Title:

Combination of hydroxychloroquine plus azithromycin as potential treatment for COVID 19 patients: pharmacology, safety profile, drug interactions and management of toxicity.

Running title:

Hydroxychloroquine-Azithromycin and COVID-19

Authors :

Guillaume Hache[1,4] PharmD, Jean Marc Rolain[2,6] PharmD, Philippe Gautret[2,7] MD, Jean-Claude Deharo MD[3,4], Philippe Brouqui[2,6] MD, Didier Raoult[2,6] MD, Stéphane Honoré[1,5,8] PharmD.

1-Service de Pharmacie, Hôpital de la Timone, APHM, 278 rue Saint Pierre, 13005-Marseille, France

2-IHU-Méditerranée Infection, 19-21 Bd Jean Moulin, 13005-Marseille, France

3-Service de Cardiologie, Hôpital de la Timone, APHM, 278 rue Saint Pierre, 13005-Marseille, France

4-Aix Marseille Univ, INSERM, INRAE, C2VN, Marseille, France

5-Aix Marseille Univ, Laboratoire de Pharmacie Clinique, Marseille, France

6-Aix Marseille Univ, IRD, APHM, MEPHI, Marseille, France

7-Aix Marseille Univ, IRD, AP-HM, SSA, VITROME, Marseille, France

8-Aix-Marseille Univ, CNRS, INP, Inst Neurophysiopathol, Marseille, France

Corresponding author :

Pr. Stéphane Honoré

Service de Pharmacie, Hôpital de la Timone, AP-HM.

278, rue saint Pierre

13006 Marseille - FRANCE.

Mail : Stephane.honore@ap-hm.fr

Phone : +33(0)491387066

ABSTRACT

The coronavirus disease COVID-19, caused by infection with SARS-CoV2, has recently emerged worldwide. In this context, there is an urgent need to identify safe and effective therapeutic strategies for treatment of such highly contagious disease. We recently reported promising results of combining hydroxychloroquine and azithromycin as an early treatment option. Ongoing clinical trials are challenging the efficacy of this combination, many clinicians claim the authorization to- or have already begun to use it to treat COVID-19 patients worldwide. The aim of this article is to share pharmacology considerations contributing to the rational of this combination, and to provide safety information in order to prevent toxicity and drug-drug interactions, based on available evidence.

INTRODUCTION

The coronavirus disease COVID-19, caused by infection with SARS-CoV2, has recently emerged worldwide. In this context, there is an urgent need to identify safe and effective therapeutic strategies for treatment of this new and highly contagious disease. Such highly contagious outbreaks are usually very sudden and spread for a relative short period of time. Albeit the clinical development of new molecules is needed for post pandemic cases and potential epidemic recurrences, clinicians have to cope with the immediate problem according to best scientific knowledge and medical experience. As time required to conduct well designed clinical trials is not compatible with the clinical management of the first wave of infection, the only available pharmacological tools are medications already approved for other diseases, candidate for a drug repositioning. Drug repositioning is thus an approach which is currently being pursued to identify safe and effective treatments against COVID 19.

In COVID 19 patients, the transition from the first symptoms of this viral infection to acute respiratory distress syndrome is likely due to uncontrolled cytokine release(*1*). Hydroxychloroquine which is better tolerated than Chloroquine in humans, exhibits both an antiviral activity against SARS-CoV2 *in vitro* and strong immunomodulatory capacities that can be useful in COVID-19(*2*). Potential mechanisms of action of hydroxychloroquine in COVID-19 disease have been reviewed recently (*3*). In a single-center non-randomized trial conducted at IHU-Méditerranée Infection /APHM in which 24 positive COVID-19 patients were treated with hydroxychloroquine 600 mg/day for ten days and antibiotic therapy if necessary (amoxicillin-clavulanic acid or azithromycin), 70% of patients who received Hydroxychloroquine were PCR negative at day six, compared to 12% for the controls. In addition, all patients who received hydroxychloroquine and azithromycin at the dosage recommended by the Marketing Authorization for the indication of superinfections of acute bronchitis were tested negative on day 6 suggesting a potential benefit of the association as compared with amoxicillin-clavulanic acid (*4*). While this study has been criticized for methodology and statistics and notably the lack of size estimates, a secondary analysis has been performed by an external non-related expert (*5*). The conclusion of this second statistical analysis was that the study does not provide sufficient evidence to support any effect of hydroxychloroquine monotherapy for treatment in COVID-19 and larger randomized studies should be considered. However, the data of Gautret et al. do suggest that the drug combination therapy associating hydroxychloroquine and azithromycin is of great interest in COVID 19 and should be prioritized as soon as possible. Then, an observational study was also conducted at IHU-Mediterranee Infection /APHM on 80 patients treated with hydroxychloroquine-

azithromycin combination and has confirmed the previous observation (*6*). Indeed, a rapid fall of nasopharyngeal viral load tested by qPCR was noted, with 83% negative at day seven, and 93% at day eight. Virus cultures from patient respiratory samples were negative in 98% patients at day five which is higher than percentage observed in the literature. From these observations, 58 trials involving hydroxychloroquine and/or azithromycin have been registered in clinicaltrials.gov so far (*13th of April 2020*) and 14 trials worldwide aim to evaluate the combination of both, with various dose regimen (see table 1). More recently, we provided the clinical and viral outcomes of our cohort of 1061 COVID-19 patients, treated at least three days with the hydroxychloroquine-azithromycin combination (*7*). We described good clinical outcomes with virological cure obtained for 91.7% of the patients, and with prolonged viral carriage at completion of the treatment for 4.4% of them. Poor clinical outcomes were described for 4.3% of the patients, including five death (0.5%). These observations suggest that the combination is safe and may avoid worsening, virus persistence and subsequent contagiosity.

Whereas ongoing clinical trials are challenging the efficacy of this combination, many clinicians claim the authorization to- or have already begun to use it to treat COVID-19 patients worldwide. Thus, the aim of this article is to describe pharmacology considerations contributing to the rational of this combination, and to provide safety information in order to prevent toxicity and drug-drug interactions, based on available evidence.

DOSE REGIMEN

We initially suggested hydroxychloroquine sulfate at a dose of 200 mg morning, noon and evening at the end of meals for ten days in accordance with the daily dose recommended in the marketing authorization for initial treatment for rheumatoid polyarthritis. In addition, azithromycin was given at a dose of 500 mg on the first day, then 250 mg in the morning from day two to day five, in accordance with the marketing authorization for superinfections of acute bronchitis. From this initial protocol, different variations have been registered in clinicaltrial.gov database. Respective dose regimen are summarized in table 1.

PRESENTATION OF MEDICATIONS

1) Hydroxychloroquine

Description

Hydroxychloroquine is a drug originally used since 1952 in the treatment of malaria in the form of hydroxychloroquine sulfate. Its use as an antimalarial has greatly decreased due to the

development of resistance in *Plasmodium*, the parasite responsible for malaria. The current use is mainly focused in rheumatology, for the treatment of rheumatoid arthritis and systemic lupus erythematosus due to its anti-inflammatory and immunomodulatory properties.

Pharmacokinetics of hydroxychloroquine

Hydroxychloroquine is well absorbed within two to four hours when given orally in doses from 100 mg to 1200 mg daily and the fraction absorbed is estimated to be around 75% (*8*). Hydroxychloroquine binds to both albumin and alpha-glycoprotein (50%) and blood concentration peaks shortly after the absorption phase and falls relatively quickly due to rapid partitioning into organs. Indeed, the accumulation of hydroxychloroquine in lysosomes appears to drive the large volume of distribution in plasma, while binding to melanin contributes to the long terminal half-life with is estimated between 30 to 50 days (*9*). The metabolism of hydroxychloroquine has been extensively studied in humans. 60% is excreted unchanged in urine and the remaining is dealkylated by cytochrome P450 (CYP) to pharmacological active monohydroxylhydroxychloroquine and N-desethylhydroxychloroquine (16 and 18% respectively) (*9,10,11)*. Thus hydroxychloroquine and metabolites are renally excreted and consequently renal impairment is likely to increase the circulating concentration of the drug and risk of toxicity. In a large study evaluating the systemic factors that determine serum concentration of hydroxychloroquine, renal failure was associated with a significantly higher serum hydroxychloroquine concentration. Moreover, no association of ethnicity or smoking with blood hydroxychloroquine concentrations was found (*12*).

Daily dose of hydroxychloroquine

Hydroxychloroquine dose regimen has been estimated according to marketed authorization and to data published about rheumatology protocols, in order to ensure safety in our initial and published experimentations. However, the effect of different daily doses of hydroxychloroquine have been investigated in a randomized, double-bling clinical trials over a period of six weeks in patients treated for rheumatoid arthritis (*13*). Dose levels tested were 400 mg/day; 800 mg/day; 1200 mg/day. Discontinuations of treatment due to adverse events appeared dose related (4% at 400 mg/day, 7% at 800 mg/day, and 9% at 1200 mg/day) without any statistical difference between the three groups of patients. Reasons for discontinuations were mostly for gastrointestinal symptoms. The only significant difference between the three groups were for nausea and vomiting occurrence. Overall it seems that toxicity of hydroxychloroquine was not dose related (in this range of doses) and dose up to 1200 mg /day for 6 weeks was well tolerated except for the gastrointestinal tract. Moreover, ophthalmologic adverse events were not dose related in this study. In fact, retinal toxicity prevalence is 8% in patients taking

hydroxychloroquine for more than five years, rising to almost 20% after 20 years of treatment (*13*). Risk factors for this retinal toxicity are treatment duration (> five years), daily dose (>5 mg/kg/day based on actual body weight), and cumulative dose > 1000g (*14*). Thus short treatment prescribed in our protocol may not lead to retinopathy. Finally, antimalarial agents are associated with oxidative hemolysis, especially in patients with severe variants of glucose-6-phosphate dehydrogenase deficiency. However, such events were not reported in a survey of 275 rheumatology patients treated with hydroxychloroquine, with established G6PD deficiency (*15*).

2) Azithromycin

Description

Azithromycin, is an azalide and is structurally related to the macrolide family of antibiotics. Macrolides have received considerable attention for their anti-inflammatory and immunomodulatory actions beyond the antibacterial effect. These two properties may ensure some efficacy in a wide spectrum of respiratory viral infections; for review see (*16*).

Pharmacokinetics of azithromycin

After oral administration, azithromycin is widely distributed in tissues and particularly in lung with an apparent steady-state volume of distribution of 31.1L/kg. The major route of elimination is biliary excretion of azithromycin as unchanged drug, and 6% of administered dose is found as unchanged drug in urine over one week after administration. Terminal elimination half-life is estimated around 68h [official drug label FDA] (*17*).

Dose of azithromycin

The dose regimen choose in our initial protocol is in accordance with the marketing authorization for superinfections of acute bronchitis.

PHARMACOLOGICAL CONSIDERATIONS FOR COMBINATION OF HYDROXYCHLOROQUINE AND AZITHROMYCIN

Based on our preliminary results suggesting a potential benefit of the association to reduce viral load of SARS- CoV2, Samarth Sandeep and Kirk McGregor performed energetics based modeling of hydroxychloroquine and azithromycin binding to the SARS-CoV-2 spike (S) protein- ACE2 complex (*4,18*). Based on the binding results they provide, hydroxychloroquine may be ineffective in directly inhibiting the SARS-CoV-2 spike-ACE2 interaction by itself. Instead, it seems to increase the acidity of the ACE2 system in the interaction between the

ACE2 and SARS-CoV-2 spike that could result in the degradation of the spike, and potentially to decrease virus dissemination. On the other hand, azithromycin provides high binding affinity and may directly target the binding interaction point between the SARS-CoV-2 spike and ACE2 (*18*). This, coupled with its ability to increase pH, may be responsible for the apparent synergism between hydroxychloroquine and azithromycin that we observed (*4,5*). Recently, our team at IHU-Méditerranée Infection demonstrate that the combination of hydroxychloroquine and azithromycin has a synergistic effect *in vitro* on SARS-CoV-2 at concentrations compatible with that obtained in human lung (*19*). These data give a pharmacological rationale for using this association in the context of COVID-19.

On the other side, some reports described ineffectiveness of macrolides in some viral infection such as rhinovirus infections (*20*), MERS (*21*) and H1N1 patients (*22*); and even detrimental effect of hydroxychloroquine in some viral infections such as Chikungunya virus and HIV (*23,24*). The suspected mechanism was that hydroxychloroquine inhibit the effect of T-cells by interfering by interfering on interleukin 2 production (*25*), fundamental in priming and maintaining T-helper 2 cell response (*26*). Azithromycin may also exert immunomodulatory effects by inhibiting T-helper 2 cytokines (*27*). Our report on 1061 COVID19 treated patient did not unveil such detrimental effect(*7*).

HYDROXYCHLOROQUINE / AZITHROMYCIN CONTRAINDICATIONS

Contraindications for this combination are those reported for each individual drug and presented in table 2 (*28*).

ASSOCIATION OF HYDROXYCHLOROQUINE AND AZITHROMYCIN, DRUG-DRUG INTERACTION AND CARDIAC TOXICITY

Both medication have been widely used over the last decades. For example in the US, 52.5M prescriptions were written for azithromycin in 2012 and 4.5M for hydroxychloroquine in 2013 according to IMS health. To date, there are very limited data about safety of the proposed protocol in COVID-19 patients. Thus, we initially assessed the safety of the protocol indirectly, in regard with the available literature about toxicity for each medication in their respective therapeutic areas, not given in association. Azithromycin and chloroquine do not exhibit any direct pharmacokinetic interaction (*29*). In addition, azithromycin plus chloroquine combination therapy was well tolerated for the treatment of uncomplicated *Plasmodium falciparum* malaria in two multi-country randomized clinical trials in African adults and can be used safely during pregnancy (*30,31*). The European Respiratory Society chILD guidelines

recommend the use of either hydroxychloroquine or azithromycin as second line to treat childhood interstitial lung disease and side effects and monitoring are very well documented (*32*,*33*).

Chloroquine is known to increase the risk of prolongation of the QTc interval (*34*). A recent systematic review of the literature, has investigated the cardiac complications attributed to hydroxychloroquine and chloroquine (*35*). Only 127 reported cases were identified and for most of them they were treated for long time treatment with a median of seven years (three days-35 years) and for a very high cumulative dose. The median cumulative dose was 1235 g for hydroxychloroquine and 803 g for chloroquine much higher than the cumulative dose in our protocol for hydroxychloroquine (i.e six grams) (*35*). A risk of QTc prolongation also exist for azithromycin, particularly for the elderly aged 60-79 years (*36*). According to the thesaurus of drug interactions from the French agency of drugs (ANSM) the interaction was classified in the stress level "precaution for use". Thus, clinical and electrocardiographic monitoring is recommended when prescribing the association (*37*). A recent report about 84 patients described a major QT prolongation (>500ms) in 11% of patients with SARS-CoV-2 infection treated with hydroxychloroquine and azithromycin, leading to treatment discontinuation; no *torsades de pointe* was reported (*38*). In addition, a large cohort study, which include nearby 1 million patients, did not identified any increased risk of severe adverse events at 30-day with hydroxychloroquine compared to sulfasalazine in patients with rheumatoid arthritis (*39*). However, in patients treated by hydroxychloroquine, their meta-analysis reported 1.8 cardiovascular related death per 1,000 patients co-treated with azithromycin compared to 0.7 per 1,000 patients co-treated with amoxicilline. The authors concluded that the addition of azithromycin may induce cardiovascular mortality, potentially due to synergistic effect on QT prolongation. These conclusions should be taken with caution. First, the prevalence of acute respiratory disease appeared higher in hydroxychloroquine + azithromycin group suggesting that patient were more exposed to cardiac events related to respiratory disease. For example, myocarditis were reported in pulmonary infections, including COVID-19, and may cause sudden death (*40,41)*. Based on our experience including 3,000 patients COVID-19, we reported one COVID-19 related myocarditis leading to death; a woman, 28 years old, non-treated by hydroxychloroquine nor azithromycin. Secondly, the exposition to treatment in terms of dosing and length were not documented which does not allow to estimate the contribution to dose-dependent toxicities. And last but not least, there may be a confusing message about a putative "synergistic" QT prolongation, which might suggest an increased mortality related to proarrhythmic effect. As a matter of fact, there was a small absolute increase in cardiovascular

mortality after five days of azithromycin in an observational cohort (*42*) and azithromycin was associated with a mild and dose-dependant prolongation of QT interval in healthy subjects treated by the combination of azithromycin and chloroquine, compared to chloroquine alone (*43*). The elevation reported for chloroquine-azithromycin in this study was in the same range than for azithromycin alone (*44*). It is important to note that most of drug-induced QT prolongations result from blocking hERG potassium canal, which slows cardiac repolarization and may lead to sudden death. However, azithromycin has a low affinity for the hERG channel (*45*) and preclinical studies demonstrated that excessive doses of azithromycin failed to cause torsade de pointes (*46*). Indeed, instead of slowing repolarization, supratherapeutic dose of azithromycin prolonged the potential of action itself without signs of proarrhytmia (*47*). Interestingly, we did not observe any torsade de pointe nor fatal cardiac event in our cohort (*7*).

POTENTIAL DRUG-DRUG INTERACTIONS WITH CONCOMITANT TREATMENTS

Potential drug-drug interactions may occur between hydroxychloroquine/azithromycin combination and other ongoing treatments, by either pharmacokinetic interactions or additive/synergistic toxicity.

Pharmacokinetic interactions

The main CYP isoform involved in the metabolism of hydroxychloroquine is CYP 3A4. Thus hydroxychloroquine may be substrate of kinetic interactions with inducers and inhibitors of CYP3A4. However, regarding the complex pharmacokinetic profile including active metabolites, and long half-life of hydroxychloroquine, it is rather unlikely that these interactions may have relevant clinical consequences with the short term treatment. Also, it has been postulated that proton-pump inhibitors, such as omeprazole and pantoprazole, may affect the activity of hydroxychloroquine raising the possibility that oral bioavailability of hydroxychloroquine may be affected by the changes in intragastric pH (*48*). Similarly, azithromycine does not illustrate opportunity for clinically relevant pharmacokinetic drug-drug interactions (*49*).

Hydroxychloroquine and azithromycin may interfere with the metabolism of other common drugs. For example, hydroxychloroquine interacts with metoprolol as a consequence of the effects of both of these on CYP2D6 (*50*). This leads to increased maximal plasma concentrations (Cmax) and thus the bioavailability of metoprolol.

The effect of hydroxychloroquine in causing increased levels of digoxin has been noted and this is clearly an important drug interaction that may result in increased cardiotoxicity of

digoxin when used in combination with hydroxychloroquine (RxFiles Detailing Program 2008). Another significant drug interaction of relevance is the wide spread use of anti-malarials with methotrexate (MTX) (*51,52*). Indeed, co-administration of hydroxychloroquine with MTX causes reduced Cmax and increased Tmax. It has been suggested that this effect of hydroxychloroquine on the PK of MTX may explain the decrease of acute liver effects due to MTX (*53,54*).

In regards with azithromycin drug-drug interactions, azithromycin is a weak inhibitor of CYP 3A4. However, no clinically relevant interaction has been highlighted so far (*49*). In addition, it should be noted that azithromycin is a potent inhibitor of the drug transporter P glycoprotein and some reports have suggested that azithromycin may rarely increase the blood concentration of cyclosporine (*55,56,57*). Caution and therapeutic drug monitoring of cyclosporine are thus recommended during co-administration of azithromycin and cyclosporine. Caution may also be applied with other Pgp substrate, especially if their therapeutic index is narrow; for example, immunosuppressive tacrolimus, everolimus, and anticoagulant such as apixaban and dabigatran.

Potential synergistic toxicity

Most of drug-drug interactions potentially associated with synergistic toxicity with concomitant treatments are related to risk of QT prolongation. They may increase the risk of cardiac arrhythmia and *torsades de pointe* (*58*). Thus, precaution has to be taken with other treatments at risk of QT prolongation. For example, antidepressants such as citalopram or escitalopram are contraindicated and tricyclic should be used with caution.[24] Most antipsychotic drugs are also at risk of QT prolongation, including antidopaminergic antiemetics such as domperidone and metoclopramide. Importantly, unbalanced kaliemia (hypo- or hyperkaliemia) may increase the risk of cardiac arrhythmia. Thus, potential cardiac toxicity of hydroxychloroquine and azithromycin can be prevented by a systematic ECG and ionogram analysis. In addition, pathogenic effect of COVID19 can be expected, potentially contributing to disease outcome. (*59*). In this objective, Canadian Heart Rhythm Society recommend that the risk of drug proarrhythmia may be minimized during the pandemia by (i) discontinuing unnecessary medications which may also increase the QT interval (ii) identifying outpatients who are likely at low risk and do not need further testing (no history of prolonged QT, unexplained syncope or family history of premature sudden cardiac death, no medications which may prolong the QT interval, and/or prior known normal QTc), and (iii) performing baseline testing in hospitalized patients or those who may be at higher risk. If baseline ECG testing reveals a

moderately prolonged QTc, optimization of medications and electrolytes may permit therapy. If the QTc is markedly prolonged, drugs which further prolong it should be avoided, or expert consultation may permit administration with mitigating precautions(*60*).

Besides this well-known cardiac toxicity, sparse reports described other kind of non-expected toxicities that might be cited to prevent any toxicity addition when used with other medication. For example, hydroxychloroquine may exert anticoagulant effect if high doses are prescribed (*61*). Some case reports described hemorrhage in patient treated by hydroxychloroquine for rheumatic diseases without being able to input causality relationship (*62,63,64*). Albeit hydroxychloroquine causality was difficult to document, the use of hydroxychloroquine may increase bleeding risk of patient under anticoagulant therapy. In addition, case reports have described neuromyotoxicity and were consistent with studies highlighting the blockage of neuromuscular junction by hydroxychloroquine (*65,66*). These cases suggest that hydroxychloroquine may have synergistic effects and enhance curare action (*67*). Then, hydroxychloroquine can lower the convulsive threshold and there are some reports of seizure unveiled under hydroxychloroquine therapy (*68*). Co-administration of hydroxychloroquine with other drugs known to lower the convulsion threshold may increase the risk of convulsions. Also, the activity of anti-epileptic drugs might be impaired if co-administered with hydroxychloroquine. Finally, some studies showed that treatment with hydroxychloroquine for a period of 6 months can effectively decrease blood glucose level and also hemoglobin A1c probably due to increased insulin production and secretion from B cells, or to decreased insulin clearance (*69*). There is no report of such hypoglycemic effect with short treatment with hydroxychloroquine but it may be taken in consideration for patients with antidiabetic treatment.

CONCLUSION

According to these data, the combination of hydroxychloroquine and azithromycin appears to have a theoretical safe profile with few clinically relevant drug-drug interactions. The main side-effects related to hydroxychloroquine are gastrointestinal symptoms and mainly nausea, vomiting and diarrhea. The main risk of the drug combination remains the risk of cardiac toxicity which can be prevented by respecting the contraindications of each drug and monitoring through systematic electrocardiogram and ionogram during the association. Our current observations and practices illustrate the efficacy of risk management. Data about safety

of alternative dose regimen of this protocol, ongoing in clinical trials with COVID-19 patients are needed.

STATEMENT

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- First authors biography: GH is a clinical pharmacist in the University hospital of Marseille, with a daily practice in prevention and management of iatrogeny. GH is also associate professor in pharmacology in the school of pharmacy.

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Table 1. Ongoing trials investigating hydroxychloroquine and azithromycin in the treatment of COVID-19.

Identifier	Title	country	regimen
NCT04341870	Study of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients: Sarilumab, Azithromycin, Hydroxychloroquine Trial - CORIMUNO-19 – VIRO	FRANCE	HCQ: 600mg/day for 10 days Azithro: 500mg D1 then 250mg/day for four days.
NCT04341727	Hydroxychloroquine, azithromycin in the treatment of SARS CoV-2 infection	UNITED STATES	HCQ: 800mg on D1, then 400mg/day for four days Azithro: 500mg D1 then 250mg/day for four days.
NCT04341207	Epidemiology of SARS-CoV2 and mortality to COVID-19 disease in French cancer patients	FRANCE	HCQ: 600mg/day for ten days Azithro: 500mg D1 then 250mg/day for four days.
NCT04339816	Azithromycn added to hydroxychloroquine in patient admitted to intensive care with COVID-19 randomised controlled trial	CZECH REPUBLIC	HCQ: 800mg on D1, then 400mg/day for four days Azithro: 500mg D1 then 250mg/day for four days.
NCT04338698	Hydroxychloroquine, oseltamivir and azithromycin for the treatment of COVID-19 infection: a RCT	PAKISTAN	HCQ: 600mg/day for five days Azithro: 500mg D1 then 250mg/day for four days.
NCT04336332	Randomized comparison of combination azithromycin and hydroxychloroquine vs. hydroxychloroquine alone for the treatment of confirmed COVID-19	UNITED STATES	HCQ: 600mg/day for 10 days Azithro: 500mg D1 then 250mg/day for four days.
NCT04335552	Pragmatic factorial trial of hydroxychloroquine, azithromycin, or both for treatment of severe SARS-CoV-2 infection	UNITED STATES	HCQ: 800mg on D1, then 600mg/day for four days Azithro: 500mg D1 then 250mg/day for four days.
NCT04334512	A study of quintuple therapy to treat COVID-19 infection	UNITED STATES	*Dose regimen not specified* Length: 24weeks
NCT04332094	Clinical trial of combined use of hydroxychloroquine azithromycin and tocilizumab for the treatment of COVID-19	SPAIN	HCQ: 800mg on D1, then 400mg/day for six days Azithromycin: 500mg/day for three days
NCT04329572	Efficacy and safety of hydroxychloroquine and azithromycin for the treatment of hospitalized patients with moderate to severe COVID-19	BRAZIL	HCQ: 800mg on D1, then 400mg/day for four days Azithromycin: 500mg/day for five days
NCT04328272	Effectiveness of hydroxychloroquine in COVID-19 patients	PAKISTAN	HCQ: 1200mg on D1 then 400mg/day for six days Azithro: 500mg D1 then 250mg/day for six days
NCT04322396	Proactive prophylaxis with azithromycin and chloroquine in hospitalized patients	DENMARK	*Dose regimen not specified* Length: 15 days
NCT04322123	Safety and efficacy of hydroxychloroquine associated with azithromycin in SARS-CoV-2 virus (COVID-19)	BRAZIL	HCQ: 800mg/day for seven days Azithromycin: 500mg/day for seven days
NCT04321278	Safety and efficacy of hydroxychloroquine associated with azithromycin in SARS-CoV-2 Virus (Coalition Covid-19 Brasil II)	BRAZIL	HCQ: 800mg/day for ten days Aeithromycin: 500mg/day for ten days

Consulted on the 13th of April 2020

Table 2. Main contra-indications of both hydroxychloroquine and azithromycin.

	Hydroxychloroquine	**Azithromycine**
Absolute contra indications	- Hypersensitivity to active substances (cross reactivity): hydroxychloroquine or chloroquine, amino-4 quinoleines, amodiaquine, mefloquine, glafenine, floctafenine, antrafenine. - Increased risk of cardiac arrhythmia: citalopram, escitalopram, hydroxyzine, domperidone and piperaquine. - Pathophysiology: retinopathy, age < 6 years, weight<35kg	- Hypersensitivity to active substances (cross reactivity): azithromycin, erythromycin, chlarithromycin, dirithromycin, josamycin, midecamycin diacetate, roxithromycin, telithromycin, macrolides, ketolides, everolimus, pimecrolimus, sirolimus, temsirolimus, fidaxomicine. - Hypersensitivity to excipient: peanut oil and soy. - hypersensitivity to lactose, abnormality of galactose metabolism, lactase deficiency, and digestive malabsorption / intolerance syndrome because of the presence of lactose as excipient. - Pathophysiology: pseudomembranous colitis, anaphylactic shock, severe skin involvement, acute exanthematic pustulosis, DRESS syndrome, severe liver failure, patient taking colchicine, cisapride, dihydroergotamine and ergotamine
Relative contraindication or not recommended	hepatic porphyria, lactation, G6PD deficiency, psoriasis, hypersensitivity to lactose, abnormality of galactose metabolism, lactase deficiency, and digestive malabsorption / intolerance syndrome because of the presence of lactose as excipient	Cholestase, Colchicine, cisapride, dihydroergotamine and ergotamine