



Is there a role for macrolides in severe asthma?

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Purpose of review

Severe asthma is a heterogeneous syndrome, encompassing several distinct clinical phenotypes. Different molecular and cellular pathways or endotypes determine the type of underlying airway inflammation in patients with severe asthma, which can be categorized as eosinophilic asthma (allergic and nonallergic) or noneosinophilic asthma (neutrophilic and paucigranulocytic). In this review, we discuss the potential role of macrolides in the treatment of severe asthma in adults.

Recent findings

Maintenance treatment with low-dose macrolides such as erythromycin and azithromycin provides clinical benefit in several chronic neutrophilic airway diseases, including cystic fibrosis (CF), non-CF bronchiectasis and exacerbation-prone chronic obstructive pulmonary disease. Although several short-term studies of macrolides in mild-to-moderate asthma have failed to improve lung function, the Azithromycin in Severe Asthma trial has demonstrated a significant reduction in the rate of exacerbations in patients with exacerbation-prone noneosinophilic severe asthma. As chronic macrolide use is associated with the risks of population antimicrobial resistance, this add-on treatment should be restricted to severe asthma patients at greatest unmet need despite optimal asthma management.

Summary

Further clinical, translational and basic research is needed to better phenotype patients with severe asthma, to determine the risk–benefit ratio of macrolide maintenance treatment in neutrophilic severe asthma and to elucidate the principal mechanisms of action of macrolides.

Keywords

asthma, asthma phenotypes, azithromycin, macrolides, neutrophilic airway inflammation, severe asthma

INTRODUCTION

Before we summarize the clinical studies of macrolides in adult asthma, it is important to emphasize that severe asthma is a heterogeneous syndrome and that macrolides have many pleiotropic effects.

Severe asthma is a heterogeneous syndrome

Asthma is characterized by a chronic inflammation of the lower airways, which is associated with bronchial hyperresponsiveness, variable airflow limitation and variable symptoms of shortness of breath, coughing and wheezing. Asthma is a heterogeneous syndrome, encompassing different clinical phenotypes that have been linked to different underlying pathophysiologic and pathogenetic mechanisms (molecular phenotypes and endotypes) [1–3]. Important clinical characteristics to determine the different phenotypes of severe asthma in adults are the age at onset of the disease, the presence or absence of allergy, the frequency of exacerbations

and the severity of airflow limitation. Whereas in the past asthma has been considered as an allergen-driven, T helper two (Th2)-mediated eosinophilic airway disease, it has become clear that this phenotype corresponds only with one particular phenotype of asthma, that is, early-onset allergic asthma. This allergic eosinophilic asthma phenotype is very responsive to treatment with inhaled corticosteroids (ICS) [2]. Indeed, the majority of patients with mild-to-moderate asthma [Global Initiative of Asthma

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KEY POINTS

- Severe asthma is a heterogeneous syndrome, encompassing eosinophilic and noneosinophilic (neutrophilic and paucigranulocytic) asthma.
- Macrolides such as erythromycin, clarithromycin and azithromycin have both antimicrobial and anti-inflammatory effects.
- The AZISAST trial has demonstrated that maintenance treatment with low-dose azithromycin significantly reduces the rate of exacerbations in patients with exacerbation-prone noneosinophilic severe asthma.
- As macrolides can be proarrhythmic, a prolonged corrected QT interval on electrocardiography or the use of drugs known to cause QT prolongation are contraindications for macrolide treatment.

(GINA) steps 2 and 3] can be well controlled with maintenance treatment with ICS, with or without long-acting beta₂-agonists (LABA), provided that the inhalation technique and the adherence are optimal (www.ginasthma.com). Early-onset allergic eosinophilic asthma has been mirrored in numerous experimental studies in mice using ovalbumin or house dust mite as model allergens [4,5]. However, based upon the type of the underlying inflammation, the age at onset of the disease and the associated conditions, at least four other asthma phenotypes have been discerned, including non-allergic eosinophilic asthma (which starts typically in adulthood, often after the age of 40 years), neutrophilic asthma, mixed eosinophilic and neutrophilic asthma and paucigranulocytic asthma [2]. A simplified overview of the different asthma phenotypes/endotypes is shown in Table 1.

Macrolides have pleiotropic effects

Macrolides such as erythromycin, clarithromycin and azithromycin are antibiotics that have anti-inflammatory and immunomodulatory effects in addition to their antibacterial effects [6,7]. Maintenance treatment with low-dose macrolides has been proved to be effective, well tolerated and safe in several chronic neutrophilic airway diseases, including cystic fibrosis (CF), diffuse panbronchiolitis and exacerbation-prone non-CF bronchiectasis and chronic obstructive pulmonary disease (COPD). Neutrophilic chronic airway diseases with proven efficacy of chronic macrolide treatment are as follows:

- (1) CF, specially when chronically infected with *P. aeruginosa*;

- (2) Non-CF bronchiectasis, with frequent exacerbations;
- (3) COPD with frequent exacerbations;
- (4) diffuse panbronchiolitis;
- (5) bronchiolitis obliterans syndrome after lung transplantation, especially if neutrophilic reversible allograft dysfunction;
- (6) noneosinophilic severe asthma, with frequent exacerbations.

First, erythromycin treatment has been shown to be able to cure diffuse panbronchiolitis, a severe life-threatening disease mainly occurring in Japan in 40–50-year-old patients, who are frequently colonized with (or infected by) *Haemophilus influenzae* in the lower airways and suffer from chronic rhinosinusitis [8–10]. Second, maintenance treatment with azithromycin in children and adults with CF was demonstrated to significantly reduce the rate of exacerbations, especially if these patients were chronically infected with *Pseudomonas aeruginosa* [11–14]. Thirdly, in the past year, three randomized placebo-controlled trials (RCTs) have demonstrated that macrolide treatment significantly prevents exacerbations in patients with non-CF bronchiectasis [15,16,17[■]]. Fourthly, erythromycin and azithromycin, as add-on therapy to usual therapy, have been shown to reduce exacerbations in patients with COPD, which is also associated with neutrophilic inflammation of the lower airways and lungs [18,19]. Moreover, *H. influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* are the most frequent bacterial infections causing acute exacerbations of COPD [20]. Lastly, azithromycin has been used successfully in the treatment of bronchiolitis obliterans after lung transplantation [21]; again, the therapeutic efficacy of azithromycin in this disease has been linked to the presence of neutrophilic inflammation in the bronchoalveolar lavage (BAL) fluid [22]. In summary, the common denominator of these diseases is the presence of neutrophilic airway inflammation, frequently elicited or amplified by chronic bacterial infections (especially by proteobacteria such as *H. influenzae* and *P. aeruginosa*). Intriguingly, also in patients with asthma, alterations in the airway microbiome have been discerned, including increased numbers of proteobacteria [23].

The need for a noninvasive biomarker of neutrophilic airway inflammation

The gold standard methods to study the underlying airway inflammation in asthma, including severe asthma, are bronchial biopsies and induced sputum. Bronchoscopy with bronchial biopsies, however, is

Table 1. Simplified overview of asthma phenotypes in adults

Pathobiological phenotype	Eosinophilic		Noneosinophilic	
	Allergic eosinophilic	Nonallergic eosinophilic	Neutrophilic	Paucigranulocytic
Age at onset	Early onset	Late onset	Late > early onset	?
Asthma severity	Most frequently mild-to-moderate; infrequently severe	Often severe	Severe > mild-to-moderate	?
Associated conditions	Allergic rhinitis and eczema	Chronic rhinosinusitis ± nasal polyps	Microbiome, aging, obesity, smoking, air pollutants	Airway remodeling? (e.g. airway smooth muscle?)
Response to therapy	Usually responsive to ICS; usually responsive to anti-Th2 cytokine (IL-4, IL-13, IL-5) mo abs and anti-IgE mo ab.	Refractory to ICS; needing OCS; responsive to anti-IL-5 mo ab.	Responsive to macrolides. Responsive to weight loss if obese.	Possibly responsive to bronchial thermoplasty?

ICS, inhaled corticosteroids; IL, interleukin; mo ab, monoclonal antibody; OCS, oral corticosteroids.

an invasive procedure that is mainly used in specialized centers in the context of clinical or translational research. Although sputum induction can be performed safely in patients with asthma, the procedure and the processing of induced sputum samples is labor-intensive and time-consuming. Therefore, other noninvasive tests are much needed to phenotype patients with severe asthma. For eosinophilic asthma, the fractional excretion of nitric oxide in the exhaled air (FeNO) and peripheral blood eosinophilia are used as indicators of airway eosinophilia. A FeNO higher than 50 ppb or a blood eosinophilia higher than 300/μl are suggestive of the presence of airway eosinophilia [24[■],25]. In contrast to the significant association between blood eosinophilia and airway eosinophilia in patients with asthma (who are not treated with systemic corticosteroids), there is no correlation at all between blood neutrophilia and airway neutrophilia [26]. Therefore, clinically applicable, noninvasive biomarkers of neutrophilic airway inflammation are urgently needed.

MECHANISMS OF ACTION

Both antimicrobial and anti-inflammatory effects are supposed to mediate the efficacy of macrolides in neutrophilic chronic airway diseases, including the neutrophilic phenotype of severe asthma. Potential mechanisms of action of macrolides in severe asthma are as follows:

(1) Antimicrobial effects:

- (a) killing of pathogenic bacteria (e.g. *Chlamydia pneumoniae* or *Mycoplasma pneumoniae*);

- (b) interfering with quorum sensing and biofilm formation by bacteria such as *P. aeruginosa*;
 - (c) enhancing phagocytosis of bacteria by alveolar macrophages;
 - (d) influencing the disturbed bronchial microbiome in asthmatic airways.
- (2) Anti-inflammatory and immunomodulatory effects:
- (a) decreasing mucus production by inhibiting neutrophil elastase;
 - (b) attenuating the production of pro-inflammatory mediators [e.g. interleukin (IL)-8] by bronchial epithelial cells;
 - (c) stimulating phagocytosis of apoptotic cells (e.g. neutrophils) by alveolar macrophages.
- (3) Extrapulmonary effects:
- (a) increasing gastrointestinal motility (in patients with gastro-oesophageal reflux, which can aggravate asthma);
 - (b) modulating chronic rhinosinusitis and/or nasal polyposis.

The antimicrobial effects of macrolides are diverse (Fig. 1). First, macrolide antibiotics can directly kill bacteria (e.g. atypical bacteria such as *C. pneumoniae* and *M. pneumoniae*). However, although severe asthma has been associated with these atypical bacterial infections, there is controversy whether the treatment effects of macrolides are dependent on the presence of chronic airway infection with atypical bacteria [27–29]. Second, macrolides have been shown to interfere with quorum-sensing, and thereby disrupt biofilm formation of bacterial species such as *P. aeruginosa*. This might

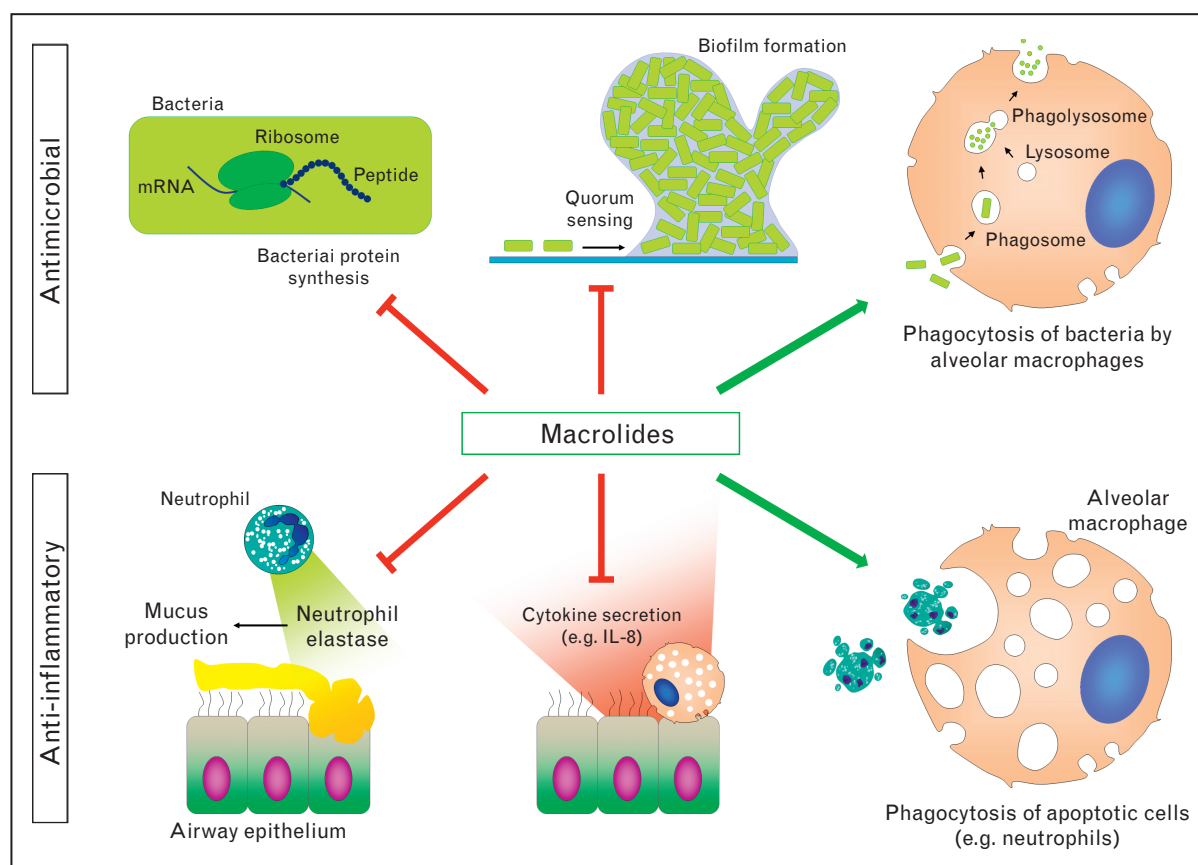


FIGURE 1. Macrolides have both antimicrobial and anti-inflammatory effects. The antimicrobial effects of macrolides encompass a direct antibiotic effect through inhibition of bacterial protein synthesis, as well as indirect antimicrobial effects by inhibiting quorum sensing and biofilm formation, and by enhancing the phagocytosis of bacteria by alveolar macrophages. In addition, macrolides have anti-inflammatory effects by stimulating the phagocytosis of apoptotic cells (i.e. efferocytosis) and by inhibiting neutrophil elastase and the production of cytokines by the respiratory epithelium.

explain the beneficial effect of azithromycin treatment *in vivo* in patients with CF or non-CF bronchiectasis who are chronically infected with *P. aeruginosa*, although this bug is resistant to macrolides *in vitro*. Thirdly, macrolides enhance phagocytosis of bacteria such as *S. pneumoniae* and *H. influenzae* by alveolar macrophages [30,31].

In addition to the antimicrobial effects, macrolides have also numerous anti-inflammatory and immunomodulatory effects. First, macrolides are partial antagonists of neutrophil elastase. As neutrophil elastase is an important stimulator of mucus production by epithelial cells (goblet cells), the inhibition of neutrophil elastase by macrolides might be responsible for the decreased volume of sputum and coughing in patients with bronchiectasis (both CF and non-CF bronchiectasis) [32,33]. Second, preclinical in-vitro and in-vivo studies demonstrate that the administration of macrolides decreases the production of proinflammatory mediators by alveolar macrophages and bronchial

epithelial cells. In a proof-of-concept study in patients with refractory asthma, treatment with clarithromycin for 8 weeks has been shown to attenuate sputum levels of IL-8, an important chemo-attractant for neutrophils [34]. Thirdly, macrolides are also able to stimulate the phagocytosis of apoptotic cells (i.e. efferocytosis) by macrophages and bronchial epithelial cells, leading to effective clearance of apoptotic neutrophils [30]. Efficient apoptotic cell clearance by bronchial epithelial cells has been shown to critically influence airway inflammation [35].

Lastly, macrolides might be beneficial in severe asthma patients via extrapulmonary effects. Erythromycin significantly increases gastrointestinal motility. As obesity and gastroesophageal reflux are both linked with asthma severity, treatment with macrolides might be helpful in obese severe asthma patients by promoting esophageal motility and preventing gastroesophageal reflux. In addition, many patients with severe asthma suffer

from chronic rhinosinusitis and/or nasal polyps [2,36]. In the Macrolides in Chronic Rhinosinusitis (MACS) study, prolonged treatment with azithromycin (500 mg per week) did not provide significant benefit over placebo; possible reasons could be the heterogeneous nature of chronic rhinosinusitis, under-dosage of azithromycin and under-powering of the study [37].

TRIALS OF MACROLIDES IN SEVERE ASTHMA

Several studies, including Cochrane meta-analyses, have examined the therapeutic efficacy of macrolides in patients with asthma, both in children and adults [27,28,34,38–42]. In this review, we focus on the clinical studies of maintenance treatment with macrolides in adults with asthma. The story of macrolide treatment in asthma is reminiscent of the development of anti-IL-5 monoclonal antibodies as add-on treatment in asthma. The first RCTs with anti-IL-5 studied patients with mild-to-moderate asthma, without subphenotyping the enrolled patients, and used lung function as primary outcome [43,44]. These studies proved that anti-IL-5 did not improve lung function in patients with mild-to-moderate asthma, who were already treated with ICS, probably because the ICS treatment had already abolished the Th2-mediated production of IL-5 [44]. Thanks to targeting anti-IL-5 treatment to patients with severe asthma and refractory airway eosinophilia, and thanks to choosing the correct primary outcome (i.e. asthma exacerbations), several investigators have shown that anti-IL-5 significantly reduces exacerbations in patients with refractory eosinophilic severe asthma [45,46^{***}]. The clinical development pathway of anti-IL-5, thus, underlines the importance of subphenotyping patients with severe asthma and of targeting specific add-on therapies to the correct severe asthma phenotype.

Similarly, the first studies of macrolides have been performed in small numbers of patients with mild-to-moderate asthma, had short study durations (less than 12 weeks) and focused on lung function as primary outcomes [27,28]. Taking these limitations into account, it is not surprising that most studies were negative. Indeed, the role of neutrophilic airway inflammation becomes more prominent in severe asthma, and the optimal primary endpoint in longer term studies of severe asthma should be the effect on asthma exacerbations (expressed as the rate of exacerbations, the total number of exacerbations or the time to the first exacerbation) [47]. In the 'Azithromycin for prevention of exacerbations in Severe Asthma (AZISAST)' study, we performed a randomized,

double-blind, placebo-controlled trial in adult patients with exacerbation-prone severe asthma [48^{***}]. Although maintenance treatment with low-dose azithromycin (250 mg three times a week) for 6 months did not affect the rate of primary endpoints compared with placebo, azithromycin treatment was associated with a significantly lower rate of exacerbations in the predefined subgroup of patients with noneosinophilic severe asthma [48^{***}]. Importantly, azithromycin was well tolerated and improved quality of life (Asthma Quality of Life Questionnaire), but there were no significant differences in lung function between the azithromycin group and the placebo group. In the 'Azithromycin-Asthma Trial in Community Settings' study, the individuals with more severe asthma in the open-label arm had clinical improvements in asthma symptoms and asthma control that persisted after the completion of azithromycin treatment, whereas the milder asthma patients randomized to azithromycin in the double-blind study did not show significant improvement in asthma outcomes [49]. Whether these differences in treatment response are related to differences in patient characteristics (e.g. asthma severity) or in study design (i.e. open label versus double-blind), is not clear.

In conclusion, similar to the development of anti-IL-5 as targeted add-on therapy in eosinophilic severe asthma, we are convinced that targeted add-on treatment with macrolides such as azithromycin is beneficial in selected patients with noneosinophilic (especially neutrophilic) severe asthma and a history of frequent exacerbations. For add-on therapy with macrolides, it is crucial to target the correct subphenotype of severe asthma and to investigate exacerbations instead of lung function as primary outcome. However, the clinical benefit of macrolide treatment comes with a resistance price.

RISKS OF AND CONTRAINDICATIONS FOR MAINTENANCE TREATMENT WITH MACROLIDES

The risks of chronic treatment with macrolide antibiotics include not only the classical personal risks of side-effects and toxicity of drugs, but also the potential to influence the antimicrobial resistance rates of a range of respiratory pathogens at the population level [50]. Particularly, the use of azithromycin and clarithromycin has been linked with the development of population macrolide resistance. For mechanisms of macrolide resistance and their clinical and ecological consequences, we refer the interested reader to a recent review [50]. Short-term use of azithromycin and clarithromycin in healthy volunteers has been associated with the

occurrence of macrolide resistance in the oral streptococcal flora [51]. In the AZISAST study, severe asthma patients had an increased proportion of oropharyngeal streptococci resistant to macrolides upon long-term treatment with azithromycin compared with placebo [48^{***}]. However, in the AZISAST study [48^{***}] and in the study by Albert *et al.* [19] in COPD, the increased occurrence of macrolide-resistant streptococci was restricted to colonization of the oropharynx or nasopharynx; there was no increase – and even a tendency to a decrease – in the rate of acute lower respiratory tract infections (bronchitis or pneumonia) and in the incidence of respiratory infections with resistant pathogens. However, proactive and intense monitoring of microbial resistance of common respiratory pathogens – both in individual patients and in the community – is mandatory [50].

Azithromycin use is associated with an increased risk of death from cardiovascular causes among older patients (>65 years old) at high baseline risk of cardiovascular disease [52]. In contrast, azithromycin use is not associated with an increased risk of cardiovascular death in a general population of young and middle-aged adults [53]. As macrolides can be proarrhythmic and induce torsade de pointes, the following criteria for selecting patients for long-term macrolide treatment have been proposed: pulse below 100 beats per minute, corrected QT interval of less than 450 ms on electrocardiography and no use of drugs known to cause QT prolongation [54]. Other contraindications for macrolide use include allergy to macrolides and the clinical suspicion of a pulmonary infection with mycobacteria (especially nontuberculous mycobacteria, as monotherapy with azithromycin will lead to the development of macrolide-resistant mycobacteria). Lastly, chronic macrolide use has been associated with liver toxicity and ototoxicity. In older individuals, formal audiography may be warranted to detect hearing loss as early as possible, as permanent hearing loss may occur upon continued use of macrolides.

FUTURE DIRECTIONS

Many research questions remain to be addressed. First, which macrolide should be preferred? Whereas azithromycin has a better pharmacokinetic profile and demonstrates less drug–drug interactions than erythromycin, one recent review suggested that the widespread use of azithromycin has a greater risk of adversely affecting macrolide resistance in the community [17^{***}]. Second, what is the optimal duration of chronic macrolide use? As exacerbations of asthma are more common

during the winter season – triggered by viral respiratory infections – restricting the maintenance treatment with macrolides to the winter period seems an interesting option in severe asthma patients with frequent viral-induced exacerbations. Moreover, in-vitro studies suggest that azithromycin induces antiviral responses against rhinovirus in bronchial epithelial cells [55]. Lastly, will newer macrolides without antibiotic effect have equal efficacy, but a better safety profile than current macrolides, as these nonantibiotic macrolides will not be associated with the risk of inducing antibiotic resistance?

CONCLUSION

In patients with uncontrolled severe asthma (GINA steps 4 and 5), targeted therapies should be added on top of high-dose fixed combinations of ICS and LABA according to the underlying clinical phenotype and pathophysiological endotype. The AZISAST study has shown that targeted add-on therapy with azithromycin provides clinical benefit in patients with exacerbation-prone, noneosinophilic severe asthma. These results need to be confirmed in larger long-term RCTs in well phenotyped patients with severe asthma (one such RCT is currently ongoing in Australia). In addition to this evidence-based medicine, we have also personal expertise in using macrolides in adults with severe asthma and patients with non-CF bronchiectasis [38]. In several patients with severe asthma, we have witnessed impressive responses to macrolide treatment, preventing exacerbations and offering the opportunity to taper – and even stop – maintenance treatment with oral corticosteroids. We hypothesize that the presence of neutrophilic airway inflammation in patients with severe asthma is a predictor of response to macrolides. However, we need confirmation that neutrophilic airway inflammation in severe asthma is indeed an accurate predictor of response to chronic low-dose macrolide treatment.

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Conflicts of interest

There are no conflicts of interest.

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