INCLUSION OF IVERMECTIN IN THE FIRST LINE OF THERAPEUTIC ACTION FOR COVID-19.

A very significant decrease in Mortality Rate reported with its use.

Aguirre Chang, Gustavo A. Research Gate. May 2, 2020.

English translation copy edited by Madeline Oh

doi: http://dx.doi.org/10.13140/RG.2.2.26424.57600/2

SUMMARY

Current evidence until April 30, 2020 regarding the use of Ivermectin in COVID-19 is reviewed.
A case series report is also made of 7 patients treated locally to date.
A study made available online on April 3, 2020 in the Journal of Antiviral Research found that in vitro, a single dose of Ivermectin reduced SARS-CoV-2 by 99.8% after 48 hours. Subsequently, on April 19, 2020, a study was made available on the SSRN website. This study, which included participants from 169 hospitals around the world, evaluated 704 patients treated with Ivermectin and compared them with their corresponding 704 controls. The result of the study demonstrated that the Mortality Rate in patients who took Ivermectin was 6.1 times lower than that of patients who did not take Ivermectin (1.4 vs 8.5%).
In addition, in the Dominican Republic, the Pulmonologist Johnny Tavares C. reported that he had treated 247 patients with Ivermectin and a favorable response was observed in all cases, and there were no fatalities.
Similarly, although there had not been many documented cases locally to date, it is evident that the use of Ivermectin results in very significant decrease in the Fatality Rate. It has also been observed that in 100% of the cases treated with Ivermectin, there was improvement in the disease and resolution of fever was seen within 48 hours of starting the treatment.
A New Therapeutic Scheme is presented here as it relates to Severity of disease and the Response to Treatment. This scheme has been developed based on the experience of patients treated locally.
In the final section, a Risk-Benefit analysis on the use of Ivermectin is performed with the Conclusion that, since there is practically no risk to its use, it is recommended to formalize its inclusion as first line therapeutic for COVID-19.
Finally, Recommendations are given related to its supply in Healthcare Facilities throughout the country.

Faced with the current COVID-19 Pandemic, it is necessary to disseminate scientific evidence and clinical experiences that we accumulate every day. Based on these, our Therapeutic Plans and Schemes must be updated.

THERAPEUTIC PLAN FOR COVID-19

Results of Autopsies in patients with COVID-19 have demonstrated Diffuse Alveolar Damage (DAD) and hyaline membranes in the alveoli of lungs, both of which are characteristic findings of Severe Acute Respiratory Syndrome (SARS). However, evidence has also shown greater degree of micro and macrothrombosis, as well as endothelitis in multiple organs and systems, compared to what was found in the Pathological Anatomy studies of cases with SARS Cov-1. This has allowed us to attain better knowledge of the Physiopathological Stages of Infection by SARS Cov-2, establishing a Therapeutic Plan with 3 main lines of action (see Table 1 and Annex Tables).

TABLE 1. THERAPEUTIC PLAN FOR COVID-19

3 LINES OF ACTION OF THE THERAPEUTIC PLAN
1) REDUCE THE VIRAL LOAD AND REPLICATION.
2) REDUCE THROMBOPHILIA RELATED TO ENDOTHELLITIS, PLATELET HYPERACTIVITY AND MICROVESICLE RELEASE.
3) TREAT NUTRIENT DEFICIENCY, OXIDATIVE STRESS AND INMUNE HYPERRESPONSE.

The First Line of Therapeutic Action for COVID-19 is aimed at reducing the Viral Load and Replication, with emphasis on early treatment as being crucial at this level. The evidence to date mentions several therapeutic alternatives. In this document, we will discuss Ivermectin, due to the important impact that we have observed in reducing the Fatality Rate and the need for Mechanical Ventilation (MV).

BACKGROUND AND SAFETY OF THE USE OF IVERMECTIN

Ivermectin is an antiparasitic considered by the WHO as an essential medicine, approved by the FDA of the USA, and widely used in humans worldwide for almost 40 years. Until 2008, about 2 billion tablets had been administered to more than 68 million people in Africa, Latin America and Yemen, with which Onchocerciasis had been eradicated. The drug was considered by the WHO in 2009 as a triumph of humanity in the face of adversity. It is a drug for which there is extensive knowledge of its use in humans. It is not an experimental drug, it is free of patents, easily available, and with Good safety profile. It is also very well tolerated at the usual dose of 200 mcg per kilogram of weight (0.2 mg / kg) and has had no significant side effects, even when given in much higher doses than the usual dose (Ref. 1,2,3).
In summary, we have data that this is a drug for which there is already a lot of experience in its use, that no toxicity has been reported in the millions of treatments already carried out and that it can be given safely even at doses well above the usual dose (Ref. 1 to 7).

ANTIVIRAL ACTIVITY OF IVERMECTIN

Several studies have shown that Ivermectin has a broad spectrum antiviral activity. In vitro, it has been found to have an effect against HIV-1 and Dengue (8). According to published studies, Ivermectin can dissociate the preformed IMPα / β1 heterodimer, responsible for the nuclear transport of viral protein loads (9). The nuclear transport of viral proteins is essential for its replication cycle and inhibition of the host's antiviral response. Therefore, action at this nuclear transport process may be a viable therapeutic approach against RNA viruses (8,10,11).

REDUCTION OF VIRAL REPLICATION OF SARS COV-2 WITH IVERMECTIN

The first study on the effect of Ivermectin on COVID-19 had been directed by Kylie Wagstaff of the Biomedicine Discovery Institute (BDI) at Monash University in Melbourne, Australia. This study, published by Leon Caly (12), was made available online on April 3, 2020 as a preliminary or preprint version on the Antiviral Research journal website. The study, performed on vitro in cell cultures, found that a single 5 mM dose of Ivermectin, given 2 hours after infection with SARS-CoV-2, reduced viral RNA by 93% after 24 hours and by 99.8% after 48 hours. This equates to approximately a 5,000-fold reduction in coronavirus RNA in 48 hours. At 72 hours no major reductions were observed. The IC50 of treatment with Ivermectin was determined to be ~ 2mM under these conditions, and the authors reported that no toxicity was observed with any of the concentrations used.
The authors also stated that it can be widely used to treat affected populations since Ivermectin is already approved for use in humans by the FDA.

FIRST STUDY OF THE USE OF IVERMECTIN IN COVID-19

The first study on the use of Ivermectin in patients sick with COVID-19 was titled: “Usefulness of Ivermectin in COVID-19 Illness” (14,15). It was made available online on April 19, 2020 on the SSRN website : Social Science Research Network (Note: this article was removed later in June 2020 due to criticism from another publication of its data source).
This was a multicenter, observational study that used data collected prospectively from hospitalized patients diagnosed with COVID-19 between January 1 and March 31, 2020. The disease was confirmed by molecular laboratory PCR testing.
The publication mentions that a multi-institutional, unidentified, international healthcare outcomes database was used that met FDA requirements for data collection.
Participants were obtained from 169 hospitals around the world. The study included high number of patients with COVID-19 treated with Ivermectin: 704 and their corresponding 704 controls. Of the 704 treated with Ivermectin, 64.1% were from North American Hospitals, 17.0% from Europe, 8.7% from Asia, 5.1% from Africa, 5.0% from South America and 0.1% from Australia. To obtain the 704 controls, data from 68,230 hospitalized patients who were not treated with Ivermectin were reviewed. They were matched to corresponding groups for age, sex, race / ethnicity, comorbidities, and a severity of illness score (SOFA). The average age was 53.7 years (+/- 17 years). The average dose of Ivermectin that each patient received was 150 mcg per kilogram of weight in a single dose.
The results of the study indicated that, in those patients who required mechanical ventillation, the Fatality Rate was significantly lower in the patients in the Ivermectin group (7.3% vs 21.3%) and the General Fatality Rate was also lower in the Ivermectin group (1.4 vs 8.5%, p <0.0001).
The results of this first study are significant in terms of the reduction in Overall Fatality Rate of 6.1 times compared to that of patients who did not use Ivermectin (1.4 vs 8.5%). In the analysis of the Fatality Rate of only those who required mechanical ventillation, we found that the Fatality Rate was reduced 2.9 times (7.3% vs 21.3%). This was also significant, despite being at an advanced stage of the disease. It should also be noted that these results have been obtained with an average dose of 150 mcg / kg, which is below the usual dose of 200 mcg / kg.

REPORT OF 247 CASES WITH COVID-19 TREATED WITH IVERMECTIN BY A PNEUMOLOGIST IN THE DOMINICAN REPUBLIC

The Dominican Republic Pulmonologist, Johnny Tavárez Capellán from the city of Puerto Plata, who has almost 30 years of professional experience, started giving interviews to the media from April 18, 2020, stating that he was using the Ivermectin to treat patients with COVID-19 (15,16).

He stated that the treatment he uses consists of giving 2 tablets of 6 mg (12mg of Ivermectin) a day for 2 days (this is equivalent to a dose per day of between 150 to 200 mcg per kilogram). And for those weighing more than 80 kilograms, the dose used is 3 tablets of 6 mg (18mg) a day for 2 days (this is equivalent to a dose per day of between 150 to 225 mcg per kilogram) (16).

The Doctor pointed out that the Ivermectin given during the first stages of the disease was very effective and the results were very Good. In most cases, symptoms were resolved within 24 hours. He also commented that even cases with more than 50% lung involvement responded very well to treatment. None of the treated patients had complications. He had not had any fatality, and therefore his treatment had a fatality rate of 0%. Side effects were minimal, most frequent ones being nausea and gastric discomfort. One patient had urticaria.

The Doctor indicated that 247 patients had been treated with Ivermectin as of April 28, 2020 (17), all with favorable results. Of the 247 cases, more than 100 received only Ivermectin. In the remaining cases patients initially received Hydroxychloroquine but was discontinued as this drug was sold out in the city. This was also one of the reasons why Ivermectin was started. They are currently conducting an informational survey for a retrospective study. In the follow-up of the treated cases, none had returned with complications and they are all apparently healthy.

DEVELOPMENT STUDIES

The Clinicaltrials.gov website (18) is a database of clinical studies. As of 05/01/20, there are 4 studies that include ivermectin awaiting to patient recruitment. The first is a double-blind trial that will combine Hydroxy-chloroquine with Ivermectin, the second and third will combine Nitaxozanide with Ivermectin, and the fourth is a real life study36 testing various drugs against COVID-19.

At the local level, in Peru, a Research Protocol has been developed to carry out a study to evaluate the efficacy and safety of Ivermectin against Hydroxychloroquine as a first-line treatment in patients with COVID-19 infection. It was mentioned that the study would be carried out at the Edgardo Rebagliati Martins National Hospital of EsSalud (19). Regarding the doses to be used in this study, for Mild cases a single dose of 300 mcg per kg of fasting weight would be considered, and for Moderate cases 2 doses of 300 mcg per kg of fasting weight every 24 hours would be used.

On a website of a media outlet in Argentina, a news item "Researchers promote certain drugs for the treatment of COVID 19" (20) was published. Its desribed a study to be carried out at a Hospital in Argentina by a group of Doctors led by Dr. Héctor E. Carvallo. In the protocol presented, for Moderate cases, the established dose of 24 mg or 400 mcg per kilogram would be given orally, in a single dose. For severe cases, it was indicated to give 24 mg. or 400 mcg per kilogram via nasogastric tube. A dose of 200 mcg per kilogram would be used for Mild cases.

Finally, a biotechnology company MedinCell had been working on a long-acting injectable version of Ivermectin for use against Malaria. They noted that it is a well-known drug which had been used for a long time with few side effects. It was now in the company's interest to investigate its potential efficacy against SARS CoV-2 (21).

DEVELOPMENT OF A FIRST TREATMENT SCHEME WITH IVERMECTIN

At the local level in the City of Lima, some individual Doctors began treating patients with Ivermectin from mid-April 2020. Based on study results and experiences aforementioned, a group of Doctors who had graduated in 1983 from the School of Medicine in San Fernando of the Universidad Nacional Mayor de San Marcos (UNMSM), all with more than 27 years of professional experience, started reviewing the safety of Ivermectin's use. A consensus developed that no major side effects were reported, and that side effect are rare and mild such as stomach discomfort or pain, dizziness, blurred vision, nausea, diarrhea and decreased apetite. A First Ivermectin Treatment Scheme for COVID-19 was then developed (see Table 2).

This Scheme was included in a broader table in which the Therapeutic Plan and Potential Therapies for COVID-19 is described, which was then disseminated both within the group of Physicians who had graduated from UNMSM, as well as outside the group. Based on our experience with cases that had been treated with the use of Ivermectin, we proceeded to update the Table of the Therapeutic Plan which was shared with many more Doctors. It is included here in the Ivermectin Treatment Schedule. To date, several Hospitals and Health Establishments of the MINSA, EsSalud and Private in the country, as well as Doctors in their individual practices, have begun using Ivermectin as a firstline agent as part of Therapeutic Action against COVID-19.

In our country the most widely available form of Ivermectin is in 6 mg/ ml bottles. In the insert of this bottle it is indicated that 30 drops are equivalent to 1 mililiter. Therefore for bioequivalent dosing, 20 drops and 1 milliliter are equivalent.

Each drop contains 200 mcg, and therefore 30 drops is equivalent to 6 mg of Ivermectin. It is important to be clear on these equivalent doses to make sure that proper doses are given indicated in the Scheme.

Table 2. FIRST TREATMENT SCHEME WITH IVERMECTIN FOR COVID-19 (Version 04/22/20)

IVERMECTIN FOR COVID-19
Presentation: 6 mg/ ml bottle. **General dose: 1 drop per Kilogram of weight.** **1 time a day for 2 days.**
Presentation: 6 mg. tablets. **Dosage for Adults: 2 tablets a day for 2 days.** **If you weigh between 80 to 110 Kg: give 3 tablets per day x 2 days.** **If you weigh more than 110 kg: give 4 tablets per day x 2 days.**
Do not take it together with orange juice (reduces its effect), lemonade or other citrus fruits. Best to take it alone and then have a glass of wáter. Take it after meals.
For patients with history of peptic ulcer, gastritis, gastric discomfort, nausea or some reason for not tolerating oral medicine, give the dose divided into 2 doses, 2 hours apart to reduce possible gastrointestinal side effects **In Severe and Critical Cases, where the viral load is higher and persistent, if there is no complete resolution after the 2nd dose, it is recommended that additional daily doses be given until there are no symptoms or signs of the disease such as dyspnea, chest pain, fatigue, or pathologic X-ray or ultrasound findings.**

Another thing to keep in mind is that, although it might be indicated on the bottle that there are 150 total drops, in practice the true yield may range from 130 to 160 drops, and more frequently may actually yields between 140 to 145 drops.

So, if a patient weighs more than 74 kg, one bottle will not be sufficient to complete the 2nd dose. If the patient has only mild or moderate case and the disease progression is not unfavorable, it is very likely that with the 1st dose alone, the improvement might be significant and therefore it may be fine that the 2nd dose be less in the number of drops than the 1st (the remainder of the bottle).

It is important to note that orange juice has been shown to decrease the oral bioavailability of ivermectin (22). Therefore, it should not be given with orange juice or other fruits since these contain elements that are inhibitors of certain transporters of Ivermectin and thus will reduce its efficacy.

Patients and family members should be instructed not to take antipyretics such as Paracetamol, because these mask disease progression and do not allow a good assessment of response to treatment. The disease progresses stealthily and can cause viral load to continue to rise uncontrollably.

In the medical literature, Drug Interactions with Ivermectin are mentioned with drugs that enhance GABA activity, such as Barbiturates, Benzodiazepines and sodium Valproate. It is therefore recommended not to use these drugs. Alcohol also increases the plasma concentration of Ivermectin.

CLASSIFICATION OF CASES ACCORDING TO SEVERITY, FOR TREATMENT WITH IVERMECTIN

To indicate the doses of Ivermectin Treatment, the case must first be classified according to its severity. With this information the treatment begins.

Regarding the classification according to the severity of the case, we made the following classification for types of cases, going from less to greater severity:

a) Asymptomatic
b) Mild
c) Moderate
d) Severe
e) Critical

a) ASYMPTOMATIC: without symptoms, they do not need to be treated with Ivermectin. Verify that they are not taking Antipyretics or Anti-inflammatories, as these reduce fever and discomfort and therefore symptoms can be masked.

b) MILD: to determine that a case is mild, it is important to confirm that the patient does not present with symptoms of dyspnea, or has signs of pulmonary involvement and that the respiratory rate is less than 22 per minute.

c) MODERATE: a patient who already presents with dyspnea or respiratory distress, but only with effort (when climbing stairs, walking, bathing), and presents with an increase in respiratory rate of greater than 22 per minute.

d) SEVERE: in these cases the presence of acute respiratory infection with bilateral lung involvement is evident. Dyspnea is almost constant, and occurs when performing activities with little effort, and also when talking or eating. Patients may present with clinical signs of muscle fatigue such as nasal flapping, use of accessory muscles (pulling), and thoracic-abdominal imbalance.

e) CRITICAL: these are patients who qualify for ICU care with Mechanical Ventilation (MV).

In the study by Liu Y. et al. Viral load in Severe cases was found to be 60 times that of Mild cases. Severe cases, apart from the higher viral load, have a longer period of virus shedding.

EVALUATION OF RESPONSE TO TREATMENT AND ESTIMATION OF THE VIRAL LOAD LEVEL

The day after starting treatment, response to treatment with Ivermectin should be assessed, and accordingly it is n whether it will be necessary to add, increase or

reduce other medications such as Anti-inflammatory, Low Molecular Weight Heparin, Antibiotics, etc.
Based on the response to treatment, one can estimate the Viral Load. If there is a significantly favorable response within 12 hours with resolution of all or most of the symptoms, Viral Load is estimated to have been low.
If the response is only partial on the 3rd day, after 2 days of treatment with Ivermectin, the Viral Load is estimated to be high and with a tendency to be persistent.

REPORT OF COVID-19 CASES TREATED WITH IVERMECTIN IN PERU

Regarding the cases treated by our group of Physicians who had graduated from the San Fernando Faculty of Medicine of the UNMSM, to date there are 36 cases. Following is a case series report of 7 of the patients who had been treated locally to date:

Case 1: Reported by Dr. Gustavo Aguirre Chang.
A 86-year-old man, who lives close a Hospital in Lima. He had histopry of well controlled Diabetes and Hypertension. Developed 8 days of fever between 38 and 39° C. He did not present dyspnea on exertion. He stayed home on those days and took Paracetamol for fever and gargled 3 times a day. He weighed 74 kg. He was instructed to discontinue antipyretics so as not to mask the response to treatment.
On the 8th day of the onset of symptoms, he took his 1st dose of 70 drops of Ivermectin at 4 pm and Dexamethasone 1 tab. of 4 mg. at 6 pm. At 7 pm he began to have sweats. At 7:30 pm he no longer had fever and did not have it again later. At 11 pm the same day, he again presented sweating.
On the next day he woke up without discomfort and without fever. At 9am he took the 2nd dose of only 64 drops which is what was left of the bottle. At 11:30 am he called by phone stating that he already felt like he was cured. On the next day, he did not report any symptoms.
This patient is classified as: a) Mild Case, with Risk Factors and b) With Very Rapid Response to Treatment (3.5 hours), with low Viral Load. The gargles performed 3 times a day have helped lower the Viral Load, and this made it posible for a very quick response in reducing fever and general discomfort.

Case 2: Reported by Dr. George Bernui Velarde.
62-year-old woman, with HT and Ca in treatment, with 3 days with a sore throat and headache that became intense from the 2nd day. On the 3rd day symptoms increased and she developed cough, myalgia and dyspnea on exertion (the doctor listening to her confirmed dyspnea when communicating with her).
She has not reported fever, most likely because she was taking 1 gram of Paracetamol for severe headache. She weighed 65 kg. She was started with the first dose of Ivermectin on the 3rd day at 4 pm (60 drops). The next day at 9 am, she took the 2nd dose (55 drops) as well as 4 mg of Dexamethasone for 2 days. She had progressive clinical improvement. Two days after taking the 2nd dose (6th day from the onset of symptoms) she reported only mild headache and mialgia and there was no longer dyspnea. On the 7th day, she reported a feeling of well-being on a scale of 8 out of 10. She was instructed to take the remainder of the ivermectin bottle on the 3rd dose with 35 drops.
This case was evaluated with Dr. Gustavo Aguirre, and the patient is classified as: a) Moderate to Severe Case (due to dyspnea when talking), with Risk Factors and b) With 70% Response in 2 days and Total Response in 8 days, Intermediate Viral Load, with a tendency to persistence.

Case 3: Reported by Dr. Ruth Araníbar Rivero and Dr. Martín Santos Reyes.
60-year-old man with controlled diabetes. The disease began with aphonia, a sensation of slight discomfort in the pharynx and slight nasal congestion. He gargled water with lemon and salt, went to a pharmacy where he was prescribed an antibiotic with which he showed improvement when he no longer had aphonia. On the 6th day from the onset of symptoms, he begins to develop back pain that progressively intensified and presented with general discomfort. From the 9th day from the onset of symptoms, he developed night sweats which was unusual for him (temperature was not measured on those days). When he did not improve, on the 13th day in the morning he went to the Clinic in SJL. Upon entering the Clinic, he stated that he had a feeling of intense shortness of breath. A Rapid Serological Test for COVID-19 was done that came out Positive. A lung CT scan was done which was reported as the Diagnosis of Atypical Pneumonia: COVID-19 vs Influenza. He was prescribed 500mgs of Azithromycin for 5 days and Paracetamol. He was told that his oxygen saturation level was normal. At home he felt tired, and on the night of the 13th day he developed a fever with an axillary temperature of 38.5 ° C and a Glucose level of 130 (he had not taken his medicine in the morning because he felt rushed). Dr. Araníbar presented this case to Dr. Martin Santos and it is decided to start treatment with Ivermectin. He weighed 78 kg and on the 14th day at 2 pm he took his 1st dose of 78 drops (without food 2 hours before or after). In addition he was given 2 doses of 4 mg of Dexamethasone orally and Azithromycin was continued. At 8 pm on the same day he no longer had a fever, and almost without any discomfort. On a telephone communication around 10pm he did not have any cough or dyspnea.
The next day (15th day), he stated that after several days, he finally slept continuously from 12 pm to 5 am, and he no longer had a fever or cough. He has gotten up to clean and tidy his room. He did not feel tired and he requested permission to bath.
At 11 am he took the 2nd dose of Ivermectin to complete his treatment.
After reviewing this case, we have classified this patient as: a) Moderate Case (for presenting Dyspnea), with

Risk Factors and b) With Rapid Response to Treatment (6 hours). Low to Intermediate Viral Load. The gargles he performed have helped him lower the Viral Load, which in turn made possible a quick response in reducing the fever and other symptoms.

Case 4: Reported by Dr. Fernando Zarzosa Salcedo
A 70-year-old woman, diagnosed with mild bronchiectasis, began having symptoms of fever and general malaise. After 6 days she developed dyspnea, chest pain and a fever of 38 ° C.
On the 8th day of the onset of symptoms she took her 1st Dose of 80 drops, and on the next day she took 2nd Dose of 65 drops (what was remaining in the bottle). After taking the 2nd Dose, the fever dropped, the dyspnea persists, however she states that she was feeling better. On the 10th day, she had a temperature of 38 ° C and mild generalized malaise.
The case was evaluated with Dr. Gustavo Aguirre, and was classified as: a) Moderate to Severe Case, with Risk Factors and b) With a 70% Response in 2 days, a High Viral Load and tendency to persistence. 2 additional doses of Ivermectin were given. The day after taking the 3rd dose, the patient reported feeling better and no longer having fever or generalized malaise.

Case 5: Reported by Dr. Miguel Zapata Rojas.
60-year-old male, with obesity weighing 86 kg presented with 5 days of fever between 38 to 39 ° C. He also developed cough, sore throat and dyspnea on the 5th day and these symptoms increased progressively. He was taken to the Emergency Room of a National Hospital, where he was admitted with a diagnosis of Pneumonia, COVID-19 and Acute Respiratory Failure. He was given Oxygen. Shortly before admission to the Hospital, he took the 1st dose of 80 drops of Ivermectin. 7 hours after admission, a CT scan was performed that showed bilateral pulmonary infiltrates. Positive PCR Test was confirmed as well. Results on the day of admission were as follows: D-Dimer 1.12, DHL: 521, PCR: 362, Hb: 11.8, Plaq: 349, Leuc: 17,020 (Eos: 0%, Lnf: 10%, Abast. 0%).
The day after he was admitted to the Hospital (6th day from the onset of symptoms) he received a 2nd dose in the morning consisting of 70 drops (what was remaining in bottle). He then showed progressive clinical improvement with significant reduction in dyspnea and stopped requiring oxygen after 2 days.
Results on the 4th day were as follows: D-Dimer 0.62, DHL: 482, PCR: 186, Hb: 11.8, Plaq: 413, Leuc: 9.850 (Abast. 0%). Ferritin; 1,650, FA: 114, GCTP: 373, CPK: 95. He did not take additional doses of Ivermectin as there was opposition from the doctors in the hospital against giving more doses. On days 9 and 10 from the onset of symptoms, he had more episodes of dyspnea with a oxygen desaturation to levels between 90 to 94%, and on one occasion after exertion down to 84%.
The case is evaluated with Dr. Gustavo Aguirre and is classified as: a) Severe to Critical Case, with Risk Factors and b) With a 70% Response in 2 days, 75% in 3 days, 70% in 7 days and 50% in 9 days. There was also High Viral Load and Persistence. He showed improvement after the 2 doses of Ivermectin, but without resolution of the symptoms. At least 4 additional doses of Ivermectin were required to reduce the Persistent Viral Load. 129 drops (300mcg / kg) were indicated.

Case 6: Reported by Dr. Manuel Yui Cerna.
83-year-old male, with a diagnosis of prostate adenoma had to postpone his surgical treatment due to the State of Emergency. He reported having fever, cough and general malaise for 7 days. He went to a Private Physician on the 3rd day of the onset of symptoms and was prescribed Penicillin for 3 days. His symptoms worsened and he subsequently developed dyspnea on day 6.
On the 7th day from the onset of his initial symptoms, he was advised to go to the local Hospital in the district where he resided (VES). There, he was told that he was too sick and was referred to the National Hospital. However, his family reported that they chose not to take him to the National Hospital. His family member communicated with Dr. Manuel Yui, who recommended starting Ivermectin. The patient and his family made the decision to take the treatment at home. He took the 1st dose on the 7th day at 9pm. He weighed 70 kg, so the first 5 doses administered were 70 drops.
On the 8th day from the onset of symptoms, he took the 2nd dose at 10am, and in the afternoon his fever was gone and his dyspnea was reduced.
On the 9th day, a chest radiograph was performed, which showed a bilateral pulmonary infiltrate with involvement of about 40% of the lung fields.
The case is reviewed with Dr. Gustavo Aguirre, and is classified as: a) Severe to Critical Case, with Risk Factors and b) With 65% Response in 2 days and 75% in 4 days, with High Viral Load and Persistent in a patient who responded to treatment with ivermectin, with resolution of fever, but with continuing dyspnea and pulmonary involvement evidenced by radiographic findings.
The Family asked to continue with home management, but it is explained to them that treatment must be rendered under the Local Hospitalization Model, that is, with oxygen supplementaton and with more frequent medical check-ups. To reduce pulmonary compromise and Viral Load, consensus was reached that at least 2 more doses of Ivermectin were required, in addition Azithromycin is indicated.
On the 10th day he received 4th dose of 70 drops of Ivermectin. On the 11th day, he still had dyspnea and also reported a little diarrhea. He began to report measurements with a Pulse Oximeter and had Saturations of between 90 to 91% without Oxygen. With Supplemental Oxygen it rose to 98%. The 1st ampule of Enoxaparin was given, and 50 mg of Oral Prednisone and gargles were continued. For his 5th dose

of Ivermectin,100 drops were indicated instead of 70 (300 mcg/kg). It was recommended that the dose be divided into 2 parts as he had reported having diarrhea that day, and also to reduce other adverse effects. He reported that 8 people live in his home. They are instructed to ventilate and disinfect the home environment. He stopped taking Azithromycin.
On the 12th day, his Oxygen Saturation improved to 92-94%. On the 13th day, he took his 6th Dose with 100 drops. A control X-ray was performed where a 15-20% involvement of both lung fields was observed. His Oxygen Saturation was 94%. On the 15th day, already being without oxygen therapy, his Oxygen Saturation was at 95%. He completed his 10th day of Hydroxychloroquine and 3rd day with Ceftriaxone 1gram IM per day. A control X-ray was performed.
This case, to date, is the only one in which 6 doses had been required. It was recognized by the severity of the disease progression for which he was instructed to go to a National Hospital to be admitted. After his 2nd dose the fever disappeared. However the dyspnea remained. He required additional doses of Ivermectin to reduce the High Viral Load and we observed him for several more days in case he progressed to Severe or Critical condition.

Case 7: Reported by Dr. Eduardo A. Castillo Saavedra. 58-year-old male patient developed illness on April 13 with generalized malaise, body aches predominantly of large joints.
Day 2: Fever started with peaks from 38.4 to 39.6 ° C.
Day 3 Diarrhea is added. Isolation began. Treatment was given with Paracetamol 4 grams daily.
Day 4: Nausea started. Day 5: Diarrhea was associated with tenesmus. He had 2 episodes of emesis and fever spikes became more frequent. Dry cough started.
Day 6: He developed sudden chest pain in the early morning. His respiratory frequency of between 30 to 32 rpm and Oxygen Saturation was 92%. He was taken to National Hospital, and a Rapid Serological Test was performed which was not reactive. Outpatient treatment with Azithromycin 500mg per day was prescribed and he was sent to home. Day 7: He took 2nd dose of Azithromycin, continued with paracetamol. Respiratory distress increased even with small efforts (when brushing teeth). Crackles appear on the left base.
Day 8: Dyspnea was more severe and was present at rest. Runs developed, O2 Saturation (SatO2): 89%, crackles developed on the right base. Febrile peaks subsided; diarrhea and vomiting persisted (2 times). He was taken to the National Hospital, his Molecular Test (PCR) result was Positive, he went to emergency room with diagnosis of Pneumonia. Low flow oxygen therapy fiO2: 40% by CBN was started.
Day 9: Family, by their own initiative, gave Ivermectin 90 drops (the 2nd bottle remained in the patient's pocket with the indication to take it after 24 hours, but it was not taken). In emergency room, they started Hydroxychloroquine, Enoxaparin and continued with Azithromycin. He was given Oxygen with Venturi mask at FiO2 100%
Day 10: AGA: PaO2 / FiO2 (PaFiO2): 308, SatO2 95% with Venturi Mask at FiO2 100%. Laboratory results were as follows: LDH: 680, Ferritin 1993, Lymphopenia 645. The CT scan showed CORADS 6.
Day 13: During the night, the Family gave him a 2nd Dose of Ivermectin, they gave him the entire content of 1 bottle that is equivalent to 30mg (150 drops). Day 14: PaFi dropped to 211, sedation with Haloperidol and pronation was started. Day 15: SatO2 was 100% with Venturi Mask, he went to CBN 5 liters, began to tolerate food. AGA showed increased PaFiO2.
Day 16: Continued in pronation. With Sat 02: 97%, went to CBN with 4 liters, began to speak without dyspnea. Day 17: Lowered CBN to 1 liter: with Sat02: 98% at rest. He could go to the bathroom without desaturating, and was able to eat normally. He ate all his food. Day 18: Very favorable laboratory controls. The Rapid Serologic Test for COVID with IgM and IgG were Positive. Day 19: He is discharged from the National Hospital, and recovered.
Upon reviewing, we have classified this patient as: a) Severe Case and b) With Total Response (100%) to Treatment in 6 days. Median Viral Load.

Apart from the cases treated by our group of Physicians graduated from UNMSM, in a recent radio interview (23), Walter Mogrovejo, a Cardiologist, stated that he had treated 12 patients with Ivermectin, all with a favorable response and did not have any fatality among those who received treatment. He stated that "no patient has reported that it had not been beneficial" and that the use of Ivermectin is very safe. The Doctor reported that after receiving report of 3 patients treated with Ivermectin by Dr. Gil Malca, he began his own treatment experience. He also stated that Doctors Antonio Camargo and Hudson Oliva have also successfully treated patients with Ivermectin. Adding up the cases treated by all the aforementioned Doctors, the total amount to 46 patients. All the mentioned cases have had informed consent, and received the treatment as compassionate use, as had been indicated.
Upon reviewing the cases treated locally with Ivermectin, it has been found to date that the Percentage of patients with disease improvement was 100%, fever resolution rate at 24 hours was 94% and 100% at at 48 hours, dyspnea resolution rate at 48 hours was 86%, case fatality rate was 0%, and the percentage of patients with disease progression was 0%.
The Percentage of patients who required admission to the ICU and / or Mechanical Ventilation (MV) was 0%. Statistically the number of patients treated are few, but evidente is clear that the use of Ivermectin results in a very significant decrease in Fatality Rate.
We must also mention that a progressive shortage of the drug was observed in pharmacies, which may continue as long as the favorable results of its use are made known.

Table 3
NEW IVERMECTIN TREATMENT SCHEME FOR COVID-19 *ver 30.06.20*

PRESENTATION / SEVERITY	TABLETS of 6 mg., if they are 3mg TB, divide Weight by 15 = TB number to give. (Dose for people with more than 56 Kg.**)	BOTTLE at 1%, in which 1 ml. equivalent to 10mg. and 0.1 ml. equivalent to 1 mg.
MILD	2 TB or 12 mg. after lunch and dinner (2 times a day) for 2 to 4 days. * If you weigh more than 85 kg, give 3 TB or 18 mg. 2 times a day for 2 to 4 days.	0.02 ml. x kilo of weight (or 0.1 ml e/ 5 kg.) after lunch and dinner for 2 to 4 days *
MODERATE	2 TB or 12 mg. after breakfast, lunch and dinner (3 times a day) for 5 to 9 days, depending on response to treatment and presence of side effects * If you weigh 85 to 115 kg, give 3 TB or 18 mg. after breakfast, lunch and dinner. If you weigh more than 115 kg, give 4 TB or 24 mg. after breakfast/ lunch/ dinner.	0.02 ml. per kilo of weight after breakfast, lunch and dinner (3 times a day) for 5 to 9 days, depending on response to treatment and presence of side effects.*
SEVERE	2 TB or 12 mg. after brea., lunch, dinner and 11.30pm (4 times a day) for 7 to 12 d. Reduce the dose according to response to treatment and presence of side effects* If you weigh 85 to 115 kg, give 3 TB or 18 mg. after break., lunch, dinner, 11.30pm. If you weigh more than 115 kg, give 4 TB or 24 mg. after break/lunch/dinn/11.30pm.	0.02 ml. per kilo of weight after brea, lunch, dinner and 11.30pm (4 times a day) for 7 to 12 d. Reduce the dose according to response to treatment and presence of side effects*
CRÍTICAL (hospitalized)	3 TB or 18 mg. every 6 hours (4 times a day) after meals for 9 to 15 days. Reduce the dose according to response to treatment and presence of side effects* If you weigh from 85 to 115 kg, give 4 TB or 24 mg. every 6 to 8 h. (3-4 times a day). If you weigh more than 115 kg, give 5 TB or 30 mg. every 6 to 8 h. (3-4 times a day).	0.03 ml. per kilo of weight (or 0.13 ml for every 5 kg.) every 6 h. (4 times a day) x 9 to 15 d. Reduce the dose according to response to treatment and presence of side effects*

* If symptoms persist, treatment should continue for more days up to 2 days after no symptoms, including general malaise, hyposmia, semi-liquid stools, sweating. The side effects that are reason to reduce doses are: blurred vision, dizziness, confusion and hives.
** For lower weights calculate the dose per kg: in Light give 0.4 mg/kg/d., In Moderate 0.6 mg/kg/d., In Severe 0.8 mg/kg/d. Critical 1.0 or + mg./kg/d.
*** For bottles without perforation, use a 3 or 5 ml syringe to measure the dose, and work with the equivalence of: 1 ml. 0.6% Fco = 1 tab of 6mg.
Do not take it with fruit juice, lemonade, milk or foods that contain orange or lemon (reduces effect). Consider that in Severe and Critical cases the Viral Load (total body) is High and Persistent, and the virus is present in various organs (lungs, intestines, heart, pericardium, kidney, etc).

Source: Aguirre-Chang Gustavo A. Inclusion of Ivermectin in the first therapeutic line of action for COVID-19. A very significant decrease in the Mortality Rate is reported with its use. Research Gate. May 2, 2020. doi: http://dx.doi.org/10.13140/RG.2.2.26424.57600/2

RISK VS BENEFIT EVALUATION OF THE USE OF IVERMECTIN

Adding the reported cases, to date there are more than 1,000 cases treated with Ivermectin worldwide (704 from the multicenter study, 247 in the Dominican Republic and at least 82 cases in Peru).
Because it is an approved drug that has been widely used in humans for the last 40 years, no major cases of toxicity have been reported and only minor side effects have been reported. This gives us confidence in its use, and in view of the high severity to which the COVID-19 disease can progress, with the consequent requirement of ICU beds, MV and the high fatality rate that this disease entails, the inclusion of Ivermectin within of the Therapeutic Plan for COVID-19 is amply justified.

DEVELOPMENT OF A NEW TREATMENT SCHEME WITH IVERMECTIN

Based on the experience with the treated cases, a new Ivermectin Treatment Scheme is developed.
In mild cases, it was observed that there was good response to treatment with the usual average dose of 0.2 to 0.4 mg (or 200 to 400 mcg) per kg of weight.
In mild cases, within 4 to 12 hours after the 1st dose, patients began to have significant decrease in fever, general malaise and other symptoms of COVID-19 that patient presented with before taking the 1st dose treatment. In these cases, due to the rapid response, it is estimated that the Viral Load had been low. It has been observed that it helps to reduce the Viral Load by gargling 1 glass of water with half a teaspoon of salt between 4 to 6 times a day during the first 4 days of the illness.
In cases where Medium Viral Load was estimated, the decrease in fever, general malaise and other symptoms occured within 12 to 48 hours.
In case where response was only partial after 2 days of treatment with Ivermectin, the Viral Load was estimated to be high. In Severe and Critical cases, partial improvement of between 50 to 80% occured within 48 hours, and it was necessary in these cases to give higher doses, for more days, according to response.
Table 3 shows the New Therapeutic Scheme with Ivermectin according to the Degree of Severity and the Response to Treatment.
This New Scheme has been included in the latest update of the broader Table in which the Therapeutic Plan and Potential Therapies for COVID-19 are described with the detail of the main lines of action mentioned in Table 1. This Table goes as Addendum 2 of this document. In addition, the Table that includes the Laboratory Diagnosis, Phases, Days of greatest transmission, Stages, Location, Viral Load, Severity, Place of Attention, Symptoms and findings, and Therapeutic Plan has been included as Addendum 1. It should be taken into account that the negativization of molecular tests and IgM frequently occurs several days later in Severe and Critical patients.

IMPACT ON THE FATALITY RATE AND MV REQUIREMENT

From the experiences of the cases treated with Ivermectin at the local level, those that completed the recommended treatment and underwent medical

follow-up, none progressed to requiring MV or died. This indicates that it has a great impact on reducing the Fatality Rate and the requirement of MV. For this reason, it is recommended to incorporate the use of Ivermectin to treat all Mild and Moderate cases, before they progress to Severe disease.

For patients that present with Severe and Critical cases to your practice, in the same way you should resort to using Ivermectin, since it has been observed that there is a direct relationship between the Viral Load and the severity of the disease. Therefore it is very likely that Ivermectin, in these advanced cases of the disease, will have an important impact on the Fatality Rate.

RECOMMENDATIONS

- Guide the logistical processes aimed at guaranteeing the supply of Ivermectin in Health Establishments in the country, including those of the First Level of Care, with the aim of facilitating the start of treatment as early as possible in Mild cases, and in Moderate cases who are initiating symptoms of pulmonary involvement, and before these progress to Severe and Critical cases that require referral for Hospitalization.
- For a better supply chain and distribution of Ivermectin at the national level, the purchases to be made must include Tablet forms, since these forms have a lower weight and volumen, and are not in fragile material as is the case with bottles.
- It is recommended to work with the Pharmaceutical Industry in order to guarantee the continuity of supply necessary to satisfy the demand in this country for this medicine.

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