Review

Clinical effectiveness of macrolides in diseases of the airways: beyond the antimicrobial effects

Maria Kryfti[1], Konstantinos Bartziokas[2], Andriana I. Papaioannou[3], Alexis Papadopoulos[2], Konstantinos Kostikas[4]

[1]6th Department of Respiratory Medicine, Sotiria Hospital of Chest Diseases, Athens;
[2]Department of Respiratory Medicine, Amalia Fleming General Hospital, Athens;
[3]2nd Department of Respiratory Medicine, Sismanogleio General Hospital, Athens;
[4]Editorial Board Pneumon

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Corespondence:
Dr Konstantinos Kostikas, MD, PhD, FCCP
3 Stamouli street, Karditsa 43100, Greece
Tel.: +30-6944780616, Fax: +30-2441022370
e-mail: ktk@otenet.gr

SUMMARY. The beneficial effect of long-term treatment with macrolides in patients with diffuse panbronchiolitis has raised interest in the use of these antibiotics in other chronic inflammatory airway diseases. Recent clinical trials have provided new evidence for a possible role of macrolides in the treatment of airway diseases related to their potential immunomodulatory and anti-inflammatory properties. Macrolides have been shown to reduce the incidence of exacerbations in patients with severe chronic obstructive pulmonary disease (COPD) and frequent exacerbations. In the treatment of idiopathic bronchiectasis, macrolide administration is associated with a reduction in sputum volume and decreased frequency and intensity of exacerbations. Conversely, current evidence is insufficient to support the use of macrolides in the treatment of asthma, although a specific subgroup of patients with refractory asthma and neutrophilic inflammation may derive some benefit. Finally, long-term prophylactic therapy with macrolides may be beneficial for lung transplant recipients, as recent evidence indicates that macrolides are effective in lowering the incidence of bronchiolitis obliterans (BO). This is a review of current evidence on the potential clinical use of macrolides in the long-term treatment of inflammatory airway disorders. *Pneumon 2013, 26(1):33-46.*

INTRODUCTION

Macrolides are macrocyclical lactones that belong to a very large class of compounds consisting of rings with greater than 8 members[1]. The most widely used macrolide antibiotics in clinical practice have lactone rings that contain 14 members (erythromycin, roxithromycin, clarithromycin and troleandromycin), 15 members (azithromycin) or 16 members (spiramycin, josamycin, and midecamycin)[2]. Macrolide antibiotics bind to the 50S unit of ribosomes of both prokaryotic and eukaryotic organisms, inhibiting

transpeptidation or translocation of nascent peptides[1]. Their broad antibiotic efficacy against Gram-positive and Gram-negative bacteria, Mycobacteria, Chlamydia, Mycoplasma and Legionella species explains why macrolides constitute a popular option in the management of respiratory infections. In addition to their broad efficacy in the control of microorganisms affecting the lung, macrolides also show good bioavailability when administered via the oral route, excellent tissue penetration, prolonged tissue persistence and a favourable side-effect profile[2].

Although macrolides are used mainly for their antibiotic properties, there is increasing documentation also of their immunomodulatory effects (i.e. ability to suppress hyperimmunity and inflammation without overt immunosuppression)[2]. These non-ribosomal effects of macrolides include immunomodulation, decrease in bacterial virulence and biofilm formation, and reduction of mucus hypersecretion[2]. The non-antimicrobial effects of macrolides (Table 1) take several weeks to be manifested and are limited to the 14 and 15 member macrolides[2]. The beneficial effect of long-term macrolide therapy observed in diffuse panbronchiolitis[3,4] has raised interest in their use for other chronic inflammatory airway diseases. This is a review of the current evidence on the efficacy of macrolides in airway diseases beyond their antibiotic effects.

IMMUNOMODULATORY EFFECTS OF MACROLIDE ANTIBIOTICS

In addition to their established antimicrobial activity, macrolides have been observed to possess immune-modifying properties[5,6]. These properties are related to their ringed structure, with immunomodulatory effects being associated with 14-membered (e.g., erythromycin, clarithromycin, roxithromycin) and 15-membered (e.g., azithromycin) macrolides[7]. Several studies have evaluated a broad range of immunomodulatory effects of macrolides on mammalian cells *in vitro* and *in vivo* (Figure 1)[8]. Macrolides exert effects in a wide variety of cells (nasal and bronchial epithelial cells, alveolar macrophages, monocytes, eosinophils, and lymphocytes) and on signaling pathways (e.g. NF-κβ, AP-1). They limit tissue damage by neutrophils, decrease mucus viscosity and suppress microbial virulence factors and angiogenesis. These immunomodulatory properties are evident at concentrations clinically achievable by low doses of macrolides, which thus have the potential to play a unique role in the management of adult chronic inflammatory airway diseases, including chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, and bronchiolitis.

COPD

A number of studies support the significant role of chronic inflammation of the airways and lung parenchyma in COPD[9-11]. Although the exact mechanism has not been elucidated, it appears that macrophages and CD8+ T-cells may contribute to progressive lung destruction in COPD in several ways[12]. A variety of infectious and noninfectious stimuli can initiate the inflammatory response associated with acute exacerbations of COPD (AECOPD). AECOPDs

TABLE 1. Non antimicrobial effects of macrolides

Effects of macrolides on:	Bacteria (non-ribosomal effects)	Mucus layer (reduction of mucus hypersecretion)	Inflammatory cells (decrease of hyperimmunity)	Normal cells (normalization without overt immunosuppression and immunomodulation)
	Reduction in bacterial adherence	Decrease in mucus protein	Reduction of reactive oxygen species	Reduction of cytokine and chemokine formation
	Reduction in biofilm formation	Decrease in water secretion	Reduction of adhesion molecules	Increase of adhesion molecules
			Reduction of cytokine and chemokine formation	Increase of constitutive NO synthase (cNOS)
			Reduction of neutrophil migration	Reversible retardation of cell proliferation
			Increase in apoptosis of inflammatory cells	

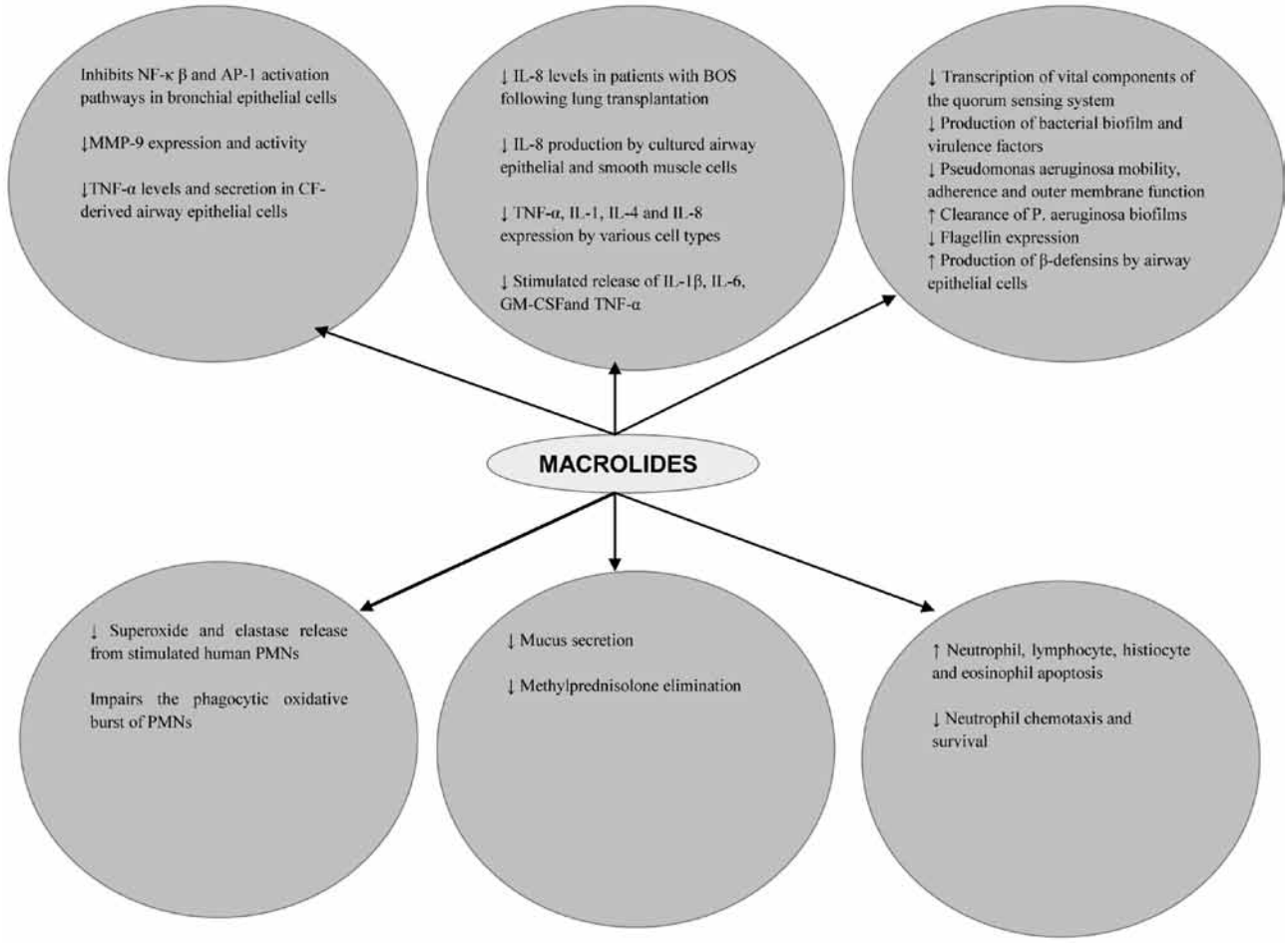

FIGURE 1. The *in vitro* and *in vivo* immunomodulatory effects of macrolides
AP: ACTIVATOR protein; BOS: bronchiolitis obliterans syndrome; CF: cystic fibrosis; GM-CSF: granulocyte-macrophage colony-stimulating factor; MMP: matrix metalloproteinase; NF-κB: nuclear factor κ-light-chain-enhancer of activated B cells; PMNs: polymorphonuclear leukocytes; TNF-α: tumour necrosis factor- α; IL: interleukin

are characterized by increased oxidative stress and both neutrophilic and eosinophilic inflammation, involving several inflammatory mediators[13-16]. AECOPD may worsen the health-related quality of life (HRQoL) of the patient and result in measurable, acute effects on pulmonary function[17,18]. The importance of chronic inflammation and infection in the pathogenesis of COPD indicate that macrolides may have a role to play in the treatment of COPD as disease modifying agents. The major studies of the efficacy of macrolides in COPD in humans are presented in Table 2.

One prospective, double-blind controlled trial examined the effect of clarithromycin treatment in moderate to severe COPD[19]. This study randomized 67 patients with a mean age of 67years, suffering from moderate to severe COPD [mean forced expiratory volume in 1 second (FEV_1) 43% predicted], to either 3 months of clarithromycin treatment (500mg of sustained release preparation daily) or placebo. Oral clarithromycin had no significant effect on sputum neutrophil numbers or cytokine levels in patients with moderate-to-severe stable COPD and no difference was observed in their overall QoL score, shuttle walk distance, spirometry or blood levels of C-reactive protein (CRP). Clarithromycin treatment, however, was associated with a significant improvement in HRQoL, as expressed by the St George's Respiratory Questionnaire Symptom Score and the Physical Function Score SF-36, and resulted in a small reduction in the neutrophilic differential count and neutrophilic chemotaxis.

In a randomized double-blind placebo-controlled

TABLE 2. Major studies of efficacy of macrolides in chronic obstructive pulmonary disease (COPD) in humans

Author/ Reference	Study population	Type of study	Macrolide	Major results
Banerjee D et al[19]	Stable COPD (moderate to severe): 67 patients	Prospective, double-blind, randomized-controlled trial	Clarithromycin (500mg/ day of sustained release preparation for 3 months)	No effect on sputum neutrophil numbers, cytokine levels, exercise capacity, PFTs, LTB4: leukotriene B4, or CRP level Improvement in HRQoL Reduction in neutrophilic differential and chemotaxis
Seemungal TA et al[20]	Stable COPD (moderate to severe): 109 patients	Randomized, double-blind, placebo-controlled study	Erythromycin (250mg b.i.d. for 12 months)	Fewer total AECOPDs and shorter duration of AECOPDs No differences in the changes in FEV_1, sputum and serum inflammatory markers or bacterial flora
Pomares X. et al[21]	COPD (frequent exacerbations and/ or colonization with *Pseudomonas aeruginosa*): 20 patients	Retrospective study	Azithromycin (500mg 3 times weekly for 12 months)	Reduction in AECOPDs, hospitalizations, and length of hospital stay.
Albert RK et al[22]	COPD (frequent exacerbations):1,142 patients	Randomized, double-blind, placebo-controlled study	Azithromycin (250mg daily for 1 year)	Prolonged median time to first exacerbation. Improvement of HRQoL No difference in survival Greater hearing decrement in the azithromycin group Decrease in colonization with selected respiratory pathogens Increase in colonization with macrolide-resistant organisms

PFT: Pulmonary function test, CRP: C-reactive protein, FEV_1: Forced expiratory volume in 1 second, AECOPD: acute exacerbation of COPD, HRQoL: Health related quality of life

study, Seemungal and colleagues examined the effect of erythromycin treatment on AECOPD[20]. Erythromycin (250mg bid) or placebo was administered for 12 months to 109 patients with moderate to severe stable COPD (mean age 67 years, FEV_1 50% pred.). Almost 80% of the patients enrolled were using inhaled corticosteroids (ICS) and many were on long-acting β2-agonist (LABA) and/ or inhaled anticholinergic medication. The macrolide-treated patients had fewer total AECOPDs (rate ratio 0.648, range 0.489-0.859; 95%CI, P=0.003) and shorter duration of AECOPDs than the placebo-treated patients. No differences were observed between the macrolide and the placebo treated patients for changes in FEV_1, sputum and serum inflammatory markers or bacterial flora. This study supports the theory that a low dose of erythromycin may reduce the number and duration of acute exacerbations[20].

The results of a recent retrospective study on a small number of patients with frequent AECOPDs and/or colonization by *Pseudomonas aeruginosa*[21] suggest that long-term intermittent treatment with azithromycin 500mg 3 times weekly is well tolerated and associated with significant reduction in AECOPD, hospitalization, and length of hospital stay in patients with severe COPD. Such studies indicate the need for larger prospective randomized controlled trials to assess the effect of regular macrolide treatment on clinically important outcomes, including AECOPD, in patients with different degrees of severity of COPD.

In a recent large prospective randomized placebo-

controlled 1-year trial, Albert and co-workers evaluated the efficacy of azithromycin 250 mg daily on the reduction of AECOPD in a population of exacerbation-prone patients with COPD[22]. The patients receiving azithromycin experienced a more prolonged median time to first exacerbation (266, range 227 to 313; 95%CI) than those on placebo (174, range143 to 215; 95% CI) days ($p<0.001$), and a lower risk for AECOPD (hazard ratio 0.73, range 0.63 to 0.84; 95% CI, $P<0.001$). The number of patients needed to treat (NNT) with azithromycin compared to placebo to prevent one ECOPD was 2.86, and macrolide treatment was associated with a greater improvement in HRQoL. There were no differences in the rates of deaths or serious adverse events between azithromycin and placebo; however, an audiogram-confirmed hearing decrement occurred in 25% of the participants receiving azithromycin compared with 20% of the placebo group ($p=0.04$). Azithromycin use was associated with a decrease in the incidence of colonization with selected respiratory pathogens, but led to a doubling in the incidence of colonization with macrolide-resistant organisms in the azithromycin group (81%) compared with the placebo group (41%) in patients not colonized with selected respiratory pathogens at the time of enrolment[23]. The use of azithromycin for the prevention of COPD exacerbations has not been endorsed by current expert guidelines, however, possibly because of the unfavourable balance between reported benefits and side effects[24]. The possible role of macrolides in the prevention of AECOPD will have to be evaluated in individual patients with frequent exacerbations despite optimal treatment[25].

CYSTIC FIBROSIS (CF)

The first trial of macrolides in CF was described in a case report in the 1990s, according to which treatment of a patient with 600mg of erythromycin daily for 12 months resulted in a decrease in sputum production and a resolution of reticulonodular densities on the chest X-ray[26]. Three years later, a study of children with CF infected with *P. aeruginosa* who received azlthromycin for 3 months showed significant improvement in both FEV_1 and forced exhaled vital capacity (FVC)[27]. The major studies of the efficacy of macrolides in CF in humans are presented in Table 3.

Three randomized controlled trials have been conducted to explore the benefits of the use of azithromycin in CF. The first was a 3-month, prospective, randomized, double blind, placebo controlled trial on 60 patients, documenting the use of azithromycin (250mg/day) on lung function, weight, and QoL[28]. This study showed that the use of azithromycin was associated with significant improvement in QoL, reduction in blood level of CRP and in the number of respiratory exacerbations and the rate of decline in lung function[28]. The second study was a 15-month randomized double blind, placebo controlled crossover trial[29]. The patients received either azithromycin (250 mg daily for body weight ≤40 kg, or 500 mg daily for body weight >40 kg) or placebo, for 6 months and then after 2 months of washout, the treatments were crossed over. The primary outcome of this study was the difference in median FEV_1 between the azithromycin and placebo treatment periods. Secondary outcome measures were sputum culture, sputum interleukin 8 (IL8) and neutrophil elastase, exercise testing, QoL, antibiotic use and pulmonary exacerbation rates. This study showed that the mean change in FEV_1 was greater at all points in the azithromycin treatment periods. Sputum bacterial density, inflammatory markers, exercise tolerance, and subjective well-being showed no difference[29].

In order to confirm the benefits of azithromycin treatment in CF a large multicentre placebo controlled trial was performed in 23 CF centres in the USA[30]. The subjects received azithromycin (250 mg daily for body weight <40 kg or 500 mg daily for body weight ≥40 kg) 3 days/week for 168 days. The patients receiving azithromycin showed an increase in FEV_1 and FVC, while both functional parameters declined in those who received placebo. In addition, patients in the azithromycin group had fewer exacerbations and reported improvement in physical activity and HRQoL[30]. The adverse effects of azithromycin recorded in all the above clinical trials in CF were nausea, diarrhoea, wheezing and hearing impairment, but these were generally mild and self-limiting. According to the above findings, although further studies are still needed, it appears that the use of azithromycin in patients with CF is a reasonable consideration.

NON CF BRONCHIECTASIS

Bronchiectasis is characterized by permanent dilatation of bronchi, usually with excessive mucopurulent secretions[31], which is the result of inflammation-related destruction of structural components of the bronchial wall[32]. CD4+ T lymphocytes, macrophages and neutrophils contribute to an intense cellular infiltrate in the airways of

TABLE 3. Major studies of the efficacy of macrolides in cystic fibrosis (CF) in humans

Author/ Reference	Study population	Type of study	Macrolide	Major results
Nakanishi N *et al*[26]	CF:1 patient	Case report	Erythromycin (600mg daily for 12 months)	Decrease in sputum production and resolution of reticulonodular densities on chest X-ray
Jaffe A *et al*[27]	CF (children infected with *Pseudomonas. aeruginosa*): 7 patients	Open label	AzIthromycin (for 3 months)	Improvement in both FEV_1 and FVC
Wolter J *et al*[28]	CF: 60 patients	Prospective, randomized, double-blind, placebo controlled trial	AzIthromycin (250mg/day for 3 months)	Improvement in HRQoL, lowering of CRP level, reduction in number of respiratory exacerbations and rate of decline in lung function
Equi A *et al*[29]	CF: 41 patients	Randomized double-blind, placebo-controlled crossover trial	Azithromycin (250 mg daily for body weight ≤40 kg, or 500 mg daily for body weight >40 kg, for 6 months)	Mean change in FEV_1 greater at all points in the azithromycin treatment groups. No difference in sputum bacterial density, inflammatory markers, exercise tolerance and subjective well-being
Saiman L *et al*[30]	CF: 185 patients	Multicentre placebo controlled trial	Azithromycin (250 mg daily for body weight <40 kg, or 500 mg daily for body weight ≥40 kg, 3 days/week for 168 days)	Increase in FEV_1 and FVC. Fewer exacerbations Improvement in physical activity and HRQoL

CRP: C- reactive protein, FEV1: Forced expiratory volume in 1 second, FVC: forced exhaled vital capacity, HRQoL: Health Related Quality of Life

patients with bronchiectasis[33], while increased expression of IL8, tumour necrosis factor-α (TNF-α)and leukotriene B4 (LTB4) has also been observed[34-36]. Experimental data have shown that a recently recognized type of T-cells, the Th17 cells, may play an important role in the induction of neutrophilic inflammation, through the production of cytokines, including IL17 and IL22[37]. Th17 lymphocytes are not the only source of IL17 in the CF airway; IL17+ neutrophils, γδT cells, and natural killer T cells have also been identified as producers of IL17[38]. This is especially important in the setting of chronic infections, such as in the case of bronchiectasis, where Th17 cells may be key contributors of tissue injury[39]. Chronic bacterial infection is common in patients with bronchiectasis, and stimulates bronchial inflammation, which is implicated in the progression of the disease. Investigators have confirmed that colonized patients have a higher neutrophil count in their BAL as well as higher BAL concentrations of elastase, myeloperoxidase, TNF-α and IL8[34]. Patients with non-CF bronchiectasis have a high rate of infection with *Ps. aeruginosa*, which is associated with increased disease severity and poorer QoL[40]. Patients colonized with *Ps. aeruginosa* also have a higher concentration of TNF-α and LTB4 in the bronchoalveolar lavage (BAL)[36]. The major studies on the efficacy of macrolides in non-CF bronchiectasis in humans are presented in Table 4.

The effect of long-term macrolide treatment in non-CF bronchiectasis has been explored in only a few studies, with small numbers of patients. A randomized double placebo-controlled trial conducted by Koh and colleagues[41] showed improvement in airway responsiveness and sputum purulence, but not in lung function, in children with bronchiectasis and increased airway responsiveness who received roxithromycin (4mg/kg b.i.d.) for 12 weeks. Tsang and colleagues found a significant improvement in the spirometric results and 24-hour sputum volume in adults with stable severe idiopathic bronchiectasis who received a low dose of erythromycin (500mg b.i.d.) for 8

TABLE 4. Major studies of the efficacy of macrolides in non-cystic fibrosis (CF) bronchiectasis in humans

Author/Reference	Study population	Type of study	Macrolide	Major results
Koh YY *et al.* [41]	Non CF bronchiectasis (children with airway hyperresponsiveness): 25 patients	Randomized, double-blind placebo-controlled trial	Roxithromycin (4mg/kg b.i.d. for 12 weeks)	Improvement in airway responsiveness and sputum purulence No effect on lung function
Tsang KW et al. [42]	Non CF bronchiectasis (adults with stable severe idiopathic bronchiectasis): 21 patients	Randomized double-blind placebo-controlled trial	Erythromycin (500mg b.i.d. for 8 weeks)	Significant improvement in spirometric results and 24-hour sputum volume. No change in sputum pathogens, leukocyte count or levels of IL1A, IL8, TNF-α or LTB4
Yalcin E et al. [43]	Non CF bronchiectasis (children with stable idiopathic bronchiectasis): 34 patients	Randomized, placebo-controlled trial	Clarithromycin (15mg/kg for 3 months)	Reduction in daily sputum production Reduction in IL8 level, total cell count and neutrophils in BAL fluid; No change in FEV_1
Serisier DJ et al [44]	Non-CF bronchiectasis subjects with frequent exacerbations- 24 patients	Prospective cohort study	Erythromycin (250 mg daily for 12 months)	Decrease of exacerbation frequency
Wong C et al. [45]	Non-CF bronchiectasis-141 patients	Randomized double blind, placebo controlled trial	Azithromycin (500 mg three times a week for 6 months)	Fewer exacerbations No significant difference in pre-bronchodilator FEV_1 No difference on HRQoL

BAL: Bronchoalveolar lavage, FEV1: Forced expiratory volume in 1 second, HRQoL: Health Related Quality of Life, PEF: Peak expiratory flow, PFT: Pulmonary Function Test, IL: interleukin, TNF- α: Tumour Necrosis Factor-α, LTB4: leukotriene B4

weeks compared with those given placebo[42]. No change was observed in sputum pathogens, leukocyte count or levels of IL1A, IL8, TNF-α or LTB4 in either group[42]. In a more recent randomized, placebo-controlled trial, Yalcin and co-workers administered clarithromycin (15mg/kg) to 34 children with stable idiopathic bronchiectasis for 3 months[43]. Patients receiving clarithromycin had less daily sputum production and lower levels of IL8, total cell count and neutrophils in BAL fluid; however, no change in FEV_1 was observed in either group[43].

Most studies of the long-term use of macrolides in patients with idiopathic bronchiectasis provide insufficient data because of the small sample sizes and short periods of treatment and follow up. A recent 12-month study has provided evidence that low-dose erythromycin may have a robust effect upon exacerbation frequency in subjects with non-CF bronchiectasis with frequent exacerbations[44]. There is therefore a need for randomized controlled trials of long-term, low-dose macrolide treatment to be conducted, focusing on aspects such as efficacy, safety, development of microbiological resistance and cost-effectiveness.

Wong and colleagues recently conducted a randomized double blind, placebo controlled trial, on 141 patients with non-CF bronchiectasis confirmed by high resolution computed tomography (HRCT) who reported at least one pulmonary exacerbation requiring antibiotic treatment in the past year. The patients were randomized to treatment with 500 mg azithromycin or placebo 3 times a week for 6 months. Those who received azithromycin had significantly fewer exacerbations during the follow-up period. Pre-bronchodilator FEV_1 did not change from baseline in the azithromycin group and decreased by 0.04 L in the placebo group, but the difference was not significant (0.04 L, range 0.03 to 0.12 L, 95% CI; p=0.251), and no difference was elicited between the azithromycin and placebo groups on HRQoL questionnaires[45].

The use of macrolides, especially azithromycin, appears to decrease the frequency and intensity of exacerbations and diminish sputum volume in patients with non-CF

idiopathic bronchiectasis, and may thus represent an effective treatment option. As in the case of COPD, the use of macrolides in bronchiectasis should be restricted to selected cases and take into account their potential side effects.

The macrolides that have been most widely studied in clinical trials are clarithromycin and azithromycin. The use of azithromycin appears to be more common in long-term studies, probably because of its particular pharmacokinetic characteristics. The structure of azithromycin results in a pharmacokinetic profile distinct from that of other macrolides such as erythromycin and clarithromycin. Even with low plasma concentrations, azithromycin shows good tissue penetration and high concentrations can be achieved in the airway secretions. Consequently, a short course of once daily treatment has been advocated for soft tissue and respiratory tract infections[46]. This advantage may be offset by development of resistance by the target pathogens because of the widespread use and long tissue half-life of azithromycin[47]. Current evidence shows that azithromycin, through its pharmacokinetic effects, may have the same efficacy in patients with CF, at lower doses[48]. From a recent meta-analysis the authors concluded that a dose level of 22-30 mg/kg/week is the lowest dose level with proven efficacy, and that even small doses of the drug can achieve low plasma levels, but for a period which may exceed 20 days[48]. It is therefore possible that azithromycin in even smaller doses than studied to date may have the same positive effects with less risk of development of resistant strains.

ASTHMA

Asthma is characterized by persistent airway inflammation that produces airway hyperresponsiveness and recurrent episodes of airway obstruction. Eosinophils are a major component of the inflammation of bronchial mucosa in asthma[49], and it is possible that chronic infection with *Chlamydia pneumoniae* and/or *Mycoplasma pneumoniae* may contribute to its pathophysiology[50]. Proposed mechanisms of action of the macrolide antibiotics in asthma include alteration of steroid metabolism, direct antimicrobial activity and anti-inflammatory effects[51]. A few randomized double-blind, placebo-controlled trials have investigated the effects of macrolides in the treatment of patients with chronic asthma. The major studies of the efficacy of macrolides in asthma in humans are presented in Table 5.

The alteration of steroid metabolism may be a reason for the use of macrolides as steroid-sparing agents in some earlier studies[52]. Kamada and colleagues examined the effects of troleandomycin in 18 children with severe steroid-dependent asthma in a small randomized, double-blind trial[53]. They observed a significant reduction in steroid requirement in the group treated with troleandomycin and methylprednisolone group compared with the group given placebo, although no improvement was observed in FEV_1. Another double-blind trial, however, in which 75 patients with steroid-dependent asthma received troleandomycin with methylprednisolone, showed no benefits in the reduction of the steroid dose needed to control asthma symptoms[54].

One mechanism of macrolide action proposed to explain a beneficial effect in asthma is direct antimicrobial activity[51]. Chronic infection with atypical microorganisms may play a role in the pathogenesis and severity of chronic asthma[55,56], and evidently macrolides exert antimicrobial activity against these pathogens[57-59]. Black and colleagues randomized 232 adult patients with asthma who had serological evidence of infection with *C. pneumoniae* to treatment with roxithromycin (150mg, bid) or placebo[60]. After 6 weeks of treatment, no significant change was noted in morning peak expiratory flow (PEF) or asthma symptom score, but there was an improvement in nighttime PEF[60]. A smaller study examined the effect of clarithromycin (500mg bid or placebo for 6 weeks) on 55 adult patients with asthma[61]. This study showed that in patients with BAL fluid positive for either *C. pneumoniae* or *M. pneumoniae* the FEV_1 was significantly improved in those taking clarithromycin[61]. In another study, patients with stable persistent asthma and serological evidence of *C. pneumoniae* infection showed clinical and spirometric improvements after receiving azithromycin for 6 weeks[62].

Many investigators have evaluated the effect of macrolides on bronchial hyperresponsiveness. Amayasu and co-workers randomized 17 adults with allergy-induced asthma to clarithromycin 200mg, or placebo twice daily for 8 weeks[63]. They reported a statistically significant reduction in bronchial hyperresponsiveness in the clarithromycin group, along with a significant decrease in symptoms and in blood and sputum eosinophil counts, sputum eosinophilic cationic protein[63]. In a study from Greece, Kostadima and colleagues observed a significant reduction in bronchial hyperresponsiveness in patients with asthma receiving clarithromycin for 8 weeks[51]. In spite of these important results, neither of these two studies documented a significant change in FEV_1 [51,63]. Simpson and co-workers confirmed the above findings regarding

TABLE 5. Major studies of the efficacy of macrolides in asthma in humans

Author/ Reference	Study population	Type of study	Macrolide	Major results
Kamada AK et al[53]	Asthma (children with severe steroid-dependent asthma): 18 patients	Randomized, double-blind placebo-controlled trial	Troleandomycin (250mg daily or every other day for 12 weeks)	Reduction in steroid requirement No improvement in FEV_1.
Nelson HS et al[54]	Asthma (steroid-dependent): 75 patients	Randomized, double-blind placebo-controlled trial	Troleandomycin (250mg once daily for 2 years)	No benefits in steroid dose reduction
Black PN et al[60]	Asthma (adult patients with *C. pneumoniae* infection): 232 patients	Randomized, double-blind placebo-controlled trial	Roxithromycin (150mg, bid for 6 weeks)	No change in morning PEF No change on asthma symptom score Improvement in nighttime PEF
Kraft M et al[61]	Asthma (adults): 55 patients	Randomized, double-blind, placebo-controlled trial	Clarithromycin (500mg b.i.d. for 6 weeks)	FEV_1 significantly improved in patients with PCR–positive BAL fluid for either *C. pneumoniae* or *M. pneumoniae*
Hahn DL et al[62]	Asthma (stable, persistent, with *C. pneumoniae* infection): 36 patients	Randomized, placebo-controlled, blinded trial.	Azithromycin (600 mg daily for 3 days - 600mg weekly for 6 weeks)	Clinical and spirometric improvements
Amayasu H et al[63]	Asthma (allergy-induced): 17 patients	Randomized, double-blind, placebo-controlled trial	Clarithromycin (200 mg twice daily for 8 weeks)	Reduction of bronchial hyperresponsiveness Decrease in blood and sputum eosinophil counts, sputum eosinophilic cationic protein Improvement of symptoms No change in FEV_1
Kostadima E et al[51]	Asthma (adults): 63 patients.	Randomized, double-blind, placebo-controlled trial	Clarithromycin (250 mg bid for 8 weeks)	Reduction in bronchial hyperresponsiveness in patients with asthma - No change on FEV_1
Simpson JK et al[64]	Asthma (refractory): 45 patients	Randomized, double-blind, placebo-controlled trial	Clarithromycin (500 mg twice daily)	No change in FEV_1 No change in bronchial hyperresponsiveness Improvement of symptoms and HRQoL Modulation of IL-8 levels and neutrophil accumulation and activation in the airways

BAL: Bronchoalveolar lavage, FEV1: Forced expiratory volume in 1 second, FVC: forced exhaled vital capacity, HRQoL: Health Related Quality of Life, PEF: Peak expiratory flow, PFT: Pulmonary Function Test, IL: interleukin, TNF- α: Tumour Necrosis Factor-α

absence of effect on FEV_1, but conversely reported no change in bronchial hyperresponsiveness in patients with asthma who received clarithromycin for 8 weeks[64]. The Simpson study, however, documented improvements in QoL and symptoms, and provided evidence of a modulation in IL8 levels and neutrophil accumulation and activation in the airways of patients with refractory asthma[64]. These authors suggest that macrolide therapy may be an important additional treatment for reducing non-eosinophilic airway inflammation, particularly neutrophilic inflammation, in patients with refractory asthma.

A Cochrane review[77] concluded that there is insufficient

documented evidence to either support or refute the use of macrolides in the treatment of asthma. It appears, however, that certain subgroups of patients with asthma may benefit from long-term macrolide treatment, especially those with neutrophilic inflammation that does not respond to regular guideline-directed treatment. Further studies are needed to establish the possible role of macrolides in the management of difficult-to-treat asthma.

POST-TRANSPLANT OBLITERATIVE BRONCHIOLITIS

Bronchiolitis obliterans syndrome (BOS) is the clinical manifestation of chronic airways rejection[66]. It is estimated that up to 50% of lung transplant recipients who survive for at least 3 months will develop BOS[67]. BOS is associated with a progressive decline in FEV_1 and mortality rates of 25-50% have been reported[67,68]. The major studies of the efficacy of macrolides in post-transplant BOS in humans are presented in Table 6.

An observational study by Gottlieb and co-workers was the first to show an improvement in FEV1 after long-term macrolide administration in a subgroup of patients with BOS[69]. In a prospective study, 7 patients with BOS who were randomized to treatment with azithromycin (loading dose followed by 250mg three times a week) for at least 3 months showed a trend towards improvement in FEV_1 that was not, however, statistically significant[70]. Benden and colleagues explored the effects of clarithromycin (250-500 mg b.i.d.) on 31 patients with BOS for 6 months, and observed an increase in FEV_1 of more than 10% in 12 patients[71]. Another prospective study following 14 patients with BOS treated with azithromycin (250mg 3 times weekly) for 12 weeks showed an increase of 13% in FEV_1 in the group as a whole (absolute increase of 310 ml, p=0.0007)[72]. In addition, 3 months after treatment, the patients with an improvement in FEV_1 of more than 10% had less neutrophils and decreased levels of IL8 and -17 in BAL fluid[72]. The authors concluded that a significant response to azithromycin treatment in patients with BOS can be predicted by BAL fluid neutrophilia of >15%[72].

Kotsimbos and colleagues examined the possible role of *C. pneumoniae* infection in the development of BOS after lung transplantation[73]. They demonstrated that a mismatch of a positive donor and a negative recipient in *C. pneumoniae* serology was an independent risk factor for the development of BOS. The risk of BOS was lower with a negative donor and positive recipient. These findings were mirrored by another study that also showed *C. pneumoniae* in lung transplants to be associated with

TABLE 6. Major studies of the efficacy of macrolides in post-transplant bronchiolitis obliterans syndrome (BOS) in humans

Author/ Reference	Study population	Type of study	Macrolide	Major results
Gottlieb J et al[69]	Bronchiolitis obliterans:81 patients	Observational study	Azithromycin	Improvement in FEV_1
Porhownik NR et al[70]	Bronchiolitis obliterans: 7 patients	Prospective cohort study	Azithromycin (loading dose followed by 250mg 3 times weekly for 3 months)	Statistically significant improvement in FEV_1
Benden C et al[71]	Bronchiolitis obliterans: 31 patients	Prospective cohort study	Clarithromycin (250-500 mg b.i.d. for 6 months)	Improvement in FEV_1
Verleden GM et al[72]	Bronchiolitis obliterans: 14 patients	Prospective cohort study	Azithromycin (250mg three times a week for 12 weeks)	Improvement of FEV_1 Decrease in neutrophils and levels of IL8 and -17 in BAL fluid.
Vos R et al[75]	Bronchiolitis obliterans: 83 patients	Randomized, double-blind, placebo-controlled trial	AzIthromycin (250 mg daily for 5 days followed by 250mg daily 3 times weekly for two years)	Fewer patients with BOS Better BOS free survival Better FEV_1, lower systemic CRP levels, lower airway neutrophilia. No improvement in overall survival

CRP: C- reactive protein, BAL: Bronchoalveolar lavage, FEV1: Forced expiratory volume in 1 second, FVC: forced exhaled vital capacity, IL: interleukin

increased risk of BOS[74].

Vos and co-workers conducted the largest double-blind randomized controlled trial investigating the effect of azIthromycin given as prophylaxis to lung transplant recipients to prevent the development of BOS[75]. In this trial, 540 patients were treated with azithromycin administered 3 times weekly for two years after surgery and 543 patients received placebo. BOS occurred less frequently in the group on azithromycin (12.5% versus 44.2%) and BOS free survival 2 years post-transplant was better with azithromycin[75]. The patients receiving azithromycin had better FEV_1 and lower blood CRP and airway neutrophilia, but there was no difference in the overall survival between the two study groups[75]. This trial provided the most robust data to date to show that the prophylactic use of azithromycin reduces the incidence of BOS in lung transplant recipients.

CONCLUSIONS

Recent clinical trials have provided new insight into the possible role of macrolides in the treatment of airway diseases. The beneficial effects of these drugs are plausibly attributed to their immunomodulatory and anti-inflammatory properties. Current evidence confirms that macrolides, particularly azithromycin, reduce the incidence of exacerbations in patients with severe COPD and frequent exacerbations. Unfortunately, the rate of isolation of macrolide-resistant pathogens increases with such treatment, which should therefore be limited to a subgroup of patients with well-characterized COPD who have frequent exacerbations despite optimal treatment. In the treatment of idiopathic bronchiectasis with macrolides, studies show evidence of diminished sputum volume and decreased frequency and intensity of exacerbations. Conversely, there currently insufficient evidence to support the general use of macrolides in the treatment of asthma, although a specific subgroup of patients with refractory asthma and neutrophilic inflammation may derive some benefit. Finally, long-term prophylactic therapy with macrolides may be beneficial in lung transplant recipients, as recent evidence indicate their effectiveness in lowering the incidence of BOS.

The major concerns about macrolides are related to the side effects associated with their long-term use, mainly hearing impairment, but also the risk of arrhythmia, especially in patients taking other medication that prolong the QT interval, and the possible emergence of bacterial resistance. The prophylactic long-term treatment of patients with airway diseases with macrolides cannot be routinely recommended. Currently treatment should be restricted to selected cases of patients with COPD or non-CF bronchiectasis with frequent exacerbations despite optimal management, and always taking into account the potential side effects. Finally, the potential for emergence of bacterial resistance with very long-term use of macrolides may be overcome by the development of novel non-antibiotic macrolide compounds possessing only anti-inflammatory and immunomodulatory actions [76].

In conclusion, the macrolides provide a potential new option for the management of patients with chronic inflammatory airway disorders who are not adequately controlled with treatment recommended by the conventional guidelines. Future studies are needed to facilitate the appropriate selection of candidate patients for long-term macrolide use, balancing the potential benefits against the risks of administration of macrolides in specific chronic inflammatory airway diseases.

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