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## SARS CoV-2 Dispatches

## Azithromycin and SARS-CoV-2 infection: Where we are now and where we are going

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Azithromycin is a macrolide antibiotic with a 15-membered lactone ring. It has excellent tissue penetration and its antimicrobial activity is due to inhibition of the 50S ribosomal subunit that prevents the synthesis of proteins in a wide range of Gram-positive and Gram-negative bacteria. Anti-inflammatory effects of azithromycin include modulating the production of pro-inflammatory cytokines such as interleukin-6 (IL-6) and IL-1 $\beta$  and acceleration of phagocytosis by macrophages, classifying azithromycin as a senolytic drug that selectively attacks and kills senescent cells with an efficiency of almost 97% [1–3].

This macrolide has also been shown to have antiviral properties for respiratory viruses, such as rhinoviruses, by decreasing the synthesis of intercellular adhesion molecules such as ICAM-1 that are used by the virus for adhesion [4]. All of the abovementioned has generated new hypotheses and opened a new prospect for older adult patients with high mortality from coronavirus disease 2019 (COVID-19), which should be evaluated in future research.

In an open-label clinical trial conducted in France, it was recently shown that azithromycin, in combination with hydroxychloroquine (HCQ), inhibits replication of the novel coronavirus severe acute

respiratory syndrome coronavirus 2 (SARS-CoV-2) [5]. However, the effects of azithromycin alone were not evaluated. The study included 36 patients (20 HCQ-treated and 16 control patients) who were positive for SARS-CoV-2 by PCR. The researchers demonstrated that HCQ (14/20; 70.0%) was superior to standard management (2/16; 12.5%) for the eradication of SARS-CoV-2 ( $P = 0.001$ ). Among the HCQ-treated patients, azithromycin was prescribed to six patients with the initial goal of preventing bacterial superinfection and it was found that in this subgroup viral eradication was much higher (6/6; 100%) on Day 6 of treatment compared with those who received HCQ as monotherapy (8/14; 57.1%). The azithromycin dose was 500 mg on Day 1 followed by 250 mg/day for the next 4 days. However, these data must be interpreted with caution. The group of patients who received HCQ as monotherapy had significantly higher viral loads than those who received the combined therapy with azithromycin, so the true adjuvant efficacy of this drug may be overestimated in the virus eradication rates [5].

Other authors suggest that with the findings of this study, together with previous research on the effect of macrolides on rhinoviruses, respiratory syncytial virus, influenza virus and Zika virus, among others, make drugs such as erythromycin conspicuous for future research in COVID-19 [6]. However, the mechanism by which the combination of a macrolide with HCQ prevents production of the SARS-CoV-2 virus remains unknown, and to date no in vitro studies have been reported with results in this regard.

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**Table 1**Summary of clinical trials for azithromycin (AZM) in coronavirus disease 2019 (COVID-19) (*n* = 21).

NCT ID	Recruiting status	Location	Design/phase	Country	Population	Intervention group(s)	Comparison group(s)	Primary outcome	Safety outcome
NCT04329832	Recruiting	MC	Open-label, RCT/phase 2	USA	Confirmed or suspected COVID-19, age $\geq 18$ years ( <i>n</i> = 300)	HCQ 400 mg PO b.i.d. for 1 day, then 200 mg PO b.i.d. for 4 days	AZM 500 mg PO on Day 1, then 250 mg PO daily on Days 2–5	COVID-19 ordinal outcomes scale at 14 days	No data
NCT04334382	Recruiting	MC	Open-label, RCT/phase 3	USA	COVID-19-confirmed adults, age $>44$ years ( <i>n</i> = 1550)	HCQ 400 mg PO b.i.d. for 1 day, then 200 mg PO b.i.d. for 4 days	AZM 500 mg PO on Day 1, then 250 mg PO daily on Days 2–5	Hospitalisation within 14 days of enrolment	No data
NCT04332107	Recruiting	SC	Quadruple blinded <sup>a</sup> , RCT/phase 3	USA	Positive SARS-CoV-2 test, age $\geq 18$ years ( <i>n</i> = 2271)	Single 1 g dose of AZM PO	Placebo	Hospitalisation	No data
NCT04339426	Recruiting	SC	Open-label, non-RCT <sup>b</sup> /phase 2	USA	COVID-19 confirmed, age $\geq 18$ years ( <i>n</i> = 25)	Atovaquone 750 mg PO b.i.d. for up to 10 days/AZM 500 mg PO for 1 day, then 250 mg PO daily for up to 10 days	–	Virology cure rate; COVID-19 serology testing	Incidence of gastrointestinal adverse events; cardiac toxicity
NCT04329572	Suspended	MC	Open-label, non-RCT <sup>b</sup> /early phase 1	Brazil	SARS-COV-2 infection confirmed by RT-PCR, age $\geq 18$ years ( <i>n</i> = 400)	HCQ 400 mg PO b.i.d. for 1 day, then 400 mg/day PO for 4 days/AZM 500 mg PO daily for 5 days	–	Evolution of acute respiratory syndrome, oxygen saturation, haemodynamic stability	No data
NCT04339816	Recruiting	MC	Triple blinded <sup>c</sup> , RCT/phase 3	Czech Republic	Proven or suspected COVID-19 infection, age $>18$ years ( <i>n</i> = 240)	AZM 500 mg PO or via NG tube for 1 day, then AZM 250 mg PO or via NG tube daily for 4 days (with first daily dose of HCQ)/HCQ 400 mg PO or via NG tube b.i.d., then 200 mg PO b.i.d. or via NG tube for 4 days	Active comparator: HCQ 400 mg PO or via NG tube b.i.d., then 200 mg PO b.i.d. or via NG tube for 4 days/placebo daily PO or via NG tube (with the first daily dose of HCQ). Placebo comparator: placebo PO or via NG tube b.i.d., and one extra dose of placebo once in 24 h per 5 days	Proportion of alive patients free of mechanical ventilation	No data
NCT04341870	Suspended	SC	Bayesian, open-label, RCT/phase 2 and phase 3	France	COVID-19, age 18–80 years ( <i>n</i> = 60)	Sarilumab 400 mg i.v. in 1 h for 1 day/AZM 500 mg PO for 1 day, then 250 mg daily for 4 days/HCQ 200 mg PO t.i.d. for 10 days	Sarilumab 400 mg i.v. in 1 h for 1 day	Need for ventilation	No data
NCT04336332	Recruiting	MC	Open-label, RCT/phase 2	USA	SARS-CoV-2 infection, age 18–89 years ( <i>n</i> = 160)	HCQ 200 mg PO t.i.d. for 10 days/AZM 500 mg PO for 1 day, then 250 mg PO daily for 4 days	Group B: HCQ 200 mg PO t.i.d. for 10 days/Group C: supportive care for 6 days; if patient still has COVID-19 symptoms, they will receive HCQ 200 mg PO t.i.d. for 10 days	Changes in patient's viral load	No data
NCT04332094	Recruiting	MC	Open-label, RCT/phase 2	Spain	SARS-CoV-2 infection confirmed, age $\geq 18$ years ( <i>n</i> = 276)	Tocilizumab 162 mg s.c. $\times$ 2 doses, then tocilizumab 162 mg s.c. $\times$ 2 doses at 12 h (Day 1)/HCQ 400 mg PO b.i.d. for 1 day, then 200 mg PO b.i.d. for 6 days/AZM 500 mg VO daily for 3 days	HCQ 400 mg PO b.i.d. for 1 day, then 200 mg PO b.i.d. for 6 days/AZM 500 mg PO daily for 3 days	In-hospital mortality; need for mechanical ventilation in the ICU	No data
NCT04335552	Recruiting	SC	Open-label, RCT/phase 2	USA	Symptoms suggestive of COVID-19 infection or develop symptoms of COVID-19 during hospitalisation, age $\geq 18$ years ( <i>n</i> = 500)	Group A: SOC/HCQ 800 mg PO or via feeding tube for 1 day, then 600 mg daily for 4 days. Group B: SOC/AZM 500 mg PO or via feeding tube for 1 day, then 250 mg PO daily for 4 days. Group C: SOC/HCQ 800 mg PO or via feeding tube, then 600 mg daily for 4 days/AZM 500 mg PO or via feeding tube for 1 day, then 250 mg daily for 4 days	SOC	World Health Organization ordinal scale measured at 14 days after enrolment	Rates of severe adverse events

Table 1 (Continued)

NCT ID	Recruiting status	Location	Design/phase	Country	Population	Intervention group(s)	Comparison group(s)	Primary outcome	Safety outcome
NCT04341207	Recruiting	SC	Open-label, non-RCT/phase 2	France	All types of locally advanced and metastatic malignancy, age $\geq 18$ years ( $n = 1000$ )	Cohort 1: HCQ 200 mg PO t.i.d. for 10 days/AZM 500 mg PO for 1 day, then 250 mg daily for 4 days. Cohort 4: HCQ 200 mg PO t.i.d. for 10 days	Cohort 2: no intervention, advanced cancer patients with SARS-CoV-2-negative test and COVID-19 symptoms Cohort 3: no intervention, advanced cancer patients with SARS-CoV-2-positive or -negative test and no COVID-19 symptoms	Prevalence and 3-month incidence of SARS-CoV-2 in cancer patients; COVID-19-specific mortality rate in cancer patients treated with HCQ and AZM	No data
NCT04328272	Not yet recruiting	SC	Single masking <sup>d</sup> , RCT/phase 3	Pakistan	COVID-19 confirmed by RT-PCR, age 18–50 years ( $n = 75$ )	HCQ 800 mg PO first dose, then after 6 h 600 mg PO (Day 1), followed 200 mg PO b.i.d. for 6 days	Active comparator: AZM 500 mg PO for 1 day, then 250 mg PO daily for 6 days. Placebo comparator: placebo (sugar tablet) b.i.d. for 7 days	National Early Warning Score equal to zero	No data
NCT04338698	Not yet recruiting	SC	Double blinded <sup>e</sup> , RCT/phase 3	Pakistan	Confirmed SARS-CoV-2, age $\geq 18$ years ( $n = 500$ )	HCQ 200 mg PO t.i.d. for 5 days	Comparator 1: AZM 500 mg PO for 1 day, then 250 mg PO daily for 4 days. Comparator 2: oseltamivir 75 mg PO b.i.d. for 5 days. Comparator 3: HCQ 200 mg PO t.i.d. for 5 days/ AZM 500 mg PO for 1 day, then 250 mg PO daily for 4 days. Comparator 4: HCQ 200 mg PO t.i.d. for 5 days/oseltamivir 75 mg PO b.i.d. for 5 days. Comparator 5: oseltamivir 75 mg PO b.i.d. for 5 days/ AZM 500 mg PO for 1 day, then 250 mg PO daily for 4 days. Comparator 6: HCQ 200 mg PO t.i.d. for 5 days/ oseltamivir 75 mg b.i.d. for 5 days/AZM 500 mg PO for 1 day, then 250 mg PO daily for 4 days	Laboratory results; clinical outcomes	No data
NCT04321278	Completed	MC	Open-label, RCT/phase 3	Brazil	Probable or confirmed infection by SARS-CoV2, age $\geq 18$ years ( $n = 440$ )	HCQ 400 mg PO b.i.d./AZM 500 mg PO daily for 10 days	HCQ 400 mg PO b.i.d. for 10 days	Evaluation of clinical status	QT prolongation; gastrointestinal intolerance; laboratory abnormalities; adverse events
NCT04322396	Recruiting	SC	Quadruple blinded <sup>a</sup> , RCT/phase 2	Denmark	Positive COVID-19 test/diagnosis during hospitalisation, age $> 18$ years ( $n = 226$ )	AZM and HCQ in 15 days	Placebo in 15 days	Number of days alive and discharged from hospital within 14 days	No data
NCT04322123	Active, not recruiting	MC	Open-label, RCT/phase 3	Brazil	Suspected or confirmed COVID-19 admitted to inpatient units and ICUs, age $\geq 18$ years ( $n = 630$ )	HCQ 400 mg PO b.i.d. for 7 days HCQ 400 mg PO b.i.d./AZM 500 mg PO daily for 7 days	Standard treatment protocol for COVID-19	Evaluation of clinical status	Safety outcome on QTc
NCT04324463	Recruiting	SC	Open-label, RCT/phase 3	Canada	COVID-19 confirmed, age $\geq 18$ years ( $n = 1500$ )	CQ 500 mg PO b.i.d. for 7 days (bodyweight $\geq 50$ kg) or CQ 500 mg PO b.i.d. for 2 days, then 500 mg daily for 5 days (bodyweight $< 50$ kg)/AZM 500 mg PO for 1 day, then 250 mg daily for 4 days	SOC	Outpatients: hospital admission or death. Inpatients: invasive mechanical ventilation or mortality	No data

NCT04334512	Recruiting	SC	Open-label single-group clinical trial/phase 2	USA	Diagnosis of COVID-19 by RT-PCR, age 18–55 years ( <i>n</i> = 60)	Quintuple therapy for 24 weeks (HCQ, AZM, vitamin C, vitamin D, zinc)	–	Successful treatment as determined by negative RT-PCR test and resolution of symptoms; safety of quintuple therapy	Assess the safety of quintuple therapy; assess the safety of quintuple therapy via pulse; assess the safety of quintuple therapy via oxygen saturation; assess the safety of quintuple therapy via ECG; assess tolerability of quintuple therapy
NCT04341727	Suspended	MC	Open-label, RCT/phase 3	USA	Positive SARS-CoV-2 test, age ≥18 years ( <i>n</i> = 500)	Arm 1: HCQ 400 mg PO b.i.d. for 1 day, then 200 mg PO b.i.d. for 4 days. Arm 2: HCQ 400 mg PO b.i.d. for 1 day, then 200 mg PO b.i.d. for 4 days/AZM 500 mg PO for 1 day, then 250 mg PO daily for 4 days. Arm 3: CQ 1000 mg PO once, followed in 12 h by 500 mg, then 500 mg PO b.i.d. for 4 days. Arm 4: CQ 1000 mg PO once, followed in 12 h by 500 mg, then 500 mg PO b.i.d. for 4 days/AZM 500 mg PO for 1 day, then 250 mg PO daily for 4 days	–	Hours to recovery	No data
NCT04332835	Not yet recruiting	SC	Open-label, RCT/phase 2 and phase 3	Colombia	Diagnosis of COVID-19 by RT-PCR, age 18–60 years ( <i>n</i> = 80)	Day 1: CP 250 mL. Day 2: CP 250 mL/HCQ 400 mg PO b.i.d. for 10 days/AZM 500 mg daily for 10 days	HCQ 400 mg PO b.i.d. for 10 days/AZM 500 mg daily for 10 days	Change in viral load; change in IgM COVID-19 titres; change in IgM and IgG COVID-19 titres	No data
NCT04323345	Recruiting	SC	Single masked <sup>f</sup> , RCT/phase 3	Egypt	COVID-19, age 5–75 years ( <i>n</i> = 1000)	Natural honey supplement 1 g/kg/day PO or NG tube divided into 2–3 doses for 14 days/SOC	SOC	Rate of recovery from positive to negative swabs; resolution of lung inflammation on CT or radiography	No data

b.i.d., twice a day; CP, convalescent plasma; CQ, chloroquine; CT, computed tomography; ECG, electrocardiogram; HCQ, hydroxychloroquine; ICU, intensive care unit; Ig, immunoglobulin; i.v., intravenous; MC, multicentre; NG, nasogastric; PO, orally; RCT, randomised clinical trial; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; s.c., subcutaneous; SC, single centre; SOC, standard of care; t.i.d., three times a day; VO,? .

<sup>a</sup> Participant, care provider, investigator, outcomes assessor.

<sup>b</sup> Single group assignment.

<sup>c</sup> Participant, care provider, outcomes assessor.

<sup>d</sup> Participant.

<sup>e</sup> Investigator, outcomes assessor.

<sup>f</sup> Investigator.

Another study by Molina et al. also evaluated the efficacy of the combination of azithromycin and HCQ using the same doses [7]. Eleven patients positive for SARS-CoV-2 by PCR were included in this study. All were given HCQ plus azithromycin combined therapy and 10 underwent repeat PCR on the sixth day after starting treatment; 8/10 patients (80%) had no virological clearance and continued to test positive for SARS-CoV-2. These data are inconsistent with those reported by Gautret et al. [5] and raise doubts about the true antiviral efficacy of this combination. On the other hand, a case series carried out in a single centre in Wuhan, China, that included 138 patients, of which 36 (26.1%) required intensive care unit (ICU) management and 6 (4.3%) died, it was found that the majority of patients received oseltamivir (124; 89.9%) and only 25 (18.1%) received azithromycin [8].

A wide variety of azithromycin-related adverse effects involving all the systems of the human body have been described, which vary in severity and frequency. Among the most frequent are gastrointestinal disorders such as nausea, vomiting and diarrhoea, which are seen in up to 10% of cases. Albeit at low frequency, severe side effects can predispose patients to life-threatening scenarios and arrhythmias such as QT prolongation. The mechanism by which the QT interval is prolonged is by blocking the external flow of potassium ions from ventricular myocytes to the extracellular fluid that stimulates ventricular repolarisation.

HCQ has also been shown to have cardiac effects including QT prolongation, therefore concomitant use of HCQ with azithromycin could potentiate these effects, an aspect that should be considered when prescribing this combination. The potential of HCQ to prolong ventricular repolarisation is not as well documented, but cases of QT prolongation have been reported during chronic treatment [9].

Only a few clinical studies have analysed the cardiovascular effects of these drugs in the past [10] and they concluded that indeed they have an effect on the QT interval and, when combined, this effect is increased. Recent studies in COVID-19 patients show this additive effect; for example, a study conducted in Boston (USA) showed that in a cohort of 90 patients given HCQ, those receiving concomitant azithromycin (53 patients) had a greater median (interquartile range) change in QT interval [23 (10 to 40) ms] compared with those receiving HCQ alone [5.5 (−15.5 to 34.25) ms] ( $P = 0.03$ ) [11].

Despite the mentioned cardiac effects, their appearance may be reduced in a controlled clinical setting. Giudicessi et al. proposed that together with other parameters such as electrolytes and co-morbidities, depending on the length of the QT interval, it can be determined whether or not the patient is a candidate for use of these drugs [12]. Patients with a QT interval of <460 ms are candidates for pharmacological therapy categorised in the 'green light' category, whilst those with a QT interval of >460 ms (categorised as 'yellow' or 'red light' status) are at greater risk of complications such as torsade de pointes, therefore the cost-benefit ratio of the management should be very well evaluated. Their data are encouraging since they estimate that the vast majority of patients (90%) will be categorised as 'green', making them candidates [12].

Finally, regulatory entities such as the European Medicines Agency (EMA), although not fully recommending the use of the aforementioned combination of drugs owing to their adverse effects, support their use under strict medical supervision and always considering the possibility of the aforementioned adverse effects. Therefore, in the context of COVID-19, these drugs should only be used as part of clinical trials or parallel to national security protocols [13]. Future research should consider, in addition to their combined efficacy, their combined safety profile.

There are currently 21 clinical trials registered on ClinicalTrials.gov for azithromycin related to COVID-19 (see Table 1). Thirteen studies have already started the patient recruitment process,

twelve will be carried out in a single centre, and eight will be carried out in the USA. Ongoing trials vary in design, comparison group, drug dose and duration, target population and primary endpoints. Only five studies include safety outcomes. The foregoing is an international call and effort to seek therapeutic strategies to control the COVID-19 pandemic that currently affects 180 countries on all continents. Based on these results, therapeutic guidelines can be established for patients with COVID-19 based on scientific evidence and will clarify the effectiveness of azithromycin against SARS-CoV-2.

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None declared.

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