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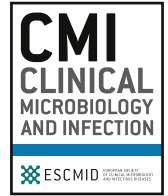
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Original article

Hydroxychloroquine in mild-to-moderate coronavirus disease 2019: a placebo-controlled double blind trial

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ABSTRACT

Objectives: To determine whether hydroxychloroquine decreases the risk of adverse outcome in patients with mild to moderate coronavirus disease 2019 (COVID-19) at high risk of worsening.

Methods: We conducted a multicentre randomized double-blind placebo-controlled trial evaluating hydroxychloroquine in COVID-19 patients with at least one of the following risk factors for worsening: need for supplemental oxygen, age ≥ 75 years, age between 60 and 74 years and presence of at least one co-morbidity. Severely ill patients requiring oxygen therapy >3 L/min or intensive care were excluded. Eligible patients were randomized in a 1:1 ratio to receive either 800 mg hydroxychloroquine on day 0 followed by 400 mg per day for 8 days or a placebo. The primary end point was a composite of death or start of invasive mechanical ventilation within 14 days following randomization. Secondary end points included mortality and clinical evolution at days 14 and 28, and viral shedding at days 5 and 10.

Results: The trial was stopped after 250 patients were included because of a slowing down of the pandemic in France. The intention-to-treat population comprised 123 and 124 patients in the placebo and hydroxychloroquine groups, respectively. The median age was 77 years (interquartile range 58–86 years) and 151/250 (60.4%) patients required oxygen therapy. The primary end point occurred in 9/124 (7.3%) patients in the hydroxychloroquine group and 8/123 (6.5%) patients in the placebo group

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(relative risk 1.12; 95% CI 0.45–2.80). The rates of positive SARS-CoV-2 RT-PCR tests at days 5 and 10 were 72.8% (75/103) and 57.1% (52/91) in the hydroxychloroquine group, versus 73.0% (73/100) and 56.6% (47/83) in the placebo group, respectively. No difference was observed between the two groups in any of the other secondary end points.

Conclusion: In this underpowered trial involving mainly older patients with mild to moderate COVID-19, patients treated with hydroxychloroquine did not experience better clinical or virological outcomes than those receiving the placebo.

Trial registration: ClinicalTrials.gov Identifier: NCT04325893 (<https://clinicaltrials.gov/ct2/show/NCT04325893>). **Vincent Dubée, Clin Microbiol Infect** 2021;27:1124

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Introduction

Hydroxychloroquine, a derivative of chloroquine that is commonly used in certain autoimmune diseases, has been proposed as a possible treatment of coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Preliminary studies suggested that this drug inhibits SARS-CoV-2 replication *in vitro* [1] and could play a role in shortening viral shedding [2]. However, clinical trials evaluating the efficacy of hydroxychloroquine in COVID-19 subsequently reported controversial and often disappointing results [3–11].

The aim of the HYCOVID trial was to evaluate the efficacy and safety of hydroxychloroquine in adult patients with mild to moderate COVID-19 at risk of worsening.

Materials and methods

Trial design

HYCOVID was a double-blind, placebo-controlled, randomized trial conducted from 2 April to 21 May 2020 in 48 hospitals in France and the Principality of Monaco. Eligible patients were randomly assigned in a 1:1 ratio to receive either hydroxychloroquine (200 mg tablets, orally) or its matching placebo at a dose of two tablets twice daily on the first day followed by one tablet twice daily for 8 days (total hydroxychloroquine dose of 4 g) plus standard care as needed.

Patients were randomized immediately after their inclusion into the study using an online application on the study website. Treatment assignment was performed according to a 1:1 ratio by means of dynamic randomization (randomization by minimization), considering the following eight criteria: age ≥ 75 years, need for supplemental oxygen therapy, diagnostic criteria for COVID-19 (positive SARS-CoV-2 RT-PCR test or chest CT scan), initial symptoms of COVID-19 for less than 7 days, hospitalization, concomitant treatment with azithromycin, concomitant treatment with lopinavir/ritonavir, treatment with corticosteroids and centre. The allocation arm was concealed for the patient and for all medical and paramedical staff.

Patients

Men and non-pregnant women aged ≥ 18 years with a diagnosis of COVID-19 confirmed by positive SARS-CoV-2 RT-PCR test on a nasopharyngeal swab within the previous 2 days were assessed for eligibility. In centres where RT-PCR could not be performed because of a shortage of swabs or RT-PCR material, the diagnosis could be made based on a chest CT scan showing typical features of COVID-19. Patients were eligible if they had at least one of the following risk factors for worsening: (a) need for supplemental oxygen to

reach a peripheral capillary oxygen saturation of more than 94% ($SpO_2 > 94\%$) or a ratio of oxygen partial pressure to fractional inspired oxygen less than or equal to 300 mmHg ($P_{aO_2}/F_{iO_2} \leq 300$ mmHg); (ii) age ≥ 75 years; (iii) age between 60 and 74 years and presence of at least one of the following co-morbidities: obesity (body mass index ≥ 30 kg/m²), arterial hypertension requiring treatment, or diabetes mellitus requiring treatment.

Patients requiring more than 3 L/min of oxygen to reach an SpO_2 of 94% were excluded, as were those with a clinical condition necessitating admission to intensive care unit, a negative SARS-CoV-2 RT-PCR test, a short-term life-threatening co-morbidity (life expectancy < 3 months), any condition contraindicating hydroxychloroquine treatment (known hypersensitivity or allergy, retinopathy, concomitant treatment associated with a risk of ventricular arrhythmias, use of medications that are contraindicated with hydroxychloroquine and cannot be replaced or stopped during the trial), or conditions associated with an increased risk of adverse event (see [Supplementary material](#) study protocol for details). Of note, concomitant treatment with azithromycin was allowed.

Clinical and laboratory monitoring

For patients with an initial positive SARS-CoV-2 RT-PCR, nasopharyngeal swabs were sampled on days 5 and 10 after randomization, and SARS-CoV-2 RT-PCR was performed using the same local technique as the initial RT-PCR.

All adverse events that occurred during a patient's participation were declared to the sponsor, with the exception of adverse events linked to the COVID-19 itself (for details, see the study protocol, available in the [Supplementary Materials](#)).

Outcome measures

The primary end point was a composite of death and the need for invasive mechanical ventilation within 14 days following randomization. Secondary efficacy outcomes included the rate of mortality or invasive ventilation within 28 days following treatment initiation, clinical evolution using the World Health Organization nine-point Ordinal Scale for Clinical Improvement for COVID-19 (with scores ranging from 0 (patients at home without any clinical or biological sign of infection) to 8 (death) [12]) at days 14 and 28, all-cause mortality at days 14 and 28, the rate of RT-PCR tests positive for SARS-CoV-2 on nasopharyngeal swab samples at days 5 and 10. Three criteria were used for clinical evolution: the absence of deterioration (stability or decrease of at least one point on the ordinal scale), clinical improvement (decrease of at least one point on the ordinal scale) and recovery (score of 0, 1 or 2 on the ordinal scale). The secondary safety outcome was the rate of serious adverse events at day 28. Clinical events were adjudicated by an

independent event adjudication committee, whose members were unaware of group assignments.

Trial oversight

The protocol was approved by an independent protection committee and by the French National Agency for Medicines and Health Products Safety, according to French regulations. Written informed consent was obtained before any study procedure from each patient or from the patient's legal representative if the patient was unable to provide consent.

Statistical analysis

Based on the first available epidemiological data on COVID-19 [13,14], we estimated the rate of the primary outcome to be 20%. A headcount of 615 patients per group allows the demonstration, under a bilateral hypothesis, of an absolute difference of 6% between the two groups (relative difference of 30%), with an α risk of 5% and a power of 80%. To allow for up to 5% non-evaluable or lost-to-follow-up patients, we set the sample size at 1300 patients in total.

Our main analysis was performed in the intention-to-treat population. Interim analyses were performed by conducting the triangle test on every 50 patients and were submitted to the Independent Data and Safety Monitoring Board that was formed for this study. A sensitivity analysis was performed in the per-protocol population, i.e. patients with no major deviation from the study protocol. For the safety analysis, all patients who received at least one dose of hydroxychloroquine were included in the intervention group.

The rates of the primary outcome were compared between the two groups using the χ^2 test. The relative risks for each clinical event at days 14 and 28 and their 95% CI were calculated with an adjustment taking into account the baseline status using a Mantel–Haenszel estimation.

A sequential analysis based on the triangle test was performed using R software, version 3.6.3. STATA software (version 13; Stata-Corp, College Station, TX, USA) was used for other analyses. Further details regarding the statistical analysis are provided in the statistical analysis plan, available in the Supplementary material (Appendix).

Results

Patients

The trial started on 1 April 2020 and was suspended on 26 May 2020 by the French regulatory authority because of reports of hydroxychloroquine toxicity in pharmacovigilance databases [15] and observational studies [16]. It was definitively stopped by the sponsor on 9 June 2020 because of a low inclusion rate in the context of the slowdown of the pandemic in France (see Supplementary material, Fig. S1).

In the 33 centres that completed the screening survey, 11% (202 patients out of 1822 patients) of the patients assessed for eligibility were included in the study. In total, 250 patients were randomized, of whom 125 were assigned to receive hydroxychloroquine and 125 the placebo (Fig. 1). Among them, one and two patients withdrew consent in the hydroxychloroquine and placebo groups, respectively. The per-protocol population comprised 226 patients: 116 in the placebo group and 110 in the hydroxychloroquine group. A summary of the major violations that led to exclusion from the per-

protocol population is provided in the Supplementary material (Table S1).

The median age was 77 (interquartile range 58–86) years (see supplementary data, Fig. S2), and 60% of the patients required supplemental oxygen at baseline (Table 1). The median time from symptom onset to randomization was 5 days (interquartile range 3–9). The treatment groups were well balanced for baseline demographic and clinical characteristics, as well as for the treatments of interest received at randomization.

Primary outcome

There was no significant difference in the rate of the primary end point, which occurred within 14 days following randomization in 8 of 123 patients assigned to the placebo group (6.5%) and 9 of 124 patients assigned to the hydroxychloroquine group (7.3%) (relative risk 1.12; 95% CI 0.45–2.80; p 0.82) (Table 2 and see Supplementary material, Fig. S3). At 28 days after randomization, 9.8% (12/123) of the patients in the placebo group had died or had been intubated compared with 7.3% (9/124) in the hydroxychloroquine group (relative risk 0.74; 95% CI 0.33–1.70; Table 2). Details about the cause of death can be found in the Supplementary material (Table S3).

In the per-protocol population, death or requirement for invasive mechanical ventilation within 14 days was observed in 6 of the 116 patients (5.2%) who received the placebo and in 7 of the 110 patients treated with hydroxychloroquine (6.4%). The relative risk for death or invasive mechanical ventilation was 1.23 (95% CI 0.43–3.55) (see Supplementary material, Table S2). No significant difference between the treatment groups was observed at day 28.

Secondary outcomes

The clinical evolution assessed by the change in ordinal scale score between day 0 and day 14 and between day 0 and day 28 did not differ between the two groups (Table 2 and Fig. 2). At day 14, 68 of the 123 patients assigned to the placebo had returned home (55.3%) compared with 71 of the 124 patients assigned to hydroxychloroquine (57.3%). The rate of clinical improvement was 65.9% (81/123) in the placebo group and 67.7% (84/124) in the hydroxychloroquine group. At day 28, 68.3% (84/123) and 73.4% (91/124) of patients had been discharged from hospital in the placebo and hydroxychloroquine groups (Table 2), and the rate of clinical improvement was 75.6% (93/123) and 79.0% (98/124), respectively.

Viral shedding could be assessed by RT-PCR in 203 and 174 patients at day 5 and day 10, respectively (Table 2). The rate of SARS-CoV-2-positive RT-PCR did not differ significantly between the two groups.

Analysis of the different outcomes in predefined subgroups can be found in the Supplementary material (Fig. S4).

Adverse events

Adverse events occurred in 70 of the 124 patients treated with hydroxychloroquine (56.5%) compared with 61 of the 120 patients who received the placebo (50.8%) (see Supplementary material, Table S4). Serious adverse events were infrequent and occurred at the same frequency in both groups (three patients in the hydroxychloroquine group (2.4%), and four patients in the placebo group (3.3%); see Supplementary material, Table S4).

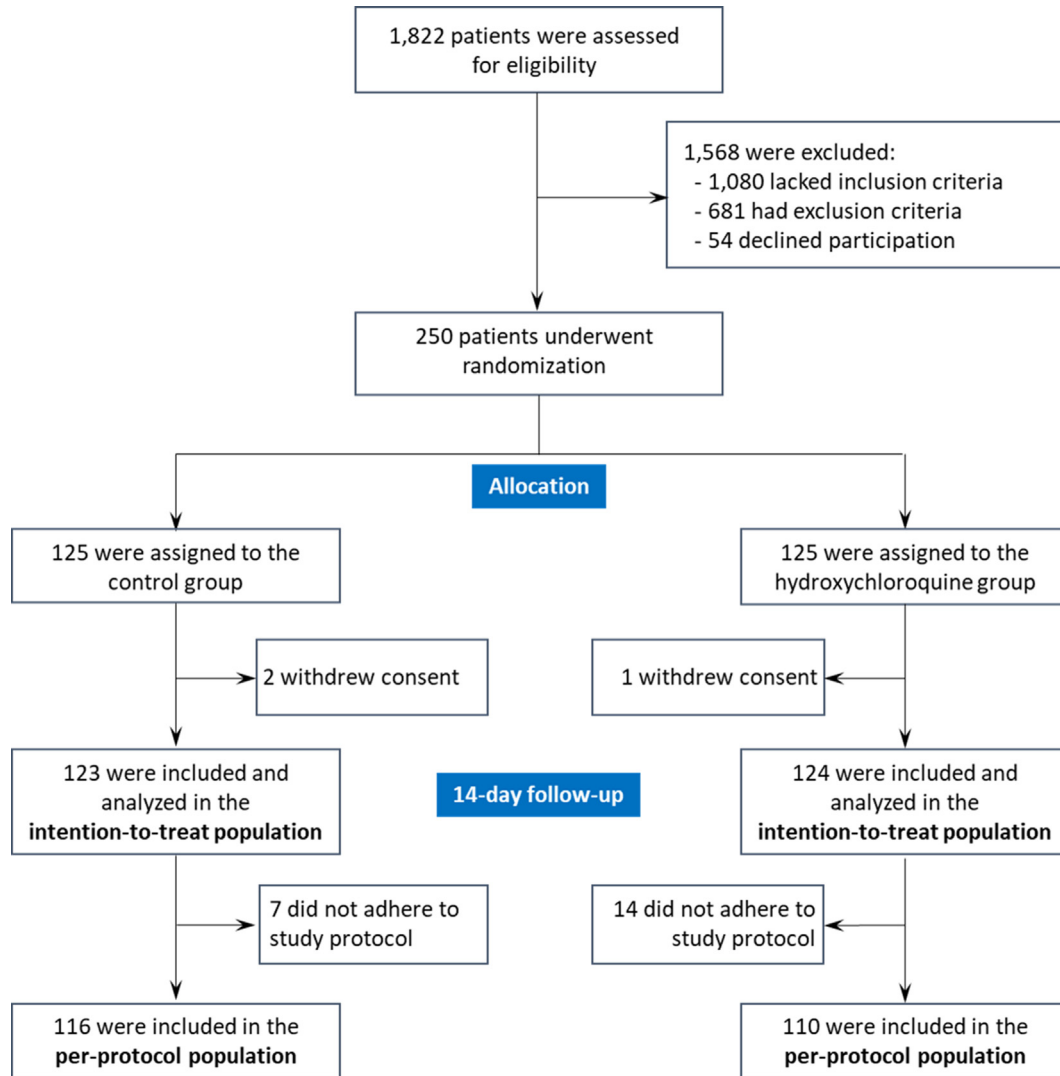


Fig. 1. Patient selection, treatment allocation and follow up. Assessment of eligibility criteria in all consecutive patients admitted for coronavirus disease 2019 (COVID-19) was reported in 33 of the 48 participating centres. Among the 1822 patients assessed for eligibility in these 33 centres, 202 patients were included leading to an inclusion rate of COVID-19 patients in the HYCOVID trial of 11%.

Discussion

In this trial involving individuals with mild to moderate COVID-19 at higher risk of worsening, we did not observe a significant difference in the rate of death or the start of mechanical ventilation at 14 days following inclusion between patients treated with hydroxychloroquine and those who received the placebo. The rate of serious adverse events was also similar in the two groups.

This is in line with the results observed in randomized open-label studies involving hospitalized patients [3,7], as well as with a double-blind, placebo-controlled trial evaluating early hydroxychloroquine treatment in ambulatory [4] and hospitalized [17] patients. All of these trials involved younger patients with a median age of 40 to 58 years. In our trial, the median time from symptom onset to treatment initiation was 5 days; in the other aforementioned studies, it ranged from 2 to 7 days.

Similarly, we observed no benefit of hydroxychloroquine therapy on the duration of RT-PCR positivity. Previous data concerning the impact of hydroxychloroquine on the duration of viral shedding were conflicting. Although an uncontrolled study found that the drug alone or combined with azithromycin induced a rapid

decrease in the rate of RT-PCR positivity [2], another found a decreased speed of viral clearance [18], and two randomized open-label studies showed no effect [7,19]. Of note, the decrease in the rate of positive RT-PCR tests observed in our study is in agreement with previous studies, which reported a median duration of detectable viral shedding of 14 days after symptom onset in mild COVID-19 and 21 days in severe cases [20–22].

The lack of power is the main limitation of our trial. The study was prematurely stopped after the inclusion of 19% of the planned number of patients because of the slowdown of the epidemic and following the publication of a subsequently retracted study raising concerns over hydroxychloroquine cardiovascular toxicity [16]. Severe cardiovascular adverse events with hydroxychloroquine were also reported by the French Network of Pharmacovigilance Centres [15]. Finally, an open labelled study and a retrospective study provided negative results on the clinical efficacy of hydroxychloroquine in individuals with mild to moderate COVID-19 [5,7]. All have contributed to an important decrease of inclusions, questioning study feasibility and justifying an early termination of the trial. Indeed, the daily number of new COVID-19 cases had dramatically decreased in France (see

Table 1
Baseline demographic, biological and clinical characteristics of the patients

Characteristic	Hydroxychloroquine	Placebo
	(n = 125)	(n = 125)
Age (years), median (IQR)	76 (60–85)	78 (57–87)
Male sex, n (%)	65 (52.0)	56 (44.8)
Diagnostic criteria, n (%)		
Positive RT-PCR SARS-CoV-2	124 (99.2)	123 (98.4)
Positive CT-scan (RT-PCR not done)	1 (0.8)	2 (1.6)
Severity risk criteria n (%) ^a		
Age ≥75 years	66 (52.8)	68 (54.4)
Age ≥60 years and co-morbidity ^a	1 (0.8)	0
Supplemental oxygen requirement	77 (61.6)	74 (59.2)
Comorbidities, n (%)		
Chronic respiratory disease	15 (12.0)	13 (10.5)
Diabetes	20 (16.0)	23 (18.6)
Arterial hypertension	65 (52.0)	68 (54.8)
Heart disease	34 (27.2)	38 (30.7)
Cerebrovascular disease	21 (16.8)	22 (17.7)
Obesity (BMI >30 kg/m ²)	25 (22.1)	40 (32.8)
Active smoker	3 (2.4)	3 (2.4)
Score on ordinal scale, n (%)		
1. Ambulatory, no limitation of activity	1 (0.8)	1 (0.8)
2. Ambulatory, limitation of activity	1 (0.8)	0 (0.0)
3. Hospitalized, no oxygen therapy	46 (36.8)	50 (40.0)
4. Hospitalized, oxygen therapy (≤3 L/min)	77 (61.6)	74 (59.2)
Concomitant treatment n (%)		
Azithromycin	10 (8.0)	11 (8.8)
Other antibiotics	62 (49.6)	60 (48.0)
Lopinavir-ritonavir	1 (0.8)	2 (1.6)
Corticosteroids	13 (10.4)	11 (8.8)
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	43 (34.4)	39 (32.2)
Symptoms, n (%)		
Body temperature >38°C	28 (22.4)	25 (20.2)
Diarrhoea	22 (17.6)	12 (9.6)
Rhinitis	9 (7.2)	7 (5.6)
Anosmia or hyposmia	19 (15.2)	17 (13.7)
Confusion	16 (12.8)	17 (13.6)
Time from onset of symptoms to inclusion (days), median (IQR)	5 (3–9)	5 (3–8)

Abbreviations: BMI, body mass index; IQR, interquartile range.

^a One patient may have several severity risk criteria.

Table 2
Outcomes in the intention-to-treat population

Outcomes	Hydroxychloroquine	Placebo	Relative risk (95% CI)
	(n = 124)	(n = 123)	
Primary outcome			
Day 14	9 (7.3)	8 (6.5)	1.12 (0.45–2.80)
Day 28	9 (7.3)	12 (9.8)	0.74 (0.33–1.70)
Mortality			
Day 14	6 (4.8)	6 (4.9)	0.99 (0.33–2.99)
Day 28	6 (4.8)	11 (8.9)	0.54 (0.21–1.42)
Use of intubation and mechanical ventilation			
Day 14	3 (2.4)	3 (2.4)	0.99 (0.20–4.82)
Day 28	3 (2.4)	4 (3.3)	0.74 (0.17–3.26)
Clinical evolution, as compared to Day 0			
Day 14			
Absence of deterioration	112 (90.3)	111 (90.2)	1.01 (0.93–1.09)
Clinical improvement	84 (67.7)	81 (65.9)	1.01 (0.86–1.18)
Recovery	71 (57.3)	68 (55.3)	1.03 (0.83–1.27)
Day 28			
Absence of deterioration	115 (92.7)	112 (91.1)	1.02 (0.95–1.10)
Clinical improvement	98 (79.0)	93 (75.6)	1.03 (0.90–1.16)
Recovery	91 (73.4)	84 (68.3)	1.06 (0.91–1.24)
Positive SARS-CoV-2 RT-PCR ^a			
At Day 5	75/103 (72.8)	73/100 (73.0)	1.00 (0.84–1.18)
At Day 10	52/91 (57.1)	47/83 (56.6)	1.01 (0.78–1.31)

^a RT-PCR could not be performed in all patients. Data are no. of positive RT-PCR/no. of RT-PCR performed (% of positive RT-PCR).

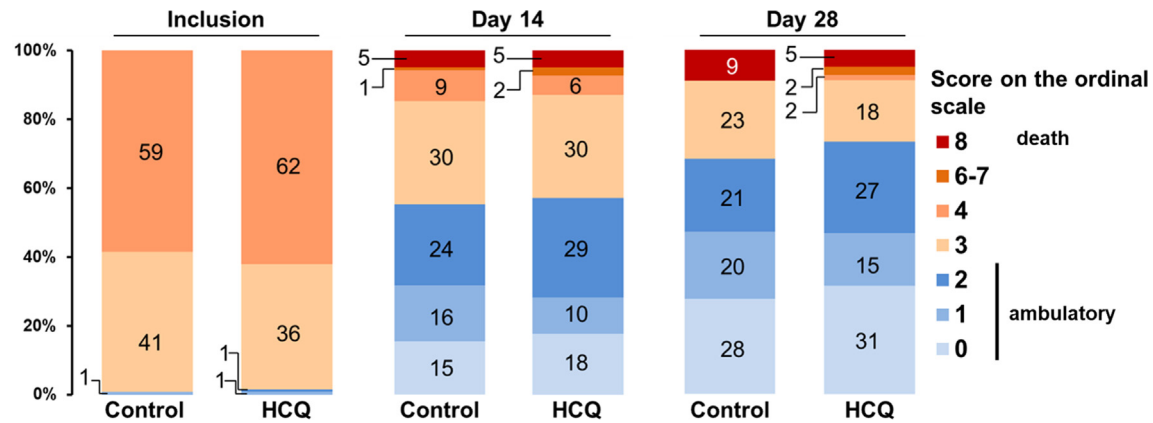


Fig. 2. Clinical status at inclusion, day 14 and day 28 according to treatment group. Clinical status of patients allocated to the placebo ($n = 123$) or hydroxychloroquine (HCQ) at inclusion, day 14 and day 28. Data are missing at days 14 and 28 for two patients in each group. No patient had a score of 5 (non-invasive ventilation or high-flow oxygen) at day 14 or day 28. The Ordinal Scale for Clinical Improvement is proposed by the World Health Organization as an outcome measure. The score reads as follows: 0: patient uninfected, no clinical or virological signs of infection; 1: patient at home, without limitation of activities; 2: patient at home, with limitation of activities; 3: patient hospitalized without oxygen therapy; 4: patient with oxygen therapy by mask or nasal prongs; 5: patient under non-invasive ventilation or high-flow oxygen; 6: patient under invasive mechanical ventilation; 7: patient under invasive mechanical ventilation and additional organ support, including vasopressors, renal replacement therapy and extracorporeal membrane oxygenation; 8: death.

Supplementary material, Fig. S1), which led to the decision that it would be impossible to achieve the planned number of inclusions.

We did not identify any safety concerns related to hydroxychloroquine use. However, we excluded patients with conditions that put them at risk of increased hydroxychloroquine toxicity, such as hypokalaemia, prolonged corrected QT interval or concomitant treatment with an increased risk of torsade de pointes, with the exception of azithromycin. Of note, hypokalaemia has been identified as a frequent complication of COVID-19 [23], and its presence is associated with disease severity. The exclusion of hypokalaemic patients may have contributed to the low rate of adverse course that we observed.

The frequency of the primary end point, a composite of death or the need for invasive mechanical ventilation at day 14, was much lower than expected (6.9% versus 20%). This result, in addition with the premature stopping of the inclusions, impairs the statistical power of our trial. This discrepancy may arise from several factors. First, recent data have demonstrated mortality rates lower than those observed in the early phases of the epidemic in Wuhan, on which we based the estimate of the number of needed patients [13,14]. Second, 15% of the patients included in this study have been treated with corticosteroids during the disease course, and it has been recently demonstrated that dexamethasone decreases mortality in severe COVID-19 [24]. Finally, we excluded patients with an organ failure requiring intensive care or needing more than 3 L/min of oxygen during the initial evaluation. This was based on the hypothesis that antiviral agents are more likely to be effective if they are prescribed early in the course of the disease. On the basis of epidemiological studies, we suspected that COVID-19 patients with advanced age and/or with serious co-morbidity would frequently worsen, even if they had no sign of severity at baseline. Our results show that most of them had an uncomplicated course with or without hydroxychloroquine.

In conclusion, because of the premature discontinuation of the inclusions and a rate of primary outcome lower than expected, this study did not achieve enough power to make a statement on the efficacy of hydroxychloroquine in patients with mild to moderate COVID-19. Nevertheless, no effect of hydroxychloroquine on clinical evolution or on the kinetics of viral shedding was observed. In line with other recent studies on this topic, these results do not support the use of hydroxychloroquine alone in this population.

Transparency declaration

The authors have declared that there are no conflicts of interest in relation to this work. Disclosure forms provided by the authors are available as Supplementary material.

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Authors' contributions

VD, PMR, HP, EPS and AM conceptualized the study and its methodology, VD and PMR supervised the conduct of the study and wrote the original draft of the manuscript. BV was in charge of data curation and formal analysis. SB, ED, OR, PR, TG, EA, SD and MAC participated in data collection. AD was responsible for preparation and shipping of study drugs. CL and OB were in charge of biological samples. CA was responsible for drug safety. All authors reviewed and edited the manuscript and approved its final version. All authors contributed significantly to the study and agree to be accountable for all aspects of the work. VD, PMR, IP and AM take responsibility for the publication.

Access to data

Anonymized individual data are available upon reasonable request to DataManagement.DRCI@chu-angers.fr.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cmi.2021.03.005>.

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