A randomised, double-blind, placebo-controlled study to evaluate the efficacy of oral azithromycin as a supplement to standard care for adult patients with acute exacerbations of asthma (the AZALEA trial)

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Scientific summary

The AZALEA trial

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Scientific summary

Background

Asthma is the most prevalent respiratory disease. Major asthma morbidity and mortality result from acute exacerbations: 5–10% of asthmatics have been hospitalised with an exacerbation and more than half of asthma patients reported having an exacerbation in the last year, with more than one-third of children and more than one-quarter of adults requiring urgent medical care visits as a result.

Respiratory viral infections are the major cause of asthma exacerbations in children (80–85%) and adults (75–80%). However, non-viral respiratory pathogens such as *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* have also been associated with wheezing episodes and asthma exacerbations in both adults and children.

There is little published evidence that standard bacterial infections are important in the aetiology of asthma exacerbations; however, patients with asthma have an increased susceptibility to respiratory bacterial infections, increased carriage of pathogenic respiratory bacteria identified by culture and molecular techniques and impaired interferon responses to bacterial polysaccharides. There is good evidence that bacterial respiratory infections are both more common and more severe in asthma.

A recent study of 361 children reported that acute wheezing episodes were associated with both bacterial infection [odds ratio 2.9, 95% confidence interval (CI) 1.9 to 4.3; $p < 0.001$] and viral infection (odds ratio 2.8, 95% CI 1.7 to 4.4; $p < 0.01$). We therefore hypothesised that standard bacterial infections are also likely to be important in the aetiology of asthma exacerbations in adults.

Current asthma guidelines recommend specifically that antibiotic therapy should *not* be administered routinely in asthma exacerbations. Adults with acute exacerbations of asthma and treated with telithromycin (a ketolide antibiotic closely related to macrolides, with both classes being highly active against *M. pneumoniae* and *C. pneumoniae*) as a supplement to standard care showed a significantly greater reduction in asthma symptoms ($p < 0.005$), greater improvement in lung function ($p = 0.001$) and faster recovery ($p = 0.03$) than those treated with placebo. This treatment, therefore, had a clear therapeutic effect; however, this study requires confirmation in a second similar study before revision of guidelines can be considered. Ideally, confirmation would be with a further study with telithromycin; however, issues with toxicity have limited the use of telithromycin to severe life-threatening infections.

The macrolide antibiotic azithromycin is an alternative that has been used for many years in the treatment of respiratory disease but which has thus far not been studied in acute exacerbations of asthma. We therefore hypothesised that treatment with azithromycin might be of benefit in the treatment of acute asthma exacerbations. The AZALEA (AZithromycin Against pLacebo for acute Exacerbations of Asthma) study therefore investigated the effectiveness of azithromycin added to standard care for adult patients with acute exacerbations of asthma.

A further mechanistic aim of our study was to investigate the frequencies of standard bacterial, atypical bacterial and viral infections in these exacerbations to determine the relative importance of each of these infections and to perform subgroup analyses to determine whether or not any treatment benefit observed is greater in those with evidence of one or more of these infections, with the aim of shedding some light on the possible mechanism(s) of action of azithromycin.

Different patterns of airway inflammation have been identified in asthma exacerbations – these have been classified as neutrophilic, eosinophilic, mixed granulocytic or pauci-granulocytic. However, it is not known whether or not these different patterns of inflammation are associated with different aetiologies of exacerbation, nor whether or not they are related to treatment outcome. We therefore finally aimed to characterise the inflammatory cell profiles in sputum at presentation, to determine whether or not exacerbation aetiology as well as any possible treatment benefit are related to the types of airway inflammation present.

Objectives

Primary objective

The primary objective was to assess treatment efficacy using a diary card summary symptom score, with symptoms including wheezing, breathlessness and coughing, at 10 days after randomisation.

Secondary objectives

The secondary objectives of the study were to evaluate:

- the following additional efficacy end points assessed at baseline and 5 and 10 days post randomisation:
  - health status assessed by the Acute Asthma Quality of Life Questionnaire (Acute AQLQ)
  - health status assessed by the Mini AQLQ
  - pulmonary function tests [forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1 : FVC ratio, peak expiratory flow (PEF), forced mid-expiratory flow rate ($FEF_{25–75\%}$) and forced expiratory flow rate at 50% expiration ($FEF_{50\%}$)].
- primary and secondary outcomes assessed 5 and 10 days post randomisation to permit better estimation of the optimum timing of assessment of primary/secondary outcome variables in future similar studies
- time to a 50% reduction in symptom score.

Exploratory analyses

- Assessment of efficacy outcomes in relation to initial standard bacteriological (*C. pneumoniae* and/or *M. pneumoniae*) and virological status.
- Assessment of efficacy outcomes in relation to initial sputum inflammatory cell status.

Methods

Trial design

This was a multicentre, randomised, double-blind, placebo-controlled study. Eligible patients were randomised within 48 hours of initial presentation to medical care with an acute deterioration in asthma control and requiring a course of oral steroids. Patients were randomised to receive either (1) azithromycin or (2) placebo for 3 days, with post-therapy assessments at 5 and 10 days and a follow-up visit at 6 weeks.

Participants

Adult patients with a documented history of asthma for > 6 months and presenting within 48 hours (of initial presentation to medical care) with an acute deterioration in asthma control and requiring a course of oral steroids.

Main inclusion criteria

- Adults of either sex aged 18–55 years or aged 56–65 years with a < 20 pack-year smoking history or aged > 65 years with a < 5 pack-year smoking history.
- Patients with a documented history of asthma for > 6 months and presenting within 48 hours (of initial presentation to medical care) with an acute deterioration in asthma control (increased wheeze, dyspnoea and/or cough and/or reduced PEF) and requiring a course of oral steroids.
- Patients with a PEF or FEV_1 of < 80% of predicted normal or patient's best at presentation, at recruitment or in the time elapsed between presentation and recruitment.

Main exclusion criteria

- Patients with known prolongation of the QT interval, with a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure or on drugs known to prolong the QT interval.
- Smokers aged 56–65 years with a ≥ 20 pack-year history or aged > 65 years with a ≥ 5 pack-year history.
- Patients requiring immediate transfer or referral to an intensive care unit.
- Patients who took oral or systemic antibiotics within 28 days prior to enrolment.
- Patients with known impaired hepatic function (alanine aminotransferase/aspartate aminotransferase) more than two times the upper limit of normal.
- Patients with significant lung disease (including chronic obstructive pulmonary disease) other than asthma.
- Patients on > 20 mg of oral corticosteroid maintenance therapy.
- Patients receiving other medications or who have other disease conditions or infections that could interfere with the evaluation of drug efficacy or safety.
- Women who are breastfeeding or pregnant women.
- Patients with suspected or known hypersensitivity to, or a suspected serious adverse reaction to, azithromycin or any of the macrolide or ketolide class of antibiotics, erythromycin or any excipients thereof.
- Patients who have received treatment with any other investigational drug within 1 month prior to study entry or who have such treatment planned for the study period during the treatment or follow-up phase.
- Patients with a concomitant condition making implementation of the protocol or interpretation of the study results difficult.
- Patients with mental conditions rendering them unable to understand the nature, scope and possible consequences of the study.
- Patients unlikely to comply with the protocol.
- No patient was allowed to enrol in this study more than once.

Interventions

All patients in the study received treatment with either azithromycin or placebo, as per randomised allocation. The identity of the treatment regimen was blinded by encapsulating active medication in opaque capsules to match the placebo.

Those randomised to azithromycin received 500 mg of azithromycin (two 250-mg capsules) once a day for 3 days. Patients randomised to placebo received two placebo capsules once a day for 3 days. Patients were instructed to take the study medication at least 1 hour before or 2 hours after food or antacids.

The time of administration of the study medication was documented on the electronic case report form for patients throughout the study. The first dose was given in the presence of a member of the research team.

Outcomes

Primary outcome

The primary outcome was a diary card summary symptom score, with symptoms including wheezing, breathlessness and coughing, assessed at 10 days after randomisation.

Secondary outcomes

- Additional efficacy end points assessed at baseline and 5 and 10 days post randomisation were:
  - health status assessed by Acute AQLQ
  - health status assessed by Mini AQLQ
  - pulmonary function tests (FEV_1, FVC, FEV_1 : FVC ratio, PEF, $FEF_{25–75\%}$, $FEF_{50\%}$).
- Primary and secondary outcomes assessed 5 and 10 days post randomisation to permit better estimation of the optimum timing of the assessment of primary/secondary outcome variables in future similar studies (the efficacy of telithromycin was assessed at 10 days only).
- Time to a 50% reduction in symptom score.

Exploratory analyses

- Trends in primary and secondary outcomes over the time course of the exacerbation up to 10 days.
- Assessment of efficacy outcomes in relation to initial *C. pneumoniae* and/or *M. pneumoniae* status.
- Assessment of efficacy outcomes in relation to initial standard bacteriological status.
- Assessment of efficacy outcomes in relation to initial virological status.
- Assessment of efficacy outcomes in relation to initial sputum inflammatory cell status.

Sample size and statistical analysis

The sample size calculations were based on the primary outcome: change in diary card summary symptom score from baseline to 10 days after randomisation. Our previous study [the Telithromycin, *Chlamydophila*, and Asthma trial (TELICAST)] found a mean decrease in symptom score of 1.3 in the treatment group and 1.0 in the control group, a difference of –0.3 [standard deviation (SD) 0.783] between the groups at 10 days. Using a two-sided *t*-test at a 1% significance level with 80% power, 161 patients in each group were required to detect the same difference in asthma scores between the groups. A significance level of 1% in the above calculation was chosen to provide greater certainty in the assessment of the primary outcome variable, as well as to provide greater power for the subgroup exploratory analyses, as those subgroup analyses that were performed were uninformative in the 280-patient TELICAST study.

Taking into account a dropout rate of 15% in the study, we aimed to recruit 190 patients in each arm of the study.

The clinical efficacy analyses were carried out on an intention-to-treat basis. Outcomes that were recorded at multiple time points (diary card symptom scores, quality-of-life questionnaires and pulmonary function tests) were analysed using a three-level hierarchical model to take account of the structure in the data.

Results

Recruitment was from 31 sites, the majority ($n = 30$) of which were secondary care hospitals, with one primary care centre. Recruitment lasted for 2.5 years, from September 2011 to April 2014. A total of 4582 patients were screened, of whom 390 met the eligibility criteria; of these, 199 were randomised to treatment, 193 (97%) from the secondary care hospitals and six (3%) from the primary care centre. The major reasons for non-recruitment were already receiving antibiotics ($n = 2044$; 44.6% of screened

patients), discharged/unable to contact ($n = 315$; 6.9%), declined participation ($n = 191$; 4.2%) and other (e.g. underlying health condition, on steroids; $n = 1833$; 40.0%).

The mean age of study participants was 39.9 years and 69.8% of participants were female ($n = 139$). Underlying asthma severity was classified by treatment before exacerbation: mild intermittent asthma [10.1% ($n = 20$)], regular preventer therapy [28.3% ($n = 56$)], initial add-on therapy [29.3% ($n = 58$)], persistent poor control [22.2% ($n = 44$)] and continuous or frequent use of oral steroids [10.1% ($n = 20$)]. The smoking status of participants was as follows: never smoked 61.1% ($n = 121$), former smoker 22.7% ($n = 45$) and current smoker 16.2% ($n = 32$) (mean pack-years 3.45). Exacerbation severity was categorised as near-fatal asthma [0.5% ($n = 1$)], life-threatening asthma [5.6% ($n = 11$)], acute severe asthma exacerbation [59.1% ($n = 117$)], moderate asthma exacerbation [30.8% ($n = 61$)] and mild asthma exacerbation [4.0% ($n = 8$)]. The median time from presentation to trial drug administration was 22 hours. Lung function at baseline (exacerbation) included PEF 69.4% predicted, FEV_1 64.8% predicted and FEV_1 : FVC ratio 69.2%. Baseline characteristics were well balanced across treatment arms and centres.

Mean (SD) scores for the primary outcome of asthma symptom score [from 0 (no symptoms) to 6 (severe symptoms)] were 4.14 (1.38) at baseline and 2.09 (1.71) at the end of treatment for the azithromycin group and 4.18 (1.48) at baseline and 2.20 (1.51) at the end of treatment for the placebo group. Using multilevel modelling for the primary outcome, there was no statistically significant difference in symptom score between the groups at day 10 (difference –0.166, 95% CI –0.670 to 0.337). Similarly, no significant between-group differences were seen in symptom scores on any other day between baseline and day 10.

No significant between-group differences were seen in the Acute AQLQ and Mini AQLQ or in any measure of lung function on any day between baseline and day 10, and there was no difference in the time to a 50% reduction in symptom score.

Only 105 (52.8%) patients provided sputum samples for sputum bacterial culture and/or sputum cell counts, whereas 191 (96.0%) patients provided nasal/throat swabs for virus/atypical pathogen polymerase chain reaction (PCR) analysis and 183 (92.0%) patients provided acute (immunoglobulin M) or acute and convalescent (immunoglobulin G, immunoglobulin A) sera for atypical pathogen serology.

Sputum bacterial culture was positive in 6% of subjects (4.1% active group, 7.8% placebo group), nasal/throat swabs and/or sputum atypical pathogen PCR analysis and/or atypical pathogen serology were positive in 4.5% of patients (5.2% active group, 3.9% placebo group) and nasal/throat swabs and/or sputum virus PCR analysis were positive in 18.1% of patients (16.5% active group, 19.6% placebo group). There were no differences in the primary outcome of asthma symptom score between the active group and the placebo group in patients with a positive sputum bacterial culture or atypical bacterial PCR or serology (including any bacterial or viral PCR positive tests), although patient numbers for these analyses were low. No subgroup analyses, defined on sputum cell count characteristics, were performed as the numbers per group were too low to be meaningful.

Conclusions

In the population of patients randomised to treatment, the addition of azithromycin to standard medical care resulted in no demonstration of a statistically significant or clinically important benefit but, as the 95% CIs for the primary outcome include a difference as great as –0.3, we were unable to provide strong evidence to rule out the possibility of significant clinical benefit. For each patient randomised, approximately 10 were excluded because they had already received antibiotic therapy, despite guideline recommendations that such therapy should not be routinely used. The study may, therefore, have been underpowered to detect a therapeutic benefit in the minority of patients randomised to treatment.

Trial registration

This trial is registered as ClinicalTrials.gov NCT01444469 and EudraCT 2011–001093–26.

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