

Azithromycin Efficacy in Adults with Severe Persistent Uncontrolled Asthma

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Practice Options from Beyond Our Pages focuses on identifying, critiquing, and placing into context research studies published in other journals that have the potential to change our clinical practices. It is written by Allergy-Immunology Fellows partnered with faculty members, and does not require an invitation for submission. This feature is coordinated by Editorial Board members Matthew Rank, MD and Julie Wang, MD.

REFERENCE

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

BACKGROUND

Severe asthma is a heterogeneous chronic disease associated with significant morbidity and mortality. Severe asthma accounts for 10% of all patients with asthma and affects approximately 2.5 million Americans.¹ Patients with severe asthma have poor quality of life (QOL), impaired lung function, and higher risk of acquiring respiratory infections. These patients by definition have increased need for medications and increased health care utilization, often requiring recurrent or chronic use of systemic corticosteroids due to frequent exacerbations.² These exacerbations contribute distinctly to the morbidity of severe asthma. Distinct molecular mechanisms can be identified among patients with asthma, and include those mediating type 2-helper T-cell-mediated (Th2) or eosinophilic inflammation, neutrophil-predominant non-Th2 inflammation, and noninflammatory phenotypes.³ Phenotypic characteristics and expression of certain biomarkers can help to distinguish among these phenotypes. These pathways are being targeted in severe asthma to apply personalized therapy to individual asthmatics. However, a significant proportion of patients with severe asthma do not benefit from, or show evidence of inflammatory pathways related to, the available targeted biologic therapies.

Severe asthma characterized by predominantly neutrophilic inflammation in the airways, as measured by sputum or

bronchoalveolar lavage, has been associated with chronic infection with atypical bacteria.⁴ Macrolide antibiotics exert antibacterial, antiviral, immunomodulatory, and anti-inflammatory effects and may benefit patients with pulmonary disorders including cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary diseases.⁵ The utility of macrolide therapy in asthma to prevent exacerbations and improve QOL has not been conclusively determined.^{6,7}

METHODS

Adults with objective evidence of severe persistent asthma that was uncontrolled despite being on medium-high dose inhaled corticosteroids (ICS) and long-acting beta-agonist bronchodilator (LABA) and who had no hearing impairment or prolonged corrected QT intervals were randomized (1:1) for 48 weeks to treatment with oral azithromycin (n = 213) or placebo (n = 207), after a 2-week run-in period wherein exacerbation and inflammation phenotypes (eosinophilic vs noneosinophilic) were assessed. Azithromycin dosing was 500 mg by mouth, 3 times per week in this randomized, double-blind, placebo-controlled trial (AMAZES trial). Follow-up in-office visits and telephone assessments were done at intervals. Pathogens and cellularity were examined in sputum before randomization and at the end of the study. For safety assessments, ECG and liver function tests were monitored. The primary efficacy endpoints were the number of moderate and severe asthma exacerbations over 48 weeks and asthma QOL as measured by the Asthma-Quality-of-Life Questionnaire score. Major secondary outcomes examined were asthma control reflected by the Asthma-Control Questionnaire (ACQ6) score, lung function, induced sputum cell counts, the number of antibiotic courses for respiratory tract infection (RTI), microbial assessments, and adverse events.

RESULTS

Study participants were 60 years old on average, carrying the diagnosis of asthma for a median of 32 years. A total of 86% of all participants were prescribed high-dose ICS and LABA as a maintenance therapy, and yet their asthma remained uncontrolled with significant airflow obstruction. The addition of azithromycin reduced significantly the total incidence of moderate and severe exacerbations in the treatment group (1.86 exacerbations per person-year, 95% confidence interval [CI] 1.54-2.18, vs 1.07 exacerbations per person-year, 95% CI 0.85-1.29), and it improved asthma-related QOL questionnaire. Time to asthma exacerbation was associated with a reduced hazard ratio in the

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azithromycin group (0.65, 95% CI 0.50-0.85); $P = .001$. The beneficial effects of azithromycin remained significant after adjusting for history of frequent exacerbations, differences in ICS dose, presence of chronic cough and sputum production and positive sputum cultures. Interestingly, azithromycin treatment resulted in decreased exacerbations compared with placebo in both eosinophilic and noneosinophilic asthma phenotypes (eosinophilic defined as $>3\%$ sputum eosinophils or if not available, >300 eosinophils per microliter of blood). Decreased upper airway symptoms, cough and sputum production along with fewer RTI requiring antibiotics and improvement in asthma control measured by ACQ6 were reported in the treatment group compared with the placebo group. In the azithromycin treatment group, the average number of sputum eosinophils ($\times 10^4$ per mL) at the end of treatment were less than seen in the placebo group (median 6.89 eosinophils in the azithromycin group vs 11.05 in the placebo group), whereas sputum neutrophil count did not change. Although azithromycin was well tolerated with no significant increase in overall rate and type of serious adverse events, compared to the placebo-treated group, diarrhea was significantly more common in the azithromycin treatment group. A nonsignificant increase in azithromycin-resistant bacteria was observed in the sputum of the azithromycin group compared with the placebo group. However, sputum cultures at the end of the study period showed similar rates of pathogenic organisms in both the treatment and placebo groups.

CRITICAL APPRAISAL

The unique properties that macrolides have as immunomodulatory, antibacterial, antiviral, and anti-inflammatory medications have led many investigators to assess their efficacy in different pulmonary diseases, including severe asthma.⁶⁻⁹ A previous study, azithromycin for prevention of exacerbations in severe asthma, enrolled a small cohort of severe asthmatics experiencing frequent asthma exacerbations and/or lower RTI, and observed on a predefined subgroup analysis a reduction in both asthma exacerbations and lower RTI in patients with noneosinophilic asthma (defined as blood eosinophilia 200/mL or less, exhaled nitric oxide lower than upper limit of normal) receiving azithromycin 250 mg 3 times a week for a 6-month period when compared with placebo.⁶ This primary outcome was however not observed in the eosinophilic subgroup treated with azithromycin.

AMAZES' strength lies in the enrollment of a larger cohort of adults with severe asthma failing high dose of ICS/LABA combination therapy, and in using a higher dosage of macrolides over a longer duration (12-month period) to better determine changes in the rate of exacerbations. With this protocol, azithromycin did not only reduce the frequency of asthma exacerbations in eosinophilic and noneosinophilic asthma when compared with placebo but also reduced the rate of RTI—an outcome that is not seen with the newer, targeted biologics/monoclonal antibodies. The relative effect on those patients with paucigranulocytic asthma, representing more than a third of the cohort, compared with those with neutrophilic inflammation, was not clearly presented in this paper. Very few participants in this study were using chronic systemic steroids, so the impact of azithromycin treatment on steroid reduction is not known. Importantly, the above-mentioned impacts of azithromycin on severe asthma may not apply to children, adolescents, and asthmatics with tobacco use.

Despite not reaching statistical significance, the AMAZES study did detect an increase in microbial resistance in the microbiome (a microbiome that is already altered in severe asthmatics) in the azithromycin-treated group, an observation that was reported in prior studies as well.⁶ The clinical significance of this increased resistance remains unclear.¹⁰

The mechanisms responsible for the clinical outcomes seen in AMAZES are not well understood. Macrolides are known to inhibit T-cell and basophil activation and can attenuate neutrophil activity.¹¹ They have been shown to reduce interleukin-5 gene expression and can shut off the mammalian target of the rapamycin pathway, leading to inhibition of eosinophil production, differentiation, and maturation—a mechanism that might explain the lower sputum eosinophil count detected in the azithromycin group at the end of the study. Macrolides decrease bacterial adhesion and increase innate epithelial bactericidal functions,¹² and have antichlamydial and mycoplasma activity, which may partially explain the lower frequency of RTI seen in the azithromycin-treated group and the benefit seen in the neutrophilic-predominant subgroup. However, positive IgG antibodies to atypical bacteria do not necessarily predict the therapeutic efficacy of azithromycin in asthma in prior studies.^{6,9}

Although the use of chronic macrolide antibiotics in severe asthma is not yet recommended by guidelines, the data from AMAZES suggest that the addition of azithromycin, 500 mg orally 3 times per week, to maintenance asthma medications for 1 year may reduce exacerbations and improve QOL for patients uncontrolled on medium- to high-dose combination therapy. This benefit is not limited to one inflammatory subtype of asthma. Furthermore, the therapy was reported to be relatively well tolerated.

From a practical prospective, we are still lacking a standardized regimen of macrolides for add-on therapy in severe uncontrolled asthma. Furthermore, the efficacy of macrolides will need to be determined for patients already using biologics whose asthma continues to be uncontrolled, as there may be synergistic effects for example with anti-interleukin 5 agents. Trials using inhaled macrolides or non-antimicrobial macrolides as an add-on therapy in severe asthma may be warranted to reduce side effects and potentially target different airway pathogens. Finally, the best implementation of macrolide therapy may require the development of biomarkers that will accurately target the subgroup of individuals who will derive the most benefit from this treatment.

RECOMMENDATION

Azithromycin as an add-on therapy administered 500 mg 3 times a week for 48 weeks may be useful in reducing exacerbations, lowering frequency of RTI, and improving QOL in adults with severe asthma regardless of their inflammatory phenotype. More and larger studies are needed to replicate macrolides' efficacy in asthma, understand its mechanisms, and examine safety profile when used chronically. The yet-to-be-examined clinical significance of induction of microbial resistance to macrolides would remain a legitimate concern.

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