

Statistical review of *Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial*.

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The following review has been prepared by members of the MRC-NIHR Trials Methodology Research Partnership¹. The reviewers named above, and other, unnamed discussants of the paper, are all qualified statisticians with experience in clinical trials. Our objective is to provide a rapid review of publications, preprints and protocols from clinical trials of COVID-19 treatments, independent of journal specific review processes. We aim to provide timely, constructive, focused, clear advice aimed at improving both the research outputs under review, as well as future studies. Given our collective expertise (clinical trial statistics) our reviews focus on the designs of the trials and other statistical content (methods, presentation and accuracy of results, inferences).

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Study Summary

Here we review *Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial*, by Gautret *et al*. When we started our review, the paper was being circulated via Google Drive. Shortly after, it was accepted for publication in the International Journal of Antimicrobial Agents³, and posted on MedRxiv.org⁴. However, these versions of the study report were the same as the one we reviewed, indicating no or limited external peer review for the final published version.

The paper reports a small, non-randomized trial in Marseille, France where 26 patients with PCR (nasopharyngeal sample) confirmed COVID-19 received 600mg hydroxychloroquine to treat their illness. Of these, 6 also received azithromycin, based on their clinical presentation. Outcomes in this group were compared to those of 16 control patients who were recruited from

other medical centers (Nice, Avignon and Briancon), or patients in Marseille who refused consent to hydroxychloroquine treatment. The primary outcome was viral clearance (yes/no) at 6 days post-inclusion measured with PCR. After dropping 6 patients from the analysis for incomplete data, the authors reported that patients in the active arm were more likely to have achieved viral clearance (70%; 14/20) than those in the control arm (12.5%; 2/16; $p < 0.001$). They also reported that all 6 patients who were also treated with azithromycin achieved viral clearance, vs 8/14 (57%) of patients that only received hydroxychloroquine. Based on these findings, they concluded that, “Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.”

Major comments

The lack of randomization limits the conclusions that should be drawn from this study.

To conclude that the differences in the outcomes observed between the groups receiving different treatment regimens are in fact due to differences in treatment, we need to be able to confidently assert that the groups shared a similar level of baseline risk, prior to treatment. Randomization is of course our best tool for creating such comparable groups, but not applied in this study.

This limitation is amplified by the fact that control patients were either recruited from other medical centres, or were patients that refused consent for the active treatment (more on this below). That said, control patients, despite experiencing worse outcomes, were younger on average, less likely to be male, and had a more favourable symptom profile, perhaps suggesting lower baseline risk (note: that these differences were not “significant” with a $p < 0.05$ does imply that they don’t matter with respect to interpretation outcomes). However, it’s entirely plausible that there could be other, unobserved factors leading to a control group with higher baseline risk. Unfortunately, there was no other information about the characteristics of patients, or about the clinicians and medical centres where they were treated, that would help us better judge the comparability of groups.

Recommendations:

For future studies

- Employ randomization.

For this study

- Provide more detailed information on patients in all groups, and more detail on how they were recruited, consented, and treated during the course of the study.

For the reader

- Treat this study as a case series report.

Lack of a covariate adjusted analysis

Following from the above points, it would be appropriate to treat this as the observational study it is, and use a statistical model to adjust for pre-treatment, outcome-prognostic covariates that are distributed differently among the study groups. Likely candidates from this study include age, sex, degree of illness, timing of onset of symptoms relative to study inclusion, and medical centre. Adjusted estimates could be presented alongside the unadjusted estimates reported in the paper.

Recommendations:

For future studies

- Pre-specify prognostic covariates in the registered protocol's statistical analysis plan, and adjust for them in the statistical analysis.

For this study

- Include a post-hoc covariate adjusted analysis.

Inappropriately included control patients

Following from the points above, it's important to note that you would not normally include someone in a trial unless they consented to receive the treatment being tested. That was not the case in this study. Instead, control patients included those who refused consent for the active treatment regimen. The fact that patients who didn't give such consent is a red flag, not just for the interpretation of the trial but its ethics. We also think it is relevant to note that this is a treatment that the authors have been promoting in the months leading up to this study.

Recommendations:

For future studies

- Appropriately consent patients, excluding those who would not accept randomization onto the active arm of the study.

Patients were inappropriately dropped from the analysis

Of the 26 patients treated with hydroxychloroquine, 6 were dropped from the analysis because they didn't have complete data through day-6 post-inclusion. The authors correctly reported the reasons for the drop outs, and their outcomes at the point they dropped out. Notably, 3 dropped out because they were admitted to the ICU (all PCR positive at transfer); 1 due to death (PCR negative the day prior); 1 due to nausea (PCR positive); and 1 left the hospital (PCR negative).

Four of these patients had bad outcomes (admission to ICU or death) so it is likely that their omission made the treated group's outcomes look better.

Recommendations:

For this study

- Include a sensitivity analysis under different assumptions to see how results might be influenced.
- Employ a longitudinal model that could retain the patients with missing data due to loss-to-follow up.

Choice of outcome

The choice of presence/absence of the virus as an outcome was suboptimal. It is not clear how this outcome relates to other outcomes that are of importance to patients (e.g. 28 day mortality). Further, the outcome is a dichotomized version of continuous viral load. This dichotomization essentially discards useful information contained in the continuous measure (which also tells of the *degree* of differences among patients), resulting in a less informative set of results with greater uncertainty in estimates.

Specifying the outcome to be recorded on day-6 is also suboptimal because it led to exclusion of patients who didn't have day-6 data (noted above). Further, it is not clear (nor justified by the authors) that the outcome on day-6 is the best measure to conclude that a negative result indicates "virologically cured", especially in light of the observation that two patients who were positive on day-6 but negative by day-9, and another that was negative on day-6 but positive on day-8.

Finally, following from the raw data, it is not clear that the outcome was ascertained in the same way for both active treatment and control patients (e.g. many control patient outcome are presented as Positive vs Negative, rather than a count vs Negative, as they are for patients in the active treatment group).

Recommendations

For future studies

- Select more relevant outcomes, particularly for your primary endpoint, perhaps considering a core outcome set⁵.
- Consider the use of a composite outcome (e.g. complete viral clearance or death).
- Avoid needless dichotomization of outcomes.
- Use an appropriate longitudinal model for repeatedly measured outcomes

For this study

- Include a post-hoc longitudinal analysis of continuously measured viral load (assuming the raw viral counts are available for all patients)

The author overstate the evidence supporting azithromycin

In addition to comparing treated patients vs controls, that also looked at patients who were treated with hydroxychloroquine only and those treated with both hydroxychloroquine and azithromycin. Unfortunately, there was little information provided about the decisions being made that led to azithromycin, and thus it is not possible to evaluate the comparability of these two groups. Further, the statistical test for differences in these groups seemingly included all three groups (controls and the two active treatment groups; not enough information was provided in the study report to say exactly what was done), which resulted in a very small p-value, suggesting the data were incompatible with a null hypothesis of no difference. However, it would be appropriate to also directly compare patients on hydroxychloroquine only to those on hydroxychloroquine and azithromycin (i.e. leaving out the control group observations from the statistical test). When this is done, the p-value is much larger (X-squared = 1.92, df = 1, p-value = 0.17; Fisher's exact test p-value = 0.11).

Recommendations:

For future studies

- Plan appropriately for intercurrent events such as loss to follow up due to death, or potential changes in the treatment regime in response to outcomes. See ICH E9(R1)⁶.

The authors overstate the existing evidence of the efficacy of hydroxychloroquine for treating COVID-19

In the background of their paper, Gautret *et al* referred to “an early clinical trial conducted in COVID-19 Chinese patients, [which] showed that chloroquine had a significant effect, both in terms of clinical outcome and viral clearance, when comparing to control groups”. There were two citations for this claim. The first was a letter⁷ that doesn't report any trial data, but instead refers to a conference held in China in February, during which participants (“experts from government and regulatory authorities and organizers of clinical trials”) seemingly agreed that chloroquine was an efficacious treatment for COVID-19. The second citation (also included in the aforementioned letter) refers to a number of clinical trials registered in China, though many of these have now been suspended or closed, while the remaining trials are still recruiting (per their entries on <http://www.chictr.org.cn> as of March 21, 2020). Hence there are, to our knowledge, no other *published* reports of clinical trials testing the efficacy of chloroquine for COVID-19 treatment. Gautret *et al* cite an additional report⁸ noting that “Chinese experts recommend that patients diagnosed as mild, moderate and severe cases of COVID-19 pneumonia and without contraindications to chloroquine, be treated with 500 mg chloroquine twice a day for ten days”. However, we have not yet been able to access this paper, nor have we identified any pre-prints reporting clinical trials of chloroquine for COVID-19 treatment on the BioRxiv or MedRxiv repositories.

Minor points

The authors reported that the “Drug effect was significantly higher in patients with symptoms of URTI and LRTI, as compared to asymptomatic patients with $p < 0.05$ (data not shown).” This would have been important data to share, and the authors should have specified how this result was arrived at in the methods. Ideally, the authors would have used the appropriate model with a treatment by symptom interaction term, but we are left guessing. It is worth noting that identifying such interactions is difficult in small studies, as they are often underpowered to detect plausible interaction effects, given that they are designed to detect main effects - a quite large one in this case (see sample size calculations in the CONSORT checklist below)

The sample size calculation requires more clarity. We suspect that “50% efficacy” refers to a comparison of 75% vs 25% virologically cured (see CONSORT checklist below).

Open Data

The authors have provided data on the 36 patients included in the report’s analysis as a supplemental table. No data are reported for the 6 patients dropped from the analysis. Data includes patient age, sex, clinical status, time between onset of symptoms and study inclusion, treatment group, treatment dosage, azithromycin treatment, and days 0 - 6 for the primary outcome.

Open Analysis Code

None provided.

Pre-registered study design

No.

PubPeer

There are a number of comments on the PubPeer page for the published version of this paper. <https://pubpeer.com/publications/3B1F9EAD4982C64445A60F5E83CCFE>

References

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CONSORT CHECKLIST

To support the review, we completed the CONSORT checklist⁹ below. Material taken directly from the paper is in *italics*. Our additional comments are in **bold**.

Title and abstract

1a Identification as a randomised trial in the title

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.

1b Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)

Title: Identification of the study as randomised	NA
Authors: Contact details for the corresponding author	Yes
Trial design: Description of the trial design (eg, parallel, cluster, non-inferiority)	NA
Methods	
Participants: Eligibility criteria for participants and the settings where the data were collected	NO
Interventions: Interventions intended for each group	YES
Objective: Specific objective or hypothesis	YES
Outcome: Clearly defined primary outcome for this report	YES
Randomisation: How participants were allocated to interventions	NA
Blinding (masking): Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	NA
Results	
Numbers randomised: Number of participants randomised to each group	YES
Recruitment: Trial status	NO
Numbers analysed: Number of participants analysed in each group	YES
Outcome: For the primary outcome, a result for each group and the estimated effect size and its precision	NO
Harms: Important adverse events or side-effects	NO
Conclusions: General interpretation of the results	YES
Trial registration: Registration number and name of trial register	NO
Funding: Source of funding	NO

Introduction

Background and objectives

2a Scientific background and explanation of rationale

Yes

2b Specific objectives or hypotheses

We therefore started to conduct a clinical trial aiming at assessing the effect of hydroxychloroquine on SARS-CoV-2-infected patients after approval by the French Ministry of

Health. In this report we describe our early results, focusing on virological data in patients receiving hydroxychloroquine as compared to a control group.

Methods

Trial design

3a Description of trial design (such as parallel, factorial) including allocation ratio

Non-randomized clinical trial

Probably better described as a case series. This should not be described as a clinical trial.

3b Important changes to methods after trial commencement (such as eligibility criteria), with reasons

Not reported.

Participants

4a Eligibility criteria for participants

Hospitalized patients with confirmed COVID-19 were included in this study if they fulfilled two primary criteria: i) age >12 years; ii) PCR documented SARS-CoV-2 carriage in nasopharyngeal sample at admission whatever their clinical status.

Patients were excluded if they had a known allergy to hydroxychloroquine or chloroquine or had another known contraindication to treatment with the study drug, including retinopathy, G6PD deficiency and QT prolongation. Breastfeeding and pregnant patients were excluded based on their declaration and pregnancy test results when required.

Before being included in the study, patients meeting inclusion criteria had to give their consent to participate to the study. Written informed signed consent was obtained from adult participants (> 18 years) or from parents or legal guardians for minors (<18 years).

From the registry (EUCTR 2020-000890-25):

Principal inclusion criteria

- Women and men with documented respiratory infection with Coronavirus SARS CoV 2
- Teenager girls and boys aged more than 12 years old
- Persons who have given their free and informed consent and have signed the written form.

Principal exclusion criteria

- Pregnant woman
- Child less than 12 years-old

- Known hypersensitivity to chloroquine or hydroxy chloroquine.
- Feeding
- Retinopathy
- Known deficit in G6PD
- Refusal to participate in the study
- Patient with known QT prolongation

4b Settings and locations where the data were collected

This ongoing study is coordinated by The Méditerranée Infection University Hospital Institute in Marseille. Patients who were proposed a treatment with hydroxychloroquine were recruited and managed in Marseille centre. Controls without hydroxychloroquine treatment were recruited in Marseille, Nice, Avignon and Briançon centers, all located in South France.

Interventions

5 The interventions for each group with sufficient details to allow replication, including how and when they were actually administered

All patients in Marseille center were proposed oral hydroxychloroquine sulfate 200 mg, three times per day during ten days...

Symptomatic treatment and antibiotics as a measure to prevent bacterial super-infection was provided by investigators based on clinical judgment.

Outcomes

6a Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed

The primary endpoint was virological clearance at day-6 post-inclusion. Secondary outcomes were virological clearance overtime during the study period, clinical follow-up (body temperature, respiratory rate, long of stay at hospital and mortality), and occurrence of side-effects.

From the registry:

Primary: Results of SARS-COV2 virus detection at Day 1, Day 4, Day 7 and Day 14

Secondary: Apyrexia, normalization of respiratory rate, and average length of hospital stay and mortality at Day 1, Day 4, Day 7, Day 14, and Days of hospital discharge

Secondary outcomes were not reported in the paper.

6b Any changes to trial outcomes after the trial commenced, with reasons

None reported.

Sample size

7a How sample size was determined

Assuming a 50% efficacy of hydroxychloroquine in reducing the viral load at day 7, a 85% power, a type I error rate of 5% and 10% loss to follow-up, we calculated that a total of 48 COVID-19 patients (ie, 24 cases in the hydroxychloroquine group and 24 in the control group) would be required for the analysis (Fleiss with CC).

75% vs 25% of a binary outcome = $21 / 0.9 = 23.33 = 24 \times 2 = 48$ (with Fleiss CC)

7b When applicable, explanation of any interim analyses and stopping guidelines

Not applicable.

Randomisation

No randomization.

Blinding

No blinding.

Statistical methods

12a Statistical methods used to compare groups for primary and secondary outcomes

Statistical differences were evaluated by Pearson's chi-square or Fisher's exact tests as categorical variables, as appropriate. Means of quantitative data were compared using Student's t-test. Analyses were performed in Stata version 14.2.3.

12b Methods for additional analyses, such as subgroup analyses and adjusted analyses

Not applicable.

Results

Participant flow (a diagram is strongly recommended)

13a For each group, the numbers of participants who were randomly assigned, received

intended treatment, and were analysed for the primary outcome

We enrolled 36 out of 42 patients meeting the inclusion criteria in this study that had at least six days of follow-up at the time of the present analysis. A total of 26 patients received hydroxychloroquine and 16 were control patients. Six hydroxychloroquine-treated patients were lost in follow-up during the survey because of early cessation of treatment.

42 meeting criteria (16 control and 26 active). No info on how many were screened. 6 dropped out from the active arm. Analysis of 16 control vs 20 active. No flow diagram.

13b For each group, losses and exclusions after randomisation, together with reasons

Six hydroxychloroquine-treated patients were lost in follow-up during the survey because of early cessation of treatment. Reasons are as follows: three patients were transferred to intensive care unit, including one transferred on day2 post-inclusion who was PCR-positive on day1, one transferred on day3 post-inclusion who was PCR-positive on days1-2 and one transferred on day4 post-inclusion who was PCR-positive on day1 and day3; one patient died on day3 post inclusion and was PCR-negative on day2; one patient decided to leave the hospital on day3 post-inclusion and was PCR-negative on days1-2; finally, one patient stopped the treatment on day3 post-inclusion because of nausea and was PCR-positive on days1-2-3. The results presented here are therefore those of 36 patients (20 hydroxychloroquine-treated patients and 16 control patients). None of the control patients was lost in follow-up.

Recruitment

14a Dates defining the periods of recruitment and follow-up

French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th...

14b Why the trial ended or was stopped

Clinical follow-up and occurrence of side-effects will be described in a further paper at the end of the trial.

The study status is unclear.

Baseline data

15 A table showing baseline demographic and clinical characteristics for each group

Basic demographics and clinical status are presented in Table 1. Overall, 15 patients were male (41.7%), with a mean age of 45.1 years. The proportion of asymptomatic patients was 16.7%, that of patients with URTI symptoms was 61.1% and that of patients with LRTI symptoms was

22.2%). All patients with LRTI symptoms, had confirmed pneumonia by CTScan. Hydroxychloroquine-treated patients were older than control patients (51.2 years vs. 37.3 years). No significant difference was observed between hydroxychloroquine-treated patients and control patients with regard to gender, clinical status and duration of symptoms prior to inclusion (Table 1).

Table 1 Characteristics of the study population.

	Age (years)			Male gender		Clinical status				Time between onset of symptoms and inclusion (days)		
	Mean ± SD	t	p-value	n (%)	p-value	Asymptomatic	URTI	LRTI	p-value	Mean ± SD	t	p-value
Hydroxychloroquine treated patients (N=20)	51.2 ± 18.7	-1.95	0.06	9 (45.0)	0.65	2 (10.0)	12 (60.0)	6 (30.0)	0.30	4.1 ± 2.6	-0.15	0.88
Control patients (N=16)	37.3 ± 24.0			6 (37.5)		4 (25.0)	10 (62.5)	2 (12.5)		3.9 ± 2.8		
All patients (36)	45.1 ± 22.0			15 (41.7)		6 (16.7)	22 (61.1)	8 (22.2)		4.0 ± 2.6		

URTI: upper tract respiratory infection, LRTI: lower tract respiratory infection

Numbers analysed

16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

See below.

Outcomes and estimation

17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)

17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended

The proportion of patients that had negative PCR results in nasopharyngeal samples significantly differed between treated patients and controls at days 3-4-5 and 6 post-inclusion (Table 2). At day6 post-inclusion, 70% of hydroxychloroquine-treated patients were virologically cured comparing with 12.5% in the control group (p= 0.001).

When comparing the effect of hydroxychloroquine treatment as a single drug and the effect of hydroxychloroquine and azithromyc in combination, the proportion of patients that had negative PCR results in nasopharyngeal samples was significantly different between the two groups at days 3-4-5 and 6 post-inclusion (Table 3). At day6 post-inclusion, 100% of patients treated with hydroxychloroquine and azithromycin combination were virologically cured comparing with

57.1% in patients treated with hydroxychloroquine only, and 12.5% in the control group ($p < 0.001$). These results are summarized in Figures 1 and 2. Drug effect was significantly higher in patients with symptoms of URTI and LRTI, as compared to asymptomatic patients with $p < 0.05$ (data not show).

Table 2. Proportion of patients with virological cure (negative nasopharyngeal PCR) by day, in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.

	Day3 post inclusion			Day4 post inclusion			Day5 post inclusion			Day6 post inclusion		
	Number of negative patients/total number of patients	%	p-value	Number of negative patients/total number of patients	%	p-value	Number of negative patients/total number of patients	%	p-value	Number of negative patients/total number of patients	%	p-value
Hydroxychloroquine treated patients (N=20)	10/20	50.0	0.005	12/20	60.0	0.04	13/20	65.0	0.006	14/20	70.0	0.001
Control patients (N=16)	1/16	6.3		4/16	25.0		3/16	18.8		2/16	12.5	

^acontrol patients from centers other than Marseille did not underwent daily sampling, but were sampled every other day in most cases, they were considered positive for PCR when actually positive the day(s) before and the day(s) after the day(s) with missing data.

Table 3. Proportion of patients with virological cure (negative nasopharyngeal PCR) by day, in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithromycin combination, and in COVID-19 control patients.

	Day3 post inclusion			Day4 post inclusion			Day5 post inclusion			Day6 post inclusion		
	Number of negative patients/total number of patients	%	p-value	Number of negative patients/total number of patients	%	p-value	Number of negative patients/total number of patients	%	p-value	Number of negative patients/total number of patients	%	p-value
Control patients	1/16	6.3	0.002	4/16	25.0	0.05	3/16	18.8	0.002	2/16	12.5	<0.001
Hydroxychloroquine treatment only	5/14	35.7		7/14	50.0		7/14	50.0		8/14	57.1	
Hydroxychloroquine and azithromycin combined treatment	5/6	83.3		5/6	83.3		6/6	100		6/6	100	

Figure 1. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.

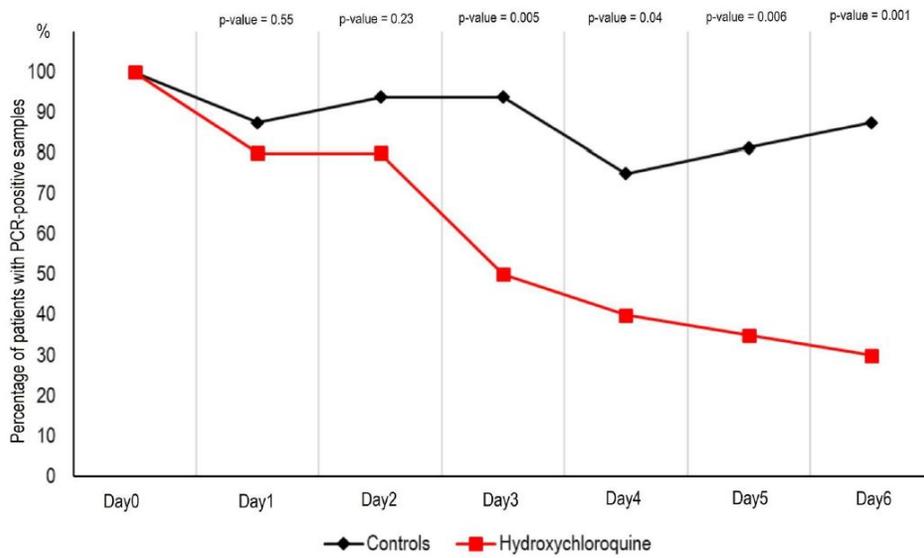
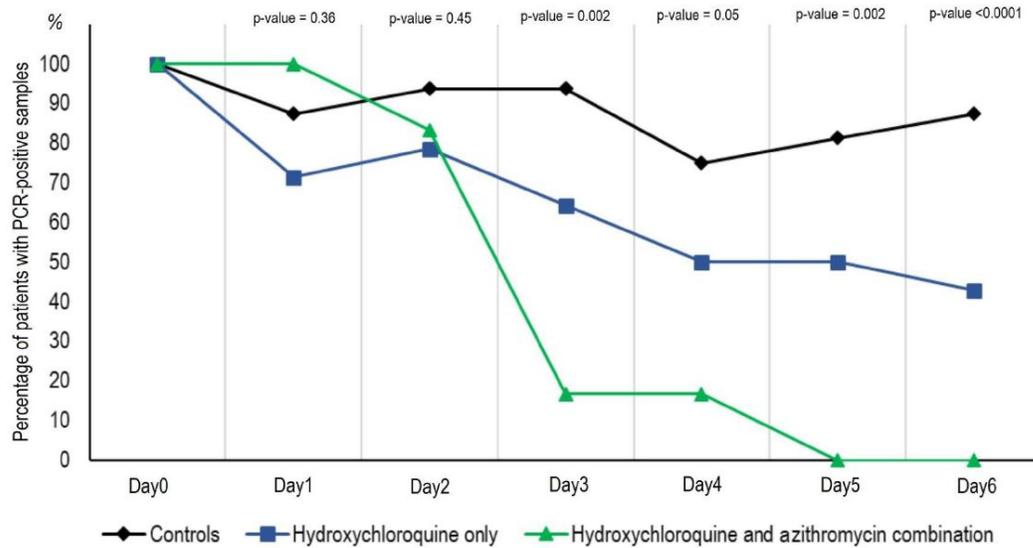


Figure 2. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine only, in COVID-19 patients treated with hydroxychloroquine and azithromycin combination, and in COVID-19 control patients.



Ancillary analyses

18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

Drug effect was significantly higher in patients with symptoms of URTI and LRTI, as compared to asymptomatic patients with $p < 0.05$ (data not show).

No details given on how this was done.

Harms

19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms⁴²)

No data shown.

Discussion

Limitations

20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant,

multiplicity of analyses

Our study has some limitations including a small sample size, limited long-term outcome follow-up, and dropout of six patients from the study, however in the current context, we believe that our results should be shared with the scientific community.

Generalisability

21 Generalisability (external validity, applicability) of the trial findings

No discussion of the external validity of the trial results. The authors suggest universal applicability:

We therefore recommend that COVID-19 patients be treated with hydroxychloroquine and azithromycin to cure their infection and to limit the transmission of the virus to other people in order to curb the spread of COVID-19 in the world

Interpretation

22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

In our opinion, the conclusions are not supported by the reported results.

Other information

Registration

23 Registration number and name of trial registry

The protocol, appendices and any other relevant documentation were submitted to the French National Agency for Drug Safety (ANSM) (2020-000890-25) and to the French Ethic Committee (CPP Ile de France) (20.02.28.99113) for reviewing and approved on 5th and 6th March, 2020, respectively. This trial is registered with EU Clinical Trials Register, number 2020-000890-25.

[2020-000890-25](#)

Protocol

24 Where the full trial protocol can be accessed, if available

Not found.

Funding

25 Sources of funding and other support (such as supply of drugs), role of funders

This work was supported by the French Government under the « Investissements d'avenir » (Investments for the Future) program managed by the Agence Nationale de la Recherche (ANR, fr: National Agency for Research), (reference: Méditerranée Infection 10-IAHU-03).