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Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial



Remo H M Furtado*, Otavio Berwanger*, Henrique A Fonseca, Thiago D Corrêa, Leonardo R Ferraz, Maura G Lapa, Fernando G Zampieri, Viviane C Veiga, Luciano C P Azevedo, Regis G Rosa, Renato D Lopes, Alvaro Avezum, Airton L O Manoel, Felipe M T Piza, Priscilla A Martins, Thiago C Lisboa, Adriano J Pereira, Guilherme B Olivato, Vicente C S Dantas, Eveline P Milan, Otavio C E Gebara, Roberto B Amazonas, Monalisa B Oliveira, Ronaldo V P Soares, Diogo D F Moia, Luciana P A Piano, Kleber Castilho, Roberta G R A P Momesso, Guilherme P P Schettino, Luiz Vicente Rizzo, Ary Serpa Neto, Flávia R Machado, Alexandre B Cavalcanti, for the COALITION COVID-19 Brazil II Investigators†

Summary

Background The efficacy and safety of azithromycin in the treatment of COVID-19 remain uncertain. We assessed whether adding azithromycin to standard of care, which included hydroxychloroquine, would improve clinical outcomes of patients admitted to the hospital with severe COVID-19.

Methods We did an open-label, randomised clinical trial at 57 centres in Brazil. We enrolled patients admitted to hospital with suspected or confirmed COVID-19 and at least one additional severity criteria as follows: use of oxygen supplementation of more than 4 L/min flow; use of high-flow nasal cannula; use of non-invasive mechanical ventilation; or use of invasive mechanical ventilation. Patients were randomly assigned (1:1) to azithromycin (500 mg via oral, nasogastric, or intravenous administration once daily for 10 days) plus standard of care or to standard of care without macrolides. All patients received hydroxychloroquine (400 mg twice daily for 10 days) because that was part of standard of care treatment in Brazil for patients with severe COVID-19. The primary outcome, assessed by an independent adjudication committee masked to treatment allocation, was clinical status at day 15 after randomisation, assessed by a six-point ordinal scale, with levels ranging from 1 to 6 and higher scores indicating a worse condition (with odds ratio [OR] greater than 1.00 favouring the control group). The primary outcome was assessed in all patients in the intention-to-treat (ITT) population who had severe acute respiratory syndrome coronavirus 2 infection confirmed by molecular or serological testing before randomisation (ie, modified ITT [mITT] population). Safety was assessed in all patients according to which treatment they received, regardless of original group assignment. This trial was registered at ClinicalTrials.gov, NCT04321278.

Findings 447 patients were enrolled from March 28 to May 19, 2020. COVID-19 was confirmed in 397 patients who constituted the mITT population, of whom 214 were assigned to the azithromycin group and 183 to the control group. In the mITT population, the primary endpoint was not significantly different between the azithromycin and control groups (OR 1.36 [95% CI 0.94–1.97], $p=0.11$). Rates of adverse events, including clinically relevant ventricular arrhythmias, resuscitated cardiac arrest, acute kidney failure, and corrected QT interval prolongation, were not significantly different between groups.

Interpretation In patients with severe COVID-19, adding azithromycin to standard of care treatment (which included hydroxychloroquine) did not improve clinical outcomes. Our findings do not support the routine use of azithromycin in combination with hydroxychloroquine in patients with severe COVID-19.

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Introduction

As of July 3, 2020, COVID-19, the disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in more than 10 million reported infections and almost 520 000 deaths worldwide.¹ Although novel treatments are being developed, there is increased interest in repurposing existing medications for COVID-19.

Azithromycin is a widely available drug that might decrease viral load when added to hydroxychloroquine in patients with non-severe COVID-19, based on a preliminary non-randomised report.² Furthermore, previous preclinical studies have suggested that azithromycin and other macrolides might exert immunomodulatory effects.^{3–6} These effects could halt intense inflammatory responses that might cause progression to organ failure

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*Contributed equally

†Investigators are listed in the appendix (pp 8–12)

Hospital Israelita Albert Einstein, São Paulo, Brazil (R H M Furtado MD, Prof O Berwanger MD, H A Fonseca PhD, T D Corrêa MD, L R Ferraz MD, M G Lapa BSc, A J Pereira MD, G B Olivato MD, R V P Soares PharmD, D D F Moia PharmD, L P A Piano PhD, K Castilho MBA, R G R A P Momesso PhD, G P P Schettino MD, Prof L V Rizzo MD, Prof A S Neto MD); **Instituto do Coração, Hospital das Clínicas da Faculdade de Medicina, Universidade de São Paulo, Brazil** (R H M Furtado); **Brazilian Research in Intensive Care Network, São Paulo, Brazil** (T D Corrêa, F G Zampieri MD, V C Veiga MD, Prof L C P Azevedo MD, R G Rosa MD, Prof A S Neto, Prof F R Machado MD, A B Cavalcanti MD); **HCoRe Research Institute, São Paulo, Brazil** (F G Zampieri, A B Cavalcanti); **BP—A Beneficência Portuguesa de São Paulo, São Paulo, Brazil** (V C Veiga); **Hospital Sírio Libanês Research and Education Institute, São Paulo, Brazil** (Prof L C P Azevedo); **Hospital Moinhos de Vento, Porto Alegre, Brazil** (R G Rosa); **Brazilian Clinical Research Institute, São Paulo, Brazil** (Prof R D Lopes MD); **Duke University Medical Centre, Duke Clinical Research**

Institute, Durham, NC, USA (Prof R D Lopes); International Research Center, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil (Prof A Avezum MD); Hospital Moyses Deustche (MBoi Mirim), São Paulo, Brazil (A L O Manoel MD, F M T Piza MD); Hospital Estadual Jayme dos Santos Neves, Serra, Brazil (P A Martins MD); Hospital de Clínicas, Porto Alegre, Brazil (T C Lisboa MD); Hospital Vila Santa Catarina, São Paulo, Brazil (A J Pereira, G B Olivato); Hospital Naval Marçílio Dias, Rio de Janeiro, Brazil (V C S Dantas MD); Hospital Giselda Trigueiro, Natal, Brazil (E P Milan MD); Hospital Santa Paula, São Paulo, Brazil (O C E Gebara MD); EMS Pharma, Hortolândia, Brazil (R B Amazonas MD, M B Oliveira MD); Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia (Prof A S Neto); and Department of Anesthesiology, Pain and Intensive Care Medicine, Universidade Federal de São Paulo, São Paulo, Brazil (Prof F R Machado)

Correspondence to: Dr Otavio Berwanger, Hospital Israelita Albert Einstein, São Paulo 05652-900, Brazil otavio.berwanger@einstein.br

See Online for appendix

Research in context

Evidence before this study

We searched MEDLINE, the Cochrane Central register of Controlled Trials (CENTRAL), Web of Science, and Scopus with the terms (“azithromycin”) AND (“SARS-CoV-2” OR “COVID” OR “coronavirus” OR “COVID-19”) AND (“randomised” OR “clinical trials”), with no date or language restrictions.

We identified 44 studies, among which there was one completed randomised trial of hydroxychloroquine with azithromycin in patients with mild to moderate COVID-19.

Although the use of azithromycin (with or without hydroxychloroquine) has been frequently discussed as a potential therapy for patients with COVID-19, we identified no randomised trials in patients with severe COVID-19.

Added value of this study

To the best of our knowledge, this study is the first randomised clinical trial assessing the effect of azithromycin added to a standard of care regimen that includes hydroxychloroquine,

and death in COVID-19.⁷ However, azithromycin might increase the risk of life-threatening ventricular arrhythmias or cardiac arrest due to corrected QT (QTc) interval prolongation,⁸ and this risk might be enhanced in the presence of other drugs known to prolong QTc interval, such as hydroxychloroquine.^{9–11}

To date, evidence on the efficacy and safety of adding azithromycin to the treatment regimen for COVID-19 is limited by low-quality studies.^{2,12,13} Thus, we did a randomised, open-label (with assessment of the primary outcome by an independent adjudication committee masked to treatment allocation) clinical trial (COALITION II) to test the hypothesis of whether adding azithromycin to a standard of care regimen with hydroxychloroquine was superior to standard of care alone in improving 15-day clinical status and 29-day survival of patients hospitalised with severe COVID-19.

Methods

Study design and patients

COALITION II was an open-label, randomised clinical trial done at 57 centres in Brazil. The trial was approved by national and institutional research ethics boards and was conducted in compliance with Good Clinical Practice guidelines and local regulatory requirements. Informed consent was obtained from each patient or from the patient’s legal representative when applicable. The protocol and statistical analysis plan are in the appendix (pp 32–115).

We included patients who were at least 18 years and were admitted to hospital with suspected or confirmed COVID-19 with fewer than 14 days since symptom onset. Additionally, patients needed to have at least one of the following severity criteria: use of oxygen supplementation of more than 4 L/min flow; use of high-flow

on a patient-centred outcome in patients with severe COVID-19. We provided detailed and clear descriptions of clinical parameters, and clinical outcomes. In patients admitted to hospital with severe COVID-19, addition of azithromycin to a standard of care that included hydroxychloroquine did not result in clinical improvement or mortality reduction. Furthermore, contrary to what has been shown in observational studies, adding azithromycin to hydroxychloroquine did not result in higher rates of reported prolongation of QTc interval, cardiac arrest, or ventricular arrhythmias.

Implications of all the available evidence

Because azithromycin is among the most widely prescribed drugs worldwide to treat COVID-19, our results showing that it did not improve outcomes compared with standard of care will inform physicians and might affect clinical practice and future research in this field.

nasal cannula; use of non-invasive positive-pressure ventilation; or use of mechanical ventilation. Key exclusion criteria included use of hydroxychloroquine, chloroquine, or macrolides for more than 48 h before enrolment and since symptom onset (ie, patients could be enrolled if treated for index COVID-19 infection with one of those drugs as long as treatment duration was not longer than 48 h); history of severe ventricular cardiac arrhythmia or electrocardiogram with QTc interval of at least 480 ms or longer; and known allergy to any of the trial drugs. A detailed list of the exclusion criteria is in the appendix (p 13). The exclusion criterion of QTc interval of at least 480 ms was applied for any electrocardiogram (ECG) before randomisation. If a participant had an ECG with QTc less than 480 ms during the same hospital stay, a new ECG was not required before randomisation.

Several sites enrolling patients in this trial were also participating in the COALITION I trial, another randomised study from our group that tested hydroxychloroquine, with or without azithromycin, in patients with mild to moderate COVID-19.¹⁴ Investigators were not allowed to transfer patients between trials, and co-enrolment was also not possible because the trials’ inclusion criteria were mutually exclusive.

Randomisation and masking

Patients were randomly assigned (1:1) to either azithromycin plus standard of care or standard of care alone. Randomisation in blocks of variable size (4, 6, and 8) was performed in an electronic case report form system and stratified by site, age (≥ 60 years vs < 60 years), and respiratory status (use of oxygen at more than 4 L/min, high-flow nasal cannula, non-invasive positive-pressure ventilation, or mechanical ventilation). Allocation was done by a centralised, web-based,

automated randomisation system. Patients, investigators, and health-care providers were not masked to study drug assignment.

Procedures

Patients in the azithromycin group received 500 mg azithromycin once daily (by oral, nasogastric, or intravenous route) plus standard of care for 10 days and those in the control group received standard of care without macrolides, at the discretion of treating physicians and according to local guidelines. Use of corticosteroids, other immunomodulators, antibiotics, and antivirals was allowed. However, use of macrolides was not allowed after randomisation in the control group.

We collected demographic and clinical data for all patients, including results of molecular tests for COVID-19. Additionally, we collected daily data regarding the use of concomitant therapies, blood tests, and the patient's clinical condition up to 7 days after enrolment or hospital discharge. Additional visits were done at 15 days and 29 days.

At the time the trial was being designed and conducted, health authorities in Brazil issued a recommendation to treat all patients with severe COVID-19 using chloroquine or hydroxychloroquine. This recommendation was based on preliminary in-vitro evidence¹⁵ and implemented because of the scarcity of tested effective therapies for COVID-19 and public health urgency amid the pandemic. Of note, during the period when the trial was being done, there was no available data on proven effective therapies for COVID-19 except for remdesivir,¹⁶ which was not available in Brazil. Therefore, after discussion with research ethics boards, regulatory agencies, and health authorities, in order to standardise the control group, the executive committee chose to provide hydroxychloroquine 400 mg twice daily (by oral or nasogastric route) for 10 days as part of the treatment regimen for both groups. This decision was made before the start of the study. Study drugs were recommended for 10 days and guidance was provided to investigators about how to adjust or interrupt treatment according to side-effects and laboratory abnormalities (appendix pp 14–15). For safety reasons, sites were instructed to perform ECGs at least every 3 days after initiation of therapy, and daily if any prolongation of QTc interval occurred. However, there was no instruction to perform ECGs after the 10-day treatment period.

Outcomes

The primary outcome was clinical status, measured at 15 days using a six-level ordinal scale as follows: (1) not admitted to hospital; (2) admitted to hospital and not using supplemental oxygen; (3) admitted to hospital and using supplemental oxygen; (4) admitted to hospital and using non-invasive positive-pressure ventilation or high-flow nasal cannula; (5) admitted to hospital and on mechanical ventilation or extracorporeal membrane

oxygen support; or (6) death. The key secondary outcome was mortality at 29 days after randomisation.

Other secondary outcomes were clinical status assessed by the six-point ordinal scale at 7 days and 29 days; length of hospital stay among survivors; incidence of secondary infection (ie, new infections arising after randomisation, whether nosocomial or not); and number of ventilator-free days by day 29. Safety outcomes were prolongation of the QTc interval (defined as QTc \geq 470 ms for women or \geq 450 ms for men, in patients whose baseline QTc was below those thresholds, or QTc \geq 480 ms if baseline QTc was above those thresholds); gastrointestinal intolerance (meaning diarrhoea, nausea, abdominal pain, or vomiting); laboratory changes in blood counts and bilirubin levels; acute kidney failure (as reported by site investigators); and overall serious adverse events.

Statistical analysis

We established that across the six levels of ordinal outcomes, with probabilities of 35% for 1, 15% for 2, 20% for 3, 10% for 4, 10% for 5, and 10% for 6, a sample of 197 patients per group (394 patients) would have 85% power to detect an average odds ratio (OR) of 0.57 between the groups with a 5% significance level, based on a previous randomised trial in COVID-19.¹⁷ Considering a dropout rate of about 10%, our target sample size was set at 440 patients. In this scenario, an OR of less than 1.00 represents a clinical improvement assessed on the ordinal scale in the azithromycin group compared with the control group.

The data safety monitoring board planned three interim analyses, after 110, 220, and 330 patients had completed the 15-day follow-up. The interim analyses stopping rules are in the statistical analysis plan (appendix p 95).

For the analysis of the primary outcome, the ORs were derived from a mixed-effect ordinal logistic regression, assuming proportional ORs, adjusted for age and baseline severity (according to the ventilatory support), and with site as a random effect. The effect of the intervention on mortality at 29 days is presented in Kaplan-Meier curves and compared with the hazard ratio (HR) and 95% CI calculated using a Cox proportional hazards model. The effect of the intervention on the number of mechanical ventilation-free days at 29 days was compared by median differences calculated with a quantile regression based on an asymmetric Laplace distribution, with p values from Wilcoxon rank-sum test. Incidences of secondary infections are reported as proportions and differences between groups as risk ratios (RRs), with CIs calculated using the Wald likelihood test. The same analyses were also done in the intention-to-treat (ITT) population comprised of all randomised patients, and in the efficacy ITT (eITT) population, comprised of all randomised patients who received at least one dose of the medication to which they were allocated.

The primary and secondary efficacy outcomes were analysed following prespecified hierarchical closed

testing to adjust for multiplicity. If one endpoint did not meet significance, all the following endpoints in the hierarchical sequence were deemed exploratory. The safety outcomes were not adjusted for multiplicity. Exploratory analyses were done considering effect of the intervention within prespecified subgroups and testing effect modification with an interaction term in the model. Safety analyses were done in all patients who received at least one dose of study treatment, considering the patient in the group of medication that was administered, regardless of the group to which the patient was allocated.

A p value less than 0.05 was considered statistically significant in all analyses. No imputation was used for missing values, since missing for the primary outcome was less than 1%. Analyses were done using SAS software, version 9.4. The trial was designed and supervised by an

academic executive committee who had full access to study data before publication and was overseen by an independent data safety monitoring board. The primary outcome and causes of deaths were determined by a clinical events classification committee whose members were unaware of study drug assignment. This trial was registered at ClinicalTrials.gov, NCT04321278.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. RHMf, OB, ABC, VCV, LCPV, RGR, FRM, RDL, and AA had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From March 28 to May 19, 2020, 835 patients were screened, of whom 388 were excluded and 447 were enrolled in the trial (figure 1; appendix p 19). Two of the 447 patients were lost to follow-up (both after 15 days) and one patient who did not have confirmed COVID-19 withdrew consent.

As of May 13, 2020, the protocol was amended so that the main analysis would be done in a modified ITT (mITT) population that included only patients diagnosed with COVID-19 confirmed through molecular methods or serological testing. This decision was made by the executive committee before the first interim analysis from the data safety monitoring board while masked to study results. The reason for this decision was to include in the primary analysis only those patients more likely to benefit from the study intervention, (ie, those ones with confirmed SARS-CoV-2 infection). Therefore, considering the actual aggregated distribution of the ordinal outcome across the six levels up to that time-point (appendix p 18), we adjusted the sample size to 380 patients with confirmed COVID-19, which would provide 85% power to detect the same magnitude of effect favouring the intervention. Assuming a 15% rate of patients without confirmed COVID-19 infection, the original planned sample size of 440 patients was kept unchanged.

Because of faster than anticipated enrolment, the trial terminated recruitment soon after the first interim analysis. After discussion with the data safety monitoring board, the second and third interim analyses were deemed unnecessary.

In total, the protocol was amended four times while the trial was ongoing to reflect adaptations of entry criteria and analytical issues. The final amendment was a modification of the statistical analysis plan, but regulatory ethical agencies from Brazil required our group to submit a new version to incorporate that (appendix pp 45–47).

Among the 447 patients, 397 patients had confirmed COVID-19 infection and constituted the mITT population

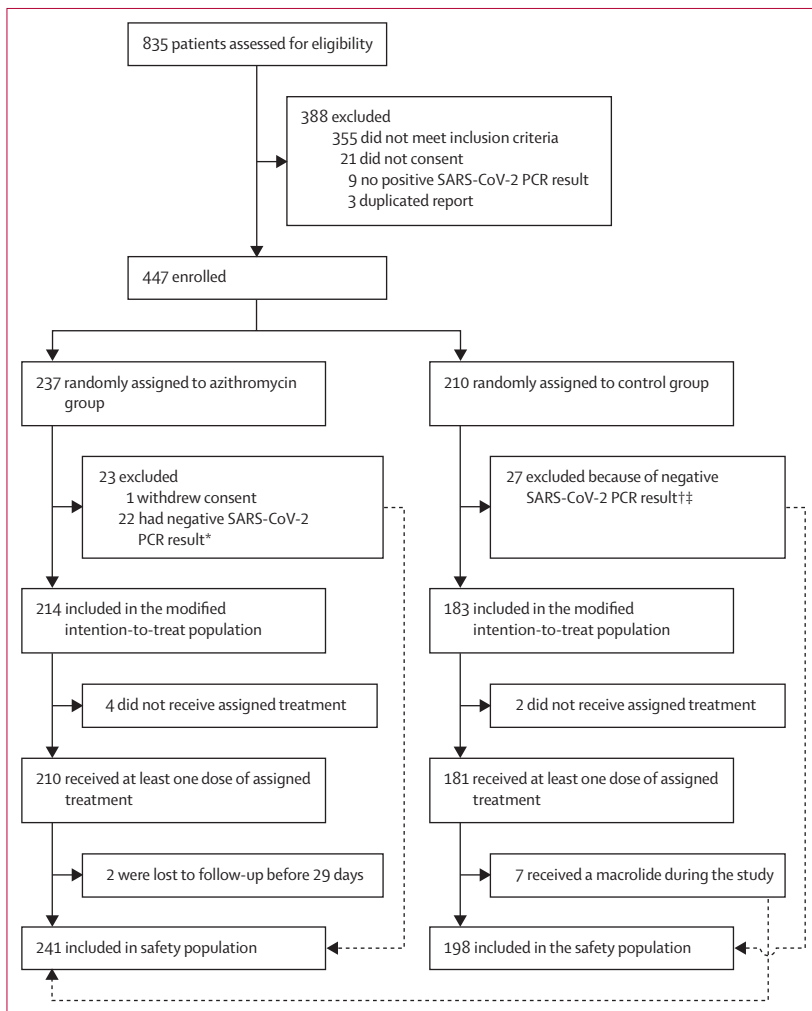


Figure 1: Trial profile
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *One of these patients did not receive at least one dose of assigned treatment so was not included in safety analyses. †One of these patients did not receive at least one dose of assigned treatment so was not included in safety analyses. ‡Two of these patients received a macrolide and so were included in the azithromycin group instead of the control group for safety analyses.

for the main analysis (214 in the azithromycin group and 183 in the control group). Groups were well matched with respect to baseline characteristics (table 1). Median age was 59.8 years (IQR 50.6–70.1), 262 (66%) patients were men, and 135 (34%) patients were women; 196 (49%) patients were on mechanical ventilation at baseline and 93 (23%) presented with shock. The median time from symptom onset to randomisation was 8.0 days (IQR 6.0–10.0). Baseline characteristics were also similar in the ITT population (appendix p 20).

In the mITT population, 210 (98%) patients in the azithromycin group received at least one dose of study treatment, and 166 (78%) patients received more than 80% of planned doses of the study drugs. In the control group, 181 (99%) received at least one dose and 149 (81%) received more than 80% of planned doses of hydroxychloroquine during follow-up. Nine (4%) patients from the control group in the ITT population received a macrolide during the course of the study, seven (4%) of whom were in the mITT population. During the index hospitalisation, the proportions of patients administered new antibiotics or vasoactive drugs were similar between the two randomised groups (appendix p 21).

The primary outcome was ascertained in all patients in the mITT population. Among patients with confirmed COVID-19 (mITT population), there was no difference in the proportional odds of being in higher categories in the six-point ordinal scale at 15 days between the azithromycin and control groups (OR 1.36 [95% CI 0.94–1.97], $p=0.11$; table 2; appendix p 27). Sensitivity analyses considering in the ITT and eITT populations had similar results (appendix pp 22–25, 28).

Among the 214 patients in the azithromycin group, 90 (42%) had died by 29 days, compared with 73 (40%) of 183 patients in the control group (HR 1.08 [95% CI 0.79–1.47], $p=0.63$; figure 2, table 2). Results were similar in the ITT population (appendix p 29).

At 7 days after the start of treatment, the proportional odds of being in a higher level in the six-point ordinal scale was greater in the azithromycin group (OR 1.60 [95% CI 1.08–2.35] $p=0.018$). There were no differences between groups at 29 days (OR 1.43 [95% CI 0.96–2.12; $p=0.081$).

Among patients assigned to the azithromycin group and on mechanical ventilation at baseline, the median number of ventilator-free days was 0 days (IQR 0–14) compared with 1 day (0–18) in the control group (mean difference -3.33 [95% CI -5.89 to -0.77]; $p=0.37$). Among survivors, the median duration of hospital stay was 26 days (IQR 11–29) in the azithromycin group compared with 18 days (11–29) in the control group (median difference 8.00 [95% CI 0.81 to 15.19]; $p=0.064$). In the azithromycin group, 87 (41%) of 214 patients had a secondary infection versus 65 (36%) of 183 in the control group (RR 1.11 [95% CI 0.92 to 1.33]; $p=0.29$). Results were similar in the other study populations (appendix pp 22–25).

	Azithromycin group (n=214)	Control group (n=183)
Age, years	59.4 (49.3–70.0)	60.2 (52.0–70.1)
Sex		
Men	140 (65%)	122 (67%)
Women	74 (35%)	61 (33%)
Smoker	18 (8%)	18 (10%)
Body-mass index, kg/m ²	26.4 (23.5–31.8)	27.2 (23.7–31.7)
Comorbidities		
Hypertension	126 (59%)	115 (63%)
Diabetes	81 (38%)	71 (39%)
Heart failure	14 (7%)	9 (5%)
Previous stroke	10 (5%)	5 (3%)
Previous myocardial infarction	8 (4%)	9 (5%)
Chronic obstructive pulmonary disease	12 (6%)	12 (7%)
Active cancer	10 (5%)	4 (2%)
Chronic kidney failure	26 (12%)	18 (10%)
Concomitant medications		
Corticosteroids	45 (21%)	27 (15%)
Oseltamivir	95 (44%)	88 (48%)
Lopinavir-ritonavir	1 (<1%)	1 (1%)
Antibiotics	179 (84%)	157 (86%)
Previous use of hydroxychloroquine and azithromycin or macrolide*	43 (20%)	30 (16%)
Time from symptom onset to randomisation, days	8 (6–11)	8 (6–10)
Need for oxygen of more than 4 L/min†	90 (42%)	75 (41%)
High-flow nasal cannula	6 (3%)	5 (3%)
Non-invasive ventilation	17 (8%)	8 (4%)
Mechanical ventilation	101 (47%)	95 (52%)
Shock at presentation	48 (22%)	45 (25%)
Arterial pressure at baseline, mm Hg	87 (75–99)	87 (80–100)
Dialysis at presentation	19 (9%)	9 (5%)
White cell count, $\times 10^9$ per L	8.38 (6.41–12.6)	9.00 (6.74–12.2)
Lymphocyte count, $\times 10^9$ per L	1.00 (0.65–1.43)	1.02 (0.74–1.42)
Creatinine, mg/dL	1.02 (0.80–1.80)	1.00 (0.80–1.57)

Data are median (IQR) or n (%). Standard of care includes hydroxychloroquine.
*This means prior use for treating the current COVID-19 infection in an outpatient basis or during the index hospitalisation. †Excludes other categories of oxygen support.

Table 1: Baseline characteristics and concomitant treatments during index of hospitalisation in the modified intention-to-treat population

The safety population consisted of 439 patients, of whom 241 were in the azithromycin group and 198 were in the control group. 177 (40%) patients had a serious adverse event (table 3). The proportion of patients with any serious adverse event was similar between the groups: 102 (42%) in the azithromycin group and 75 (38%) in the control group ($p=0.35$). There was no difference between groups with respect to the proportion of patients with QTc interval prolongation (47 [20%] in

	Azithromycin group (n=214)	Control group (n=183)	Difference (95% CI)	p value
Primary outcome				
Score on six-point ordinal scale at day 15	1.36 (0.94 to 1.97)*	0.11
1: not admitted to hospital	46 (21%)	49 (27%)
2: admitted to hospital, not requiring supplemental oxygen	7 (3%)	15 (8%)
3: admitted to hospital, requiring supplemental oxygen	21 (10%)	9 (5%)
4: admitted to hospital, requiring HFNC or NIPPV	5 (2%)	3 (2%)
5: admitted to hospital, requiring ECMO, invasive mechanical ventilation, or both	69 (32%)	52 (28%)
6: death	66 (31%)	55 (30%)
Key secondary outcome				
Death at 29 days	90 (42%)	73 (40%)	1.08 (0.79 to 1.47)†	0.63
Secondary outcomes				
Score on six-point ordinal scale at 7 days	1.60 (1.08 to 2.35)*	0.018
1: not admitted to hospital	9 (4%)	15 (8%)
2: admitted to hospital, not requiring supplemental oxygen	12 (6%)	8 (4%)
3: admitted to hospital, requiring supplemental oxygen	31 (14%)	32 (17%)
4: admitted to hospital, requiring HFNC or NIPPV	9 (4%)	14 (8%)
5: admitted to hospital, requiring ECMO, invasive mechanical ventilation, or both	119 (56%)	86 (47%)
6: death	34 (16%)	28 (15%)
Score on six-point ordinal scale at 29 days	1.43 (0.96 to 2.12)*	0.081
1: not admitted to hospital	69 (32%)	76 (42%)
2: admitted to hospital, not requiring supplemental oxygen	12 (6%)	6 (3%)
3: admitted to hospital, requiring supplemental oxygen	16 (7%)	7 (4%)
4: admitted to hospital, requiring HFNC or NIPPV	2 (1%)	5 (3%)
5: admitted to hospital, requiring ECMO, invasive mechanical ventilation, or both	23 (11%)	16 (9%)
6: death	90 (42%)	73 (40%)
Ventilation-free days (n=310)	0 (0 to 14)	1 (0 to 18)	-3.33 (-5.89 to -0.77)‡	0.37
Duration of hospital stay among survivors, days (n=234)	26 (11 to 29)	18 (11 to 29)	8.00 (0.81 to 15.19)‡	0.064
Incidence of secondary infections	87 (41%)	65 (36%)	1.11 (0.92 to 1.33)§	0.29

Data are n (%) or median (IQR), unless otherwise indicated. ECMO=extracorporeal membrane oxygenation. HFNC=high-flow nasal cannula. NIPPV=non-invasive positive-pressure ventilation. *Odds of a patient in the azithromycin group having a worse status than a patient in the control group; an odds ratio >1.00 represents a clinical worsening assessed on the ordinal scale in the combination group compared with the monotherapy group; likelihood ratio test of the proportional odds assumption was not significant (p=0.099); two patients, both in the combination therapy group, did not have ordinal scale or vital status ascertained at 29 days because they were lost to follow-up; however, both had clinical status ascertained at 15 days. †Hazard ratio estimated from a Cox proportional hazards model. ‡Median difference with corresponding 95% CI calculated as an asymmetric Laplace distribution. §Risk ratio with 95% CI calculated with the Wald likelihood test.

Table 2: Study efficacy outcomes in the modified intention-to-treat population

the azithromycin group vs 42 [21%] in the control group; p=0.66); the proportions of patients with ventricular arrhythmias or resuscitated cardiac arrest were also similar between the groups. There were no adjudicated deaths due to ventricular arrhythmia. There were also no significant differences between groups in the incidence of other safety outcomes (table 3; appendix p 26).

Results for the primary endpoint stratified by subgroups according to demographics, disease severity, and comorbidities were generally consistent with the main analysis. However, there was significant heterogeneity according to age (p_{interaction}=0.033) and concomitant use of antiviral therapy (p_{interaction}=0.033; appendix p 30).

Discussion

In this trial, addition of azithromycin to standard of care treatment was not superior to standard of care alone (standard of care included hydroxychloroquine according to local guidelines) in improving the clinical status in patients with severe COVID-19. Moreover, patients in the azithromycin group had similar mortality and incidence of secondary infections, duration of hospital stay, and time free from mechanical ventilation compared with patients in the control group. In patients younger than 60 years or in those administered antiviral drugs (mostly oseltamivir), patients in the azithromycin group had worse outcomes in terms of the primary endpoint of clinical status at day 15. However, subgroup analyses should be interpreted with caution because those differences could be due to chance.

According to a survey of more than 6000 physicians in 30 countries, azithromycin was the second most commonly prescribed treatment for COVID-19.¹⁸ Use of the combination of azithromycin and hydroxychloroquine has been reported in non-randomised studies,^{11-13,19} most of which have not suggested any associated benefit in terms of mortality or viral clearance. Previous reports of macrolides to treat other types of viral pneumonia also had mixed results.²⁰⁻²² In Middle East respiratory syndrome (MERS), a disease caused by another beta-coronavirus similar to SARS-CoV-2, a retrospective observational report did not find any association between use of macrolides (mostly azithromycin) and improvement of clinical outcomes or decreases in viral shedding.²² Conversely, in another retrospective observational report, adjunctive therapy with azithromycin was associated with improved 90-day survival and a shorter time to discontinuation of mechanical ventilation among patients with acute respiratory distress syndrome of different causes.²³ Until recently, no randomised trials analysing azithromycin in COVID-19 or other diseases caused by betacoronaviruses have been published. In the COALITION COVID-19 Brazil I trial, addition of hydroxychloroquine with or without azithromycin to standard of care did not result in clinical improvement in patients admitted to hospital with mild to moderate COVID-19.¹⁴ The results of the present study expand those findings,

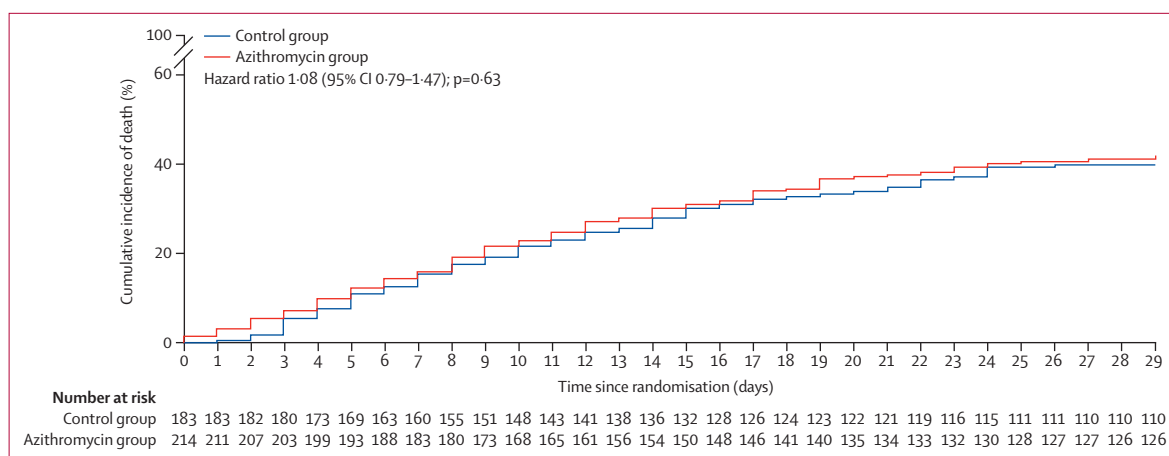


Figure 2: Cumulative incidence of all-cause mortality at 29 days after randomisation

Numbers estimated by the Kaplan-Meier method, and hazard ratio with corresponding 95% CI calculated from a Cox proportional hazards model.

suggesting that in patients with severe COVID-19, addition of azithromycin to a regimen that included hydroxychloroquine does not result in improvement of clinical outcomes. The absence of any clinical benefit suggests that the routine use of this strategy should be avoided, unless there is evidence of concomitant bacterial pneumonia, for which current guidelines recommend a combination therapy of a β lactam with a macrolide in severe cases.²⁴ However, in COVID-19 cases where radiological and laboratory data suggest an isolated viral pneumonia, azithromycin probably has no effect in terms of improving clinical outcomes. Moreover, our results can inform future research in this area, because the body of evidence from randomised clinical trials so far suggests that it is unlikely that azithromycin combined with hydroxychloroquine is a useful treatment option for patients admitted to hospital with COVID-19.

The mortality rates in our trial are higher than in previous randomised trials in patients with COVID-19.^{16,25} We understand that this high mortality rate might be partially explained by the selection criteria for our trial. Because entry criteria required patients to be on oxygen of more than 4 L/min, this resulted in inclusion of a very high-risk population, with almost half of our patients on mechanical ventilation and about a quarter in shock at baseline. Although the mortality rate in this study was higher than in a retrospective study from China,²⁶ our patients had a higher prevalence of hypertension, diabetes, and chronic kidney disease, which might explain the worse outcomes in our cohort. Health-care capacity restrictions and inequalities in the context of a pandemic might also have contributed to these high mortality rates. However, our pragmatic study reproduces the reality from many countries, including some high-income countries, where health-care resources shortages have occurred because of the high numbers of patients with severe COVID-19 admitted simultaneously to hospitals.

	Azithromycin group (n=241)	Control group (n=198)	p value
Serious adverse events	102 (42%)	75 (38%)	0.35
Serious adverse events suspected to be related to study drug	12 (5%)	8 (4%)	0.64
QTc interval prolongation*	47 (20%)	42 (21%)	0.66
Gastrointestinal intolerance	61 (25%)	48 (24%)	0.80
Clinically relevant ventricular arrhythmias†	8 (3%)	5 (3%)	0.63
Resuscitated cardiac arrest	16 (7%)	13 (7%)	0.98
Death due to ventricular arrhythmia	0	0	..
Acute kidney failure	147 (61%)	103 (52%)	0.059
Need for dialysis (in patients not on dialysis at baseline)	86/222 (39%)	64/189 (34%)	0.27
Death due to acute kidney failure	2 (1%)	3 (2%)	0.66
Decrease in white blood cell count of >50% on at least one occasion	10 (4%)	4 (2%)	0.32
Decrease in lymphocytes >50% on at least one occasion	27 (11%)	21 (11%)	0.96
Decrease in platelets >50% on at least one occasion	10 (4%)	8 (4%)	0.99
Increase in bilirubin >50% on at least one occasion	10 (4%)	6 (3%)	0.71

Data are n (%). Safety outcomes were assessed in the safety population, which was all patients who received at least one dose of study treatment, considering the patient in the group of medication that was actually administered, regardless of the group to which the patient was allocated. QTc=corrected QT. *Defined as QTc \geq 470 ms for women or \geq 450 ms for men in patients whose baseline QTc was below those thresholds, or QTc \geq 480 ms if baseline QTc was above those thresholds. †Events that resulted in death or cardiac arrest, prompted medical intervention (such as electrical or chemical cardioversion or defibrillation), or fulfilled criteria of a serious adverse event.

Table 3: Safety outcomes

One of the concerns with azithromycin and its combination with drugs that prolong QTc interval such as hydroxychloroquine is related to cardiovascular safety.^{8,27} Although observational studies have reported increased incidence of QTc interval prolongation with combination therapy compared with hydroxychloroquine alone,^{9,10} there were no significant differences between groups in our trial. This finding is also in disagreement with other previous reports suggesting an association of azithromycin with increased risk of ventricular arrhythmias or cardiovascular death.^{8,28} The discrepancy in the results

might be related to the fact that we excluded patients with prolonged QTc interval at baseline or those taking medications known to increase QTc interval, or to the confounders and ascertainment bias present in retrospective, observational studies. Notably, the incidence of clinically relevant ventricular arrhythmias and cardiac arrest was not increased with the addition of azithromycin in our study. Nevertheless, it should be acknowledged that a rare event such as ventricular arrhythmia might not be captured by a moderately sized, randomised clinical trial.

We provided hydroxychloroquine for all patients in the control group as part of standard of care. We considered that, given the absence of proven effective therapies for COVID-19 when our trial was being conducted and in a scenario of a pandemic and public concern with mounting numbers of deaths, it was conceivable to proceed with such a design.²⁹ This same approach has been used previously in a randomised trial testing combination therapy with interferon beta-1b, lopinavir-ritonavir and ribavirin versus lopinavir-ritonavir and ribavirin, which had no standard of care group without active comparators,³⁰ despite the fact that lopinavir-ritonavir did not result in improvement in clinical outcomes in another trial in patients with COVID-19.¹⁷ Moreover, contrary to that study, which included patients with mild to moderate COVID-19, our trial included a very-high risk population. By the time our trial was designed, health authorities in Brazil issued a protocol that recommended chloroquine or hydroxychloroquine for patients with severe COVID-19. Thus, when this trial was started, hydroxychloroquine or chloroquine became routine practice for patients with severe COVID-19 in Brazil, making recruitment into a trial with a standard of care regimen without hydroxychloroquine unfeasible. However, it should be noted that the interpretation of our safety results is especially limited by the absence of a randomised group taking neither drug.

This trial has other limitations that also merit consideration. First, we included only patients with severe COVID-19 infection, so our findings cannot be extrapolated to patients with less severe disease. Second, it is possible that the absence of difference between groups was due to type 2 error, especially because our sample size calculation was based on a large magnitude of effect (OR 0·57), not previously seen in other positive trials in patients with COVID-19.^{16,25} However, given that the point estimate for the primary endpoint is in the opposite direction from favouring the addition of azithromycin to the standard of care, and that the lower boundary of the 95% CI for the OR is 0·94, our results probably exclude a meaningful clinical benefit from this strategy. Third, we cannot ascertain from our results whether azithromycin should be used as standalone therapy for COVID-19 without hydroxychloroquine. Fourth, 4% of patients from the control group broke protocol and received a macrolide at some point during the course of the study, which could

have biased our results towards the null. Fifth, the open-label design might have led to reporting bias, although we attempted to control for ascertainment bias by having masked adjudication of the primary outcome and causes of death.

In conclusion, in patients admitted to hospital with severe COVID-19, adding azithromycin to a standard of care (a regimen that included hydroxychloroquine) did not result in clinical improvement or mortality reduction. These findings do not support the routine use of azithromycin in combination with hydroxychloroquine for this patient population and can inform clinical practice and guidelines.

Contributors

RHMF contributed to the literature search, figures, study design, selecting participating sites, data collection, data interpretation, and drafting the manuscript. OB contributed to the literature search, study design, selecting participating sites, data collection, obtaining funding, data interpretation, and drafting the manuscript. HAF contributed to the study design, selecting participating sites, data interpretation, and drafting of the manuscript. TDC contributed to data collection, data interpretation, and critical review of the manuscript. LRF contributed to data interpretation and critical review of the manuscript. MGL contributed to statistical analysis, figures, and critical review of the manuscript. FGZ contributed to data collection, data interpretation, and critical review of the manuscript. VCV, RGR, LCPA, AA, and RDL contributed to study design, data collection, data interpretation, and critical review of the manuscript. ALOM, FMTP, PAM, TCL, AJP, GBO, VCSD, EPM, and OCEG contributed to data collection, data interpretation, and critical review of the manuscript. RBA and MBO contributed to critical review of the manuscript. RVPS, DDFM, LPAP, KC, and RGRAPM contributed to trial operations, site monitoring, data management, and critical review of the manuscript. GPPS and LVR contributed to data collection, data interpretation, and critical review of the manuscript. ASN contributed to study design, data collection, statistical analysis, data interpretation, and critical review of the manuscript. FRM contributed to study design, data collection, data interpretation, and critical review of the manuscript. ABC contributed to study design, selecting participating sites, data collection, data interpretation, and critical revision of the manuscript.

Declaration of interests

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