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REVIEW

Long-term macrolide therapy in chronic inflammatory airway diseases

P.A.J. Crosbie and M.A. Woodhead

ABSTRACT: In addition to direct antibacterial actions, 14- and 15-member-ring macrolides have immune modulating effects that appear to be the reason for clinical benefit in diffuse panbronchiolitis.

A literature search was conducted for studies of the clinical effectiveness of macrolides in other chronic lung conditions.

A number of studies were identified that showed short-term beneficial outcomes or the potential for such outcomes in cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease, asthma and post-transplant obliterative bronchiolitis. The studies were limited by small patient numbers, different outcome measures and short-term follow-up, and were not designed to assess potentially harmful effects.

Further large prospective and long-term studies are required in order to identify potential benefit and harm before these agents can be recommended routinely for these conditions.

KEYWORDS: Airway, anti-inflammatory, ketolide, macrolide

Macrolide antibiotics are used as first-line agents in the treatment of acute bacterial infections, such as community-acquired pneumonia [1]. In addition to direct antimicrobial activity, macrolides also exert immune modifying effects [2, 3]. The potential clinical benefit of these properties was first investigated in steroid-dependent asthma [4]. In one study, patients concurrently treated with the macrolide troleandomycin were able to significantly reduce their total steroid dose without a significant decrease in asthma control [5]. Subsequently, this was shown to be due, at least in part, to alterations in steroid metabolism, with troleandomycin reducing methylprednisolone clearance by 60% [6]. NELSON *et al.* [7], in a 2-yr double-blind placebo-controlled study, showed that the combination of macrolide and methylprednisolone produced no significant clinical benefit in steroid-dependent asthma but, instead, resulted in an increase in steroid-induced side-effects, *e.g.* accelerated loss of bone density and increased sugar levels.

The chance finding that erythromycin treatment radically improved the clinical outcome of a patient with diffuse panbronchiolitis rekindled interest in the use of macrolides as a potential treatment in other inflammatory airway disorders, *e.g.* cystic fibrosis [8]. Diffuse panbronchiolitis is a progressive inflammatory disorder of lung airways found almost exclusively in Japan. Clinically it is characterised by chronic cough, excessive sputum production, exertional breathlessness, chronic sinusitis and Pseudomonas colonisation [9]. Untreated, the prognosis of diffuse panbronchiolitis is poor, with progressive deterioration of lung function, the development of diffuse bronchiectasis and death caused by respiratory failure. The introduction of long-term macrolide therapy has resulted in dramatic improvements in survival, with 5-yr survival rates increasing from 63 to 92% [9, 10]. Significant symptom reduction and improved pulmonary function have also been achieved [11–14]. The mechanism of action is thought to be due to immune modifying effects rather than direct antimicrobial activity. Clinical improvement has been reported independent of the presence or absence of chronic airway infection [11] and with antibiotic levels below the minimum inhibitory concentrations of several pathogenic bacteria [15].

The anti-inflammatory properties of macrolides are related to structure, with immunomodulatory effects seen with 14- (erythromycin, clarithromycin and roxithromycin) and 15- (azithromycin) but not 16-member (josamycin) macrolides [16].

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Macrolides are postulated to reduce airway inflammation *via* several mechanisms. These effects include reduced airway mucus secretion [17] and anti-inflammatory properties, including decreased airway neutrophil accumulation through a reduction in expression of pro-inflammatory cytokines, *e.g.* interleukin (IL)-8, and adhesion molecule production, *e.g.* macrophage adhesion molecule-1 [18–20]. Antipseudomonal activity may also be important [3].

In addition to the potential benefit, use of these agents also has the potential for harm. In addition to many of the usual risks from antimicrobial therapy, macrolides also have clinically significant effects on cardiac conduction [21] and may be important promoters of antimicrobial resistance [22].

The role of macrolides in the treatment of diffuse panbronchiolitis is well established. What is less clear is the evidence for a role of macrolides in the treatment of other chronic inflammatory airway diseases, *e.g.* cystic fibrosis, bronchiectasis, asthma, obliterative bronchiolitis, chronic obstructive pulmonary disease (COPD) and chronic rhinosinusitis. The possible anti-inflammatory mechanisms of macrolide action have recently been reviewed [3]. The aim of the present review was to examine clinical studies regarding macrolide treatment in such inflammatory conditions in order to identify evidence of a significant clinical benefit, and, where possible, to balance this against the potential for harmful effects of these agents.

METHODS

A literature search was conducted using PubMed/MEDLINE. The terms macrolide OR erythromycin OR clarithromycin OR azithromycin OR roxithromycin OR troleandomycin OR telithromycin were used in conjuncture with each condition: asthma, bronchiectasis, cystic fibrosis, panbronchiolitis, obliterative bronchiolitis, chronic rhinitis, chronic obstructive pulmonary disease and COPD. Only double-blind placebo-controlled trials were included in the review of asthma since many more such studies were available.

CLINICAL TRIALS

Cystic fibrosis

A number of clinical trials, including four randomised double-blind placebo-controlled trials comprising 368 patients, have shown evidence of beneficial effects of macrolide treatment in both adults and children with cystic fibrosis (table 1). The largest clinical trial of azithromycin treatment in cystic fibrosis studied 185 patients aged >6 yrs who were chronically infected with *Pseudomonas aeruginosa* and had a forced expiratory volume in one second (FEV_1) of >30% of the predicted value [27]. Patients were randomised to receive either azithromycin (250 or 500 mg dependent on body weight) or placebo three times a week for 24 weeks. There was a 4.4% relative improvement in FEV_1 in the azithromycin group and a 1.8% decline in the placebo group ($p=0.001$). A similar improvement was seen in forced vital capacity (FVC). FEV_1 returned to baseline 4 weeks after treatment was discontinued. Patients in the treatment group gained significantly more weight than those in the placebo arm (0.7 kg; 95% confidence interval (CI) 0.1–1.4; $p=0.02$) and were less likely to suffer an exacerbation (hazard ratio 0.65; 95% CI 0.44–0.95; $p=0.03$). A reduction in exacerbation rate was also seen in patients in the treatment arm who had not shown a significant improvement in FEV_1 [31]. A reduction in hospital days (47%) and days of intravenous antibiotic use (39%) was also reported but did not reach significance. Reported adverse events that were significantly more common in the treatment group included nausea (17% more; $p=0.01$), diarrhoea (15% more; $p=0.009$) and wheezing (13% more; $p=0.007$).

The finding of a beneficial effect of azithromycin on pulmonary function has been reported in several smaller studies [26, 28–30]. A Cochrane review of macrolide therapy undertaken in 2004 concluded that treatment with azithromycin had a small but significant effect on pulmonary function in patients with cystic fibrosis [23]. However, more recent data have suggested that the initial benefit in pulmonary function seen with the commencement of azithromycin treatment may not be maintained over the long term. CLEMENT *et al.* [25] studied the effect of azithromycin therapy over 12 months in 82 patients with cystic fibrosis, 19 of whom were infected with *P. aeruginosa*. There was no significant difference in FEV_1 between the treatment and control group at the end of the study; although the treatment arm initially showed a significant improvement in FEV_1, measurements were similar in both groups by 10 months. However, the number of pulmonary exacerbations, time until the first exacerbation and number of additional courses of antibiotics were significantly reduced in the treatment arm. These findings were independent of Pseudomonas status. A retrospective study by TRAMPER-STRANDERS *et al.* [24] reported that, although significant improvements in FEV_1 were measured up to 1 yr after commencement of azithromycin in 100 patients with cystic fibrosis, this improvement was not maintained in the longer term and FEV_1 fell in the second and third years of follow-up. This study also reported marked increases in *Staphylococcus aureus* resistance to macrolides, up to 83% after 1 yr, 97% after 2 yrs and 100% after 3 yrs of azithromycin therapy. Increased macrolide resistance in *S. aureus* and *Haemophilus* spp. was also reported by PHAFF *et al.* [32] in a population receiving azithromycin maintenance therapy over a 4-yr period.

There is consistent evidence that macrolide therapy reduces infective exacerbations, decreases the requirement for additional antibiotics and improves nutritional measures in patients with cystic fibrosis. However, short-to-medium term improvements in lung function may not be maintained in the longer term. Whether infective exacerbations are reduced in frequency over the long term and what clinical impact increased macrolide bacterial resistance has requires further study.

Bronchiectasis

The role of macrolide therapy in bronchiectasis treatment has been examined only in five small studies, with a maximum of 39 patients (table 2). Only two were randomised double-blind placebo-controlled trials. KOH *et al.* [37] showed a significant decrease in airway responsiveness to methacholine in children with bronchiectasis (and increased airway responsiveness) who received roxithromycin ($n=13$) for 12 weeks compared to controls ($n=12$). There was no change in spirometric results, but, by 6 weeks, significant improvements in sputum purulence scores were observed in the treatment arm. The clinical significance of reduced airway responsiveness in bronchiectasis is unclear. TSANG *et al.* [36] studied the effect of

TABLE 1 Summary of studies examining the clinical effectiveness of macrolide therapy in cystic fibrosis

First author [ref.]	Study design	Azithromycin regimen	Adults/ children n	Length of study	Benefit?	Adverse effects (treatment arm)
SOUTHERN [23]	Meta-analysis	Azithromycin	296	⩽6 months+	↑ FEV_1	No serious events
TRAMPER-STRANDERS [24]	Prospective, open-label	5–10 mg·kg^{-1} *o.d.*	0/100	3 (0.9–7) yrs	↑ FEV_1 in year 1 and ↓ FEV_1 in years 2 and 3	Macrolide-resistant *Staphylococcus aureus* (100%)
CLEMENT [25]	Multicentric, randomised, double-blind, placebo-controlled	250–500 mg three times weekly	82#	12 months	FEV_1 unchanged; ↓ exacerbation rate/number oral antibiotics	No difference in minor adverse events between groups
HANSEN [26]	Observational cohort	250 mg *o.d.*	45/0	12 months	↑ FEV_1+FVC; ↑ weight; ↓ mucoid *Pseudomonas aeruginosa*	Tinnitus (n=2)
SAIMAN [27]	Multicentric, randomised, double-blind, placebo-controlled	250 or 500 mg three times weekly	185¶	24 weeks	↑ FEV_1; ↓ exacerbation rate; ↑ weight; ↑ adverse events	↑ Nausea (17% more); ↑ diarrhoea (15% more); ↑ wheezing (13% more)
PIRZADA [28]	Retrospective	250 mg *o.d.*	20/0	21 months	↑ FEV_1+FVC; ↓ *i.v.* antibiotics; ↑ weight	Not specifically mentioned; one subject withdrew because of abdominal pain
EQUI [29]	Randomised, double-blind, placebo-controlled, crossover	250–500 mg *o.d.*	0/41	Two 6-month blocks	↑ FEV_1; ↓ oral antibiotics	Subjects reported no significant side-effects (LFT results abnormal (n=1))
WOLTER [30]	Randomised, double-blind, placebo-controlled	250 mg *o.d.*	60/0	3 months	↓ FEV_1 decline rate; ↑ QoL score; ↓ *i.v.* antibiotics	No difference between groups (urticaria (n=1), neutropenia (n=1), rash (n=1))

FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; LFT: liver function test; QoL: quality of life. #: mostly children; ¶: all chronically infected with Pseudomonas; +: follow-up.

erythromycin (500 mg twice daily) for 8 weeks on adult subjects with stable severe idiopathic bronchiectasis. A significant improvement in FEV_1, FVC and sputum volume was seen in subjects receiving erythromycin (n=11) compared to controls (n=10). Measurements of sputum pathogens and pro-inflammatory mediators (IL-8, tumour necrosis factor-α, IL-1α and leukotriene B_4) did not change in either group during the study [36].

A placebo-controlled trial of children with bronchiectasis treated with clarithromycin for 3 months showed no change in FEV_1, although maximal mid-expiratory flow (FEF_{25-75}) was significantly improved and there was a significant reduction in sputum volume [33]. A reduction in bronchoalveolar lavage (BAL) fluid IL-8 concentration was seen in the treatment arm, but no change in pathogens or other measures of inflammation, including IL-10 and tumour necrosis factor-α, was measured. CYMBAALA *et al.* [34] showed a reduction in sputum volume and infectious exacerbation frequency in adults (n=11) treated with azithromycin in a randomised crossover study design. A quarter of the study population complained of diarrhoea as a side-effect of azithromycin treatment, with one individual withdrawing from the study. A prospective cohort study of 39 patients with frequent exacerbations of bronchiectasis (more than four exacerbations in 12 months), showed significant improvements in exacerbation frequency, use of intravenous antibiotics, sputum production and symptom scores when subjects received 4 months of azithromycin treatment [35].

The trials of macrolide treatment in bronchiectasis are limited in number, size of study population, and length of treatment and follow up. However, there is consistent evidence of a decrease in exacerbation frequency and sputum volume. These findings would need to be confirmed in much larger studies with longer follow-up times and careful assessment of harmful effects in order to define a role for macrolides in bronchiectasis treatment.

Chronic obstructive pulmonary disease

One published study has examined the effect of clarithromycin treatment in COPD [38]. This was a prospective double-blind randomised controlled trial of 67 patients with moderately severe COPD. The effects of 3 months' clarithromycin therapy on health status, exacerbation rate and sputum bacterial numbers were measured. Overall, no significant benefit was seen in any measure. However, significant improvements in both the St George's Respiratory Questionnaire symptom score and 36-item short-form health survey physical function score were seen.

TABLE 2 Summary of studies examining the clinical effectiveness of macrolide therapy in bronchiectasis

First author [ref.]	Study design	Drug regimen	Adults/ children n	Length of study	Benefit?	Adverse effects (treatment arm)
YALCIN [33]	Randomised, placebo-controlled	Clarithromycin 15 mg·kg^{-1}	0/34	3 months	↓ Sputum volume; ↑ FEF_{25-75}; FEV_1 unchanged	Not examined
CYMBALA [34]	Randomised, open-label, crossover	Azithromycin 500 mg twice weekly	11/0	6 months	↓ Exacerbation frequency; ↓ sputum volume	No serious events (diarrhoea in 25%)
DAVIES [35]	Prospective, open-label	Azithromycin 250 mg three times weekly	39/0	10 months	↓ Exacerbation frequency; ↓ *i.v.* antibiotics; ↑ $T_{L,CO}$; ↓ symptoms	Drug stopped due to abnormal LFT results (n=2), diarrhoea (n=2), rash (n=1), tinnitus (n=1)
TSANG [36]	Randomised, double-blind, placebo-controlled	Erythromycin 500 mg twice daily	21/0	8 weeks	↑ FEV_1 + FVC; ↓ sputum volume	One withdrawal due to rash
KOH [37]	Randomised, double-blind, placebo-controlled	Roxithromycin 4 mg·kg^{-1} twice daily	0/25#	12 weeks	↓ Airway responsiveness; FEV_1 unchanged	Not examined

FEF_{25-75}: maximal mid-expiratory flow; FEV_1: forced expiratory volume in one second; $T_{L,CO}$: transfer factor of the lung for carbon monoxide; LFT: liver function test; FVC: forced vital capacity. #: with increased airway responsiveness.

WILKINSON *et al.* [39] recently presented results of a similarly designed study in abstract form. This study measured the number of treated exacerbations as a primary outcome in 109 patients with COPD treated with erythromycin for 1 yr. Patients in the placebo arm were significantly more likely to be treated for an exacerbation than subjects treated with erythromycin (odds ratio 1.48; p=0.004). The number of studies investigating macrolide therapy in COPD is clearly extremely limited (table 3), but the positive benefit seen in the most recent study suggests that more work should be undertaken.

Chronic rhinosinusitis

Macrolide treatment of chronic rhinosinusitis has been investigated in several open-label studies [40–42]. For example, a prospective open-label study of 17 patients with persistent sinusitis following sinus surgery, using erythromycin treatment, showed significant improvements in saccharin transit time and symptoms, including nasal congestion, rhinitis and headache, at 3 and 12 months of follow-up [41]. The first double-blind randomised placebo-controlled study examining the effects of low-dose macrolide therapy in chronic rhinosinusitis was reported in 2006 [43]. This study investigated the effects of 3 months' roxithromycin treatment in 64 patients with chronic rhinosinusitis. Significant improvements were measured in rhinosinusitis-specific quality-of-life scores (20-item Sino-Nasal Outcome Test (SNOT-20)), saccharin transit time, nasal endoscopic scoring and nasal lavage levels of IL-8. Outcomes were better in patients with low immunoglobulin E levels. A further SNOT-20 assessment was then carried out 3 months after cessation of macrolide therapy, and improvements in scores were not maintained. The results from this study are encouraging but further work is required in order to define a role for macrolide therapy in the treatment of chronic rhinosinusitis.

Asthma

Several randomised double-blind placebo-controlled trials have examined the role of macrolide therapy in the management of

TABLE 3 Summary of studies examining the clinical effectiveness of macrolide therapy in chronic obstructive pulmonary disease

First author [ref.]	Study design	Drug regimen	Adults/ children n	Length of study	Benefit?	Adverse effects (treatment arm)
BANERJEE [38]	Block, randomised, prospective, double-blind, placebo-controlled	Clarithromycin 500 mg once daily	67	3/12 months	Health status unchanged; exacerbation rate unchanged; sputum bacterial numbers unchanged	One withdrawal due to gastrointestinal upset
WILKINSON [39]	Randomised, double-blind, placebo-controlled	Erythromycin 250 mg twice daily	109	1 yr	↓ Incidence of exacerbations	Not presented

chronic asthma (table 4). Proposed mechanisms of macrolide action in asthma include direct antimicrobial activity, alteration of steroid metabolism and anti-inflammatory effects [47]. Early studies of troleandomycin in oral steroid-dependent asthmatics suggested a significant steroid-sparing role. For example, an open-label study of ZEIGER *et al.* [5] showed significant symptom and spirometric improvements along with a reduction in steroid dose. A small study of KAMADA *et al.* [52], of 18 severe steroid-dependent asthmatic children, showed a significant decrease in oral steroid requirement in the troleandomycin and methylprednisolone group compared to placebo; however, no improvement in FEV1 was seen. Troleandomycin reduces methylprednisolone clearance; this mechanism is thought to be a factor in the reduced steroid requirement in these patients [6]. However, a double-blind placebo-controlled trial of troleandomycin added to methylprednisolone in 75 steroid-dependent asthmatics over a 2-yr period showed no benefit in reducing steroid dose to control asthma symptoms [7]. However, there was a significant reduction in bone density in the macrolide group.

Chronic infection with atypical organisms may play a role in the pathogenesis or severity of chronic asthma [53, 54]. Two studies have examined the effects of macrolide therapy in asthmatics with serological or PCR evidence of infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. The largest study of BLACK *et al.* [49] examined the effect of 6 weeks' roxithromycin or placebo treatment on 232 asthmatics with serological evidence of infection with *C. pneumoniae*. No significant change in the primary end-points of mean morning peak expiratory flow (PEF) or symptom score was observed. There was a significant improvement in evening PEF by 6 weeks, but this was nonsignificant after 6 months' follow-up [49]. This was in direct contrast to a smaller study of KRAFT *et al.* [48], who measured significant improvements in FEV1 only in asthmatics whose BAL fluid was PCR-positive for either *M. pneumoniae* or *C. pneumoniae* compared to PCR-negative subjects.

The lack of a gold standard for proof of *C. pneumoniae* infection may be one reason for the inconsistent findings. The use of serology, by BLACK *et al.* [49], to define infected and noninfected populations may have resulted in a dilution of subjects with true chronic infection with those previously exposed but not currently infected. By contrast, KRAFT *et al.* [48] used PCR to define their populations and probably had a higher chance of delineating between truly infected and noninfected individuals. A further confounding factor may have been differences in numbers treated with inhaled corticosteroid (30% of subjects in the study of KRAFT *et al.* [48] compared to >75% in the study of BLACK *et al.* [49]).

Two studies have shown significant reductions in bronchial hyperresponsiveness in patients with asthma after 8 weeks' treatment with clarithromycin; neither showed any significant change in FEV1 [47, 50]. The first study examined 17 patients with allergy-induced asthma and demonstrated a significant reduction in blood and sputum eosinophil counts, suggesting a possible anti-inflammatory role for clarithromycin [50]. Patients taking oral or inhaled corticosteroid were excluded. The second study examined asthmatics taking 800 μg budesonide daily; serum-free cortisol levels showed no change from baseline levels after treatment with clarithromycin, suggesting that altered steroid metabolism was not the effect mechanism [47]. Evidence for reduced bronchial hyperresponsiveness has also been demonstrated after treatment with erythromycin, roxithromycin and azithromycin [55–57]. A more recent study of SIMPSON *et al.* [45] showed improvements in quality-of-life scores and significant reductions in wheezing in patients with refractory asthma. No improvement in bronchial hyperresponsiveness or FEV1 was seen. Improvement in quality-of-life scores was matched by significant reductions in induced sputum neutrophil numbers and IL-8 and neutrophil elastase levels. The authors reported that improvements in quality of life and measures of inflammation were most apparent in non-eosinophilic asthmatics.

Interpretation of the studies as a whole is difficult because of the heterogeneous nature of the study populations, the small number of patients studied and the short study durations (⩽12 weeks). This was reflected in the conclusion of a Cochrane review of RICHELDI *et al.* [44], which stated there was insufficient evidence to support or refute the use of macrolides in the management of chronic asthma.

A recent study of JOHNSTON *et al.* [46] examined the effect of the ketolide telithromycin on the management of acute exacerbations of asthma. This was a double-blind placebo-controlled study of 278 adults who were randomised to receive 10 days of either oral telithromycin or placebo. The primary outcomes were change from baseline asthma symptoms and home-recorded morning PEF. Patients in the treatment arm showed a significant reduction in asthma symptoms compared to placebo ($p=0.004$), but no difference in home-recorded PEF was seen. Significant improvements in symptom-free days (16 *versus* 8%; $p=0.006$) and other measures of pulmonary function were seen in the treatment arm when measured in the clinic at the end of treatment but not at a 6-week follow-up (including FEV1, PEF, FVC and $FEF_{25–75}$). There was evidence of *C. pneumoniae* or *M. pneumoniae* infection in 61% of the study population; however, bacteriological status was not related to telithromycin response. Nausea was reported significantly more frequently in the telithromycin group ($p=0.01$), and elevation of liver enzyme levels was seen in two patients in the telithromycin group who had shown abnormal enzyme levels prior to commencement of treatment. This study shows some benefit with ketolide treatment in acute asthma; the high apparent prevalence of *C. pneumoniae* or *M. pneumoniae* suggests that the mechanism of action may be related to direct antimicrobial activity. It is unclear whether the benefit measured translates into a clinical benefit, and more studies are clearly required.

Post-transplant obliterative bronchiolitis

Bronchiolitis obliterans is a significant cause of long-term morbidity and mortality in patients following lung transplantation. Bronchiolitis obliterans syndrome (BOS) is the clinical manifestation of chronic airways rejection [58]. A progressive decline in FEV1 is often seen, and mortality rates of 25–50% have been reported [59, 60]. Several small studies (maximum 20 patients) have examined the potential benefit of azithromycin in the treatment of post-transplant obliterative bronchiolitis (table 5). Five prospective open-label studies have been

TABLE 4 Summary of randomised-controlled studies examining the clinical effectiveness of macrolide therapy in asthma

First author [ref.]	Study design	Drug regimen	Adults/ children n	Length of study	Benefit?	Adverse effects (treatment arm)
RICHELDI [44]	Meta-analysis				Insufficient evidence for a conclusion	No difference in drug withdrawals or GI events
SIMPSON [45]	Randomised, double-blind, placebo-controlled	Clarithromycin 500 mg *b.i.d.*	45/0	8 weeks	↑ QoL; ↓ wheeze; FEV_1 unchanged; BHR unchanged	Not reported
JOHNSTON [46]	Randomised, parallel group, double-blind, placebo-controlled	Telithromycin 800 mg daily for 10 days	278/0	6 weeks	↓ Symptom score; home PEF unchanged	No overall difference between groups (nausea more common (5.3%), ↑ ALT+AST (n=2))
KOSTADIMA [47]	Randomised, double-blind, placebo-controlled	Clarithromycin 250 mg *b.i.d./t.i.d.*	63/0 (all ICS)	8 weeks	↓ BHR; FEV_1 unchanged	Not examined (GI disorder (n=1))
KRAFT [48]	Randomised, double-blind, placebo-controlled	Clarithromycin 500 mg *b.i.d.*	55/0 (32% ICS)	6 weeks	↑ FEV_1 in PCR+ subjects (*Mycoplasma pneumoniae* or *Chlamydia pneumoniae*)	Not examined
BLACK [49]	Randomised, double-blind, placebo-controlled	Roxithromycin 150 mg *b.i.d.*	232/0 (>75% ICS)	6 weeks (6 month follow-up)	Morning PEF unchanged; ↑ evening PEF; symptom score unchanged	No overall difference between groups (diarrhoea/nausea more common, ↑ ALT+AST (n=2))
AMAYASU [50]	Randomised, double-blind, placebo-controlled, crossover	Clarithromycin 200 mg *b.i.d.*	17/0 (no ICS)	8 weeks	FEV_1 unchanged; ↓ BHR; ↓ symptom score	None
SHOJI [51]	Randomised, double-blind, placebo-controlled, crossover	Roxithromycin 150 mg *b.i.d.*	14/0 (no ICS)	Two 8-week blocks	FEV_1 unchanged; BHR unchanged; ↓ symptom score	None
KAMADA [52]	Randomised, double-blind, parallel treatment arms	Troleandomycin + methylprednisolone; troleandomycin + prednisone; methyl-prednisolone	0/19 (all ICS)	12 weeks	All ↓ steroid dose; ↓ symptom score#; pulmonary function unchanged	One withdrawal due to abnormal LFT results
NELSON [7]	Double-blind, placebo-controlled	Troleandomycin + methylprednisolone; methylprednisolone	75/0	2 yrs	No benefit	↓ Bone density; ↑ glucose+cholesterol

GI: gastrointestinal; QoL: quality of life; FEV_1: forced expiratory volume in one second; BHR: bronchial hyperresponsiveness; PEF: peak expiratory flow; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ICS: inhaled corticosteroid; LFT: liver function test. #: troleandomycin/methylprednisolone group.

undertaken, with four showing significant improvements in FEV_1 with azithromycin treatment [61, 62, 65, 66] and one showing no significant effect [63]. One retrospective study also showed a significant increase in FEV_1 with azithromycin treatment [64]. The largest prospective study treated 14 patients with azithromycin three times weekly for 12 weeks [66]. A 13% increase in FEV_1 was seen in the group as a whole, an increase of 0.31 L ($p=0.007$). Only six out of the 14 study subjects showed an improvement in FEV_1 of >10%. All of the subjects underwent BAL prior to and after 3 months of treatment. Absolute BAL fluid neutrophil count, the proportion of neutrophils, and levels of IL-8 and -17 were significantly reduced in the patients with significant changes in FEV_1 but not in the eight subjects who had shown no response. The authors stated that a BAL fluid neutrophilia of >15% predicted a significant response to azithromycin treatment (positive predictive value 85%). There was no difference in colonisation with Pseudomonas between the groups.

Two studies have examined the possible role of *C. pneumoniae* infection in the development of BOS after lung transplantation. KOTSIMBOS *et al.* [67] showed that a mismatch in donor–recipient *C. pneumoniae* serology (*i.e.* donor positive/recipient negative) was an independent risk factor for the development of BOS. With the reverse mismatch (*i.e.* donor negative/recipient positive) the risk of BOS was reduced. GLANVILLE *et al.* [68] showed that *C. pneumoniae* infection in lung transplants was associated with a worse outcome and increased risk of BOS. One mechanism by which macrolide therapy may benefit lung transplant patients could be in the treatment of *C.*

TABLE 5 Summary of studies examining the clinical effectiveness of macrolide therapy in post-transplant obliterative bronchiolitis

First author [ref.]	Study design	Drug regimen	Adults/ children n	Length of study	Benefit?	Adverse effects (treatment arm)
GERHARDT [61]	Prospective, open label	Azithromycin 250 mg daily for 5 days then three times weekly	6	Mean 13 weeks	↑ FEV_1 (significant in 5/6 patients)	Not examined
VERLEDEN [62]	Prospective, open label	Azithromycin 250 mg daily for 5 days then alternate days	8	Min 12 weeks; max 36 weeks	↑ FEV_1 (4 responders)	Not examined
SHITRIT [63]	Prospective, open label.	Azithromycin 250 mg alternate days	11	10 months	No improvement in lung function	Not examined
YATES [64]	Retrospective, case series	Azithromycin 250 mg alternate days	20	Mean 26 weeks	↑ FEV_1 (sustained beyond 3 months in 12/17 patients)	None
KHALID [65]	Prospective, open label	Azithromycin 500 mg *q.i.d.* for 3 days then 250 mg three times weekly	8#	12 weeks	↑ FEV_1+FVC	None
VERLEDEN [66]	Prospective, open label	Azithromycin 250 mg daily for 5 days then three times weekly	14	12 weeks	↑ FEV_1 (6/14 responded; responders had higher neutrophil and IL-8 levels)	Not examined

FEV_1: forced expiratory volume in one second; min: minimum; max: maximum; FVC: forced vital capacity; IL: interleukin. #: allogenic bone marrow transplant.

pneumoniae infection, but this issue remains bedevilled by the lack of a gold standard for this infection, as indicated earlier.

Other

BALLARD *et al.* [69] conducted a study of azithromycin in extremely low birthweight babies to assess its impact on the incidence and severity of bronchopulmonary dysplasia. This was a double-blind randomised placebo-controlled trial of neonates admitted to an intensive care unit to receive mechanical ventilation. No difference in mortality, incidence of bronchopulmonary dysplasia, duration of mechanical ventilation or other morbid conditions was seen. Post-natal steroid use in the whole study population and duration of ventilation in survivors was significantly less in the treatment group.

DISCUSSION

The dramatic improvement in the mortality and morbidity of diffuse panbronchiolitis with the introduction of macrolide therapy has increased interest in the potential use of macrolides in the treatment of other chronic inflammatory airway conditions. The aim of the present review was to examine the current evidence for a role of long-term macrolide therapy in the clinical management of these chronic diseases.

The use of azithromycin in cystic fibrosis has shown short-term improvements in pulmonary function (FEV_1), although more recent data suggest that this improvement is not maintained in the long term. However, there is some evidence for a reduction in exacerbation rate, decreased additional antibiotic usage and improvements in nutritional measures. How these potential benefits compare to the risks of increased bacterial resistance and whether clinical benefit is maintained over the long term requires further evaluation.

In the treatment of bronchiectasis with macrolides, studies show consistent evidence of decreased sputum volume and two studies also show decreased exacerbation frequency. The studies are very limited in terms of size, duration of follow-up and design. Larger studies of longer duration are required. The number of studies in COPD is even fewer. However, the positive finding of decreased exacerbation frequency, recently reported by WILKINSON *et al.* [39], suggests that further work in this area may be warranted. Two clinical trials examining the effects of azithromycin therapy on lung function and time to first exacerbation in COPD patients are currently under way; both are large studies with >800 and >1,000 patients, respectively (registered at ClinicalTrials.gov (trial numbers NCT00325897 and NCT00132860)). Data from these trials may help in determining whether or not long-term macrolide therapy has a role in the treatment of COPD.

There is currently no clear evidence that the use of macrolides in the treatment of chronic asthma results in significant clinical benefits. The use of the ketolide antibiotic telithromycin in the treatment of acute exacerbations of asthma showed significant improvements in symptom scores and laboratory-measured pulmonary function test results. However, it is not clear whether this translates into a significant clinical benefit and more studies are, therefore, required. Findings from open-label studies of macrolide therapy in post-transplant obliterative bronchiolitis are promising but require validation in long-term double-blind randomised placebo-controlled trials prior to routine use of this treatment. The role of *C. pneumoniae* infection also needs to be further investigated.

In all of the above studies, assessment of macrolide impact is confused by the heterogeneous nature of both study populations and outcome measures, both beneficial and harmful. Spirometric measures of lung function as a primary outcome

may not be the best indicator of the benefits of macrolide therapy. Clinically relevant end-points, such as reductions in exacerbation frequency, requirement for additional antibiotics, hospital stays, improved nutritional measures, symptom scores and quality-of-life assessments, should be the goal of future studies.

With very few exceptions, the studies identified were not designed to explore the potential for significant side-effects caused by the prolonged use of macrolides. The potential benefits need to be balanced against the risks, to both the individual and the population as a whole, of introduction of these new treatments. Increased bacterial macrolide resistance in common respiratory pathogens is increasing in Europe [70, 71]. In the UK, although penicillin resistance in *Streptococcus pneumoniae* may be declining, macrolide resistance continues to slowly increase [72]. This may lead to clinical failure in acute infection [73]. Macrolide use is the most important driver of macrolide resistance, with azithromycin selecting quantitatively more resistant organisms and clarithromycin selecting a higher-resistance-coding gene mutation [22]. The risk of macrolide resistance in nontuberculous mycobacteria that may be prevalent in cystic fibrosis populations should also be explored [74]. Long-term use of macrolides in a rare condition, such as diffuse panbronchiolitis, may generate resistant bacteria in the individual without causing significant harm to the population at large. Their use for much more common conditions, such as asthma and COPD, may have an impact on macrolide resistance in bacteria in the general population. This needs to be explored by further research.

Macrolides possess the potential to have significant electrophysiological effects on the heart, including prolonged cardiac repolarisation (QT prolongation) [75], with resultant proarrhythmogenic effects [76, 77] leading to potentially fatal ventricular tachycardias (torsades de pointes) [78]. RAY *et al.* [76] reported that the use of erythromycin was associated with a doubling in the risk of sudden cardiac death. The risk increased five-fold if patients were concurrently taking drugs that inhibit cytochrome P_{450} 3A, *e.g.* selective serotonin reuptake inhibitor antidepressants, calcium channel antagonists, amiodarone, certain antiretroviral drugs and various others. It is also possible that this effect is under-reported since sudden death in patients with chronic respiratory diseases may well be assigned to the underlying respiratory condition as opposed to a cardiac arrhythmia. The risk related to a short course of macrolide for an acute infection in a young person might, therefore, be different to that related to prolonged use in an older patient with COPD or bronchiectasis, who is more likely to both have structural cardiac disease and be taking other commonly used drugs that prolong the QT interval [79]. Other drug interactions may also be important. For example, the increased risk of statin-induced myopathy reported with concurrent erythromycin or clarithromycin therapy [80, 81].

If macrolides are to be used for their anti-inflammatory effects, which macrolide is preferable? Comparative studies of the relative clinical efficacy of macrolide therapy have not yet been performed. Choice may be determined as much by potential harm as benefit. The use of newer macrolides, *e.g.* azithromycin, may be associated with a reduced risk of cardiac arrhythmias than use of older macrolides, *e.g.* erythromycin and clarithromycin [82–84], and may, therefore, be the drug of choice. However, there are case reports of QT prolongation and cardiac arrest with azithromycin [85, 86]. However the potential for resistance development may be greater [22].

Macrolides provide an exciting potential new approach to the management of a number of diverse chronic inflammatory lung conditions. The possible beneficial effect across a number of diverse lung conditions is intriguing and perhaps comparable to the effects across a range of diseases found with corticosteroid therapy. This may relate to an as yet undescribed impact on a fundamental intracellular signalling pathway or possibly relates to a combination of factors, *e.g.* immunemodulatory and antimicrobial properties including antipseudomonal activity.

Initial studies show promise, but this promise has yet to be realised. The temptation for premature clinical use should be resisted as there is an as yet unquantified risk of harm. Further large controlled trials in these conditions, carefully measuring both benefit and harm, are required before they become established as part of routine therapy. In the long term, if the benefits are proven, the identification of the precise mechanisms of anti-inflammatory action of these molecules may lead to the synthesis of immunolides, anti-inflammatory macrolides without the potential for antibacterial effect, resistance generation or cardiac side-effects [85], which might then be ideal therapies for these chronic inflammatory airway diseases.

REFERENCES

1 Gould IM. BTS guidelines on CAP. *Thorax* 2002; 57: 657.
2 Tamaoki J, Kadota J, Takizawa H. Clinical implications of the immunomodulatory effects of macrolides. *Am J Med* 2004; 117: Suppl. 9A, 5S–11S.
3 Parnham MJ. Immunomodulatory effects of antimicrobials in the therapy of respiratory tract infections. *Curr Opin Infect Dis* 2005; 18: 125–131.
4 Itkin IH, Menzel ML. The use of macrolide antibiotic substances in the treatment of asthma. *J Allergy* 1970; 45: 146–162.
5 Zeiger RS, Schatz M, Sperling W, Simon RA, Stevenson DD. Efficacy of troleandomycin in outpatients with severe, corticosteroid-dependent asthma. *J Allergy Clin Immunol* 1980; 66: 438–446.
6 Szefler SJ, Rose JQ, Ellis EF, Spector SL, Green AW, Jusko WJ. The effect of troleandomycin on methylprednisolone elimination. *J Allergy Clin Immunol* 1980; 66: 447–451.
7 Nelson HS, Hamilos DL, Corsello PR, Levesque NV, Buchmeier AD, Bucher BL. A double-blind study of troleandomycin and methylprednisolone in asthmatic subjects who require daily corticosteroids. *Am Rev Respir Dis* 1993; 147: 398–404.
8 Kudoh S, Uetake T, Hagiwara K, *et al.* [Clinical effects of low-dose long-term erythromycin chemotherapy on diffuse panbronchiolitis]. *Nihon Kyobu Shikkan Gakkai Zasshi* 1987; 25: 632–542.
9 Kudoh S. Applying lessons learned in the treatment of diffuse panbronchiolitis to other chronic inflammatory diseases. *Am J Med* 2004; 117: Suppl. 9A, 12S–19S.
10 Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse

panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med* 1998; 157: 1829–1832.
11 Fujii T, Kadota J, Kawakami K, *et al.* Long term effect of erythromycin therapy in patients with chronic *Pseudomonas aeruginosa* infection. *Thorax* 1995; 50: 1246–1252.
12 Ichikawa Y, Hotta M, Sumita S, Fujimoto K, Oizumi K. Reversible airway lesions in diffuse panbronchiolitis. Detection by high-resolution computed tomography. *Chest* 1995; 107: 120–125.
13 Kadota J, Mukae H, Ishii H, *et al.* Long-term efficacy and safety of clarithromycin treatment in patients with diffuse panbronchiolitis. *Respir Med* 2003; 97: 844–850.
14 Shirai T, Sato A, Chida K. Effect of 14-membered ring macrolide therapy on chronic respiratory tract infections and polymorphonuclear leukocyte activity. *Intern Med* 1995; 34: 469–474.
15 Nagai H, Shishido H, Yoneda R, Yamaguchi E, Tamura A, Kurashima A. Long-term low-dose administration of erythromycin to patients with diffuse panbronchiolitis. *Respiration* 1991; 58: 145–149.
16 Rubin BK. Immunomodulatory properties of macrolides: overview and historical perspective. *Am J Med* 2004; 117: Suppl. 9A, 2S–4S.
17 Tamaoki J, Takeyama K, Tagaya E, Konno K. Effect of clarithromycin on sputum production and its rheological properties in chronic respiratory tract infections. *Antimicrob Agents Chemother* 1995; 39: 1688–1690.
18 Takizawa H, Desaki M, Ohtoshi T, *et al.* Erythromycin modulates IL-8 expression in normal and inflamed human bronchial epithelial cells. *Am J Respir Crit Care Med* 1997; 156: 266–271.
19 Desaki M, Okazaki H, Sunazuka T, Omura S, Yamamoto K, Takizawa H. Molecular mechanisms of anti-inflammatory action of erythromycin in human bronchial epithelial cells: possible role in the signaling pathway that regulates nuclear factor-κB activation. *Antimicrob Agents Chemother* 2004; 48: 1581–1585.
20 Kusano S, Kadota J, Kohno S, *et al.* Effect of roxithromycin on peripheral neutrophil adhesion molecules in patients with chronic lower respiratory tract disease. *Respiration* 1995; 62: 217–222.
21 McComb JM, Campbell NP, Cleland J. Recurrent ventricular tachycardia associated with QT prolongation after mitral valve replacement and its association with intravenous administration of erythromycin. *Am J Cardiol* 1984; 54: 922–923.
22 Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2007; 369: 482–490.
23 Southern KW, Barker PM, Solis A. Macrolide antibiotics for cystic fibrosis. *Cochrane Database Syst Rev* 2004; Issue, 2: *CD002203.*
24 Tramper-Stranders GA, Wolfs TF, Fleer A, Kimpen JL, van der Ent CK. Maintenance azithromycin treatment in pediatric patients with cystic fibrosis: long-term outcomes related to macrolide resistance and pulmonary function. *Pediatr Infect Dis J* 2007; 26: 8–12.
25 Clement A, Tamalet A, Leroux E, Ravilly S, Fauroux B, Jais JP. Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax* 2006; 61: 895–902.
26 Hansen CR, Pressler T, Koch C, Høiby N. Long-term azitromycin treatment of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection; an observational cohort study. *J Cyst Fibros* 2005; 4: 35–40.
27 Saiman L, Marshall BC, Mayer-Hamblett N, *et al.* Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA* 2003; 290: 1749–1756.
28 Pirzada OM, McGaw J, Taylor CJ, Everard ML. Improved lung function and body mass index associated with long-term use of macrolide antibiotics. *J Cyst Fibros* 2003; 2: 69–71.
29 Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. *Lancet* 2002; 360: 978–984.
30 Wolter J, Seeney S, Bell S, Bowler S, Masel P, McCormack J. Effect of long term treatment with azithromycin on disease parameters in cystic fibrosis: a randomised trial. *Thorax* 2002; 57: 212–216.
31 Saiman L, Mayer-Hamblett N, Campbell P, Marshall BC. Heterogeneity of treatment response to azithromycin in patients with cystic fibrosis. *Am J Respir Crit Care Med* 2005; 172: 1008–1012.
32 Phaff SJ, Tiddens HA, Verbrugh HA, Ott A. Macrolide resistance of *Staphylococcus aureus* and *Haemophilus* species associated with long-term azithromycin use in cystic fibrosis. *J Antimicrob Chemother* 2006; 57: 741–746.
33 Yalcin E, Kiper N, Ozcelik U, *et al.* Effects of clarithromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. *J Clin Pharm Ther* 2006; 31: 49–55.
34 Cymbala AA, Edmonds LC, Bauer MA, *et al.* The disease-modifying effects of twice-weekly oral azithromycin in patients with bronchiectasis. *Treat Respir Med* 2005; 4: 117–122.
35 Davies G, Wilson R. Prophylactic antibiotic treatment of bronchiectasis with azithromycin. *Thorax* 2004; 59: 540–541.
36 Tsang KW, Ho PI, Chan KN, *et al.* A pilot study of low-dose erythromycin in bronchiectasis. *Eur Respir J* 1999; 13: 361–364.
37 Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: a double-blind, placebo-controlled study. *Eur Respir J* 1997; 10: 994–999.
38 Banerjee D, Khair OA, Honeybourne D. The effect of oral clarithromycin on health status and sputum bacteriology in stable COPD. *Respir Med* 2005; 99: 208–215.
39 Wilkinson TMA, Seemungal TAR, Sapsford R, Hurst JR, Perera W, Wedzicha JA. Effect of Long-term Erythromycin in COPD Trial (ELECT): exacerbations and inflammation. *Thorax* 2007; 62: Suppl. 3, A15.
40 Hashiba M, Baba S. Efficacy of long-term administration of clarithromycin in the treatment of intractable chronic sinusitis. *Acta Otolaryngol Suppl* 1996; 525: 73–78.
41 Cervin A, Kalm O, Sandkull P, Lindberg S. One-year low-dose erythromycin treatment of persistent chronic sinusitis after sinus surgery: clinical outcome and effects on mucociliary parameters and nasal nitric oxide. *Otolaryngol Head Neck Surg* 2002; 126: 481–489.
42 Kimura N, Nishioka K, Nishizaki K, Ogawa T, Naitou Y, Masuda Y. Clinical effect of low-dose, long-term

roxithromycin chemotherapy in patients with chronic sinusitis. *Acta Med Okayama* 1997; 51: 33–37.
43 Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope* 2006; 116: 189–193.
44 Richeldi L, Ferrara G, Fabbri LM, Lasserson TJ, Gibson PG. Macrolides for chronic asthma. *Cochrane Database Syst Rev 2005; Issue*, 4: CD002997.
45 Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. *Am J Respir Crit Care Med* 2008; 177: 148–155.
46 Johnston SL, Blasi F, Black PN, Martin RJ, Farrell DJ, Nieman RB. The effect of telithromycin in acute exacerbations of asthma. *N Engl J Med* 2006; 354: 1589–1600.
47 Kostadima E, Tsiodras S, Alexopoulos EI, *et al.* Clarithromycin reduces the severity of bronchial hyperresponsiveness in patients with asthma. *Eur Respir J* 2004; 23: 714–717.
48 Kraft M, Cassell GH, Pak J, Martin RJ. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in asthma: effect of clarithromycin. *Chest* 2002; 121: 1782–1788.
49 Black PN, Blasi F, Jenkins CR, *et al.* Trial of roxithromycin in subjects with asthma and serological evidence of infection with *Chlamydia pneumoniae*. *Am J Respir Crit Care Med* 2001; 164: 536–541.
50 Amayasu H, Yoshida S, Ebana S, *et al.* Clarithromycin suppresses bronchial hyperresponsiveness associated with eosinophilic inflammation in patients with asthma. *Ann Allergy Asthma Immunol* 2000; 84: 594–598.
51 Shoji T, Yoshida S, Sakamoto H, Hasegawa H, Nakagawa H, Amayasu H. Anti-inflammatory effect of roxithromycin in patients with aspirin-intolerant asthma. *Clin Exp Allergy* 1999; 29: 950–956.
52 Kamada AK, Hill MR, Ikle DN, Brenner AM, Szefler SJ. Efficacy and safety of low-dose troleandomycin therapy in children with severe, steroid-requiring asthma. *J Allergy Clin Immunol* 1993; 91: 873–882.
53 Martin RJ, Kraft M, Chu HW, Berns EA, Cassell GH. A link between chronic asthma and chronic infection. *J Allergy Clin Immunol* 2001; 107: 595–601.
54 Daian CM, Wolff AH, Bielory L. The role of atypical organisms in asthma. *Allergy Asthma Proc* 2000; 21: 107–111.
55 Miyatake H, Taki F, Taniguchi H, Suzuki R, Takagi K, Satake T. Erythromycin reduces the severity of bronchial hyperresponsiveness in asthma. *Chest* 1991; 99: 670–673.
56 Shimizu T, Kato M, Mochizuki H, Tokuyama K, Morikawa A, Kuroume T. Roxithromycin reduces the degree of bronchial hyperresponsiveness in children with asthma. *Chest* 1994; 106: 458–461.
57 Ekici A, Ekici M, Erdemoglu AK. Effect of azithromycin on the severity of bronchial hyperresponsiveness in patients with mild asthma. *J Asthma* 2002; 39: 181–185.
58 Boehler A, Kesten S, Weder W, Speich R. Bronchiolitis obliterans after lung transplantation: a review. *Chest* 1998; 114: 1411–1426.
59 Bando K, Paradis IL, Similo S, *et al.* Obliterative bronchiolitis after lung and heart–lung transplantation. An analysis of risk factors and management. *J Thorac Cardiovasc Surg* 1995; 110: 4–13.
60 Sundaresan S, Trulock EP, Mohanakumar T, Cooper JD, Patterson GA. Prevalence and outcome of bronchiolitis obliterans syndrome after lung transplantation. *Ann Thorac Surg* 1995; 60: 1341–1346.
61 Gerhardt SG, McDyer JF, Girgis RE, Conte JV, Yang SC, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. *Am J Respir Crit Care Med* 2003; 168: 121–125.
62 Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2004; 77: 1465–1467.
63 Shitrit D, Bendayan D, Gidon S, Saute M, Bakal I, Kramer MR. Long-term azithromycin use for treatment of bronchiolitis obliterans syndrome in lung transplant recipients. *J Heart Lung Transplant* 2005; 24: 1440–1443.
64 Yates B, Murphy DM, Forrest IA, *et al.* Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2005; 172: 772–775.
65 Khalid M, Al Saghir A, Saleemi S, *et al.* Azithromycin in bronchiolitis obliterans complicating bone marrow transplantation: a preliminary study. *Eur Respir J* 2005; 25: 490–493.
66 Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2006; 174: 566–570.
67 Kotsimbos TC, Snell GI, Levvey B, *et al. Chlamydia pneumoniae* serology in donors and recipients and the risk of bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2005; 79: 269–275.
68 Glanville AR, Gencay M, Tamm M, *et al. Chlamydia pneumoniae* infection after lung transplantation. *J Heart Lung Transplant* 2005; 24: 131–136.
69 Ballard HO, Anstead MI, Shook LA. Azithromycin in the extremely low birth weight infant for the prevention of bronchopulmonary dysplasia: a pilot study. *Respir Res* 2007; 8: 41.
70 Reinert RR, Reinert S, van der Linden M, Cil MY, Al-Lahham A, Appelbaum P. Antimicrobial susceptibility of *Streptococcus pneumoniae* in eight European countries from 2001 to 2003. *Antimicrob Agents Chemother* 2005; 49: 2903–2913.
71 Malhotra-Kumar S, Lammens C, Chapelle S, *et al.* Macrolide- and telithromycin-resistant *Streptococcus pyogenes*, Belgium, 1999–2003. *Emerg Infect Dis* 2005; 11: 939–942.
72 Livermore DM, Reynolds R, Stephens P, *et al.* Trends in penicillin and macrolide resistance among pneumococci in the UK and the Republic of Ireland in relation to antibiotic sales to pharmacies and dispensing doctors. *Int J Antimicrob Agents* 2006; 28: 273–279.
73 Daneman N, McGeer A, Green K, Low DE. Macrolide resistance in bacteremic pneumococcal disease: implications for patient management. *Clin Infect Dis* 2006; 43: 432–438.
74 Olivier KN, Weber DJ, Wallace RJ Jr, *et al.* Nontuberculous mycobacteria. I: multicenter prevalence study in cystic fibrosis. *Am J Respir Crit Care Med* 2003; 167: 828–834.
75 Russo V, Puzio G, Siniscalchi N. Azithromycin-induced QT prolongation in elderly patient. *Acta Biomed* 2006; 77: 30–32.
76 Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *N Engl J Med* 2004; 351: 1089–1096.

77 Milberg P, Eckardt L, Bruns HJ, *et al.* Divergent pro-arrhythmic potential of macrolide antibiotics despite similar QT prolongation: fast phase 3 repolarization prevents early afterdepolarizations and torsade de pointes. *J Pharmacol Exp Ther* 2002; 303: 218–225.

78 Schoenenberger RA, Haefeli WE, Weiss P, Ritz RF. Association of intravenous erythromycin and potentially fatal ventricular tachycardia with Q-T prolongation (torsades de pointes). *BMJ* 1990; 300: 1375–1376.

79 Shaffer D, Singer S, Korvick J, Honig P. Concomitant risk factors in reports of torsades de pointes associated with macrolide use: review of the United States Food and Drug Administration Adverse Event Reporting System. *Clin Infect Dis* 2002; 35: 197–200.

80 Medicines and Healthcare products Regulatory Agency, Commission on Human Medicines. Drug safety advice. Statins: interactions, and updated advice for atorvastatin. *Drug Safety Update* 2008; 1: Issue 6, 2–4.

81 Lee AJ, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. *Ann Pharmacother* 2001; 35: 26–31.

82 Corrao G, Botteri E, Bagnardi V, *et al*. Generating signals of drug-adverse effects from prescription databases and application to the risk of arrhythmia associated with antibacterials. *Pharmacoepidemiol Drug Saf* 2005; 14: 31–40.

83 Owens RC Jr. QT prolongation with antimicrobial agents: understanding the significance. *Drugs* 2004; 64: 1091–1124.

84 Harris S, Hilligoss DM, Colangelo PM, Eller M, Okerholm R. Azithromycin and terfenadine: lack of drug interaction. *Clin Pharmacol Ther* 1995; 58: 310–315.

85 Samarendra P, Kumari S, Evans SJ, Sacchi TJ, Navarro V. QT prolongation associated with azithromycin/amiodarone combination. *Pacing Clin Electrophysiol* 2001; 24: 1572–1574.

86 Arellano-Rodrigo E, Garcia A, Mont L, Roque M. [Torsade de pointes and cardiorespiratory arrest induced by azithromycin in a patient with congenital long QT syndrome.] *Med Clin (Barc)* 2001; 117: 118–119.

87 Fecik RA, Nguyen PL, Venkatraman L. Approaches to the synthesis of immunolides: selective immunomodulatory macrolides for cystic fibrosis. *Curr Opin Drug Discov Devel* 2005; 8: 741–747.