

Long-term macrolide antibiotics in asthma therapy

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Abstract

Macrolide antibiotics drew worldwide attention when their use was dramatically successful in the treatment of diffuse panbronchiolitis in 1980s. The success was attributed to their immunomodulatory effects, rather than their antimicrobial properties. Since then, studies have shown that macrolides exert their immunomodulatory effects through several mechanisms, including suppression of proinflammatory cytokines, promoting apoptosis of inflammatory cells, improving phagocytic function, ameliorating airway hypersecretion, and inhibiting production of reactive oxygen species. Macrolides have also been studied in the treatment of asthma. This review highlights the role of macrolides in the treatment of asthma, presenting an overview of the main clinical trials. Despite favourable preclinical data and reports of anecdotal successes, the results of clinical trials are conflicting. This may be due to the heterogeneous nature of asthma. Further studies are needed to identify particular subgroup of asthma that will respond to macrolides.

Keywords

Macrolide; Asthma; Chronic inflammation; Immunomodulation; Noneosinophilic asthma

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Introduction

Macrolides consist of an expansive family of compounds characterised by the presence of a macrocyclic lactone ring. Interestingly, two broadly used immunosuppressive agents, sirolimus (rapamycin) and tacrolimus (FK-506), are also members of macrolide family. However, these agents are not included when we use the term “macrolides” in this review unless otherwise indicated.

Macrolides are classified according to the size of the lactone ring. Erythromycin-derived 14- and 15-member macrolides draw particular interest due to their immunomodulatory function [1]. The immunomodulatory effect first drew considerable attention in the 1980s when long-term low-dose erythromycin treatment achieved large success in the treatment of diffuse panbronchiolitis [1]. Diffuse panbronchiolitis is a disease that is almost exclusively found in East Asia, especially in Japan. It is characterised by chronic cough, chronic sinusitis, sputum production, and progressive dyspnoea that eventually lead to respiratory failure and death. This was previously a commonly fatal disease with a five year survival rate of only 63%. The survival rate has improved to more than 90% since the introduction of long-term low-dose erythromycin treatment [1-3]. This dramatic success was attributed to its immunomodulatory effects rather than its antimicrobial effect, because clinical improvement has been reported regardless of the state of chronic infection and despite the observation that antibiotic concentrations were frequently well below the minimum inhibitory concentration of several pathogenic bacteria [4]. Persistent airway colonization with bacteria despite the improvement was also demonstrated.

Given this success, large efforts have been devoted to elucidate the mechanism of macrolide immunomodulatory effects. Clinically, macrolides have also been employed to treat other chronic inflammatory lung diseases, including cystic fibrosis, bronchiectasis, chronic obstructive pulmonary disease (COPD), post-transplantation bronchiolitis obliterans, chronic rhinosinusitis, and asthma, with varied results.

In this review, we will first outline the current understanding of asthma pathogenesis. Next, we summarise how macrolides affect the immune system in the context of asthma. Finally we present an overview of the results of clinical trials, and speculate on future directions for investigation.

Pathogenesis of asthma

Asthma is a chronic inflammatory disease of the airways, characterised by airflow obstruction and bronchial hyper-responsiveness. Autopsy and biopsy studies demonstrate airway infiltration with lymphocytes, eosinophils, and degranulated mast cells, denudation of airway epithelium, sub-basement-membrane collagen deposition, and goblet cell hyperplasia [5]. Neutrophil infiltration is also seen in certain subgroups of patients [6-8]. An abnormal immune response, mediated by type 2 helper (Th2) cells, underlies this complex inflammatory process [9]. When a genetically susceptible individual is exposed to a certain antigen, the antigen is taken up, processed, and presented by antigen presenting cells such as dendritic cells. Upon stimulation by antigen presenting cells, Th2 cells excrete various cytokines and promote the immune reaction characteristic of asthma. The major cytokines excreted from Th2 cells are IL-4, IL-5, IL-6, IL-9 and IL-13 [5,10]. These cytokines stimulate IgE production by B cells. IgE binds to IgE receptors on mast cells. Mast cells are located mainly on the epithelial surface areas of the body such as bronchial mucosa. Cross linkage of the mast cell bound IgE by the antigen causes degranulation of the mast cells and release of preformed and newly formed bioactive mediators, including histamine and leukotrienes which in the lung cause bronchoconstriction and glandular secretion. Mast cells also produce several cytokines, including IL-1, IL-2, IL-3, IL-4, IL-5, granulocyte-macrophage colony-stimulating factor, interferon- γ , and tumor necrosis factor, which promote proliferation and survival of T cells, eosinophils, and mast cells (positive feedback) and contribute

to persistence of the inflammation. Cytokines produced by Th2 and mast cells promote eosinophil proliferation and infiltration. Activated eosinophils produce inflammatory proteins, including major basic protein, eosinophil-derived neurotoxin, peroxidase, and cationic protein. Reactive oxygen species are also produced. These chemicals directly injure airway epithelium. Eosinophils also produce leukotrienes, which contract airway smooth muscles, increase vascular permeability and may recruit more eosinophils [5,9-11].

The airway epithelial cells play an important role in initiation and maintenance of the inflammation in asthma [10,11]. Tight junctions between asthmatic epithelial cells are disrupted and allow easier entry of allergens and microbes into the subepithelial space, which leads to immune activation. Activated epithelial cells produce chemokines, such as eotaxin-1 and -2, RANTES and monocyte chemoattractant proteins-3 and -4, which attract eosinophils, lymphocytes, and mast cells. Airway epithelial cells also produce nitric oxide, which contributes to airway inflammation [9].

The end result of these processes is persistent inflammation of the airways leading to airflow obstruction and bronchial hypersensitivity. If these processes are allowed to persist, airway remodelling characterized by subepithelial thickening and smooth muscle hyperplasia and hypertrophy ensues [10]. These changes result in irreversible airflow obstruction.

Recently, the contribution of neutrophilic inflammation in asthma is drawing special attention [6-8,12]. It is not uncommon and is often seen in patients with severe and poorly controlled asthma. Neutrophils are the most common inflammatory cells seen in adult asthma exacerbations.

Macrolide effects in asthma

Major macrolides immunomodulatory effects relevant to asthma are summarized in Table I.

Cytokines

A number of studies since the 1990s have demonstrated that administration of various macrolides suppresses proinflammatory cytokine production in asthma and non-asthma, *ex vivo* and *in vivo*, both in animal and human subjects [13-71]. Proinflammatory cytokines in the lung demonstrated to be suppressed by macrolides include IL-1, 2, 3, 4, 5, 6, 8, 10, 13, TNF α , eotaxin, GM-CSF, RANTES, CCL20 (CTACK), CCL27 (MIP-3 α), MIP-2, and VEGF. As noted above, Th2-type cytokines (IL-4, 5, 6, 9, and 13), especially IL-5 as an eosinophil promoter, play a major role in pathogenesis of asthma.

Noma et al. collected peripheral blood T cells from paediatric asthmatic patients who were sensitized by *Dermatophagoides farimae* and demonstrated roxithromycin suppressed antigen-stimulated T cell proliferation and production of IL-4 and IL-5 in a dose dependent fashion [13]. Lyn et. al similarly demonstrated azithromycin suppressed IL-5 production by T cells from asthmatic children *ex vivo* [14]. Beigelman et al. used an ovalbumin-sensitized mouse model of asthma and demonstrated that azithromycin attenuated leukocytosis in bronchoalveolar lavage (BAL) caused by antigen administration [15]. Furthermore, analysis of the BAL leukocyte differential demonstrated that azithromycin attenuated all inflammatory cell types including eosinophils, macrophages, lymphocytes, and neutrophils. However, the largest fold-reduction was noted in eosinophils. BAL cytokine levels of IL-5 and

Immunomodulatory effect	Reference
Suppression of proinflammatory cytokines	13-71
Promote apoptosis of neutrophils and lymphocytes	74-82
Improve amount and quality of airway secretion	73,87-92
Improve phagocytotic function	72,83-85
Antimicrobial effect	93-95
Suppresses ROS/NOS production	107-113

Table I. Immunomodulatory effects of macrolides

IL-13, as well as chemokines, CCL2 (also known as monocyte chemoattractant protein-1, MCP-1), CCL3 (also known as macrophage inflammatory protein-1 α , MIP-1 α), and CCL4 (also known as macrophage inflammatory protein-1 β , MIP-1 β) were also suppressed. Amayasu et al. showed asthmatic human subjects treated with 200 mg of clarithromycin twice daily for 8 weeks had significantly decreased blood and sputum eosinophils [16].

Even though these data indicate that macrolides do suppress Th2-type cytokines (IL-4, 5, 6, and 13), the immunomodulatory effect of macrolides is most established in their suppression of IL-8 and TNF- α which are more closely linked with neutrophilic inflammation. Simpson et al. demonstrated that clarithromycin 500 mg twice daily can suppress IL-8 levels, neutrophil accumulation and activation in the airways in patients with noneosinophilic asthma [17]. It is increasingly known that non-eosinophilic asthma is common and neutrophilic inflammation plays an important part in the pathogenesis of this asthma variant [6-8,12]. Studies have demonstrated that neutrophilic inflammation is more resistant to corticosteroid treatment, and elevations of IL-8 level are found in these patients. Additionally, common irritants associated with asthma exacerbations such as air pollution, bacterial endotoxins, viral infections, and ozone, also cause neutrophilic inflammation [12]. Therefore, macrolides are attractive agents that may prove efficacious in both noneosinophilic and irritant asthma.

Survival of inflammatory cells, hypersecretion and phagocytosis

The mechanism of persistent inflammation in asthma is unclear. However, it has been proposed that pre-programmed apoptosis and the phagocytosis of these apoptotic cells by macrophages (efferocytosis) play an important role in the resolution of inflammation [72,73]. Mucus hypersecretion and ciliary dysfunction, which are characteristic of asthma, also impair clearance of the inflammatory cells which provides a nidus for bacterial colonization that further promotes persistence of inflammation [72]. Macrolides may work on each component of these processes.

There is some evidence showing that macrolides can promote apoptosis of neutrophils and lymphocytes. Erythromycin, roxithromycin, clarithromycin, and azithromycin are shown to promote neutrophil apoptosis [74-76]. Suppression of lymphocytic survival is also shown in azithromycin and roxithromycin [77-79]. Some studies also suggest that macrolides may influence eosinophil survival [80,81]. However, it is not clear if these effects are through direct effects or above-mentioned suppression of cytokines and growth factors. Interestingly, some researchers have reported enhanced apoptosis in bronchial smooth muscle cells [82].

Clearance of the apoptotic cells is mainly carried out by macrophages (efferocytosis). Disturbance of this process can lead to secondary necrosis of inflammatory cells and exacerbation and persistence of inflammation. In COPD (chronic obstructive pulmonary disease), there is evidence that this pathologic process is important [72]. In asthma, the evidence is scarce, but Huynh et al. did demonstrate fewer phagocytic bodies in BAL from patients with severe asthma compared with control patients or patients with mild to moderate asthma [83]. They also demonstrated that macrophages from patients with severe asthma have decreased phagocytotic function *in vitro*. Together, these data indicate that this pathologic process may also play a role in asthma. Macrolides were shown to improve phagocytotic function of alveolar macrophages in healthy volunteers [84] and in COPD patients [85]. Therefore, macrolides may improve clearance of inflammation by improving inflammatory cell clearance via phagocytosis.

Airway mucus hypersecretion is an important pathophysiological feature of asthma. Excessive mucus can obstruct airways and impairs clearance of inflammatory cells which leads to persistence of inflammation [73,86]. Macrolides decrease mucus secretion via several mechanisms such as suppression of NF- κ B, cytokine production, and direct inhibition of chloride channels [87-89]. Macrolides not only

decrease the amount of secretion but also alter the rheological character of the mucus and making it easier to expectorate [90-92].

Chronic infection

Macrolides may also improve asthma through their intrinsic antimicrobial effect. Persistent atypical bacterial infections, especially with *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, have been implicated in the pathogenesis of asthma. Martin et al. examined clinical specimens from the nasopharynx, the oropharynx, and the lung (BAL, brushing, and endobronchial biopsy) for the presence of clamydial or mycoplasmal infection from 55 stable asthmatic patients and 11 healthy controls in the United States [93]. Thirty-one asthmatic patients (56.4%) were found to have positive PCR results for either *M. pneumoniae* (25 patients or 45.5%) or *C. pneumoniae* (6 patients or 10.9%). A study from Turkey also reports higher rates of PCR positivity for *C. pneumoniae* in stable asthmatic patients compared with healthy subjects [94]. These data suggest that chronic atypical bacterial infection is common in asthmatic patients and it may contribute to the pathogenesis of asthma.

Macrolides are well known for their superior coverage of atypical organisms. Simply eradicating chronic infection through the use of macrolides, therefore, may significantly improve asthma control in these patients. Kraft et al. conducted a randomized placebo-controlled trial of clarithromycin treatment in 55 stable asthmatic patients [95]. All of the patients underwent bronchoscopy and were evaluated for *C. pneumoniae* and/or *M. pneumoniae* PCR positivity. Clarithromycin treatment resulted in a significant improvement in the FEV₁ only in the PCR-positive subjects (2.50 ± 0.16 l, to 2.69 ± 0.19 l, mean \pm SEM; $p = 0.05$). Clarithromycin-treated PCR positive patients also demonstrated a greater reduction in inflammatory cytokines in the lung than PCR-negative patients.

Viral infection

Viral infection is a major cause of asthma exacerbations (80-85% in children, 70-75% in adults [96]). There is some evidence that macrolides can ameliorate respiratory viral infection [97-103]. However, there are few data about macrolide effect specifically on virus-induced asthma exacerbation. One randomized controlled trial evaluated a group of patients with asthma exacerbation of whom 60% had serological evidence of *Mycoplasma* or *Chlamydia* infection. In this population, telithromycin treatment did demonstrate a decrease in asthma symptom scores [104]. While many of these patients may have had viral infections, it is difficult to assess the specific benefit of macrolides in regards to viral infection in this study.

Reactive oxygen/nitrogen species (ROS/RNS) production

ROS/RNS are produced by inflammatory cells (neutrophils, eosinophils, and alveolar macrophages) and contribute to airway inflammation in asthma [105,106]. Data suggest that macrolides interfere with ROS/RNS production [107-113]. For example, Borszcz et al. demonstrated that the human eosinophil and neutrophil respiratory burst was inhibited by up to 54% with clarithromycin [113].

Clinical trials

Despite the above mentioned promising results from various experimental models and anecdotal successes, clinical trials are somewhat disappointing. A summary of randomized controlled trials is presented in Table II.

Author, year [ref.]	Patients	Study design/ interventions	Main outcomes	Note
Nelson, 1993 [117]	75 adult patients with steroid-dependent asthma	Double-blinded, randomized, placebo-controlled study. Troleandomycin plus methylprednisolone vs. methylprednisolone alone	No difference in steroid dose reduction More steroid-related adverse events in troleandomycin group	See note from Kamada, 1993 section
Kamada, 1993 [115]	18 children with severe, steroid-requiring asthma	Double-blinded, randomized, 3-arm parallel study. Troleandomycin plus methylprednisolone vs. troleandomycin plus prednisone vs. methylprednisolone only	No difference in pulmonary function nor PC ₂₀ -methacholine between 3 treatment arms. Significant decrease in steroid requirement in all treatment arms compared within the groups vs. baseline. Only significant difference noted between troleandomycin + methylprednisolone group and methylprednisolone only group: 80% ± 6% vs. 44% ± 14%, respectively	Troleandomycin is noted to increase bioavailability of methylprednisolone [121] and also reduce elimination of theophylline [122,123]
Shoji, 1999 [118]	14 adult patients with mild to moderate aspirin-intolerant asthma	Double-blinded, randomized, crossover study Roxithromycin 150 mg/ bid vs. placebo, for 8 weeks	No improvement in PFT. Improvement in symptom score. Decrease in blood eosinophils and ECP (roxithro vs. placebo: 12.4 ± 2.3 vs. 42.8 ± 7.6 x10 ⁴ /ml, 3.6 ± 1.4 vs. 14.8 ± 7.6 mg/l) Decrease in sputum eosinophils and ECP (roxithro vs. placebo: 10 ± 6 x10 ⁴ /ml vs. 90 ± 33 x10 ⁴ /ml, 0.4 ± 0.1 vs. 1.7 ± 0.9 mg/l)	
Amayasu, 2000 [16]	17 adult patients with mild to moderate stable asthma	Double-blinded randomized, crossover study Clarithromycin 200 mg bid vs. placebo, for 8 weeks	No improvement in PFTs. Improvement in symptom score. Decrease in sputum and blood eosinophils: sputum 11 ± 6 x10 ⁴ /ml vs. 88 ± 36 x 10 ⁴ /ml, blood 12.0 ± 2.4 x 10 ⁴ /ml vs. 47.5 ± 6.6 x 10 ⁴ /ml, clarithromycin vs. placebo, mean ± SD. Decrease in hyper-reactivity: Log (PC ₂₀ -methacholine) 2.96 ± 0.57 vs. 2.60 ± 0.51, clarithromycin vs. placebo	
Black, 2001 [114]	232 adult patients with asthma and IgG/IgA to <i>C. pneumoniae</i>	Double-blinded randomized, placebo-controlled study. Roxithromycin 150 mg/ bid vs. placebo, for 6 weeks	Improvement in evening PEF (change in evening PEF, roxithromycin vs. placebo = 15 l/min vs. 3 l/min, p = 0.02). No improvement in FEV ₁ . Nonsignificant improvement in symptom score	
Kraft, 2002 [95]	55 adults patients with stable asthma	Double-blinded, randomized placebo-controlled study, clarithromycin 500 mg/ bid vs. placebo. The patients were evaluated by PCR for infection with <i>Chlamydia</i> or <i>Mycoplasma</i>	Improvement in FEV ₁ found only in PCR-positive patients in treatment group: mean ± SEM, 2.50 ± 0.16 l to 2.69 ± 0.19 l. More decrease in inflammatory cytokines (TNF-α, IL-5, IL-12 mRNA in BAL) in PCR-positive group	PCR for <i>Chlamydia</i> or <i>Mycoplasma</i> was positive in 31 out of 55 patients

Author, year [ref.]	Patients	Study design/ interventions	Main outcomes	Note
Kostadima, 2004 [116]	75 adult patients with stable asthma on moderate dose of inhaled budesonide	Double-blinded randomized placebo-controlled study with 3 arms. Clarithromycin 250 mg/bid vs. clarithromycin 250 mg/tid vs. placebo, for 8 weeks	No difference in spirometry findings. Improvement in PC ₂₀ -methacholine only in clarithromycin treated groups with trend favouring higher dose group (before vs. after, median: clarithro bid 0.3 mg vs 1.3 mg, clarithromycin 250 mg/tid 0.4 mg vs.2 mg, and placebo 0.4 mg vs. 0.3 mg)	
Strunk, 2008 [120]	55 children with moderate-to-severe asthma who require inhaled steroid for control	Double-blinded randomized placebo-controlled study, 3 arms azithromycin, montelukast, or placebo. Primary outcome was time to inadequate control as inhaled steroid dose was gradually tapered	No difference were noted for either treatment compared with placebo in time to inadequate control status: azithromycin vs. montelukast vs. placebo = 8.4 wks (95%CI 4.3-17.3) vs. 13.9 wks (95%CI 4.7-20.6) vs. 19.1 wks (95%CI = 11.7-infinity)	The study was prematurely terminated due to futility
Simpson, 2008 [17]	45 adult patients with severe refractory asthma	Double-blinded, randomized placebo-controlled study. Clarithromycin 500 mg bid vs placebo, for 8 weeks	Decrease in IL-8: clarithro vs. placebo, 3.9 (IQR = 1.8-5.4) vs. 6.4 (IQR = 3.7-11.3), p < 0.05 Decrease in MMP-9 (ng/ml): clarithro vs. placebo, 3074 (IQR = 1,806-7,084) vs. 6724 (IQR = 3620-14,335), p < 0.05. No difference in FEV ₁ and symptoms score. No significant improvement in sputum neutrophil counts and neutrophil elastase level. These trends are more pronounced in noneosinophilic asthma patients	
Sutherland, 2010 [119]	92 adult patients with mild-to-moderate asthma that was not well controlled	Double-blinded randomized placebo-controlled study. Stratified according to PCR result for <i>M. pneumoniae</i> or <i>C. pneumoniae</i> . Clarithromycin 500 mg/bid vs. placebo, for 16 weeks	No difference in ACQ score. No difference in PFTs. No difference in exhaled nitric oxide Improvement in bronchial hyper-responsiveness measured in PC ₂₀ -methacholine: mean ± SE, 1.2 ± 0.5 doubling doses (p = 0.02)	Originally planned to recruit approximately 75 patients in each arm. However, the recruitment for PCR-positive patients did not reach the goal due to lower-than-expected PCR positivity. Only 12 out of 92 patients were PCR positive

Table II. Summary of clinical trials: double-blinded randomized controlled trials whose treatment duration is at least 4 weeks with clinical outcomes

95%CI = 95% confidence interval; ACQ = asthma control questionnaire; BAL = bronchoalveolar lavage; ECP = eosinophil cationic protein; FEV₁ = forced expiratory volume at 1 second; IQR = interquartile range; PC₂₀-methacholine = provocative concentration of methacholine causing a 20% fall in FEV₁; PEF = peak expiratory flow; PFT = pulmonary function test; SD = standard deviation; SE = standard error

The most recently published Cochrane systematic review on macrolides for chronic asthma summarised all relevant randomized controlled trials (RCTs) up to May 2007 [124]. This review identified 7 RCTs in which asthma was treated with a macrolide for at least 4 weeks. A total of 416 patients were recruited. The meta-analysis demonstrated no significant difference in FEV₁, despite significant differences noted in markers of eosinophilic inflammation and symptoms. The authors concluded that «these data are insufficient to recommend the routine use of macrolides for control of asthma at present, even though some clinical data indicate a positive effect». They pointed out that the quality of these studies was generally low and that the patient samples were heterogeneous. They concluded that larger well designed studies are needed.

Since the Cochrane review, there have been 3 RCTs. One involved children and the others included adult patients. These three new RCTs are also not encouraging.

Strunk et al. included 55 children 6 to 17 years of age with moderate-to-severe persistent asthma [66]. They were randomized to 3 groups: 1. placebo, 2. azithromycin (250 mg for those 25-40 kg or 500 mg for those > 40 kg once daily), and 3. montelukast 5 mg or 10 mg once daily (based on age). The primary outcome was time from randomization to inadequate asthma control. The protocol included a sequential budesonide dose reduction after 6 weeks of treatment with investigation medications. The study was originally designed to recruit 210 randomized children. However, the study was terminated after randomized 55 patients due to futility (median time to inadequate control status: azithromycin median 8.4 weeks (95%CI = 4.3-17.3), montelukast 13.9 weeks (95%CI = 4.7-20.6), placebo 19.1 weeks (95%CI = 11.7-infinity). Of note, the well accepted treatment with montelukast also did not show benefit in this study.

Simpson et al. randomized 46 adult patients with symptomatic refractory asthma to clarithromycin 500 mg/bid vs. placebo for 8 weeks [17]. The randomization was stratified according to high and low neutrophil counts in the sputum. The treatment group demonstrated significant reduction in airway IL-8 levels and MMP-9 levels compared with placebo (IL-8, ng/ml: 3.9 (IQR = 1.8-5.4) vs. 6.4 (IQR = 3.7-11.3); MMP-9, ng/ml: 3074 (IQR = 1,806-7,084) vs. 6724 (IQR = 3620-14,335)). There was also a trend towards decreased sputum neutrophil counts and improvement in asthma control scores in the treatment group; however, these values were not statistically significant when compared to placebo. There was also no improvement in spirometric findings. Of the 46 patients, 28 patients had noneosinophilic asthma and the above mentioned findings were more pronounced in this subgroup.

Sutherland et al. recruited 92 adult asthma patients with mild-to-moderate persistent asthma that was not well controlled despite treatment with low-dose inhaled corticosteroids [119]. The patients were divided based on the result of lower airway PCR for *M. pneumoniae* or *C. pneumoniae* (there were 80 patients in PCR negative group and 12 in positive group). Within each group, patients were randomized to either clarithromycin (500 mg/bid) or placebo. The primary outcome was the change in the Asthma Control Questionnaire (ACQ) score after 16 weeks of study treatment. Although underpowered, no beneficial effect of clarithromycin was noted in the ACQ score in either patient group or overall. The authors also observed no difference in pulmonary function tests, in exhaled nitric oxide concentration, or in Asthma Quality of Life Questionnaire Score which were secondary outcomes. There was a small improvement in PC₂₀ doubling dose (1.2 ± 0.5 , $p = 0.01$).

Potential adverse effects

A well written summary article by Altenburg et al. finds that gastrointestinal complaints are the most common adverse effects of macrolide therapy [1]. Other infrequently reported side effects are rash and hepatotoxicity. Rare but well known and potentially significant adverse reactions include ototoxicity and cardiac toxicity. Development of antibiotic resistance is also a concern. Given that the benefit of chronic macrolide use for asthma is still uncertain, clinicians should use careful judgment in case-by-case bases.

Conclusion and future directions

Asthma has been recognized as a heterogeneous disease [6]. Corticosteroids have been a mainstay of asthma treatment for years. However, it is well recognized that there are subgroups of patients who are resistant or not well controlled with corticosteroids and there is a strong need for other effective therapies. Recently, newer agents that are more focused on specific pathologic processes are increasingly available. Anti-IgE monoclonal antibody (omalizumab), anti-IL5 monoclonal antibody (mepolizumab), anti-TNF- α agents (such as infliximab, etanercept, adalimumab, golimumab), and anti-leukotriene agents (such as montelukast, zileuton) are some examples. Even though these agents may not be as effective as corticosteroids in the general asthma population, they can be very effective in certain subgroups of asthma patients. Macrolides have been recognised for their immunomodulatory effects and have attracted great interest as an additional asthma treatment. However, clinical trials conducted on general asthma populations have been conflicting. It may be that there are not enough well designed RCTs, but it may also be the case that macrolides are only effective in certain subgroups of asthma patients. Macrolides exert their immunomodulatory effects through a wide range of mechanisms as discussed above. However, suppression of neutrophilic inflammation through inhibition of NF- κ B and AP-1 pathways seems to be a major mechanism [78,125-132]. Hence, the most promising asthma subpopulations in which macrolides may be most effective are patients with noneosinophilic asthma and patients with chronic airway infection. Additional well designed clinical trials are needed to answer this question. Until then, macrolides will remain as a potentially attractive but not yet proven treatment option of asthma.

Questions for further research

It is important to identify subgroup of asthma patients who benefit from macrolide antibiotics. Asthmatics with evidence of chronic atypical infection or patients with noneosinophilic asthma are the most promising.

The review in brief

Clinical question	Overview of the current knowledge on macrolide antibiotics in asthma therapy
Type of review	Narrative
Search of the literature	PubMed, with keywords: Macrolide; Asthma; Chronic inflammation; Immunomodulation; Noneosinophilic asthma
Conclusions	Macrolides have immunomodulatory property, which acts on various aspect of immune system. Despite anecdotal success, they lack definitive evidence in asthma therapy. Results of randomized controlled trials are conflicting. Further studies are necessary, which are focused on particular subgroups of asthma patients.
Limitations	Clinical trials on specific subgroup of asthma are limited.

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