Chloroquine and hydroxychloroquine as potential therapies against COVID-19

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***Abstract*- The desperate search to find effective treatments for coronavirus disease 2019 (COVID-19), 2 generic drugs, used largely by rheumatologists and dermatologists to treat immune-mediated diseases, have entered the spotlight. The antimalarials hydroxychloroquine (HCQ) and chloroquine (CQ) have demonstrated antiviral activity against severe acute respiratory syndrome–coronavirus 2 (SARS–CoV-2) in vitro and in small, poorly controlled or uncontrolled clinical studies (1–3). Normally, such research would be deemed hypothesis-generating at best. Here, we try to provide guidance regarding clinical decision making both for patients with COVID-19 and those with immune-mediated conditions, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), and strategies to mitigate further harm to these patients.**

***Index terms*- chloroquine clinical research clinical trials corona virus in COVID-19 disease & medicine hydroxychloroquine malaria nut shell SARS-CoV-2**

INTRODUCTION

On 16 April, the Spanish Agency for Medicines and Healthcare Products (AEMPS) updated a document analysing different available alternatives, existing presentations, degree of evidence, access requirements, proposed doses and most common adverse effects for every assessed drug (1). The chloroquine/hydroxychloroquine section provides interesting information taking into account these aspects, highlighting its important role against malaria, lupus or rheumatoid arthritis.

With regard to the scientific evidence, CRQ and HCQ have shown in vitro activity against SARS-CoV-2, but so far no published clinical trials have been carried out to confirm this effect. In other contexts, CRQ has not been shown to be effective in treating other viruses in animal or human models such as influenza, dengue or Chikungunya (1). Despite the limited evidence, the FDA has issued an emergency use authorization for the use of CRQ and HCQ in hospitalized patients with COVID-19 (2).

Hydroxychloroquine (HCQ):-

Hydroxychloroquine (HCQ), sold under the brand name Plaquenil among others, is a medication used to prevent and treat malaria in areas where malaria remains sensitive to chloroquine. Other uses include treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda. It is taken by mouth. It is also being studied as a treatment for coronavirus disease 2019 (COVID-19). Common side effects include vomiting, headache, changes in vision, and muscle weakness. Severe side effects may include allergic reactions, vision problems, and heart problems. Although all risk cannot be excluded, it remains a treatment for rheumatic disease during pregnancy. Hydroxychloroquine is in the antimalarial and 4-aminoquinoline families of medication. was approved for medical use in the United States in 1955. It is on the World Health Organization's List of Essential Medicines, the safest and most effective medicines needed in a health system. In 2017, it was the 128th most commonly prescribed medication in

the United States, with more than five million prescriptions. • Classification: Antimalarial
• Rationale for Use: Hydroxychloroquine has in vitro activity against SARS-CoV-2 and may have immunomodulating properties. • Mechanism of Action: Mechanisms may include inhibition of viral enzymes or processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release. Other mechanisms may also involve ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release. • FDA Emergency Use Authorization (EUA) (66) (68) o Hydroxychloroquine is not FDA-approved for the treatment of COVID-19. o The EUA states treatment is for adult and adolescent patients weighing 50 kg or more who are hospitalized with COVID-19. o Authorized hydroxychloroquine is limited to product supplied from the Strategic National Stockpile (SNS) and will be distributed to authorized heath care systems and providers.

Medical use:-
Hydroxychloroquine is used to treat systemic lupus erythematosus, rheumatic disorders like rheumatoid arthritis, porphyria cutanea tarda, and Q fever, and certain types of malaria. It is considered the first-line treatment for systemic lupus erythematosus.[10] Certain types of malaria, resistant strains, and complicated cases require different or additional medication.
It is widely used to treat primary Sjögren syndrome, but has not been shown to be effective. Hydroxychloroquine is widely used in the treatment of post-Lyme arthritis. It may have both an anti-spirochaete activity and an anti-inflammatory activity, similar to the treatment of rheumatoid arthritis.

Adverse effect
The most common adverse effects are nausea, stomach cramps, and diarrhea. The most serious adverse effects affect the eye, with dose-related retinopathy as a concern even after hydroxychloroquine use is discontinued. For short-term treatment of acute malaria, adverse effects can include abdominal cramps, diarrhea, heart problems, reduced appetite, headache, nausea and vomiting. For prolonged treatment of lupus or rheumatoid arthritis, adverse effects include the acute symptoms, plus altered eye pigmentation, acne, anemia, bleaching of hair, blisters in mouth and eyes, blood disorders, convulsions, vision difficulties, diminished reflexes, emotional changes, excessive coloring of the skin, hearing loss, hives, itching, liver problems or liver failure, loss of hair, muscle paralysis, weakness or atrophy, nightmares, psoriasis, reading difficulties, tinnitus, skin inflammation and scaling, skin rash, vertigo, weight loss, and occasionally urinary incontinence.
Hydroxychloroquine can worsen existing cases of both psoriasis and porphyria. Children may be especially vulnerable to developing adverse effects from hydroxychloroquine.

Pharmacology
Pharmacokinetics
Hydroxychloroquine has similar pharmacokinetics to chloroquine, with rapid gastrointestinal absorption, large distribution volume,[26] and elimination by the kidneys. Cytochrome P450 enzymes (CYP2D6, 2C8, 3A4 and 3A5) metabolize hydroxychloroquine to N-desethylhydroxychloroquine.[27]

Pharmacodynamics
Antimalarials are lipophilic weak bases and easily pass plasma membranes. The free base form accumulates in lysosomes (acidic cytoplasmic vesicles) and is then protonated,[28] resulting in concentrations within lysosomes up to 1000 times higher than in culture media. This increases the pH of the lysosome from four to six.[29] Alteration in pH causes inhibition of lysosomal acidic proteases causing a diminished proteolysis effect.[30] Higher pH within lysosomes causes decreased intracellular processing, glycosylation and secretion of proteins with many immunologic and nonimmunologic consequences.[31] These effects are believed to be the cause of a decreased immune cell functioning such as chemotaxis, phagocytosis and superoxide production by neutrophils.

Mechanism of action
Hydroxychloroquine increases[34] lysosomal pH in antigen-presenting cells. In inflammatory conditions, it blocks toll-like receptors on plasmacytoid dendritic cells (PDCs).[citation needed] Toll-like receptor 9

(TLR 9), which recognizes DNA-containing immune complexes, leads to the production of interferon and causes the dendritic cells to mature and present antigen to T cells. Hydroxychloroquine, by decreasing TLR signaling, reduces the activation of dendritic cells and the inflammatory process.[medical citation needed

In 2003, a novel mechanism was described wherein hydroxychloroquine inhibits stimulation of the toll-like receptor (TLR) 9 family receptors. TLRs are cellular receptors for microbial products that induce inflammatory responses through activation of the innate immune system.

A CRITICAL READING OF THE CLINICAL EVIDENCE At present, numerous clinical trials are underway with CRQ and HCQ (3) such as SOLIDARITY (4) or EPICOS (5), among the most important projects in Spain. Nevertheless, the first published article mentioning the use of CRQ in patients with COVID-19 was a letter to the editor (6) where no verifiable data is provided about its potential benefits in more than 100 infected patients, as stated in that document.

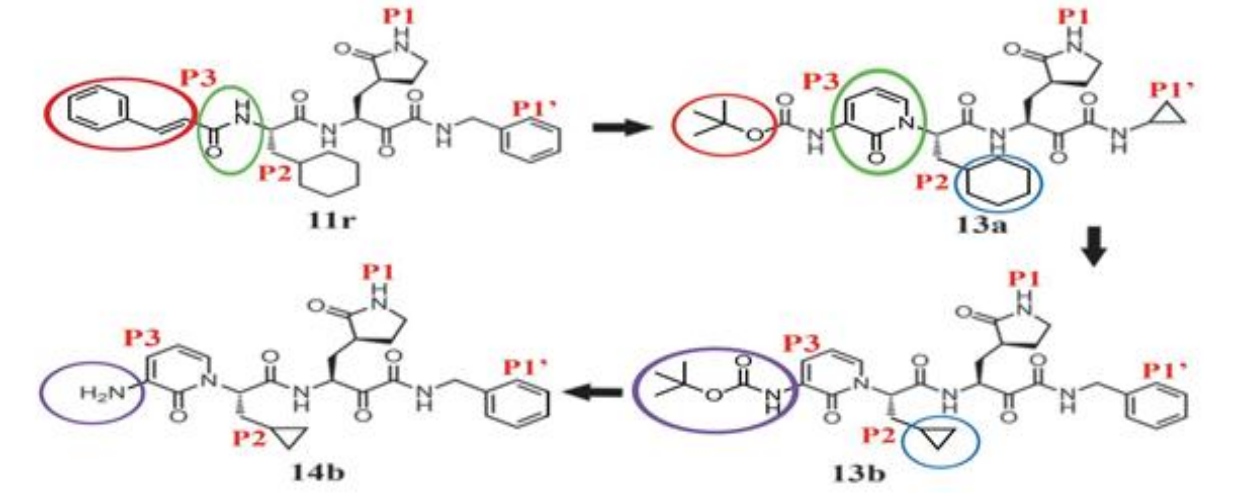
Nowadays, information can be extracted from three clinical trials (7,8,9), two of which have not been published yet, and three studies with an observational design (10,11,12), one of which has not been published yet (Table 1).

Table 1. Hydroxychloroquine studies with available results in COVID-19 patients.

Study	Design	Patients	Intervention	Main outcome	Result	Comments
Chen (7)	Open Controlled Randomized 1:1 Unicentric	N=30 (15 HCQ, 15 control) Age, mean 50 years, males 70%, COVID-19 admission, with no serious concomitant disease	HCQ 400mg/24h vs control for 5 days (all with STD)	Viral clearance at Day 7 or death in two weeks	No differences in the main outcome HCQ (86,7%) STD (93,3%)	Clinical trial with low statistical power and no positive results. All patients improve their basal condition.
Chen (8)	Open Controlled Randomized 1:1:1 Unicentric	N=62 (31 HCQ, 31 control) Age, mean 45 years, males 47%, COVID-19 with pneumonia but without serious hypoxia	HCQ 200mg/24h HCQ 400mg/24h Placebo for 5 days	Time to viral clearance and T cell recovery time	No data provided on main outcomes	**NOT PUBLISHED YET** Clinical trial with wide discrepancy between protocol and article. Uncertain findings in secondary outcomes.
Tang (9)	Open Controlled Randomized 1:1 Multicentric	N=150 (75 HCQ, 75 control) Age, mean 46 years, males 55%, mild-moderate COVID-19 admission.	HCQ 1200-800mg /24h vs control for 2-3 weeks. (all with STD)	Viral clearance within 28 days	No differences in the main outcome HCQ (85,4%) STD (81,3%)	**NOT PUBLISHED YET** Clinical trial with no positive results. Uncertain post-hoc finding.
Gautret (10)	Not controlled Not randomized With external control group	N=42 (26 HCQ, 16 control) Age, mean 45 years, males 42%, COVID-19, any level of severity	HCQ 600mg/24h (+ AZT if needed) for 10 days	Viral clearance at Day 6	HCQ+AZT (100%) HCQ (57,1%) No HCQ (12,5%) N=36 assessed	Quality of evidence low Some patients excluded Publicación bias. Conflict of interests.
Gautret (11)	Not controlled Not randomized	N=80 Age, median 53 years, males 53%, COVID-19, with or without comorbidities	HCQ 600mg/24h + AZT for ≥3 days	Clinical course Contagiousness Length of stay in the ID ward	81,3% favourable outcome; 83% negative PCR at Day 7; Mean lenght of stay of 4,6 days	**NOT PUBLISHED YET** Quality of evidence low 6 patients already assessed in other study Protocol not provided.
Molina (12)	Not controlled Not randomized	N=11 Age, mean 59 years, males 64%, COVID-19, with or without comorbidities	HCQ 600mg/24h + AZT for 10 days	Viral clearance at Day 5/6	HCQ+AZT (20%)	Quality of evidence low Protocol not provided.

The virus has been named severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) (3) because the RNA genome is about 82% identical to that of the SARS coronavirus (SARS-CoV); both viruses belong to clade b of the genus Betacoronavirus (1, 2). The disease caused by SARS-CoV-2 is called coronavirus disease 2019 (COVID-19). Whereas at the beginning of the outbreak, cases were connected to the Huanan seafood and animal market in Wuhan, efficient human-to-human transmission led to exponential growth in the number of cases. On 11 March 2020, the World Health Organization (WHO) declared the outbreak a pandemic. As of 9 April, there were >1,500,000 cumulative cases globally, with a ~5.9% case fatality rate.

Fig. 1 Chemical structures of α-ketoamide inhibitors 11r,



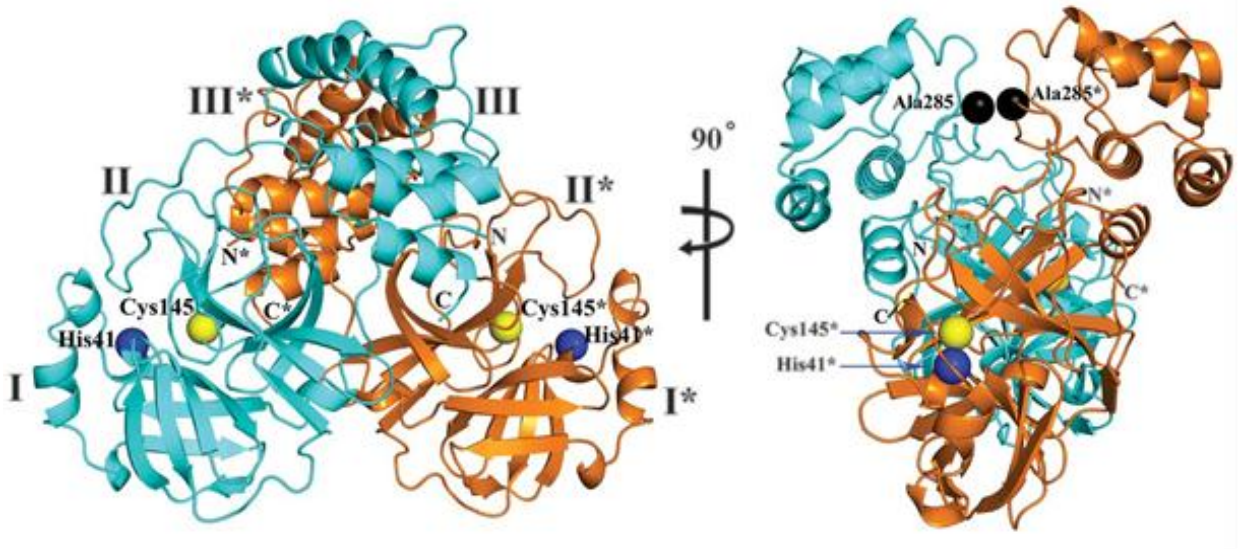


Fig. 2 Three-dimensional structure of SARS-CoV-2 Mpro in two different views

Previously, we designed and synthesized peptidomimetic α-ketoamides as broad-spectrum inhibitors of the main proteases of betacoronaviruses and alphacoronaviruses as well as the 3C proteases of enteroviruses (6). The best of these compounds (11r; Fig. 1) showed an half-maximal effective concentration (EC50) of 400 pM against Middle East respiratory syndrome–coronavirus (MERS-CoV) in Huh7 cells as well as low-μM EC50 values against SARS-CoV and a whole range of enteroviruses in various cell lines, although the antiviral activity seemed to depend to a great extent on the cell type used in the experiments (6). To improve the half-life of the compound in plasma, we modified 11r by hiding the P3-P2 amide bond within a pyridone ring (Fig. 1, green ovals) in the expectation that this might

prevent cellular proteases from accessing this bond and cleaving it. Further, to increase the solubility of the compound in plasma and to reduce its binding to plasma proteins, we replaced the hydrophobic cinnamoyl moiety by the somewhat less hydrophobic Boc group (Fig. 1, red ovals) to give 13a (see scheme S1 for synthesis).

REFERENCES

[1] a b c "Hydroxychloroquine Use During Pregnancy". Drugs.com. 28 February 2020. Retrieved 21 March 2020.

[2] a b c d e f g h i j k l m n o p q "Hydroxychloroquine Sulfate Monograph for Professionals". The American Society of Health-System Pharmacists. 20 March 2020. Archived from the original on 20 March 2020. Retrieved 20 March 2020.

[3] a b Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S (March 2020). "A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19". Journal of Critical Care. doi:10.1016/j.jcrc.2020.03.005. PMID 32173110.

[4] Grady D (1 April 2020). "Malaria Drug Helps Virus Patients Improve, in Small Study". The New York Times. Archived from the original on 1 April 2020. Retrieved 1 April 2020.

[5] a b "Guidance on patients at risk of drug-induced sudden cardiac death from off-label COVID-19 treatments". newsnetwork.mayoclinic.org. 25 March 2020.

[6] Flint J, Panchal S, Hurrell A, van de Venne M, Gayed M, Schreiber K, et al. (September 2016). "BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding-Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids". Rheumatology. 55 (9): 1693–7. doi:10.1093/rheumatology/kev404. PMID 26750124. Archived from the original on 8 April 2020.

[7] World Health Organization (2019). World Health Organization model list of essential medicines: 21st list 2019. Geneva: World Health Organization. hdl:10665/325771. WHO/MVP /EMP/IAU/2019.06. License: CC BY-NC-SA 3.0 IGO.

[8] "The Top 300 of 2020". ClinCalc. Retrieved 18 March 2020.

[9] "Hydroxychloroquine Sulfate - Drug Usage Statistics". ClinCalc. Retrieved 7 April 2020.

[10] Chew CY, Mar A, Nikpour M, Saracino AM (October 2019). "Hydroxychloroquine in dermatology: New perspectives on an old drug". The Australasian Journal of Dermatology.