Hydroxychloroquine
in the treatment
of adult patients
with COVID-19

Update: 22 December 2020
(previous publications: 2 April 2020; 29 April 2020;
29 May 2020; 22 July 2020; 25 November 2020)

AIFA

ITALIAN MEDICINES AGENCY

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

Useful information is hereby provided to guide the prescription and to define a risk/benefit balance for the individual patient.	
For which patients is it recommended?	In light of the evidence that has progressively become available, showing a complete lack of efficacy and an increase in adverse events, although not serious, AIFA does not recommend the use of hydroxychloroquine in hospitalised COVID-19 patients. Additionally, AIFA does not consider it useful or appropriate to authorise new clinical trials on hospital patients. Regarding low-severity home patients with SARS-CoV-2 infection in the early stages of the disease, more limited data exist on the lack of efficacy against an increase in adverse events. Therefore, AIFA does not recommend the use of hydroxychloroquine. Prescriptions made on a case-by-case basis would represent an off label use of the medicine. In light of the above, randomised controlled clinical trials cannot be authorised to make available data conclusive. By analogy, this conclusion shall also apply to chloroquine.
At which dosages is it preferably prescribed and in which forms?	Use of high doses of HCQ increases the risk of adverse events. For this reason, even in clinical trials, the use is recommended at the lowest dose and for the shortest time possible (5-7 days).
Who can prescribe the medicine during this emergency phase?	In accordance with the applicable legislation, the off-label use is not reimbursed by the NHS and is subject to specific rules on prescription. The administration of HCQ and CQ to home patients with COVID-19 is therefore the responsibility of the prescribing doctor and shall take place after each single patient has given their informed consent.
What are the major risks in terms of adverse events?	**Warning** (from fact sheet) It is essential that clinical trials using HCQ and CQ include appropriate risk minimisation measures and careful monitoring of the following aspects. • Prolongation of congenital or acquired QT interval and/or with known risk factors that may prolong this interval, such as: heart failure, acute myocardial infarction (AMI), bradycardia (<50 bpm), previous ventricular arrhythmias, not corrected hypokalaemia and/or hypomagnesemia. • Hypoglycaemia also in the absence of hypoglycaemic therapy (please warn patients of this risk). • Hepatic or renal failure. • Glucose-6-phosphate dehydrogenase deficiency (G6PD), porphyria, psoriasis. • Psychiatric disorders. For further details consult the fact sheet and AIFA's notice dated 31 March 2020. https://www.aifa.gov.it/documents/20142/1097058/2020.03.31_NII_clorochina_idrosssiclorochina_GP_consolidata+COVID-19.pdf/c928750d-dcb2-f38a-41a1-1fbf6af7a767.

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

Can it be prescribed in combination with other medicines?	*Main interactions* (Liverpool drug Interaction group): **According to the fact sheet, the main interactions concern:** - digoxin (increases plasma concentrations) - hypoglycaemic agents (decrease blood sugar) - QT prolonging medicines (particularly antiarrhythmic agents, tricyclic antidepressants, antipsychotics, certain anti-infective agents) - anti-epileptics - ciclosporin For further information on pharmacological interactions*: https://www.covid19-druginteractions.org/*.

Background

Hydroxychloroquine (Plaquenil® tablets 200 mg or generic correspondent) is a chemically similar chloroquine analogue that shares the same mechanism of action. It is an antimalarial, currently used in Italy in rheumatology at a dosage of 200 mg x 2 even for very long periods. There is therefore extensive clinical experience (higher than chloroquine) with regard to its tolerability.

Rationale

Hydroxychloroquine (HCQ) and chloroquine (CQ) (and their active metabolites) showed to have an antiviral effect in vitro or in animal models by altering (increasing) the endosomal pH which is essential for the virus cell fusion. In addition, they interfere with the glycosylation of SARS-COV-2 cell receptors.

In vitro data indicate that CQ is capable of blocking viral replication of SARS-COV-2 at doses used in clinical practice. In addition to their antiviral action, both medicines have immunomodulant activity that could synergistically enhance the in vivo antiviral effect.

It also appears from in vitro studies that the effects on cells can be observed when the medicine is present both before and after the viral inoculum.

Various studies on animal models have highlighted a lack of efficacy in reducing SARS-CoV-2 infection (*Kaptein SJF et al. 2020; Maisonnasse P et al. 2020*).

CQ and HCQ are distributed throughout the body, including the lung where they appear to be concentrated. The choice of HCQ is the result of increased in vitro efficacy. According to a recent study, HCQ could be active against SARS-COV-2 at lower concentrations than CQ.

Main evidence available

Randomised clinical trials

At the beginning of the pandemic, only small controlled studies were available that were characterised by a poor methodology (*Chen J et al. 2020; Chen Z et al. 2020; Tang W et al. 2020*).

Subsequently, more robust evidence emerged from numerous clinical trials. The main results are given below in chronological order:

- 05/06/2020: a press release disseminated the results of RECOVERY (Randomised Evaluation of COVid-19 thERapY), a large multi-arm, adaptive trial aimed at evaluating the efficacy of different therapeutic options for hospitalised COVID-19 patients. Investigators reported that data from an interim analysis, assessing 1542 patients randomised to hydroxychloroquine and 3132 randomised to usual care, did not show any difference in terms of mortality after one month between the two groups (25.7% vs 23.5%; HR 1.11; 95% CI 0.98-1.26), nor difference in hospital stay duration or other outcomes (https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf).

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

- 17/07/2020 *Skipper C et al. 2020:* this was an internet-based randomised, double-blind, placebo-controlled trial, evaluating the efficacy and safety of HCQ in an early use setting represented by symptomatic, nonhospitalised subjects with confirmed or probable diagnosis (defined as onset of symptomatology after high-risk contact with a reliable source) of COVID-19 (*Skipper C et al. 2020*). HCQ or placebo therapy had to be initiated within 4 days of symptom onset. The administered dose was 800 mg (1st dose), then 600 mg (after 6-8 hours), then 600 mg daily for an additional 4 days. The study, conducted in the US and Canada, enrolled 491 subjects, 423 of whom were included in the primary analysis, the endpoint of which was the change in the severity score of symptoms on a visual analogue scale of 10 points over 14 days. No statistically significant differences were observed between the two study groups in terms of change in symptom severity score over 14 days (in the HCQ group, the mean reduction from baseline was 2.60 points compared to a 2.33 point reduction in the placebo group with an absolute difference of -0.27 points [95 % CI -0.61 -0.07]; P = 0.117). Over the 14-day observation period, 24% of HCQ-treated patients had persistent symptoms compared with 30% in the placebo group. There were no statistically significant differences in the incidence of hospitalisations or deaths (P = 0.29). In the HCQ group, there were 4 admissions and 1 non-hospital deaths, while in the placebo group there were 10 admissions (2 unrelated to COVID-19), including 1 death in hospital. Side effects of medicines occurred in 43% (92 out of 212) of participants treated with hydroxychloroquine compared with 22% (46 out of 211) treated with placebo (P < 0.001). No serious adverse events attributed to the medicine were observed. The study has some limitations: a certain diagnosis was possible only in 58% of participants; evaluations were made online or by telephone; the primary outcome was modified during the study to allow the study to be concluded with a smaller sample size. Despite these limitations, the results appear to indicate that HCQ is not effective in reducing the severity or persistence of symptoms in an early use setting for the treatment of mild forms of COVID-19.

- 03/06/2020 *Boulware DR et al. 2020*: this was a randomised double-blind placebo-controlled study evaluating the efficacy of hydroxychloroquine taken as post-exposure prophylaxis. The study was conducted in the United States and Canada according to a pragmatic approach, whereby both recruitment and follow-up were carried out online, while treatment was delivered directly to the participants' homes. Adult subjects exposed to people with confirmed COVID-19 diagnosis, for reasons of cohabitation or work, were enrolled. Within 4 days of exposure, subjects were randomised to receive placebo or HCQ (800 mg for the first administration, followed by 600 mg over the next 6-8 hours and then 600 mg daily for the next 4 days). 821 subjects (87.6% of cases with high risk exposure) were enrolled in the study. Symptoms compatible with COVID-19 were reported in 107 subjects (13.0%), but virological confirmation by PCR was available in less than 3% of subjects. The incidence of new symptoms compatible with a COVID-19 diagnosis was not significantly different between subjects taking HCQ (49/414 [11.8%]) and those who were randomised to the placebo arm (58/407 [14.3%]). Side effects were more frequent in the treated group compared with the placebo group (40.1% vs. 16.8%), although no serious adverse events were reported. Overall, the study showed important methodological limitations, specifically: the definition of the endpoint was not supported by a virological diagnosis; the method of collecting information was subject to an unavoidable recall bias; it was impossible to verify the intervention adherence; there was an important selection bias for which all young subjects in relatively good health were enrolled. Further studies are needed to clearly define the medicine's role in the prophylaxis of SARS-CoV-2 infection.

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

- *16/07/2020 - Mitjà O et al.*: this was the first multicentre, open-label, randomised controlled trial conducted in a non-hospital setting on a population with mild disease. The study enrolled non-hospitalised adult patients with confirmed SARS-CoV-2 infection and less than five days of symptoms. Patients were assigned to receive HCQ (800 mg on day 1, followed by 400 mg once daily for 6 days) or no antiviral treatment. The primary endpoint was the reduction of viral RNA load in nasopharyngeal swabs up to 7 days after treatment start, disease progression using the WHO scale up to 28 days, and time to complete resolution of symptoms. The trial was conducted in Catalonia (Spain) between 17 March and 26 May 2020. A total of 293 patients were enrolled: 157 in the control arm and 136 in the intervention arm with HCQ. The mean age was 41.6 years (SD 12.6), mean viral load at baseline was 7.90 (SD 1.82) Log10 copies/mL, and median time from symptom onset to randomization was 3 day. No significant differences were found in the mean reduction of viral load at day 3 (-1.41 vs. -1.41 Log10 copies/mL in the control and intervention arm, respectively; difference 0.01 [95% CI -0.28;0.29]) or at day 7 (-3.37 vs. -3.44; d –0.07 [-0.44;0.29]). In addition, treatment with HCQ did not reduce the risk of hospitalization (7.1%, control vs. 5.9%, intervention; RR 0.75 [0.32;1.77]) nor shortened the time to complete resolution of symptoms (12 days, control vs. 10 days, intervention; p = 0.38). Although a higher percentage of participants experiencing adverse events was found in the HCQ arm, no major treatment-related AEs were reported.
  Main limitations:
    - The trial used a surrogate endpoint, for which the ideal utilization timing and the threshold value were still unknown for defining its clinical utility
    - The trial was not strengthened to assess more robust endpoints from a clinical point of view (hospitalisation or symptom resolution)
    - The trial had an open-label design.

- *23/07/20202 - Cavalcanti A et al.*: this was a randomised, open label, three-group controlled trials involving standard of care (SOC), SOC plus HCQ (400 mg for 7 days) and SOC plus HCQ (400 mg BID for 7 days) and azithromycin (500 mg/die for 7 days). Eligible participants were hospitalised patients with suspected or confirmed COVID-19 who were receiving either no supplemental oxygen or ≤ 4 L/min of supplemental oxygen. The trial was conducted in Brazil and enrolled 665 patients of which 504 had a confirmed diagnosis of COVID-19 (representing the reference population for the primary analysis; modified intention-to-treat population): 217 patients were randomised to receive HCQ+AZT, 221 to receive HCQ and 229 to receive the SOC. The mean age was 50 years, the average time from symptom onset to randomisation was 7 days and 42% of participants were receiving supplemental oxygen at baseline. The primary outcome was clinical status at 15 days, evaluated with the use of a WHO seven-level ordinal scale. Among patients with a confirmed diagnosis of COVID-19, no significant differences emerged in terms of worse score at 15 days (HCQ+AZT vs SOC: OR 0.99; 95% CI 0.57-1.73; P = 1.00; HCQ vs SOC: OR 1.21; 95% CI 0.69- 2.11; P=1.00; HCQ+AZT vs HCQ: OR 0.82; 95% CI 0.47-1.43; P = 1.00). There were no significant differences in any of the secondary outcomes, including: clinical status at 7 days, intubation, need for high-flow supplemental oxygen or non-invasive ventilation, duration of hospital stay and in-hospital death. Conversely, adverse events such as prolongation of QT interval and hypertransaminasemia were more common in patients receiving HCQ compared to SOC.
  Main limitations:
    - The trial had an open-label design
    - The trial used very wide confidence intervals

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

- *14/08/2020 - Abd-Elsalam S et al. 2020*: this was a multicentre, randomised, open-label, SOC controlled study conducted in Egypt. A total of 194 patients with a confirmed COVID-19 diagnosis were enrolled: 97 patients were randomised to HCQ (400 mg BID (day 1) followed by 200 mg BID (days 2-15)) and 97 patients were randomised to SOC. The primary endpoints were recovery within 28 days, need for mechanical ventilation or death. At the time of enrolment, O_2 saturation ranged between 95 and 90% in 16.0% of participants, between 90 and 85% in 7.4% of participants and was <85% in 6.9% of all participants. After 28 days, no significant differences emerged between the two groups in terms of clinical outcome (P = .07). Complete recovery after 28 days was achieved for 53.6% of patients in the HCQ group and 34.0% of patients in the control group. Both groups did not differ as regards the use of mechanical ventilation (4.1% in the HCQ group and 5.2 in the control group; P=.75), ICU admission (11.3% vs 13.4%; P=.83), and mortality (6.2% vs 5.2%; P= .77).
  Main limitations:
  - The trial had an open-label design
  - The number of patients included in the trial was limited
  - Information regarding concurrent treatment was missing.
- *23/09/2020 - TEACH Study (Ulrich RJ et al. 2020)*: this was a multicentre, double-blind, randomised clinical trial conducted in the United States. Enrolled subjects were hospitalised patients with confirmed COVID-19 diagnosis with at least one of these symptoms: cough, dyspnoea, nausea, diarrhoea, myalgia, anosmia, dysgeusia. Subjects admitted to ICU, receiving mechanical ventilation, ECMO or using vasopressors were excluded. Enrolled subjects were randomised 1:1 to HCQ (400 mg BID (day 1) and 200 mg BID (days 2-5) or placebo for 5 days. The primary efficacy outcome was the percentage of subjects achieving a severe disease progression composite end point (death, intensive care unit admission, mechanical ventilation, ECMO, and/or vasopressor use) at day 14. The trial was terminated early. In the period between April and May 2020, 128 subjects were randomised: 67 to the HCQ arm and 61 to the placebo arm. The mean age of enrolled subjects was 66 years and the median time to symptom onset was 7 days, without statistically significant differences between subjects receiving HCQ and subjects receiving placebo. In total, 48% of participants were classified in WHO category 4 ("*Hospitalized, on supplemental oxygen*"), 33.6% were classified in category 5 ("*Hospitalized, not on O2, requiring ongoing medical care*") and 16% were classified in category 3 ("*Hospitalized, on non-invasive ventilation or high-flow nasal cannula*"). More than 34% of subjects were receiving an additional COVID-19 investigational or off-label treatment . At day 14, 11 (16.4%) subjects assigned to HCQ and 6 (9.8%) subjects assigned to placebo met the severe disease progression end point, but this did not achieve statistical significance (P = .35). There were no significant differences in COVID-19 clinical scores, number of oxygen-free days, SARS-CoV-2 clearance, or adverse events between HCQ and placebo. HCQ was associated with a slight increase in mean corrected QT interval, an increased D-dimer, and a trend toward an increased length of stay.
  Main limitations:
  - The trial was terminated early
  - There was extensive use of other investigational medicinal products or off-label use for COVID-19
  - The sample size was based on the prevalence of primary endpoint that was overestimated compared with the real clinical situation, with consequent uncertainty as for the calculation of the sample power and internal validity of the study.
- *30/09/2020: Abella BS et al. 2020*: this was a randomised, double-blind, placebo-controlled trial that aimed at assessing the efficacy of treatment with HCQ as a pre-exposure prophylaxis strategy in

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

healthcare professionals exposed to COVID-19 patients. A dose regimen of HCQ 600 mg/die for 8 weeks was studied. The trial was terminated early after enrolling 132 subjects due to lack of efficacy. The enrolled subjects were randomised to the prophylaxis with HCQ arm (n=66) or the control arm without HCQ (n=66). At the time of enrolment, the mean age was 33 years. During follow-up no differences were found in the rate of infection among participants randomised to treatment with HCQ and those randomised to placebo (4/64 [63%] vs 4/61 [6.6%]; P>0.99). Conversely, subjects treated with HCQ reported more adverse events (45% vs 26%; P=0.04) and discontinued treatment early (19% vs 16%; P=0.81).

Main limitation:
  o The trial was terminated early
  o The number of participants was limited.

- *15/10/2020 – SOLIDARITY trial*: this was an adaptive, multicentre trial, coordinated by the WHO, aimed at testing the efficacy and safety of different anti-COVID strategies (including, originally, HCQ, remdesivir, lopinavir/ritonavir and interferon). Eligible patients were aged ≥18 years, hospitalized with a diagnosis of COVID-19, naïve for any study medicine. HCQ was used with the following dosage: 4 tablets at the beginning of the trial, followed, after 6 hours, by 2 tablets/BID for a total of 10 days. Between March and April, more than 11,330 subjects were randomised by 405 hospitals in 30 different countries across 6 continents. The primary analysis was carried out on 11,266 participants, of which 954 were assigned to the HCQ arm. The mortality rate of HCQ vs control, equal to RR=1.19 (95%CI 0.89-1.59, p=0.23; 104/947 vs 84/906), allowed to confirm that the treatment was overall ineffective.

Main limitations:
  o The trial had an open-label design
  o The HQC dosage was higher than the protocol previously recommended in Italy, and therefore results could not be generalised.

- *17/10/2020 – Rajasingham R et al. Clin Infect Dis 2020*: this is a randomised, double-blind, placebo-controlled clinical trial conducted in the United States and in the Canadian province of Manitoba, totally implemented online (from enrolment of patients to self-reported evaluation of the outcome). The trial enrolled healthcare workers who had been constantly exposed to SARS-CoV-2. Participants were randomised 2:2:1:1 to receive (i) HCQ (loading dose of 400mg BID (two 200mg tablets) separated by 6-8 hours followed by 400 mg once weekly for 12 days or (ii) HCQ 400 mg 2 twice weekly for 12 weeks, or to placebo which was prescribed in a matched fashion, including a loading dose of two tablets followed by two tablets once or twice weekly for 12 weeks. 1,483 healthcare workers were enrolled (in 79% of cases they were exposed to aerosol-generating procedures). The incidence of COVID-19 (laboratory-confirmed or symptomatic compatible illness) was 0.27 events per person/year (RR 0.72; 95% CI 0.44-1.16; P = 0.18) with HQC once weekly, and 0.28 events per person/year (RR 0.74; 95% CI 0.46-1.19; P = 0.22) with HQC twice weekly, compared with 0.38 events per person/year with placebo. These results were confirmed even narrowing the analysis down to the 97 subjects with a confirmed diagnosis of COVID-19.

Main limitations:
  o The endpoint was not defined based on a virologic diagnosis
  o The gathering of information was subject to an inevitable recall bias
  o Selection bias due to the fact that young and healthy subjects were enrolled.

- *09/11/2020 – Self Wh et al. JAMA 2020*: this was a multicentre, randomised, double-blind, placebo-controlled trial conducted at 34 hospitals in the US. Adults hospitalized with respiratory symptoms from severe acute respiratory syndrome coronavirus 2 infection were enrolled. Treatment with HCQ

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

involved the following dosage: 400mg BID for the first 2 doses, followed by 200mg BID for 8 doses. The trial was interrupted for futility after enrolling 479 subjects (242 randomised to HCQ and 237 to placebo), compared with 510 subjects originally estimated. The primary outcome was clinical status 14 days after randomization as assessed with a 7-category ordinal scale. The enrolled population had a median age of 57 years, 46.8% were receiving supplemental oxygen without positive pressure, 11.5% were receiving non-invasive ventilation or high-flow oxygen, and 6.7% were receiving invasive mechanical ventilation or ECMO. In both arms, the median time to symptom onset was 5 days (IQR 3-7). The primary analysis did not show any differences in both arms in terms of clinical status at 14 days (median [IQR] score 6 in both groups; aOR, 1.02 [95%CI, 0.73 to 1.42]). None of the 12 secondary outcomes were significantly different between groups, including in terms of mortality at 28 days (10.4% vs 10.5%; aOR, 1.07 [95%CI, 0.54- 2.09]).
Main limitations:
  o   The trial was interrupted early
  o   A primary endpoint was used which was difficult to interpret from a clinical point of view in terms of clinically relevant minimum difference.

- *24/11/2020 – Mitja O et al. NEJM 2020*: this was an open-label, cluster-randomised trial involving asymptomatic contacts of patients with confirmed SARS-CoV-2 infection. Participants were randomised to HCQ (800 mg followed by 400 mg/die for 6 days) or to usual care. The primary outcome was PCR-confirmed, symptomatic Covid-19. The analysis included 2314 contacts of 672 index case patients: 1116 received HCQ, while 1198 were randomly assigned to the control arm. Both arms did not show significant differences in terms of incidence of symptomatic and PCR-confirmed COVID-19 infection (5.7% and 6.2% in the HCQ and SOC arms, respectively; RR 0.86 [95%CI 0.52-1.42]), and in terms of SARS-CoV-2 infection (18.7% and 17.8%, respectively). The incidence of adverse events was higher in the hydroxychloroquine group than in the usual-care group (56.1% vs. 5.9%), but no treatment-related serious adverse events were reported.
Main limitations:
  o   The trial had an open-label design.

- *December 2020 – Ormani AS et al. EClin Med 2020*: this was a randomised, double-blind, placebo-controlled study carried out in Qatar (Qatar Prospective RCT of Expediting Coronavirus tepering – Q-PROTECT). It included three treatment arms: placebo, HCQ (600 mg/day for 6 days), and HCQ plus azithromycin (HCQ-AZ). The study enrolled non-hospitalised, asymptomatic or mildly ill adult patients with laboratory-confirmed SARS-CoV-2 infection. 456 patients (152 per arm) were randomised, with a median age of approximately 41 years. The study population did not show significant differences in terms of primary endpoint, that is day 6 virologic cure: HC+AZ 16/152 (10.5%), HC 19/149 (12.8%), placebo 18/147 (12.2%). Similar results were achieved in the assessment of the primary outcome at day 14: HC+AZ 30/149 (20.1%,), HC 42/146 (28.8%), placebo 45/143 (31.5%).

- *8/12/2020 – Barnabas R et al. Ann Intern Med 2020*: this was a randomised, double-blind, placebo-controlled study carried out in the US. The study aimed at assessing the safety and effectiveness of HCQ (440 mg/day for 3 days followed by 200 mg/day for 11 days) as post-exposure prophylaxis in close contacts recently exposed to persons with diagnosed SARS-CoV-2 infection. Participants were recruited online, with the primary endpoint being PCR–confirmed SARS-CoV-2 infection assessed via samples collected daily through day 14. The study enrolled 689 subjects (353 in the HCQ group and 336 in the placebo group), with a median age of 39 years (IQR 27-51). 18 % of the enrolled population included healthcare professionals, and the median duration of the last exposure to the index case

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

was 2 days (IQR 1-3). At day 14, the group treated with HCQ had a cumulative incidence of infections equal to 15.1% (95%CI 110-18.9) compared to 13.5% (95%CI 9.7-17.1) in the placebo group (Adj HR 1.10; 95%CI 0.73-1.66; P>0.20). No statistically significant difference emerged for secondary endpoints, i.e. infection rate at day 28, and onset of clinically manifest COVID-19. Conversely, the frequency of adverse events was higher in the HCQ group compared with the placebo group (16.2% vs 10.9%; P=0.0026).

Overall, the results from randomised trials seem to show a clear lack of clinical benefit linked to the use of HCQ both in the hospitalised population with moderate/severe disease and in the population with less advanced disease. In the latter case, although limited evidence exists, data from the small number of clinical trials conducted do not seem to show any benefit linked with the medicine (Mitja O et al. Clin Infect Dis 2020; Ormani AS et al. EClin Med 2020). As for safety, RCT data do not seem to confirm the higher risk of serious cardiac toxicity emerging from observational studies and, in no case, an excess mortality was evidenced. Randomised studies conducted within the SARS-CoV-2 infection prevention setting showed that that prophylaxis with hydroxychloroquine was ineffective both pre- and post-exposure.

Observational studies

Concerning the analysis of observational studies, the most clinically relevant studies are summarised below, which feature a control group, the mortality endpoint and are published in international peer-reviewed journals:

- *10/04/2020 Lane J et al. 2020:* the results of an international, multicentre trial were made available at an earlier stage, before publication on *Lancet Reumathology*. The trial was conducted on a cohort of 956,374 rheumatic patients predominantly using HCQ. The comparison with those who were concurrently taking azithromycin (323,122 cases) and those who incidentally added amoxicillin (351,956 cases) show that the HCQ + azithromycin combination was associated with an increased risk of 30-day cardiovascular mortality [HR 2.19 CI: 1.22-3.94]. Moreover, in the same case series, the risk of serious adverse events did not appear to be higher in short-term HCQ (956,374) concurrent treatments (30 days) than the treatment with sulfasalazine (310,350). These findings were confirmed by a secondary analysis of self-controlled case series.

- *23/04/2020 Magagnoli et al.* 2020: multicentre study conducted in the US, whose preliminary results had already been made available as a pre-print. Updated data were published concerning 807 male patients who were admitted for SARSCoV-2 infection and exposed to HCQ (198 patients), to HCQ + azithromycin (214 patients), or not exposed to HCQ (395 patients). The analysis showed that HCQ, with or without azithromycin, did not reduce the risk of mechanical ventilation. On the contrary, there was an increase in the overall mortality risk [aHR 1.83; 95 % CI: 1.16-2.89; p = 0,009] in patients treated with HCQ alone compared with patients not treated with HCQ. In addition, no difference in mortality between patients exposed and those not exposed to HCQ was observed in the group of patients under mechanical ventilation.

- *18/06/2020 Paccoud et al 2020.*: small study (n=84) reporting a retrospective analysis in which data from 38 subjects treated with HCQ (200 mg tid for 10 days) in addition to SOC were compared with 46 subjects with no contraindications to the use of HCQ, treated with SOC alone. The study evaluated a composite endpoint combining multiple outcomes (death, admission to intensive care, or decision to discontinue life-saving treatments), with no significant impact of HCQ (HR 0.90 [0.38; 2.1], p = 0.81). Cumulative survival was also not different between the two study groups (HR 0.89 [0.23; 3.47], p = 1).

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

- *15/05/2020 Yu et al. 2020*: multicentre study conducted in China, whose preliminary results had already been made available as a pre-print. This was a retrospective analysis of 550 patients admitted to hospital with severe respiratory failure and the need for mechanical ventilation. Comparing data from the 48 subjects treated with HCQ (200 x2 mg/day for 7-10 days)+SOC against the other subjects, the authors reported a benefit in terms of mortality (9/48 in the HCQ group and 45.8% (238/520) in the untreated group (p<0.001). The low quality of the study, characterised by important biases and inaccuracies, make the results obtained difficult to interpret.

- *29/06/2020 Arshad et al*. 2020: retrospective, multicentre, observational study, conducted in the US, including all subjects hospitalised from 10 March to 2 May 2020 with a COVID-19 diagnosis. A total of 2,541 subjects were included in the analysis. The total mortality rate was 18.1% and was significantly lower (13.5%) in HCQ-treated subjects. In a multivariable analysis, treatment with HCQ (HR 0.34; 95% CI 0.25-0.45) and HCQ+azithromycin (HR 0.29; 95 %CI 0.22-0.40) was significantly associated with a lower risk of death than the untreated subjects. In 91% of cases, treatment was initiated within 48 hours of hospitalisation. As pointed out by the authors themselves, in an uncontrolled study model and subject to an important risk of allocation bias, these results need to be confirmed in prospective, randomised, controlled studies.

- *20/08/2020 - CORIST Study (CORIST Collaboration, 2020)*: this was a retrospective, observational study including 3,451 hospitalised patients with a confirmed diagnosis of infection in 33 clinical centres in Italy, of which 2,634 had received HCQ. In a multivariable analysis, the use of hydroxychloroquine was associated with a reduction in death risk equal to 30% (HR 0.70; 95%CI 0.59 - 0.84). When interpreting these data, a number criticalities need to be taken into account: the non-homogeneous distribution of pre-existing risk factors and concurrent treatments (patients treated with hydroxychloroquine were younger and had less comorbidities. Additionally, they were more frequently treated with other concurrent medicines), the absence of data concerning adverse events (therefore it cannot be ruled out that the medicinal product was discontinued for toxicity, or that deaths could depend on adverse events), and the possible existence of other confounding factors linked to the design of the observational study. Such criticalities make the results of a retrospective observational study difficult to interpret and to apply to the clinical practice.

- *24/08/2020 - Catteau L et al. 2020:* this was a retrospective analysis of COVID-19 in-hospital mortality in the Belgian national hospital network. Patients treated with HCQ were compared with patients treated with supportive care (no-HCQ group). Out of 8,075 diagnosed before 1 May 2020 and for whom complete discharge data were available at 24 May 2020, 4542 received HCQ in monotherapy and 3533 were in the no-HCQ group*.* The two groups were not well balanced at baseline for important elements such as: patients in the HCQ group were younger and overall showed less comorbidities, including cardiovascular disease, arterial hypertension, chronic renal disease, neurological and cognitive disorders, malignancies, obesity and smoking status. However, at the time of hospitalisation, the HCQ group had a higher rate of radiological pneumonia, ARDS and ICU transfer within the 24 h after admission, as well as a higher frequency of elevated LDH and CRP levels. Finally, use of steroids was more frequent in the HCQ group (8.1% vs 5.9%). In the HCQ group, a lower proportion of deaths was observed (804/4542; 17.7%) compared with the control group (957/3533; 27.1%). In the multivariable analysis, mortality was lower in the HCQ group [adjusted hazard ratio (aHR) = 0.684; 95%CI 0.617-0.758]. Such reduction was observed both in patients diagnosed ≤5 days (n = 3975) and > 5 days (n = 3487) after symptom onset [aHR = 0.701 (95% CI 0.617-0.796) e aHR = 0.647 (95% CI 0.525-0.797), respectively]. These data cannot be easily interpreted due to a significant imbalance of the two study cohorts in relation to important clinical characteristics.

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

Further evidence emerged with regard to the evaluation of a possible indirect prevention effect deriving from the use of HCQ in subjects with rheumatic disease. Recently, a retrospective study was published which was conducted on the US Veterans Health Administration administrative databases. Investigators analysed information concerning adult patients with rheumatoid arthritis or associated rheumatological conditions, who were alive on 1 March 2020 (*Gentry CA et al. 2020*). By using a propensity March score statistical method, each subject treated with HCQ was associated with two non-treated control subjects, and both groups were compared to assess any difference in terms of incidence of documented SARS-CoV-2 infection (primary outcome of the study).

The study included 10,703 subjects treated with HCQ and 21,406 controls. Despite the matching, both groups were slightly different for the prevalence of younger subjects in the HCQ group compared with the control group. The incidence of SARS-CoV-2 infection was similar in both groups (31/10.703 [0.3%] vs 78/21.406 [0.4%]; OR 0.79%; 95%CI 0.52-1.20). In a multivariate analysis, the use of HCQ was not associated with a preventive effect against the infection (OR 0.79%; 95% 0.51-1.42). No difference emerged in the main secondary outcomes, such as hospital admission associated with SARS-CoV-2 infection, intensive care requirement associated with SARS-CoV-2 infection, mortality associated with COVID-19. Conversely, a lower mortality for all cause was observed (OR 0.70; 95%CI 0.55-0.89). This was a secondary outcome not directly related to COVID-19, and, as the investigators pointed out, might have been determined by confounding factors such as underlying conditions and the efficacy of HCQ on these, in addition to the younger age of subjects. The authors highlighted that the limitations of a retrospective study using an administrative database applied to their study. However, the data collected add up to literature evidence suggesting that hydroxychloroquine might not be effective in fighting COVID-19. Similar results also emerged from other studies (*Gendelmand O et al. 2020; Konig MF et al. 2020; Jung SY et al. Clin Microbiol Infect. 2020*).

Overall, the results of the main observational studies provide ambiguous evidence of the possible clinical benefits of hydroxychloroquine. The limitations related to the observational design of the studies and the numerous possible confounding effects within a complex condition such as COVID-19 make the results difficult to interpret.

Scientific review and meta-analysis

Living systematic reviews and network meta-analyses conducted by major research groups have been published. They summarise the results of clinical studies as they become available.

- In one of the main living systematic review available, edited by the Cochrane group in collaboration with various universities and research institutions (https://covid-nma.com/living_data/index.php), the analysis of data available, updated at 27 October 2020, confirms that hydroxychloroquine has no clinical benefit in terms of mortality, clinical improvement (assessed based on different parameters and timelines) or viral clearance. Conversely, a positive correlation to an increased risk of adverse events is evident (RR 2.16; 95%CI 1.21-3.86 in the evaluation at 14-28 days).

- *30/07/2020 - Siemieniuk RAC et al. BMJ 2020*: the results of one of the first living systematic reviews and network meta-analyses, conducted in the context of the BMJ Rapid Recommendations project, was published. The results indicate that there is an increased risk of adverse events, with an absolute risk difference equal to 985.06 (95% credible interval CI 24.68 - 985.10) per 1000 subjects, and a modest improvement (-4.53 days) in symptom resolution.

- 26/08/2020 - *Fiolet T et al. 2020:* this meta-analysis considered 29 clinical studies (4 clinical trials, including 3 randomised, and 25 observational studies) in which chloroquine or hydroxychloroquine were evaluated (used with or without azithromycin). The results showed that the use of hydroxychloroquine was not associated with a reduction in the risk of death, while the combination of hydroxychloroquine and azithromycin in COVID-19 patients was associated with a statistically significant increase in mortality (+27% compared with controls, RR 1.27; 95 %CI 1.04-1.54). When discussing the work, the authors

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

concluded that in light of the large number of studies evaluating hydroxychloroquine alone or in combination with another medicine, it seems unlikely that any efficacy will ever emerge.

- 22/10/2020 - *Axfors C et al. 2020*: the results of a meta-analysis conducted at Stanford University's Meta-Research Innovation Center (METRICS) have been made available (as a pre-print and therefore not yet peer-reviewed). The meta-analysis, conducted on 7,659 subjects treated with HCQ, did not show any benefit of the medicine in reducing mortality after 28 days (OR 1.08; 95%CI 0.99-1.18).

In conclusion, literature data show that prospective randomised clinical trials clearly indicate that hydroxychloroquine does not bring significant benefits to hospitalised patients. In the case of non-hospitalised patients, although data not suggesting a benefit, the level of uncertainty may justify further evaluation in randomised clinical trials.

Recommendations by international organisations

EMA: On 24 April, the European Medicines Agency drew attention on the risks of adverse events, including serious, associated with the use of HCQ and CQ. In particular, while serious adverse events can occur at recommended doses, higher doses can further increase the risk of abnormal heart rhythm (QT-prolongation). EMA is aware that HCQ is currently being used in the context of COVID-19 pandemic, and calls on prescribers to perform a close monitoring, and soliciting clinical studies on the efficacy of the medicine in the context of COVID-19.

On 29 May, EMA informed that, given the emergence of new evidence relating to the safety of chloroquine and hydroxychloroquine, such medicines should only be used in clinical trials or in national emergency use programmes on hospitalised patients under close supervision. On 27 November 2020, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended updating the product information for all chloroquine or hydroxychloroquine-containing medicines following a review of all available data that confirmed a link between the use of these medicines and the risk of psychiatric disorders and suicidal behaviour. Reminding that CQ and HCQ did not show any beneficial effects in treating COVID-19 in large randomised clinical trials, EMA underlined that chloroquine and hydroxychloroquine, even used in approved doses for authorised indications, can cause a wide spectrum of psychiatric disorders. Psychotic disorders and suicidal behaviour are listed in the product information of some chloroquine or hydroxychloroquine-containing medicines as rare side effects or side effects occurring at an unknown frequency. The review confirmed that psychiatric disorders have occurred and may sometimes be serious, both in patients with and without prior mental health problems.

FDA: On 28 March 2020, the FDA issued an emergency use authorisation (EUA) in those cases where clinical trials could not be performed. On 24 April, it informed that it was aware of reports of serious heart rhythm problems in patients (hospitalised and not) with COVID-19 treated with HCQ or CQ, often in combination with azithromycin and other QT prolonging medicines, particularly in patients with renal impairment. Such reports of adverse events included tachycardia or ventricular fibrillation or torsades de pointes and some fatal cases. The recommendation was to limit the use of HCQ to clinical trial or hospital settings, where close monitoring could be ensured. On 15 June 2020, the FDA revoked the previously granted EUA (Emergency Use Authorisation).

- **WHO:** The World Health Organisation informed that the use of high doses of HCQ or CQ may be associated with serious health-negative adverse events. Antibiotics should not be used as a means to prevent or treat COVID-19. On 26 May 2020, the WHO discontinued the hydroxychloroquine arm of the SOLIDARITY study. However, it should be noted that in this study the dosage of hydroxychloroquine was considerably higher than that recommended in the previous version of the sheet. On 4 June 2020, the

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

hydroxychloroquine treatment arm of the SOLIDARITY study was reopened for enrolment, and was finally closed on 17 June 2020.

- **National Institutes of Health (NIH)**: NIH published the following recommendations [Coronavirus Disease 2019 (COVID-19) Treatment Guidelines (update: 9 October 2020)]:
  1. The Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19 in hospitalized patients (AI).
  2. In nonhospitalized patients, the Panel recommends against the use of chloroquine or hydroxychloroquine with or without azithromycin for the treatment of COVID-19, except in a clinical trial (AI).
  3. The Panel recommends against the use of high-dose chloroquine (600 mg twice daily for 10 days) for the treatment of COVID-19 (AI).

- **Infectious Diseases Society of America (IDSA):** the American society published its Guidelines on the Treatment and Management of Patients with COVID-19 (last access: 26 October 2020)
  1. Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine. (Strong recommendation, Moderate certainty of evidence).
  2. Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine plus azithromycin. (Strong recommendation, Low certainty of evidence).

All major international bodies and major scientific societies agree not to recommend the use of hydroxychloroquine in hospitalised subjects, considering its possible use in non-hospitalised subjects only in clinical trials.

Warning (from fact sheet)

It is essential that clinical trials using HCQ and CQ include appropriate risk minimisation measures and careful monitoring of the following aspects:
- Prolongation of congenital or acquired QT interval and/or with known risk factors that may prolong this interval, such as: heart failure, acute myocardial infarction (AMI), bradycardia (<50 bpm), previous ventricular arrhythmias, not corrected hypokalaemia and/or hypomagnesemia.
- Hypoglycaemia also in the absence of hypoglycaemic therapy (please warn patients of this risk).
- Hepatic or renal failure.
- Glucose-6-phosphate dehydrogenase deficiency (G6PD), porphyria, psoriasis.
- Psychiatric disorders.

For further details consult the fact sheet and AIFA's notice dated 31 March 2020.
https://www.aifa.gov.it/documents/20142/1097058/2020.03.31_NII_clorochina_idrosssiclorochina_GP_consolidata+COVID-19.pdf/c928750d-dcb2-f38a-41a1-1fbf6af7a767

Main interactions
According to the fact sheet, the main interactions concern:
- digoxin (increases plasma concentrations)
- hypoglycaemic agents (decrease blood sugar)
- QT prolonging medicines (particularly antiarrhythmic agents, tricyclic antidepressants, antipsychotics, certain anti-infective agents)
- anti-epileptics
- ciclosporin.

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

For further information on pharmacological interactions, consult the following link*:* https://www.covid19-druginteractions.org/.

References

- Abd-Elsalam S, Esmail ES, Khalaf M, et al. Hydroxychloroquine in the Treatment of COVID-19: A Multicenter Randomized Controlled Study. Am J Trop Med Hyg. 2020 Oct;103(4):1635-1639. doi: 10.4269/ajtmh.20-0873. PMID: 32828135; PMCID: PMC7543820.
- Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and Safety of Hydroxychloroquine vs Placebo for Pre-exposure SARS-CoV-2 Prophylaxis Among Health Care Workers: A Randomized Clinical Trial [published online ahead of print, 2020 Sep 30]. JAMA Intern Med. 2020;e206319. doi:10.1001/jamainternmed.2020.6319.
- Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19 [published online ahead of print, 2020 Jul 2]. Int J Infect Dis. 2020;S1201-9712(20)30534-8. doi:10.1016/j.ijid.2020.06.099.
- Aviña-Zubieta J A et Al: Long term effectiveness of antimalarial drugs in rheumatic diseases. *Ann Rheum Dis* 1998;**57**:582–587 .
  https://www.researchgate.net/publication/13394691_Long_term_effectiveness_of_antimalarial_drugs_in_rheumatic_diseases
- Axfors C, Schmitt AM, Janiaud P, et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials. medRxiv 2020.09.16.20194571; doi: https://doi.org/10.1101/2020.09.16.20194571European Medicine Agency. COVID-19: reminder of risk of serious side effects with chloroquine and hydroxychloroquine https://www.ema.europa.eu/en/news/covid-19-reminder-risk-serious-side-effects-chloroquine-hydroxychloroquine
- Barnabas RV, Brown ER, Bershteyn A, et al. Hydroxychloroquine as Postexposure Prophylaxis to Prevent Severe Acute Respiratory Syndrome Coronavirus 2 Infection : A Randomized Trial. Ann Intern Med. 2020 Dec 8:M20-6519. doi: 10.7326/M20-6519. Epub ahead of print. PMID: 33284679; PMCID: PMC7732017.
- Bessière F, Roccia H, Delinière A, et al. Assessment of QT Intervals in a Case Series of Patients With Coronavirus Disease 2019 (COVID-19) Infection Treated With Hydroxychloroquine Alone or in Combination With Azithromycin in an Intensive Care Unit [published online ahead of print, 2020 May 1]. JAMA Cardiol. 2020;e201787. doi:10.1001/jamacardio.2020.1787. https://jamanetwork.com/journals/jamacardiology/fullarticle/2765633
- Boulware DR, Pullen MF, Bangdiwala AS, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19 [published online ahead of print, 2020 Jun 3]. N Engl J Med. 2020;10.1056/NEJMoa2016638. doi:10.1056/NEJMoa2016638.
- Catteau L, Dauby N, Montourcy M, et al.; Belgian Collaborative Group on COVID-19 Hospital Surveillance. Low-dose hydroxychloroquine therapy and mortality in hospitalised patients with COVID-19: a nationwide observational study of 8075 participants. Int J Antimicrob Agents. 2020 Oct;56(4):106144. doi: 10.1016/j.ijantimicag.2020.106144. Epub 2020 Aug 24. PMID: 32853673; PMCID: PMC7444610.
- Cavalcanti AB, Zampieri FG, Rosa RG, et al.; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med. 2020 Jul 23:NEJMoa2019014. doi: 10.1056/NEJMoa2019014. Epub ahead of print. PMID: 32706953; PMCID: PMC7397242.

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

- Chen J et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirusdisease-19 (COVID-19). J Zhejiang Univ (Med Sci); 2020.
- Chen Z et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020.03.22.20040758; doi: https://doi.org/10.1101/2020.03.22.20040758
- Cohen MS. Hydroxychloroquine for the Prevention of Covid-19 - Searching for Evidence [published online ahead of print, 2020 Jun 3]. N Engl J Med. 2020;10.1056/NEJMe2020388. doi:10.1056/NEJMe2020388
- COVID-19 RISK and Treatments (CORIST) Collaboration. Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study. Eur J Intern Med. 2020 Aug 25:S0953-6205(20)30335-6. doi: 10.1016/j.ejim.2020.08.019. Epub ahead of print. PMID: 32859477; PMCID: PMC7446618.
- DEPLAZIO. Efficacia comparativa dei trattamenti farmacologici per il trattamento delle persone affette da COVID-19. https://www.deplazio.net/it/component/content/article/78-area-covid-19/342-efficacia-comparativa-dei-trattamenti-farmacologici-per-il-trattamento-delle-persone-affette-da-covid-19
- EMA. COVID-19: reminder of the risks of chloroquine and Hydroxychloroquine. https://www.ema.europa.eu/en/documents/press-release/covid-19-reminder-risks-chloroquine-hydroxychloroquine_en.pdf
- FDA Drug Safety Communication https://www.fda.gov/media/137250/download
- FDA Drug Safety Communication https://www.fda.gov/drugs/drug-safety-and-availability/fda-cautions-against-use-hydroxychloroquine-or-chloroquine-covid-19-outside-hospital-setting-or
- Fiolet T, Guihur A, Rebeaud ME, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis [published online ahead of print, 2020 Aug 26]. Clin Microbiol Infect. 2020;S1198-743X(20)30505-X. doi:10.1016/j.cmi.2020.08.022.
- Gao J et Al: letter: Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies BioScience Trends. 2020; 14(1):72-73. https://www.jstage.jst.go.jp/article/bst/14/1/14_2020.01047/_pdf/-char/en
- 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;NEJMoa2012410. doi:10.1056/NEJMoa2012410. https://www.nejm.org/doi/full/10.1056/NEJMoa2012410
- Gendelman O, Amital H, Bragazzi NL, Watad A, Chodick G. Continuous hydroxychloroquine or colchicine therapy does not prevent infection with SARS-CoV-2: Insights from a large healthcare database analysis. Autoimmun Rev. 2020 Jul;19(7):102566. doi: 10.1016/j.autrev.2020.102566. Epub 2020 May 5. PMID: 32380315; PMCID: PMC7198406.
- Gentry CA, Humphrey MB, Thind SK, Hendrickson SC, Kurdgelashvili G, Williams RJ 2nd. Long-term hydroxychloroquine use in patients with rheumatic conditions and development of SARS-CoV-2 infection: a retrospective cohort study. Lancet Rheumatol. 2020 Nov;2(11):e689-e697. doi: 10.1016/S2665-9913(20)30305-2. Epub 2020 Sep 21. PMID: 32984847; PMCID: PMC7505552.
- Idrossiclorochina (Plaquenil®) scheda tecnica: https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_008055_013967_RCP.pdf&retry=0&sys=m0b1l3
- Jung SY, Kim MS, Kim MC, et al. Effect of hydroxychloroquine pre-exposure on infection with SARS-CoV-2 in rheumatic disease patients: A population-based cohort study. Clin Microbiol Infect. 2020 Dec 11:S1198-743X(20)30752-7. doi: 10.1016/j.cmi.2020.12.003. Epub ahead of print. PMID: 33316402.
- Kaptein SJF et al. Favipiravir at high doses has potent antiviral activity in SARS-CoV-2–infected hamsters, whereas hydroxychloroquine lacks activity; PNAS 117: 26955–26965; 2020.

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

- Konig MF, Kim AH, Scheetz MH, Graef ER, Liew JW, Simard J, Machado PM, Gianfrancesco M, Yazdany J, Langguth D, Robinson PC; COVID-19 Global Rheumatology Alliance. Baseline use of hydroxychloroquine in systemic lupus erythematosus does not preclude SARS-CoV-2 infection and severe COVID-19. Ann Rheum Dis. 2020 Oct;79(10):1386-1388. doi: 10.1136/annrheumdis-2020-217690. Epub 2020 May 7. PMID: 32381561.

- Lane JCE, Weaver J, Kostka K, et al; OHDSI-COVID-19 consortium. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. Lancet Rheumatol. 2020 Nov;2(11):e698-e711. doi: 10.1016/S2665-9913(20)30276-9. Epub 2020 Aug 21. PMID: 32864627; PMCID: PMC7442425.

- 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

- Mahévas M. et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data *BMJ* 2020; 369 :m1844. https://www.bmj.com/content/369/bmj.m1844

- Maisonnasse P et al. Hydroxychloroquine use against SARS-CoV-2 infection in non-human primates. Nature 585: 584-587; 2020

- Mercuro NJ, et al. Risk of QT Interval Prolongation Associated with Use of Hydroxychloroquine with or Without Concomitant Azithromycin Among Hospitalized Patients Testing Positive for Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. doi:10.1001/jamacardio.2020.1834. https://jamanetwork.com/journals/jamacardiology/fullarticle/2765631

- Mitjà O, Corbacho-Monné M, Ubals M, et al; BCN PEP-CoV-2 RESEARCH GROUP. Hydroxychloroquine for Early Treatment of Adults with Mild Covid-19: A Randomized-Controlled Trial. Clin Infect Dis. 2020 Jul 16:ciaa1009. doi: 10.1093/cid/ciaa1009. Epub ahead of print. PMID: 32674126; PMCID: PMC7454406.

- Mitjà O, Corbacho-Monné M, Ubals M, et al., for the BCN-PEP-CoV2 Research Group. A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19. New Engl J Med [on line] November 24, 2020. DOI: 10.1056/NEJMoa2021801. https://www.nejm.org/doi/full/10.1056/NEJMoa2021801

- Mohammad S. Et Al. Examination of Hydroxychloroquine Use and Hemolytic Anemia in G6PDH-Deficient Patients Arthritis Care & Research2018; 70, 481–485 https://onlinelibrary.wiley.com/doi/epdf/10.1002/acr.23296

- National Institutes of Health. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Available at https://www.covid19treatmentguidelines.nih.gov/ . Accessed October 26, 2020.

- Omrani AS, Pathan SA, Thomas SA, et al. Randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin for virologic cure of non-severe Covid-19. EClinicalMedicine. 2020 Dec; 29:100645. doi: 10.1016/j.eclinm.2020.100645. Epub 2020 Nov 20. PMID: 33251500; PMCID: PMC7678437.

- Paccoud O, Tubach F, Baptiste A, et al. Compassionate use of hydroxychloroquine in clinical practice for patients with mild to severe Covid-19 in a French university hospital [published online ahead of print, 2020 Jun 18]. Clin Infect Dis. 2020;ciaa791. doi:10.1093/cid/ciaa791.

- RECOVERY Trial. No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19. https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19. Rosenberg ES et al. 2020 Association of Treatment with Hydroxychloroquine or Azithromycin With In-Hospital Mortality in

Hydroxychloroquine
in the treatment of adult patients with COVID-19
Update: 22 December 2020 (previous publications: 2 April 2020; 29 April 2020; 29 May 2020; 22 July 2020, 25 November 2020)

Patients With COVID-19 in New York State. JAMA 10.1001/jama.2020.8630 https://jamanetwork.com/journals/jama/fullarticle/2766117

- Self WH, Semler MW, Leither LM, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. JAMA. 2020 Nov 9:e2022240. doi: 10.1001/jama.2020.22240. Epub ahead of print. PMID: 33165621; PMCID: PMC7653542.

- Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ. 2020;370:m2980. Published 2020 Jul 30. doi:10.1136/bmj.m2980.

- Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. A randomized trial. Ann Intern Med. 2020. [Epub ahead of print]. doi:10.7326/M20-4207.

- Tang W et Al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1

- Ulrich RJ, Troxel AB, Carmody E, et al. Treating Covid-19 With Hydroxychloroquine (TEACH): A Multicenter, Double-Blind, Randomized Controlled Trial in Hospitalized Patients. Open Forum Infect Dis. 2020;ofaa446. Published 2020 Sep 23. doi:10.1093/ofid/ofaa446.

- Living mapping and living systematic review of Covid-19 studies. https://covid-nma.com/living_data/index.php.

- Wang M, et Al Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020. https://doi.org/10.1038/s41422-020-0282-0

- WHO Solidarity trial consortium, Pan H, Peto E, Abdool Karim Q, et al. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. medRxiv 2020.10.15.20209817; doi: https://doi.org/10.1101/2020.10.15.20209817.

- World Health Organization https://www.who.int/news-room/q-a-detail/malaria-and-the-covid-19-pandemic

- World Health Organization https://www.who.int/news-room/q-a-detail/q-a-hydroxychloroquine-and-covid-19.

- Xueting Yao 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) https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa237/5801998.

- Yu B, Li C, Chen P, et al. Low dose of hydroxychloroquine reduces fatality of critically ill patients with COVID-19 [published online ahead of print, 2020 May 15] [published correction appears in Sci China Life Sci. 2020 Jun 18;:]. Sci China Life Sci. 2020;1-7. doi:10.1007/s11427-020-1732-2.