Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Letter to the Editor

Antimalarials (chloroquine and hydroxychloroquine) in the COVID-19 pandemic☆

Los antimaláricos (cloroquina e hidroxicloroquina) en la pandemia COVID-19

The new coronavirus that started as an outbreak in China in December 2019, has rapidly expanded worldwide. On March 11, 2020, the World Health Organization declared the disease a pandemic. The emergency confronted by the planet today, requires us to develop effective measures to protect people with high risk of transmission.

Chloroquine, a widely used drug as antimalarial agent and in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematous, has been recently reported as a potential broad spectrum antiviral agent. Chloroquine blocks the viral infection, increasing the endosomal pH needed for the virus/cell fusion, in addition to interfering with the glycosylation of the SARS-CoV cellular receptors. Chloroquine is an inexpensive and safe medication, and it has been used for over 70 years.[1,2] Hydroxychloroquine (a chloroquine analogue) has an *in vitro* anti-SARS-CoV activity. The clinical safety profile of hydroxychloroquine is better than chloroquine (over its long-term use) and allows for a higher daily dose, with less concerns about pharmacological interactions.[3]

There are *in vitro* reports suggesting the antiviral efficacy of chloroquine that date back to 1969,[4] and more recently *in vitro* efficacy with regards to the COVID-19 infection, as shown in the systematic review published by Cortegiani et al.[5] In a trial published by Wang et al., as a letter to the editor in the *Cell Research* journal, they showed that chloroquine was effective both during the entry and post-entry stages of the 2019-nCoV infection, on Vero E6 cells.[1] Its immunomodulatory activity may be effective *in vitro*, synergically increasing its antiviral effect *in vivo*. Following its oral administration, it is widely distributed throughout the body, including the lungs, and may be clinically applicable against the 2019-nCoV since it has shown to be highly effective *in vitro*. Hence, there is justification, clinical evidence of effectiveness and safety with the long-term clinical use for other indications, to justify clinical research on chloroquine in patients with COVID-19.[1,5,6]

Up to this date, with the scientific information available, we do not have conclusive evidence to recommend the prescription of chloroquine or hydrochloroquine as prophylaxis for the infection; however, as the COVID-19 pandemic evolves, there are already 4 worldwide studies to assess its prophylactic efficacy: NCT04318444, NCT04318015, NCT04303507 and NCT04308668.[7] The Indian Council of Medical Research recommends the use of hydroxychloroquine for prophylaxis, as follows[7]:

- All healthcare workers involved in the care of suspicious or confirmed cases of COVID-19: 400 mg twice a day on day one, followed by 400 mg once a week with a meal, for the next 7 weeks.
- Asymptomatic household contacts of laboratory confirmed cases may be prescribed 400 mg twice a day for day one, followed by 400 mg once a week with a meal, for the next 3 weeks.

Moreover, in view of the recent, scarce and non-conclusive clinical scientific evidence, antimalarial agents are suggested as a therapeutic strategy in moderate to severe COVID-19 cases. In the absence of effective strategies, based on the recent study conducted by Gautret et al., in patients with confirmed COVID-19 infection, with significant methodological limitations, hydroxychloroquine was used at a dose of 200 mg, 3 times per day for 10 days, in 6 asymptomatic patients, 22

PII of original article: S0121-8123(20)30055-4

☆ Please cite this article as: Jáuregui E. Los antimaláricos (cloroquina e hidroxicloroquina) en la pandemia COVID-19. Rev Colomb Reumatol. 2021;28:156–158.

patients with symptoms of upper respiratory tract infection, and other 8 with lower respiratory tract infection. They submitted the results of just 20 cases that showed a significant reduction in viral load by day 6 after inclusion, as compared to controls, and a much shorter average duration in non-treated patients than what is reported in the literature. Azithromycin added to hydroxychloroquine was significantly more effective to clear the virus.[3]

Another recent randomized clinical trial conducted by Chen et al. included 62 patients with COVID-19 infection, of which 31 were assigned to receive hydroxychloroquine and the rest were assigned to the control group. They showed that the use of hydroxychloroquine could significantly shorten the clinical recovery times and promote the resolution of pneumonia (80.6% *vs.* 54.8%).[8]

In view of the scarce evidence, China made an expert consensus publication which is available in English as an abstract, recommending the use of chloroquine phosphate 500 mg 2 times per day for 10 days, in patients diagnosed with mild, moderate and severe coronavirus-associated pneumonia, if no contraindications exist.[9]

In response to the anticipation generated by the antimalarial agents, the authorities in various countries (Italy, Spain, France and even Colombia) have included chloroquine or hydroxychloroquine as one of the treatment options in their management protocols for patients with COVID-19 infection. These recommendations are being constantly reviewed and may change if the epidemiological situation and the therapeutic options require changes.[10,11]

Therefore, in order to be able to make a strong recommendation about the use of antimalarial agents for the treatment of COVID-19 infection, we must wait for the results of the clinical trials conducted with high methodological quality, many of which are already under way.

It is important to recall that in case these medications are used, antimalarial agents are contraindicated in patients with a history of hypersensitivity to chloroquine and to the 4-aminoquinolines, in patients with retinopathy or visual field impairment, hematopoietic disorders, glucose-6-phosphato dehydrogenase deficit (hemolytic anemia, favism) and myasthenia gravis. These drugs must be used with caution in patients with mild to moderate kidney or liver failure, who may even require dose adjustments.[12,13]

Antimalarial agents may cause severe hypoglycemia[12] and prolongation of the QTc-interval,[12,13] so they must be used with caution in patients with congenital or acquired and documented QT prolongation, or known risk factors of QT prolongation such as:

- Cardiac disorders, *i.e.*, hear failure, myocardial infarction;
- Pro-arrhythmic conditions, *i.e.*, bradycardia (<50 bpm);
- A history of ventricular arrhythmia;
- Uncorrected hypomagnesemia or hypopotassemia;

And during the concomitant administration of drugs that cause QT prolongation, since this may result in an increased risk of ventricular arrhythmia, that sometimes may be lethal. Some of these drugs include the anti-arhythmic class IA and III agents, tricyclic antidepressants, antipsychotic agents, and some anti-infectives.[12,13]

In conclusion, the option of using antimalarial drugs in the treatment of COVID-19 should be carefully pondered, in accordance with the recent announcements with regards to their efficacy and potential adverse effects. The recommendation is to limit its prescription exclusively to healthcare workers. The review of the results of the clinical trials should be very critical, to be able to make recommendations about their use, if efficacy is confirmed both for the prevention and treatment of this 21st Century pandemic, to guide clinical practice.

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Edwin Jáuregui
ASOREUMA, Reumatología, Riesgo de fractura S.A-CAYRE IPS, Bogotá, Colombia

E-mail address: edwinjaureguic69@gmail.com
2444-4405/

https://doi.org/10.1016/j.rcreue.2021.04.002