South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: AZITHROMYCIN FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 11 May 2020

Key findings

- We conducted a rapid review of the available clinical evidence pertaining to the use of azithromycin with or without other medicines for patients with suspected or confirmed COVID-19.
- We did not find any systematic reviews or randomised controlled studies which assessed the direct efficacy of azithromycin for COVID-19. In one randomised trial both arms received azithromycin; in three observational studies there was no comparator group.
- One randomised clinical trial and two observational studies in COVID-19 patients found that azithromycin, in combination with other medicines such as chloroquine, was associated with clinically significant QTc prolongation. A large observational study in people with rheumatoid arthritis found that azithromycin plus hydroxychloroquine increased the risk of cardiovascular mortality relative to amoxicillin and hydroxychloroquine.
- We did not identify any reports on the use of azithromycin in children with COVID-19 and its use in children is discouraged outside of a clinical trial setting, except where indicated for other reasons (e.g. to treat bacterial co-infections).
- There is currently insufficient evidence to support the inclusion of azithromycin in treatment guidelines for COVID-19 in South Africa.
- Azithromycin should only be considered for use in the treatment of COVID-19 within the context of clinical trials.

THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:
There is currently insufficient evidence to recommend routine use of azithromycin in children or adults with COVID-19.
Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish, Helen Rees, Gary Reubenson.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated when sufficient additional evidence becomes available.

BACKGROUND

The novel human respiratory coronavirus (SARS-CoV-2), which causes COVID-2019, was declared a pandemic by the World Health Organization on 11 March 2020. There are currently more than 3.5 million confirmed COVID-19 cases in over 200 countries, areas or territories. Moreover, SARs-CoV-2 has caused almost 250 000 deaths (WHO, https://covid19.who.int/; Johns Hopkins, https://coronavirus.jhu.edu/map.html, as at 4 May 2020).

In patients infected with SARS-CoV-2, disease severity and outcomes are believed to be related to characteristics of the immune response.[1,2] The inclusion of an immunomodulant macrolide antimicrobial such as azithromycin in the treatment of COVID-19 has therefore been suggested.[3,4,5] Macrolides have shown some antiviral activity against rhinovirus, influenza virus, respiratory syncytial virus, Zika virus, and Ebola virus.

Azithromycin is currently included in many South African standard treatment guidelines, including for the treatment of bacterial infections in penicillin-allergic patients, for rickettsial infections in patients unable to take tetracyclines, and specifically for the management of atypical bacterial infections, including nosocomial pneumonia. However, azithromycin is associated with a number of adverse effects, including QTc prolongation, which can result in ventricular arrythmias.[6] Concomitant administration with other QTc-prolonging drugs, such as chloroquine or hydroxychloroquine, may increase the risk of significant QTc prolongation. A recent study in rheumatoid arthritis patients in Germany, Japan, Netherlands, Spain, UK, and the USA compared 323 122 users of hydroxychloroquine-azithromycin to 351 956 users of hydroxychloroquine-amoxicillin.[7] After adjusting for confounders, there was an increased risk of 30-day cardiovascular mortality (Calibrated HR2.19 [95% CI 1.22-3.94]) in those receiving the azithromycin combination with hydroxychloroquine compared to the combination with amoxicillin. Azithromycin is an inhibitor of various cytochrome P450 isozymes, in particular CYP3A4, and of p-glycoprotein, and so can increase plasma concentrations of concomitant medicines that are predominantly metabolised via these pathways. These drug-drug interactions can be clinically relevant, especially where additive effects on cardiac rhythms are expected.

Note: Due to the continuous emergence of new evidence, this rapid review will be updated as and when more evidence becomes available. It was noted that, as of 4 May 2020, 44 clinical trials investigating the role of azithromycin in the treatment of COVID-19 are registered on clinicaltrials.gov. Two clinical trials investigating azithromycin with hydroxychloroquine (NCT04348474; NCT04329572) were suspended as the contracted clinical research organisation was no longer interested in conducting the studies; no additional reasons were provided (clinicaltrials.gov).

RESEARCH QUESTION:

Should azithromycin be used to treat suspected or confirmed COVID-19, with or without other medicines?

METHODS

We conducted a rapid review of the evidence including systematic searching of four electronic databases (PubMed, Cochrane COVID Study Register, Clinicaltrials.gov and WHO ICTRP). Screening of records and data extraction was conducted by one reviewer, with results reviewed and checked by another reviewer. Relevant records were extracted in a narrative table of results. No appraisal or meta-analysis was done. The search strategy is shown in Appendix 1.

Eligibility criteria for review

Population: Patients with suspected or confirmed COVID-19, no restriction to age or disease severity.

Intervention: Azithromycin either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator)

Outcomes: Mortality; progression to hospitalisation (for ambulant patients); duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse events, adverse reactions.

Study designs: Case series, non-randomised cohorts as well as randomised controlled trials, and systematic reviews of studies in humans. Single case reports were excluded.

RESULTS

We searched PubMed, as well as the Cochrane COVID Study Register, WHO ICTRP and Clinicaltrials.gov on 24 April 2020. We did an updated search on Clinicaltrials.gov on 4 May 2020. Details of each search are provided in Appendix 1. One reviewer screened 34 records and identified five potentially eligible articles. Three additional sources were identified from medRxiv, one of which was subsequently published in JAMA. Data in **Table 1** report the main characteristics and outcomes of the included studies. We excluded a case series where outcomes were not reported separately for the groups treated with different agents.[2]

We found only one randomised controlled trial which included azithromycin in both experimental arms.[8] The high-dose chloroquine arm of this study was prematurely stopped, due to increased adverse effects and lethality. We included six observational studies in which patients took azithromycin, in all studies this was in combination with other drugs. In all studies the treatment regimen included either chloroquine or hydroxychloroquine.[9,10,11,12,13,14] No studies compared patients treated with azithromycin alone with those treated with placebo or standard of care, excluding specific agents for COVID-19.

None of the included studies provide good quality data to inform assessment of the efficacy of azithromycin in the treatment of COVID-19.

The studies to date suggest that some of the predicted safety concerns have been encountered.[15] In particular, the risk of QTc prolongation needs to be considered, especially if azithromycin is used with other QTc prolonging agents.

Use of azithromycin in COVID-19 is an area of considerable research interest, as shown in the number of trials registered with WHO ICTRP or Clinicaltrials.gov, or recorded in the Cochrane COVID Study Register. The evidence is thus expected to change rapidly, as more trials are completed and reported.

The conclusion of this rapid review is similar to that reached by The COVID-19 LOVE Working Group (https://www.epistemonikos.cl/2020/04/03/is-it-true-that-azithromycin-and-other-macrolides-are-useful-for-covid-19-treatment/), which stated: "The results of the studies carried out to date do not confirm any kind of benefits derived from the use of azithromycin or other macrolides for treating patients with COVID-19."

CONCLUSION

There is currently insufficient evidence to support the use of azithromycin in the management of COVID-19 in South Africa outside of a clinical trial setting. Eligible patients in South Africa should be considered for enrolment in randomised clinical trials of potential therapies for COVID-19, so that robust data on efficacy and safety of interventions can be generated to inform treatment policies.

Reviewers: Andy Gray (AG): Division of Pharmacology, University of KwaZulu-Natal; Karen Cohen (KC): Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town; Gary Maartens (GM): Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town.

Declaration of interests: AG, KC and GM have no interests to declare in respect of azithromycin therapy for COVID-19.

Table 1. Characteristics of included studies (for safety analysis only)

Citation	Study design	Population (n)	Treatment	Main findings
Borba et al JAMA 2020	Double-blind, placebo controlled RCT	Hospitalised patients 18 years and older with ARDS (respiratory rate >24 rpm AND/OR heart rate >125 bpm (in the absence of fever) AND/OR peripheral oxygen saturation <90% in ambient air AND/OR shock (defined as mean arterial pressure lower than 65 mmHg, with the need for vasopressors medicines or oliguria or a lower level of consciousness) secondary to presumed SARS-CoV-2, in a single referral hospital Enrolled prior to laboratory confirmation of COVID-19; all retained in safety analysis (49.4% RT-PCR positive) Planned n=440	High dose (600mg CQ twice daily for 10 days or total dose 12g) or low dose (450mg for 5 days, twice daily only on the first day, or total dose 2.7g). As standard of care all participants received **azithromycin (500mg daily for 5 days)** and ceftriaxone (1g every 12 hours for 7 days) and oseltamivir (75mg every 12 hours for 5 days, if influenza suspected)	Safety data presented for the first 81 randomised participants (41 high dose, 40 low dose) High dose CQ presented more QTc>500ms than low dose (25% vs 10.7%). In the text, a "trend toward higher lethality (17%)" was noted in the high dose CQ group. However, a table shows that death occurred in 17.5% of the low dose vs 9.7% high dose recipients **The Data Safety and Monitoring Board stopped recruitment to the high dose arm** All patients over 75 years of age were randomized to the high dose arm
Gautret P et al. 2 International Journal of Antimicrobial Agents 2020 Journal pre-print	Open-label, non-randomised clinical trial (all patients at 1 hospital received HCQ; patients at other participating hospitals didn't)	N = 42 (26 on HCQ; 16 controls) Hospitalised: but some were asymptomatic, some had upper respiratory tract symptoms only; some had pneumonia or bronchitis. SARS-CoV-2 PCR positive Age >12 years (mean age 45.1 years) Patients with contra-indications to chloroquine were excluded	All received symptomatic treatment at the discretion of the investigators; 6 HCQ-treated patients also received **azithromycin (500mg on day1, followed by 250mg per day for 4 days)**. Intervention arm: hydroxychloroquine sulfate 200 mg 8 hourly orally for 10 days (HCQ group)	Day 6 results presented for 36 patients; 6 HCQ patients were considered LTFU and were excluded from analysis (3 transferred to ICU, 1 died (cause not specified), 1 left hospital on Day 3, 1 stopped HCQ on Day 3). Negative SARS-CoV-2 on Day 6 nasopharyngeal swab: 70% in HCQ group and 12.5% in control group (p=0.001). 1 patient who was still PCR-positive at day 6-post inclusion on HCQ treatment only, received azithromycin in addition to HCQ at day 8-post

Citation	Study design	Population (n)	Treatment	Main findings
				inclusion and cured her infection at day-9 post infection; 1 patient on the HCQ and azithromycin combination who tested negative at day 6 post-inclusion was tested positive at low titer at day 8 post-inclusion
Gautret P et al. Travel Medicine and Infectious Disease 2020	Case series	N = 80 (all hospitalised, PCR-documented SARS-CoV-2 RNA from a nasopharyngeal sample) Includes the 6 patients treated with HCQ and azithromycin reported previously in IJAA paper	HCQ 200 mg three times per day for ten days combined with **azithromycin 500 mg on D1 followed by 250 mg per day for the next four days**. For patients with pneumonia and NEWS score≥5, a broad spectrum antibiotic (ceftriaxone) was added	The planned primary endpoints were (i) an aggressive clinical course requiring oxygen therapy or transfer to the ICU after at least three days of treatment, (ii) contagiousness as assessed by PCR and culture, and (iii) length of stay in the ID ward. In the case series, all patients improved clinically except one 86 year-old patient who died, and one 74 year-old patient still in intensive care. A rapid fall of nasopharyngeal viral load was noted, with 83% negative at Day 7, and 93% at Day 8. Virus cultures from patient respiratory samples were negative in 97.5% of patients at Day 5. Mean length of stay in the ID ward was 5 days. Twelve-lead ECG were performed before treatment and two days after treatment began; treatment was either not started or discontinued when the QTc (Bazett's formula) was >500 ms. No data were reported on the number of patients in whom treatment was not started or discontinued.
Molina JM, et al. Médecine et Maladies Infectieuses. 2020. Pre-proof publication	Open label, single arm cohort	N = 11 7 men, 4 women 10/11 had fever	All received same medical management as Gautret study: HCQ 600 mg/d for 10 days and **azithromycin 500 mg day 1 and 250 mg days 2 to 5**	Within 5 days, 1 died, 2 were in ICU. 1 patient discontinued hydroxychloroquine and azithromycin at 4 days because of prolonged QT (from 405 ms to 470 ms)

Citation	Study design	Population (n)	Treatment	Main findings
		Mean age of 58.7 years (range: 20-77) 8 had significant comorbidities associated with poor outcomes (obesity: 2; solid cancer: 3; hematological cancer: 2; HIV-infection: 1)	10/11 with fever received nasal Oxygen when initiating treatment	Repeated nasal swabs in 10 that were alive were still PCR positive for SARS-CoV-RNA at days 5-6 after treatment started.
The Columbia University Kidney Transplant Program, . Journal of the American Society of Nephrology, 2020	Case series	N=15 kidney transplant recipients hospitalised for confirmed COVID-19	13 (87%) patients received HCQ, with 9 also treated with **azithromycin**, 1 with tocilizumab	Of those treated with HCQ and azithromycin, 2 died, 4 were discharged and 3 remained in hospital No other safety data reported (but azithromycin was specifically avoided in patients with QT prolongation on admission)
Chorin, medRxiv 2020 Preprint, not peer-reviewed	Case series	N=84 adult patients with SARS-CoV-2 infection treated with hydroxychloroquine/ azithromycin combination	All were treated with hydroxychloroquine/ **azithromycin** combination, but no doses were stated	QTc prolonged maximally from baseline between days 3 and 4; in 30% of patients QTc increased by greater than 40ms; in 11% of patients QTc increased to >500 ms
Magagnoli, medRxiv 2020 Preprint, not peer-reviewed	Retrospective cohort analysis, using propensity scores	N= 368 male patients treated in United States Veterans Health Administration medical centers	Patients were treated with either hydroxychloroquine (HC, n=97), hydroxychloroquine and **azithromycin** HC+AZ, n=113) or no hydroxychloroquine (no HC, n=158) It is unclear whether patients in the no HC cohort might have received azithromycin	Using propensity scores to take into account clinical characteristics, the risk of death from any cause was higher in the HC group (adjusted hazard ratio, 2.61; 95% CI, 1.10 to 6.17; P=0.03) but not in the HC+AZ group (adjusted hazard ratio, 1.14; 95% CI, 0.56 to 2.32; P=0.72), compared to the no HC group. The risk of ventilation was similar in the HC group (adjusted hazard ratio, 1.43; 95% CI, 0.53 to 3.79; P=0.48) and in the HC+AZ group (adjusted hazard ratio, 0.43; 95% CI, 0.16 to 1.12; P=0.09), compared to the no HC group. The possibility of non-respiratory toxicity, including cardiotoxicity was raised, including with hydroxychloroquine alone.

Appendix 1: Search strategy

PubMed

#3: Search ((#1 AND #2) NOT (animals[mh] NOT humans[mh]))

#2: Search (coronavir*[tiab] OR coronovirus*[tiab] OR corona virus[tiab] OR virus corona[tiab] OR corono virus[tiab] OR virus corono[tiab] OR COVID-19[tiab] OR COVID19[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR cv-19[tiab] OR n-cov[tiab] OR ncov*[tiab] OR hCOV*[tiab] OR SARS cov-2[tiab] OR SARS-coronavirus[tiab] OR SARS-cov[tiab] OR (wuhan*[tiab] AND (virus[tiab] OR viruses[tiab] OR viral[tiab])) OR (COVID*[tiab] AND (virus[tiab] OR viruses[tiab] OR viral[tiab])) OR MERS-cov[tiab] OR MERS cov[tiab] OR COVID-19[NM] OR severe acute respiratory syndrome coronavirus 2[nm])

#1: Search (azithromycin[mh] OR azithromycin[tiab] OR sumamed[tiab] OR zithromax[tiab] OR azitrocin[tiab] OR azadose[tiab] OR zitromax[tiab] OR macrolide[tiab] OR macrolides[tiab] OR macrolides[mh])

Records retrieved from search #3: 34 (5 relevant to PICO question)

WHO ICTRP

Downloaded Excel file from their website (1528 trials in file) – searched for azithromycin and retrieved

Records retrieved: 45

Cochrane COVID Study Register (https://covid-19.cochrane.org/)

azithromycin OR azithromycin OR sumamed OR zithromax OR azitrocin OR azadose OR zitromax OR macrolides

Records retrieved: 45

Clinical trials.gov

azithromycin OR azithromycin OR sumamed OR zithromax OR azitrocin OR azadose OR zitromax OR macrolides | SARS-COV-2 OR COVID-19 OR 2019-nCOV OR 2019 NOVEL CORONAVIRUS OR SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Records retrieved: 53 (44 for treatment of Covid-19)

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