



Early treatment of COVID-19 based on scientific evidence

Tratamento precoce para COVID-19 baseado em evidência científica

Tratamiento precoz para COVID-19 basado en evidencia científica

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ABSTRACT

Objective: To present a proposal for early treatment of patients with COVID-19 in a Primary Health Care (*Unidade Básica de Saúde - UBS*) center. **Methods:** This is a proposed treatment protocol for COVID-19 using hydroxychloroquine or chloroquine based on the currently (June 13, 2020) available scientific literature. PubMed database was searched for studies using the descriptors COVID-19, hydroxychloroquine, and chloroquine. Five studies were selected from the 645 studies found as they addressed the use of hydroxychloroquine or chloroquine in the treatment of COVID-19 in early stages. **Results:** The proposed early treatment protocol for patients with suspected COVID-19 includes guidance on the main symptoms, general guidelines for the population, medical evaluation, examination considerations, recommended therapy, post-prescription guidelines and criteria for hospitalization. **Conclusion:** According to the studies, early outpatient treatment of COVID-19 with hydroxychloroquine or chloroquine seems to decrease the risk of hospitalization and the need for intensive care beds. The decision to adopt the proposed treatment is made by the patient, and the physician should only conduct the treatment after obtaining written informed consent from the patient, as it is an off-label prescription. Randomized studies are needed to confirm this hypothesis.

Descriptors: Protocols; Therapeutics; Coronavirus Infections.

RESUMO

Objetivo: Apresentar uma proposta de tratamento precoce para pacientes com COVID-19 em Unidade Básica de Saúde (UBS). **Métodos:** Trata-se de uma proposta de protocolo de tratamento para COVID-19 com hidroxicloroquina ou cloroquina com base na literatura científica disponível no momento (13 de junho de 2020). O levantamento dos estudos ocorreu na base PubMed, por meio dos descritores COVID-19, hydroxychloroquine e chloroquine. Foram selecionados cinco artigos, dos 645 artigos



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encontrados, por abordarem o uso de hidroxicloroquina ou cloroquina no tratamento da fase precoce da COVID-19. **Resultados:** A proposta de protocolo para tratamento precoce para pacientes com suspeita de COVID-19 envolve orientações sobre os principais sintomas, orientações gerais à população, avaliação médica, considerações sobre exames, terapia recomendada, orientações pós-prescrição e critérios para internação. **Conclusão:** Baseado em estudos, o tratamento precoce ambulatorial da COVID-19 com hidroxicloroquina ou cloroquina parece diminuir o risco de internação e, assim, a necessidade de leitos de terapia intensiva. A decisão de adoção do tratamento a ser proposto é do paciente, e o médico só deve adotar após o paciente assinar o consentimento livre e esclarecido, por tratar-se de prescrição off label. Estudos randomizados são necessários para confirmar essa hipótese.

Descritores: Protocolos; Terapêutica; Infecções por Coronavírus.

RESUMEN

Objetivo: Presentar una propuesta de tratamiento precoz para pacientes con la COVID-19 en Unidad Básica de Salud (UBS). **Métodos:** Se trata de una propuesta de protocolo de tratamiento para la COVID-19 con hidrocloroquina o cloroquina basado en la literatura científica disponible en el momento (13 de junio de 2020). La recogida de los estudios se dio en la base de datos PubMed a través de los descriptores COVID-19, hydroxychloroquine y chloroquine. De los 645 artículos encontrados se ha elegido cinco de ellos sobre el uso de la hidrocloroquina o cloroquina para el tratamiento de la fase precoz de la COVID-19. **Resultados:** En la propuesta del protocolo para el tratamiento precoz de pacientes con sospecha de la COVID-19 hay orientaciones de los síntomas principales, las orientaciones generales para la población, la evaluación médica, las consideraciones de las pruebas, la terapia recomendada, las orientaciones post prescripción y los criterios para el ingreso hospitalario. **Conclusión:** Basados en estudios, el tratamiento precoz de ambulatorio de la COVID-19 con hidrocloroquina o cloroquina parece disminuir el riesgo de ingreso hospitalario y la necesidad de camas de la unidad de cuidados intensivos. La decisión para la adhesión al tratamiento propuesto es del paciente y el medico solo debe iniciarlo tras la firma del consentimiento libre esclarecido de parte del paciente una vez que se trata de prescripción off label. Son necesarios estudios randomizados para confirmar esa hipótesis.

Descriptores: Protocolos; Terapêutica; Infecciones por Coronavirus.

INTRODUCTION

The growing COVID-19 pandemic is generating a global crisis that has already become a health, economic and humanitarian disaster. SARS-CoV-2 is a betacoronavirus first described after the diagnosis of pneumonia of unknown cause in Wuhan province, China, in November 2019⁽¹⁾.

The sequencing of the virus was released on January 10, 2020, and its genome is now available on GenBank⁽²⁾. It is a simple RNA virus that has spikes on its surface, seen under electron microscopy, resembling a crown. SARS-CoV-2 predominantly infects the lower respiratory tract by binding to the receptors of alveolar epithelial cells, thereby inducing an intense inflammatory cytokine response. The cytokine storm is the postulated mechanism for organ damage^(3,4).

The World Health Organization (WHO) declared, on January 30, 2020, that COVID-19 was a global emergency, and on March 11, 2020 the WHO stated that the disease was already a new pandemic, with many countries already affected⁽⁵⁾.

Until June 12, 2020 at 9:00 pm, there were 7,553,182 confirmed cases worldwide, with 423,349 deaths and 216 countries, areas or territories affected by COVID-19⁽⁶⁾. In Brazil, until June 12, 2020 at 6:30 pm, there were 828,810 confirmed cases, 25,982 new cases and 41,828 deaths, with 909 new deaths. Fortunately, until June 12, 2020 at the same time, 365,063 people had recovered in the country and another 421,919 were still being monitored⁽⁷⁾.

COVID-19 is predominantly a respiratory disease, with severity ranging from mild to fatal and transmission occurring mainly through the spread of respiratory droplets⁽⁸⁾. In addition to airborne droplets, in vitro experiments have shown that the SARS-CoV-2 virus can survive for up to four days when these respiratory droplets are deposited on surfaces⁽⁹⁾.

These characteristics make the virus highly transmissible. In mathematical models based on outbreak data from clusters in Singapore and Tianjin (China), the rates of transmission in pre-symptomatic and symptomatic cases were estimated to be 45% (95%CI 32-67) and 62% (95%CI 50-76), respectively⁽¹⁰⁾.

Chinese studies estimate that the mortality rate of COVID-19 is 0.25-3%⁽¹¹⁾. However, given its high transmission rate, the WHO risk assessment considers it to be a "very high risk at the global level"⁽⁵⁾. In Brazil, the lethality rate of COVID-19 was 5% according to data published on June 12, 2020 at 8:15 pm by the Ministry of Health⁽⁷⁾.

COVID-19 evolves in well-defined clinical phases: Phase I, Phase II and Phase III. Phase I (mild infection/early infection) occurs at the time of inoculation and early onset of the disease. For most infected patients, this involves an incubation period associated with mild and generally nonspecific symptoms, such as malaise, fever, and dry cough⁽¹²⁾.

Phase II (moderate, with pulmonary involvement without hypoxia - IIA and pulmonary involvement with hypoxia - IIB) is the stage at which lung disease is established and viral multiplication and localized inflammation in the lung occur. In this phase, patients develop viral pneumonia, with cough, fever, and hypoxia in phase IIB (defined as PaO₂/FiO₂ <300 mmHg). Chest X-ray or computed tomography reveal bilateral infiltrates or ground-glass opacities. Blood tests show an increase in lymphopenia and transaminases. Systemic inflammation markers may be elevated, although unnoticeable. It is at this stage that most patients with COVID-19 need to be hospitalized for observation and treatment⁽¹²⁾.

Systemic hyperinflammation occurs in Phase III (severe). A minority of patients with COVID-19 will make the direct transition to this stage of the disease, which manifests itself as an extrapulmonary systemic hyperinflammation syndrome. At this stage, the markers of systemic inflammation rise significantly. A form similar to hemophagocytic lymphohistiocytosis (sHLH) can occur at this advanced stage of the disease, and patients may experience shock, vasoplegia, respiratory failure, myocarditis and cardiopulmonary collapse. Phase III therapy depends on the use of immunomodulating agents to reduce systemic inflammation before it progresses to dysfunction of multiple organs and systems and hence death⁽¹²⁾.

The infectious or viral replication phase of the disease usually lasts for about seven days. From the 7th to the 10th day, the patient enters the inflammatory or pulmonary inflammation phase⁽¹³⁾. In the first phase of pulmonary inflammation (IIA), there is no hypoxia, that is, the patient does not experience dyspnea, but pulmonary inflammation already exists, that is, the cytochemical storm process is already beginning⁽¹²⁾.

An aggravating factor observed in clinical practice are patients with dyspneic sensation that is disproportionate to the radiological image. In addition, no reliable prognostic marker has yet been found to detect patients who will progress to the stage of pulmonary inflammation. According to a systematic review, the most reported predictors of severe prognosis in patients with COVID-19 are: age, sex, characteristics derived from CT scans, presence of C-reactive protein, lactic dehydrogenase and lymphocyte count. However, researchers state that more accurate prediction models are needed to avoid overtreatment or undertreatment, which may cause unnecessary risks or compromise prognosis. These facts confirm the need for good guidance for patients to access the health service before dyspnea and start treatment early⁽¹⁴⁾.

Although there is no specific treatment for SARS-CoV-2 so far, several alternatives have been proposed: antivirals, hydroxychloroquine, chloroquine, corticosteroids, tocilizumab, ivermectin, immunoglobulin and plasmapheresis, among others⁽¹⁵⁻¹⁸⁾.

However, for treatment at advanced stages of the disease, unsustainable financial and physical resources are needed, in a pandemic context, for any country in the world. Thus, the most efficient strategies would be prevention and early treatment of the disease. Preliminary data on early treatment are promising and have shown a decrease in the severity of the disease and the need for intensive care beds⁽¹⁹⁾. In addition, important randomized and observational studies⁽²⁰⁻²⁵⁾, which used chloroquine or hydroxychloroquine in Phase II and III of COVID-19, did not show a decrease in mortality. In one of these studies⁽²¹⁾, which used 12g of chloroquine, there was an increase in mortality.

The role of hydroxychloroquine and chloroquine in the treatment of Phase I of COVID-19 will be evaluated in the present study in order to present a proposal for early treatment in Primary Health Care (*Unidade Básica de Saúde - UBS*) centers.

METHODS

This is a proposal for a protocol for the early treatment of patients with COVID-19 carried out by means of an exploratory bibliometric study of the scientific literature currently available (June 13, 2020) on the use of hydroxychloroquine or chloroquine, whether associated or not with a macrolide.

The studies were searched on PubMed using controlled and uncontrolled descriptors: COVID-19, hydroxychloroquine and chloroquine combined by the Boolean operators OR and AND. The search yielded 645 studies: five clinical trials, three of which were randomized studies; 34 case studies, and others. Only five studies were selected as they addressed the use of hydroxychloroquine or chloroquine, whether associated or not with macrolides, in the treatment of the early phase of COVID-19. In addition, a study from the medRxiv platform (papers not certified by peer review) was included as it was a randomized study.

The selected studies that guide the preparation of the proposal for early treatment of patients with COVID-19 are presented below.

One of the first studies published was a letter reporting “more” than 100 patients treated with 500 mg of chloroquine orally every 12 hours for pneumonia cause by SARS-Cov-2. Patients receiving chloroquine showed significant improvement in symptoms and radiological image compared to controls who did not use it. The researchers also reported that the protocol was incorporated into the Chinese Guidelines on COVID-19 after a meeting on February 15, 2020 with government and regulatory authorities⁽²⁶⁾. However, the researchers did not present the rates of complications and mortality, as well as the clinical details of patients in each group.

Another study, which was randomized but published as a preprint, included 62 patients and evaluated the administration of 400 mg of hydroxychloroquine a day for five days or placebo in patients with COVID-19. The researchers evaluated the radiological findings at admission and five days later all the patients were admitted to the ward. In addition to hydroxychloroquine in the intervention group, all the patients received oxygen, antiviral agents, antibiotics and immunoglobulin, with or without corticosteroids. Recovery from cough and fever was faster in the hydroxychloroquine intervention group. The rate of radiological improvement of pneumonia was 80.6% in the intervention group and 54.5% in the control group. The four patients who progressed worse were in the control group. Only two adverse effects were reported: a case of headache and a skin rash. The mortality rate and number of hospitalization days were not reported in this study⁽¹⁸⁾.

A small French observational study⁽¹⁷⁾ evaluated the use of 600 mg of hydroxychloroquine a day, with or without azithromycin, in 20 patients. They evaluated viral clearance using RT-PCR (Reverse Transcription Polymerase Chain Reaction) obtained from nasopharyngeal swab. There was elimination of the virus in 100% of the cases of patients who used hydroxychloroquine and azithromycin until the sixth day, in 57.1% of those who used only hydroxychloroquine, and in 12.5% of the control patients on the sixth day. No other important outcomes, such as mortality and hospitalization days, were reported.

In another uncontrolled observational study⁽²⁷⁾ of a cohort of 80 patients with relatively mild infection and treated with a combination of hydroxychloroquine and azithromycin for a period of at least three days, all the patients improved clinically, except one patient aged 86 who died and a 74-year-old patient who was still in intensive care. There was a rapid drop in nasopharyngeal viral load, with 83% of the participants testing negative on the 7th day and 93% on the 8th day. Virus cultures from patients' respiratory samples were negative in 97.5% of the patients on the 5th day. Patients could be discharged quickly from the infectious disease center, with an average stay of five days.

The main study published to date, which evaluated early treatment in Phase I of COVID-19, was the study conducted in Marseille, France⁽¹⁹⁾. The researchers assessed 1,061 people who tested positive for SARS-CoV-2 through RT-PCR collected from a nasal swab and treated for at least three days with hydroxychloroquine (200 mg three times daily for ten days) and azithromycin (500 mg on the first day, followed by 250 mg daily for the next four days). Viral clearance determined by RT-PCT occurred in 973 patients in 10 days (91.7%). Adverse clinical outcomes (admission to the Intensive Care Unit – ICU, death or hospitalization for 10 days or more) were observed in 46 patients (4.3%) and 8 patients died (0.75%, aged 74 to 95 years). All the deaths resulted from respiratory failure and not from cardiac toxicity.

Five patients were still hospitalized (however, 98.7% of the patients were cured) at the time of submission of the study for publication. The adverse clinical outcome was associated with advanced age (OR 1.11), severity of the disease at admission (OR 10.05) and low serum hydroxychloroquine concentration. The poor clinical outcome was also independently associated with the use of selective beta-blocking agents and angiotensin II receptor blockers ($p < 0.05$). A total of 2.3% of patients reported mild adverse events (gastrointestinal or skin symptoms, headache, insomnia, and transient blurred vision).

Thus, the combined administration of hydroxychloroquine and azithromycin before the occurrence of COVID-19 complications is safe and associated with a very low mortality rate in patients. Although the study was not randomized and did include historical controls who did not receive hydroxychloroquine, it is hypothesized that early treatment could shorten hospitalization in the ward and ICU and decrease the death rate. These data need to be confirmed by randomized controlled trials.

Also based on clinical experience, the multicenter collaboration group of the Department of Science and Technology of the Guangdong Province and Health Commission of Guangdong Province states that treating patients diagnosed with coronavirus pneumonia with chloroquine improves the treatment success rate, decreases the mean stay and decreases the likelihood of sequelae in patients. In order to guide and regulate the use of chloroquine in patients with new SARS-CoV-2 pneumonia, the group developed a consensus document, after extensive discussion, in

which it recommends chloroquine phosphate tablet for mild, moderate and severe cases of the novel SARS-CoV-2 pneumonia without contraindications to chloroquine⁽²⁸⁾.

It should be noted that there is no level 1A scientific evidence on the efficacy or contraindication of hydroxychloroquine, as seen in the studies presented. In the latest studies that contraindicated the use of medication, the drug was not used in Phase I of the disease⁽²⁰⁻²⁵⁾. Thus, the use of hydroxychloroquine in Phase I is an option.

In this context, we hereby propose a protocol primarily aimed at contributing with strategies that can avoid or decrease the probability of a patient with COVID-19 in the infectious or viral replication phase evolving to the inflammatory phase, in which the probability of recovery is lower in the current context, and, thus, reduce mortality and the likelihood of permanent sequelae, such as pulmonary fibrosis, in these patients. This could additionally contribute to reducing the demand for ward and ICU beds.

Another aim of early treatment is to try to reduce acute symptoms in those patients who, statistically, would have self-limited disease.

RESULTS

The proposal for an early treatment protocol for patients with suspected COVID-19 in Phase I of the disease is presented below (Table I).

Table I - Protocol for the early treatment of COVID-19.

Main clinical symptoms (flu-like syndrome)	Considerations
Fever; dry cough; persistent headache; throat discomfort (“difficulty swallowing”); myalgia, chest pain; asthenia; nausea, vomiting and diarrhea; anosmia (up to 20-25% of patients experience loss of smell); ageusia (loss of taste) ^(3,8,13,29) .	These are very suggestive signs of COVID-19: persistent fever (90% of cases), associated with dry cough and gastrointestinal symptoms. Patients with anosmia, more than 80% of cases, have positive PCR for SARS-CoV-2, so it is a symptom that should be considered ^(3,8,13) .
When to seek medical assistance	
In case of fever and two or more of these symptoms that persist without improvement for more than 3 to 4 days, the patient should be instructed to seek medical assistance ⁽¹⁹⁾ . If the fever disappears, but the other symptoms do not improve, it may be one of the signs that the patient is entering the inflammation phase and requires extra attention from the physician to avoid missing the window of opportunity for early treatment ⁽¹⁹⁾ .	
Medical assessment in the emergency room	
Ideally, clinical, radiological and laboratory assessment should be performed ⁽⁸⁾ . If it is impossible to perform all the ideal exams, considering the pandemic situation and the risk of unfavorable and rapid evolution, it is recommended that the patient and family be informed and that they sign an informed consent form to start early treatment with hydroxychloroquine and azithromycin ⁽²⁹⁾ . The scientific evidence to date is from small studies with inappropriate methodologies. Randomized studies are underway in several countries and, once published, the recommendations may be updated ⁽²⁹⁾ . Immediate prescription of the recommended therapeutic regimen for the treatment of COVID-19 ⁽²⁹⁾ .	
Exam considerations	
Patients with risk factors, such as age 60+, SAH (systemic arterial hypertension), DM (diabetes mellitus), obesity, heart disease, pneumopathy, liver disease, neoplasia, immunosuppression, should, if possible, have basic laboratory tests performed: blood count, electrolytes, blood glucose, GAMA-GT, PCR, transaminases, urea and creatinine. Additional tests for follow-up should also be performed: D-dimer, DHL, CPK and ferritin ⁽²⁹⁾ . Collection of RT-PCR nasal and oropharynx swab: collect from all suspects, according to availability ⁽²⁹⁾ . Electrocardiogram (ECG) ⁽²⁹⁾ . Chest x-ray and/or chest computed tomography (CT), according to medical assessment and health care service conditions ⁽²⁹⁾ .	

Recommended therapy	Considerations
<p>Hydroxychloroquine^(18,19,27,29,30)</p> <p>1st day: 400 mg, orally, every 12 hours.</p> <p>2nd to 7th day: 400 mg, orally, daily.</p> <p>The duration of use may vary according to medical assessment. It may last from 5 to 10 days depending on the case^(18,19,27,29,30).</p> <p>In case of renal failure: no adjustment is required if FG>30 mg/dl. If FG between 15 and 30 mg/dl, do not give a full dose. If <15 mg/dL, give a dose every other day⁽²⁹⁾.</p> <p>Contraindicated in case of maculopathies and pigmentary retinosis⁽²⁹⁾.</p> <p>Azithromycin^(19,27,29)</p> <p>1st to 5th day: 500 mg, orally, in a single daily dose for 5 days.</p> <p>Pregnant women, nursing mothers and children have no contraindications to the use of the recommended regimen! Children: 6.5 mg/kg/day of hydroxychloroquine. Consider the hospitalization of pregnant women according to the severity and evolution of the case⁽²⁹⁾.</p> <p>Observations: if flu-like symptoms predominate, in the absence of specific manifestations of COVID-19 (such as nausea, diarrhea and anosmia), 75 mg of oseltamivir should be administered orally every 12 hours for five days⁽⁸⁾.</p> <p>Contraindication: allergic reaction to the use of hydroxychloroquine and azithromycin⁽²⁹⁾.</p> <p>Attention should be paid to patients with heart disease, retinopathies, maculopathies, liver failure, epilepsy, or hypersensitivity to the drug^(29,30).</p> <p>In patients with and without liver disease, the increase in liver enzymes may be due to viral action. It is not an absolute contraindication to the proposed regimen, preferably in hospital⁽²⁹⁾.</p> <p>In the case of epileptic patients, consider hospitalization and start the protocol according to a medical decision⁽³¹⁾.</p>	<p>The regimen should last only three days in mild cases^(18,19,27,29,30).</p> <p>Avoid in patients with renal failure with FG <10mg/dL^(18,19,27,29,30). Do not use amiodarone or sotalolol, as they increase digoxin levels^(29,30).</p> <p>In the absence of hydroxychloroquine, chloroquine can be chosen^(26,28,29,30).</p> <p>Patients over 60 years old^(29,32).</p> <p>Patients with history of heart disease and use of medications that can prolong internal QT^(29,32).</p> <p>Patients with a heart rate below 60 bpm⁽³²⁾.</p> <p>These patients should, if possible, perform ECG and, if changes that may predispose to arrhythmias are found, request an assessment by a cardiologist, whether in person or via telemedicine. After proper assessment, consider therapy with a hospitalized patient. If the cardiologist or telemedicine cannot be accessed, calculate the frequency-corrected QT interval, so that⁽³²⁾:</p> <p>If QTc interval (corrected QT) <450 ms, hydroxychloroquine and azithromycin may be indicated.</p> <p>If QTc interval is between 450-500 ms, use only hydroxychloroquine.</p> <p>If QT interval > 500 ms, refer for hospitalization and do not prescribe hydroxychloroquine and azithromycin.</p>
Additional therapy	Considerations
<p>Thromboprophylaxis for all patients^(19,33-36).</p> <p>Unfractionated heparin subcutaneously: 5,000 IU, every 12 hours, if weight <70 kg, and every 8 hours if weight >70 kg, for 7 days for all patients and for 15 days if patients present a high baseline thrombosis risk^(19,33-36).</p> <p>Or</p> <p>Enoxaparin subcutaneously: 40 mg, if weight <70 kg, and 60 mg, if weight >70 kg, for 7 days for all patients and for 15 days if there is a high baseline thrombosis risk^(19,33-36).</p>	<p>If renal failure (FG<30, 20 mg of enoxaparin subcutaneously)^(19,33-36).</p> <p>Observations: if the D-dimer is greater than 1.5 times the normal reference value, start anticoagulation immediately on an inpatient basis and carry out D-dimer control.</p> <p>In such cases, if access to the hospitalization service is not immediate, start intravenous corticosteroids (80 mg of methylprednisolone intravenously). If possible, admit the patient immediately. This intervention must be performed by the hospital team⁽²⁹⁾.</p>

Post-prescription guidelines	Considerations
<p>Stable patients without dyspnea, radiological changes and comorbidities can be sent home with a prescribed therapeutic regimen⁽³⁰⁾.</p> <p>They should be instructed to keep social distancing and self-isolate at home for 14 days, use their own bedroom and bathroom, separate objects for personal use from those of other residents^(8,30).</p> <p>Maintain remote monitoring and surveillance via messages, calls or telemedicine⁽⁶⁾.</p> <p>Return to the medical service if signs of clinical worsening occur⁽⁶⁾.</p>	<p>The start of treatment should not be delayed, unless the physician believes that the harm is greater than the benefit^(19,29,30).</p>
Criteria for hospitalization	
Hospitalization criteria will follow the protocols adopted by hospital institutions.	

DISCUSSION

Brazil's Federal Council of Medicine proposed, on April 16, 2020, that the attending physician should consider the use of chloroquine and hydroxychloroquine in patients with mild symptoms at the beginning of the disease in cases where other viruses are ruled out and the diagnosis of COVID-19 is confirmed. This decision should be made jointly with the patient.

The physician should tell the patient that no studies to date have proven the benefit of using the drug and explain potential side effects prior to obtaining written informed consent from the patient or family. The physician should also consider its use in patients who present with important symptoms, but who are not yet in need of intensive care, whether they need hospitalization or not. The professional should also consider its compassionate use in critical patients receiving intensive care⁽³⁰⁾.

The understanding of COVID-19 is still incomplete, especially with regard to sequelae and long-term results. In addition, little has been written about the rehabilitation needs of patients with COVID-19 after discharge from acute care. Cardiac, neurological, respiratory, cognitive and psychological sequelae and sequelae in other systems, such as kidney and tracheal problems, and other injuries have been reported in the literature. The different sequelae range from those associated with the viral disease to a prolonged stay in the ICU. In addition, many patients have pre-existing comorbidities, which can potentiate such sequelae⁽³⁷⁾. Thus, in view of these uncertainties, early treatment seems to be important to minimize possible disabilities and maximize the function and quality of life of the affected people⁽³⁷⁾.

The management of COVID-19 determined by the Ministry of Health of Brazil was modified on May 20, 2020. The use of hydroxychloroquine/chloroquine and azithromycin in Phase I of COVID-19 was then included in the treatment throughout the national territory⁽²⁹⁾.

It should be noted that hydroxychloroquine is a drug that has been used for more than 70 years, with well-described dose and side effects^(26,30,38). The Brazilian Society of Rheumatology (*Sociedade Brasileira de Reumatologia – SBR*) warns that chloroquine and hydroxychloroquine, since they have been used for a long time, have a known safety profile^(30,38). Antimalarials are considered immunomodulatory and non-immunosuppressive medications.

The most common side effects are related to the gastrointestinal tract, such as abdominal discomfort, nausea, vomiting and diarrhea. Ocular, cardiac, neurological and skin toxicity may also occur^(30,38). In addition, patients with psoriasis, porphyria and alcoholism may be more susceptible to adverse skin events, usually without severity. In rare cases, hemolysis may occur in patients with glucose-6-phosphate dehydrogenase deficiency. The SBR also calls for special attention to be given to interaction with other drugs, such as macrolides, quinolones, antivirals and antipsychotics, which can lead to heart problems (QT interval prolongation)^(30,38).

The patients in the main studies that used hydroxychloroquine or chloroquine in the early phase of the disease showed: better clinical and radiological response, faster viral elimination, shorter hospital stay, reduced mortality, less admission to the ICU and reduced likelihood of sequelae^(17-19, 26,28).

Other therapeutic alternatives are being evaluated in prospective studies using antiviral, anti-inflammatory and immunomodulatory drugs, cell therapy, antioxidants, and other therapies. Anticoagulant therapy has been recommended in patients with early-stage COVID-19⁽³⁹⁾.

The SARS-CoV-2-induced infection may be associated with coagulopathy. Initial coagulopathy features of COVID-19 include prominent elevation of D-dimer and fibrin/fibrinogen degradation products, while abnormalities in

prothrombin time, partial thromboplastin time and platelet count are relatively uncommon in initial presentations^(33,34). Screening with coagulation tests is suggested, including the measurement of D-dimer and fibrinogen levels^(33,34).

COVID-19-associated coagulopathy should be managed as it would be for any seriously ill patient. The treatment should follow the established practice of using thromboembolic prophylaxis for critically ill inpatients and standard supportive care measures for those with coagulopathy or disseminated intravascular coagulopathy sepsis. However, there is little information on the management of thrombotic risk, coagulation disorders and anticoagulant therapy in a patient with COVID-19^(33,34).

Therefore, the risks and benefits for outpatients should be discussed, especially when there are doubts about the diagnosis along with dengue, when the use of anticoagulation can be catastrophic⁽³⁰⁾.

Two randomized Brazilian studies are in progress: one has already started (*Coalisão Brasil 2*) and is registered at ClinicalTrials.gov⁽⁴⁰⁾. It is a randomized study comparing the use of hydroxychloroquine and hydroxychloroquine + azithromycin. The study is expected to end on August 30, 2020, according to the Clinical Trials website.

The other Brazilian study is the RBR-3cbs3w, which will recruit outpatients with mild disease. The study is designed to include 1,300 patients and randomly assign them to the hydroxychloroquine group or a control group. As of April 12, 2020, the study was still not recruiting patients⁽⁴¹⁾.

Thus, the present study has an important limitation, since no randomized study with adequate methodology using hydroxychloroquine or chloroquine in Phase 1 of COVID-19 has yet been published.

There are many clinical trials currently underway, but the results are unlikely to be fully or partially released before the second half of 2020^(40,41). Taking into account the severity of the pandemic and the initial results of observational studies with a lethality rate of 0.7%, such as that of the French study using hydroxychloroquine associated with azithromycin⁽¹⁹⁾, and also that the lethality rate in Brazil is 5.0 %⁽⁷⁾, perhaps many deaths could be avoided by adopting the protocol proposed for primary care. This could also reduce the number of hospitalizations in hospital wards and ICUs⁽¹⁹⁾.

CONCLUSION

There is no level 1A evidence that the combination of chloroquine or hydroxychloroquine + azithromycin is effective in the treatment of COVID-19.

Given these initial data from observational studies, which generate a hypothesis that hydroxychloroquine and azithromycin may alter the course of the disease, with a probable decrease in morbidity and perhaps mortality, it would certainly be more beneficial for patients if they were offered this off label treatment as the disease has a high lethality and morbidity.

Also, these two drugs have been used for decades in various clinical settings with minor side effects and very rare mortality.

However, the decision on whether or not to take the medication is up to the patient, and the physician should only prescribe it after the patient gives written informed consent. The autonomy of the physician and the patient must be preserved, as it has always been in Medicine. In addition, randomized studies can be conducted to confirm or refute this hypothesis.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

CONTRIBUTIONS

Sabas Carlos Vieira, Danilo Rafael da Silva Fontinele and **Marina Bucar Barjud** contributed to the study conception and design; acquisition, analysis and interpretation of data; and writing of the manuscript. **Justino Moreira de Carvalho Junior, Lina Madeira Campos Melo, José Wilson Fonseca Filho, Gerson Luís Medina Prado** and **Alexandre Adad Alencar** contributed to the acquisition, analysis and interpretation of data; and writing of the manuscript.

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