MACROLIDE-CLARITHROMYCIN TASK-FORCE FOR THE TREATMENT AND PROPHYLAXIS OF COVID-19 AS A SINGLE AGENT.

Eduardo Mansilla[1]

[1]Affiliation not available

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Mansilla E[1], Rangel R[2], Marín GH[3], Zotarelli Filho I[4], Rivas E[5], Rivas J[6], Carvalho KAT[7], Dayer MR[8] and Samadikuchaksaraei A[9].

1.Eduardo Mansilla, MD.

Professor and Head Internal Medicine, School of Medical Sciences, UNLP, Argentina.

Correspondence Author.

E-mail: *mansillaeduardo1@gmail.com*

Tel: +5492214280275

2.Ricardo Rangel Martínez, BSB.

General Director ExomePharma, Ciudad de México DF, México.

3. Gustavo Horacio Marín, MD.

Professor of Pharmacology, School of Medical Sciences, UNLP,

Argentina.

4.Idiberto Zotarelli Filho, Ph.D.

Professor of Faceres Medical School, São José do Rio Preto, São Paulo, Brazil.

5.Elsa Rivas, MD.

Intensive Care Units-Hospital de la Amistad Perú Corea II, Santa Rosa and Salvador University Hospital, Piura, Perú.

6.Jaime Rivas, MD.

Intensive Care Unit, Hospital de la Amistad Perú Corea II, Santa Rosa, Piura, Perú.

7. Katherine Athayde Teixeira de Carvalho, MD, Ph.D. Professor of Pequeno Príncipe Faculty & Pelé Pequeno Príncipe Institute Curitiba, Paraná, Brazil.

8.Mohammad Reza Dayer, Ph.D.

Associate Professor, Department of Biology, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran. n un rato te mando el trabajo.

9. Alí Samadikuchaksaraei, MD, PhD. Professor and Head Department of Tissue Engineering & Regenerative Medicine, Iran University of Medical Sciences, Tehran, Iran.

Abstract:

SARS-CoV-2 is a novel RNA coronavirus responsible of a deadly pandemic: the clinical illness COVID-19. With only one authorized drug for emergency use in critically ill patients: Remdesivir, there is not any other approved drug or vaccine yet with proven potential to overcome this infection. We exposed here many scientific evidences to support our novel idea that a macrolide, basically Clarithromycin, could be effective as a single agent for treatment and prophylaxis of COVID-19. Clarithromycin could change the history of this pandemic. It could reduce the costs of treatment and the potential adverse effects when combining more than one drug such as with Hydroxychloroquine. Clarithromycin treatment and prophylaxis as a single agent could be much more simple, safe and cheaper as giving Chloroquine or Hydroxychloroquine alone or in combination with Azithromycin as well as other therapeutic options.

Keywords: COVID-19, Macrolides, Clarithromycin, Single Agent, Therapy, Prophylaxis

Introduction:

SARS-CoV-2 (previously named 2019-nCoV), the virus that causes the clinical illness COVID-19, is a novel RNA virus belonging to the coronavirus family (1). With more than three million confirmed cases worldwide and more than 200000 deaths at this moment and growing up these numbers constantly, various treatments are being tried clinically or undergoing evaluation (1)(2) (3) (4). The greatest risk of spread worldwide of Covid-19 involves serious life-threatening problems against human security. Fever, cough, and shortness of breath are the main symptoms of the disease that can lead to pneumonia or other organs compromised with a mortality rate of 5% or higher (1) (2) (5). Currently, there is only one authorized drug, but for emergency use in critically ill patients: Remdesivir (6). There are no other approved medications for infectious coronavirus, despite the fact that antiviral drugs such as protease inhibitors, integrase and / or polymerase enzymes are designed and are in advanced studies (3) (4) (7). Among these inhibitors, antiprotease inhibitors appear to work effectively in blocking virus replication and provide promising treatment for Covid19 disease but not yet advisable in a systematic way (3) (8) (9). The majority of published evidence that have suggested treatments for COVID-19 has been extrapolated from experience with SARS, MERS or limited to case-series (10) (11). Randomized-controlled trials are ongoing, most notably with three agents: 1. Remdesivir, actually one of the novel investigational drugs with possible greatest potential as an anti-Covid-19 (6)(12)(13)(14). 2. Lopinavir/Ritonavir, an anti-retroviral used for treatment of HIV; (11)(12). 3. Chloroquine and Hydroxychloroquine, antimalarial drugs with antiviral activity in-vitro, especially when associated with a macrolide antibiotic, azithromycin, in vivo (15)(16)(17). All these have probably been the most mentioned and promising compounds for Covid19 treatment. Other agents also under investigation including immunomodulatory

drugs have been used to attenuate COVID-19-associated cytokine storm such as tocilizumab and sarilumab (18)(19)(20) as well as the mesenchymal stem cell therapy described by Atluri et al (2020) (21).

The Macrolide-Clarithromycin Project:

By middle of March 2020, we presented to the Argentine National Health Ministry our novel idea to treat COVID-19 infected patients with only a Macrolide, Clarithromycin, as a single agent. Also we proposed to use it for the prophylaxis of medical personnel largely exposed and at high risk. Even as a strategy to eradicate the virus from earth. In a way to rapidly make public this information and central idea: the use of clarithromycin as single agent for treatment and prophylaxis of COVID-19 we made a video and a special page for internet as well as a short preliminary communication on a special-scientific site of the web (22)(23)(24). Until that date, in which we presented this project to our regulatory authorities, and according to the available scientific literature and published information, no other research medical group in the world had previously done or proposed a controlled clinical trial to test the pure antiviral efficacy of any macrolide for COVID-19, as a single agent, without the association of any other drug with it. Up to date we have not received any answer yet from our Ministry of Health in this direction and in this short period of time several other groups from different parts of the world started thinking in similar but not identical ideas.

Other COVID-19 Interventional Studies with Macrolides:

As of May 3, 2020, the Cochrane COVID-19 Study Register lists 490 interventional studies of which 285 are randomized trials (25). In the https://www.ncbi.nlm.nih.gov/pubmed site there are 7947 published papers on Covid-19 (26) and at US ClinicalTrials.gov, which is a resource provided by the U.S. National Library of Medicine, only 3 clinical trials were found for macrolides, all for azithromycin and non for clarithromycin, but only one using azithromycin as single agent for Covid-19 (27). This is a short description of these trials: 1. Hydroxychloroquine vs. Azithromycin for Hospitalized Patients With Suspected or Confirmed COVID-19 (HAHPS). This is a Phase2 randomized Interventional study in which 300 patients will be enroll. Patients in the Hydroxychloroquine arm will receive Hydroxychloroquine 400 mg by mouth twice daily for 1 day, then 200 mg by mouth twice daily for 4 days (dose reductions for weight $<$ 45 kg or GFR (glomerular filtration rate)$<$50ml/min). Patients in the Azithromycin arm will receive Azithromycin 500 mg on day 1 plus 250 mg daily on days 2-5 (may be administered intravenously per clinician preference). If the patient has already received azithromycin prior to randomization, the prior doses will count toward the 5 day total. It is now recruiting. It was First Posted : April 1, 2020, and it is done by the University of Utah (ClinicalTrials.gov Identifier: NCT04329832) (28). 2. Azithromycin for COVID-19. Treatment in Outpatients Nationwide (ACTION). This individually randomized telemedicine-based trial organized by University of California, San Francisco will evaluate the efficacy of a single dose of 1 gr Azithromycin for prevention of progression of COVID-19 in patients with a recent positive SARS-CoV-2 test who are not currently hospitalized. Was First Posted on April 2, 2020 and is not still recruiting patients. They have an estimated enrollment of 2271 participants. They propose an individually-randomized, placebo-controlled trial to determine the efficacy of a single dose of 1gr Azithromycin for prevention of COVID-19 progression to hospitalization (ClinicalTrials.gov Identifier: NCT04332107)(29). 3. Azithromycin in Hospitalized COVID-19 Patients (AIC). The present study is a randomized, double-blind, controlled, clinical trial, with the approval of the ethics committee will be conducted on patients who have a positive test confirming COVID-19 in Shahid Modarres Medical Education Center and Hospital in Tehran. Patients will be randomly assigned to the two arms of the study and after completing the course of treatment and collecting and analyzing the necessary information from each patient, the results of the study will be published both on this site and in the form of an article in a reputable international journal. It is not yet recruiting and was First Posted on April 24, 2020. Shahid Modarres Hospital, Shahid Beheshti University of Medical Sciences and Health Services. Tehran, Iran, Islamic Republic of, (ClinicalTrials.gov Identifier: NCT04359316) (30). No paper or study at this time was found either in any of these sites for Clarithromycin and COVID-19 (25) (26) (27).

General Mechanism of Action of Macrolides:

The macrolide family of antibiotics is widely used for bacterial infections and especially those produced

by Mycoplasmas and Atypical bacteria. They include several drugs such as erythromycin, azithromycin, clarithromycin, and telithromycin between others (31) (32). Side effects of these drugs are rare but may include stomach upset, diarrhea, nausea, vomiting, or abdominal pain. Much more less common but serious side effects include hearing damage or deafness, drooping eyelids and blurred vision, difficulty swallowing or speaking, muscle weakness, and liver damage. It is contraindicated for people allergic to erythromycin, clarithromycin, azithromycin and/or telithromycin. It is also contraindicated in people with severe liver and kidney disease (33). Clarithromycin is several-fold more active in vitro than Erythromycin against gram-positive organisms, while Azithromycin is 2- to 4-fold less potent. Clarithromycin has a longer serum half- life and better tissue penetration than erythromycin, allowing twice-a-day or once-a-day long acting formulation dosing for most common infections (32)(33). In addition to common bacteria, Azithromycin and Clarithromycin have demonstrated to be also active as single agents against some unexpected pathogens (e.g., Borrelia burgdorferi, Toxoplasma gondii, Mycobacterium avium complex, and M. leprae), Zica Virus and maybe also, against SARS-CoV-2 as we are postulating (34) (35) (36) (37). Efficacy of Clarithromycin has been examined against H5N1 highly pathogenic and H7N9 low pathogenic avian influenza virus infections in cynomolgus monkeys, showing viral suppression and clinical improvement (38) (39). A study assessed the efficacy and safety of a Clarithromycin-Naproxen-Oseltamivir combination for the treatment of serious influenza, also showing good results reducing both 30- and 90-day mortality and length of hospital stay (40).

Clarithromycin is also used in conjunction with other medications to treat stomach ulcers caused by Helicobacter pylori (41); and it has been used as an anti-cancer agent especially for Lymphomas (42).

It is usually administered as 500 mg oral dose every 12 hours or as a 500 mg long acting formulation once a day, both for 8 days (32).

It is several folds more active and has a better bioavailability than Azithromycin (55% vs 37%), it is resistant to gastric acid and its absorption and bioavailability are enhanced by food (70% vs 55%) while a decrease of 52% is recorded for Azithromycin, its metabolite in human, the 14-Hydroxy-Clarithromycin, is also microbiologically active thus enhancing the activity of the parent molecule, it reaches peak serum concentration faster than Azithromycin (1.8 hr. vs 2.5 hr.), it attains higher peak concentration than Azithromycin (3 mg/L vs 0,4 mg/L) and it has a better concentration in the nasal mucosa, tonsils and lung tissue (33) (43).

Macrolides as Antivirals:

The novel antiviral mechanism of action of macrolides was discovered when a significant improvement in the survival of patients with diffuse pan-bronchiolitis (DPB) receiving low dose of Erythromycin was observed, and when their beneficial effect was found to be independent of their anti-microbial activity. Their administration was associated with reduced inflammatory response in chronic airway diseases including upper and lower respiratory tract infections (44) (45).

Clarithromycin as an Antiviral:

Both in vitro and in vivo studies have provided evidence of their efficacy in viral respiratory infections including rhinovirus (RV), respiratory syncytial virus (RSV), and influenza virus (45) (46) (47) (48) (49) (50) (51) (52) (53).

Clarithromycin can inhibit the duplication of some influenza viruses. In concentrations of 12.5 and 25 μg/mL, this drug reduces the duplication of H1N1 influenza virus in vitro (54).

It acts at the middle and late stages of virus replication to reduce the duplication of progeny virus in the infected cell (55).

In the early stage of virus infection (2-3 d), the secretion of IL-12 is increased to promote the production of interferon (IFN)-γ and immunoglobulin (Ig) A on the mucous membrane of the respiratory tract in order to enhance the immunity of the mucous membrane (56) (57) (58). During the middle and late stages (after 6d) of a deadly influenza infection model, excess IFN-γ is produced (59). The clinical significance of reducing this

immune reaction and its ability to affect the fatality rate are currently being investigated and are expected to be future targets of Macrolide therapy (60)(61).

Clarithromycin as well as other macrolides can inhibit the activation of NF-ϰB in cell nuclei to reduce transcription and promote anti- inflammatory action (59).

In summary, clarithromycin, a clinically used macrolide, reduces FluA viral titers and cytokines secretion in supernatant fluids, FluA virus RNA replication in the cells, and susceptibility of the cells to infection by the virus (62) (63) (64).

Clarithromycin also reduced the expression of SA 2,6Gal, a receptor for human influenza, on the mucosal surface of human tracheae, and reduced the number of acidic endosomes from which viral RNPs enter into the cytoplasm (63).

Those clarithromycin mechanisms were explained by actions on inhibition protein synthesis by reversibly binding to the 50S ribosomal subunits. This action share with the macrolides that inhibit the translocation of aminoacyl transfer-RNA, and prevents peptide chain elongation. Perhaps this may could acting and explaining the antiviral properties; the SARS-CoV-2 is an RNA virus (65) (66).

Otherwise, the macrolide antibiotics, especially Clarithromycin can decrease the hypersecretion of proinflammatory cytokines and chemokines in vitro, in preclinical models, and chronic inflammatory pulmonary diseases. Other proprieties of the macrolides that could aid their action in pulmonary injuries are the airway epithelial barrier that is due to the stabilization of the epithelial cell membrane, the entry of the virus into the cell (67).

All these findings suggest that a clinically used macrolide antibiotic, clarithromycin, may inhibit many virus, including type A seasonal human influenza virus infection, via reducing its receptor on the airway epithelial cells and via reducing entry of viral RNPs, which contain viral RNA, into the cytoplasm (57)(68)(69).

Macrolides have received considerable attention for their anti-inflammatory and immunomodulatory actions beyond the antibacterial effect. These two properties may ensure some efficacy in a wide spectrum of viral infections (70) (71) (72) (73). They downregulate the inflammatory cascade, attenuate excessive cytokine production in viral infections, and they may reduce virus-related exacerbations (72) (73). The effects of Clarithromycin in patients with Covid-19 and pulmonary disease appear to be also independent of its antimicrobial properties, and maybe more related to immunomodulating pathways that do not affect its antibiotic mechanism. This action could also be required for COVID-19 as there are many descriptions of "cytokines storms" syndromes (67)(68)(69)(70)(73).

Clarithromycin inhibit airway inflammation and may modulate also the severity of influenza infection induced by influenza virus infection. (71).

Much data showed that macrolides reduced different viral titers of ICAM-1, as well as the release of many pro-inflammatory viral infection-induced cytokines including IL-1β, IL-6, IL-8, and TNF-α. Also, lowering of viral titers and RNA of viral replication as well as augmentation of the IL-12 by macrolides, which is essential in reducing virus yield were revealed (59) (62) (64) The demonstration that the macrolides, particularly clarithromycin, have a role on immunomodulation, could also be seen in the potential case of a patient receiving a mesenchymal cell therapy simultaneously attenuating pro-inflammatory cytokines secretion, inflammatory cell recruitment and/or increased alveolar macrophages content specially if that patients could have respiratory distress (21)(73)(74)

Based on all this existing evidence, macrolides, especially Clarithromycin maybe considered as a promising treatment option in treatment of respiratory viral infections and have encouraged a number of researchers to explore further this potential application even us for Covid-19 Treatment and Prophylaxis (22) (23) (24)(74)(75).

Azithromycin pharmacologically is very similar to Clarithromycin (32), but, according to our experience and that of the scientific literature, Clarithromycin, as an antiviral, anti-inflammatory and/or immunomodulatory

drug seems to be a lot much better (22) (23) (33) (34) (74) (75).

That's why it should be better or even essential to use Clarithromycin in any proposed trial of this kind in which a Macrolide would be given as a single agent.

Macrolides Used for MERS:

In patients with Middle East Respiratory Syndrome (MERS), macrolides are often prescribed as part of the empiric treatment regimen for pneumonia, often before the detection of MERS coronavirus (MERS-CoV). Using a cohort of critically ill patients with MERS, the aim of one study was to determine whether there was an association between macrolide therapy and 90-day mortality and RNA clearance in critically ill patients with MERS. Of 349 critically ill MERS patients, 136 (39%) received macrolide therapy. Azithromycin was most commonly used (97/136; 71.3%). Macrolide therapy was commonly started before the patient arrived in the intensive care unit (ICU) (51/136; 37.5%), or on day1 in ICU (53/136; 39%). Patients received macrolide treatment (Azithromycin, Clarithromycin) within three days before admission to ICU, or at any time during their stay in ICU, up to 28 days and a 'no macrolide therapy' (control) group. Macrolide therapy was not independently associated with a significant difference in 90-day mortality or improvement in MERS-CoV RNA clearance (76). But due to the nature of the population of this study (critically ill patients), this study did not measure the difference in symptoms improvement between the group who received macrolides and the group who did not. Also the category of these patients as they were all critically ill, might have not been, the best one to start with this kind of treatment. If the patients could have received the treatment before being critically ill maybe the results could have been completely different. Also, this study was a retrospective one.

The French Studies with Hydroxychloroquine and the Macrolide Azithromicyn for COVID-19 (17) (77) (78):

The small studies using the combination of Hydroxychloroquine and Azithromycin "showed a significant reduction in viral load" after six days of treatment and a "much shorter average viral load duration" compared to patients who received another treatment. Six patients in one of the trials were asymptomatic and 22 had symptoms of upper respiratory tract infection. Eight patients had lower respiratory tract infections. Twenty cases were treated in the study, with untreated patients acting as negative controls. Hydroxychloroquine treatment was found to significantly reduce viral load in patients with COVID-19, and had an improved effect when azithromycin was included in the treatment. Interestingly, a patient who continued to test positive after being treated with Hydroxychloroquine alone was given Azithromycin starting on the eighth day and tested negative the following day (79).

This fact is of outmost importance since it would be inferred from said results that macrolide drugs could have an antiviral effect inherent to them.

However, Hydroxychloroquine an antimalarial and antirheumatic drug has many adverse reactions such as cardiac, liver and eye disorders among others. Thus, checkups are needed before using Hydroxychloroquine in patients with chronic diseases who are the most affected by COVID-19 (16) (17)(78) (79) (80).

This risk could have been lowered by using Hydroxychloroquine at a lower dosage but still achieving a good, and more stable concentration in the blood. This fact could have been better achieved combining Hydroxychloroquine with Clarithromycin which is in many ways superior to Azithromycin (33) (81).

Also, that risk is no longer a problem, if Hydroxychloroquine is not used in such a combination and, any macrolide specially Clarithromycin alone could be left as a single agent as we have postulated (22) (23) (24).

It has been usually wrongly believed that azithromycin, in all those different COVID-19 clinical studies, has mainly acted as an antibacterial agent especially for associated-pneumonias (77) (78) (81).

When comparing the effect of Hydroxychloroquine treatment as a single drug and the effect of Hydroxychloroquine and Azithromycin in combination, the proportion of patients that had negative PCR results

in nasopharyngeal samples was significantly different between the two groups at days 3-4-5 and six post-inclusion. At day six post-inclusion, 100% of patients treated with Hydroxychloroquine and Azithromycin combination were virologicaly cured comparing with 57.1% in patients treated with Hydroxychloroquine only, and 12.5% in the control group ($p<0.001$). Of note, one patient who was still PCR-positive at day 6-post inclusion under Hydroxychloroquine treatment only received Azithromycin in addition to hydroxychloroquine at day eight post inclusion and cured her infection at day-9 post-infection (77) (78).

How did Hydroxychloroquine and Azithromycin Worked Together and Could have Azithromycin Been the Most Active Drug in that Combination? :

The results obtained in those Hydroxychloroquine-Azithromycin studies (77) (78), could only be explained by three simple possible ways:

1) Azithromycin only acts as an antibacterial agent for associated pneumonia;

2) Azithromycin acts synergistically with Hydroxychloroquine;

3) Azithromycin has an antiviral effect independent of that of Hydroxychloroquine.

No one has come out to completely open the scene on this yet.

" From all the cited scientific literature and our own clinical experience we are more inclined to think that the action of macrolides in these situations could have been basically antiviral " (48) (22).

Other Studies Indicating that Clarithromycin is a Good Option for Covid-19:

Another exciting study made in Iran, experienced docking experiments using the newly released coordinate structure for COVID-19 protease as a receptor and nine drugs were selected from HIV-1 protease inhibitors and twenty-one candidates from anti bronchitis drugs, based on their chemical structures and enrolled them in blind and active site-directed dockings in different modes and native-like conditions of interactions. These experiments suggested that the binding capacity and the inhibitory potency of those candidates were as follows: Tipranavir >Indinavir>Atazanavir>Darunavir>Ritonavir>Amprenavir for HIV-1, and Cefditoren>Cefixime>Erythromycin>Clarithromycin for anti-bronchitis medicines (82). In this context the author imagines that a successful treatment regime should contain multi drugs of protease inhibitors, spike shielding drugs, and immunomodulatory drugs in early steps of the disease and Ivermectin>heparin (as intravenous or nebulized)>macrolides seemed to them to be good adjuvant candidates in all anti 2019-nCov regimes to shield S protein even for prophylactic purposes (83).

Other small experiences appeared in the scientific literature later on in a similar direction. One study in Taiwan, reported two cases with community-acquired pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) who returned from Wuhan, China. In hospital, one patient positive for the virus remained febrile, malaise and poor appetite. Follow-up CXR revealed increasing opacity at right middle and lower lung fields. Levofloxacin was initiated. On hospital day 12, after a 6-day course of Levofloxacin, her fever abated with improved appetite and physical activity. She became free of symptoms afterward. The second patient on day 6 in hospital, remained febrile, malaise and poor appetite. She reported worsening of cough. Follow-up CXR revealed patchy consolidation over bilateral lower lung field. Parenteral Cefepime and oral Clarithromycin therapy were initiated. On day 9, she was afebrile with improved general condition. Antimicrobial therapy was shifted to oral Moxifloxacin. She remained free of symptoms afterward (84).

In Colombia, as published, one patient received clarithromycin instead of azithromycin, in combination with chloroquine with the successful recovery of COVID-19 pneumonia, without any side adverse effects and become negative for the SARS-CoV-2 infection, as observed in the RT-PCR test. (85).

In Ecuador 12 patients were treated with a combination of Clarithromycin, N-acetilcystine and an antiviral nutraceutical (Virusid) with excellent outcomes (86).

Clarithromycin should be the best candidate to be tried for COVID-19 from all this evidence is obvious for us.

"The Macrolide-Clarithromycin Task-Force for the Treatment and Prophylaxis of Covid19 ".

Scientists and clinicians especially in Latin American countries, have many different difficulties, mainly economical, to implement innovative concepts in Medicine or to carry on control clinical trials. Also it seems that we are bound to many bureaucratic barriers and very slow motion of our health authorities to test novel medical strategies in this urgent situation.

However, as it is observed in Brazil, our countries and people could be damaged more strongly by the virus than in other parts of the world and maybe suffering the worst consequences even in a second possible wave of this virus (87).

For this purpose, we have interested and joined several medical groups from different South and Central American countries in what we have called the "Macrolide-Clarithromycin Task-Force for the Treatment and Prophylaxis of COVID-19 ".

The main objective of this Task-Force is to use a Macrolide: Clarithromycin, as a single agent for the treatment and prophylaxis of the COVID-19 pandemic and perform a multi-national collaborative project and at least two controlled Clinical Trials in this direction: one therapeutic and the other prophylactic.

With this novel concept in mind, that Clarithromycin could not only be an antibacterial agent but also a strong immunomodulatory, anti-inflammatory and anti-viral one, very active for COVID-19, we got in contact as we said with medical groups in Argentina, México, Perú, Brazil, Colombia, Ecuador, and Venezuela, that were very enthusiastic to hear and share this idea.

This Task Force is now opened to all the interested groups not only in Latin America but also from the rest of the world, such as it was the case of Iran that early joined the Force. Also the United States has been invited to participate.

Extenuating Clinical Circumstances and the Possible Use of Clarithromycin:

It is well recognized that there may be extenuating clinical circumstances where clinicians decide to use unproven therapies when clinical trials are unavailable. In those circumstances where unproven therapies are used, the WHO has provided a standardized case report form for data collection to ensure that there is a contribution to scientific research and the clinical community (88).

As with any viral pneumonia, COVID-19 itself up to here has not been an indication for antibiotics. However, patients who present with respiratory symptoms and pulmonary infiltrates on imaging may meet the diagnostic criteria for COVID-19 and Bacterial Pneumonia or just Bacterial Pneumonia without COVID-19 when the diagnostic tests are done and the results are obtained (100). Typical or Atypical pulmonary Infection without COVID-19 or COVID-19 with pulmonary co-infection with any bacterial pathogen can be possible, and as per standard therapy, antibiotics should be indicated in both situations. Losing time until the initial antibiotic treatment or non-response to initial antimicrobial therapy will increase mortality in both situations. Then, the initial and urgent selection of antimicrobials is critical. According to NICE (89), to cover atypical and multiple pathogens in older patients with pneumonia and at risk of severe complications, the recommended choices of antibiotics in the community are:

Amoxicillin with	500 mg 3 times a day (higher doses can be used – see BNF) for 5 days
Clarithromycin (if atypical pathogens)	500 mg twice a day for 5 days

An example of standard therapy for in-patient treatment for community acquired pneumonia is ceftriaxone 1-2 g IV daily with a macrolide, usually azithromycin 500mg IV/PO x 3 days or azithromycin 500mg PO x 1 day followed by 250mg PO x 4 days (89).

In these situations, in the context of the COVID-19 pandemic, with or without prior testing results, especially in poor undeveloped countries, we propose to urgently use in patients with cough and fever with or without signs and images of pneumonia, as first choice, a Macrolide, the Clarithromycin antibiotic, not only as an anti-bacterial but also as an antiviral, anti-inflammatory, and immune-modulating agent.

Apart from penicillin allergy, adverse reactions to the recommended antibiotics, e.g. macrolides, are generally mild and uncommon. The main disadvantage of this proposed strategy is that it could tend to drive increased bacterial resistance. However, in a pandemic like this one, with a high mortality rate in a specific subpopulation, in this case the very elderly people, this needs to be weighed against the benefits of the policy (88)(89).

If Clarithromycin could have the desired anti SARS-CoV-2 effect, then, rescue prescribing strategies, initiated by the own patient at an early stage with this macrolide Clarithromycin, could aid effective delivery not only of an outstanding antimicrobial but also of an antiviral in the same tablet, significantly reducing hospital admissions, and lowering mortality.

While less antimicrobial resistance should remain a global priority, the current pandemic highlights the need for unprecedented management strategies. For example, in the current context, it may be entirely appropriate for nursing homes to have routine stockpiles of antibiotics (89), but as we have said, specifically clarithromycin. Rapid interventions like this could be life-saving, allowing rapid and appropriate prescribing decisions that could minimize morbidity and mortality of COVID-19, as well as reducing the impact of the pandemic on health services most exposed to this virus.

In this context, equipping patients and medical personnel in the first lines with rescue clarithromycin for Primary Prophylaxis as we have proposed for the first time, may be a legitimate strategy to consider in this pandemic, and should be tried in a Controlled Clinical Trial.

Primary Purposes of our Two Proposed Protocols for Covid19:

Treatment.

Objective: To detect and early diagnose a possible new case of coronavirus (COVID-19) patient and even healthy carriers, in order to allow their inclusion in a research protocol with the exclusive use as single agent, of Clarithromycin 500 mg long acting oral formulation that allows its administration once a day for 8 days and see if this treatment per-se is able to reduce and/or disappear the viral load in that new case or healthy carrier and stop the progression of the disease to more severe stages, as well as lowering mortality.

Primary Prophylaxis:

Current evidence suggests that person-to-person spreading among first-line healthcare workers caring for patients suffering from COVID-19 is a dangerous situation that could leave people without primary or specialized care and treatment. So far, no drugs or combinations have been fully recommended, nor are vaccines approved for the use of antiviral prophylaxis before or after exposure to COVID-19 available, since there is no evidence to support their use yet.

Objective: to test the Clarithromycin 500 mg long acting oral formulation that allows its administration once a day for 15 days as a single agent could have a prophylactic effect on members of the health team directly involved in the care of patients with COVID-19 and highly exposed to this virus, reducing the possibility of their infection as well as progression, and permitting to protect themselves.

Discussion:

Considering the amount of death and the catastrophic consequences in the global economy that this COVID-19 pandemic is leaving behind all over the planet, we think this strategy is worth convenient to at least be tried in controlled clinical trials.

Clarithromycin could change the history of this disease. It could reduce the costs of treatment and the potential adverse effects when combining more than one drug such as with Hydroxychloroquine. Clar-

ithromycin treatment as a single agent could be much more simple, safe and cheaper as giving Chloroquine or Hydroxychloroquine alone or in combination with Azithromycin as well as other therapeutic options.

Clarithromycin would be immediately available globally and could protect all health workers from COVID-19. It would avoid patients to be sent to Intensive Care Units if used as soon as they start with the first symptoms or even at diagnosis in asymptomatic patients. It would reduce the high mortality rate associated with the disease. It would accelerate the inactivation of the viral load. I would avoid the economic debacle of the world.

If these results would be encouraging, it could then be possible to propose to the governments of the world to quickly implement a "whole-earth-all-persons-treatment-prophylaxis strategy with Clarithromycin as a single agent, to reduce the mortality, and maybe eradicate the virus from our planet. This proposition would keep waiting for the development of vaccines, as they are not available at the moment and need to follow the course of the research phases, especially to completely ensure the safety of humanity.

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Conflicts of Interest: The authors declare no conflict of interest.

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