Summary

Although the use of anti-inflammatory therapies in bronchiectasis remains an attractive proposition, there is currently insufficient evidence to support the use of inhaled and oral corticosteroids, non-steroidal anti-inflammatory drugs and macrolides. Individual patient trials may be warranted for inhaled corticosteroids and macrolides. It is hoped that recently completed and ongoing randomised control trials of macrolides will better define the use and safety in bronchiectasis. There remains an urgent need to perform adequately powered multicentre trials of other potentially useful therapies.

It is anticipated that specialised bronchiectasis clinics will provide greater opportunities to study disease epidemiology and pathogenesis and allow better definition of study population for inclusion within future trials. There is a need for a more defined study population and a widely accepted definition of a pulmonary exacerbation in bronchiectasis which may be applied uniformly across studies to allow direct comparison of study outcomes. Finally, care should be taken to ensure adequate follow-up to detect potential adverse effects of new therapies, particularly on microbial resistance patterns.

Keywords: Anti-inflammatory therapy, bronchiectasis, inflammation, inhaled corticosteroids, macrolides

Bronchiectasis is an under-recognised condition characterised by pathological dilatation of bronchi, persistent neutrophilic airway inflammation and, in many, chronic bacterial infection. Bronchiectasis develops in the susceptible host through a vicious cycle of airway infection and inflammation [1]. The causes of non-cystic fibrosis (CF) bronchiectasis are diverse, the cohort populations are heterogeneous and the evidence to support therapies limited [2]. Factors which may have contributed to the limited evidence for treatment are likely to include population and disease severity heterogeneity, limited funding sources for clinical trials and the diverse manner that patients with bronchiectasis are managed. This appears to be changing with...
the advent of specialised bronchiectasis clinics which are providing an opportunity to develop focused research programmes. There are a limited number of high-quality randomised controlled trials (RCT’s) cited in recently published management guidelines for bronchiectasis [3–5].

Airway biology in bronchiectasis

Cohort studies of patients with bronchiectasis reveal *Haemophilus influenzae* and *Pseudomonas aeruginosa* to be the most frequently isolated organisms from airway secretions. *Streptococcus pneumoniae*, *Moraxella* species and nontuberculous mycobacteria (NTM) are reported less commonly [6–8]. Although infection triggers inflammation, ongoing neutrophilic infiltration of the airways is apparent even in the absence of persistent infection, suggesting dysregulation of immune responses [9]. Neutrophils are the predominant inflammatory cell found in sputum and bronchoalveolar lavage fluid (BALF) in patients with bronchiectasis [9, 10]. It is hypothesised that neutrophil apoptosis and clearance may be defective in bronchiectasis [11]. Non-apoptosed cells die by necrosis leading to exudation of toxic products (e.g. exoenzymes, oxygen free radicals, myeloperoxidase, etc.) which cause both localised tissue damage and provide an ongoing stimulus for the inflammatory response. Macrophages, lymphocytes and eosinophils are similarly present in increased number in the bronchiectatic airway, however, their role is poorly defined [12].

Acute respiratory exacerbations in patients with bronchiectasis are poorly understood but are thought to be related, in part, to increased load of existing airway bacteria and/or infection with a new bacterial pathogen. These changes provide rationale for the use of targeted antibiotics in patients with bronchiectasis during respiratory exacerbations which are discussed in detail in the chapter by Fowleraker and Wat [13].

Targeting inflammation in bronchiectasis

An alternative approach to targeting infection with antimicrobial agents is to attempt to modify the immune response to infection. In this chapter we focus on the use of anti-inflammatory agents and examine the evidence for the use and potential pitfalls of these therapies. We also explore future treatment options and studies that are in progress.

Anti-inflammatory therapies will be discussed in one of three broad categories: 1) general anti-inflammatory therapies which have broad immunosuppressive effects on inflammatory pathways (e.g. corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDS)); 2) novel anti-inflammatory therapies which have immunomodulatory properties in addition to the cellular effects for which they are conventionally utilised (e.g. macrolides and hydroxy-methyl-glutaryl-coenzymeA (HMGCoA) reductase inhibitors); and 3) targeted anti-inflammatory therapies which block a specific mediator of the immune response (e.g. anti-immunoglobulin E or anti-tumour necrosis factor (TNF)-α).

General anti-inflammatory agents

Corticosteroids

Corticosteroids have broad anti-inflammatory effects through inhibition of inflammatory mediator synthesis and release and impairment of inflammatory cell migration [14]. Corticosteroids stimulate eosinophil apoptosis but paradoxically inhibit neutrophil apoptosis which, in part, possibly explains their variable anti-inflammatory effectiveness in different clinical settings [15]. Inhaled corticosteroids improve asthma control [16, 17] and are associated with reduction in exacerbation frequency in chronic obstructive pulmonary disease (COPD) [18], yet their withdrawal in patients with CF has minimal impact on symptoms, lung function or exacerbations [19]. Short courses of oral steroids have an established role in the treatment of exacerbations of asthma and COPD [20, 21]; however, their role in CF is more controversial [22].
Inhaled corticosteroids

Recently, Kapur et al. [23] identified six RCTs of inhaled steroids in non-CF bronchiectasis (table 1). The meta-analysis of these studies failed to provide conclusive evidence that inhaled corticosteroids result in a clinically significant improvement in lung function, affect exacerbation rates or improve quality of life in patients with bronchiectasis (fig. 1).

The earliest study, published in 1992 by Elborn et al. [24], enrolled 20 patients in a 12-week crossover trial of high-dose beclomethasone dipropionate/placebo (6 weeks drug, 6 weeks placebo). Despite five patients dropping out of the study, the authors reported an 18% reduction in volume of sputum and reduced bronchoprovocation during histamine challenge testing. A subsequent study demonstrated inhaled fluticasone dipropionate reduced sputum levels of pro-inflammatory mediators (interleukin (IL)-8, leukotriene B4 (LTB4) and IL-1β) and sputum leukocyte density in bronchiectasis [25]. Combined with the consistent finding that inhaled steroids have no effect on sputum bacterial load [25], this suggests that any beneficial effect they may exert is most likely explained by anti-inflammatory as opposed to antimicrobial activity. Studies by Tsang et al. [26] and Joshi and Sundaram [27] reported no change in exhaled nitric oxide and no change in lung function, respectively.

Two larger and longer trials studying fluticasone dipropionate (500 μg b.i.d.) in adults with bronchiectasis, demonstrated a reduction in sputum quantity [28, 29]. In a post hoc analysis Tsang et al. [28] observed that this effect was most pronounced in those patients with chronic P. aeruginosa infection. However, each of these studies had significant limitations including no placebo arm in the former and variable baseline sputum production in the treatment arms in the latter, precluding their data from being included in the assessment of this outcome measure in the Cochrane Review. Although therapy was generally well tolerated for the duration of the trials, long-term safety is uncertain in dosage regimens which would currently be considered to be high. In addition, one short-term study [25], the data on density of total bacteria, commensal bacteria and P. aeruginosa in sputum showed an increasing trend after 4 weeks of therapy with inhaled steroids.

Based on the available evidence from these published studies, Kapur et al. [23] concluded that there is currently insufficient evidence of both benefit and safety to recommend routine use of inhaled corticosteroids in patients with bronchiectasis, however, it may be appropriate to consider a trial in severely symptomatic patients on a case by case basis, with close monitoring for adverse effects.

Oral corticosteroids

There is currently no evidence supporting the use of oral corticosteroids. A Cochrane Review by Lasserson et al. [30] failed to identify any RCTs in non-CF bronchiectasis either for short-term (during an exacerbation) or long-term use. The only evidence of potential benefit is from the paediatric CF literature in which prednisolone at a dose of 1 mg·kg⁻¹ on alternate days was associated with reduced rate of lung function decline [22]. The long-term adverse effects including effects on growth and cataract resulted in the early termination of the trial.

NSAIDS

NSAIDS non-selectively block the activation of the cyclo-oxygenase pathway of pro-inflammatory prostaglandins. A landmark placebo controlled RCT examined the effects of ibuprofen in people with CF [31]. The study included 85 patients (age range 5–39 years) and demonstrated that those treated with high-dose ibuprofen (dose range 16.2–31.6 mg·kg⁻¹) experienced a slower rate of decline in forced expiratory volume in 1 second (FEV1), as well as improved maintenance of weight when compared with control subjects over the 4-year study period. Post hoc analysis revealed these effects to be most pronounced in those participants <13 years of age at study commencement. Ibuprofen therapy was well tolerated with only one patient withdrawing due to side-effects clearly attributable to ibuprofen (conjunctivitis and epistaxis).
Table 1. Randomised controlled trials of inhaled corticosteroids in bronchiectasis

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Drug</th>
<th>Placebo</th>
<th>Duration</th>
<th>Subjects</th>
<th>Outcome measures</th>
<th>Findings</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELBORN [24]</td>
<td>UK</td>
<td>DBRCT (crossover)</td>
<td>Adults (30–65 yrs)</td>
<td>Bronchiectasis, no prior oral/inhaled corticosteroids</td>
<td>Beclomethasone dipropionate (750 μg b.i.d.)</td>
<td>Yes</td>
<td>12 weeks</td>
<td>20</td>
<td>Lung function, PD20 metacholine, sputum production, pulmonary symptoms</td>
<td>Improved FEV1, improved morning PEFR, improved cough, reduced sputum volume</td>
<td>Oral candidiasis (n=1)</td>
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<td></td>
<td></td>
<td>24 h sputum (volume/leukocyte counts/microbial concentrations/IL-1/IL-8/TNF-α/LTB4, lung function)</td>
<td>Reduced sputum leukocyte density, reduced IL-1β, IL-8 and LTB4, no change in sputum volume, no change in lung function</td>
<td>None reported but trend towards increased sputum density of commensal flora and P. aeruginosa</td>
</tr>
<tr>
<td>TSANG [25]</td>
<td>China (HK)</td>
<td>DBRCT (parallel)</td>
<td>Adults (mean age 55 yrs)</td>
<td>Bronchiectasis &gt;10 mL sputum per 24 h</td>
<td>Fluticasone propionate (500 μg b.i.d.)</td>
<td>Yes</td>
<td>4 weeks</td>
<td>24</td>
<td></td>
<td></td>
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<tr>
<td>TSANG [26]</td>
<td>China (HK)</td>
<td>RCT</td>
<td>Adults (mean age 56 yrs)</td>
<td>Bronchiectasis, nonsmokers</td>
<td>Fluticasone propionate (500 μg b.i.d.)</td>
<td>Yes</td>
<td>52 weeks</td>
<td>60</td>
<td>eNO</td>
<td>No change in eNO</td>
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<td>JOSHI [27]</td>
<td>India</td>
<td>DBRCT (crossover)</td>
<td>Adults/children (15–60 yrs)</td>
<td>Bronchiectasis, 12% improvement post-bronchodilator FEV1</td>
<td>Beclomethasone dipropionate (400 μg b.i.d.)</td>
<td>Yes</td>
<td>8 weeks</td>
<td>20</td>
<td>Lung function</td>
<td>No change in lung function</td>
<td>None</td>
</tr>
<tr>
<td>TSANG [28]</td>
<td>China (HK)</td>
<td>DBRCT (parallel)</td>
<td>Adults (mean age 58 yrs)</td>
<td>Bronchiectasis, no prior oral/inhaled corticosteroids</td>
<td>Fluticasone propionate (500 μg b.i.d.)</td>
<td>Yes</td>
<td>52 weeks</td>
<td>86</td>
<td>Sputum volume and purulence, exacerbation rates, lung function</td>
<td>Reduced sputum volume, no change in exacerbation rates, sputum purulence, lung function</td>
<td>Sore throat (n=7)</td>
</tr>
<tr>
<td>MARTINEZ-</td>
<td>Spain</td>
<td>RCT-non DB³ (parallel)</td>
<td>Adults (mean age 69 yrs)</td>
<td>Bronchiectasis</td>
<td>Fluticasone propionate (500 μg b.i.d. or 250 μg b.i.d.)</td>
<td>Yes</td>
<td>36 weeks</td>
<td>93</td>
<td>HRQoL</td>
<td>Improved dyspnoea, reduced sputum volume, reduced β-agonist use (high-dose group)</td>
<td>Dry mouth (n=8), local irritation (n=4), dysphonia (n=4), oral candidiasis (n=2), aphthous ulcer (n=1)</td>
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<tr>
<td>GARCIA [29]</td>
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DBRCT: double-blind (DB) randomised controlled trial (RCT); b.i.d.: twice daily; FEV1: forced expiratory volume in 1 second; PD20: provocative dose causing a 20% fall in FEV1; PEFR: peak expiratory flow rate; IL: interleukin; TNF-α: tumour necrosis factor-α; LTB4: leukotriene B4; P. aeruginosa: Pseudomonas aeruginosa; eNO: exhaled nitric oxide; HRQoL: health-related quality of life. ³: the only blinded component of this study was for the dose of inhaled corticosteroids.
A Cochrane Review by Lands and Stanojevic [32] of NSAIDs in CF, including four RCTs, concluded that high-dose ibuprofen is capable of slowing disease progression; whilst NSAIDs are an attractive potential therapy in patients with bronchiectasis the benefits of treatment...
demonstrated in patients with CF cannot necessarily be extrapolated. This has been demonstrated with the use of human recombinant DNase, which when trialled in non-CF bronchiectasis resulted in increased pulmonary exacerbations and greater decline in lung function [33].

Two recent Cochrane Reviews of oral and inhaled NSAID therapy in non-CF bronchiectasis were able to identify only one study suitable for inclusion [34, 35]. In this study 25 adults with chronic lung disease (eight bronchiectasis, 12 chronic bronchitis and five diffuse panbronchiolitis) received inhaled indomethacin or placebo for 14 days. In the treatment group (inhaled indomethacin) compared with placebo, there was a significant reduction in sputum production over 14 days (difference -75 g·day⁻¹; 95% CI -134.61– -15.39) and significant improvement in dyspnoea score (difference -1.90; 95% CI -3.15– -0.65). There was no significant difference between groups in lung function or blood indices [36].

**Novel immunomodulatory agents**

**Macrolides**

Macrolides have been in clinical use as antimicrobial agents for >50 years. There are three classes of macrolides based on the central ring structure: 14-membered ring macrolides (e.g. erythromycin, roxithromycin and clarithromycin); 15-membered ring macrolides (also known as “azolides”, e.g. azithromycin); and 16-membered ring macrolides (e.g. spiramycin and josamycin) (fig. 2). The variation in structure of each class influence pharmacokinetic and pharmacodynamic properties [38]. Importantly, compared with other classes, the 15-membered ring structure azolides have less drug interaction, improved gastrointestinal tolerance and enhanced ability to concentrate within the neutrophil [39].

**Antimicrobial properties**

Macrolides exert their antimicrobial action against Gram-positive, Gram-negative and intracellular organisms by binding to ribosomal subunits required for protein replication. Of particular relevance to their use in bronchiectasis is their antimicrobial activity against *H. influenzae, Moraxella catarrhalis* and *S. pneumoniae*. Similarly their activity against “atypical” respiratory pathogens (including *Legionella pneumophila, Chlamydia* spp. and *Mycoplasma pneumoniae*) has led to their widespread usage in the treatment of community-acquired pneumonia [40, 41].

At least two compounds (clarithromycin and azithromycin) have demonstrated activity in NTM infection and are important components of multi-drug regimes for treatment of *Mycobacterium avium* complex [42]. If adherence to treatment regimens is poor or if macrolide monotherapy is administered, NTM species may develop resistance. This may result in poorer clinical outcome [43]. This is a major concern when macrolides are prescribed in disease processes where mycobacterial infections can co-exist. The recently published Australia and New Zealand bronchiectasis guidelines recommend screening for NTM prior to initiation of macrolide therapy and regular sputum surveillance during treatment [5].

**Anti-pseudomonal properties**

The reported prevalence of *P. aeruginosa* infection in bronchiectasis varies from 12% to 33% [8] and is associated with radiological disease severity [44], increased lung function decline [45] and mortality [46]. Mucoid transformation of *P. aeruginosa* allows alginate secretion and biofilm production which provides a physical barrier from the immune system and contributes to persistent airway infection and inflammation [47]. *P. aeruginosa* within biofilms can communicate through quorum sensing systems (las and rhl) which are important in coordination of the expression of virulence factors and biofilm maturation [48]. Azithromycin has been shown to suppress both lasI and rhlI in vitro [49].
*P. aeruginosa* is considered to be inherently resistant to macrolides as the *in vitro* minimal inhibitory concentration (MIC) is significantly higher than the concentration achievable *in vivo* [50]. However sub-MIC concentrations of macrolides may inhibit *P. aeruginosa* virulence. Type IV pili on the surface membrane of *P. aeruginosa* increase the organism’s motility and are believed to be critical in adhesion of *P. aeruginosa* to epithelial cells and colony expansion, and in facilitating biofilm formation. Sub-MIC concentrations of clarithromycin inhibit adherence of *P. aeruginosa* to cell surface pili and retard biofilm maturation *in vitro* [50].

Macrolides have also been shown to suppress various *P. aeruginosa* virulence factors including protease, elastase, leucocidin, pyocyanin, phospholipase C and exotoxin A [51–53]. Suppression of *P. aeruginosa* virulence varied depending on *P. aeruginosa* strains studied and the specific macrolide used. In general, azithromycin has been shown to be more effective than other macrolides [51, 52]. Azithromycin has also been shown to inhibit *P. aeruginosa* antibiotic efflux pumps thereby potentially contributing to synergy and increasing the efficacy of other classes of antimicrobials [54]. Although these studies suggest macrolides are capable of impairing *P. aeruginosa* virulence, it is important to highlight that most of these studies were performed with laboratory strains of *P. aeruginosa* using *in vitro* systems.

**Anti-inflammatory properties**

Anti-inflammatory properties of macrolides were first considered in the 1970s when observational studies noted that steroid-dependent asthmatics were able to reduce their dose of oral corticosteroid dose while prescribed erythromycin and triacetyleandomycin [55]. The steroid sparing effect was later confirmed in prospective studies in patients with severe corticosteroid dependent asthma [56]. Furthermore, a reduction in bronchial hyperreactivity in asthmatic subjects was seen in patients receiving erythromycin, clarithromycin or roxithromycin [57–59].

However, it was in the 1980s when use of macrolides revolutionised the treatment of diffuse panbronchiolitis (DPB) that their immunomodulatory properties came under closer scrutiny. DPB is an idiopathic inflammatory airway condition found almost exclusively within the South East Asian populations (especially in Japan), which histologically is characterised by intense neutrophilic inflammation of the bronchioles [60]. Its typical onset is in the second to fifth decade of life which, when untreated, progresses to severe bronchiectasis, chronic airway infection and...
ultimately respiratory failure. Prior to the introduction of macrolides in the mid 1980s, 10-year survival rates were low (~33%) [61], and even lower in those patients with chronic *P. aeruginosa* infection [62]. Since the introduction of erythromycin and subsequently other macrolides, survival has improved dramatically achieving 10-year survival rates >90% [61].

**Immunomodulatory properties**

Herin we briefly review the supportive evidence with more comprehensive reviews in the literature [63, 64]. While anti-inflammatory actions of macrolides are well established, the differences seen in some studies are probably attributable to variance in methodology, model system used and the macrolide agent studied.

Endotoxins produced by invading bacteria stimulate human epithelial cells both directly and through toll-like receptors, triggering an inflammatory cascade leading to the activation of nuclear factor (NF)-κβ [65]. NF-κβ is central in regulating transcription of genes which encode pro-inflammatory mediators, including IL-6, IL-8, TNF-α (cytokines) and the intercellular adhesion molecule-1 (ICAM-1). *In vitro* studies have demonstrated both erythromycin and clarithromycin to be capable of inhibiting NF-κβ activation [66, 67] and complimentary studies have independently demonstrated release of lower levels of IL-1, IL-6, IL-8 and ICAM-1 from activated bronchial epithelial cells when exposed to macrolides [68–70].

Neutrophils recruited to the site of inflammation become activated allowing phagocytosis of microorganisms and production of proteases (including neutrophil elastase and matrix-metalloproteinases (MMP)-9), and reactive oxygen species (ROS) responsible for the “oxidative burst” believed to be fundamental to killing the phagacytosed microorganism [71, 72]. In the setting of infection, spillage of these proteases and ROS from necrotic neutrophils contributes towards localised tissue damage and provides ongoing stimulus to the inflammatory process. Macrolides are able to modulate neutrophil function by several mechanisms. In an animal model of bronchiectasis, macrolides inhibit ICAM-1 expression which may reduce neutrophil migration to the site of inflammation [64]. Various 14-membered macrolides have been shown to inhibit the oxidative burst [72] and similarly erythromycin and flurythromycin inhibit the release of neutrophil elastase [73].

Interestingly, macrolides are associated with increased neutrophil degranulation [63]. A short-term study of the effect of azithromycin (3 days) in healthy volunteers demonstrated an immediate increase in neutrophil degranulation and circulating ROS, but decreased IL-8. This was followed by a delayed inhibitory effect on oxidative burst, myeloperoxidase, IL-6 and increased neutrophil apoptosis [74]. These *in vitro* studies provide impetus for studying the potential impact of macrolides on neutrophil dominated airway diseases such as bronchiectasis.

**Macrolides and mucus hypersecretion**

Mucus hypersecretion is a hallmark of bronchiectasis, which in combination with impaired mucociliary clearance produces a local environment conducive to chronic infection. Mucins (macromolecular glycoproteins) are major constituents of mucus and are encoded by a number of genes. One such gene, MUC5AC is specifically expressed by bronchial epithelial goblet cells [75] and *in vitro* studies demonstrate erythromycin and clarithromycin attenuate lipopolysaccharide-induced increased MUC5AC gene expression [64]. Azithromycin demonstrates similar effects on the MUC5AC gene in *P. aeruginosa* quorum sensing mediator stimulated human epithelial cells [76]. These effects are supported by *in vivo* responses to macrolides in varied animal models [77, 78].

In summary, the potential benefits of macrolide therapy in patients with bronchiectasis may result from antimicrobial properties and effects on biofilm development in patients with *P. aeruginosa* infection, by down-regulating acute and chronic inflammatory responses and limiting mucus hypersecretion.
**Clinical trials of macrolides**

To date there have been limited studies examining the effectiveness of macrolides for treatment of non-CF bronchiectasis. Those published studies have been performed in small patient populations and have varied considerably in study design including duration, dose and specific macrolide, outcome measures and whether a control group was used as a comparator (table 2).

The first double-blind, placebo-controlled RCT of macrolides in non-CF bronchiectasis compared the effect of roxithromycin (4 mg·kg⁻¹ b.i.d./placebo for 12 weeks in children with a clinical diagnosis of bronchiectasis and evidence of airway hyperreactivity [79]. There was a significant reduction in sputum purulence, leukocyte concentration and a reduction in airway reactivity (provocative dose causing a 20% fall in FEV₁ to metacholine). However, there was no change in lung function when compared with placebo.

In a second macrolide trial also in children with stable non-CF bronchiectasis, YALCIN et al. [80] compared the impact of clarithromycin with conventional treatment administered for 3 months on immune mediators within BALF. The study demonstrated greater reduction in sputum volume and BALF total cell counts, neutrophil ratios and IL-8 levels in the clarithromycin group. Interestingly, there was no significant change in sputum microbiology. This study had the major limitation of the lack of a placebo.

A double-blind RCT of erythromycin in adults with non-CF bronchiectasis compared 8 weeks of erythromycin (500 mg b.i.d., n=14) with placebo (10 patients) during a period of clinical stability [81]. Three patients, each receiving erythromycin withdrew (adverse effect n=1, poor adherence n=2). A “per protocol” analysis based on those who completed the trial demonstrated an improvement in lung function (mean increase in FEV₁ and forced vital capacity of 140 mL and 120 mL, respectively) and decreased sputum production in those receiving erythromycin. There were no differences in levels of inflammatory cytokines (IL-8, TNF-α or LTB₄) in sputum.

Several uncontrolled studies have also been reported. An open label, randomised, crossover study of 6 months of azithromycin 500 mg twice weekly and standard treatment in 12 patients (11 included in analysis) demonstrated a reduction in the number of exacerbations requiring antibiotics (five versus 16, p<0.019) and sputum volume during azithromycin therapy and no change in lung function [82]. Notably, the investigators aimed to recruit 30 subjects for the study based on pre-study power estimates.

A prospective cohort study of azithromycin in adult patients with frequent pulmonary exacerbations (>4 in the year prior to enrolment), employed a treatment protocol of azithromycin 500 mg·day⁻¹ for 6 days, then 250 mg·day⁻¹ for 6 days, followed by maintenance treatment of 250 mg three times per week [83]. Six (15%) of the 39 patients recruited withdrew due to adverse effects. Analysis based on those who tolerated therapy demonstrated a reduction in exacerbation rate (from 0.71 to 0.13 per month, p<0.001), reduction in number of courses of antibiotics (0.08 to 0.003 per month, p<0.001) and a trend to improvement in lung function parameters. Respiratory symptoms improved in those treated with azithromycin over a mean follow-up period of 20 months (in-house symptom questionnaire).

Finally a cohort study of 56 adult patients treated with azithromycin 250 mg three times per week, of which 50 patients completed a minimum of 3 months (mean duration 9.1 months), demonstrated a reduction in exacerbation rate and sputum production (compared with the 6 months prior to treatment) and an improvement in FEV₁ (only 29 patients assessable) [84].

In summary, these small studies have demonstrated that macrolide therapy is generally well tolerated and reduces sputum volume, however, effect on pulmonary function is unclear. Several studies have reported significant participant dropout due to gastrointestinal adverse events. Routine use of macrolides cannot be supported based on current evidence and there is an urgent need for large randomised placebo controlled trials to assess tolerability, clinical impact, which
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Drug</th>
<th>Placebo</th>
<th>Duration</th>
<th>Subjects</th>
<th>Outcome measures</th>
<th>Findings</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koh [79]</td>
<td>South Korea</td>
<td>DBRCT (parallel)</td>
<td>Children (mean age 13 yrs)</td>
<td>Bronchiectasis, airway hyperreactivity</td>
<td>Roxithromycin (4 mg·kg⁻¹ b.i.d.)</td>
<td>Yes</td>
<td>12 weeks</td>
<td>25</td>
<td>Sputum purulence/WCC, FEV₁, PD₂₀ metacholine</td>
<td>Reduced sputum purulence/leukocyte counts, reduced airway reactivity, fall in FEV₁</td>
<td>None</td>
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<tr>
<td>Yalcin [80]</td>
<td>Turkey</td>
<td>RCT (parallel)</td>
<td>Children (7–18 yrs)</td>
<td>Bronchiectasis, no antibiotics in prior 16 weeks</td>
<td>Clarithromycin (15 mg·kg⁻¹ b.i.d.)</td>
<td>No</td>
<td>12 weeks</td>
<td>34</td>
<td>Sputum volume, lung function, BALF (leukocyte counts, microbial cultures, IL-8, IL-10, TNF-α)</td>
<td>Reduced sputum volume, reduced BALF neutrophil ratio, IL-8, increased FEF₂₅–₇₅%, No change in FEV₁</td>
<td>None</td>
</tr>
<tr>
<td>Tsang [81]</td>
<td>China (Hong Kong)</td>
<td>DBRCT (parallel)</td>
<td>Adult (mean age 55 yrs)</td>
<td>Bronchiectasis &gt;10 mL sputum per 24 h</td>
<td>Erythromycin (500 mg b.i.d.)</td>
<td>Yes</td>
<td>8 weeks</td>
<td>24</td>
<td>24 h sputum (volume/WCC/microbial concentrations/immune mediators), lung function</td>
<td>Reduced sputum volume, improved FEV₁ and FVC, no change in microbial concentration, no change in immune mediators</td>
<td>Withdrew due to rash (n=1)</td>
</tr>
<tr>
<td>Cymbala [82]</td>
<td>USA</td>
<td>Open label (crossover)</td>
<td>Adult (mean age 71 yrs)</td>
<td>Bronchiectasis</td>
<td>Azithromycin (500 mg b.i.d.)</td>
<td>No</td>
<td>Mean 52 weeks (26 weeks each arm, 4 weeks washout)</td>
<td>12</td>
<td>Sputum volume, exacerbation rates, lung function</td>
<td>Reduced sputum volume, reduced exacerbations, no change in lung function</td>
<td>Diarrhoea (n=3)</td>
</tr>
<tr>
<td>Davies [83]</td>
<td>UK</td>
<td>Cohort</td>
<td>Adult (18–77 yrs)</td>
<td>Bronchiectasis, &gt;4 exacerbations prior 52 weeks</td>
<td>Azithromycin (500 mg q.d. 6 days, 250 mg q.d. 6 days, 250 mg MWF)</td>
<td>No</td>
<td>Mean 80 weeks</td>
<td>39</td>
<td>Exacerbation rates, antibiotic usage, lung function</td>
<td>Reduced exacerbation rate, reduced antibiotic usage, improved DL,CO, no change in FEV₁, FVC</td>
<td>Withdrew (n=6); abnormal liver function (n=2), diarrhoea (n=2), rash (n=1), tinnitus (n=1)</td>
</tr>
<tr>
<td>Anwar [84]</td>
<td>UK</td>
<td>Cohort</td>
<td>Adult (mean age 63 yrs)</td>
<td>Bronchiectasis, ≥3 exacerbations prior 26 weeks</td>
<td>Azithromycin (250 mg MWF)</td>
<td>No</td>
<td>204 weeks</td>
<td>56</td>
<td>Exacerbation rates, lung function, sputum volume/microbiology</td>
<td>Reduced sputum volume, reduced exacerbation rates, reduced positive sputum microbial cultures</td>
<td>Withdrew (n=6); diarrhoea (n=3), abdominal cramps (n=2), skin rash (n=2)</td>
</tr>
</tbody>
</table>

DBRCT: double-blind randomised controlled trial (RCT); b.i.d.: twice daily; WCC: white cell count; FEV₁: forced expiratory volume in 1 second; PD₂₀: provocative dose causing a 20% fall in FEV₁; BALF: bronchoalveolar lavage fluid; IL: interleukin; TNF: tumour necrosis factor; FVC: forced vital capacity; FEF₂₅–₇₅%: forced expiratory flow at 25–75% FVC; q.d.: once daily; DL,CO: diffusing capacity of the lung for carbon monoxide; MWF: Monday, Wednesday, Friday. #: immune mediators: IL-1α, TNF-α and leukotriene B₄; *: seven adverse events in six patients.
macrolide is most beneficial and to assess the risk of macrolide resistant infections. This latter point is important given the emerging evidence of macrolide resistance in Europe [85–87] and in the CF population [88–90]. Several studies have either recently been completed, are actively recruiting or about to commence, which will hopefully address some of these important issues (table 3).

**HMGcoA reductase inhibitors**

HMGcoA reductase inhibitors (“statins”) have established clinical utility as lipid lowering agents in patients with hyperlipidaemia. They also have widely recognised anti-inflammatory and immunomodulatory properties. In vitro studies of HMGCoA reductase inhibitors have demonstrated inhibition of neutrophil migration and epithelial cell production of chemottractants and proteases and potentiation of macrophage efferocytosis [72].

In animal models of COPD, simvastatin has been shown to inhibit airway remodelling, lower TNF-α and MMP-9 levels and reduce peribronchial and perivascular inflammation [91, 92]. A recent systematic review identified nine studies using HMGCoA reductase inhibitors in patients with COPD [93], however, only one of these was a prospective RCT. Collectively, these studies demonstrated beneficial effects on pulmonary function, exacerbation rates and mortality and provide the foundation for further study. Large, prospective RCTs are currently underway. Studies in asthmatic subjects have yielded more variable results. Reduction in airway hyperreactivity has been seen in one study [94], no benefit in another [95] and one retrospective review even suggested HMGCoA reductase inhibitor use was associated with poorer clinical outcomes [96]. A recent placebo-controlled, double-blind RCT of simvastatin 40 mg·day⁻¹ in patients with steroid responsive (eosinophilic) asthma failed to demonstrate any clinically significant steroid sparing effect from the addition of simvastatin [97].

There are currently no studies of the use of HMGCoA reductase inhibitors for bronchiectasis, however, the findings of the studies in other airway diseases suggest that future studies are worthwhile.

**Targeted agents**

There are currently no phase III trials of targeted therapies in inflammatory airway diseases, however, a number of potential candidate agents specifically targeting neutrophilic inflammation are under investigation.

The CXC chemokines and their associated receptors (CXCR1/CXCR2) are believed to have a key role in neutrophilic inflammation in pulmonary disease and recently a number of agents which inhibit this pathway have been developed [98]. A phase II study of an anti-CXCL8 monoclonal antibody in COPD has demonstrated safety and improvement in dyspnoea scores over 3 months [99]. In a complimentary in vitro study ELR-CXC antagonists inhibited neutrophil chemotactic factors in the sputum of bronchiectatic patients [100]. These studies suggest that further investigation of these agents may be valuable.

Anti-TNF-α agents have an established role in treatment of systemic inflammatory diseases, including rheumatoid arthritis [101] and Crohn’s disease [102]. In short-term trials of anti-TNF-α agents in inflammatory lung diseases variable efficacy has been reported. While improvement in exacerbation rates in asthma have been demonstrated [103], no effect was seen in patients with COPD [104]. The major concerns associated with the use of these agents in patients with pulmonary disease are the potential for the emergence of opportunistic infections, in particular the re-activation of mycobacterial disease [105] and their possible association with acute deterioration of fibrotic lung disease [106].

With the emerging array of anti-inflammatory monoclonal antibodies and targeted receptor blocker drugs, new therapeutic options will potentially become available. Carefully conducted trials will be required to support the use and examine adverse consequences. Although manipulation of the immune response is an attractive prospect for treatment of a range of
<table>
<thead>
<tr>
<th>Study acronym</th>
<th>Country</th>
<th>Design</th>
<th>Population</th>
<th>Inclusion criteria</th>
<th>Drug</th>
<th>Duration</th>
<th>Subjects</th>
<th>Outcome measures</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIS</td>
<td>International multicentre study (Australia, New Zealand)</td>
<td>DBRCT (parallel)</td>
<td>Indigenous children (1–8 yrs)</td>
<td>≥1 pulmonary exacerbation prior 52 weeks, confirmed bronchiectasis or chronic SLD</td>
<td>Azithromycin (30 mg·kg⁻¹·week⁻¹)</td>
<td>104 weeks</td>
<td>88</td>
<td>Exacerbations (time to first/rate/severity), safety/adverse events, antimicrobial resistance</td>
<td>Recruitment until Dec 2010</td>
</tr>
<tr>
<td>BLESS</td>
<td>Australia</td>
<td>DBRCT (parallel)</td>
<td>Adults (18–80 yrs)</td>
<td>Confirmed bronchiectasis (HRCT), ≥2 exacerbations in prior 52 weeks, daily productive cough, clinically stable (4 weeks)</td>
<td>Erthromycin (400 mg b.i.d.)</td>
<td>48 weeks</td>
<td>118</td>
<td>Exacerbation rate, antibiotic usage, HRQoL, sputum volume/inflammatory markers</td>
<td>Ongoing</td>
</tr>
<tr>
<td>BAT</td>
<td>The Netherlands</td>
<td>DBRCT (parallel), stratified by \textit{P. aeruginosa} status</td>
<td>Adults (&gt;18 yrs)</td>
<td>Confirmed bronchiectasis (HRCT)</td>
<td>Azithromycin (250 mg q.d.)</td>
<td>52 weeks</td>
<td>72</td>
<td>Exacerbation rate, change in lung function, change in symptom scores, change in airway microbiology, sputum inflammatory markers, HRQoL, adverse events</td>
<td>Study completed, yet to report</td>
</tr>
<tr>
<td>EMBRACE</td>
<td>New Zealand</td>
<td>DBRCT (parallel)</td>
<td>Adults (18–80 yrs)</td>
<td>Confirmed bronchiectasis (HRCT), clinically stable, ≥1 exacerbations in prior 52 weeks</td>
<td>Azithromycin (500 mg MWF)</td>
<td>26 weeks</td>
<td>140</td>
<td>Exacerbations (time to first/rate/severity), change in lung function, HRQoL, change in sputum cell count</td>
<td>Study completed, yet to report</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
<td>DBRCT (factorial design), stratified by \textit{P. aeruginosa} status</td>
<td>Adults (18–80 yrs including indigenous adults)</td>
<td>Bronchiectasis (HRCT + clinical), clinically stable, ≥2 weeks since antibiotics for exacerbation</td>
<td>Azithromycin (250 mg q.d.) or hypertonic saline 7% or both</td>
<td>26 weeks</td>
<td>130</td>
<td>HRQoL, exacerbation rate, change in lung function, change in symptoms score, change in airway microbiology, sputum inflammatory markers, adverse events</td>
<td>Recruitment to commence early 2011</td>
</tr>
</tbody>
</table>

BIS: bronchiectasis intervention study; BLESS: bronchiectasis and low-dose erythromycin study; BAT: bronchiectasis and long-term azithromycin treatment; EMBRACE: effectiveness of macrolides in patients with bronchiectasis using azithromycin to control exacerbations; DBRCT: double-blind randomised controlled trial; SLD: suppurative lung disease; HRCT: high-resolution computed tomography; \textit{b.i.d.}: twice daily; HRQoL: health-related quality of life; \textit{q.d.}: once daily; \textit{P. aeruginosa}: \textit{Pseudomonas aeruginosa}; MWF: Monday, Wednesday, Friday.
inflammatory medical conditions, history advocates caution. In March 2006, six healthy volunteers enrolled in a phase I trial were administered a first-in-man anti-CD28 humanised monoclonal antibody (TG1412) designed to modulate regulatory T-cells. Within hours of administration each volunteer experienced a severe cytokine storm resulting in multi-organ failure [107]. Although all six survived, the most severely affected subject required intensive care support for 3 weeks. Similarly, in a recent study in children and adults with CF the use of an LTB4 antagonist (BIIL284) resulted in increased respiratory exacerbations resulting in the study being prematurely terminated after interim data analysis [108].

These studies highlight that in conditions characterised by infection associated with inflammation, anti-inflammatory therapies may be associated with adverse consequences and require very careful and detailed analysis.

**Conclusion**

Evidence for the use of anti-inflammatory therapies in bronchiectasis is limited and more adequately powered studies are required [109, 110]. There is currently insufficient evidence to support the use of inhaled and oral corticosteroids, NSAIDs and macrolides. Individual patient trials may be warranted for inhaled corticosteroids and macrolides and other therapies remain unproven with no evidence to support use as anti-inflammatory therapy in bronchiectasis.

**Statement of interest**

None declared.

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**References**

Anti-Inflammatory Therapy


