Chapter 11

Long-term oral antibiotic treatment: why, what, when and to whom?

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Antibiotics are typically prescribed as short courses for acute infections, in order to reduce bacterial load, shift the balance in favour of host defences and thus help to overcome infection. Over the past decade, however, interest in the long-term anti-inflammatory and immunomodulatory effects of selected antibiotics has been on the increase. Since the clinical effectiveness of erythromycin was reported in diffuse panbronchiolitis in the 1980s, the use of macrolides has been adopted into many other chronic inflammatory airway diseases characterised by frequent exacerbations, including cystic fibrosis (CF), non-CF bronchiectasis, COPD, severe noneosinophilic asthma, bronchiolitis obliterans after lung transplantation and organising pneumonia. In this chapter, we discuss the indications and limitations of long-term macrolide treatment in these chronic respiratory conditions.

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Long-term oral antibiotic treatment: why?

Airway disorders such as COPD, cystic fibrosis (CF) and bronchiectasis, in which chronic airway inflammation and (infectious) exacerbations occur, typically result in progressive lung function decline, decreased health-related quality of life and increased risk of mortality [1–5]. The pathophysiological processes typical of these chronic inflammatory lung diseases are characterised by a vicious circle hypothesis, in which exacerbations result in increased airway inflammation, more damage to airways and therefore a higher risk for new

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exacerbations, which will finally result in progression of disease (figure 1) [4, 6, 7]. To inhibit further disease progression, interventions have to be performed directed at one of these steps of the vicious circle. Among these interventions is the implementation of long-term oral antibiotic treatment. The most widely studied class of antibiotics used for oral maintenance therapy is the macrolide group.

Long-term oral antibiotic treatment: what?

Choice of agent

Although other antibiotics, such as the tetracycline doxycycline and the fluoroquinolone moxifloxacin, have also been assigned immunomodulatory properties [8, 9], only the use of macrolides has been well documented in RCTs. Their effects in chronic inflammatory lung diseases were first studied in patients with diffuse panbronchiolitis in the 1980s [10]. Since then macrolides have been studied extensively in CF [11–14], non-CF bronchiectasis [15–17], and recently also in patients with COPD [18–20] and severe asthma [21, 22].

Structure and mechanisms of actions of macrolides

The family of macrolide antibiotics is structurally characterised by a lactone ring containing at least 12 members, with erythromycin, clarithromycin and roxithromycin containing a 14-membered lactone ring, and azithromycin (also called an azalide) containing a 15-membered lactone ring with a tertiary amino group [23, 24]. The neomacrolides azithromycin, clarithromycin and roxithromycin have excellent bioavailability with superior oral absorption and better tissue penetration than erythromycin, accumulating preferentially in (alveolar) macrophages, with azithromycin having the longest serum half-life, making it suitable for once-daily or even intermittent dosing [25–27]. Due to toxicity concerns and scarceness of data on immunomodulatory effects, the ketolide telithromycin is less convenient for long-term use and will therefore not be discussed further in this chapter [28–30].

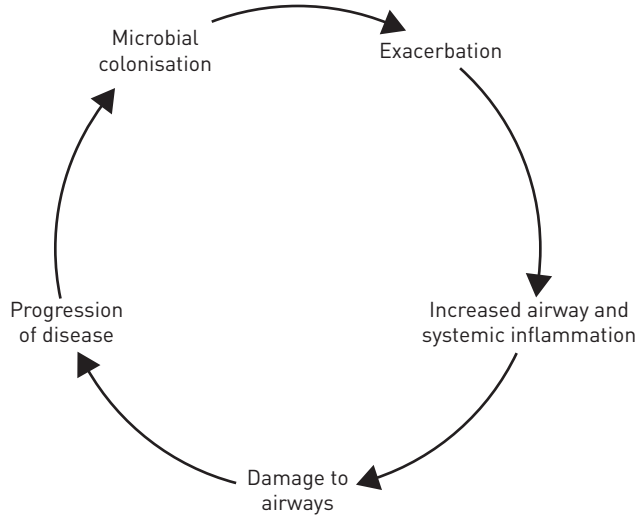

Figure 1. Vicious circle hypothesis of chronic inflammatory pulmonary disorders [6].

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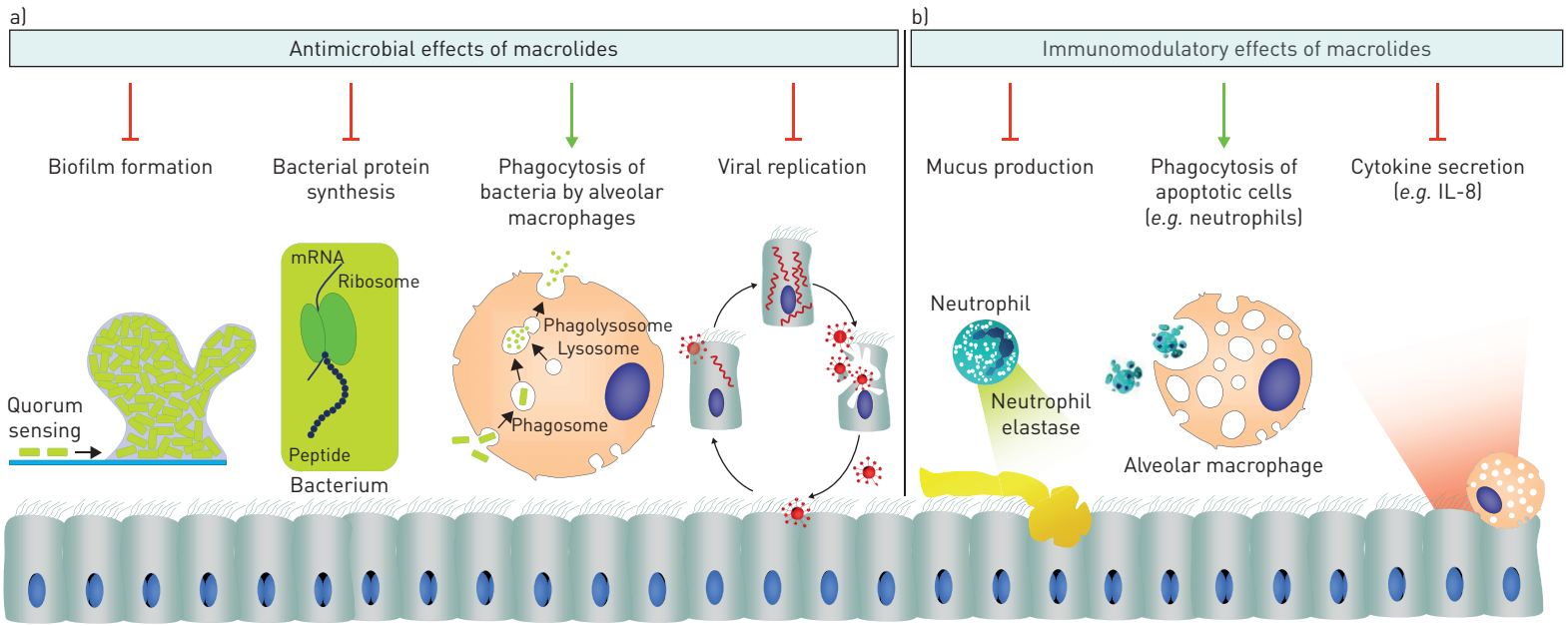

Figure 2. The antimicrobial and immunomodulatory effects of macrolides. a) Antimicrobial effects. Macrolides can directly affect bacteria by inhibiting bacterial protein synthesis, and reducing their adherence and toxin production. In addition, they are able to disrupt biofilm formation through suppression of quorum sensing proteins, in particular in the case of *Pseudomonas aeruginosa* infections. Macrolides stimulate phagocytosis of pathogenic bacteria by alveolar macrophages. In bronchial epithelial cells, they tend to induce antiviral host responses, thereby indirectly hampering viral replication. b) Immunomodulatory effects. Macrolides enhance mucociliary clearance by reducing airway secretions through inhibition of neutrophil elastase and modulation of mucin gene expression, and reduce chronic inflammation by stimulating phagocytosis of apoptotic cells and impairing the production of pro-inflammatory mediators such as IL-8 in airway epithelial cells and alveolar macrophages [53].

Antimicrobial effects of macrolides

The direct antibiotic effect of macrolides is exerted through binding to the bacterial 50S ribosomal subunit, thereby interfering with its assembly and ultimately inhibiting bacterial protein synthesis, leading to a bacteriostatic effect [25, 31, 32]. Their antibacterial spectrum primarily includes the atypical bacteria *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila*, and, although resistance is on the increase, Gram-positives such as *Streptococcus pneumoniae*, while the neomacrolides also have a better Gram-negative coverage, including susceptible strains of *Haemophilus influenzae* and *Moraxella catarrhalis* [25, 33, 34]. The neomacrolides clarithromycin and azithromycin have excellent tissue penetration, and hence form the backbone in first-line combination treatment regimens for NTM such as MAC [35, 36]. Acquired resistance to macrolides occurs through alterations in their binding site on the bacterial ribosomal RNA induced by methylases encoded by erythromycin ribosome methylase (*erm*) genes or through macrolide efflux (*mef*) genes encoding for active efflux pumps reducing intrabacterial macrolide concentrations [37, 38].

Indirect antimicrobial effects are established by stimulation of phagocytosis of bacteria by alveolar macrophages [39, 40], and *via* inhibition of quorum sensing and biofilm formation, mechanisms which have been proven particularly useful in reducing the virulence of *Pseudomonas aeruginosa* and facilitating the effects of antipseudomonal antibiotics [41–43]. At subinhibitory concentrations, azithromycin interferes with cell–cell communication through inhibition of the guanosine diphosphomannose dehydrogenase enzyme in the alginate biosynthetic pathway of mucoid *P. aeruginosa* strains, thereby mitigating biofilm production [44]. Interestingly, an increase in the expression level of type III secretion system genes, encoding for virulence factors in *P. aeruginosa*, has also been observed *in vitro*, but up to now without any clinical correlate [44, 45].

Supported by the observation that erythromycin significantly reduced the number of common colds in COPD patients [46], potential antiviral properties of macrolides have also been unravelled more recently [47–49]. *In vitro*, azithromycin decreases viral load in bronchial epithelial cells infected with rhinovirus [49]. Its antiviral effects are possibly mediated by induction of pattern recognition receptors, IFNs and IFN-stimulated genes, leading to a global amplification of the host antiviral response to human rhinoviruses [47, 48]. The antimicrobial effects of macrolides are summarised in figure 2a.

Immunomodulatory effects of macrolides

Long-term treatment courses with 14- and 15-membered-ring macrolides are known to influence chronic airway diseases mediated by neutrophilic inflammation [50–53]. In contrast to other antibiotics that have been attributed immunomodulatory effects, macrolides are known to alter a plenitude of cells within the airway, including neutrophils, alveolar macrophages, lymphocytes and epithelial cells [54, 55]. The pronounced intracellular accumulation and retention of macrolides, and in particular of azithromycin, allows prolongation of their effects within host cells [56, 57]. After an initial stimulation of neutrophil degranulation and phagocytosis-associated oxidative burst enhancing their antibacterial activity, late effects of macrolides include increased neutrophil apoptosis and attenuation of oxidative burst responses [55, 56]. Neutrophilic inflammation is further hampered by macrolide antibiotics through decreased production of chemoattractants and

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decreased expression of adhesion molecules, resulting in attenuation of chemotaxis [58, 59]. Azithromycin may also promote differentiation of monocytoid cell lines into macrophages and alter the macrophage phenotype, leading to reduced secretion of pro-inflammatory cytokines and increased production of anti-inflammatory mediators [60–62]. In addition, macrolides stimulate phagocytosis of apoptotic cells by alveolar macrophages [39, 40], attenuate type 1 T-helper cell (Th1) responses following lipopolysaccharide (LPS)- or IFN-γ-induced stimulation of macrophages, and (although conflicting observations have been reported) seem to affect the balance between Th1 and Th2 responses [63–65].

Additional modulation of host defence occurs through interaction with structural cells, such as bronchial epithelial cells, with beneficial effects on the stability of the epithelial barrier and ciliary function [54, 55]. Macrolide-induced inhibition of neutrophilic elastase and matrix metalloproteinases [66–68], and of respiratory epithelium cytokine production [56, 68, 69], is well established. Most of these effects are probably caused by modulation of mitogen-activated protein kinase and NF-κB signalling pathways [54]. In human airways, epithelial goblet cells and mucous cells synthesise gel-forming mucins such as MUC5AC and MUC5B [54]. Erythromycin and clarithromycin have been shown to inhibit this TNF-α-induced mucus secretion, resulting in improved mucociliary clearance and hence beneficial effects in various clinical conditions characterised by excessive sputum production [51, 70, 71]. The immunomodulatory effects of macrolides are summarised in figure 2b.

Dosing of macrolides

The long half-life and interesting safety profile makes azithromycin the agent of choice for long-term use. When used for its immunomodulatory purposes, azithromycin is typically dosed as 500 mg three times weekly on Monday, Wednesday and Friday (MWF), or alternatively by a daily 250 mg dose, although the AZISAST (Azithromycin in severe asthma) study has shown efficacy in noneosinophilic asthma at lower doses of 250 mg three times weekly [21]. In case of intolerance of the usual dosage, lower doses of 250 mg MWF are worth considering as, although not widely studied, they might have the advantage of inducing less adverse events without losing efficacy. In case of obstinate gastrointestinal intolerance of azithromycin, roxithromycin can be used as an alternative, at a daily dose of 150 mg [72]. As for clarithromycin, most clinical trials have been performed with doses of 500 mg twice daily, although doses as low as 200 mg daily have also proven effective [68, 73].

Other antibiotics

In addition to macrolides, other antibiotics have been investigated, although less intensively, for maintenance treatment in chronic inflammatory airway diseases. Doxycycline and other tetracyclines have been shown to regulate the host immune response, *e.g.* by targeting matrix metalloproteinases released from neutrophils and attenuating LPS-induced inflammation [8, 74, 75]. Immunomodulatory effects have also been attributed to fluoroquinolones, with moxifloxacin selectively inhibiting secretion of cytokines such as IL-8 and IL-6, and NF-κB activation in CF epithelial cell lines, and ciprofloxacin providing anti-inflammatory properties in the setting of LPS-induced lung injury in animal models [76, 77]. In *Stenotrophomonas maltophilia* infection, trimethoprim–sulfamethoxazole (cotrimoxazole) has been shown to suppress TNF-α production by human peripheral blood mononuclear cells [78]. Accumulating *in vitro* evidence suggests that cotrimoxazole is able

to enhance neutrophil chemotaxis, phagocytosis and intracellular killing by macrophages, to reduce lymphocytic proliferation [79]. As mentioned earlier, this chapter will elaborate mainly on the clinical applications of macrolides as only scarce data on the long-term use of other oral antibiotic treatment classes are available.

Long-term oral antibiotic treatment: when and to whom?

Diffuse panbronchiolitis

Diffuse panbronchiolitis is an idiopathic inflammatory disease of the respiratory bronchioles, almost exclusively occurring in Japan and other East Asian countries [80, 81]. This progressive disease is characterised by neutrophilic airway inflammation with elevated pro-inflammatory cytokines such as IL-8 and IL-1β, and often complicated by *H. influenzae* and/or *P. aeruginosa* infection [82, 83]. The prognosis of this possibly fatal disease was significantly improved by the introduction of erythromycin, leading to the suspicion of beneficial effects of erythromycin other than its antibacterial activity [10, 84]. Treatment with macrolides has been shown to decrease BAL fluid levels of neutrophils, IL-8 and pro-inflammatory β-defensins [83, 85, 86]. Nevertheless, most evidence came from retrospective or prospective open trials, suggesting not only efficacy of erythromycin [10, 84, 87, 88], but also of clarithromycin, azithromycin and roxithromycin [73, 89–91]. Only one small RCT was reported examining serial CT scans [92]. As the overt clinical success of macrolide treatment precludes placebo-controlled trials in diffuse panbronchiolitis, the authors of a systematic review instead recommended setting up comparative RCTs between different kinds or doses of macrolides in the future [93].

Cystic fibrosis

CF is a multisystem, autosomal recessive genetic disease, caused by a defect in the CF transmembrane conductance regulator (*CFTR*) gene. Its pulmonary manifestations are characterised by recurrent airway infections, chronic inflammation and progressive lung function decline, resulting in limited life expectancy [94, 95]. However, the prognosis is gradually improving due to the introduction of medication directly targeted to the genetic cause of the disease, as well as treatments directed towards infection and inflammation [96, 97]. Frequent pulmonary exacerbations are known to be associated with increased mortality. Macrolides, which in CF will mainly have anti-inflammatory and antibacterial working mechanisms by inhibiting biofilm formation (figure 2), have been investigated for their potential to improve lung function in CF in five large RCTs (table 1) [11–14, 98]. Forced expiratory volume in 1 s (FEV_1) improved in two studies and azithromycin reduced FEV_1 decline in one study. Although two other trials did not show an effect of macrolides on FEV_1, a reduction in the number of exacerbations was established. The 2012 Cochrane review on macrolide maintenance therapy in CF stated that 6-month azithromycin treatment courses can result in improved FEV_1 and reduced exacerbation rates, but that it is not clear whether this effect will be sustained [99]. What is the effect of treatment with macrolides longer than 12 months [100]? This important issue has recently been addressed in a retrospective study showing that in the 2 years following the first year of azithromycin treatment, the exacerbation rate increased again to levels similar to the period before starting the macrolide [101].

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Table 1. Randomised double-blind placebo-controlled trials with long-term macrolides in cystic fibrosis (CF) and non-CF bronchiectasis

First author [ref.]	Inclusion criteria	Intervention	Length of treatment	Primary outcome	Number of exacerbations
CF					
Saiman [12]	Age ⩾6 years; weight ⩾25 kg; chronic infection with *Pseudomonas aeruginosa*	Azithromycin 250 or 500 mg (weight <40 or ⩾40 kg) three times weekly	168 days	Significantly improved FEV1	Significantly reduced (hazard ratio 0.65)
Clement [11]	Age 6–21 years	Azithromycin 250 or 500 mg (weight <40 or ⩾40 kg) three times weekly	12 months	No significant difference in FEV1	Significantly reduced (rate ratio 0.5)
Equi [13]	Age 8–18 years	Azithromycin 250 or 500 mg (weight <40 or ⩾40 kg) once daily	6 months	Significantly improved FEV1	No significant difference
Wolter [14]	Age ⩾18 years	Azithromycin 250 mg once daily	3 months	Reduced rate of FEV1 decline	No significant difference
Saiman [98]	Age 6–18 years; weight ⩾18 kg; no *Pseudomonas* infection	Azithromycin 250 or 500 mg (weight <36 or ⩾36 kg) three times weekly	168 days	No significant difference in FEV1	50% reduction in exacerbations (hazard ratio 0.5)
Non-CF bronchiectasis					
Wong [15]	Age ⩾18 years; ⩾1 exacerbation requiring antibiotic(s) in preceding year	Azithromycin 500 mg three times weekly	6 months	Significantly reduced number of exacerbations (rate ratio 0.38)	
Serisier [17]	Age 20–85 years; ⩾2 exacerbations requiring antibiotic(s) in preceding year	Erythromycin 400 mg twice daily	48 weeks	Significantly reduced number of exacerbations (rate ratio 0.57)	
Altenburg [16]	Age ⩾18 years; ⩾3 LRTIs requiring antibiotic(s) in preceding year; ⩾1 sputum culture yielding ⩾1 bacterial pathogen in preceding year	Azithromycin 250 mg once daily	52 weeks	Significantly reduced number of exacerbations (rate ratio 0.41)	

FEV1: forced expiratory volume in 1 s.

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To whom?

As macrolides have a positive effect on lung function and exacerbation frequency, it can be suggested to start this treatment in CF patients showing lung function decline or experiencing frequent exacerbations.

Non-CF bronchiectasis

Bronchiectasis is defined as the presence of dilated thick-walled bronchi caused by chronic bronchial inflammation and recurrent airway infections [4]. Many aetiologies have been identified, with the most common causes described in the European Bronchiectasis Registry (EMBARC) being idiopathic (39%) and post-infective (27%). Long-term oral antibiotics were used in 19.4%, consisting mainly (in 74.2%) of azithromycin [102]. One RCT evaluated amoxicillin 3 g twice daily for 32 weeks in bronchiectasis patients expectorating daily purulent sputum, which resulted in a reduction in 24-h sputum volume and purulence, and in symptom awareness [103]. Most recent trials have, however, been examining macrolides mainly based on their anti-inflammatory properties and antibacterial effects by inhibiting biofilm formation (figure 2). The three main randomised double-blind placebo-controlled studies investigating the effect of azithromycin in non-CF bronchiectasis have shown significant reductions in pulmonary exacerbations (table 1) [15–17]. In the trial conducted by Wong *et al.* [15], the benefits of macrolide treatment persisted for 6 months after completion of treatment. Serisier *et al.* [17] showed that low-dose erythromycin also decreased sputum production, with a beneficial effect on lung function, and increased eradication of sputum pathogens.

To whom?

Based on the three trials [15–17], expert opinion supports macrolide maintenance treatment in patients with frequent exacerbations (at least two exacerbations in the previous year) provided their airway clearance techniques have been already optimised. Patients who are stable with good self-reported quality of life and less pulmonary complaints should not be treated with long-term azithromycin [104, 105].

COPD

COPD is defined by progressive airflow obstruction that is poorly reversible and intercurrent acute exacerbations, which have an impact on disease course and mortality risk [3, 106, 107]. Increasing evidence supports an important role for the lung microbiome in the pathogenesis of COPD [108]. Exacerbations are often caused by infectious microorganisms, accompanied by airway and systemic inflammation [109]. Prevention of exacerbations is therefore essential to inhibit further disease progression. During exacerbations, microbiome shifts have been observed, as well as differences related to the exacerbation phenotypes described as bacterial or eosinophilic, with increases in Proteobacteria (mainly *Haemophilus* and *Moraxella* spp.) or Firmicutes (mainly *Streptococcus* spp.), respectively [108, 110]. A UK retrospective cohort study demonstrated that maintenance antibiotic treatment (⩾6 months) had been prescribed only for a small proportion of COPD patients (0.61%). The antibiotics most often used were oxytetracycline, doxycycline and penicillin, with a rise in macrolide prescriptions from 2005 [111].

Many antibiotics have been assessed for long-term treatment in COPD. As early as 1956, an observational study published in *The Lancet* showed overall improvement in 60% of

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patients with chronic bronchitis receiving tetracyclines during 6 months in winter. *H. influenzae* was present in sputum cultures in almost all patients [112]. In contrast, a recent RCT examining a 3-week course of doxycycline in stable COPD patients was not able to show any anti-inflammatory effects [113]. Another observational study published in 1975 showed that an improvement in sputum production and dyspnoea was seen in 50% of COPD patients with chronic sputum production receiving trimethoprim–sulfamethoxazole 960 mg twice daily during 3 months [114]. Recently, intermittent pulsed therapy with moxifloxacin 400 mg once daily for 5 days, repeated each 8 weeks during 48 weeks, reduced the exacerbation rate in COPD patients in an RCT [115].

In addition to their anti-inflammatory functions, macrolides can play a major role in prevention of exacerbations due to their antibacterial and antiviral properties (figure 2). Three major studies have investigated the role of macrolides in reducing exacerbations (table 2). While Uzun *et al.* [18] included patients with frequent exacerbations, patients with nonfrequent exacerbations were also allowed to be enrolled in the other two studies [19, 20]. Macrolides reduced the number of exacerbations in all three trials [18–20]. The beneficial effect of macrolides can be partially explained by the presence of bronchiectasis in patients with COPD. Martínez-García *et al.* [116] showed that bronchiectasis was present in almost 60% of the COPD patients. In the COLUMBUS (COPD: influence of macrolides on exacerbation frequency in patients) trial, CT scans were performed to exclude patients with bronchiectasis [18]. A multicentre RCT examining the effect of short-term macrolide treatment in acute COPD exacerbations is currently ongoing [117].

To whom?

Criteria were proposed for selecting patients for long-term azithromycin treatment. In two reviews, the authors recommend to prescribe macrolides in patients with frequent exacerbations (at least two in the year before treatment) [17, 118]. The most pronounced effect of azithromycin was seen in patients of older age, in those classified in lower Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade and in those not actively smoking [119]. However, this analysis was performed on data which also involved patients with nonfrequent exacerbations.

Severe noneosinophilic asthma

Severe asthma is a heterogeneous syndrome characterised by chronic airway inflammation, either of eosinophilic nature or of noneosinophilic origin (neutrophilic or paucigranulocytic) [120]. In parallel to the chronic neutrophilic airway diseases mentioned previously, the effects of low-dose macrolides have also been examined in patients with severe noneosinophilic asthma [53]. Initially, the observed beneficial effects of macrolides in asthma were attributed to their antimicrobial properties directed towards intracellular pathogens, such as *Chlamydophila* and *M. pneumoniae* [121, 122]. As with respiratory viral infections, infection with and/or reactivation of these atypical bacteria has been associated with both asthma exacerbations and chronic severe asthma [123–125]. Increased susceptibility to infection in asthma probably leads to increased atypical bacterial infection (mainly with *C. pneumoniae*), which itself then further increases neutrophilic airway inflammation by eliciting acute antibody responses such as IgA, leading to aggravation of asthmatic symptoms [124, 125]. Although a partial contribution of their bacteriostatic effects cannot be excluded, it is widely assumed that the immunomodulatory properties of macrolides are the predominant mechanism of action [126, 127]. Whereas shorter-term trials were only able to show some

Table 2. Randomised double-blind placebo-controlled trials with long-term macrolides in COPD and severe asthma

First author [ref.]	Inclusion criteria	Intervention	Length of treatment	Primary outcome
COPD				
Uzun [18]	Age ⩾18 years; ⩾3 exacerbations in the preceding year	Azithromycin 500 mg three times weekly	12 months	Significantly reduced number of exacerbations (rate ratio 0.60)
Albert [19]	Age ⩾40 years; FEV_1 <80% predicted; either use of continuous supplemental oxygen or receipt of systemic corticosteroids within the previous year	Azithromycin 250 mg once daily	12 months	Significantly reduced number of exacerbations (rate ratio 0.83)
Seemungal [20]	FEV_1 30–70% predicted; no exacerbation required	Erythromycin 250 mg twice daily	12 months	Significantly reduced number of exacerbations (rate ratio 0.65)
Severe asthma				
Brusselle [21]	Age 18–75 years; persistent asthma (GINA step 4 or 5); ⩾2 severe asthma exacerbations requiring systemic corticosteroids and/or LRTIs requiring antibiotic(s) within previous year	Azithromycin 250 mg three times weekly	6 months	No difference in rate of severe exacerbations and LRTIs requiring antibiotic(s); significantly reduced number of LRTIs and exacerbations in predefined noneosinophilic severe asthma subgroup (rate ratio 0.43)
Hahn [22]	Age ⩾18 years; persistent asthma	Azithromycin 600 mg weekly	12 weeks (1 year follow-up)	No difference in symptom control, except for open-label group with more severe asthma; not powered to detect differences in exacerbation rate

FEV_1: forced expiratory volume in 1 s; GINA: Global Initiative for Asthma.

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effect of macrolides on reduction of symptoms and improvement of lung function in severe asthma, insufficient to recommend their routine use for asthma control [68, 128–132], the AZISAST study was the first to examine the prevention of exacerbations as a primary end-point in adults with exacerbation-prone severe asthma receiving long-term (6 months) macrolide maintenance therapy (table 2) [21]. In contrast, clinical trials on short-term macrolide treatment in acute asthma exacerbations yielded conflicting results [133–135].

To whom?

In the AZISAST randomised double-blind placebo-controlled trial, low-dose (250 mg three times weekly) azithromycin treatment was only associated with a significant lower exacerbation rate in the predefined subgroup of patients with noneosinophilic severe asthma [21]. The need for a careful selection of patients can also be derived from the AZMATICS (Azithromycin/asthma trial in community settings) trial, where a 12-week macrolide treatment course only showed clinical improvement in an open-label study arm encompassing individuals with severe treatment-resistant or refractory asthma [22]. However, as a recent Cochrane review points out, there is still a need for additional high-quality studies to confirm the possible benefit of macrolides in noneosinophilic severe asthma [136].

Other indications

Azithromycin has also proven useful in bronchiolitis obliterans syndrome (BOS) after lung transplantation [137, 138]. This major complication of lung transplantation is a form of chronic rejection associated with poor survival, defined as a delayed allograft dysfunction with persistent decline in FEV_1 without any other known and potentially reversible cause [139, 140]. After encouraging data showing improvements in FEV_1 in observational studies [141, 142], Corris *et al.* [143] have recently shown efficacy of azithromycin treatment in improving FEV_1 in lung allograft BOS in an RCT. In lung transplant recipients, azithromycin prophylaxis might even prevent the occurrence of BOS [144, 145]. These findings might also be extrapolated to the similar condition of BOS complicating haematopoietic stem cell transplantation; however, the scarce and rather small clinical trials available have not been able to show a significant benefit of azithromycin in this population [146–148].

Organising pneumonia, either cryptogenic, or induced by infections, drug toxicity, vasculitis or other conditions, is an inflammatory disorder characterised by buds of granulation tissue in the peripheral airways and alveoli, preferably treated with systemic corticosteroids [149]. On a case-by-case basis, chronic macrolide treatment may be adjuvant to steroid therapy or act as a steroid-sparing strategy, probably through inhibition of IL-8 release and neutrophil accumulation in the distal airways [150–154].

Long-term oral antibiotic treatment: is it safe?

Drug interactions

Drug interactions of macrolides are mainly mediated by inhibition of hepatic cytochrome CYP (P450) 3A enzymes, but are least pronounced for azithromycin compared with clarithromycin and erythromycin [155]. Through inhibition of CYP3A4, clarithromycin and erythromycin have the propensity of inducing toxic concentrations of a long list of substrates, including most statins, calcium channel blockers, amiodarone and colchicine. As an inhibitor of glycoprotein P, however, azithromycin and the other neomacrolides are able

to increase plasma concentrations of various substrates such as digoxin, everolimus, sirolimus, tacrolimus and posaconazole. All macrolides can cause altered warfarin levels to various extent. Interactions with concomitant medication should therefore always be checked before treatment initiation.

Adverse reactions

To date, no RCTs have thoroughly assessed the long-term safety of chronic macrolide therapy. Typical side-effects include gastrointestinal discomfort such as nausea, diarrhoea and abdominal pain, induced by dose-related effects on motilin receptors [156]. These mild-to-moderate symptoms seldom lead to drug discontinuation (reviewed in [157]) and are less frequently reported with the neomacrolides than with erythromycin [158, 159]. Within the neomacrolides, azithromycin and roxithromycin tend to induce fewer gastrointestinal complaints than clarithromycin.

While severe hepatotoxicity is rare during azithromycin treatment, transient cholestasis or other abnormal liver function tests have been described, although less frequently than with erythromycin [158–160]. Its propensity to induce severe hepatotoxicity excludes telithromycin from long-term treatment indications [28–30]. During long-term azithromycin treatment, monitoring of serum liver enzymes is advisable and treatment should be discontinued immediately if signs or symptoms of hepatitis occur.

The incidence of cardiac events has mainly been monitored in clinical trials on short-term macrolide use [161, 162]. In particular, macrolide antibiotics are known to potentially induce QT prolongation and torsades de pointes [161, 163]. Hence, azithromycin still needs to be used with caution in patients with pre-existing cardiovascular disease and risk factors [164, 165]. Before treatment initiation, measurement of the QT interval by electrocardiography is recommended, in particular in the case of polypharmacy or concomitant treatment with other QT-prolonging drugs such as fluoroquinolones.

Macrolide-induced ototoxicity typically affects the lower (speech) frequencies and is usually characterised by a bilateral sensorineural hearing loss, often reversible [157]. This rare side-effect is dose dependent and facilitated by risk factors such as renal impairment, as was demonstrated in one prospective case–control study in pneumonia patients treated with intravenous erythromycin [166]. Azithromycin-induced hearing loss has been reported in case of long-term high dosage (*e.g.* 500 mg daily) and mostly within a context of treatment of NTM infections [167, 168]. However, its incidence during low-dose long-term treatment still needs to be established [157], although one study in COPD patients observed more hearing decrements in participants receiving azithromycin than in those receiving placebo [19]. While routine audiometric screening is not considered mandatory, some authors suggest ordering audiometry before initiation of therapy in risk groups [169].

Long-term macrolide treatment will undoubtedly have an influence on the respiratory microbiome. A subanalysis of the BLESS (Bronchiectasis and low-dose erythromycin study) trial showed that in patients with non-CF bronchiectasis who were not colonised with *P. aeruginosa*, erythromycin caused a shift in the microbiome from a dominant presence of *H. influenzae* to an increase in concentration of *P. aeruginosa* [17]. Further research on this important area needs to be performed to investigate whether this change in the microbiome will also influence the clinical outcome.

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Macrolide resistance

Prescription of macrolides has been associated with emerging resistance, mainly in *Streptococcus* spp. and *Staphylococcus* spp. [170–174]. Unfortunately, few RCTs assessing long-term macrolide maintenance therapy have monitored for resistance induction. In CF patients, increased macrolide resistance has been observed during long-term macrolide treatment in *Staphylococcus aureus* and *H. influenzae*, particularly after multiple years of therapy [175–178]. As the clinical benefit of azithromycin in CF seems to be limited to the first 6–12 months of treatment [101], implementing shorter treatment courses and periods of treatment interruption might help to tackle resistance development. Similarly, a meta-analysis of RCTs in non-CF bronchiectasis documented an increased risk of macrolide resistance in *H. influenzae*, *S. aureus* and *S. pneumoniae* [179], while COPD trials did not find increased appearance of macrolide-resistant organisms after 3–12 months of therapy [20, 180].

Although macrolide resistance is increasing among pneumococcal isolates, literature on its clinical significance in severe infections such as pneumococcal pneumonia is inconsistent, but does not show a significant increase in mortality [181–184]. A recent retrospective study in a tertiary care hospital found no evidence suggesting that adult patients hospitalised with macrolide-resistant pneumococcal pneumonia experienced a more severe clinical presentation or worse clinical outcome than those with positive cultures for macrolide-susceptible *S. pneumoniae* [185]. From a population point of view, however, it remains important to restrict chronic macrolide use to those patients who will benefit the most in view of the increasing resistance data.

The occurrence of macrolide resistance is facilitated by macrolide monotherapy in the treatment of MAC lung disease and macrolide susceptibility is key to treatment success [186]. As azithromycin is able to block autophagosome clearance by preventing lysosomal acidification in primary human macrophages, leading to impairment of autophagy and, consequently, inhibition of intracellular killing of mycobacteria, some authors fear the induction of (macrolide-resistant) mycobacterial infection during long-term azithromycin use [187]. However, a nested case–control study in one large CF centre recently showed a reduced risk of NTM in CF adults receiving long-term azithromycin, making a plea for its use as primary prophylaxis against NTM [188]. Nevertheless, before initiating macrolide treatment, ideally three sputum samples should be delivered to exclude pre-existing NTM disease in predisposing conditions such as CF and bronchiectasis. Furthermore, current guidelines advise not to continue azithromycin treatment if a positive NTM culture is obtained in CF patients, unless as part of a multidrug treatment regimen in the context of NTM disease [189]. Recommendations for long-term macrolide treatment monitoring are summarised in table 3.

Conclusions

The pleiotropic effects of macrolides such as erythromycin, clarithromycin and azithromycin encompass anti-inflammatory and immunomodulatory capacities, in addition to their antimicrobial effects. The beneficial effects of macrolides have almost unequivocally been accepted in chronic inflammatory airway diseases such as diffuse panbronchiolitis, CF, non-CF bronchiectasis, COPD and severe noneosinophilic asthma (table 4). However, when macrolides are widely used in the community, population antimicrobial resistance will possibly increase. Therefore, indications to start macrolides should be very carefully

Table 3. Recommendations for long-term macrolide treatment monitoring

Adverse events	Timing	Recommendation
Drug hypersensitivity	At start	Absence of known allergy to macrolides
Drug interactions	Any time	Verify concomitant medication
Hepatotoxicity	At start	Aminotransferase levels <3× upper limit of normal
	At 6 weeks	Monitor serum liver enzymes
	Yearly	Monitor liver enzymes (more frequently in risk groups)
Cardiotoxicity	At start	Perform electrocardiography to assess corrected QT interval (<450 ms)
	Any time	Repeat electrocardiography if new concomitant medication influencing QT duration
Ototoxicity	At start	Audiometric screening for pre-existing hearing loss in risk groups (*e.g.* elderly)
NTM infection	At start	Perform sputum samples to exclude pre-existing NTM infection
	6 monthly	Monitor sputum cultures for NTM (particularly in risk groups, *e.g.* cystic fibrosis)

Table 4. Summary of considerations for chronic immunomodulatory therapy with macrolides

Airway disease	Subgroup of patients with expected benefit
Diffuse panbronchiolitis	
CF	Patients with FEV_1 decline and/or frequent (infectious) exacerbations, particularly in case of chronic *Pseudomonas aeruginosa* infection
Non-CF bronchiectasis	Patients with frequent (infectious) exacerbations
COPD	Patients with frequent (infectious) exacerbations
Asthma	Noneosinophilic severe asthmatic patients with frequent exacerbations
Bronchiolitis obliterans	Bronchiolitis obliterans syndrome in lung transplant recipients
Organising pneumonia	Corticosteroid-dependent patients

CF: cystic fibrosis; FEV_1: forced expiratory volume in 1 s.

considered, particularly when used in common diseases such as COPD and asthma, and well monitored (table 3). Azithromycin 500 mg three times weekly (MWF) is the regimen of first choice. In general, long-term macrolides should be considered in the described diseases when patients present with at least two exacerbations per year despite optimal treatment with the ordinary medications as recommended in the relevant guidelines.

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