SHORT COMMUNICATION

Effects of long-term low-dose azithromycin in patients with non-CF bronchiectasis

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Summary
We describe our institutional efficacy experience of azithromycin 250 mg thrice weekly in adult non-cystic fibrosis bronchiectasis.

Methods: Eligibility criteria for prophylactic azithromycin included 3 exacerbations requiring rescue antibiotics over the previous 6 months. The clinical records of 56 bronchiectasis patients on azithromycin were retrospectively reviewed. Exacerbation frequency, sputum microbiology, self-reported change in sputum volume, and spirometry results were recorded.

Results: Mean length of treatment was 9.1 months (7.5) and 50 patients had treatment ≥3 months. Spirometry, pre- and post-azithromycin in 29 patients, who had 3 or more months of treatment, showed a mean increase in FEV1 of 83 ml (0.14) (P = 0.005) from 1.560 to 1.643 l. There was a decrease in the exacerbation frequency from 0.81/month (SD) (0.32) pre-azithromycin to 0.41/month (0.45) (P < 0.001) post-azithromycin. Clinically significant suppression of previous sputum microbial isolates was also observed.

Conclusion: Azithromycin improves exacerbation frequency, spirometry, and sputum microbiology in bronchiectasis.

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Bronchiectasis is a disease characterised by recurrent bronchial sepsis and exerts considerable morbidity in many of those affected.1 In the majority of patients treatment is largely confined to “rescue” antibiotics for exacerbations. Whilst critical to abrogating individual infections, this approach has limited effect on chronic symptoms, exacerbation frequency and possibly disease progression.
Antibiotic prophylaxis, therefore, remains an appealing strategy in bronchiectasis but previous studies employing aminopenicillins and tetracyclines did not reduce exacerbation frequency. However, the proven efficacy of prophylactic macrolide antibiotics in other chronic suppurative conditions, such as diffuse pan-bronchiolitis and cystic fibrosis, has led to the frequent ad hoc usage of macrolides in bronchiectasis with apparent successes in individual patients. To date, however, there is only a small body of published evidence to support this strategy.

Tsang et al., in an 8-week placebo-controlled study in 21 patients with idiopathic bronchiectasis, found that low-dose erythromycin significantly improved lung function and reduced sputum volume. An anecdotal report in 33 bronchiectasis patients completing ≥4 months of azithromycin therapy suggested a significant reduction in infective exacerbations and improvement in symptoms. There was also a significant improvement in carbon monoxide gas transfer but only a positive trend in spirometric values. The only randomised study employing azithromycin, to date, involved only 11 patients and utilised an open-label, unblinded, 6-month active treatment phase (azithromycin 500 mg twice weekly), and crossover design without placebo. The exacerbation frequency of the patients prior to the study was unstated and the majority of patients received azithromycin in the first 6 months. In the treatment phase there was a significant reduction in exacerbations and sputum volume but there was no change witnessed in forced expiratory volume in 1 s (FEV1) or forced expiratory capacity (FVC).

We, therefore, wished to interrogate the efficacy of long-term azithromycin 250 mg thrice weekly as prophylactic therapy in patients attending our institutional bronchiectasis clinic from December 2003 to January 2007. The dose and frequency of azithromycin we employ were extrapolated from the cystic fibrosis and lung transplantation literature. Bronchiectasis was confirmed in all patients by standard high resolution CT scan criteria. Patients considered eligible for long-term low-dose azithromycin were those who, despite optimization of standard care, experienced ≥3 infective exacerbations in the previous 6 months. An exacerbation was defined as the presence of 3 or more of the following symptoms for ≥24 h: increasing cough; increasing breathlessness and/or wheezing; increase in sputum volume and/or change in sputum colour; pleuritic chest pain; haemoptysis and/or fever. Exclusion criteria included macrolide allergy and deranged liver function tests.

In patients on ≥3 months therapy, the following were compared:

1. The number of infective exacerbations 6 months prior to, and whilst on, treatment (averaged to a monthly rate).
2. FEV1 and FVC within 6 months of starting treatment and most recent on treatment where available. Results obtained during acute exacerbations were disregarded.
3. Sputum culture results 12 months prior to, and whilst on, treatment (chronic colonization defined as ≥3 positive cultures of the same organism at intervals ≥6 weeks).

Patients who had had a change in other bronchiectasis treatments within 3 months of commencing azithromycin (n = 6) were not included in the exacerbation or lung function analysis. The data was analysed by paired t-test and non-parametric Wilcoxon test.

Fifty-six Caucasian patients (18 male/38 female), mean age 63 ± 12.9 years, were assessed and 22 (39%) had idiopathic disease and 34 (61%) had disease of known cause: post-infectious (n = 10); COPD (n = 10); traction (n = 4); rheumatoid arthritis (n = 3); chronic asthma (n = 3); allergic bronchopulmonary aspergillosis (n = 2); hypogammaglobulinemia (n = 1); aspiration (n = 1).

The mean duration of treatment was 9.1 months (±7.5) with 50 (89%) patients completing ≥3 months therapy. Six (11%) patients discontinued treatment due to abdominal cramps (n = 2), skin rash (n = 2) and diarrhoea (n = 3). The effects of azithromycin on exacerbation frequency, FEV1, sputum microbiology and volume are shown in Table 1. Only 29 (58%) patients were assessable for lung function analysis due to the stringent criteria outlined previously.

There was a significant reduction in exacerbation frequency (P < 0.001) and the number of positive sputum cultures (P < 0.005) whilst using long-term low-dose azithromycin. There was a significant improvement in actual and % predicted FEV1 (1.560 vs 1.643 l, P = 0.005; 57.3% vs 60.8%, P = 0.002). There was a non-significant improvement in actual and % predicted FVC (2.511 vs 2.60 l, P = 0.132; 74% vs 77%, P = 0.108). FEV1/FVC ratio was unchanged (0.60 vs 0.61, P = 0.430).

All 50 patients were producing at least 1 tablespoon (≥15 ml) of sputum daily prior to commencing azithromycin and following treatment 18 patients (36%) became unproductive.

Our experience supports the previous observations of Davies et al. that long-term azithromycin appears to reduce infective exacerbations in bronchiectasis and supresses airway pathogens, including Pseudomonas...

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Pre-AZ</th>
<th>Post-AZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbation frequency (SD) per month (n = 44)</td>
<td>0.81 (0.32)</td>
<td>0.41* (0.45)</td>
</tr>
<tr>
<td>FEV1 – litres (n = 29)</td>
<td>1.560</td>
<td>1.643*</td>
</tr>
<tr>
<td>% predicted FEV1 (n = 29)</td>
<td>57.3%</td>
<td>60.8%^</td>
</tr>
<tr>
<td>Sputum microbiology (n = 50; C = colonized)</td>
<td>No. of positive sputum cultures</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Haemophilus influenzae</td>
<td>20 (4C)</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas aeruginosa</td>
<td>16 (9C)</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pneumoniae</td>
<td>10 (2C)</td>
</tr>
<tr>
<td></td>
<td>Moraxella catarrhais</td>
<td>10 (0C)</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
<td>2 (2C)</td>
</tr>
<tr>
<td>Sputum volume daily (n = 50) All ≥15 ml</td>
<td>18 (36%) unproductive</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.001; ^P = 0.005; **P = 0.002; ***P < 0.005; C = chronic colonization, defined as ≥3 positive cultures of the same organism at intervals ≥6 weeks.
aeruginosa (Pa). The mechanism of action of azithromycin is not fully elucidated but previous studies suggest potential immunomodulatory, as opposed to anti-microbial effects. Bronchiectatic airways are characterised by neutrophilic inflammation and high levels of the pro-inflammatory cytokines IL1, IL8 and TNF-α. Erythromycin significantly reduces the levels of these cytokines in diffuse pan-bronchiolitis and in lung transplant patients with BOS, azithromycin significantly reduces BAL neutrophilia and IL8 mRNA. Azithromycin also has proven prokinetic effects on the gut and treatment in lung allografts has been associated with lower levels of markers of aspiration.

Interestingly, azithromycin has also recently been shown to improve lung function in patients with BOS, possibly through inhibition of epithelial cell derived matrix metalloproteinases and this may resonate with the apparent beneficial effect on FEV1 witnessed in our patients.

The anti-pseudomonal effect of azithromycin may represent an inhibitory effect on quorum sensing, biofilm formation, production of immunostimulatory exoproducts and the inflammatory response to this organism. We report the efficacy of long-term low-dose azithromycin in bronchiectasis patients with frequent exacerbations. We have demonstrated beneficial effects on exacerbation frequency, sputum microbiology, FEV1 and sputum volume and we feel this therapy should be considered in the chronic management of patients with difficult to control bronchiectasis.

Conflict of interest

None of the authors have a conflict of interest to declare in relation to this work. All authors hereby certify that the attached document is our original work. Except where reference is made in the text, this document contains no material presented elsewhere or extracted in whole or in part from a document presented by any of us for another qualification at this or any other institution.

We declare that we have no conflict of interest, and in particular no financial or other interest in any commercial organisation related to this study, either in the provision of equipment or therapy.

References