVOLUTION AND SPREAD PERIODS



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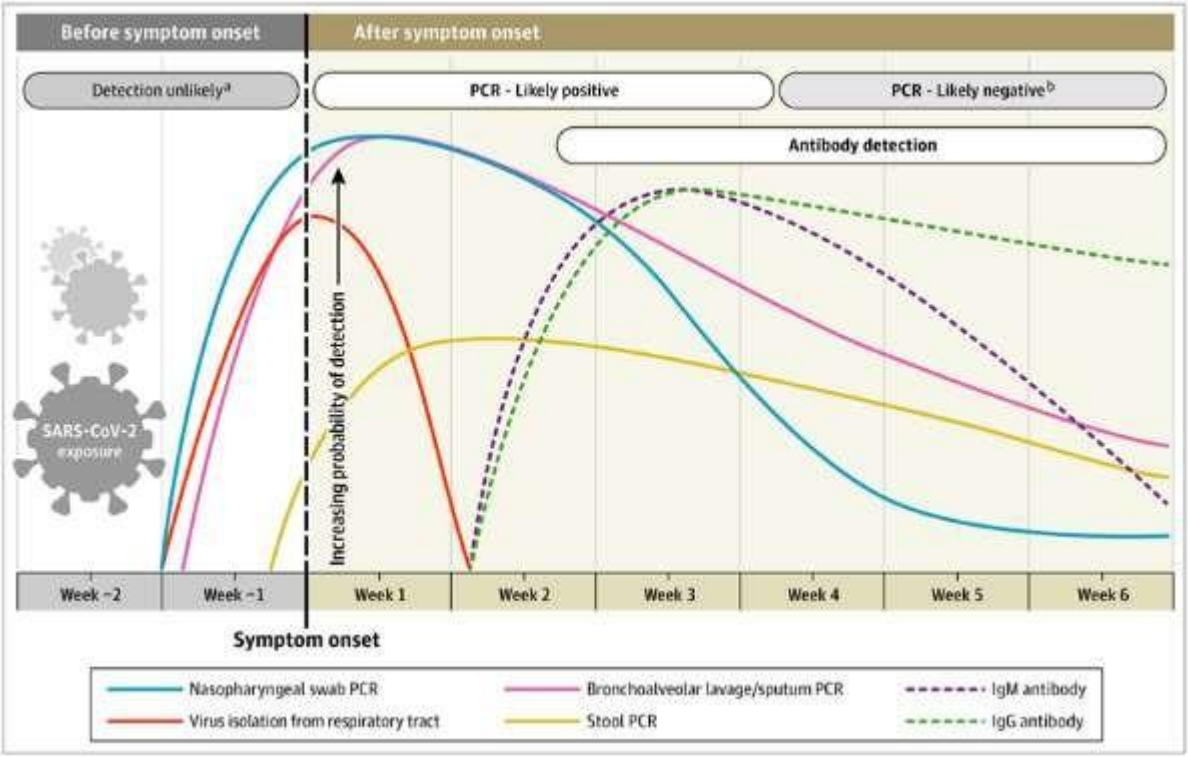
3. Viral dynamics in mild and severe cases of Covid-19. Yang Liu et al. The Lancet, March 19, 2020.

FIG. 4: GENERAL CHARACTERISTICS OF THE IMMUNE RESPONSE MECHANISM



Source: Nandini Sethuraman, Sundararaj Stanleyraj Jeremiah and AkihideRyo. Interpreting. Diagnostic Tests for SARS- CoV-2 PMID: 32374370 DOI: 10.1001 / jama.2020.8259 JAMA. 2020 Jun 9; 323 (22): 2249-2251.

Drug repositioning: Since the beginning of the pandemic despite drastic containment measures, the spread of this virus is threatening to bring down health systems around the world. For this reason, international health authorities have focused on the rapid diagnosis and isolation of patients, as well as on the search for therapies capable of counteracting the most serious effects of the disease, which constitute approximately 15% of cases. However, the lack of a specific pharmacological treatment makes it difficult to contain the pandemic. As the number of infected increases exponentially, the development of vaccines and new antiviral therapies becomes urgent. Unfortunately, these developments are outside the current timeline to contain the pandemic. In this context, it is imperative to reposition existing drugs on the market with established safety profiles that are implemented on another therapeutic indication, based on solid preclinical studies. This pragmatic strategy has been successful for many drugs and can be a key tool in emergency situations such as the current one. Considering that to date there are no specific therapies approved by the United States Food and Drug Administration (FDA) for severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), different repositionable drugs are being studied in clinical trials and compassionate use protocols based on in vitro activity (against SARS-CoV-2 or related viruses) and / or on the limited clinical experience available.

In relation to ivermectin there are many studies in progress and some completed. Either in prevention, the IVERCAR study, which evaluates the effect of the use of Ivermectin associated with iota-carrageenan in repeated doses in the oral cavity, which would reduce the probability of the appearance or progress of clinical manifestations and the appearance of severe disease, and would decrease viral load and time of virus shedding in the preclinical phase. And the IDEA protocol, which combines the administration of four drugs according to the severity of the same based on the appearance of signs and symptoms that determine criteria, to regulate the administration of the same (Ivermectin, dexamethasone, enoxaparin and acetylsalicylic acid).

Mechanisms of action of ivermectin

Ivermectin is a broad spectrum anti parasitic agent approved by the FDA (González Canga et al., 2008) that in recent years, along with other groups, has shown antiviral activity against a wide range of viruses (Gotz et al., 2016; Lundberg et al., 2013; Tay et al., 2013; Wagstaffet al., 2012) in vitro. Originally identified as an inhibitor of the interaction between the IN (IN) protein of the human immunodeficiency virus-1 (HIV-1) and the imported heterodimer (IMP) α / β1, responsible for the nuclear import of IN (Wagstaffet al., 2011), ivermectin has been confirmed to inhibit nuclear import of IN and replication of HIV-1 (Wagstaffet al., 2012). Other actions of ivermectin have been reported (Mastrangelo et al., 2012), but ivermectin has been shown to inhibit nuclear import from the host (p. g., (Kosyna et al., 2015; van der Watt et al., 2016)) and viral proteins, including the non-structural protein 5 of the simian virus SV40 (T-ag) and the dengue virus (DENV) (Wagstaffet al., 2012, Wagstaffet al., 2011). It is important to note that it has been shown to limit infection by RNA viruses such as DENV 1-4 (Tayet al., 2013), West Nile virus (Yang et al., 2020), Venezuelan echinencephalitis virus (VEEV) (Lundberg et al., 2013) and influenza (Gotzet al., 2016), and this broad spectrum activity is believed to be due to the action of many different RNA viruses on IMPα / β1 during infection (Caly et al., 2012; Jans et al., 2019).

Ivermectin has also been shown to be effective against DNA pseudo rabies virus (PRV), both in vitro and in vivo, and ivermectin treatment has been shown to increase survival in PRV-infected mice (Lv et al., 2018). The efficacy of ivermectin against Zika virus (ZIKV) was observed in mice, but the authors acknowledged that study limitations warranted reassessment of ivermectin's activity against ZIKV (Ketkar et al., 2019). Finally, ivermectin was the focus of a 2014-2017 phase III clinical trial in Thailand against DENV virus infection, where a single daily oral dose was found to be safe and lead to a significant reduction in serum levels of the viral protein NS1.

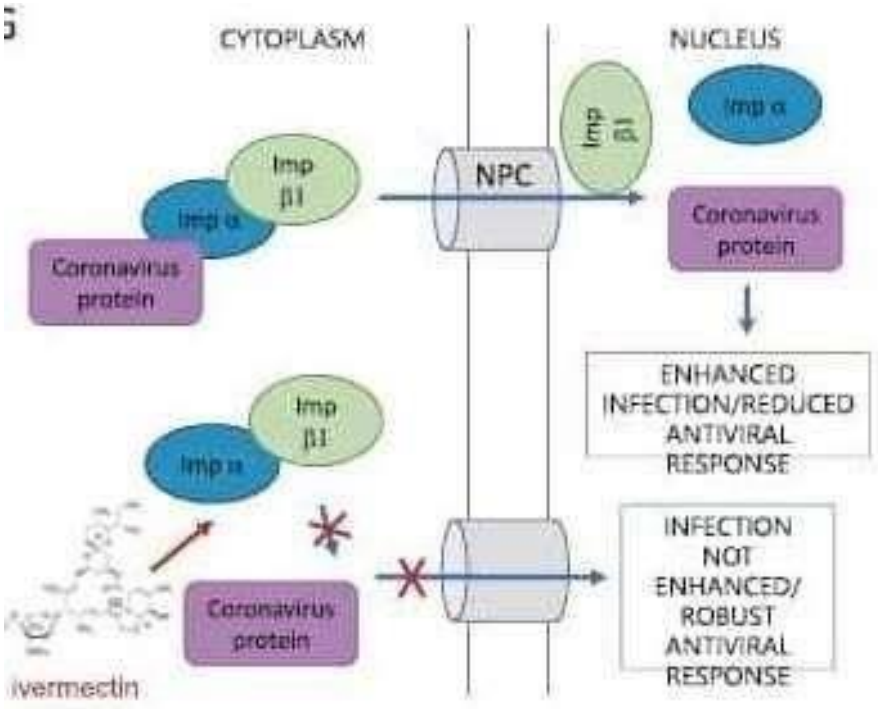
Studies on SARS-CoV proteins have revealed a possible role of IMPα / β1 during infection in the signal-dependent nucleocytoplasmatic closure of the SARS-CoV nucleocapsid protein (Rowland et al., 2005; Timani et al., 2005; Wulan et al., 2015), which can affect host cell division (Hiscox et al., 2001; Wurm et al., 2001). Furthermore, the accessory protein of SARS-CoV, the ORF6 protein, has been shown to antagonize the antiviral activity of the transcription factor STAT1 by sequestering IMPα / β1 in the ER / rough Golgi membrane (Frieman et al., 2007). Taken together, these reports suggest that the nuclear transport inhibitory activity of ivermectin may be effective against SARS-CoV-2.

Ivermectin for extended use in mild patients with Covid 19

To test the antiviral activity of ivermectin against SARS-CoV-2, Vero / hSLAM cells were infected with isolated SARS-CoV-2 Australia / VIC01 / 2020 with a MOI of 0.1 for 2 h, followed by the addition of 5µM ivermectin. The supernatant and cell pellets were harvested on days 0-3 and analyzed by RT-PCR for SARS-CoV-2 RNA replication.

In summary, on the COVID-19 virus, demonstrated studies indicate that ivermectin would have two types of action: extra and intracellular action. The extracellular action is through interaction with cavities or ionophore channels present in the sarcolemma of the cell membrane that electrolytically trap the corona of the virus capsid and prevent access to the cell. In the intracellular mechanism, it is described that it is carried out by means of a destabilization of the heterodimer complex IMPORTIN (IMPA alpha / b1), a co transporter that would carry the virus to the nucleus. When destabilized, the entry of the virus to the nucleus is blocked and thus prevents viral replication. We propose the use of Ivermectin among one of the main pharmacological options whose repositioning was proposed for the therapeutic intervention of SARS-CoV-2.

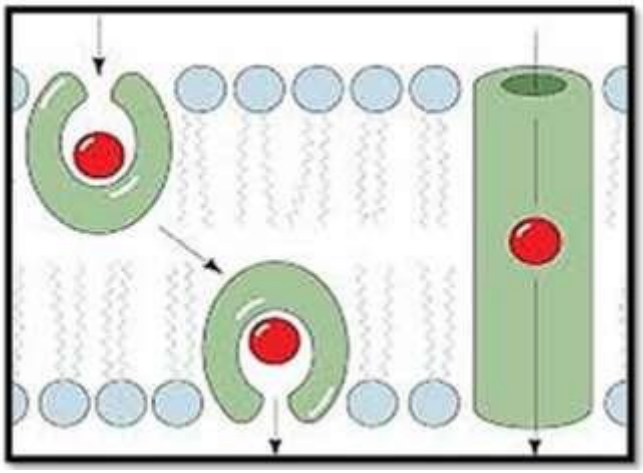
FIG. 5: Ivermectin intracytoplasmic mechanism of action to inhibit replication and decrease viral load



Source Carvallo et al. 2020 Available at https: //www.cadenanueve.com/wp-content / uploads / 2020/08 / PROPOSAL-TERAP% C3% 89UTICA-FRENTE-AL-COVID-19.pdf

Fig. 5 shows a scheme of the antiviral action proposed by ivermectin on the corona virus. IMPα / β1 binds to the corona virus load protein in the cytoplasm (top) and moves it through the nuclear pore complex (NPC) to the nucleus where the complex breaks down and the viral load can reduce the cell's antiviral response host, which leads to further infection. Ivermectin binds and destabilizes the Impα / β1 heterodimer, thus preventing it from binding to the viral protein (background) and preventing it from entering the nucleus. These likely results in a reduction in the inhibition of antiviral responses, leading to a normal and more efficient antiviral response.

FIG. 6: EXTRACELLULAR MECHANISM BY IONOPHOR FORMATION AT THE LEVEL OF THE LIPID CAPSID OF COVID 19



Recently, another mechanism of action has been proposed (Fig 6), as an ionophore agent. Ionophores have many oxygen atoms internally, and are essential for binding cations and transporting them through phospholipids bilayers (cell membranes; phospholipids capsid of the virus). As a consequence, they would determine an ionic imbalance between the external and internal environment, with the consequent osmotic lysis.

In this context, our health system considered the study of the repositioning of ivermectin to be strategic as a strategy to reduce the viral load and stop and / or reverse the progression to developing moderate or severe stages of Covid 19 disease since: a) it is a safe drug, b) available in our setting c) with preclinical evidence of prophylactic capacity and d) antecedents in other health systems of the world of its use both preventively and in empirical treatment.

Clinical studies justifying repositioning in COVID 19

The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and ability to produce high-quality evidence even in the midst of a pandemic. The therapies have not been shown to be effective to date. Based on preclinical evidence and safety profiles, some studies (IVERCAR, IDEA) have proposed the use of Ivermectin, alone and / or in combination with other drugs, to cover all phases of the pandemic, from prophylaxis to immunization, through the treatment of ongoing cases. It should be noted that, in all of them, the current ANMAT authorizations, and each and every one of the drugs used have the approval of Public Health of the Argentine Nation, appearing for decades in the national pharmacopoeia.

Pharmacodynamics: Ivermectin is a member of the avermectin class of broad spectrum ant parasitic agents that possess a single mode of action. Compounds of the class bind selectively and with a marked affinity for chloride ion channels generated by glutamate. This generates an increase in the permeability of the cell membrane towards chloride ions with hyper polarization of the cell. Used as an ant parasitic, this results in paralysis and death. Compounds in this class also interact with other ligand-generated chloride channels, such as those generated by the neurotransmitter gamma amino butyric acid

(GABA). The selective activity of compounds of this class is attributed to the fact that some mammals do not have chloride channels generated by glutamate and avermectins have a low affinity for chloride channels generated by ligands in mammals. Furthermore, Ivermectin does not easily cross the blood-brain barrier in humans. Ivermectin stimulates the release of the inhibitory neurotransmitter, gamma-amino butyric acid (GABA), from presynaptic nerve endings. Ivermectin does not penetrate the central nervous system of mammals, and therefore does not interfere in mammals with GABA-dependent neurotransmission. In adult patients, a single dose reduces the number of skin microfilaria to undetectable rates within a few days after a single dose.

Security for treatment in Humans: In our country a multicenter study has been carried out in 200 patients with scabies. The study was double-blind, randomizing, crossover, with Securo® orally compared with lindane topical solution. The treatments were carried out on days 1 and 15, with evolution controls on days 15 and 29. The results showed cures that ranged from 51.39% (15 days) to 79.17% (29 days). Laboratory tests did not show any changes or differences between the two treatments.

Side effects Side effects were few, mild, and transitory. In different countries of Europe and America, various clinical trials were carried out with ivermectin in scabies. The extensive bibliography allows to observe: the utility of Ivermectin in the therapy of human scabies. Good clinical and laboratory tolerance. The improvement of the symptoms and clinical signs of affected patients. Its comfortable and simple dosage. In the trials it was found that Ivermectin had no adverse effects, personality alterations, or systemic disorders after 4 weeks of treatment, the patients maintaining their good general condition at 6 months.

Some authors showed that Ivermectin can also be used: In elderly patients. In the treatment of endemic scabies. In immune compromised patients, in whom topical treatments for scabies may be difficult, with risk of failure. In patients with forms of scabies that do not respond to conventional therapy

Pharmacokinetics: The tablets contain a mixture of at least 80% of 22, 23-dihydroavermectin B1a, and 20% or less of 22, 23-dihydroavermectin B1b. With single oral doses of 24 mg (the one proposed in this study) of Ivermectin administered as tablets, the mean peak plasma concentration of the main compound (H2B1a) was 46.6 (+ 21.9) measured 4 hours after the administration of the product. Plasma concentration increases with increasing dose in a globally proportional manner. Ivermectin is metabolized in the human body and Ivermectin and its metabolites are almost exclusively eliminated in the faces for about 12 days after less than 1% of the administered dose is excreted in the urine. The plasma half-life of Ivermectin is around 12 hours and that of the metabolites.

Contraindications: Hypersensitivity to some of the components of this medicine. For the age group of this protocol there are none. In pregnancy and lactation, the prescription of Ivermectin is not recommended; therefore these groups do NOT enter the inclusion criteria

Collateral and secondary actions: In most cases, the side effects are mild and transient. And it is generally due to the effect of the residues of the parasites destroyed by the action of the drug.

TYPE AND DESIGN OF STUDY

- Extended access protocol, under treatment of a new indication for Ivermectin

Outcome primary

1- Decrease the number of subjects with mild symptoms and reverse symptoms by lowering viral load.

2- Avoid progression of the disease to more delicate moderate or severe states until the end of the study.

Secondary Outcomes

1- Reduce infection rate

2- Avoid overload and demand for healthcare in the healthcare system and optimize HR in the healthcare system

3- Decrease hospitalization rate for COVID-19

Procedures:

Visit 1:

1- Informed Consent signing.
2- Review of Inclusion and Exclusion Criteria
3- Filling of the clinical file for data loading and a history record of comorbidities in the clinical history.
4- Delivery of treatment 8 comp for 1st and 2nd week

Visit 2: at the 3rd week for delivery of Treatment 8 comp for 3rd and 4th week

Controls by remote monitoring in the intermediate weeks Week 2 and 4 Post intervention. Control contact or report on day 14 to review symptoms.

Unscheduled Visit:

If the subject presents suspicious symptoms of an increase in the stage of infection by Covid-19, it will be evaluated by the health team, with the standard care recommended for infection and subject to the proposed treatment for each case according to severity

1- Clinical examination
2- Adverse event evaluation
3- Nasopharyngeal swab sample
4- Optional sample for antibody Dosage IgM and IgG specific for SARS-CoV-2 at day 14 of follow-up.

INFORMED CONSENT

Following international ethical guidelines. For health-related research with human beings (Geneva 2016) prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), the informed consent process will be carried out: Consent written. Two originals will be signed and one will remain in the Health Emergencies Directorate, for legal guardianship and another will be for the participant. The data will be kept confidential and the subject may withdraw from the study at any time.

Care and monitoring of the individual in the study

At all times, the medical team responsible for this study is responsible for duly informing the participants of the drug's contraindications as well as any alarm signal that implies a relationship with the development of symptoms expected from exposure to COVID-19. Therefore, if the team decides that a deviation from the randomized treatment arm is definitely necessary, this must be adhered to.

DATA SECURITY AND PUBLICATION

Patient information will be encrypted. Analysts will use only anonymous data with no identifiable patient details in postings.

LOCAL REGULATIONS / HELSINKI STATEMENT

The researcher will ensure that this study is carried out in full compliance with the principles of the "Declaration of Helsinki" and with the laws and regulations of our country. The study will be evaluated by the Ethics Committee belonging to the Health Research Directorate of the Ministry of Health of the Province of Tucumán and by ANMAT.

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