

High-dose Hydroxychloroquine for Mild COVID-19: One Center’s Clinical Experience and Investigational Challenges

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October 5, 2020

Abstract

Aims: The recently described SARS-CoV-2 has led to a pandemic which has severe consequences for the global community. Hydroxychloroquine has been repurposed for the treatment of COVID-19 but conflicting information on its efficacy and safety has since emerged. Our group designed a trial on the use of high-dose hydroxychloroquine in a high-risk ambulatory population with mild COVID-19 (NCT04351620) and summarizes herein the clinical data of hydroxychloroquine in COVID-19. **Methods:** Single-arm and single-center study evaluating the tolerability of high-dose hydroxychloroquine, 600 mg twice daily for 5 days, in patients with mild COVID-19 and risk factors for clinical decompensation and hospitalization. Secondary objectives included maintenance of ambulatory status, defervescence, and symptom relief. **Results:** Over a six-week period, 59 patients met eligibility criteria out of 314 contacted (18.7%). Out of these 59 potentially eligible patients, 44 (74.5%) patients declined to be screened further due to concerns about its risks and unproven efficacy, referencing media accounts and politicization of the medication. Out of the 9 patients consented, 2 did not complete the therapy plan, 1 due to headaches, 1 did not follow up. Two of the 7 patients who completed the study continued to have fevers, one was admitted for pneumonia. Study was terminated early due to recruitment difficulties. **Conclusions:** The trial met pre-defined primary outcome of tolerability, but sample size was too small to allow further interpretation. The political climate and media coverage might have negatively impacted patient recruitment, which has ultimately led to its early interruption.

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PRINCIPAL INVESTIGATOR STATEMENT: The authors confirm that the Principal Investigator for this paper is Dr. Reem Jan and that she has direct clinical responsibility for the patients included in this study.

AUTHORSHIP STATEMENT: All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the concept, design analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the *British Journal of Clinical Pharmacology*.

CONFLICT OF INTEREST DISCLOSURE: The authors whose names are listed above certify that they have NO affiliations with or involvement in any organizations or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

ETHICS APPROVAL STATEMENT/ PERSONAL COSENT STATEMENT: This study was approved by the University of Chicago Institutional Review of Boards and all patients included in this study signed a consent form.

DATA AVAILABILITY STATEMENT: The data that supports the findings of this study are available on request from the corresponding author (IBV). The data are not publicly available due to their containing information that could compromise the privacy of research participants.

FUNDING STATEMENT: This study did not receive any funding outside the University of Chicago.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT04351620

KEY WORDS: hydroxychloroquine, SARS-CoV-2, COVID-19, clinical trial, tolerability, review.

WORD COUNT: 3,351

TABLE COUNT: 1 table

FIGURE COUNT: 1 figure

ABSTRACT:

Aims: The recently described SARS-CoV-2 has led to a pandemic which has severe consequences for the global community. Hydroxychloroquine has been repurposed for the treatment of COVID-19 but conflicting information on its efficacy and safety has since emerged. Our group designed a trial on the use of high-dose hydroxychloroquine in a high-risk ambulatory population with mild COVID-19 (NCT04351620) and summarizes herein the clinical data of hydroxychloroquine in COVID-19.

Methods: Single-arm and single-center study evaluating the tolerability of high-dose hydroxychloroquine, 600 mg twice daily for 5 days, in patients with mild COVID-19 and risk factors for clinical decompensation and hospitalization. Secondary objectives included maintenance of ambulatory status, defervescence, and symptom relief.

Results: Over a six-week period, 59 patients met eligibility criteria out of 314 contacted (18.7%). Out of these 59 potentially eligible patients, 44 (74.5%) patients declined to be screened further due to concerns about its risks and unproven efficacy, referencing media accounts and politicization of the medication. Out of the 9 patients consented, 2 did not complete the therapy plan, 1 due to headaches, 1 did not follow up. Two of the 7 patients who completed the study continued to have fevers, one was admitted for pneumonia. Study was terminated early due to recruitment difficulties.

Conclusions: The trial met pre-defined primary outcome of tolerability, but sample size was too small to allow further interpretation. The political climate and media coverage might have negatively impacted patient recruitment, which has ultimately led to its early interruption.

MAIN TEXT:

Introduction

In December 2019, SARS-CoV-2 was identified as a novel coronavirus implicated in a cluster of viral pneumonia cases in Wuhan, China. This pathogen has since disseminated across the world in a pandemic that has led to severe health and economic consequences for the global community. This has led to a sense of urgency in finding therapies that can alleviate the death toll and reduce the burden on hospitals, especially intensive care units with their limited and expensive resources. Drug development is a timely and painstaking process from the laboratory to the dispensary, hence creating a safe and effective antiviral *de novo* may not meet the urgency of the moment. As a result, scientific attention has been directed toward agents already widely used, with known safety and pharmacological profiles.[1]

Hydroxychloroquine received an intense amount of attention early in this pandemic, following uncontrolled data suggesting that the related compound chloroquine improved pulmonary outcomes in China.[2] Excitement mounted as the world wondered whether these cheap and safe medications would indeed save lives. Indeed, government health policies across the world promoted the immediate use of hydroxychloroquine for patients with COVID-19. Numerous clinical trials were initiated to study the safety and efficacy of hydroxychloroquine utilizing various dosing strategies (Figure 1). A majority of early trials utilized standard hydroxychloroquine doses approved for chronic treatment of rheumatic diseases ranging from 400 to 600 mg daily (Table 1). Our group hypothesized a high-dose short-term hydroxychloroquine dosing strategy would provide enhanced treatment efficacy due to more rapid increases in serum drug concentrations. We therefore proposed a study to determine if high-dose hydroxychloroquine (1200 mg daily for five days) was well tolerated and demonstrated activity in ambulatory patients with mild COVID-19.

Herein we review the pharmacologic basis and design of our trial, the outcomes of other studies investigating hydroxychloroquine in COVID19 to date as well as discuss the challenges faced by studies evaluating hydroxychloroquine in COVID-19 in the current environment.

Pharmacology and Toxicity of 4-Aminoquinones

Hydroxychloroquine and chloroquine belong to a class of drugs known as 4-aminoquinones. Hydroxychloroquine differs from chloroquine by the presence of a hydroxyl group at the end of the side chain. Hydroxychloroquine has considerable pharmacokinetic variability and the terminal half-life is 40-50 days.[3, 4] Both molecules are weak bases and can irreversibly accumulate in acidic environments, such as the lysosome, which contributes to its large volume of distribution and impacts the amount of free drug available in tissues.[5] Plasma, blood and serum concentrations can vary in individual patients and between patients after identical doses. Hydroxychloroquine has an active metabolite, desethylhydroxychloroquine (DHCQ) that is largely formed by CYP3A4.[6]

The immune modulatory mechanisms of hydroxychloroquine have not yet been fully elucidated; however, they are believed to include the reduction of Toll-like receptor and cGAS-STING signaling, attenuation of pro-inflammatory cytokine production, and inhibition of lysosomal activity and autophagy.[7-9] It is unknown whether hydroxychloroquine has a direct antiviral effect in COVID-19, and if so, what plasma concentrations of the drug and its active metabolite are efficacious. Antiviral effects of chloroquine against RNA viruses, including SARS-CoV-1, have previously been demonstrated *in vitro* including alteration of cellular pH and disruption of the endolysosomal pathway critical for viral entry, replication and assembly.[10, 11] Similar studies of hydroxychloroquine in SARS-CoV-2 indicated similar activity.[12, 13]

In designing our trial, we relied on a published randomized dose-ranging trial in rheumatoid arthritis (RA), which demonstrated that a dose of 1200 mg of hydroxychloroquine daily for up to 6 weeks was safe and achieved a more rapid response than lower daily doses.[3, 14] Previously published pharmacokinetic studies in RA patients indicate that the maximum concentration after the first dose is approximately one-third of the steady-state concentration.[15] Therefore a dose of 1200 mg daily is expected to achieve concentration achievable at 400 mg daily at steady-state, which does not occur until approximately five times the terminal

half-life of 40 days.

Shortly after our trial was initiated, physiologically based pharmacokinetic modeling performed *in vitro* identified an effective free lung tissue trough concentration/EC50 in cell culture could be reached by hydroxychloroquine loading doses on Day 1 of therapy, between 400 mg BID and 600 mg BID.[13] However, the U.S. FDA cautioned interpretation of these results as the model used severely underestimated the required intracellular EC50 for therapeutic effect *in vivo*. Rather, they concluded there was a low likelihood of achieving effective *in vivo* concentration of hydroxychloroquine with a safe oral regimen.[16] Subsequent pharmacokinetic/ pharmacodynamic (PKPD) modeling of pooled data from all *in vitro* and clinical studies of COVID-19 predicted dosing regimens of at least 800 mg/day for greater than 5 days were required to decrease viral loads compared with dosing regimens of less than 400 mg/day.[17]

Higher dosing strategies must consider incremental toxicities of hydroxychloroquine. Overdosage can occur with oral ingestion and include symptoms of headache, drowsiness, visual disturbance, cardiovascular collapse.[18] Retinal toxicity and cardiomyopathy are serious toxicities; however are believed to represent a long-term and dose-dependent cumulative phenomenon.[19, 20] Hydroxychloroquine is structurally similar to the class IA antiarrhythmic quinidine, which inhibits voltage-gated sodium and potassium channels, including the hERG cardiomyocyte Kv11.1 channel and contributes to drug-induced QTc prolongation and increases the risk of torsades de pointes and sudden cardiac death.[21]

No studies have established a concentration-dependent relationship between hydroxychloroquine and risk for QTc prolongation and most of the data supporting concerns for QTc prolongation with hydroxychloroquine have been based on studies of chloroquine.[22] Historical experience evaluating QTc in patients treated with hydroxychloroquine for rheumatologic diseases has not revealed strong association with cardiac toxicity.[23, 24] The aforementioned trial which utilized 1200 mg daily for 6 weeks in RA reported no difference in therapy discontinuation and no reports of cardiovascular events up to 24 weeks of follow up.[3, 14] In COVID-19, one model using chloroquine data to predict risk of QTc prolongation with hydroxychloroquine estimated that doses 400-600 BID for 10 days or less were unlikely to cause clinically significant QTc prolongation in patients without risk factors for QTc prolongation.[17] Recent studies evaluating QTc prolongation in hospitalized patients with COVID-19 being treated with hydroxychloroquine monotherapy, found a significant percentage of patients developed a prolonged QTc of 500 milliseconds or had a change in QTc of 60 milliseconds or more however none developed arrhythmias.[25, 26] In these studies, 75% and 50% of patients respectively were concomitantly taking one or more other medications with known QTc-prolonging effects and both studies lacked a control group.

High-Dose Hydroxychloroquine for Ambulatory Patients with COVID-19: Our Center's Experience

With this pharmacologic rationale, our group designed a single arm and single-center study evaluating the tolerability of high-dose hydroxychloroquine therapy, 600 mg twice daily for five days, in outpatient adult participants with mild COVID-19 with risks factors for clinical decompensation (NCT04351620). Our secondary objectives were to evaluate whether high-dose hydroxychloroquine lead to symptom relief, defervescence and maintenance of ambulatory status. Patients were eligible for inclusion in our trial if they were SARS-CoV-2 PCR positive, had one fever greater than 100.4 F within 48 hours of enrollment, manifested symptoms consistent with the disease, and had one additional risk factor associated with hospitalization. These risk factors included age > 55, pre-existing pulmonary, cardiovascular, kidney disease, diabetes, hypertension, or one fever every 24 hours for > 72h. Patients with history of cardiovascular disease were required to have had an electrocardiogram within the past thirty days showing a normal QT interval (QT < 500 ms). Patients with more advanced kidney disease, history of retinal disease, history of QT prolongation or other arrhythmias, use of QT prolonging medications and pregnant or lactating women were excluded from the study.

We designed our trial to enroll a high-risk ambulatory population with mild illness whom stood to benefit more from early intervention with hydroxychloroquine. Mild illness is defined by symptoms of upper respiratory tract infection, including fever, dry cough, sore throat, nasal congestion, anosmia, ageusia, fatigue,

myalgia, and headaches without pneumonia or with mild pneumonia.[27] Mild illness can progress to severe illness characterized by respiratory failure with or without shock and multi-organ failure. Although risk factors for hospitalization due to COVID-19 had not been well-defined, several studies reported similar epidemiological risk factors associated with severe disease and in-hospital mortality, including older age, and chronic medical conditions such as hypertension and diabetes.[28, 29] Screening, informed consent and entry into the trial was completed remotely allowing for patients to remain quarantined. Upon notification of a positive SARS-CoV-2 test result by the University of Chicago Infection Control, patients were asked permission to be contacted by our study team. Once contacted, formal screening and informed consent were completed over the phone by study investigators. No clinical laboratory assessments were required upon screening, during, or at end of the study. If enrolled, hydroxychloroquine was delivered to their home address by the University of Chicago Specialty Pharmacy within 24 hours of enrollment. While participating in the study, patients were asked to check and log their body temperature twice a day and record antipyretic use. A standardized symptom assessment was performed daily while the participant was taking hydroxychloroquine, 5 days, and at a pre-specified Day 14 follow up at which point their participation in the study was complete. The study was approved by the University of Chicago Institutional Review Boards.

Over a six-week period, 59 patients met eligibility criteria out of 314 patients contacted (18.7%). Out of these 59 potentially eligible patients, 44 (74.5%) patients declined to be screened further due to concerns about the risks and unproven efficacy of the medication, often referencing media accounts and touting of the drug by President of the United States. Fifteen completed the “Pre-Treatment Assessment” and 9 signed the Telephone Consent, with 7 continuing on to receive the medication. Two patients discontinued the treatment because of side effects, one of whom did not follow-up and the other was unable to tolerate either the original dose or the dose reduction protocol because of headaches. While we were unable to confirm with certainty that this was a medication effect, it was deemed prudent to end their enrollment. The remaining patients were able to complete their courses, hence meeting the primary outcome of tolerability. Two of the patients reported rapid improvement in fever and myalgia within 24 hours of starting the treatment. One patient continued to have fevers throughout the course and was admitted to hospital for pneumonitis. Incidentally, EKG obtained on admission demonstrated a normal QTc interval. Another patient had fevers through the entire study period. Hence with the small sample size, no conclusions could be drawn and the study was terminated early due to recruitment difficulties, with many patients contacted by the team citing negative media reports on the drug as the reason behind their disinterest.

Clinical data on 4-aminoquinones and SARS-CoV-2

In the early stages of the pandemic, the National Health Commission of China incorporated 4-aminoquinones into the treatment guidelines of COVID-19 after Chinese preliminary data demonstrated tolerability and efficacy of chloroquine in treating COVID-19.[2] The expectations for the effectiveness of these medications sharply increased after Gautret *et al.* published results from their small, open-label, non-randomized clinical trial from a single-center in Marseilles, France.[30] This trial concluded that hydroxychloroquine given at a dose of 600 mg a day in combination with azithromycin was effective in viral load reduction and virus elimination of SARS-CoV-2 as measured by nasopharyngeal PCR in patients across disease severity. The article received criticism for its statistical methods, and particularly for excluding 6 out of the 26 patients who received hydroxychloroquine and were lost to follow up or had a poor outcome. Shortly thereafter, the U.S. Food and Drug Administration (FDA) issued an emergency use authorization that allowed the use of hydroxychloroquine in patients hospitalized due to COVID-19 when clinical trials were not available or participation in clinical trials was not feasible.[31] Other countries, including Brazil, France, Italy, Netherlands, and South Korea issued similar recommendations.

Between March and May, 2020, the period of our trial’s design and recruitment, a myriad of hydroxychloroquine clinical studies were performed. The studies were primarily retrospective analysis reporting on the clinical outcomes of its use in hospitalized patients. In many cases, these studies were subject to confounders and selection biases. Data from randomized controlled trials has more recently become available (Table 1).

A retrospective analysis of hospitalized, non-mechanically ventilated patients across all U.S. Veteran’s Health

Administration Medical Centers revealed an association between the use of hydroxychloroquine and an increase in in-hospital mortality.[32] The authors did not specify the excess cause of death in this subgroup, but it did not seem to derive from worse respiratory failure, given that rates of mechanical ventilation were similar between subgroups. An observational study in France comparing 84 hydroxychloroquine treated individuals with 89 patients treated with usual care found similar survival without transfer to the ICU at day 21 in both groups.[33] This trial pre-specified treatment groups prior to hospital admission to minimize selection bias.

A multicenter retrospective study in the United States included 1438 patients from 25 hospitals failed to demonstrate a reduction in in-hospital mortality in patients treated with hydroxychloroquine, azithromycin or both. Combination treatment with hydroxychloroquine and azithromycin was associated with more frequent cardiac arrest (HR 2.13, CI 1.12 – 4.05).[34] A single center study from New York City found no association between hydroxychloroquine and the composite end point of intubation or death (HR 1.04, CI 0.82 – 1.32) in 1376 patients who received usual care or hydroxychloroquine alone.[35] The Henry Ford Hospital Study, a retrospective cohort study of 2541 patients, reported a mortality benefit in patients receiving hydroxychloroquine.[36] This study has been criticized for potential confounding factors including the more frequent use of corticosteroids and tocilizumab in hydroxychloroquine treatment arms, with corticosteroids now recognized as an effective form of treatment in hospitalized patients requiring supplemental oxygen.[37]

A retrospective analysis of a multinational registry including over 96,031 subjects from 671 hospitals in six continents comparing four groups, chloroquine or hydroxychloroquine with and without a macrolide, to usual care reported an increase in hospital mortality and new ventricular arrhythmias with use of hydroxychloroquine and chloroquine with or without macrolide.[38] This study was soon retracted due to questions over data integrity as a significant amount of data provided by a private company, Surgisphere, appeared to have large discrepancies and was not released for independent review citing contractual limitations.

In a retrospective study of critically ill, mechanically ventilated patients with COVID-19, hydroxychloroquine was associated with a substantial decrease in mortality (18.8% in the hydroxychloroquine group versus 47.4% in the control group) and interleukin-6 concentrations.[39] The authors did not report criteria for hydroxychloroquine use and selection bias is an important concern when interpreting these results. Preliminary results of the randomized controlled multicenter RECOVERY trial comparing 1561 patients treated with high-dose hydroxychloroquine to 3155 patients on usual care revealed hydroxychloroquine was not associated with reductions in 28-day mortality but rather with increased length of hospital stay and increased risk of progression to invasive mechanical ventilation.[40]

After review of these trials, the U. S. FDA revoked its Emergency Use Authorization of chloroquine and hydroxychloroquine to treat hospitalized COVID-19 patients. Subsequently, the World Health Organization discontinued the SOLIDARITY trial of hydroxychloroquine treatment in hospitalized COVID-19 patients after interim results revealed little or no reduction in mortality and concerning safety signals, albeit without “solid evidence of increase in mortality.”

A randomized controlled trial addressing mild to moderate hospitalized COVID-19 patients also failed to show that hydroxychloroquine alone or in combination with azithromycin improves clinical status compared to usual care.[41] The first randomized multicenter clinical trial evaluating the effect of hydroxychloroquine (n=75) in comparison to usual care alone (n=75) in mild to moderate COVID-19 did not show differences in the probability of SARS-CoV-2 PCR negative conversion or alleviation of symptoms by day 28 of follow up.[42] The median of 16 days delay between onset of symptoms and randomization could have biased the results towards the non-intervention group.

A recent randomized, double-blind, placebo-controlled clinical trial for treatment of symptomatic non-hospitalized patients with COVID-19 investigated a higher dose of hydroxychloroquine (800mg plus 600mg six to 8 hours later and 600mg daily for 4 days). This trial demonstrated that hydroxychloroquine did not substantially reduce symptom severity in outpatients with early, mild COVID-19. Adverse events were significantly higher in hydroxychloroquine group with gastrointestinal symptoms being most commonly reported.

Of note, some limitations included only 58% of patients had laboratory confirmation of SARS-CoV-2 due to testing shortages.[43]

Conflicting results from small clinical trials and a retrospective study on the benefits of hydroxychloroquine with and without azithromycin have been reported. [30, 44-48] Such studies were frequently unpowered and lacked a comparison group.[44, 45, 48] Moreover, the inclusion of individuals with mild or no symptoms and characteristics associated with better prognosis support the evidence that the prognosis in mild to moderate COVID-19 is overall good and treatment is unlikely to benefit these patients.[49]

The use of hydroxychloroquine as a prophylactic agent has been less studied. Through a creative recruitment process utilizing internet-based self-referral and online follow up surveys, Boulware *et al.* randomized asymptomatic adult individuals from Canada and the U. S. who had a high or moderate-risk exposure to confirmed cases of COVID-19 to hydroxychloroquine or placebo.[50] Hydroxychloroquine did not prevent illness compatible or confirmed to be COVID-19 infection and was associated with increased mild adverse reactions. In light of the overall younger (median age 40) and healthier population recruited, mostly women (51.6%), the question remains if more at risk populations would benefit from the intervention.

Conclusion: Research challenges on the use of 4-aminoquinones in SARS-CoV-2

The COVID-19 pandemic continues to pose a serious threat to public health. Hydroxychloroquine's established safety record and plausible efficacy supported clinical investigation of its use for treatment of COVID-19. Investigation of clinical outcomes of large numbers of patients treated with low-dose hydroxychloroquine, as a result of emergency use authorizations across the world, reached conflicting conclusions. In general, the methodology of these studies were flawed; even when randomized controlled trials have been conducted, selection bias and residual confounding bias have been observed.[51] We believe a high-dose short-term dosing of hydroxychloroquine maximizes the likelihood of efficacy for treatment of COVID-19. Unfortunately, the current climate is unlikely to allow for further rigorous and controlled testing now that the lower doses have demonstrated poor efficacy. As a result, hydroxychloroquine may never be adequately evaluated at doses or in clinical settings where it may provide the most benefit. This outcome underlies the importance of utilizing sound pharmacologic principles in the initial design in clinical trials. The risks of hydroxychloroquine at higher doses, particularly in an acutely ill population, likely contributed to reluctance to utilize high-dose regimens in initial studies. We believe the risks are not prohibitive if appropriate exclusion criteria and monitoring is utilized. In particular, real-time QTc monitoring could be considered in future studies.

Perhaps the most important lesson learnt from our collective experience with hydroxychloroquine and COVID-19 is the danger of allowing public and political pressure to influence trial design and study review processes. When there is enormous pressure to produce results in a timely fashion, any early findings are likely to receive intense interest and scrutiny, thereby impacting the feasibility of future trials. Interest in our trial declined as the media emphasized severe, but rare, side effects and spurious endorsements were made by political figures.[52] Conflicting reports of efficacy supported by results made publicly available before peer-revision heightened confusion about the efficacy and safety of the drug for treatment of COVID-19.[32] This led to correction of messaging, and in some cases retraction of published studies after receiving further scrutiny.[38] Of particular concern, the rapid ebb and flow of both positive and negative information deepens public mistrust of the scientific community. These forces had a substantial impact on the recruitment of patients to our study and contributed to its early termination.[52] This same scenario has reoccurred in the context of the Emergency Use Authorization for convalescent plasma, despite ongoing NIH-funded phase III trials to ascertain whether convalescent plasma is effective. We hope that the critical COVID-19 vaccine studies do not meet a similar fate. This experience could provide a valuable teaching module in pharmacological and medical training programs in future to highlight the pitfalls in abandoning scientific protocol and procedure, even with the best intentions of ameliorating public health.

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Table 1: Clinical studies on the use of hydroxychloroquine or chloroquine in COVID-19 disease or COVID-19 prophylaxis

Article

Single-arm interventional studies

J. M. Molina *et al.* (France, March 30th, 2020)

P. Gautret *et al.* (France, April 11th, 2020)

Retrospective studies

Table 1: Clinical studies on the use of hydroxychloroquine or chloroquine in COVID-19 disease or COVID-19 prophylaxis

- J. Magagnoli *et al.* (US, April 21st 2020)
- M. Million *et al.* (France, May 5th 2020)
- M. R. Mehra *et al.* (Multinational, May 6th 2020)
- E. S. Rosenberg *et al.* (US, May 11th 2020)
- B. Yu *et al.* (China, May 15th 2020)
- M. Mahévas *et al.* (France, May 24th 2020)
- J. Geleris *et al.* (US, June 18th 2020)
- S. Arshad *et al.* (US, July 2nd 2020)

Prospective, interventional and controlled studies:

- P. Gautret *et al.* (France, March 20th, 2020)
- Z. Chen *et al.* (China, April 1st, 2020)
- M. G. Silva Borba *et al.* (Brazil, April 24th 2020)
- W. Tang *et al.* (China, May 4th, 2020)
- D. R. Boulware *et al.* (US and Canada, June 3rd 2020)
- P. W. Horby *et al.* (UK, June 4th 2020)
- A. B Cavalcanti *et al.* (Brazil, July 23rd 2020)

HCQ: hydroxychloroquine, **CQ:** chloroquine, **AZI:** azithromycin, **SOC:** standard of care, **D (1-28):** Day (1-28), **Q8h/Q12h:** 8h/12h

Confirmed cases: confirmed by SARS-CoV-2 RNA by PCR from nasopharyngeal sample or other confirmatory laboratory

NEWS (National Early Warning Score): scoring system designed to be applied to hospitalized patients to allow for early d

