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Amazing efficacy of azithromycin in uncontrolled asthma: the AMAZES study

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COI statement:

G.B. has, within the last 5 years, received honoraria for lectures and/or advisory boards from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi, Teva and Zambon.

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Asthma is a highly prevalent chronic airway disease affecting more than 300 million subjects worldwide. Despite treatment with inhaled corticosteroids (ICS) 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 may lead to emergency room visits, hospitalizations and rarely death; they result in a huge personal and societal burden. Although targeted add-on therapy with monoclonal antibodies such as anti-IgE (omalizumab) and anti-IL5 (mepolizumab, reslizumab) have been shown to be efficacious in specific phenotypes of severe asthma, the high costs preclude widespread use in many parts of the globe. Therefore, there is a need for affordable, effective and safe add-on therapies in patients with poorly controlled asthma. Previous studies have demonstrated a beneficial effect of macrolide antibiotics such as azithromycin on asthma symptoms, but their effect on asthma exacerbations has been inconclusive due to lack of large long-term trials [1, 2].

In this issue of the Lancet, Peter Gibson *et al.* 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 [3]. 420 patients (60 years old; 40% males) with uncontrolled persistent asthma despite a maintenance treatment with medium-to-high dose ICS plus a long-acting bronchodilator (long acting beta2-agonist [98%]; long acting muscarinic antagonist [17%]) were randomised to receive azithromycin 500mg or placebo three times per week for 48 weeks. Patients with hearing impairment or a prolonged corrected QT interval were excluded in order to minimize the risk of ototoxicity and cardiac arrhythmia [4]. 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/patient-year *versus* 1.86/patient-year; incidence rate ratio [IRR] 0.59) as well as the rate of severe exacerbations (requiring treatment with systemic corticosteroids or hospitalization; 0.61/patient-year *versus* 1.07/patient-year; IRR 0.59). Azithromycin improved asthma-related quality of life across all domains of the Asthma-specific Quality of Life Questionnaire (AQLQ; symptoms, emotions and environment domains). In addition, azithromycin use was associated with improved asthma control (ACQ6), reduced the number of patients reporting a respiratory tract infection and decreased the rate of antibiotic courses for respiratory indications. Importantly, azithromycin was safe and well tolerated since there was no significant difference between azithromycin and placebo groups in the rate and type of serious adverse events, drug-related adverse events or study withdrawals due to adverse events. Diarrhoea was more frequent in users of azithromycin than placebo. Finally, there was a trend towards an increase in azithromycin resistant bacteria in surveillance sputum cultures of patients treated with azithromycin.

This landmark study has many assets. First, the large number of patients and the long duration of treatment provided sufficient power to unequivocally demonstrate that add-on therapy with azithromycin in adult patients with uncontrolled asthma reduces exacerbation rates and improves quality of life. Secondly, since asthma is a heterogeneous disease, all 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. In contrast, in the AZISAST study, azithromycin decreased the exacerbation rate in patients with non-eosinophilic but not eosinophilic asthma [5]. However, there are many differences between the AMAZES study and the AZISAST study which might explain the

discordant results regarding the effects of azithromycin in the eosinophilic asthma phenotype (see table).

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 (e.g. frequent exacerbators) and to time periods with the greatest risk of exacerbations (i.e. winter). Biomarkers which 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 [6, 7]. 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 [8]. Lastly, azithromycin stimulates phagocytosis of microbes and dead cells by macrophages (i.e. efferocytosis), an effect that is likely to be independent of the nature of the accompanying – neutrophilic or eosinophilic - airway inflammation [9].

In summary, in the large AMAZES study, Gibson and colleagues have clearly demonstrated that add-on therapy with azithromycin is effective and safe in adult patients with uncontrolled asthma despite treatment with ICS and LABA. Amazingly, azithromycin benefited both eosinophilic and non-eosinophilic asthma patients. Although not formally assessed, the treatment is likely to be cost effective, particularly when compared to expensive biological agents. Should it therefore be a pre-biological treatment option? This is more difficult question as the effects of long-term therapy with macrolides on community microbial resistance remain a public health concern. We believe that studies with potentially safer non-antibiotic macrolides in uncontrolled and/or severe asthma are warranted. It may be that these show that the antimicrobial (antibacterial and antiviral) effects contribute to the overall efficacy of macrolides in which case a committed search for treatment response biomarkers and effective targeting of treatment would be an important priority before widespread use of this treatment can be recommended.

Table: Comparison of AMAZES trial and AZISAST trial (References 3 and 5).

	AMAZES trial	AZISAST trial
I) Characteristics of trial and study drug		
Maintenance dosing of azithromycin	500mg three times per week	250mg three times per week
Duration of treatment phase	48 weeks	26 weeks
Total number of patients randomized	420	109
II) Characteristics of patients		
Age at enrolment - yr	60	53
Male sex (%)	40%	38,5%
Exacerbations in the previous year*	1	≥2
Frequent exacerbators** (%)	33%	88%
Ex-smokers: number (%)	161 (38%)	
ACQ score	1.55	1.55
FEV ₁ prebronchodilator (% predicted)	73%	82%
FeNO	Not available	FeNO < ULN
Asthma inflammatory phenotypes:	Induced sputum:	Blood:
Eosinophilic asthma	≥3% eosinophils	>200 eosinophils
Non-eosinophilic asthma	<3% eosinophils	≤200 eosinophils
III) Primary efficacy outcomes		
Moderate and severe asthma exacerbations	IRR: 0.59 (AZI: 1.07 versus PLAC: 1.86)	Not available
Severe asthma exacerbations	IRR: 0.59 (AZI: 0.61 versus PLAC: 1.07)	IRR: 1.05 (AZI: 0.55 versus PLAC: 0.52)
Severe asthma exacerbations and lower respiratory tract infections	Not available	IRR: 0.89 (AZI: 0.72 versus PLAC: 0.81)
Primary endpoint in non-eosinophilic asthma	Moderate and severe asthma exacerbations: IRR: 0.66 (AZI: 1.15 versus PLAC: 1.74)	Severe asthma exacerbations: IRR: 0.43 (AZI: 0.44 versus PLAC: 1.03)
Primary endpoint in eosinophilic asthma	Moderate and severe asthma exacerbations: IRR: 0.52 (AZI: 0.96 versus PLAC: 1.98)	Severe asthma exacerbations: IRR: 2.16 (AZI: 0.82 versus PLAC: 0.38)

AZI: azithromycin

FeNO: Fractional excretion of Nitric Oxide

IRR: incidence rate ratio

PLAC: placebo

ULN: upper limit of normal

*Exacerbations treated with oral corticosteroid courses

**Frequent exacerbators: patients with a history of ≥ 2 severe exacerbations in the previous year

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