Journal Pre-proof

No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection

Jean Michel Molina Dr Constance Delaugerre Jerome Le Goff Breno Mela-Lima Diane Ponscarme Lauriane Goldwirt Nathalie de Castro

PII: S0399-077X(20)30085-8

DOI: https://doi.org/doi:10.1016/j.medmal.2020.03.006

Reference: MEDMAL 4279

To appear in: *Médecine et Maladies Infectieuses*

Received Date: 28 March 2020

Please cite this article as: Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, de Castro N, No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection, *Médecine et Maladies Infectieuses* (2020), doi: https://doi.org/10.1016/j.medmal.2020.03.006

No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection.

Jean Michel Molina[1-3], Constance Delaugerre[2-4], Jerome Le Goff[2-4], Breno Mela-Lima[1], Diane Ponscarme[1], Lauriane Goldwirt[5], and Nathalie de Castro[1].

[1] Infectious Diseases Department, Saint Louis Hospital, 75010 Paris, France

[1]Université de Paris, 75000 Paris, France.

[3]U944 INSERM, Université de Paris, 75000 Paris, France

[4]Virology Department, APHP-Saint Louis Hospital, 75010 Paris, France

[5]Pharmacology Department, APHP, Saint-Louis Hospital, 75010 Paris, France

Corresponding author: Dr. Jean-michel Molina; Infectious Diseases Department, APHP-Saint Louis Hospital, 1 avenue Claude Vellefaux, 75010 Paris, France; Tel: +33.1.42.49.90.66;

Email : jean-michel.molina@aphp.fr

The COVID-19 epidemic is the worst worldwide pandemic in a century with more than 500,000 cases and 25,000 deaths so far. In France, more than 30,000 cases have been reported up to March 27, and nearly 2,000 have died.

Pending the availability of a vaccine, there is a critical need to identify effective treatments and a number of clinical trials have been implemented worldwide.

Chloroquine analogs have been shown to inhibit the acidification of endosomes and to exhibit in vitro a non specific antiviral activity at high micromolar concentration against a broad range of emerging virus (HIV, dengue, hepatitis C, chikungunya, influenza, Ebola, SARS and MERS viruses) and more recently COVID-19 (1-2).

In France, following the results of a clinical study in Marseille, there is considerable interest for the use of hydroxychloroquine to treat COVID-19 disease, and the French Ministry of Health recently allowed the use of hydroxychloroquine to treat COVID-19 disease pending the results of ongoing clinical trials (3).

In their study, Gautret et al. reported a 100% viral clearance in nasopharyngeal swabs in 6 patients after 5 and 6 days of the combination of hydroxychloroquine and azithromycin (3).

This rate of viral clearance was lower with hydroxychloroquine alone (57.1%) and was only 12.5% in patients who did not receive hydroxychloroquine (p< 0.001).

Such a rapid and full viral clearance was quite unexpected and we wished to assess in a prospective study virologic and clinical outcomes of 11 consecutive patients hospitalized in our department who received hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg Day 1 and 250 mg days 2 to 5) using the same dosing regimen reported by Gautret et al. (3).

There were 7 men and 4 women with a mean age of 58.7 years (range: 20-77), 8 had significant comorbidities associated with poor outcomes (obesity: 2; solid cancer: 3; hematological cancer: 2; HIV-infection: 1).

At the time of treatment initiation, 10/11 had fever and received nasal oxygen therapy. Within 5 days, one patient died, two were transferred to the ICU. In one patient, hydroxychloroquine and azithromycin were discontinued after 4 days because of a prolongation of the QT interval from 405 ms before treatment to 460 and 470 ms under the combination. Mean through blood concentration of hydroxychloroquine was 678 ng/mL (range: 381-891) at days 3-7 after treatment initiation.

Repeated nasopharyngeal swabs in 10 patients (not done in the patient who died) using a qualitative PCR assay (nucleic acid extraction using Nuclisens Easy Mag®, Biomerieux and amplification with RealStar SARS CoV-2®, Altona), were still positive for SARS-CoV2 RNA in 8/10 patients (80%, 95% confidence interval: 49-94) at days 5 to 6 after treatment initiation.

These virologic results stand in contrast with those reported by Gautret et al. and cast doubts about the strong antiviral efficacy of this combination. Furthermore, in their report Gautret et al also reported one death and three transfers to the ICU among the 26 patients who received hydroxychloroquine, also underlining the poor clinical outcome with this combination.

In addition, a recent study from China in individuals with COVID-19 found no difference in the rate of virologic clearance at 7 days with or without 5 days of hydroxychloroquine, and no difference in clinical outcomes (duration of hospitalization, temperature normalization, radiological progression) (4). These results are consistent with the lack of virologic or clinical benefit of chloroquine in a number of viral infections where it was assessed for treatment or prophylaxis with sometimes a deleterious effect on viral replication (5-8).

In summary, despite a reported antiviral activity of chloroquine against COVID-19 in vitro, we found no evidence of a strong antiviral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment of our hospitalized patients with severe COVID-19. Ongoing randomized clinical trials with hydroxychloroquine should provide a definitive answer regarding the alleged efficacy of this combination and will assess its safety.

Déclaration de liens d'intérêts : Les auteurs déclarent ne pas avoir de lien d'intérêts

Références

1. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell research 2020; 30:269-71.
2. Al-Bari AA. Targeting endosomal acidification by chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. Pharmacology research and perspectives. 2017;5:e00293
3. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents 2020 (ahead of print).
4. Chen J, Liu D, Lui L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 COVID-19). Journal of Zhejiang University 2020; 03-03
5. Roques P, Thiberville SD, Dupuis-Maguiraga L et al. Paradoxical effect of chloroquine treatment in enhancing Chikungunya virus infection. Viruses, 2018:10:268
6. Tricou V, Minh NN, Van TP et al. A randomized controlled trial of chloroquine for the treatment of dengue in Vietnamese adults. PLos Neglected tropical diseases 2010; 4:e785.
7. Paton NI, Lee L, Xu Y, et al. Chloroquine for influenza prevention: a randomised, double-blind, placebo-controlled trial. Lancet Infectious Diseases, 2011; 11:677-83
8. Paton NI, Goodall RL, Dunn DT, et al. Effects of hydroxychloroquine on immune activation and disease progression among HIV-infected patients not receiving antiretroviral therapy: a randomized controlled trial. JAMA. 2012;308 (4):353-61.