Long-term macrolide maintenance therapy in non-CF bronchiectasis: Evidence and questions

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Summary
Macrolide antibiotics have anti-inflammatory and immunomodulatory properties in addition to antibacterial activity. Until recently, only a small number of studies evaluating macrolides in patients with non-cystic fibrosis (CF) bronchiectasis had been published. These were open-label, uncontrolled, short-duration studies that included small numbers of patients. However, these studies suggested that macrolides can reduce exacerbation frequency, reduce sputum volume, and improve lung function in patients with non-CF bronchiectasis.

Three recently published randomised, double-blind, placebo-controlled studies showed that macrolides (azithromycin or erythromycin) taken for between 6 and 12 months led to significant reductions in exacerbation rate and reduced the decline in lung function. In all studies, macrolides were generally well tolerated.

The advantages of macrolide maintenance therapy need to be balanced against the risks, which include emergence of bacterial resistance, cardiotoxicity and ototoxicity. In addition, a key need is the consistent definition of endpoints for studies in non-CF bronchiectasis, particularly the definition of exacerbation, to allow systematic data analysis. Existing studies on the use of low-dose macrolides in non-CF bronchiectasis are encouraging, but further studies are needed to define the optimal agent, dose, duration for treatment, and the patients likely to benefit and long-term safety.

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Introduction

Bronchiectasis describes the pathological condition of abnormally dilated airways [1]. Cystic fibrosis (CF) is one of the leading inherited causes of bronchiectasis but there are numerous other causes, including a post-infectious aetiology (e.g. after pneumonia, pertussis, or Mycobacterium infection), connective tissue disease, allergic bronchopulmonary aspergillosis, immunodeficiency, autoimmune conditions, congenital ciliary defects or foreign body aspiration [1–3]. In 26–53% of patients, bronchiectasis is idio-pathic and has no known cause [1–3].

Bronchiectasis is increasing in prevalence in developing countries and in some indigenous groups in affluent countries [4–6]. With the increased life expectancy of the global population, there is also greater risk of chronic illness, including bronchiectasis, worldwide. Bronchiectasis is commonly reported in developed countries, with prevalence increasing with age [1]. The term ‘non-CF bronchiectasis’ has been used to describe the group of patients with bronchiectasis caused by conditions other than CF [7].

The pathophysiology of bronchiectasis involves irreversible dilation and damage to the bronchial walls (conducting airways) as a consequence of repeated infection and subsequent inflammation. Mucociliary clearance is impaired, so the airways are prone to repeated colonisation by pathogens [7]. Chronic infection promotes further neutrophilic inflammation, leading to a vicious cycle of infection and inflammation in the permanently damaged airways. Patients present with persistent cough, chronic daily sputum production and recurrent chest infections [1]. Estimates suggest that the airways of almost all patients with bronchiectasis are chronically infected with pathogenic bacteria, even among those who are clinically stable [8]. The most common infecting pathogens are Haemophilus influenzae (47–55%) and Pseudomonas aeruginosa (12–26%) [1]. Bacterial load correlates with inflammatory response, with greater numbers of neutrophils, and higher concentrations of neutrophil degradation products and inflammatory markers [1,9].

Recent studies using pyrosequencing have demonstrated a much greater diversity than was previously appreciated, including many anaerobic species. The significance of these is yet to be determined [8,10,11].

The aims of management of non-CF bronchiectasis in adults are to identify and treat any underlying causes in order to prevent disease progression; to maintain and improve pulmonary function; to reduce exacerbation frequency and severity; and to improve health-related quality of life (HRQoL) by reducing symptoms and exacerbations [7]. Management strategies include airway clearance techniques, inhaled hyperosmolar agents, mucolytics, inhaled corticosteroids, short- and long-term antibiotics (either oral or nebulised) and surgery: though the evidence base for most of these is poor [1,7]. Patient education is also a key component of non-CF bronchiectasis management and should focus on interventions that improve quality of life (QoL) and reduce exacerbation frequency along with the implementation of action plans to improve the recognition and treatment of acute exacerbations [7].

The treatment of non-CF bronchiectasis has generally consisted of treatments with proven efficacy in CF or other diseases (e.g. chronic obstructive pulmonary disease [COPD]), but this is by no means a sound strategy, as evidenced by the study of recombinant human deoxyribonuclease [12]. This treatment for CF was not only ineffective in patients with idiopathic bronchiectasis, but potentially harmful [12] and should not be used in this patient population [7].

The British Thoracic Society guidelines on the management of non-CF bronchiectasis highlight the current evidence gaps, which limit recommendations for chronic management strategies [7]. Bronchiectasis may not respond
Macrolide therapy for non-CF bronchiectasis

Review

Macrolides in chronic airways diseases

Macrolide antibiotics contain a macrocyclic lactone ring attached to a number of sugar moieties. They are classified according to the number of lactone rings into 14-, 15- and 16-member ring macrolides. Their mechanism of action is reversible binding to the 50 S subunit of prokaryocyte ribosomes, blocking ribosomal translation and, ultimately, bacterial replication [24]. Macrolides are bacteriostatic for Staphylococci, Streptococci, and Haemophilus. They are not bactericidal against P. aeruginosa but inhibit biofilm formation and toxin production [25].

The 14- and 15-member ring macrolides group include erythromycin, clarithromycin, roxithromycin and azithromycin [26]. These macrolides can down-regulate inflammation and enhance or reduce activation of the immune system in a time- and dose-dependent manner [26]. Their actions include inhibiting the synthesis of proinflammatory agents by bacteria, eosinophils, neutrophils and epithelial cells, and stimulating the phagocytic activity of alveolar macrophages. They have also demonstrated a number of immunomodulatory activities in vivo and in vitro, including a reduction in T-cell numbers and T-cell migration to the airway epithelium, inhibition of neutrophil activation and mobilisation, acceleration of neutrophil apoptosis, and a decrease in the production of reactive oxygen species (Fig. 1) [26].

In addition to the immunomodulatory properties of macrolides, there is a sound scientific rationale for studying these agents in non-CF bronchiectasis, based on their beneficial clinical effects including controlling exacerbations in patients with CF [28], COPD [29] and diffuse panbronchiolitis [26,30]. The small number of reports published before 2012 had limitations [14–19,21,23]. However, these studies and case series showed reductions in pulmonary exacerbations [14,16,17,19] and sputum volumes [14–16,21,23], and improvements in lung function [14,17,21]. One retrospective study found that older age and male gender were independent predictors of response to macrolide treatment [15]. The study of longest duration was a prospective, open-label pilot study in which 21 patients were treated for 12 months with low-dose erythromycin [19]. Compared with the preceding year, patients taking erythromycin had half the median annual number of infective exacerbations and annual days of antibiotic use.

Two of these studies investigated the potential mechanisms of action in non-CF bronchiectasis [21,23]. Yalcın et al. found that treatment with clarithromycin 15 mg/kg/day for 3 months in children with non-CF bronchiectasis significantly reduced levels of interleukin (IL)-8 in bronchoalveolar lavage (BAL) fluid (p = 0.006), but had no effect on levels of IL-10 or tumour necrosis factor-α [23]. The concentration of bacterial isolates in BAL fluid did not change in this study, suggesting that changes in neutrophil and IL-8 levels resulted from an anti-inflammatory effect of the clarithromycin [23].

In contrast to these findings, Tsang et al. found no impact of erythromycin 500 mg twice daily for 8 weeks on sputum levels of IL-1α, IL-8, tumour necrosis factor-α or leukotriene-B4 in adult patients with non-CF bronchiectasis [21]. It is not clear why there was no evidence of anti-inflammatory effect in this study, whereas there was in the study with clarithromycin in children, but it may have been because the study was too small (n = 21) or of too short a duration (8 weeks) to detect a significant effect, or that changes in levels of inflammatory markers are more easily detected in BAL fluid compared to sputum. Even without evidence of a clear anti-inflammatory effect, the clinical benefits seen with macrolides in these short-term studies suggested that these agents may have disease-modifying effects in non-CF bronchiectasis, and led to investigation in larger randomised trials.

Clinical trial data

Data from three randomised, double-blind, placebo-controlled trials have shown significant reductions in pulmonary exacerbations in non-CF bronchiectasis patients treated with long-term, low-dose macrolide therapy [13,20,22].

The EMBRACE study

The Effectiveness of Macrolides in patients with Bronchiectasis using Azithromycin to Control Exacerbations (EMBRACE) study enrolled patients who had experienced at least one respiratory exacerbation requiring antibiotics in the previous year [22]. Patients (n = 141) were randomised to treatment with azithromycin 500 mg or placebo three times a week. The study had three co-primary endpoints: (1) the rate of event-based exacerbations at the end of the 6-month treatment period (defined as an increase in or new onset of more than one pulmonary symptom: sputum volume, sputum purulence, or dyspnoea · requiring antibiotic treatment); (2) change in forced expiratory volume in 1 s (FEV₁) before bronchodilation; and (3) change in St. George’s Respiratory Questionnaire (SGRQ) total score at the end of treatment.
Treatment with azithromycin 500 mg three times weekly reduced the rate of exacerbations requiring antibiotic treatment by almost two-thirds \((p < 0.0001)\) during the 6-month treatment period. Azithromycin also increased the median time until \(\geq 25\%\) of patients had a first exacerbation \((p < 0.0001)\) and the median time to first exacerbation during the overall 12-month study period \((p < 0.0001)\) (Fig. 2(a)). The effect on exacerbations persisted over the 6 months after treatment withdrawal. Based on the reported percentage of patients with at least one event-based exacerbation, it can be estimated that the number needed to treat (NNT) with azithromycin to prevent one patient having an exacerbation in 12 months is five (Table 1).

Azithromycin did not significantly affect the rate of symptom-based (patient-reported) exacerbations. These exacerbations were defined as an increase in, or new onset of, more than one pulmonary symptom (sputum volume, sputum purulence, or dyspnoea) reported on diary cards, and the mean of the three symptom scores for the daily diary card increasing by at least one point on 2 consecutive days, compared with the same calculation in the previous week. It is not clear why there was a difference in exacerbation rates using the two definitions in this study [22], but it is possible that a higher rate of patient-reported exacerbations may have been identified if the definition included cough, which is the predominant symptom of bronchiectasis.

The EMBRACE study did not meet the other two co-primary endpoints: azithromycin had no statistically significant effect on FEV\(_1\) or HRQoL as assessed by the SGRQ total score [22]. After 6 months, symptoms were significantly improved when assessing the SGRQ responses. This improvement was no longer significant after 12 months of azithromycin treatment [22], but this finding is consistent with the effect of azithromycin in reducing the exacerbation rate, because the symptom score is one of the SGRQ components associated with exacerbation rate [31].

The BAT study

The Bronchiectasis and long-term Azithromycin Treatment (BAT) study enrolled patients who had confirmed bronchiectasis and had experienced at least three lower respiratory tract infections, and had at least one sputum culture yielding at least one bacterial respiratory pathogen, in the preceding year [13]. Patients \((n = 83)\) in this double-blind study were randomised to receive azithromycin 250 mg/day or placebo for 12 months. The primary endpoint of the
study was the number of infectious exacerbations over the 12-month treatment period. Secondary endpoints included lung infection, sputum bacteriology, inflammatory markers, adverse effects, symptom scores, and QoL.

Azithromycin treatment significantly reduced the number of exacerbations compared with placebo, with a median of 0 versus 2 during treatment ($p < 0.001$). The number of patients with at least one exacerbation during the study was 80% in the placebo group and 46.5% in the azithromycin group, corresponding to an absolute risk reduction of 34% (Fig. 2(b)), or a NNT of three to prevent one patient having an exacerbation in 12 months.

Azithromycin also significantly attenuated changes in FEV1 and forced vital capacity ($p = 0.047$ and $p = 0.020$ vs. placebo, respectively). There was no change in C-reactive protein during azithromycin therapy. In contrast to EMBRACE, azithromycin treatment was associated with significant improvements in the SGRQ score compared with placebo, and azithromycin recipients also had significantly fewer symptoms than those receiving placebo ($p = 0.047$).

There was evidence that antibacterial resistance developed during the study, with 88% of pathogens tested becoming macrolide resistant in sputum samples from the azithromycin group compared with 26% in the placebo group ($p < 0.001$) [13].

The BLESS study
At least two separate pulmonary exacerbations during the previous 12 months and daily sputum production were required for entry into this randomised, double-blind Bronchiectasis and Low-dose Erythromycin Study (BLESS) [20]. One hundred and seventeen patients received oral erythromycin ethylsuccinate 400 mg twice daily (equivalent to 250 mg of base erythromycin) or placebo for 12 months. The primary endpoint was the number of protocol-defined pulmonary exacerbations. Secondary endpoints were the rate of all pulmonary events, change in the proportion of commensal oropharyngeal streptococci resistant to macrolides, symptoms, QoL, inflammatory markers, lung function, sputum bacteriology, and exercise capacity.

The number of protocol-defined pulmonary exacerbations was 76 and 114 in the erythromycin and placebo groups, respectively, corresponding to a mean of 1.29 and 1.97 per patient per year; incidence rate ratio 0.57 ($p = 0.003$) (Fig. 2(c)). The number of patients with no exacerbations was 20 in the erythromycin group and 16 in the placebo group, resulting in an estimated NNT of 16 over a 12-month period. Like azithromycin in BAT, erythromycin significantly prevented the decline in FEV1 during the study period. In contrast, erythromycin had no significant effect on cough or QOL scores. Levels of inflammatory biomarkers [20], C-reactive protein, and exercise tolerance were also unchanged in erythromycin recipients. There was no difference between the two treatment groups with respect to emergence of new sputum pathogens, but the proportion of macrolide-resistant commensal oropharyngeal streptococci increased significantly in erythromycin, but not placebo, recipients [20].

Adverse events
Gastrointestinal side effects are the most common complaint in patients treated with macrolides, although in randomised trials of long-term, low-dose macrolide treatment in chronic pulmonary diseases, these side effects have been mild to moderate and rarely warranted treatment discontinuation [13]. Gastrointestinal adverse events were the most commonly reported adverse events in the EMBRACE and BAT trials and occurred more frequently with azithromycin than placebo (27–40% vs. 5–13% of patients) [13,22].

Key issues and controversies
The data from the EMBRACE, BAT and BLESS studies are consistent with results from studies in adults and children with CF and adults with COPD in showing that low-dose macrolide maintenance therapy reduces the incidence of exacerbations over 3 [32], 6 [33–35], or 12 [29] months of treatment (Table 2). In the EMBRACE study, azithromycin had no effect on lung function or QoL, whereas azithromycin has improved both these parameters in some [32,33], but not all, studies in patients with CF. In addition to investigating the number of exacerbations during macrolide therapy, the BAT study also investigated QoL and found this to be significantly improved in patients receiving azithromycin compared with those receiving placebo over 1 year of therapy [13]. However, this may have been a result of the longer treatment duration in BAT compared with EMBRACE (12 vs. 6 months, respectively).

While the optimal duration of treatment has not clearly been established, the Kaplan–Meier curves for remaining exacerbation-free from the EMBRACE trial continued to diverge beyond 3 months of treatment (Fig. 2(a)) [22]. This was also the case in the BLESS trial, where the difference between groups in the cumulative incidence of exacerbations continued to increase up to 1 year [20]. In BAT, differences between treatment groups in the proportion of patients who were free of exacerbations were greatest at 3–6 months, but this difference was maintained over 1 year of therapy [13]. Considering that the mechanisms of macrolides probably include immunomodulatory activity [27], and the duration of treatment in the RCTs of CF (3–6 months) [32–34], it is reasonable to assume that treatment duration should be at least 3 months. Data from clinical practice indicate that, in patients with CF, the beneficial effects of azithromycin on lung function are limited to the first 12 months of treatment [32,36,37]. Coupled with the need to balance benefit with risk of macrolide resistance, these data suggest that the optimal duration in non-CF bronchiectasis is likely to be between 3 and 12 months. Continuous treatment for longer than this requires clarification in longer-term studies.

One of the key issues in the use of macrolides for patients with non-CF bronchiectasis is who to treat. In the EMBRACE study, Wong et al. recommend that patients should only receive azithromycin if they have experienced at least one exacerbation in the previous year [22]. However, in an accompanying editorial, Wilson and Wells note that they are ‘uneasy’ about this recommendation because it may apply to almost all patients with clinically overt bronchiectasis [38]. They note that non-CF bronchiectasis generally shows one of two patterns of natural history: a progressive course with frequent exacerbations despite
standard treatment, or a long-term stable clinical course despite early major irreversible airway damage. Pulmonary function testing poorly discriminates between these two patterns of longitudinal disease progression, and therefore it is difficult to identify prospectively those patients at high risk of exacerbation [38]. Similarly, more data are required to determine if benefits are consistent across bronchiectasis phenotypes. For example, should patients with COPD-associated bronchiectasis receive different treatment strategies? In patients with COPD, long-term maintenance treatment with azithromycin benefited patients in almost all subgroups based on demographics and disease history, except for smokers [29]. Azithromycin had the greatest benefit in elderly COPD patients (>65 years), but was less effective in those with recent exacerbations requiring hospitalisation or recent use of steroids, and those taking inhaled corticosteroids, all factors indicative of a high risk of recurrent exacerbations [29]. In children

Table 1  Comparison between Phase III clinical trials.

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Azithromycin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Patient, n</td>
<td>70</td>
<td>71</td>
<td>58</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>20/50</td>
<td>23/48</td>
<td>25/33</td>
</tr>
<tr>
<td>Age, years</td>
<td>59.0</td>
<td>60.9</td>
<td>63.5</td>
</tr>
<tr>
<td>Study duration</td>
<td>6 months</td>
<td>12 months</td>
<td>12 months</td>
</tr>
<tr>
<td>FEV1 % predicted at baseline</td>
<td>67.3</td>
<td>67.1</td>
<td>70.1</td>
</tr>
<tr>
<td>Change in FEV1 from baseline, L</td>
<td>–0.04</td>
<td>0</td>
<td>–4.0</td>
</tr>
<tr>
<td>SGRQ at baseline, total score</td>
<td>36.6</td>
<td>31.9</td>
<td>38.1</td>
</tr>
<tr>
<td>Change in SGRQ total score from baseline</td>
<td>–1.92</td>
<td>–5.17</td>
<td>–1.3</td>
</tr>
<tr>
<td>Exacerbation rate in 12 months prior to trial</td>
<td>3.93</td>
<td>3.34</td>
<td>NR</td>
</tr>
<tr>
<td>Total no. exacerbations over 12 months</td>
<td>178</td>
<td>109</td>
<td>114</td>
</tr>
<tr>
<td>Annual exacerbation rate, patient/year</td>
<td>2.73</td>
<td>1.58</td>
<td>1.97</td>
</tr>
<tr>
<td>Patients with at least one exacerbation, n (%)</td>
<td>58 (82.9)</td>
<td>44 (62.0)</td>
<td>42 (72.4)</td>
</tr>
<tr>
<td>NNT to prevent one patient experiencing an exacerbation over 12 months$^d$</td>
<td>5</td>
<td>16</td>
<td>3</td>
</tr>
</tbody>
</table>

Data is mean unless otherwise stated.

$^a$ Data change per visit (every 3 months), $F_{1,78.8} = 4.085, p = 0.047$.

$^b$ BLESS study did not present exacerbation rate, but did present the number of patients with five or more exacerbations in the year preceding the trial ($n = 20$ and 22 for placebo and erythromycin respectively).

$^c$ EMBRACE was a 6-month study but presented annualised data for exacerbations.

$^d$ Calculated as 1/absolute risk reduction (proportion with event [placebo] – proportion with event [intervention]). Values presented are the published NNT for BAT and estimates by the authors for EMBRACE and BLESS, based on the percentage of patients with exacerbation events. BAT, Bronchiectasis and long-term Azithromycin Treatment study; BLESS, Bronchiectasis and Low-dose Erythromycin Study; EMBRACE, Effectiveness of Macrolides in patients with Bronchiectasis using Azithromycin to Control Exacerbations study; FEV1, forced expiratory volume in 1 s; NNT, number needed to treat; NR, not recorded; SGRQ, St. George’s Respiratory Questionnaire.

Figure 2  A Proportion of patients free from event-based exacerbations in the EMBRACE trial [22]. Shaded areas indicate 95% confidence intervals. Crosses indicate censoring. Reprinted from [22], Copyright 2012, with permission from Elsevier. 2B Proportion of patients free from exacerbations in the BAT trial [13]. Reprinted from [13]. Copyright © 2013 American Medical Association. All rights reserved. 2C Cumulative incidence of protocol-defined pulmonary exacerbations in the BLESS trial [20]. Each point represents a separate protocol-defined pulmonary exacerbation. Individual participants could account for more than one event each; $p = 0.003$ for the comparison with placebo for the rate of pulmonary exacerbations per year. Reprinted from [20]. Copyright © 2013 American Medical Association. All rights reserved. PDPE, protocol-defined pulmonary exacerbations.
with CF, there was a reduction in the frequency of exacerbations with azithromycin in patients with or without *P. aeruginosa* infection at baseline [33,35], and in all subgroups of *P. aeruginosa*-infected children, regardless of whether or not they achieved an improvement in lung function [34]. In fact, the reduction in the risk of exacerbation was greater in patients with lower FEV1 at baseline [34]. In fact, the reduction in the risk of exacerbation was greater in patients with lower FEV1 at baseline [34].

Similar data are needed from larger trials with prespecified subgroups of patients with non-CF bronchiectasis to identify patients who may achieve the greatest benefit from maintenance macrolide therapy. Limited data were obtained from the BLESS trial, which suggested that patients with *P. aeruginosa* infection at baseline or ≥4 exacerbations in the year prior to the trial demonstrated significant responses to erythromycin therapy [20]. Given the reservations about applying long-term macrolide therapy using the broad EMBRACE definition of exacerbation, it has been suggested that non-CF bronchiectasis patients who have more than two exacerbations per year may be the most appropriate group for whom to consider long-term treatment with macrolides [39].

Combined data from the EMBRACE, BAT and BLESS studies provide good RCT evidence for the use of macrolide maintenance therapy in adults with non-CF bronchiectasis (Table 1) [13,20,22]. Azithromycin was the agent used in two studies and erythromycin has been studied once. However, in the absence of any direct comparative data, there is insufficient evidence on which to base a conclusion about which macrolide regimen has the optimal risk-benefit profile in patients with non-CF bronchiectasis.

The frequency of exacerbations has been widely used as an endpoint in non-CF bronchiectasis studies, including its use as a primary endpoint in the large clinical trials, but definitions vary (Supplementary Table S1). This measure is highly relevant to patients and healthcare providers. Patients with non-CF bronchiectasis have exacerbations at the rate of 1.5–6.5 per patient per year [7,12], and these events are associated with an increased risk of admission and re-admission to hospital, as well as high healthcare costs [40,41]. Moreover, the frequency of hospitalised exacerbations is a determinant of accelerated lung function decline in adults and children [42,43], and recurrent exacerbations are a powerful predictor of poor HRQoL [44]. The three recent studies used different definitions for exacerbation. The EMBRACE study [22] defined exacerbation using the Anthonisen criteria for an exacerbation in COPD, a definition that includes changes in sputum volume and purulence, and shortness of breath, but not cough, the predominant symptom of bronchiectasis. In the BAT study, exacerbations were defined as an increase in respiratory symptoms requiring antibiotic administration for a sustained (>24-h) increase in sputum volume; or purulence accompanied by new deteriorations in at least two different symptoms (sputum volume, sputum purulence, cough, dyspnoea, chest pain, or haemoptysis). However, in this study, patients were advised to contact a trial physician who would determine whether antibiotic therapy was needed in the event of an exacerbation. This aspect of the trial design could introduce bias. EMBRACE avoided this by advising the patient’s general practitioner or physician to avoid macrolide antibiotics at the start of the trial, but otherwise had no input into treatment for exacerbations [22].

Other appropriate endpoints for RCTs in bronchiectasis need to be defined. While there are some validated endpoints (e.g. Leicester Cough Questionnaire [45]) and the SGRQ has been validated in bronchiectasis, there remains a

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### Table 2  Randomised controlled trials of azithromycin maintenance therapy in patients with CF or COPD.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients</th>
<th>Azithromycin dose</th>
<th>Duration of treatment</th>
<th>Primary endpoint</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wolter et al., 2002 [32]</td>
<td>Adults (n = 60)</td>
<td>250 mg/day</td>
<td>3 months</td>
<td>FEV1</td>
<td>Improved lung function, reduced exacerbations, improved QoL</td>
</tr>
<tr>
<td>Saiman et al., 2003 [33]</td>
<td>Children (n = 185)</td>
<td>250 or 500 mg 3 times/wk</td>
<td>168 days</td>
<td>FEV1</td>
<td>Improved lung function, reduced exacerbations</td>
</tr>
<tr>
<td>Saiman et al., 2005 [34]</td>
<td>Children (n = 185)</td>
<td>250 or 500 mg 3 times/wk</td>
<td>168 days</td>
<td>Exacerbations</td>
<td>Reduced risk regardless of change in FEV1. All subgroups benefited</td>
</tr>
<tr>
<td>Saiman et al., 2010 [35]</td>
<td>Children (n = 260)</td>
<td>250 or 500 mg 3 times/wk</td>
<td>168 days</td>
<td>FEV1</td>
<td>No FEV1 improvement but reduced exacerbations</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albert et al., 2011 [29]</td>
<td>Adults (n = 1577)</td>
<td>250 mg/day</td>
<td>1 year</td>
<td>Time to exacerbation</td>
<td>Reduced exacerbations</td>
</tr>
</tbody>
</table>

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s; QoL, quality of life; wk, week.
lack of specific valid patient-reported outcomes for bronchiectasis [1]. In contrast to previous data in other pulmonary indications, the EMBRACE study showed no change in FEV$_1$ and the EMBRACE and BLESS studies showed no change in SGRQ during macrolide therapy [20,22]. These data should be considered with care as the SGRQ was developed to assess QoL in patients with COPD [46], but has been validated for use in bronchiectasis [31]. An alternative QoL measure has been developed specifically to assess the effect of bronchiectasis (QoL-B), but this has yet to be fully validated [47]. While this may indicate that these endpoints are less reflective of clinical improvement in non-CF bronchiectasis than in other pulmonary conditions, significant attenuation in the decline of lung function were seen in both BAT and BLESS [13,20]. These findings were surprising as an earlier trial investigating response to short-term courses of antibiotics in patients with bronchiectasis found that FEV$_1$ values do not change in response to treatment (unlike in treatment for CF) [48], suggesting that FEV$_1$ is not a good clinical endpoint to use. Improvements in QoL were documented in BAT [13], further complicating the decision about the appropriateness of the different endpoints.

As described earlier, unanswered questions remain as to the optimal dosage, duration, or periodicity of macrolide regimens in non-CF bronchiectasis. While current data show that treatment is well tolerated in non-CF bronchiectasis, CF, and COPD, there are potential safety concerns associated with the long-term use of macrolides, including cardiac side effects, that have been reported [24]. Arrhythmic events are extremely rare and are unlikely to be identified in clinical trials, and there were no adverse cardiac events in EMBRACE or the study by Albert et al. in patients with COPD [22,29]. One erythromycin recipient in the BLESS study was withdrawn as a result of suspected corrected Q-T interval prolongation, but further analysis showed that this patient had been enrolled despite a corrected Q-T interval of 480 ms, and no further prolongation occurred during erythromycin therapy [20]. Post-marketing data suggest a risk of an additional 47 cardiovascular deaths per 1 million with short (5-day) courses of azithromycin, with the risk increasing in patients with cardiovascular risk factors [49]. This underlines the need to carefully consider the use of macrolide therapy, in those with cardiovascular risk factors, and for ongoing assessment of cardiac safety during clinical use. The study in patients with COPD excluded patients with QT prolongation at baseline, and it may be prudent to use similar exclusion criteria in future studies in non-CF bronchiectasis and when commencing treatment [29].

Reversible hearing loss has been associated with high-dose macrolide therapy and the incidence of this side effect with long-term low-dose macrolide treatment has not been well characterised [13]. Auditory side effects have been reported with long-term azithromycin treatment in COPD patients [29] but have not been studied properly in bronchiectasis. While data from CF studies may provide some information as to the tolerability profile of macrolides, both auditory and cardiovascular adverse events may be more relevant in a non-CF bronchiectasis population, which tends to be older than those with CF. An editorial accompanying the BAT and BLESS publications suggested that sputum culture, an electrocardiogram, and clinical assessment of hearing and liver function should be undertaken prior to initiation of macrolide therapy, and at regular intervals during treatment [39].

Development of pathogen resistance is a major concern with the use of macrolides, and this may apply to bacteria that are specific targets of macrolide therapy or commensal organisms. Azithromycin and clarithromycin are the mainstay of treatment for non-tuberculosis mycobacteria (NTM), which are commonly found in bronchiectasis patients [24]. Recent data indicate that azithromycin impairs autophagic and phagosomal degradation of macrophages, thereby compromising host defences against Mycobacterium infection [50]. This could explain why adult patients with CF on long-term azithromycin therapy are at increased risk of developing NTM infection, particularly infection with multidrug-resistant species of Mycobacterium abscessus [50]. It is not clear if long-term azithromycin predisposes to NTM infection. In a small study of 14 cases an association between azithromycin use and NTM was demonstrated, but two larger multicentre case control studies in patients with CF did not show the same finding [50–52]. Longer surveillance studies with more cases are required to determine if this is a clinical problem. RCTs in CF patients who were treated for up to 168 days with azithromycin did not show any increased risk of developing NTM infection [32,33,35], suggesting that treatment duration may be a key factor in limiting the potential for NTM development in non-CF bronchiectasis. Nevertheless, it will be important to monitor microbiology during future trials to limit the risk of NTM infections during macrolide therapy, which may severely limit future NTM treatment options.

Also of concern is the potential for development of resistance in commensal organisms, especially oropharyngeal streptococci that can then be transmitted within the community. Even a short course of azithromycin is associated with a substantial increase in resistance among patients’ oropharyngeal streptococci [8]. One study found a statistically significant 53.4% increase in macrolide-resistant streptococci after 3 days of azithromycin treatment in healthy volunteers [53]. The RCTs in patients with CF or COPD showed an increased rate of macrolide resistance among S. aureus strains after 5–12 months of treatment with azithromycin [29,35]. Data in CF patients shows that long-term azithromycin treatment reduces carriage of S. aureus but increases the rate of macrolide resistance among S. aureus strains [28,37,54]. However, resistant strains of S. aureus do not appear to be transmitted to household contacts [54]. Macrolide resistance testing was not routinely carried out in the EMBRACE study [22]. However, two patients (4%) in the azithromycin arm developed macrolide-resistant S. pneumoniae at 6 months [22]. The design of both BAT and BLESS included routine assessment of sputum samples and secondary endpoints including microbiological evaluation with susceptibility testing (BAT) and changes in the proportion of commensal oropharyngeal streptococci resistant to macrolides. The results of these trials suggested that no new pathogens emerged during macrolide therapy [13,20]. However, the proportion of macrolide-resistant commensal oropharyngeal streptococci increased significantly during erythromycin therapy and macrolide resistance of known respiratory pathogens was significantly increased in azithromycin recipients [13,20]. The clinical significance of
this is unclear. While these data provide additional information that was not available from the EMBRACE study, there are a number of concerns that remain to be addressed, including the possibility that macrolide use might increase resistance to other antibiotics and the effect of macrolides on antibiotic resistance among other pathogens [39]. Some concerns about increasing community and patient resistance have been raised, but there is little existing evidence [55].

Implications for future research

Current data on the use of low-dose macrolides in non-CF bronchiectasis are encouraging. Data in CF patients suggest that macrolide treatment may cease to provide clinical benefit after 12 months [36,37], but it remains to be determined whether this is the case for non-CF bronchiectasis.

Additional clinical trials with large patient numbers and longer follow-up periods are also needed to assess safety. Studies should be conducted in patients of different age groups, including elderly and paediatric patients. One such study, the Bronchiectasis Interventional Study (BIS), is evaluating the effect of 12–24 months of treatment with azithromycin in indigenous children with non-CF bronchiectasis in Alaska, Australia, and New Zealand [56].

Careful attention will need to be paid to the potential for cardio- and ototoxicity with long-term macrolide therapy. Until further data are available on the safety of low-dose macrolide therapy in this patient group, studies should have stringent selection criteria that include baseline electrocardiogram assessment and exclusion of anyone with cardiovascular disease or significant cardiovascular risk factors.

Routine testing of macrolide resistance should be included in future clinical trials, including macrolide susceptibility of oropharyngeal flora. Macrolide resistance in respiratory bacteria colonising the nasopharynx is a secondary endpoint in the BIS trial of long-term, low-dose azithromycin in paediatric patients described earlier [56].

Ideally, there should be consistent definitions for endpoints in non-CF bronchiectasis studies, so that the data can be systematically analysed to support evidence-based recommendations. To this end, validated patient-reported outcomes and QoL assessment tools are needed in bronchiectasis.

Researchers should also continue to investigate the mechanism of action of low-dose macrolide therapy in bronchiectasis, particularly the role of anti-inflammatory and immunomodulatory effects. A study currently underway into the effects of long-term, low-dose azithromycin on airway oxidative stress markers in exhaled breath condensate of adults with non-CF bronchiectasis, may help to clarify these mechanisms [NCT01463371; clinicaltrials.gov].

Conclusions

Macrolide antibiotics possess additional anti-inflammatory and immunomodulatory properties in addition to their antimicrobial function. There is now an evidence base from three RCTs for the long-term use of low-dose macrolides in non-CF bronchiectasis. Owing to concerns about drug resistance, it seems prudent to limit macrolide treatment to patients with functionally severe disease. Those with milder disease should only receive long-term macrolide treatment in cases of major morbidity and/or evidence of disease progression despite standard treatment [38]. Priorities for future research include identifying the optimal regimen and duration of macrolide treatment to maximise clinical efficacy and minimise emergence of resistance, direct comparisons of different macrolides in non-CF bronchiectasis, and development and validation of bronchiectasis-specific endpoints. The anti-inflammatory and immunomodulatory properties of macrolides without the antimicrobial activity and inherent risk of pathogen resistance should also be explored.

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Author contributions

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Competing interests

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Appendix A. Supplementary data

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References


