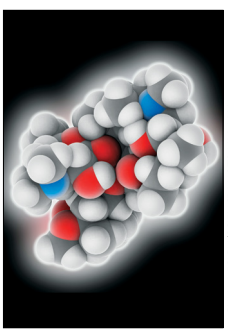
Azithromycin in uncontrolled asthma



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Asthma is a highly prevalent chronic airway disease affecting more than 300 million people worldwide. Despite treatment with inhaled corticosteroids and long-acting bronchodilators, asthma is uncontrolled in a substantial number of patients who remain symptomatic and are at risk of asthma exacerbations. These asthma attacks are often triggered by viral respiratory infections and might lead to emergency room visits, hospitalisations, and rarely, death; they result in a huge personal and societal burden.[1] Although targeted add-on therapy with monoclonal antibodies such as anti-IgE (omalizumab) and anti-IL5 (mepolizumab and reslizumab) has been shown to be efficacious in specific phenotypes of severe asthma,[2,3] the high costs preclude widespread use in many parts of the world. Therefore, affordable, effective, and safe add-on therapies in patients with poorly controlled asthma are needed. Previous studies have shown a beneficial effect of macrolide antibiotics such as azithromycin on asthma symptoms, but their effect on asthma exacerbations has been inconclusive due to a lack of large long-term trials.[4,5]

In *The Lancet*, Peter Gibson and colleagues[6] report the results of the AMAZES study, a large randomised, double-blind, placebo-controlled trial of azithromycin in adult patients with persistent uncontrolled asthma in Australia. 420 patients (median age 60 years [IQR 50–60], 40% males) with uncontrolled persistent asthma despite a maintenance treatment with medium-to-high dose inhaled corticosteroids plus a long-acting bronchodilator (long-acting beta-agonist [98%]; long-acting muscarinic antagonist [17%]) were randomly assigned to receive azithromycin 500 mg or placebo three times per week for 48 weeks. Patients with hearing impairment or a prolonged corrected QTc interval were excluded to minimise the risk of ototoxicity and cardiac arrhythmia.[7] The combined co-primary endpoints were the rate of total (moderate and severe) asthma exacerbations and asthma-specific quality of life. Azithromycin significantly reduced the rate of total asthma exacerbations compared with placebo (1·07 exacerbations per patient-year *vs* 1·86 exacerbations per patient-year; incidence rate ratio [IRR] 0·59 [95% CI 0·47–0·74]) as well as the rate of severe exacerbations (requiring treatment with systemic corticosteroids or hospitalisation; 0·61 per patient-year *vs* 1·07 per patient-year; IRR 0·59 [95% CI 0·42–0·83]). Azithromycin improved asthma-related quality of life across all domains of the Asthma-specific Quality of Life Questionnaire (AQLQ; symptoms, emotions, and environment domains). Additionally, azithromycin use was associated with improved asthma control (assessed by Asthma Control Questionnaire 6), reduced the number of patients reporting a respiratory tract infection, and lowered the rate of antibiotic courses for respiratory indications. Importantly, azithromycin was generally safe and well tolerated, though diarrhoea was more frequent in users of azithromycin than placebo (34% *vs* 19%). Finally, there was a non-significant increase in azithromycin-resistant bacteria in surveillance sputum cultures of patients treated with azithromycin.

This landmark study has many strengths. First, the large number of patients and the long duration of treatment provided sufficient power to unequivocally show that add-on therapy with azithromycin in adult patients with uncontrolled asthma reduced exacerbation rates and improved quality of life in this study. Second, since asthma is a heterogeneous disease, it is of benefit that all study patients were well phenotyped, including assessment of the asthma inflammatory phenotypes using induced sputum, the gold standard. Unexpectedly, azithromycin reduced exacerbations in both eosinophilic asthma and non-eosinophilic asthma. By contrast, in the AZISAST study, azithromycin decreased the exacerbation rate in patients with non-eosinophilic but not eosinophilic asthma.[8] However, there are many differences between the AMAZES study and the AZISAST study (eg, patient selection, dosing of azithromycin, and duration of treatment) that might explain the discordant results regarding the effects of azithromycin in the eosinophilic asthma phenotype.

What are the next steps? Since microbial resistance is a well known side-effect of antibiotic use, add-on therapy with azithromycin in asthma needs to be restricted to those patients with the highest unmet medical need (eg, frequent exacerbators) and to time periods with the greatest risk of exacerbations (ie, winter). Biomarkers that predict the therapeutic response to macrolides might facilitate optimal patient selection. Further research is needed to elucidate the most important mechanism of action of these pleiotropic

drugs. Macrolides have anti-inflammatory, antibacterial, and antiviral effects.[9,10] However, the authors did not observe a reduction in inflammatory cell counts in sputum to support a definite anti-inflammatory effect. Azithromycin was also effective in patients with and without potentially pathogenic microorganisms in sputum cultures at baseline. Since azithromycin reduced both asthma exacerbations and respiratory infections, the benefits of azithromycin might be due to preventing viral-induced attacks in asthma.[11] Azithromycin stimulates phagocytosis of microbes and dead cells by macrophages (ie, efferocytosis), an effect that is likely to be independent of the nature of the accompanying—neutrophilic or eosinophilic—airway inflammation.[12]

Gibson and colleagues have clearly shown that add-on therapy with azithromycin is effective and safe in adult patients with uncontrolled asthma despite treatment with inhaled corticosteroids and long-acting beta agonists. Azithromycin benefited patients with both eosinophilic and non-eosinophilic asthma. However, the effects of long-term therapy with macrolides on community microbial resistance remain a public health concern. Future studies with potentially safer non-antibiotic macrolides in uncontrolled severe asthma are warranted. Since the antimicrobial effects probably contribute to the overall efficacy of macrolides, the beneficial effects of non-antibiotic macrolides might be intermediate between macrolide antibiotics and placebo.

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GB has within the last 5 years received honoraria for lectures or advisory boards from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi, Teva, and Zambon. IP has within the last 5 years received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Boehringer Inglehiem, Aerocrine, Almirall, Novartis, Teva, and GlaxoSmithKline, and a payment for organising an educational event from AstraZeneca. IP has received honoraria for attending advisory panels with Almirall, Genentech, Regeneron, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp Dohme, Schering-Plough, Novartis, Dey, Napp, Teva, Merck, and Respivert, and he has received sponsorship to attend international scientific meetings from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, Teva, and Napp.

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