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Editorial article

Use of antimalarial drugs in the treatment of COVID-19: A window of opportunity?[☆]

Uso de antipalúdicos en el tratamiento del COVID-19: ¿una ventana de oportunidad?

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Since the first cases of coronavirus were reported in December 2019 in Wuhan, China, the scientific community has been searching for an effective treatment, relying largely on prior knowledge about the other 6 known human coronaviruses to date, of which, the SARS-CoV and the MERS-CoV were responsible for major epidemics in 2003 and 2012 respectively.

It was precisely in 2003 when Savarino et al. hypothesized the possible usefulness of chloroquine and hydroxychloroquine in the treatment of SARS-CoV,[1] prompting several studies in subsequent years trying to evaluate its *in vitro* antiviral efficacy against this and other human coronaviruses, collected in a review recently published by Raoult et al.[2]

The different investigations carried out since then attribute to these 2 drugs an antiviral action dependent on multiple mechanisms, sometimes replicated in *in vivo* studies, and that, in the case of COVID-19, could include interference with glycosylation of the ACE2 receptor that the virus uses to bind to cells; the inhibition of the quinone reductase 2 enzyme, involved in the synthesis of sialic acids, which act as ligands for the virus; the alkalinization of endosomes and the inhibition of kinases such as MAPK, among others.[3,4]

In addition to this direct antiviral action, its immunomodulatory effect, which justifies its use in the chronic treatment of rheumatoid arthritis and systemic lupus erythematosus, may be of special interest in SARS-CoV2 infection, especially in patients who develop a macrophage activation syndrome, extremely serious due to its common progression to multiple organ failure,[5,6] and that until now has been treated with glucocorticoids and tocilizumab.[5] Given the fact that a circular letter recently published in the *Lancet* pointed out that these drugs should be used with caution because they could prolong the infection time by depressing the immune system,[5,7]

the combined antiviral and immunomodulatory action of hydroxychloroquine makes its use pathophysiologically attractive.

The first study of the use of chloroquine in coronavirus-19 infection was conducted in China and was published on **4th February**. It analyzed the effect of various antivirals on Vero E6 cells, which come from kidney epithelial cells isolated from an African green monkey. To assess the effect, they measured EC50, the minimum concentration of chloroquine needed to inhibit 50% of the virus, and CC50, the concentration of the drug that kills 50% of the host's cells. Ideally, for a drug to be used in clinical practice, the EC50 should be as low as possible and the CC50 should be as high as possible. When this occurs, we have a remarkably high selectivity index, that is, the drug acts selectively against the virus without harming the organism, as was seen in the case of chloroquine and remdesivir.[8]

Since chloroquine works by preventing the entry of the virus into cells, 3 treatment regimens were tested that verified the inhibitory potential of chloroquine before and after the Vero cells infection, while remdesivir was only effective with the infection already established.[8]

The fact that the concentration with which chloroquine managed to inhibit 90% of the pathogen, of 6.90 μM, was previously achieved in patients with rheumatoid arthritis at doses of 500 mg[8] motivated the start of several clinical trials in China, the preliminary results of which were published on **19th February** in a review article that stated that this drug had shown benefits in 100 patients, presumably managing to prevent the exacerbation of pneumonia, improve lung CT images, promote virus suppression and shorten the duration of the disease without producing any serious adverse reaction.[9]

Given this evidence, the article itself recommended the use of chloroquine phosphate in patients with COVID-19,[9] a recommendation which was added that same day to the Chinese National Plan for Diagnosis and Treatment, version number 6, where it appears as first-line antiviral treatment, in a dose of 500 mg orally 2 times a day for 7 days.[10]

On **9th March,** the second *in vitro* clinical trial of chloroquine was published, this time comparing this drug with another from the same group, hydroxychloroquine, which differs in its molecular structure by incorporating a hydroxyl group, which gives it

a series of specific properties, such as a greater immunomodulatory effect, possibly related to its action on toll-like receptors and the decrease in the production of IL-6, the role of which becomes important in the genesis of the macrophage activation syndrome[4] in these patients; as well as a better safety profile that allows higher doses to be used, and fewer interactions,[4,11,12] which make it especially attractive in older patients with comorbidities, often exposed to polypharmacy, who are most seriously affected by the virus.

This study revealed that the EC50 of hydroxychloroquine was lower than that of chloroquine, both in therapeutic and prophylactic use, which translated into greater efficacy of hydroxychloroquine compared to its precursor. Likewise, the efficacy was greater for both drugs at 48 h that at 24 h after administration, which could reflect its ability to accumulate. Given this peculiar kinetics, a computer model calculated that the safest and most effective regimen for patients was an initial induction dose of 400 mg twice a day on day 1, followed by 200 mg twice a day for the next 4 days, managing to keep the calculated concentrations in blood and lungs relatively stable throughout the treatment.

These are the findings that precede the clinical trial led by Didier Raoult, led by Gautret and published on **20th March**, which found that, on the sixth day of the start of the study, only 12.5% of the patients in the control group had become negative compared to 57.1% of the patients who received 200 daily mg of hydroxychloroquine sulphate for 10 days, and 100% of those who received the combination of hydroxychloroquine and azithromycin, the latter at doses of 500 mg on day 1, followed by 250 mg/day during the subsequent 4 days.[13]

This study, which has been heavily criticized for not presenting results on mortality or the clinical progression of patients, as well as for an excessive speed in the review, was followed by an observational study which became available on the Internet on **29th March**, carried out by the same group, which analyses the clinical course, contagiousness (PCR < 34 or positive culture), and length of hospital stay in a sample of 80 patients ranging from 20 to 88 years of age (μ = 52.5) treated with the previous regimen (92%) or adding a broad-spectrum antibiotic (ceftriaxone). Although the discharge criteria varied during admission due to the increase in care burden, it is striking that 81.3% of patients were discharged on an average of 4.1 days from the start of therapy, and 4.6 days from admission, with a low score on the NEWS scale, which estimates the presence of disease; 16.2% and 1.2% of hospitalized patients remained in the infectious diseases department and ICU, respectively, and only one 86-year-old patient who had been admitted with advanced pneumonia died during the study. Similar to what happened in the preliminary study, contagiousness experienced a rapid and progressive decrease, with negative PCR in 83% of patients on the seventh day, and 93% on the eighth day.[14]

These findings are supported by a randomized clinical trial of 62 patients with mild pneumonia (without hypoxia) due to SARS-CoV2, published on **30th March** in China, which found significant differences in the total or partial resolution of pneumonia among the group treated with 400 mg/day of hydroxychloroquine for 5 days (80.6%) compared to the control group (54.8%), in which 4 individuals experienced progression to severe disease. Again, there were no serious adverse reactions with the administration of the drug, with only one case of rash and one of headache. It should be noted that, possibly to speed up the publication process, the article has not been peer reviewed.[15]

The importance of these findings lies in the fact that the time that a patient remains infected with the virus could be significantly reduced, from the 20 days in which the mean value is at present,[16] to about 7–8 days, decreasing the transmissibility of the disease. On the other hand, the early discharge of patients would reduce hospital saturation and optimize the treatment offered. In addition, the use of hydroxychloroquine has the incentive of its low price in

relation to the rest of the drugs being tested, since it is not subject to a patent and would not exceed a daily cost of 60 cents per patient.

However, a recent randomized clinical trial published in China examining the efficacy and safety of the administration of 400 mg of hydroxychloroquine together with the different treatments recommended by the Chinese National Plan for Diagnosis and Treatment (INFα2a, lopinavir/ritonavir, arbidol, *etc.*), compared to the exclusive use of the latter in 30 patients with COVID-19 infection, found no significant difference in viral load at 7 days of treatment, nor in the average hospital stay, the mean time of decrease in body temperature, radiological progression in computed tomography or adverse reactions, which, for both groups, consisted of transient diarrhoea and impaired liver function. It should be noted that the study itself indicates that the sample size is far from the number needed to achieve results with significant statistical power.[17]

The *in vivo* assessment of the prophylactic treatment is still pending, as well as the publication of the results of different studies that are already being carried out, such as the one led by Oriol Mitjà, of the Germans Trias Hospital in Badalona (Barcelona).

Despite these promising results, there is some controversy about the generalized use of antimalarial drugs in the treatment of COVID-19.[18] All drugs need to meet efficacy and safety criteria in order to standardize their use in humans. Although the evidence regarding efficacy, which is being evaluated in this article, is still scarce, the results of several ongoing clinical trials are expected to be published soon, which will shed light on the relevance of replacing current treatments with this new alternative. The rapid development of evidence requires that the conclusions of this editorial should be taken with caution.

Another desired criterion is that it is safe, that is, non-toxic. In this sense, we already have data on its safety at the doses it is intended to be used because chloroquine and/or hydroxychloroquine are used at high doses in the acute attack of malaria, Q fever and Whipple's disease[12,13,19] and, specifically on COVID-19 patients, the *in vivo* studies conducted so far have reported no serious adverse reactions.[9,14,15,17] In this sense, previously published studies confirm that the cardiac complications reported in case of hydroxychloroquine overdose, a risk that we can face with short regimens at high doses, could be actively prevented if its administration is avoided in patients with contraindications, intermittent electrocardiogram monitoring is used during treatment, a maintenance dose lower than that of induction is applied to prevent its accumulation, and the dose is adjusted in those patients who may require it, as specified in the drug's SmPC of the Spanish Agency of Medicines.[8,12,14] The evidence for the concomitant use of azithromycin and chloroquine is more limited. Although in a 2011 article evaluating the safety and tolerability of both drugs in combination, only minor adverse events such as the presence of nausea associated with azithromycin were reported,[20] a recent study of 84 patients with COVID-19 treated with hydroxychloroquine and azithromycin demonstrates QTc interval prolongation, from 435 ± 24 ms to 463 ± 32 ms. In 11% of patients, the maximum QTc value exceeded 500 ms, with this being an important and recognized risk factor for the development of potentially fatal malignant arrhythmias.[21] Furthermore, QTc prolongation was independent of baseline values, underscoring the importance of continuous or frequent monitoring in these patients[21] and consolidates the resounding demand for caution in the use of the combination of these drugs, as already supported by some authorities.[22] In any case, a multinational study on the safety profile of hydroxychloroquine alone and in combination with azithromycin is currently underway in more than 130,000 patients with COVID-19 pneumonia (ClinicalTrials.gov identifier: NCT04321278).[23]

The fact that, according to a recent document from the Occupational Risk Prevention Service of the Madrid health department, this drug has begun to be applied to health workers with confirmed or

probable COVID-19, suggests that, with the safety data we already have, and in the context in which we find ourselves, the general use of hydroxychloroquine is imminent, to the extent that the availability of the product allows its administration.

Conflict of interests

None declared.

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