AZITHROMYCIN

RECOMMENDATION

We recommend against the use of azithromycin among hospitalized patients with moderate-to-severe COVID-19 infection. *(Moderate quality of evidence; Strong recommendation)*

Consensus Issues

No issues were raised during the consensus panel meeting.

EVIDENCE SUMMARY

Should azithromycin be used as treatment for COVID-19?

Evidence Reviewers: Anna Maria Vida P. Garcia, RPh, D Clin Epi; Maria Vanessa Sulit, RN, Msc, Howell Henrian G Bayona, MSc, CSP-PASP

Key Findings

Moderate certainty of evidence from 3 RCTs comparing azithromycin with standard of care versus standard of care alone showed no significant benefit on all-cause mortality at day 28, 29 and 30. Results from 2 large trials (COALITION II, RECOVERY) showed no significant difference with regard to the need for ECMO or mechanical ventilation at days 28 or 29 between the two groups. Subgroup analysis showed that azithromycin worsened the clinical status of patients aged < 60 years and on antiviral therapy. However, the results should be interpreted with caution as results varied significantly across age groups and concomitant use of antiviral therapy. The proportion of adverse events were similar between azithromycin and standard of care. Most of the studies were found to be at moderate risk of bias with common issues on blinding and in two studies patients in the standard of care group had received azithromycin or other macrolides that could affect the results.

Introduction

Azithromycin is a second-generation macrolide antibiotic which acts by inhibiting bacterial protein synthesis by binding and interfering with the 50S subunit of bacterial ribosome and the growth of the nascent polypeptide chain [1]. Azithromycin has been proposed as a potential treatment for COVID-19 due to its immunomodulatory effects which include downregulation of cytokine production, maintenance of epithelial cell integrity and prevention of lung fibrosis. Moreover,

azithromycin was also reported to have anti-viral activity, in vitro study showed that azithromycin was able to inhibit SARS-COV-2 replication in Vero cells and human epithelial cell [2].

Review Methods

A literature search using PubMed and the Cochrane Library using the terms "COVID-19", "azithromycin", and "systematic review" or "randomized controlled trials" and their synonyms or MESH terms was done to update the existing guidelines. To obtain gray literature and ongoing clinical trials, (1) clinicaltrials.gov, (2) ChinaXiv.org, (3) MedRxiv.org, (4) BioRxiv.org, (5) chictr.org and (6) WHO International Clinical Trials Registry Platform (ICTRP) was searched. An update for this review will be done for any new published relevant trial.

Randomized controlled trials, systematic review or meta-analysis that reported the effect of azithromycin compared to standard of care or placebo as treatment in patients with COVID-19 were included in this review. In-vitro and in-vivo studies and those that compared azithromycin to other active ingredients (i.e., not part of standard of care) were excluded.

Results

Three RCTs assessing the effect of adding azithromycin to standard of care versus standard of care alone in patients with severe COVID-19 were found [3,4,5]. Detailed study characteristics can be found in Appendix 1. Sekhavati et al. included 111 adults with COVID-19 (unspecified severity) in one hospital in Iran [3]. COALITION II trial included 397 adults with severe COVID-19 infections admitted in 57 hospitals in Brazil [4]. The RECOVERY trial included 7,663 patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection [5]. In all 3 studies, azithromycin was given with standard of care. In the COALITION II study HCQ was part of the standard of care, while in the study of Sekhavati and colleagues the control group received oral lopinavir/ritonavir (LPV/r) and oral HCQ [3,4]. In the RECOVERY trial, standard of care given was reported to evolve over time [5].

Pooled results from the 3 trials on all-cause mortality at day 28, 29 and 30 showed no significant benefit for azithromycin (RR 0.9895% CI: 0.90 to 1.06). All-cause mortality at day 7 and day 15 was only measured in one study, which showed no significant difference between groups with RR of 1.04 (0.66, 1.64) and RR 1.03 (0.76-1.38), respectively [4].

Pooled results from COALITION II and RECOVERY trials showed no significant difference with regard to the need for ECMO or mechanical ventilation at days 28 or 29 between the two groups with a RR of 0.94 (95%CI: 0.81 to 1.09) [5, 6]. The COALITION II trial also measured this outcome for days 7 and 15, which also showed no significant difference between the two groups, RR 1.18 (0.97 to 1.44) and RR 1.13 (0.84 to 1.53), respectively [4].

All 3 RCTs also reported duration of hospitalization, but results could not be pooled. Sekhavati et. al., (2020) reported a -1.35 (mean) days (95% CI: -2.45 to -0.25) shorter duration of hospitalization in azithromycin + standard of care as compared to the standard of care group [3]. The RECOVERY trial showed no difference in the duration of hospitalization among survivors for azithromycin plus standard of care group and standard of care alone group with median 10 days (IQR: 5 to >28) and 11 days (IQR: 5 to >28), respectively [5]. In the COALITION II trial, a higher but non-significant median day of hospitalization among survivors in the azithromycin + standard

of care group as compared to the control group (Median 8 days (95%CI: 0.81, 15.19; p-value: 0.064) [4].

For ICU admission, Sekhavati et al, (2020), showed no significant difference between azithromycin and the standard of care group as compared to the standard group (RR 0.28 (0.60 to 1.29)) [3].

In terms of adverse events, the RECOVERY trial reported no significant difference between the azithromycin plus standard of care group as compared to the standard group, with frequencies of 101 (4.4%) and 224 (4.8%) respectively and RR of 0.91 (0.72, 1.14) [5]. The COALITION II trial also reported safety outcomes such as clinically relevant ventricular arrhythmias, resuscitated cardiac arrest, acute kidney failure, and corrected QT interval prolongation, and found no significant difference between the two groups [5]. For serious adverse events, the RECOVERY trial reported a case of pseudomembranous colitis which was believed to be related to azithromycin, while the COALITION II study reported no significant difference between the two groups RR 1.12 (0.89 to 1.49) [4, 5].

Subgroup analysis

In the COALITION II study, azithromycin showed worsened clinical status at day 15 of patients aged < 60 years old (OR: 1.98, 95% CI: 1.17 to 3.37) and patients on antiviral therapy (OR: 2.10, 95% CI: 1.21 to 3.65). However, the results should be interpreted with caution as results varied significantly across age groups and concomitant use of antiviral therapy ($p_{interaction}$=0·033 and $p_{interaction}$=0·03, respectively) [4].

In the RECOVERY trial, women in the azithromycin group had better outcomes in terms of hospital discharge (RR 1.16, 95% CI 1.05−1.27). However, results varied significantly across men and women e ($p_{interactio}$=0.007) [5].

The GRADE rating for this body of evidence was moderate; downgrading occurred due to serious risk of bias concerns (Appendix 2). All studies were open-label. The outcome assessors were blinded except in the Sekhavati et al. (2020) RCT. Baseline characteristics in the COALITION II and Sekhavati et al (2020) RCTs were reported to be comparable [4,5]. However, significant differences between the treatment arms were reported in the study RECOVERY trial [5]. In the study of Sekhavati et al (2020) allocation concealment was not described, and reporting bias could not be assessed as protocol was not available [3]. Moreover, in the COALITION II study, 4% of the patients received a macrolide at some point during the study period, while in the RECOVERY trial, 17% of the patients in the standard of care group were given azithromycin or another macrolide antibiotic that could bias the result [4,5].

Recommendations from Other Groups

Azithromycin is currently not recommended for the treatment of COVID-19 outside of randomized trials [6]. In other CPGs such as those by the Infectious diseases Society of America (IDSA), National Institutes of Health (NIH), the use of azithromycin alone was not mentioned or reviewed [7,8].

Research Gaps

There were 4 ongoing trials identified from various trial registries (see Appendix 4). Two trials (ATOMIC2, NCT04381962; ACTION, NCT04332107) have also been completed, but results are not yet posted as of 16 Feb 2021. An update will be done upon publication of findings from these trials. Most of the studies in this review were likely to include patients with moderate or severe COVID-19 infection. Thus, we could not address the effect of azithromycin in non-hospitalized patients with mild symptoms.

References

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Appendix 1: Characteristics of Included Studies

Author	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
Sekhavati E, 2020 [4]	N=111 ≥ 18 yrs old admitted to the hospital with lab confirmed COVID-19 and low risk for QT prolongation and arrhythmia Severity not specified	n=56 AZITHROMYCIN 500 mg daily (oral) + SOC: LPV/r 400/100 mg 2x daily and HCQ 400 mg daily for 5 days	n=55 SOC: LPV/r 400/100 mg 2x daily and HCQ 400 mg daily for 5 days	Primary: Hospital days, need for ICU admission, death Secondary: length of ICU stays; discharge body temperature; respiratory rate and SpO_2 at discharge, need for intubation
Furtado RHM, 2020 (COALITION II) [5]	N=397 (mITT)* ≥ 18 yrs old admitted to hospital with severe confirmed COVID-19 (<14 days since symptom onset	n=214 (mITT)* AZITHROMYCIN 500 mg daily (oral, NGT, IV) + SOC with HCQ 500 mg for 10 days	n=183 (mITT)* SOC including HCQ 400 mg for 10 days	Clinical Outcomes (Primary at Day 15, Secondary at Day 7): not admitted to hospital; admitted to hospital, not requiring supplemental oxygen, admitted to hospital requiring HFNC or NIPPV, admitted to hospital requiring ECMO or invasive mechanical ventilation Key secondary outcome: death at 29 days Other secondary outcomes: ventilation free days, duration of hospitalization among survivors and incidence secondary infection Safety Outcomes: Qtc prolongation, GI intolerance, laboratory changes in blood counts and bilirubin levels, acute kidney failure and overall SAE
RECOVERY Trial 2021	N=7764 Patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection admitted to the hospital About 80% of the patient received supplemental O2 (75%) and ventilation (6%) Age limit was removed	n= 2582 AZITHROMYCIN 500 mg daily (oral, NGT, IV) + std. of care Duration: for 10 days or until discharge	n= 5182 not specified was reported to evolve over time	Primary: 28-day mortality Secondary: time to being discharged alive; discharged from hospital within 28 days; Receipt of invasive mechanical ventilation or death, invasive mechanical ventilation or ECMO or both. Death Prespecified subsidiary clinical outcomes cause-specific mortality; use of hemodialysis or hemofiltration; major cardiac arrhythmia; receipt and duration of ventilation among those on invasive mechanical ventilation at randomization

Appendix 2: GRADE Evidence Profile

AZITHROMYCIN compared to Standard Care for COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Followup	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%) With Standard Care	Study event rates (%) With AZITHROMYCIN	Relative effect (95% CI)	Anticipated absolute effects Risk with Standard Care	Anticipated absolute effects Risk difference with AZITHROMYCIN
All-Cause Mortality Day 28, 29, 30											
8271 (3 RCTs)	serious [a,b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	1236/5419 (22.8%)	651/2852 (22.8%)	**RR 0.98** (0.90 to 1.06)	228 per 1,000	**5 fewer per 1,000** (from 23 fewer to 14 more)
Need for ECMO or Mechanical Ventilation or both (Day 28 & 29)											
7819 (2 RCTs) [1,2]	serious [a,b]	not serious	not serious	not serious	none	⨁⨁⨁◯ MODERATE	484/5119 (9.5%)	236/2700 (8.7%)	**RR 0.94** (0.81 to 1.07)	95 per 1,000	**6 fewer per 1,000** (from 18 fewer to 7 more)

Duration of Hospitalization Sekhavati 2020(Mean)

111 (1 RCT) [3]	serious [b,c]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	55	56	-	The mean duration of Hospitalization Sekhavati 2020(Mean) was **0**	mean **1.35 lower** (2.45 lower to 0.25 lower)

Duration of Hospitalization among survivors COALITION II Study 2020 (median)

397 (1 RCT) [2]	serious [a,b]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	183	214	-	The mean duration of Hospitalization among survivors COALITION II Study 2020 (median) was **0**	median **8 higher** (0.81 higher to 15.91 higher)

Clinical Progression (ICU admission)

111 (1 RCT)	serious [a,b]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	7/55 (12.7%)	2/56 (3.6%)	**RR 0.28** (0.06 to 1.29)	127 per 1,000	**92 fewer per 1,000** (from 120 fewer to 37 more)

Adverse Event

6984 (1 RCT) [1]	serious [a]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	224/4670 (4.8%)	101/2314 (4.4%)	**RR 0.91** (0.72 to 1.14)	48 per 1,000	**4 fewer per 1,000** (from 13 fewer to 7 more)

Serious Adverse Events

439 (1 RCT) [2]	serious [a,b]	not serious	not serious	not serious	none	⊕⊕⊕◯ MODERATE	75/198 (37.9%)	102/241 (42.3%)	**RR 1.12** (0.89 to 1.41)	379 per 1,000	**45 more per 1,000** (from 42 fewer to

											155 more)

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Some of the patients in the standard of care group received azithromycin or other macrolides that could bias the result
b. In some of the studies HCQ and/or lopinavir/ritonavir as part of the standard of care therapy
c. Unclear allocation bias

References

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Appendix 3: Forest Plot

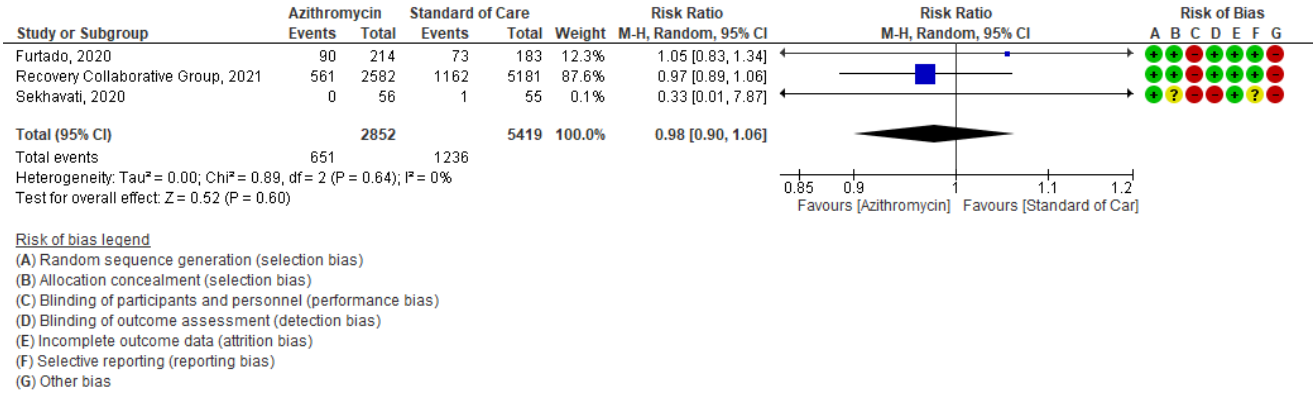

Figure 1: All-Cause Mortality at Day 28, 29, 30

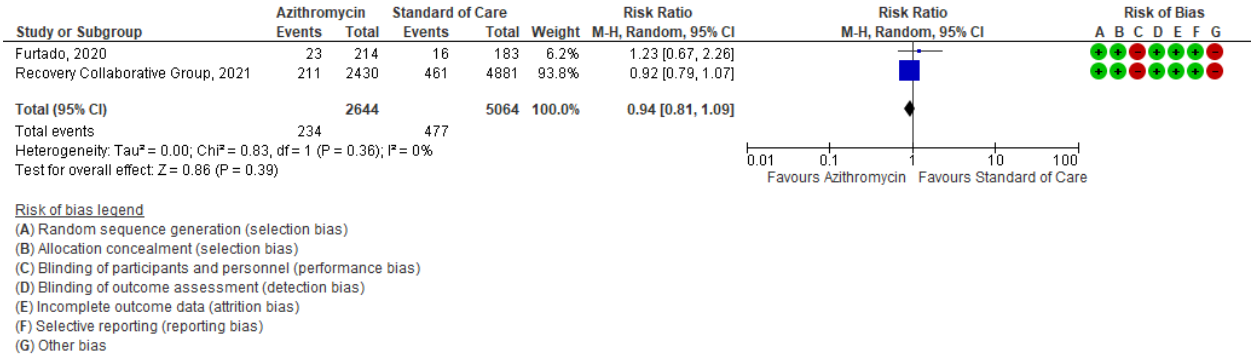

Figure 2: Need for ECMO or Mechanical Ventilation or both (Day 28 & 29)

Appendix 4: Characteristics of Ongoing Studies

Title/ Clinical Trial ID Number Completion Date	Population	Intervention Group(s)	Comparator	Outcomes
Azithromycin for COVID-19 Treatment in Outpatients Nationwide (ACTION) NCT04332107 [11] Completion date: December 30, 2021	Adult patients with a positive SARS-CoV-2 test and not hospitalized	Azithromycin 1.2g capsules (oral)	Placebo	Primary: symptoms Secondary: Viral load; all-cause Mortality; AE; + SARS-CoV-2 test (nasal, saliva. rectal swab); genetic macrolide resistance determinants; COVID-19 symptoms (cough, fever, myalgia, anosmia, shortness of breath, fatigue, conjunctivitis, and orthostatic symptoms; no. of emergency room visits; no. of household members with COVID-19 (confirmed or symptomatic); hospitalization
A Multicentre Open-label Two-arm Randomised Superiority Clinical Trial of Azithromycin Versus Usual Care In Ambulatory COVID19 (ATOMIC2) NCT04381962 [12] Completion date: October 13, 2020 (results not posted)	Adult patients with clinically-diagnosed COVID-19 but assessed as appropriate for initial ambulant (outpatient) management	Azithromycin 500 mg daily for 14 days + SOC	SOC	Primary: Progression to respiratory failure or death; Secondary: Progression to respiratory failure or death; all-cause mortality; progression to pneumonia and to severe pneumonia; peak severity of illness; safety and tolerability
Investigating the efficacy and safety of Azithromycin inhaled spray in controlling the symptoms of patients with COVID-19 IRCT20080901001165N50 [13] Completion date: not reported	Adult patients with clinical symptoms of COVID-19, confirmed diagnosis of COVID-19 (lung CT-scan or + RT-PCR test)and <7 days have passed since the onset of symptoms ●	Azithromycin inhaled spray 1 puff every 12 hours, for 7 days (In addition to routine treatment according to the latest national guideline	SOC according to the latest national guideline	Clinical symptoms changes (dry cough, respiratory distress, fever); Lab. tests changes; Side effects
PRINCIPLE: A trial evaluating treatments for suspected COVID-19 in people aged 50 years and above with pre-existing conditions and those aged 65 years and above ISRCTN86534580 [14] Completion date not reported	● Patients aged ≥50 yrs old with symptoms of possible COVID-19 that started within the last 14 days	Azithromycin capsules 500 mg for 3 days +SOC	SOC	Hospital admission; mortality; duration of severe symptoms; Time taken to self-report recovery; Oxygen use; ICU admission; mechanical ventilation; Negative effects on well-being measured using WHO-5 Well-Being Index