Macrolides and Asthma Therapy

Krishna Undela, Adil Adatia, Brian H. Rowe, and Giovanni Ferrara

Abstract Asthma is a chronic condition of the airways that is typified by bronchial hyperresponsiveness, variable airflow obstruction, and airway inflammation. Most patients can achieve disease control using inhaled corticosteroids, with some needing adjunct long-acting bronchodilator therapy. However, an important minority of patients have persistent symptoms and exacerbations despite these treatments. The landmark AMAZES study showed that the macrolide azithromycin significantly reduced the exacerbation rate in this population, using a randomized parallel group design. The efficacy of macrolides in chronic asthma was recently confirmed in a Cochrane systematic review, which analyzed 25 randomized controlled trials with a total of 1973 patients. Mechanistic studies have shown that this therapeutic effect is mediated by reduced mucosal inflammation, improved airway mucus clearance, and favorable modulation of host-pathogen interactions.

Keywords Macrolides · Acute asthma · Chronic asthma · Bacterial resistance · Asthma exacerbation

1 Introduction

Asthma is one of the most common respiratory diseases in all age groups, affecting 1–18% of the general population in different countries. The incidence of asthma has been increasing over the past several decades [1]. Asthma is characterized by airway

K. Undela
Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research (NIPER) Guwahati, Kamrup, Assam, India

A. Adatia · G. Ferrara (✉)
Division of Pulmonary Medicine, Department of Medicine, Faculty of Medicine & Dentistry, College of Health Sciences, University of Alberta, Edmonton, AB, Canada
e-mail: ferrara@ualberta.ca

B. H. Rowe
Department of Emergency Medicine, Faculty of Medicine & Dentistry and School of Public Health, both in the College of Health Sciences, University of Alberta, Edmonton, AB, Canada

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inflammation, leading to variable symptoms, often in the form of exacerbations, comprising wheezing, shortness of breath, chest tightness, and cough. A hallmark of asthma is variable and reversible expiratory airflow limitation, which is also diagnostic for this condition, although patients with untreated asthma may develop fixed airflow limitation over time [2].

Airway inflammation in asthma can be subclassified based on the presence or absence of type 2 (T2) immune signature. Asthma with elevated T2 immune response (T2-high asthma) is characterized by excessive expression of the cytokines including interleukin (IL)-4, IL-5, and IL-13, and the alarmins thymic stromal lymphopoietin (TSLP), IL-25, and IL-33. Patients with T2-high asthma typically have elevated fractional exhaled nitric oxide measurements, blood and sputum eosinophils, and/or serum immunoglobulin E (IgE). Patients with T2-low asthma are generally identified as those in whom such markers of a T2 immune signature are absent [3].

The main approach to treat asthma and prevent exacerbations is to treat airway inflammation with inhaled corticosteroids (ICS) beginning in the earliest phases of the condition, although the frequency and dosing of this treatment depend on disease severity and symptom burden. Additionally, inhaled short-acting beta 2 agonists (SABA), long-acting beta 2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) can be added to treat persistent or severe airflow limitation and symptoms [1].

The current Global Initiative for Asthma (GINA) guidelines provide guidance on how to diagnose asthma and how to treat patients experiencing different levels of severity by sequentially introducing and increasing the dosage and combination of asthma controller medications [1]. While ICS agents, often combined with LABAs and LAMAs, and novel treatments (e.g., leukotriene receptor antagonists [LTRA], biologic agents) have improved the lives of people living with the disease, symptom control has been elusive for some patients. Despite the progress achieved over the last 30 years, asthma morbidity and mortality remain a problem for national healthcare systems [4, 5]. Moreover, several questions and challenges still exist in the management of patients with asthma, especially in low- and middle-income countries.

First, asthma can present with a variety of clinical phenotypes and variable severity, and, often, inhaled drugs are unavailable or fail to achieve asthma control. In such cases, oral corticosteroids and, in patients with T2-high asthma, biologics targeting T2 inflammation such as IgE, IL-5/5R, IL-4alpha (which inhibits IL-4 and IL-13 signaling), or TSLP may be required [1, 2]. These severe cases account for a significant proportion of asthma-related morbidity and costs [6, 7], and often biologics are unavailable or prohibitively expensive [8]. Second, even inhalers are not always easy to use, especially for children and elderly patients, contributing to the main problem of nonadherence to treatment and suboptimal asthma control [9].

Therefore, there is still a need for new treatment modalities, and macrolide antibiotics have been investigated for several decades, thanks to their interesting properties [10]. Macrolides were initially investigated as potential corticosteroid-sparing agents [11]. Later, the possibility that asthma inflammation and asthma

exacerbations could be sustained by intracellular pathogens such as *Chlamydia pneumoniae* triggered interest in testing macrolides in patients with asthma [12, 13]. Finally, a well-designed, well-powered, and well-executed randomized controlled trial (RCT) demonstrated the benefit of treating with azithromycin to reduce asthma exacerbations in patients with moderate-severe asthma [14]. In this chapter, we reviewed the mechanisms behind the effect of macrolides in asthma, and the evidence for their use in acute and chronic forms of asthma.

2 Mechanisms of Action of Macrolides in Asthma

The mechanisms of macrolide therapy in asthma are incompletely understood. Myriad bioactive properties of macrolides have been described and are thought to contribute to their therapeutic effects including the modulation of mucosal inflammation, airway mucus, host-pathogen interactions, and gastrointestinal motility. Please refer to Fig. 1 for summary.

2.1 Anti-inflammatory and Immunomodulatory Effects

Macrolides have been shown in multiple small studies to attenuate eosinophilic and neutrophilic airway inflammation in T2-high and T2-low asthma, respectively

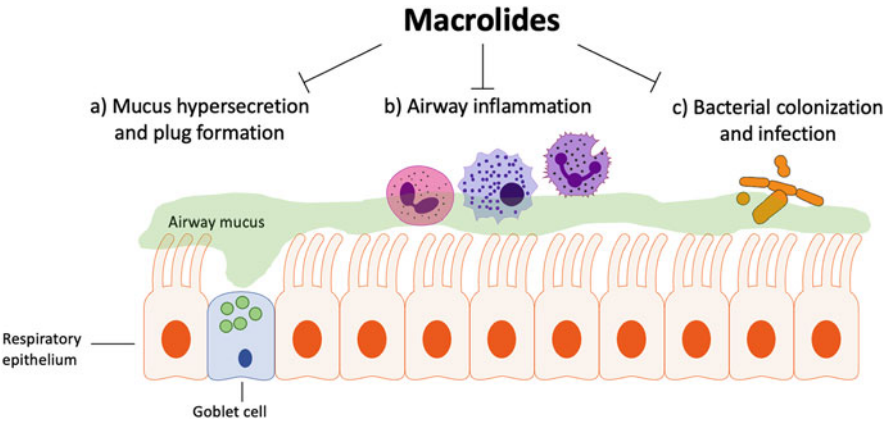

Fig. 1 Mechanisms of macrolides in asthma. Macrolides (**a**) reduce mucus hypersecretion and plug formation by inhibiting IL13-induced goblet cell hyperplasia and mucin glycoprotein MUC5AC production, (**b**) modulate airway inflammation by downregulating inflammatory cytokines (e.g., IL-1β, IL-6) and augmenting neutrophil efferocytosis, (**c**) reduce airway microbial diversity by inhibiting *Haemophilus* spp. and, in colonized patients, blocking biofilm growth of Pseudomonas aeruginosa by interrupting quorum sensing, and (**d**) may reduce asthma symptoms due to gastro-esophageal reflux by increasing gastrointestinal motility (not shown). *IL* interleukin

[15]. For example, a small RCT of clarithromycin in T2-low asthma demonstrated a reduction in the neutrophil chemoattractant IL-8 (chemokine (C-X-C motif) ligand 8, CXCL8) and total neutrophils found in sputum. Conversely, in the landmark AMAZES trial [14], a large randomized parallel-group study, azithromycin significantly reduced exacerbation rates with no apparent reduction in sputum eosinophil or neutrophil abundance. Thus, the clinical effects of azithromycin do not appear to be mediated by the amelioration of luminal granulocyte infiltration, although the sputum analysis methods used may not have fully captured the airway inflammatory endotype [16].

Azithromycin has been shown to downregulate inflammatory cytokines in the airway including IL-1β, IL-6, and extracellular DNA [17]. The decrease in sputum extracellular DNA is of particular interest given the emerging role of neutrophil extracellular traps (which are comprised of DNA, histones, and granular proteins) in asthma with sputum neutrophilia [18]. Azithromycin also augments the phagocytic function of alveolar macrophages. It promotes efferocytosis of neutrophils [19] and bronchial epithelial cells [20], and it enhances the phagocytosis of bacteria [21]. Creola bodies, which are clusters of apoptotic epithelial cells, are readily identified in sputa of patients with asthma, and their efficient clearance is important for the control of airway inflammation [22].

2.2 *Effects on Airway Secretions*

Macrolides appear to have significant beneficial effects on airway secretions. Mucus hypersecretion and altered mucus composition are well-established pathologic features of asthma [23], and recent studies have clearly demonstrated that luminal mucus plugging is a major contributor to chronic airflow obstruction in patients with asthma [24, 25]. Macrolides are partial antagonists of neutrophil elastase [26], a neutrophil granule protease that induces mucin glycoprotein MUC5AC production by goblet cells [27], and inhibiting IL13-induced goblet cell hyperplasia [28], thus attenuating mucus hypersecretion [29]. The increased mucus viscoelasticity that results from crosslinking cysteine residues on MUC5AC is also a key mechanism of mucus plug formation in asthma [24], so it is plausible that azithromycin additionally reduces luminal mucus plugging.

2.3 *Antimicrobial Effects*

Macrolides are bacteriostatic antibiotics that block protein synthesis by inhibiting the 50S ribosomal subunit. Azithromycin and clarithromycin are active against gram-positive, gram-negative, and atypical respiratory pathogens including *Streptococcus pneumoniae, Haemophilus* spp., *Mycoplasma pneumoniae, and Chlamydophila pneumoniae* [30]. Chronic azithromycin does not reduce the total bacterial load in

patients with asthma, but it does decrease respiratory microbial diversity, particularly by greatly reducing the abundance of *Haemophilus* spp. [31]. This reduction in *Haemophilus* spp. is likely clinically important given that a) the baseline abundance of *Haemophilus influenzae* in sputum appears to predict the efficacy of azithromycin [32] and b) the reduction of *Haemophilus influenzae* is associated with a reduction in pro-inflammatory cytokines, especially in patients with noneosinophilic asthma [17]. Such antimicrobial effects of macrolides are likely to play a larger role in patients predisposed to recurrent infective exacerbations such as those with comorbid primary ciliary dyskinesia and immunodeficiencies [33–35].

Azithromycin also inhibits biofilm growth of *Pseudomonas aeruginosa* by interrupting quorum sensing, the process by which bacteria modulate gene expression in response to population density [36], and by impairing twitching motility, which facilitates the formation of cell aggregates [37]. These mechanisms are thought to partly underlie the benefit of azithromycin in cystic fibrosis and noncystic fibrosis bronchiectasis [38]. Comorbid bronchiectasis and attendant *Pseudomonas* colonization is common in severe asthma [39, 40], and recent studies demonstrated that severe asthma cohorts have a significantly increased pathogenic cystic fibrosis transmembrane conductance regulator (*CFTR)* allele frequency [41, 42], suggesting a possible disease-modifying effect. Hence, the inhibition of biofilm development may be an important mechanism in such patients.

2.4 Effects on Gastrointestinal Motility

Azithromycin and erythromycin ligate the motilin receptor, resulting in increased gastrointestinal motility. Though generally viewed as an adverse off target effect (that causes diarrhea in an important minority of patients), some authors have argued that the increased gastrointestinal motility treats unrecognized gastroesophageal reflux disease (GERD) that triggers asthma symptoms and hence improves asthma control [43]. The role of GERD in triggering asthma symptoms is controversial, and a recent Cochrane review failed to demonstrate that the treatment of GERD significantly improves asthma outcomes [44]. It is plausible, nonetheless, that in a subset of patients, such as those with obesity, this mechanism plays a role.

3 Evidence of Macrolide Treatment Effectiveness

3.1 Acute Asthma

In general, acute asthma exacerbations are the result of exposures to airway irritants (i.e., air pollution, indoor fumes, viruses, environmental allergens, etc.) and/or loss of control due to management nonadherence. Consequently, the focus of treatment in acute asthma is an aggressive approach to reversing the inflammatory cause of the

exacerbation. For example, acute severe exacerbations are treated with SABA and short-acting anticholinergic (SAAC) agents, [45] systemic [46] and inhaled corticosteroids [47], and intravenous magnesium sulfate [46]. Since most patients respond to treatment and can avoid admission to hospital, current guidelines recommend the use of systemic [46] and inhaled corticosteroids [47] for all discharged patients and strategies to avoid triggers.

Since bacterial infections are thought to play a negligible role in most acute exacerbations, current guidance recommends against the universal use of antibiotics and restricts their use to cases where there are signs, symptoms, or investigations that confirm a bacterial infection. Despite these recommendations, these therapeutic agents remain prescribed in the management of patients with acute asthma. The anti-inflammatory mechanism of action of macrolides has the potential to contribute to the management of acute asthma and hence the interest in exploring the evidence.

The evidence base for this approach arises from a Cochrane systematic review that was last updated in 2018 involving 6 studies and 681 adults and children with exacerbations of asthma [48]. Importantly, most studies explicitly excluded patients with signs/symptoms of a bacterial infection. Four of the six studies involved macrolides and comparisons were made to standard of care or placebo. Overall, there was significant among-study heterogeneity, poor outcome reporting, and the evidence was imprecise. The authors concluded that there was insufficient evidence to support the use of antibiotics in adults and children with exacerbations of asthma.

An important issue to consider when prescribing antibiotics are the adverse effects such as gastrointestinal side effects, antibiotic-induced diarrhea, rash, and other allergies. The RCTs included in the systematic review reported adverse effects over the short-term and found no difference between those receiving antibiotics and those who did not. These results are imprecise and of low quality.

Given this evidence, in patients experiencing an exacerbation of asthma, we support an approach of seeking confirmation of bacterial infection and treating those patients with antibiotics. In the absence of clear bacterial infection, we recommend maximizing the anti-inflammatory management of all patients experiencing an exacerbation of asthma using systemic [46] and inhaled corticosteroids [47]. Finally, antibiotics might be a reasonable alternative in cases where patients have not fully recovered from their asthma symptoms following aggressive anti-inflammatory treatment.

3.2 Chronic Asthma

The use of macrolides for the management of chronic asthma has been a vigorously debated topic for the past three decades. Preliminary studies on macrolides in people with asthma have suggested a steroid-sparing effect [11, 49], while later reports have demonstrated an anti-inflammatory effect of this class of antibiotics, whereby macrolides also seem to decrease bronchial hyperresponsiveness associated with eosinophilic inflammation [50–53]. Recent studies have identified the effects of

macrolides on various clinical outcomes of asthma, such as exacerbations requiring hospitalization, emergency department (ED) visits, use of systemic corticosteroids [54, 55], symptoms, asthma control, quality of life [56, 57], change in rescue medication [58, 59], and/or lung function tests such as forced expiratory volume in 1 second (FEV_1) and peak expiratory flow (PEF) [54, 55, 57, 59].

Most RCTs have evaluated the efficacy of azithromycin [14, 52, 54, 57, 58, 60–63], followed by clarithromycin [50, 51, 53, 59, 62, 64, 65], roxithromycin [66–69], and oleandomycin [11, 49]. A well-designed RCT (AMAZES study) with a large sample size of well-selected participants identified that azithromycin 500 mg three times weekly for 48 weeks reduced asthma exacerbations and improved the quality of life of adults with symptomatic asthma despite the current use of moderate-to-high doses ICS and LABA therapy [14]. In another RCT, children aged 1–3 years with recurrent asthma-like symptoms responded positively to a 3-day course of an azithromycin oral solution (10 mg/kg per day). The mean duration of episodes of asthma-like symptoms after treatment with azithromycin was 3.4 days compared with 7.7 days for children receiving placebo. Evidence suggests that the effect increases with early initiation of therapy [70]. An RCT conducted to evaluate the effect of 16 weeks of clarithromycin in addition to fluticasone in adults with mild-to-moderate persistent asthma suboptimally controlled with low-dose ICS agents alone demonstrated no beneficial effect on asthma control or lung function when clarithromycin was added to fluticasone. A significant reduction in airway hyperresponsiveness, however, was observed with clarithromycin treatment in this study [59].

The most recent Cochrane systematic review on macrolides for chronic asthma included 25 RCTs and involved 1973 patients. The primary findings were that macrolides likely reduce exacerbations requiring hospitalizations, ED visits, and/or treatment with systemic corticosteroids compared with placebo, and may reduce asthma symptoms, resulting in slightly improved asthma control [10]. Another systematic review of three RCTs identified that children treated with macrolides had a significantly lower time to symptom resolution and a decrease in the severity of symptoms than controls. No difference was detected, however, in hospitalization and time to the next exacerbation between groups [71].

Overall, the current evidence suggests that macrolides provide a potential benefit to patients with moderate-severe asthma. International guidelines and consensus statements suggest adding azithromycin if a patient has persistent, uncontrolled asthma despite high-dose ICS and LABA therapy, as an alternative to biologics [1, 72, 73]. Hence, macrolide therapy may be especially useful in resource limited settings where biologics are not widely available. Macrolide therapy is also one of the only evidence-based treatments available for patients with T2-low asthma who do not adequately respond to high-dose ICS, LABA, and LAMA treatment and is thus widely used in this patient population [74].

4 Conclusions

Macrolides have been investigated in different asthma populations and in different clinical settings. There is no convincing evidence for the use of macrolides to treat acute asthma exacerbations in the absence of concurrent bacterial infection. Conversely, a large, well-designed RCT in chronic asthma clearly demonstrated that azithromycin reduces asthma exacerbation rates in patients who are inadequately controlled despite ICS and LABA therapy [14]. This finding was confirmed by a Cochrane systematic review [10] and a meta-analysis of individual patient data [75].

International guidelines and position statements recommend considering chronic azithromycin therapy in uncontrolled patients already treated with high-dose ICS and LABA therapies as an alternative to biologics [1, 72, 73]. Hence, it may be particularly useful in resource-constrained healthcare settings where the cost of biologics is prohibitive. Macrolides are generally considered to be safe, although this aspect has not been widely studied in resource-limited settings where older classes of drugs (e.g., digoxin) are still widely used.

Chronic use of antibiotics may increase the development of antibiotic-resistant bacterial strains that cause respiratory and systemic infections. Whether the use of macrolides for the treatment of asthma aggravate this problem, particularly in areas where antibiotic resistance is already a serious issue, is a question that needs to be addressed with properly designed studies and surveillance strategies. A clear risk/benefit assessment and strict patient selection criteria for the use of macrolides in chronic asthma are paramount to secure individual benefit and to avoid potential detrimental consequences for the patient and the community.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of Interest All authors declare they have no conflict of interest.

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