

# Rapid Evidence Review

## Clinical evidence for hydroxychloroquine and azithromycin combination therapy for COVID-19

Prepared by the COVID -19 Evidence Review Group

Version 2, 2<sup>nd</sup> April 2020

*Key changes between version 1 (24<sup>th</sup> March 2020) and version 2 (2<sup>nd</sup> April 2020): Updated summary and conclusion, inclusion of two new clinical studies, updated clinical guidelines, updated clinical trials information, updated ERG conclusion.*

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.



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## Summary

Two uncontrolled studies reported the use of hydroxychloroquine and azithromycin in combination (hyd/az) for the treatment of COVID-19 (1, 2). There are inconsistencies in the study findings, with one study in 80 patients reporting broadly positive outcomes from the combination therapy, including negative viral load in 83% of the cohort on day 7, while another study in 11 patients concluded there is no evidence of rapid antiviral clearance or clinical benefit, with persistence of SARS-CoV2 RNA in nasopharyngeal swabs in 8/10 surviving patients at days 5 to 6 after treatment initiation. Differences between the patient populations suggest that the patient cohort in the smaller study, which failed to show any clinical benefit, may have been predisposed to a poorer outcome e.g. greater proportion of co-morbidities, older, more males, greater need for oxygen therapy (2). Neither study can be considered to provide compelling evidence in support of or against the efficacy of combination therapy with hydroxychloroquine and azithromycin in the treatment of COVID-19. Both studies are limited by the lack of a control arm, which is required to demonstrate whether the observed clinical outcomes were a result of hyd/az combination therapy, single-agent hydroxychloroquine or azithromycin therapy, supportive care or the natural progression of the disease. The study numbers are very small, given the heterogeneous nature of the disease course. Hyd/az combination therapy is registered as an intervention in a number of ongoing COVID-19 clinical trials. There is a lack of consistency between the doses of each drug used in these trials. There is limited data evaluating the safety of hyd/az combination therapy, however the risk of QT prolongation and arrhythmias is a notable safety concern. The safety of QT prolonging drugs, such as hydroxychloroquine or azithromycin, may be maximized by close monitoring and optimisation of risk factors. Use of combination therapy with azithromycin and hydroxychloroquine should ideally occur within a clinical trial, where both efficacy and safety can be closely monitored.

## Conclusion

At the time of writing, there is no evidence to indicate that combination therapy with azithromycin and hydroxychloroquine is more effective than single-agent hydroxychloroquine for the treatment of COVID-19. Controlled trials, ideally randomised and double-blinded, are necessary to provide robust evidence for the systematic use of this treatment regimen. The risk of QTc prolongation and more serious ventricular arrhythmias should be carefully evaluated and monitored if this treatment is considered for use.

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## Background

Speculation on the potential benefit of combination therapy with hydroxychloroquine and azithromycin (hyd/az) has led to a number of case-series' reporting outcomes using this treatment regimen for COVID-19 (1, 2). The Evidence Review Group (ERG) conducted a targeted literature review to identify sources reporting clinical outcomes among patients treated with hyd/az combination therapy, and conducted a rapid critical appraisal of relevant studies. See Appendix 1 for the Search Strategy.

## Introduction

Hydroxychloroquine and chloroquine are antimalarial drugs which have been the focus of intense clinical investigation and widespread anecdotal use since the beginning of the COVID-19 outbreak (3, 4). They share similar chemical structures and mechanisms of action and have several pharmacological actions which impart therapeutic efficacy in the treatment of rheumatic disease (5). Hydroxychloroquine (Plaquenil®) is licensed in Ireland for the treatment of rheumatoid arthritis, discoid and systemic lupus erythematosus, and dermatological conditions caused or aggravated by sunlight (5)). It is unlicensed for the treatment of COVID-19. Effective in vitro inhibition of SARS-CoV-2 has been shown by chloroquine and hydroxychloroquine in pre-clinical studies (6, 7), and a number of sources have identified these drugs as effective treatments for COVID-19 (8, 9). Speculation on the potential benefit of combination therapy with hydroxychloroquine and azithromycin has led to a number of case-series reporting outcomes using this treatment regimen (1, 2). Azithromycin is a macrolide antibiotic, reported to have in vitro activity against Zika virus (10). However, in the case of the Ebola virus, a study by Madrid et al, failed to reproducibly demonstrate in vivo efficacy of azithromycin in animal models (11).

## Clinical studies

Two studies reporting the use of hyd/az combination therapy for the treatment of COVID-19 were identified. One study is the subject of two reports, firstly an interim report was published by Gautret et al (Gautret 2020a), on the incidental treatment of six patients with hyd/az therapy as part of a wider controlled study on the efficacy of hydroxychloroquine (12). The second report, from the same authors (Gautret 2020b), is a complete analysis of 80 patients (including the initial six from Gautret 2020a) who received treatment with hyd/az for at least three days and who were followed-up for at least six days (1). Another team of French investigators reported outcomes from a prospective study of 11 consecutive patients treated with hyd/az who were admitted to APHP-Saint Louis Hospital, Paris (2).

*Gautret et al. 20<sup>th</sup> March 2020*

The first report from Gautret et al, included clinical outcomes from six patients who received azithromycin (500mg on day one, followed by 250mg per day for the next four days) in addition to hydroxychloroquine sulfate (200mg three times daily for ten days) which was received as part of a controlled trial comparing hydroxychloroquine with a control group (12). Azithromycin was added to the treatment regimen of six patients to prevent bacterial super-infection, and was not specified among the original trial interventions. At day six post-inclusion, the authors reported that 70% (14/20) of the hydroxychloroquine-treated patients were virologically cured compared with 12.5% (2/16) in the control group ( $p=0.001$ ). All six patients treated with hyd/Az were virologically cured at six days however one patient who met the primary outcome of virological clearance at day 6 tested positive again at low titre at day 8. The study in which these patients were enrolled was not designed to investigate the comparative efficacy of hyd/Az and single-agent hydroxychloroquine, and may more appropriately be considered a small case-series (12). A number of limitations of this study have previously been identified including its non-randomised design, small patient numbers, absence of information on the methods of patient selection and recruitment to the treatment arms and criteria for hyd/Az combination therapy, and the post-hoc nature of the analysis comparing single-agent hydroxychloroquine therapy with hyd/Az combination therapy (13). The proportion of hydroxychloroquine-treated patients who received hyd/Az combination treatment (23%), is equivalent to the proportion of hydroxychloroquine-treated patients who were lost-to-follow-up in the study. This level of attrition limits the conclusions which can be made on the comparative efficacy of combination vs single-agent therapy.

*Gautret et al. 27<sup>th</sup> March 2020*

A second report by Gautret et al, expanded the initial case series of six patients treated with hyd/az to 80 patients. Patients with confirmed COVID-19 were admitted to the University Hospital Institute Méditerranée Infection in Marseille, France (1). Patients with no contraindications were offered combination therapy with hydroxychloroquine sulphate 200mg three times daily for ten days plus azithromycin 500mg on day 1 followed by 250mg per day for the next four days. Ceftriaxone (a broad spectrum antibiotic) was added in patients with pneumonia and NEWS score  $\geq 5$ . ECGs were performed on each patient before treatment and two days after treatment began. Hyd/az treatment was either not started or discontinued after two days on the basis of QTc risk-benefit assessment, and other abnormalities on ECG,. Eighty patients who received combination hyd/az treatment for at least three days and who were followed-up for at least six days were included in the analysis. The median age of patients was 52.5 years; 52.5% were male; 57.5% had at least one chronic condition known to be a risk factor for severe COVID-19. The mean duration between the onset of symptoms and hospitalisation was five days (range 1-17 days). 53.8%

and 41.2% of patients presented with LRTI with URTI respectively. Four patients were asymptomatic. 92% of patients had a low NEWS score (0-4), suggesting a mild disease. 53.8% of patients had LDCT compatible with pneumonia within 72 hours of admission. The mean PCR Ct value was 23.4. The mean time between the onset of symptoms and the initiation of treatment was 4.9 days. Treatment was stopped on day 4 in one patient because of the risk of a potential drug interaction. Viral load tested by qPCR was negative in 83% of patients on day 7 and 93% at day 8. Most patients (65/80, 81.3%) were discharged from the authors' unit with a favourable outcome at the time of writing. The mean time from treatment initiation to discharge was 4.1 days (SD 2.2). Three patients were transferred to the ICU, including one death. Adverse events were described as rare and minor, occurring on seven occasions (unclear if these are seven events, or seven patients) including nausea/vomiting, diarrhoea and blurred vision.

This study is limited by the lack of a control arm, which is required to demonstrate whether the observed clinical outcomes were a result of hyd/az combination therapy, single-agent hyd/az therapy, supportive care or the natural progression of the disease. The study numbers are very small, given the heterogeneous nature of the disease course. The study does not provide information on the status of all patients who were initiated on hyd/az treatment, only those who received at least three days of treatment or who were followed up for at least six days. It is possible that those patients who discontinued treatment early may have had more severe disease, necessitating a change in treatment.

#### *Molina et al. 28<sup>th</sup> March 2020*

A prospective study of 11 consecutive patients admitted to a French Hospital (APHP-Saint Louis Hospital) who received hydroxychloroquine (600 mg/d for 10 days) and azithromycin (500 mg Day 1 and 250 mg days 2 to 5) were followed up for virological and clinical outcomes (2). The mean age was 58.7 years and eight patients had significant comorbidities associated with poor outcomes. At the time of treatment initiation, 10/11 had fever and received nasal oxygen therapy. Within five days, one patient died, two were transferred to the ICU, and treatment with hydroxychloroquine and azithromycin was discontinued after four days because of QT prolongation in one patient (2). Repeated nasopharyngeal swabs were still positive for SARS-CoV2 RNA in 8/10 surviving patients at days 5 to 6 after treatment initiation (2).

As described for the Gautret study, the Molina study is limited by the lack of a control arm, which is required to demonstrate whether the observed clinical outcomes were a result of hyd/az combination therapy, single-agent hyd/az therapy, supportive care or the natural progression of the disease. The study numbers are very small, given the heterogeneous nature of the disease course.

## ERG conclusion on the clinical studies

There are inconsistencies in the conclusions drawn by authors on the efficacy of hyd/az combination treatment for COVID-19. One study reported broadly positive outcomes for a cohort of 80 patients, with 81.3% discharged with favourable outcomes and negative viral load in 83% of the cohort on day 7 (1). Conversely, another study on a smaller cohort of 11 patients, reported persistence of SARS-CoV2 RNA in nasopharyngeal swabs in 8/10 surviving patients at days 5 to 6 after treatment initiation, one death, two ICU transfers and one case of QT-prolongation (2). There may be differences between the two study populations. For example, 15% of patients in the Gautret et al study required oxygen therapy, whereas 10/11 (91%) patients in the Molina et al study received nasal oxygen therapy. 92% of patients had a low NEWS score (0-4), suggesting a mild disease. Chronic conditions or comorbidities associated with poor outcomes or severe COVID-19 were present in 57.5% of the Gautret cohort compared with 73% of the Molina cohort. The Molina cohort was also slightly older, with a greater proportion of males than the Gautret cohort. All of these factors may have predisposed the Molina cohort to a poorer outcome. qPCR results up to day 8 were reported in the Gautret cohort whereas qPCR results up to day 5 or 6 were recorded for the Molina cohort. It is difficult to predict whether longer follow-up would have resulted in greater clearance rates in the Molina cohort. Neither the Gautret nor Molina studies can be considered to provide compelling evidence in support of or against the efficacy of combination therapy with hydroxychloroquine and azithromycin in the treatment of COVID-19. Both studies are limited by the lack of a control arm, which is required to demonstrate whether the observed clinical outcomes were a result of hyd/az combination therapy, single-agent hyd/az therapy, supportive care or the natural progression of the disease. The study numbers are very small, given the heterogeneous nature of the disease course (1, 2). At the time of writing, there is no evidence to indicate that combination therapy with azithromycin and hydroxychloroquine is more effective than single-agent hydroxychloroquine for the treatment of COVID-19. Controlled trials, ideally randomised and double-blinded, are necessary to provide robust evidence for the systematic use of this treatment regimen.

## Cardiovascular safety considerations

Both hydroxychloroquine and azithromycin have been used widely for many years for other therapeutic indications, and the safety profile of both is well established (14, 15). However a notable safety concern, arising from combination use of these drugs, is the risk of QT prolongation and arrhythmias. Both hydroxychloroquine and azithromycin are known to cause QT prolongation. The concurrent use of more than one drug that prolongs the QT interval increases the risk of Torsades de pointes (TdP) and ventricular arrhythmia(15). A number of studies have quantified this risk and a 2013 Danish study which compared

azithromycin (five days) versus no antibiotic estimated the rate ratio of cardiovascular death to be 2.85 (95% CI 1.13 to 7.24) (16). There is limited data evaluating the safety of combination therapy, however in vivo studies have shown no synergistic arrhythmic effects of azithromycin with or without chloroquine(17). It should be noted that a number of studies have been published reporting the efficacy and safety of azithromycin-chloroquine combination in the treatment of malaria (18-20). However, the absence of an active drug safety surveillance system in most countries limits the reassurance which can be drawn from these observations(21). QT prolongation occurred in one patient in the Molina et al study, described above, which led to treatment being discontinued (2). An expert consensus published by a multicentre collaboration group of the Department of Science and the Technology of Guangdong Province and Health Commission of Guangdong Province, relating specifically to the use of chloroquine phosphate, was published on 20th February (8). The panel recommended avoiding concurrent administration of other drugs known to prolong the QT interval such as macrolide antibiotics, which would include azithromycin (8).

Guidance on managing the risk of ventricular arrhythmia due to hyd/az therapy for COVID-19 was published in the American College of Cardiology publication *Cardiology Magazine* on March 29<sup>th</sup> 2020(21). In this guidance, the authors advise that the safety of QT prolonging medications may be maximized by close monitoring and optimization of factors which are known to contribute to increased risk of drug-induced TdP including female sex, structural heart disease, congenital long-QT syndromes, electrolyte disturbances, hepatic/renal failure and concomitant QT prolonging medications(22, 23). The authors further suggest that mitigating factors such as the limited duration of use of these drugs for COVID-19, and the potential for individual and population-health benefits, should be taken into account when considering the safety risks (21). Recommendations from *Mayo Clinic Proceedings* (March 25 2020) proposed a risk stratification, monitoring and treatment algorithm for the use of Qtc-prolonging drugs for COVID-19 (24). This algorithm, as well as other available resources for clinical guidance is listed in Appendix 2.

## International COVID-19 Guidelines

Interim Clinical Guidance for Adults with Suspected or Confirmed COVID-19 in Belgium (Version 6, 31<sup>st</sup> March 2020) recommends that there is no sufficient evidence about activity of azithromycin and therefore no reason to associate this antibiotic to the hydroxychloroquine treatment at this moment (9). Combination therapy with Hyd/Az is not referred to in the most recent guidelines published by the WHO (13 March 2020), the Chinese Preventive Medicines Association (Seventh Edition) and the Italian Society of Infectious and Tropical Diseases (13 March 2020) (22, 25, 26).



## Clinical Trial Registers

Hyd/az combination therapy is included as an intervention in a number of ongoing COVID-19 clinical trials (ClinicalTrials.gov Identifiers: NCT04329572, NCT04329832, NCT04328272) (27). The doses of hydroxychloroquine and azithromycin registered for use in clinical trials vary, including:

- hydroxychloroquine 400mg twice daily on day 1, 400mg daily from day 2-5; azithromycin 500mg daily for 5 days
- hydroxychloroquine 400mg twice daily on day 1, 200mg daily from day 2-5; azithromycin 500 mg on day 1, 250mg daily from day 2-5
- hydroxychloroquine 600mg 1<sup>st</sup> dose, 600mg 2<sup>nd</sup> dose after 6 hours, 400mg twice daily from day 2-7

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## Appendix 1

*Search strategy 02<sup>nd</sup> April 2020*

<b>Database</b>	<b>Key terms</b>
Google Scholar	SARS-CoV-2 macrolide
PubMed	SARS-CoV-2 azithromycin (SARS-Cov-2) OR COVID-19) OR "Coronavirus"[MeSH Terms]) (SARS-Cov-2) OR COVID-19) OR "Coronavirus"[MeSH Terms]) AND (hydroxychloroquine OR chloroquine) AND azithromycin
	Azithromycin AND (chloroquine OR hydroxychloroquine)
ChinaXiv	(Covid-19) OR Title:(coronavirus) AND Category:(azithromycin)
Clinicaltrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2
EU clinical trials register	COVID-19

## Appendix 2

### Guidance on risk evaluation with combination use of hydroxychloroquine and azithromycin for COVID-19

1. Urgent Guidance for Navigating and Circumventing the QTc Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for COVID19 (Preprint from Mayo Clinic Proceedings, March 25 2020) (24)  
[https://mayoclinicproceedings.org/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp\\_covid19.pdf](https://mayoclinicproceedings.org/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp_covid19.pdf)
2. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19 (American College of Cardiology, Cardiology Magazine, March 29 2020). (21)  
<https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19>
3. CredibleMeds®. <https://www.crediblemeds.org/blog/recommendations-re-covid-19-treatments/>

**Figure A1.** Risk stratification, monitoring and treatment algorithm for the use of QTc-prolonging drugs for COVID-19 (from Giudicessi, Noseworthy, Friedman and Ackerman, Mayo Clinic Proceedings Preprint) (24)

