THE CUTTING EDGE: RESEARCH UPDATE

Hydroxychloroquine and azithromycin as a treatment of COVID-19

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Background

Since the emerging of the new coronavirus disease (COVID-19) with its staggering worldwide morbidity and mortality, the scientific community has been placed under extraordinary pressure to find safe and effective treatments, pending the availability of a vaccine. Some authors have focused their attention on the use of hydroxychloroquine, currently used in the prevention and treatment of malaria and chronic inflammatory diseases (lupus erythematosus and rheumatoid arthritis). Preclinical data suggest that hydroxychloroquine has in vitro antiviral activity blocking the entry of the virus into cells, decreasing pH within cells and attenuating cytokine production; this in vitro effect was promising against a bunch of virus (dengue, HIV, chikungunya, Ebola, SARS, and MERS) and recently, scientists have demonstrated its efficacy also against SARS-CoV-2 [1, 2]. The in vivo efficacy of hydroxychloroquine has not yet been assessed, even if several trials are ongoing (ex. trial ORCHID, NCT 04332991) [3]. Despite the lack of standardized evidences, hydroxychloroquine has been adopted by clinicians worldwide in the treatment, and in some cases, even in the prevention of patients with SARS-CoV-2 and it is still used even if some recent observational studies have confuted its usefulness [4]. The Chinese National guidelines and the US Food and Drug Administration for emergency uses have both recommended the off-label adoption of hydroxychloroquine in the treatment of COVID-19.

Summary

Gautret et al. have conducted an open-label non-randomized clinical trial to test the efficacy of the combination use of hydroxychloroquine and azithromycin in the treatment of COVID-19 patients. They recruited 42 patients with COVID-19 infection fulfilling two primary inclusion criteria: age > 12 years and PCR-documented SARS-CoV2 carriage in nasopharyngeal sample at admission, whatever their clinical status. Patients with allergy to chloroquine/hydroxychloroquine or other contraindication to treatment (retinopathy, G6PD deficiency, QT prolongation) were excluded and recruited as control patients. Patients proposed for treatment with hydroxychloroquine ± azithromycin were included and managed in the coordination centre of the study in Marseille, while controls without hydroxychloroquine treatment were followed in other hospitals all located in South France. Symptomatic treatment and antibiotics to prevent bacterial superinfection were provided by investigators based on clinical judgment. From the total 42 patients included, 26 patients received the treatment with hydroxychloroquine and 16 were control patients. 6 hydroxychloroquine-treated patients were lost to follow-up because of transfer to intensive care unit (three patients), death (one patient) or voluntary stopping of the treatment (two patients). Among hydroxychloroquine-treated patients, six patients also received azithromycin. Patients were followed for 6 days and each day, if possible, they received a standardized clinical examination and a nasopharyngeal swab. The primary outcome was virological clearance at day-6 post-inclusion. Secondary outcomes were virological clearance overtime during the period study, clinical follow-up, and occurrence of side-effects. The authors reported a 100% viral clearance in nasopharyngeal swabs after 6 days in all patients who received the combined treatment with hydroxychloroquine and azithromycin; this rate was lower with hydroxychloroquine alone (57.1%) and was 12.5% in control patients.

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Strengths of the study

– It deals with a huge, clinically relevant problem. COVID-19 is causing the death of thousands of people worldwide and changing the shape of our society, so a cure is urgently needed.
– The study has demonstrated that hydroxychlorochine alone provides viral clearance in 70% of patients at the 6-day follow-up; when azithromycin is added, this percentage raises up to 100%. If proven effective, this would be a low-cost, easily available therapeutic strategy.
– Data collection is still going on and authors, in the future, may add other important data to the ones here reported. This has been already partially done in an article from the same group published in Travel Medicine and Infectious Disease [5].

Weakness of the study

– The primary end point is viral clearance that, although important, is not as relevant as clinical outcomes in the decision-making process, especially knowing the low sensitivity of nasopharyngeal swab in detecting the presence of SARS-CoV2.
– The absence of randomization made the study vulnerable to differences in baseline risk between the subgroups. Patients were recruited in different hospitals that may have different standards of care and treatment regimens; moreover, instead of excluding patients who declined treatment, researchers assigned them to the control group.
– Patients with the most serious and clinically relevant outcomes (transfer to ICU, death) were excluded from the analysis. This leads to an inflation bias of the effect of treatment, since these patients' data may be the most interesting to assess hydroxychloroquine efficacy.
– The small sample size, especially in the setting of a worldwide pandemic disease, reduces the strengths of the results; moreover, the majority of patients enlisted have only mild upper respiratory tract symptoms. This could cause an easier resolution and a quicker clearance of the virus.

Question marks

– Authors listed as secondary end points the clinical follow-up and the occurrence of side-effects, but there is no mention of such data in the study; it would be interesting to understand if patients treated with hydroxychloro-

quine ± azithromycin had clinical benefit compared with the control group and stratifying patients according to initial clinical presentation (asymptomatic, upper and lower tract respiratory patients).
– There are no data regarding the choice of adding azithromycin in 6 out of 26 patients in the treatment group: a more precise characterization of this subgroup could help explaining the findings.

Clinical bottom line

Nowadays, there is no standardized demonstration of the efficacy of hydroxychloroquine in the prevention and treatment of patients with COVID-19 disease, even if the pre-clinical rationale and evidence are sufficient to justify clinical research on the topic. The desire to quickly find an effective treatment against SARS-CoV-2 has led to a relaxation of standards of publication, but results from well-designed randomized clinical trial are urgently needed. Since these results will be available, we think that hydroxychlorochine should not be routinely used in COVID-19 patients but only in the setting of clinical trials.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent was obtained since the study did not involve the participation of human subjects.

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