SOCIETÀ ITALIANA DI FARMACOLOGIA

Riconosciuta con D.M. del MURST del 02/01/1996
Iscritta Registro Persone Giuridiche Prefettura di Milano n. 467 pag 722 vol. 2°
C.F.: 97053420150 – P.I.: 11453180157

SISTEMA DI GESTIONE QUALITÀ CERTIFICATO
CERTIQUALITY
UNI EN ISO 9001:2015

Chloroquine/hydroxychloroquine to prevent and treat COVID-19

April 20, 2020 update

Gianluca Trifirò (trifirog@unime.it), Salvatore Crisafulli (salcrisafulli@unime.it) – University of Messina
Andrea Cignarella (andrea.cignarella@unipd.it) – University of Padova

May 12, 2020 update
May 28, 2020 update
June 9, 2020 update
October 16, 2020 update

Gianluca Trifirò, Salvatore Crisafulli, Andrea Cignarella

Overview

After the very early use of quinine extracted from *Cinchona* bark for the treatment of malaria, in the 1940s antimalarial drugs were chemically synthesized and then approved for medical use. Chloroquine and hydroxychloroquine have a long-standing history in the prevention and treatment of malaria and the treatment of chronic inflammatory diseases including systemic lupus erythematosus and rheumatoid arthritis (**Figure 1**).

Both drugs are administered orally and are well-absorbed from the gastrointestinal tract. The metabolism of hepatic CYPs produces two deaminated metabolites, with plasma terminal half-lives of up to 45 days. Both drugs are excreted mainly via the kidneys. Chloroquine and hydroxychloroquine have similar mechanisms of action including inhibition of lysosomal activity in host cells, inhibition of prostaglandin synthesis, polymorphonuclear leukocyte chemotaxis and phagocytosis, attenuation of interleukin-1 production by monocytes and inhibition of superoxide release by neutrophils (**Figure 2**).

These two drugs have been found to exert antiviral activity in *in vitro* models. The antiviral effect appears to be due to endosomal acidification, which mediates the virus-host cell fusion, as well as inhibition of host receptor glycosylation, thus blocking viral entry into cells. Beyond their antiviral action, these agents have immunomodulatory effects that may be synergistic with the antiviral action.

Scientific evidence on the benefit-risk profile of chloroquine/hydroxychloroquine in the treatment of COVID-19 patients

Although the antiviral activity of chloroquine and hydroxychloroquine has been demonstrated in several *in vitro* experimental models in the pre-COVID-19 era, in relation to different viruses such as Zika [Han et al., 2019] and Ebola [Madrid

et al., 2013], its efficacy has never been confirmed in human clinical studies in acute viral infections induced by the aforementioned viruses. Concerning SARS-CoV-2 specifically, chloroquine and hydroxychloroquine have been shown to be effective in inhibiting the replication of this virus in *in vitro* experimental models, at doses that can also be used in humans [Wang et al., 2020; swab.nl, 2020]. According to a recent study, the inhibitory effect of these drugs is dose-dependent and hydroxychloroquine could be active against SARS-CoV-2 at lower concentrations than chloroquine [Yao et al., 2020]. Moreover, after its absorption, chloroquine administered orally at a dosage of 500 mg is distributed throughout the body, including the lungs [Wang et al., 2020; Colson et al., 2020].

To date, a considerable number of clinical trials and observational studies evaluating the effects of chloroquine and hydroxychloroquine in COVID-19 patients have been published. However, they are affected by important methodological limitations that that do not allow definitive conclusions to be drawn on the efficacy of the treatment with chloroquine/hydroxychloroquine in patients with COVID-19. The steadily increasing evidence from these studies has been summarized in systematic reviews and meta-analyses, which are described below.

A recent systematic review and meta-analysis of randomized controlled trials (RCTs) and observational studies evaluated the effects of chloroquine and hydroxychloroquine, in combination with azithromycin or not, in patients with COVID-19 [Kashour et al., 2020]. In total, 5 RCTs and 14 cohort studies were included, for a total of 20,263 patients. Study outcomes were: short-term mortality (1 RCT and 12 cohort studies), viral clearance (3 RCTs) and need for mechanical ventilation/intensive care unit (ICU) admission (3 cohort studies). This meta-analysis found no significant association between treatment with chloroquine/hydroxychloroquine and mortality [odds ratio: 0.93; 95% confidence interval (CI): 0.79 - 1.11; p-value = 0.003]. The same conclusion was drawn for viral clearance. Among the 5 included studies (3 RCTs and 2 cohort studies) evaluating the effects of chloroquine/hydroxychloroquine regarding this outcome, only one RCT demonstrated a significant improvement in patients treated with these drugs. Of the 48 COVID-19 patients enrolled in this study, 18 received chloroquine (1000 mg/day on the first day, 500 mg for 9 days), 12 hydroxychloroquine (400 mg/day for 10 days), and 12 received treatment control. The time required to reach viral clearance was shorter among patients treated with chloroquine and hydroxychloroquine than in the control group (P = 0.006 and P = 0.010, respectively) [Chen et al., 2020]. Finally, none of the 3 cohort studies that evaluated the effects of hydroxychloroquine

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

on mechanical ventilation/ICU admission documented any positive effects of treatment with this drug, in combination or not with azithromycin, on this composite outcome.

Another systematic review and meta-analysis confirmed these results, demonstrating that the results of the included RCTs did not show statistically significant differences between hydroxychloroquine and comparison groups in terms of viral clearance and disease progression, highlighting the absence of robust scientific evidence that may justify the use of this drug for the treatment of SARS-CoV-2 infection [Zang et al, 2020]. Similar conclusions were drawn from a more recent systematic review of 16 RCTs, which aimed to evaluate the quality of clinical studies assessing the efficacy of chloroquine/hydroxychloroquine in patients affected by COVID-19. The results of this study demonstrated that the included studies generally had a small sample size and mixed results affected by a moderate to high risk of bias [Mazhar et al, 2020].

To confirm these results, an open-label RCT published in the New England Journal of Medicine on October 8, 2020 (*Recovery trial*) showed that, among COVID-19 hospitalized patients, mortality at 28 days was not reduced for patients treated with hydroxychloroquine (421/1561; 27.0%) as compared to those treated with standard therapy (790/3155; 25.0%) [Horby et al, 2020].

Regarding the potential prophylactic effect of these drugs, a double-blind RCT showed that 821 asymptomatic subjects exposed to SARS-CoV-2 did not benefit from hydroxychloroquine received within 4 days after the exposure as compared with placebo in preventing illness compatible with COVID-19 [Boulware et al., 2020]. Such results were confirmed by a cohort study and a double-blind RCT, which evaluated the prophylactic effect of hydroxychloroquine in patients with rheumatic diseases [Rentsch, 2020] and in health care workers [Abella, 2020], respectively. Specifically, in the cohort study conducted by Rentsch et al, no statistically significant association was observed between treatment with hydroxychloroquine and the reduction in the mortality rate from COVID-19 (standardized cumulative mortality: 0.23% [95% CI: 0.18-0.29] among hydroxychloroquine users vs 0.22 [95% CI 0.20-0.25] among non-users). Similarly, the double-blind, placebo-controlled RCT conducted on health care workers demonstrated that prophylactic treatment with hydroxychloroquine 600 mg daily for 8 weeks was not effective in preventing SARS-CoV-2 infection (infection rate: 6.3% among subjects treated with hydroxychloroquine vs. 6.6% among subjects treated with placebo; p-value> 0.99).

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

As regards experimental investigations, to date 291 clinical trials on chloroquine/hydroxychloroquine are currently ongoing, as registered on www.clinicaltrials.gov, the American site of clinical trials (update to October 15, 2020). Also in Italy, several clinical trials on medicines for the treatment of COVID-19 patients have been approved by the Italian Medicines Agency (AIFA). To date, 2 ongoing clinical trials in Italy are currently registered on clinicaltrials.gov. In particular, they are (i) an open-label phase II clinical trial with the aim of evaluating the efficacy of hydroxychloroquine in the prevention of COVID-19 and in the treatment of the disease in the early stages and (ii) a phase II open-label clinical trial in which hydroxychloroquine is used as an active comparator to evaluate the effectiveness of the combination of ozone therapy and probiotics in the management of the initial stages of the disease.

Methods of prescribing and reimbursement of chloroquine/hydroxychloroquine in COVID-19

In light of recent evidence on little or no benefits and potential risks associated with the use of chloroquine/hydroxychloroquine in patients with COVID-19, on May 26, 2020, AIFA suspended the authorization for the use (and reimbursement) of these drugs for the treatment of SARS-CoV-2 infection, outside of clinical trials, both in hospital and in the home setting. A similar measure was ordered by the Food and Drug Administration (FDA), which on 1 July 2020 revoked the authorization for the use of chloroquine/hydroxychloroquine in COVID-19 patients outside the hospital or clinical trial settings, due to the risk of adverse cardiovascular effects.

Monitoring of drug toxicity

Chloroquine and hydroxychloroquine are generally well-tolerated, even after prolonged use. Itching frequently occurs, as well as nausea, vomiting, abdominal pain, headache, anorexia, malaise and blurred vision rarely occur. Hemolysis in patients with glucose 6-phosphate dehydrogenase deficiency, hearing reduction, confusional state, psychosis, convulsions, agranulocytosis, exfoliative dermatitis, hypotension and QT prolongation can be rare serious adverse reactions. For this reason, chloroquine should not be administered in patients receiving other concomitant drugs that can prolong the QT interval (e.g. amiodarone). Since this drug is often administered in covid-19 in combination with antibiotic therapy, special attention should be paid to antibacterials that may cause QT prolongation. The appendix lists the drugs potentially interacting with chloroquine, stratified by level of risk.

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

Hydroxychloroquine was proven to be two to three times less toxic than chloroquine in experimental *in vivo* models [McChensey, 1983]. Specifically, hepatic, renal and cardiac side effects were milder in hydroxychloroquine treated albino rats compared to those treated with chloroquine [El Shishtawy, 2015]. Hydroxychloroquine has a similar, albeit slightly milder, toxicity profile in humans, where retinal toxicity was lower than that of chloroquine [Finbloom, 1985]. Hydroxychloroquine may infrequently alter liver enzymes and rarely cause severe hypoglycemia.

High doses intramuscularly administered or rapid intravenous administration of these drugs can cause severe hypotension and respiratory and cardiac arrest. These drugs are also contraindicated in patients affected by psoriasis or porphyria, in which they can precipitate acute attacks of these diseases. They should not be used in patients with retinal or visual field abnormalities, or in the case of myopathies. They should be cautiously used in patients with a history of liver, neurological or hematological diseases. The use of chloroquine in pregnant women should be avoided, except in the prophylaxis or treatment of malaria. It was demonstrated that radioactively tagged chloroquine administered intravenously to pregnant pigmented CBA mice passed rapidly across the placenta and accumulated selectively in the melanin structures of the fetal eyes. It was retained in the ocular tissues for five months after the drug had been eliminated from the rest of the body. To date, there are no adequate and well-controlled studies evaluating the safety and efficacy of chloroquine in pregnant women (ARALEN – Summary of product characteristics). There is insufficient clinical data on the use of hydroxychloroquine in pregnant women. Like chloroquine, hydroxychloroquine crosses the placenta. 4-aminoquinolines in therapeutic doses caused damage to the central nervous system, including ototoxicity (auditory and vestibular toxicity, congenital deafness), retinal hemorrhages and abnormal retinal pigmentation. Hydroxychloroquine is contraindicated during pregnancy. Before treatment is started a pregnancy has to be excluded (Quinoric – Summary of product characteristics).

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

References

Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med*. DOI: 10.1056/NEJMoa2016638.

Cao B, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020; 382:1787-1799

Chen L, et al. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. medRxiv 2020.06.19.20136093; doi: https://doi.org/10.1101/2020.06.19.20136093

Colson P, Rolain JM, Lagier JC, Brouqui P, Raoult D. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020;55(4):105932.

Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care* 2020; S0883-9441(20)30390-7.

El Shishtawy MA, Haidar Hassan K, Ramzy R, Berri F, Mortada M, Nasreddine S, Ezzedine M. Comparative toxicity study of chloroquine and hydroxychloroquine on adult Albino Rats. European Scientific Journal 2015.

Finbloom DS, Silver K, Newsome DA, Gunkel R. Comparison of hydroxychloroquine and chloroquine use and the development of retinal toxicity. *J Rheumatol*. 1985;12(4):692-4.

Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72–73.

Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19 [published online ahead of print, 2020 May 7]. N Engl J Med. 2020;10.1056/NEJMoa2012410. doi:10.1056/NEJMoa2012410

Han Y, Pham HT, Xu H, Quan Y, Mesplède T. Antimalarial drugs and their metabolites are potent Zika virus inhibitors. J Med Virol. 2019 Jul;91(7):1182-1190. doi: 10.1002/jmv.25440. Epub 2019 Mar 4. PMID: 30801742.

RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, Wiselka M, Ustianowski A, Elmahi E, Prudon B, Whitehouse T, Felton T, Williams J, Faccenda J, Underwood J, Baillie JK, Chappell LC, Faust SN, Jaki T, Jeffery K, Lim WS, Montgomery A, Rowan K, Tarning J, Watson JA, White NJ, Juszczak E, Haynes R, Landray MJ. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med. 2020 Oct 8. doi: 10.1056/NEJMoa2022926. Epub ahead of print. PMID: 33031652.

https://swab.nl/nl/covid-19 (accesso: 19 marzo 2020)

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

https://www.aifa.gov.it/documents/20142/1131319/AZI-RCT-COVID-19_documenti.zip

Kashour ZT et al. Efficacy of Chloroquine or Hydroxychloroquine in COVID-19 Patients: A Systematic Review and Meta-Analysis. https://www.medrxiv.org/content/10.1101/2020.07.12.20150110v2

Madrid PB, Chopra S, Manger ID, Gilfillan L, Keepers TR, Shurtleff AC, Green CE, Iyer LV, Dilks HH, Davey RA, Kolokoltsov AA, Carrion R Jr, Patterson JL, Bavari S, Panchal RG, Warren TK, Wells JB, Moos WH, Burke RL, Tanga MJ. A systematic screen of FDA-approved drugs for inhibitors of biological threat agents. PLoS One. 2013;8(4):e60579.

Magagnoli J et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2

Mazhar F, Hadi MA, Kow CS, Marran AMN, Merchant HA, Hasan SS, Use of hydroxychloroquine and chloroquine in COVID-19: How good is the quality ofrandomized controlled trials?, International Journal of Infectious Diseases(2020),doi:https://doi.org/10.1016/j.ijid.2020.09.

McChansey EW. Animal toxicity and pharmacokinetics of hydroxychloroquine sulphate. *The American Journal of Medicine* 1983. 75(1):11-18

Multicenter Collaboration Group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for Chloroquine in the Treatment of Novel Coronavirus Pneumonia Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia [in Chinese; abstract in English]. *Zhonghua Jie He He Hu Xi Za Zhi* 2020;43(3):185–188.

Rentsch CT, Devito NJ, Mackenna B, Morton CE, Bhaskaran K, Brown JP, et al. Hydroxychloroquine for prevention of COVID-19 mortality: a population-based cohort study. medRxiv. 2020

Abella BS, Jolkovsky EL, Biney BT, Uspal JE, Hyman MC, Frank I, et al. Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers. JAMA Intern Med. 2020

Tang et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 2020; 369: m1849

Touret F, de Lamballerie X. Of chloroquine and COVID-19. *Antiviral Res*. 2020; 177:104762.

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020;30(3):269-271.

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [published online ahead of print, 2020 Mar 9]. *Clin Infect Dis*. 2020; ciaa237.

Zang Y, Han X, He M, Shi J, Li Y. Hydroxychloroquine use and progression or prognosis of COVID-19: a systematic review and meta-analysis. Naunyn Schmiedebergs Arch Pharmacol. 2020 Sep 6:1–8. doi: 10.1007/s00210-020-01964-5. Epub ahead of print. PMID: 32892293; PMCID: PMC7474863.

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

Figure 1. Timeline of empiric introduction of chloroquine and hydroxychloroquine.

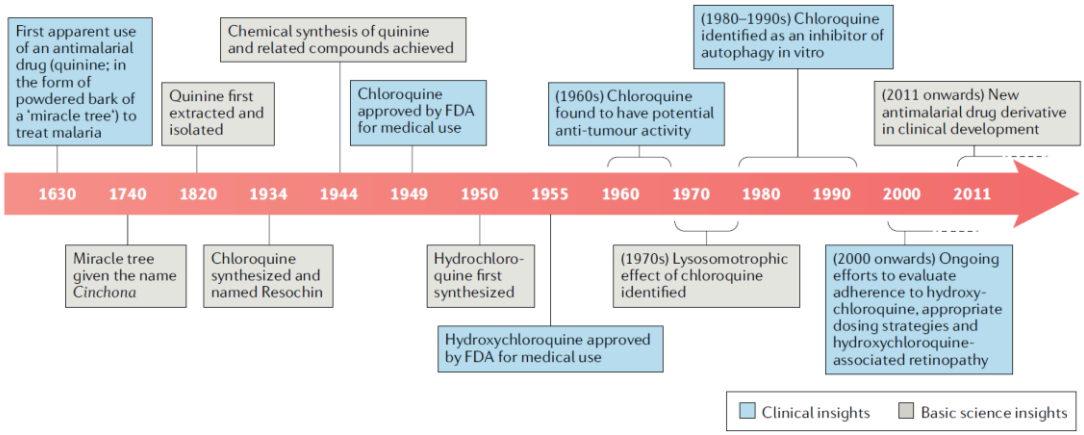
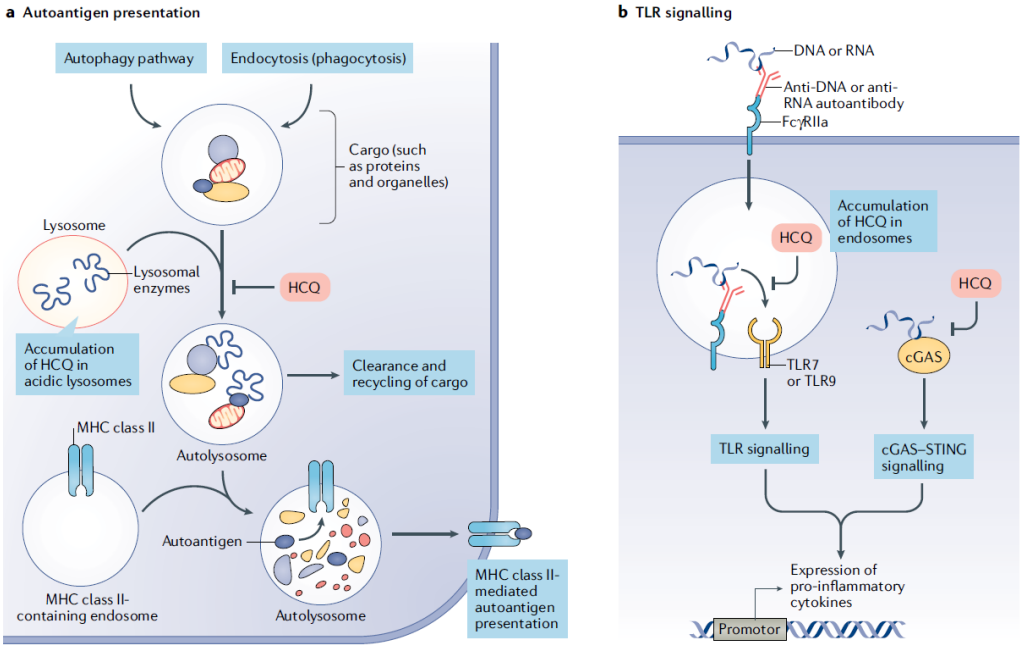


Figure 2. Potential molecular mechanisms of chloroquine/hydroxychloroquine.



Legend: HCQ = Hydroxychloroquine; MHC = Major histocompatibility complex; TLR= Toll- like receptor; cGAS = cyclic GMP-AMP synthase; STING= stimulator of interferon genes.

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

SOCIETÀ ITALIANA DI FARMACOLOGIA

Riconosciuta con D.M. del MURST del 02/01/1996
Iscritta Registro Persone Giuridiche Prefettura di Milano n. 467 pag 722 vol. 2°
C.F.: 97053420150 – P.I.: 11453180157

SISTEMA DI GESTIONE QUALITÀ CERTIFICATO
CERTIQUALITY
UNI EN ISO 9001:2015

Appendix. Potential chloroquine/hydroxychloroquine pharmacological interactions, stratified by grade of recommendation) (adapted from http://www.covid19-druginteractions.org/)

Table 1. Potentially interacting drugs that should not be co-administered with chloroquine/hydroxychloroquine.

Pharmacological class	Molecule
Antibacterials	Rifampicin
	Rifapentine
Analgesics	Dextropropoxyphene
Antiarrhythmics	Amiodarone
	Bepridil
	Flecainide
	Mexiletine
Antidepressants	St. John's wort
Antipsychotics	Ziprasidone

Table 2. Drugs with potential risk of interaction with chloroquine/hydroxychloroquine and that may require a dose adjustment or close monitoring.

Pharmacological class	Molecule
Anaesthetics and muscle-relaxants	Propofol
	Sevoflurane
	Tizanidine
Analgesics	Hydrocodone
	Methadone
Antiarrhythmics	Disopyramide
	Dofetilide
	Propafenone
	Quinidine
Antibacterials	Azithromycin
	Bedaquiline
	Claritrhomycin
	Clofazimine
	Delamanid
	Erythromycin
	Levofloxacin
	Moxifloxacin
	Ofloxacin

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

	Rifabutin
	Telithromycin
Anti-coagulant/Anti-platelet and fibrinolytics	Betrixaban
	Dabigatran
	Edoxaban
Antidepressants	Amitriptyline
	Citalopram
	Clomipramine
	Desipramine
	Escitalopram
	Imipramine
	Lithium
	Maprotiline
	Nortriptyline
	Trazodone
Antipsychotics	Chlorpromazine
	Clozapine
	Fluphenazine
	Haloperidol
	Iloperidone
	Levomepromazine
	Perphenazine
	Pimozide
	Pipotiazina
	Quetiapine
	Risperidone
	Sulpiride
	Thioridazine
	Tiapride
	Zotepine
	Zuclopenthixol
Antivirals	Lopinavir/ritonavir
Broncodilators	Salmeterol
Gastrointestinal agents	Antacids
	Cisapride
Anti-emetics	Dolasetron
	Domperidone
	Granisetron
	Ondansetron
	Prochlorperazine
Hypertension/Heart failure	Digoxin

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/

	Ivabradine
	Ranolazine
Immunosuppressants	Adalimumab
	Azathioprine
	Ciclosporin
	Sirolimus
	Tacrolimus

Table 3. Drugs with low risk of interaction with chloroquine/hydroxychloroquine for which dosage adjustment or other actions are probably not necessary.

Pharmacological class	Molecule
Anti-coagulants	Apixaban
	Rivaroxaban
Beta blockers	Metoprolol
	Nebivolol
	Propranolol
	Timolol
Broncodilators	Umeclidinium bromide
Calcium channel blockers	Verapamil

Segreteria Organizzativa: Ida Ceserani – SIF - Sede Legale e Operativa: Via G. Pascoli, 3 – 20129 Milano, Italia
Tel. +39 02 29520311 – Fax +39 02 700590939 – E-mail: presidente@sif-farmacologia.it – sif.farmacologia@segr.it

Sede del Presidente: Dipartimento di Scienze Farmacologiche e Biomolecolari – Università di Milano – Via G. Balzaretti, 9 – 20133 Milano, Italia
Tel + 39 0250318332/331 – Fax +39 0250318278 - E-mail: giorgio.racagni@unimi.it

Sede del Presidente Eletto: Dipartimento di Farmacia – Università degli Studi di Napoli Federico II – Via D. Montesano, 49 – 80131 Napoli, Italia
Tel. +39 081678442 – E-mail: cirino@unina.it

Sede del Segretario: Dipartimento NeuroFarBa – Sezione di Farmacologia - Università di Firenze – Viale G. Pieraccini, 6 – 50139 Firenze, Italia
Tel. +39 0552758 196 - E-mail: carla.ghelardini@unifi.it

Sito Web: https://www.sifweb.org/