

Azithromycin reduced exacerbations and improved QoL in symptomatic asthma despite inhaled maintenance therapy

Gibson PG, Yang IA, Upham JW, et al. **Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial.** *Lancet.* 2017;390:659-68.

Clinical impact ratings: **GM** ★★★★★★ **HO** ★★★★★★ **PM** ★★★★★★

Question

In patients who have symptomatic asthma despite inhaled maintenance therapy, does azithromycin reduce exacerbations and improve quality of life (QoL)?

Methods

Design: Randomized placebo-controlled trial. Australian and New Zealand Clinical Trials Registry ACTRN12609000197235.

Allocation: Concealed.*

Blinding: Blinded* (patients, clinicians, investigators, and research staff).

Follow-up period: 52 weeks.

Setting: 8 clinical centers in Australia.

Patients: 420 adults ≥ 18 years of age (median age 60 y, 61% women) who had symptomatic asthma (Asthma Control Questionnaire [ACQ6] score ≥ 0.75) despite use of maintenance inhaled corticosteroids or long-acting bronchodilators, and remained stable (change in ACQ6 score < 0.5) after completion of a 2-week optimized asthma treatment run-in with > 80% adherence. Exclusion criteria included exacerbations, infections, or changes in maintenance medication in the past 4 weeks; current smoking; former smoking of > 10 pack-y and diffusing capacity for carbon monoxide < 70% predicted; hearing impairment; or abnormally prolonged QTc interval.

Intervention: Oral azithromycin, 500 mg 3 times/wk (*n* = 213), or placebo (*n* = 207), added to maintenance controller therapy for 48 weeks.

Outcomes: Severe and moderate asthma exacerbations and asthma QoL (Asthma Quality of Life Questionnaire [AQLQ]) at 48 weeks. Secondary outcomes included azithromycin-resistant pathogens in sputum, adverse events, and treatment discontinuation due to adverse events.

Patient follow-up: 80% (intention-to-treat analysis).

Main results

Azithromycin reduced severe and moderate exacerbations and improved asthma-related QoL (Table). The improvement in QoL from baseline reached the minimal important difference of 0.5 units in the symptoms domain but not the activity, emotions, or environment

domains. Azithromycin increased risk for diarrhea (Table) but not azithromycin-resistant pathogens in sputum (Table) (based on 81 patients), other treatment-related adverse events, serious adverse events, or treatment discontinuation due to adverse events.

Conclusion

In patients who have symptomatic asthma despite inhaled maintenance therapy, azithromycin reduced exacerbations and improved quality of life.

*See Glossary.

Sources of funding: National Health and Medical Research Council of Australia and John Hunter Hospital Charitable Trust.

For correspondence: Dr. P.G. Gibson, Hunter Medical Research Institute, New Lambton Heights, NSW, Australia. E-mail peter.gibson@hnehealth.nsw.gov.au. ■

Commentary

Azithromycin is known to reduce exacerbations in selected patients with chronic obstructive pulmonary disease (COPD) (1). The randomized controlled trial by Gibson and colleagues provides the first clear evidence that azithromycin confers similar benefits in asthma that is inadequately controlled with first-line therapies. The adjusted mean difference between groups in AQLQ score, while statistically significant, is smaller than the established minimal clinically important difference of 0.5 (2), suggesting that the average patient did not experience an important QoL benefit with azithromycin. The reduction in exacerbations is far more relevant, as exacerbations can be life-threatening and place an important burden on both patients and the health care system. Azithromycin also increased the risk for diarrhea, but this was rarely severe enough to result in study withdrawal and would be expected to resolve promptly with treatment cessation.

Although azithromycin was not observed to produce significant antimicrobial resistance, the trial was too small and too brief to assess this adequately. Because chronic bacterial airway infection is not a typical feature of asthma, potential antimicrobial resistance might be less consequential to patients with asthma than to patients with COPD or bronchiectasis, in whom azithromycin is already indicated. However, the established population risk for increasing antimicrobial resistance in the community with more widespread long-term azithromycin use (1) must also be considered.

Most patients in this trial received high-dose inhaled corticosteroids, and nearly all received a long-acting β -agonist. However, only a few received a long-acting muscarinic antagonist or a leukotriene modifier and none received a biologic. Any of these agents would be a valid alternative to adding azithromycin in this context. Head-to-head trials among these agents are needed.

Matthew B. Stanbrook, MD, PhD
Toronto Western Hospital, University
of Toronto
Toronto, Ontario, Canada

References

1. Parameswaran GI, Sethi S. Long-term macrolide therapy in chronic obstructive pulmonary disease. *CMAJ.* 2014;186:1148-52.
2. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol.* 1994;47:81-7.

Azithromycin vs placebo in adults who have symptomatic asthma despite inhaled maintenance therapy†

Outcomes	Events/person-y		RRR (95% CI)	NNT (CI)
	Azithromycin	Placebo		
Exacerbations (severe and moderate)	1.07	1.86	25% (10 to 38)	7 (5 to 17)
	Mean scores		Adjusted mean difference between groups (CI)	
Asthma-related quality of life (AQLQ)‡ at 48 wk	5.73	5.55	0.36 (0.21 to 0.52)	
	Event rates		RRI (CI)	NNH (CI)
Azithromycin-resistant pathogens in sputum§	49%	29%	71% (–3 to 206)	Not significant
Diarrhea	34%	19%	79% (28 to 152)	7 (5 to 16)

†AQLQ = Asthma Quality of Life Questionnaire; other abbreviations defined in Glossary. RRR, NNT, and CI calculated from data in article.

‡Score range 1 to 7, higher scores indicate better quality of life (score information obtained from www.thoracic.org/members/assemblies/assemblies/srn/questionnaires/aqlq.php). Positive between-group difference favors azithromycin.

§Assessed in 81 patients.

doi:10.7326/ACPJC-2017-167-8-042